PHYSIOLOGYNEWS

spring 2005 | number 58

IUPS 2005
Images of the Bristol, Nottingham, Oxford and KCL Meetings

Also featuring:
Living history – the case of the misbehaving circuit
50 years of caveolae
Obesity – why all the noise?
From tadpole to frog: a tale of two networks
The Nobel Prize

A publication of the Physiological Society

King's College London

Images from and around King's College London, venue for the Physiological Society Meeting 17-20 December, 2004

(photos by Prem Kumar)

More images from the KCL Meeting appear on the inside back cover

The Society's dog. 'Rudolf Magnus gave me to Charles Sherrington, who gave me to Henry Dale, who gave me to the Physiological Society in October 1942'

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Contributions and Queries

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Cover photo

Cover illustration from Combes *et al.* p. 17

Ventral view of metamorphosing stage 61 *Xenopus* tadpole. Background activity is rhythmic spinal ventral root discharge simultaneously driving tail oscillations during swimming (top trace) and limb extension-flexion thrusts (lower traces). *Photography courtesy of Sean Earnshaw, University of St Andrews, using a Nikon FM SLR camera with 110 mm macro lens.*

PHYSIOLOGYNEWS

Action points

Grants

For full information on Members' and Affiliates' Grants, Pfizer *in vivo* Physiology Grants, Network Interaction Grants, Non-Society Symposia Grants, Postgraduate Support Fund information and the Vacation Studentship Scheme visit: http://www.physoc.org/grants

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Applications for Full and Affiliate Membership are received throughout the year and have no deadlines. A decision is normally made within 8-10 weeks of the Administration Office receiving the application. For full details please visit: http://www.physoc.org/join

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Changes can be emailed to: jgould@physoc.org or updated online at http://www.physoc.org

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Physiology News

Deadlines

Letters and articles and all other contributions for inclusion in the Summer 2005 issue, No. 59, should reach the Publications Office (lrimmer@physoc.org) by 20 April, 2005. Short news items are encouraged and can usually be included as late copy if space permits.

Suggestions for articles

Suggestions for future articles are welcome. Please contact either the Editorial Administrator or a member of the Editorial Group of *Physiology News* (see contents page for details).

Physiology News Online

Physiology News is now available on our website: http://www.physoc.org.

Guidelines for contributors

These guidelines are intended to assist authors in writing their contributions and to reduce the subsequent editing process. The Editorial Group of *Physiology News* tries to ensure that all articles are written in a journalistic style so that they will have an immediate interest value for a wide readership and will be readable and comprehensible to non-experts. In particular, scientific articles should give a good overview of a field rather than focus entirely on the authors' own research.

Format of articles

The main message or question posed should be introduced in the first paragraph. The background for the topic should then be established, leading up to the final conclusion.

Length of articles

This will be determined by the subject matter and agreed with the Editorial Administrator.

Submission of articles

Authors should submit articles as a Word document attached to an email. Illustrations should be sent as separate attachments (see below) and not embedded in the text.

Illustrations and authors' photographs

Authors are encouraged to submit diagrams, drawings, photographs or other artwork with their articles or to suggest appropriate illustrations. A photograph of the author(s) should also accompany submissions, if possible. Illustrations and photographs may be colour or black and white, prints, transparencies or tif/jpeg files with a **minimum resolution of 300 dpi**. Electronic colour figures should be saved in **CMYK mode**.

References

Authors are requested to keep the number of references to a minimum – preferably no more than two or three. Please cite all references in the style of *The Journal of Physiology* (see *Instructions to Authors 2005* at http://www.physoc.org)

In this issue

This issue of *Physiology News* contains several examples of the serendipity on which science often depends. A trained mind asking the right questions is essential in research, but serendipity and chance play a role too. A thought in the right place; a totally unexpected observation; a chance finding that leads somewhere unforeseen.

For me personally this is a big part of the attraction of doing research, and also part of what makes research and its history interesting to read about. In Living History, Stanley Salmons gives an example of serendipity when he describes how a simple malfunctioning circuit took him down many new scientific avenues, and even into cardiac surgery.

Sometimes, of course, it can take a long time for a serendipitous finding to be fully appreciated. As Mike Taggart describes on p. 13, it has taken caveolae 50 years, but they definitely seem to have made it from morphological curiosity to centre stage in cell biology.

Another of the charms of research is that nothing is ever set in stone. Paradigms change, and even in the best-explored areas there are new ideas to be found, and new ways of looking at things, as Fraser and Huang explore for the GHK equation (p. 21).

Aside from those brief highlights, we have a full issue's worth of science News and Views, Features, and Society news. We preview some IUPS and San Diego attractions, introduce you to your new Council members on p. 34 and highlight what the Council has been talking about on p. 49. Plus the joys (?) of research committees and themes in Unbelievable! **Happy Easter**.

Austin Elliott

THE SOCIETY'S COUNCIL SEARCHES FOR A NEW DIRECTION!

Democracy? Ho hum

At its 2004 Annual General Meeting in Cork, the Members of the Physiological Society voted to abolish voting on oral communications and posters.

Well, I say 'the Members'. I could (more accurately) have said 'well under 5% of the Members'.

No precise numbers – the scrutineers winced at the prospect of them being repeated here, and had a lapse of memory.

Given the 100-plus years that the Society's tradition of voting on communications had existed, it might seem pretty surprising that so few of the Society's Members could rouse themselves to vote.

One rather expects that few people will trudge along to AGMs, whether for Trades Unions, learned Societies or residents associations. Unless they are, respectively, trying to stop your university being closed, trying to triple your membership charges, or opposing the construction of a railway line at the end of your garden.

But less than 5% of the Society's Members could even be bothered to vote via a postal ballot that had been mailed out to them.

Reading something, ticking a few boxes, and stuffing the piece of paper in an envelope. How difficult or time-consuming is that?

If one is being charitable, one can read the (lack of) response of the membership as being a tacit approval of the change. People probably see that the motion is being proposed by the Society's Council, assume it will go through, and approve by doing nothing.

NB to Council: could be time to triple the membership charges.

Note, though, that there was more on the relevant voting paper than just the changes in voting on communications. There were also some changes in the make-up of the group of Trustees who are legally responsible for running the Society (*Physiology News*, **57**, 41). So on the above reasoning we would have to conclude that the Members wanted those to go through too.

Or that we don't care. Take your pick.

One thing this is not, though, is fully-functional Society democracy. Misfunctioning, or even dysfunctional, maybe.

To repeat: it is only functioning if we – the Members – all are 100% happy that our not voting means we don't care what the result is.

As I have written before, I find this hard to believe, given what an argumentative bunch physiologists are. In my experience most scientists prefer to spend their free time, like their lunch hours, debating, arguing, grumbling and, occasionally, eating. Put half a dozen of them in a bar during a Society Meeting, start an argument about whether voting on communications is a waste of time, and watch them go.

So what makes us so vote-shy?

The major changes in Governance at the Society a few years ago, in particular the change to a fully-elected Council, were a laudable attempt to make the Society more democratic and give the Members more of a direct say in how the Society was run. The Society's Council should be a bit like the Society's parliament, it was felt, directly elected by the membership and therefore accountable to them. In addition, really significant changes in how the Society's rules were drawn would require a vote of the Members. A referendum, in effect.

Unfortunately, aspects of this don't seem to be working.

Perhaps an incentive is needed. Maybe the Society should offer a £5 discount off the annual membership fee to people who actually send back their ballot papers.

NB to Council: how about this: put the annual membership fee up £10, and then offer £5 off if they vote.

Whatever the Society decides to do (or doesn't decide, or decides not to do) about this, there is one point that cannot be reiterated enough.

In a democracy, people get to think for themselves. But if what they think is that they're not bothered, then they can have no complaints if they don't like what gets done in their name.

'Well I didn't vote for any of them, so you can't blame me.'

Wrong.

There is an apt quote for this sort of ailing democratic-but-participation-light process, usually attributed to the American politician Adlai Stevenson:

'In a democracy, people get the government they deserve.'

Remember that when you get this year's voting papers.

Austin Elliott

IUPS 2005

As a decent number of Physiological Society Members troop off to the IUPS meeting in San Diego, we preview some of the attractions...

First - the meeting!

… of course, the biggest attraction is the IUPS conference itself. After all, what could be more enticing than the prospect of meeting up with 2000+ other bioscientists from all around the world? Well, the prospect of meeting up with 2000+ scientists somewhere sunny. IUPS conferences have a long and distinguished history – this one is the 35th, with the first having taken place in Basel in 1889 - and have visited many locations around the world, but sunshine **and** an exotic location is always a plus. The last three meetings, for those that weren't there, were a slightly damp and chilly Glasgow in 1993 (the last time the IUPS came to Britain), St Petersburg in 1997 (described by participants as 'unforgettable', for a whole range of reasons) and most recently Christchurch in 2001. For anyone interested, a report on this last meeting can still be found on our website in issue 45 (Winter 2001).

Second, the city

San Diego has many visitor attractions, and as a small service we have provided a brief list of must-visits/must-dos (purely for those who have spare days, of course).

IUPS 2005

35th Congress of the International Union of Physiological Sciences
San Diego, CA, USA

31 March – 5 April, 2005

(http://www.IUPS2005.org)

Two *Journal of Physiology* symposia will take place at the IUPS:

***PDZ domain scaffolding proteins and their functions in polarized cells* (4 April)**
***TRP channels: physiological genomics and proteomics* (5 April)**

(http://www.jphysiol.org)

From the top:
Physiology News Editor Austin Elliott visits the Hotel del Coronado; life's a beach in San Diego; beware of killer whales at Sea World.

You should…

• Have dinner on a restaurant terrace overlooking the ocean (or at least within earshot of the sea) in La Jolla

• Have lunch at the famous Hotel del Coronado (The 'Del') on Coronado Island. The 'Del' is where the future Edward VIII of England first met Mrs Simpson, and will also be immediately recognisable to anyone who has seen the movie *Some Like It Hot*. True movie buffs can buy a blue blazer and yachting cap at one of San Diego's first-rate thrift stores and try pretending to be Tony Curtis pretending to be Cary Grant. Don't blame us if you get arrested, though.

• Visit Sea World; entrance is a slightly painful $50, but the Killer Whale show is quite something (word of warning; wear something waterproof if you are going to sit in one of the first 10 rows). For a preview visit the webcam at: http://www.shamu.com/ca/shamu-cam/index.htm

• For the young (or at least young-at-heart), wander down to Pacific Beach ('PB') to take in the nightlife. Don't forget to rehydrate afterwards. Alternatively, go there in the day to stroll along the beach. For a 'Surfcam' preview and other local surf info have a look at: http://scilib.ucsd.edu/sio/ocean/

• Visit Balboa Park for a day to do the museums (multi-museum day tickets available for around $30), go to the zoo, or just stroll around. *NB: Some bus routes from the hotel district to Balboa Park do go through 'interesting' parts of town; watch out for bus-stop benches with signs like: 'In jail? Make bail! – call 1-800-BOND-OUT'*

• Take the coast light railway - the 'San Diego trolley' - down to Tijuana and stroll over into Mexico for duty-free shopping, Mexican food, and 'other attractions'.

Want to try your hand as a writer?

Due to scheduling conflicts none of the regular *Physiology News* team will be reporting from the IUPS. We would therefore welcome brief reports (300 words) on the meeting from anyone who would like a shot at being a stand-in Conference/Foreign Correspondent, and thinks they could be both entertaining and informative. We will pay £50 for any pieces published and are keen to get views from physiologists of all ages - so come on, get your reporter's notebook out.

Oxford Focused Meeting

The Society's first meeting on modelling in physiology

I built my first cardiac cell model in 1960 (Noble, 1960) following the discovery of the potassium channels, i_{K1} and i_K, in cardiac Purkinje fibres (Hutter & Noble, 1960). In October 2004, the Society held its first ever meeting devoted to modelling in physiology. There can't be many other areas of our science that have waited 44 years for a dedicated meeting! One could argue that it is 52 years, since the paradigm model was that of Hodgkin and Huxley (Hodgkin & Huxley, 1952). It was therefore a great pleasure to be able to welcome Sir Andrew Huxley to introduce the Hodgkin-Huxley-Katz lecture on the first day of the meeting.

Why such a long delay? One reason is that, until fairly recently, the Society has not held focused meetings on any subject. When I started work as Meetings Secretary in 1974 all the Society's meetings were general. Moreover, the Secretary was required to mix all the topics up in each meeting by arranging the abstracts in the order in which they were received. I was the first to break this tradition by organising abstracts into sessions with oral presentations on similar topics forming each session. So, it is only during the last 30 years that focused sessions, and then complete focused meetings, have been held.

But I think there is also a deeper, philosophical reason. British physiology has been so keen on its empirical tradition, reflected also in the strength of empiricism in British philosophy, that it has been fairly antipathetic to theoretical work. Notice, in the title of Hodgkin and Huxley's paper, that they refer to 'a quantitative *description'* rather than to 'a quantitative *theory'*.

Nevertheless, the early papers on nerve and heart cell models were nearly all published in *The Journal of Physiology*. That tradition was broken in 1985 when the work that Dario DiFrancesco and I published on the first simulations of calcium transients and calcium handling was published instead by *The Royal Society* (DiFrancesco & Noble, 1985). I believe that was also the point at which the traditional 'British' approach to the life science started to lose ground to the more pragmatic style championed in the United States, where Bioengineering groups at various universities took up the challenge, including notably the work of Luo and Rudy (1994) and of Raimond Winslow (Rice *et al*. 1999). The preferred key journals now include the *American Journal of Physiology* (where my latest modelling work has been published), the *Journal of General Physiology, Circulation Research* and the *Biophysical Journal*. These are all published in the USA. It is worth noting, though, that *Philosophical Transactions of the Royal Society* and *Progress in Biophysics and Molecular Biology* continue to be active in this area.

In fact, we now find ourselves having to catch up. The Oxford meeting was an excellent contribution to achieving that, since it showed how strong the field still is here in the UK, but it was also a strongly international one, with presentations from countries as far flung as the USA, Japan, Russia, Canada and New Zealand. There were roughly equal numbers of talks presented from the UK and from abroad. The meeting attracted 127 participants, and was sponsored by the British Heart Foundation, Pfizer and Novartis, as well as by the Physiological Society. *Philosophical Transactions of the Royal Society* will be publishing around 30 papers in a volume arising from the meeting, while the Hodgkin-Huxley-Katz lecture will be published in *The Journal of Physiology.*

A second significant sign lies in the strategy of the *Journal of Experimental Physiology*, whose Editorial Board has announced that it wishes to foster quantitative integrative physiology, including modelling. A future focused volume will be devoted to this field. A journal of *experimental* physiology sponsoring theoretical work?! I like both the irony and the significance of that. The irony is obvious. The significance lies much deeper and is more important. As Hodgkin and Huxley's work showed: the best simulation work in physiology is strongly based experimentally, and it succeeds to the extent that it interacts further with experimental work, both by suggesting new experiments and by itself developing in iterative interaction with them.

This strategy can also be linked to the growing popularity of what has come to be called 'systems biology'. No-one is quite sure what the term means, but physiologists can be clear that, at the least, it includes quantitative analysis of the areas that are traditionally called systems physiology. It also includes what molecular and genomic biologists now refer to as the theory of interactions. The distinguished geneticist Gabriel Dover (2000) goes as far as to say: 'We don't have a theory of interactions and until we do we cannot have a theory of development or a theory of evolution'. This is therefore also the route by which physiology can reconnect with the mainstream of biological thought, including developmental biology and evolutionary biology (Diamond, 1993).

Finally, I hope we don't have to wait a further 44 years before the next Society meeting on modelling work (I might not be around to witness that!).

Denis Noble
University of Oxford, UK

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Nottingham Focused Meeting

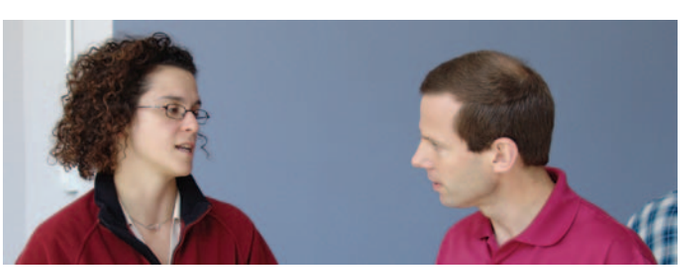
Responsiveness of muscle, bone and connective tissue to physical activity: genetic and molecular integration

Over 60 delegates attending found the new Meeting format highly enjoyable and productive

The first Focused Meeting of the Physiological Society took place at the University of Nottingham Graduate Entry Medical School in Derby from 12-13 July, 2004

It's clear that the application of modern techniques in physiology is providing us with unforeseen knowledge concerning the way in which our musculo-skeletal mass maintains itself and adapts under both catabolic (immobilisation, space flight, hospitalisation) and anabolic (growth in childhood, strength training/body building, rehabilitation) conditions. Some remarkable physiological phenomena have been discovered recently, e.g. the marked anabolic response of bone to vibration, the linking of changes in muscle myo-filament turnover with the turnover of extra-cellular matrix, the marked response of tendon to exercise, the existence of genetic traits which make human beings good or poor responders to exercise, etc.

This, the first Focused Meeting of the Physiological Society, organised by Paul Greenhaff and Mike Rennie, was hosted by the Centre for Integrated Systems Biology and Medicine (http://www.nottingham.ac.uk/cisbm/) at the University of Nottingham. It highlighted recent research addressing the responsiveness of muscle, bone and connective tissue to physical activity, and in particular recent genetic and molecular advances to our understanding of what controls tissue mass under these conditions.

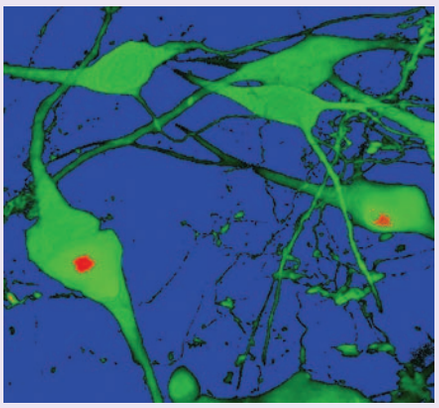


Top left: .Marco Narici, Martin Thompson and Mike White enjoying lunch (left to right)
Top right and centre: Delegates engrossed in informal discussions
Left: Arnold de Haan, David Jones and Michael Rennie (left to right) debate the merits of the new focused meeting format of the Society.

The 2 day event allowed contemporary physiological findings to be set in a context of transcriptional and translational control of the tissues of the musculo-skeletal system, some of which like bone and tendon had hitherto been thought only to respond weakly and slowly. The meeting was attended by over 60 delegates, and lecture presentations by an international panel of symposium speakers were accompanied by original communications by attendees.

The overwhelming opinion from Members was that this new format of Meeting was highly enjoyable and productive, facilitating detailed discussion in an informal and friendly environment (particularly in the bar following the symposium dinner). Clearly this new initiative of the Society should go from strength to strength… (please pardon the pun).

Paul Greenhaff
School of Biomedical Sciences, University of Nottingham, UK



Central neurones transduced with cell-type specific viral vectors

Viral gene transfer in neuroscience: new tricks of the trade

A Physiological Society Focused Meeting held at the University of Bristol (4-5 September, 2004)

The University of Bristol hosted this 2 day meeting sponsored by the Physiological Society, with additional contributions from Pfizer UK and the Department of Physiology. The aims were to raise awareness in the physiological community of the recent achievements of this rapidly developing technology, to give researchers an opportunity to interact with some of the world's leaders working in the area and, finally, to facilitate collaborations between laboratories around the world. Gratifyingly, this turned out to be a truly international meeting with contributions from Germany, Singapore, Switzerland, the UK and the USA. Bristol seemed to be the right place for this event given that several large research groups in this University are using viral vectors in a variety of research programmes ranging from central control of blood pressure to gene transfer into transplanted blood vessels.

Viral vectors provide an excellent opportunity to address the major challenge presented by the topic of physiological genomics. As Boron and Boulpaep recently put it: 'Physiological genomics (or functional genomics) is a new branch of physiology devoted to understanding the roles genes play in physiology… In order to grasp the function of a gene product, the physiologist must retrace his steps back up the reductionistic road and achieve an integrated inderstanding of that gene's function at the level of the cells, organs and whole body' (Boron WF, Boulpaep EL (2002). *Medical Physiology*. Saunders). Indeed, being exceptionally efficient gene delivery vehicles, viral vectors allow both expression of a transgenic protein or suppression of an endogenous gene/protein in gain-of function or loss-of function experiments. Moreover, targeted viral vectors open a whole new method for specific genomic experiments on phenotypically identified neuronal sub-populations.

The meeting ran over 2 days. On 4 September the invited speakers gave their presentations. First, Markus Ehrengruber (University of Zürich, Switzerland) addressed some new developments in the alfavirus family of vectors and described recent Semliki Forest virus vectors that have decreased cytotoxicity. This development is important because the original versions of these vectors, used in previous studies, are highly toxic for the transduced cells, which clearly compromises the credibility of the results that may be obtained. This lecture was followed by Wang Shu (Institute of Bioengineering and Nanotechnology, Singapore) who works on new transcriptional and transductional strategies for targeting neurones. In his presentation, Dr Shu described advantages of the recombinant baculoviruses for neuronal gene transfer. Presently, this type of vector is seldom used in neuroscience but this might change given the relative ease of its production, efficient gene delivery into central neurones and relatively large packaging capacity. Sebastian Kügler (Department of Neurology, University of Göttingen, Germany) then gave an overview of his work on adeno-associated viral vectors. This vector is currently one of the favourites in the field of gene therapy. Dr Kügler illustrated its use in his studies on neuroprotection. After the lunch break and poster session, Beverley Davidson (University of Iowa, USA) spoke of virally mediated expression of RNAi *in vivo*, which she is developing as a gene therapy tool for neurodegenerative diseases. Gene suppression using RNA interference has been one of the hottest scientific topics of the last few years and Dr Davidson's work on siRNA has been published in the most prestigious biomedical journals. James Uney (University of Bristol) then spoke about regulatable gene expression and presented his studies on tetracycline-regulatable viral gene expression systems. His talk was followed by Andy Baker (University of Glasgow) who is developing an interesting strategy to alter the tropism of viral vectors. This is achieved by modifications to the capsid proteins of adenoviral and adeno-associated viral vectors using peptide sequences derived from a phage display approach. Nicholas Mazarakis (Oxford Biomedica, Cambridge) presented recent developments in his company for using lentiviral vectors for gene therapy treatment of neurodegeneration in man. He focused on feline immunodeficiency virus derived vectors with transductional properties altered using alternative coat proteins. Lentivirus-derived vectors were also the topic of Mohan Raizada's talk (University of Florida, USA). The University of Florida is one of the leading world centres for viral vector development

From the left: Nicholas Mazarakis, Stephen White, Markus Ehrengruber and Sebastian Kügler relaxing at the symposium dinner

and Dr Raizada spoke on his work using lentiviral vectors to study mechanisms underlying the generation of essential hypertension. The final speaker, A G Teschemacher (University of Bristol), presented a wide variety of applications of both adeno- and lentivirus derived vectors based on her own studies and those performed in collaboration with Sergey Kasparov and Julian Paton in the Department of Physiology, University of Bristol. Specifically, she described studies where phenotypically identified neuronal populations were genetically targeted using adeno- and lentiviral vectors for dynamic confocal imaging and functional studies at the cellular and systems level.

In addition to these presentations, about two dozen posters were presented during the lunch and tea breaks by various researchers attending the symposium, as well as by the speakers. This provided a further opportunity to meet the speakers and discuss issues relating to viral gene delivery from the experts. The meeting was followed by dinner at one of Bristol's finest harbour-side restaurants.

On Sunday morning Bristol-based groups (Kasparov-Paton viral laboratory in the School of Medical Sciences and James Uney's laboratory in the Dorothy Hodgkin Building) opened their doors to the speakers and any delegates. This provided a further chance to see first hand experiments with viral vectors and to discuss the different technologies being applied.

We believe that this meeting provided a great opportunity to gain novel insights into the rapidly developing world of viral gene transfer and to discuss the newest developments in the field with some of the world's leaders and to establish closer contacts and new collaborations.

Sergey Kasparov
Julian F.R. Paton
Department of Physiology, University of Bristol, UK

Papers from the Bristol symposium were published in the January issue of *Experimental Physiology* (2005, 90.1)

The Journal of Physiology symposium 'The Senses'

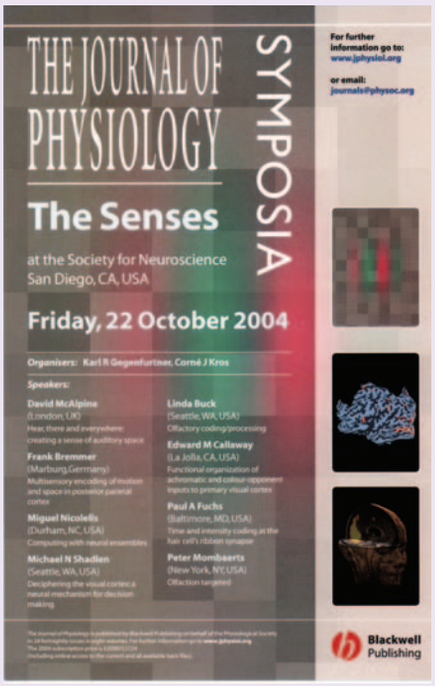
A *Journal of Physiology* symposium on sensory physiology was held in San Diego on 22 October, 2004. The satellite symposium to the annual meeting of the Society for Neuroscience brought together leading experts to highlight the similarities and differences in processing strategies for a variety of sensory systems such as vision, audition, somatosensation and olfaction.

A lot of progress has been made on the very early stages of sensory processing, as indicated by a number of Nobel Prizes over the past few decades. As a consequence, the process of converting physical energy into the excitations of sensory nerves is quite well understood. The biggest current questions are what kinds of features are extracted from the information stream and how these are used to recognize objects and guide actions.

Several of the talks dealt with the question of how elementary features are conveyed to the central nervous system. Ed Callaway (La Jolla, USA) pointed out how luminance and chromatic information are conveyed to the visual cortex in separate pathways. Paul Fuchs (Baltimore, USA) presented a detailed model of time and intensity coding at the hair cell's ribbon synapse in the inner ear.

Linda Buck (Seattle, USA), who was just recently awarded this year's Nobel Prize for physiology or medicine,* discussed how the excitations of olfactory receptors are converted into smells. Peter Mombaerts (New York, USA) presented work on the genetic basis of olfactory maps.

Probably even more important than recognizing things, sensory information is used to enable orientation in space and to form decisions about future actions. David McAlpine (London, UK) presented a new model of auditory space perception and supporting



empirical evidence. Along the same lines of space perception, Frank Bremmer (Marburg, Germany) showed how information from visual, auditory and somatosensory systems is integrated in the parietal cortex of monkeys and humans.

One of the current core questions in sensory physiology is how computations are performed in neural ensembles. Miguel Nicolelis (Durham, USA) showed state dependent responses in the barrel cortex of awake behaving rats. Michael Shadlen is investigating similar questions in awake behaving monkeys, tracing the complete sequence of steps from sensory processing to decision making.

The symposium was a big success in pointing out similar coding strategies for converting elementary sensory information into features for quite different sensory modalities. However, it also made clear that we have quite a long way to go towards understanding the crucial next steps from features to objects and actions.

Karl R Gegenfurtner
Justus-Liebig-University, Giessen, Germany and member of the Editorial Board, The Journal of Physiology

*See Tim Jacob's article on the Nobel Prize winners Linda Buck and Richard Axel on p. 12 of this issue

The case of the misbehaving circuit

Stanley Salmons recalls the accident that replaced a paradigm

Above: Brenda Russell (around 1976)
Below: Jan Henriksson (1998)

In 1965 I was pursuing a PhD in Eric Ashton's anthropometry group in the Department of Anatomy at the University of Birmingham, developing micropower radiotelemetric techniques for recording muscle activity from freely moving primates. On 15 September that year I tried a new type of single-pulse generator. It proved hard to keep it stable, so it was unsuitable for this application. It struck me, however, that it could form the basis of an implantable stimulator, with which one could resolve the controversy about the nature of the neural influence on muscle.

At that time there was a good deal of interest in the cross-reinnervation experiments of Buller, Eccles and Eccles. These, it was widely believed, showed that the contractile characteristics of fast and slow muscles were determined by chemotrophic factors delivered via the motor nerves. A competing view, championed by Gerta Vrbová, held that this neural influence was mediated by the different frequencies of impulse activity in these nerves. Dr Vrbová had just joined the Department, so I suggested to her that we use the (as yet unbuilt) stimulator to activate a fast muscle with the continuous, low-frequency pattern normally found in slow muscle nerves.

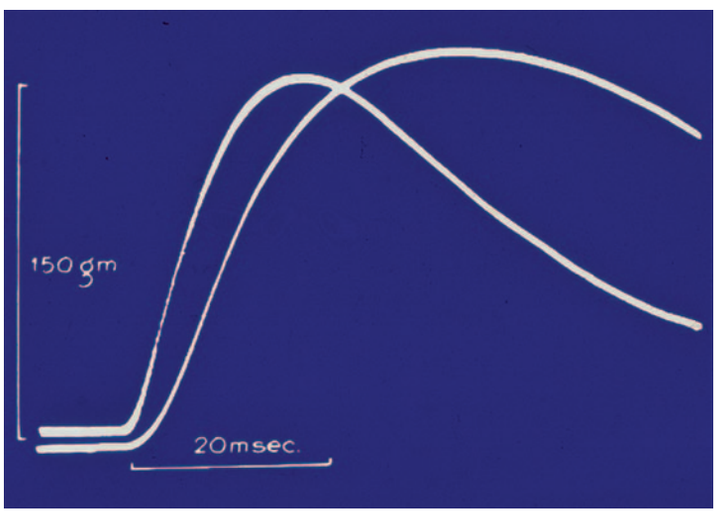


Figure 1. Single twitch contractions of rabbit tibialis anterior muscles. Upper trace: control. Lower trace: stimulated at 10 Hz for 6 weeks (Salmons & Vrbová, 1969).

The fast muscle nerve would still carry intermittent high-frequency bursts, but I believed that the much greater activity imposed by the stimulator would have the dominant effect. I developed the stimulator and we did the experiment. The stimulated fast muscle became slower (Fig. 1). Later Frank Sréter and I were to show that the physiological and biochemical effects of cross-reinnervating a slow muscle could be nullified if stimulation was used to restore its normal activity pattern (Salmons & Sréter, 1976). I put forward the notion of functional adaptation, and this became the more favoured paradigm (Salmons & Henriksson, 1981).

Where are they now?

Gerta Vrbová is Emeritus Professor of Developmental Neuroscience in the Department of Anatomy & Developmental Biology, University College London.

John Gergely is Senior Scientist at the Boston Biomedical Research Institute.

Jan Henriksson is Professor and Joint Head of the Section for Exercise Physiology, Department of Physiology and Pharmacology, Karolinska Institute, Stockholm.

Brenda Russell is Professor of Physiology, Biophysics, Bioengineering and Medicine, and Associate Vice Chancellor for Research at the University of Illinois at Chicago.

Larry Stephenson is Ford-Webber Professor of Surgery and Chief of Cardiothoracic Surgery for Wayne State University, the Detroit Medical Center and Harper Hospital.

Jonathan Jarvis is Reader in the Department of Human Anatomy and Cell Biology, University of Liverpool.

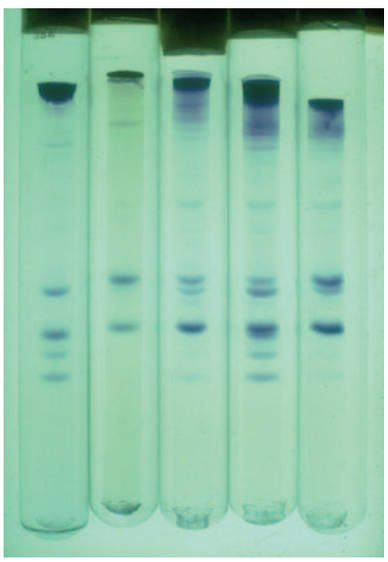


Figure 2. SDS-PAGE (tube gels) demonstrating the expression of slow myosin light chains (MLCs) after 10 weeks of stimulation; co-electrophoresis was used to confirm the identity of the bands. From left to right: control rabbit tibialis anterior muscle (TA), control soleus (SOL), stimulated TA, mixed TA + SOL, mixed stimulated TA + SOL (Sréter et al. 1973).

In Boston I worked with Frank Sréter and John Gergely on the newly discovered myosin light chains (MLCs). We found that slow MLCs were induced by stimulation (Fig. 2). This was an exciting observation because it showed that muscle stimulation elicited qualitative, as well as quantitative, changes in protein expression. My group and others, particularly Dirk Pette's in Konstanz, subsequently added many other proteins to this list. The underlying changes at gene level have yet to be unravelled, so the story is far from over.

In 1977 I met Jan Henriksson, an exercise biochemist, at an IUPS meeting in Szeged. In discussion we realized that exercise-induced and stimulation-induced changes differed only in degree (Salmons & Henriksson, 1981). Brenda Russell (at that time Eisenberg), who had been a colleague at University College London, was at the same meeting; we decided to establish the time course of ultrastructural changes during fast-to-slow transformation (Eisenberg & Salmons, 1981). Subsequently Jan, working in Oliver Lowry's lab, confirmed that oxidative enzyme activity rose and fell in the same way as Brenda had shown for mitochondrial density (Henriksson *et al*. 1986). During transformation to a stable 2A phenotype this biphasic response was absent, evidence of interaction between the pathways underlying adaptive change (Mayne *et al*. 1996). At first it was hard to reconcile the adaptive capacity of muscle with the existence of discrete fibre types, but I used a threshold model to explain both this and the sequence of changes that followed the onset and cessation of stimulation (Salmons, 1990).

A feature of the adaptive response of muscle to increased use was a dramatic increase in fatigue resistance (Salmons & Sréter, 1976). In 1979 Larry Stephenson, a cardiothoracic surgeon then in Philadelphia, asked me if such a muscle could do cardiac work. That was the beginning of a 25-year collaboration on cardiac assist from

Jonathan Jarvis and Stanley Salmons at the World Cardiac Bioassist Meeting, Paris, 2003

Larry Stephenson, a contemporary portrait

skeletal muscle, a technique that still has immense potential for patients with heart failure, and in which my colleague, Jonathan Jarvis, has played a major role. Other clinical applications have been: stimulation of paralysed (including denervated) muscles to restore posture, movement, or ventilation lost through stroke or spinal-cord injury; pacing of the diaphragm in apnoeic babies; and configuration of conditioned muscle grafts as artificial sphincters. But it all started with a badly behaved circuit.

Stanley Salmons
Emeritus Professor of Applied Myology, Department of Human Anatomy and Cell Biology, University of Liverpool, UK

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A summer in the life of...

The Society's Executive Committee Chairman shares some of his scientific journeys

David Yudilevich and Giovanni in the company of Albert Einstein

I am currently Chairman of the Executive Committee of the Physiological Society and Head of Graduate Research Studies in the Guy's, King's & St Thomas' School of Biomedical Sciences at King's College London. The majority of my time is spent on research, though I do thoroughly enjoy interacting with the staff in the London and Cambridge offices of our Society. I am fortunate to have excellent research links with friends in Spain (Jose 'Pepe' Viña), Italy (Guiseppe Poli), Japan (Tetsuro Ishii and colleagues), Brazil (Claudio Mendes Ribeiro), Oxford (Clive Ellory), Edinburgh (Richard Sharpe) and numerous colleagues at King's and my closest collaborator Richard Siow.

Rather than a 'week in the life of ...', I thought I would share some of my scientific journeys during May to August 2004. Before I start reminiscing about scientific travels, the photograph of colleagues in front of the poster of Albert Einstein is quite dear to me. David Yudilevich cherished this poster brought from Chile to Queen Elizabeth College, where he was Head of Department of Physiology until 1985. We spent many hours in his office at Kensington discussing and arguing about science! On his retirement he presented the poster to me and it now hangs in my office at Guy's Campus. The recent joint meeting of the Physiological Society and Chilean Physiological Society at King's bears testimony to David's unique ability to foster links between Chile and the UK.

Thanks to sponsorship from the Society, Pepe and I co-organized a symposium entitled *Phytoestrogens and isoflavones: cell signalling and physiological action* at the International Society for Free Radical Research (SFRR-I) meeting in Buenos Aires, Argentina in May. As with most of my trips abroad, I find moments to explore memorable sites. On arrival in Buenos Aires, I had 45 min to find my way from the international to the national airport to fly on to Iguazu falls. A relatively stressful journey by bus through what seemed like a never ending line of traffic, but in the end I never expected to be so overwhelmed by the thundering noise of the numerous waterfalls. Other attractions of Buenos Aires included sight-seeing at night, excellent steak, and impressive displays of tango!

In June Tetsuro Ishii and I travelled to Berlin as invited guests of the Hydroxynonenal Society. There we were accommodated in the Hilton just opposite the German and French Cathedrals and Katharina Mahn provided an eye-opening tour of what was East Berlin, including the Berliner Dom and other sites.

I flew to Valencia in July to meet up with Jose Viña's research group in the Departamento de Fisologia. On this occasion, my wife Lynn travelled with me. Pepe took us on an inspired tour of Valencia, and we particularly appreciated the visit to the market in the old part of town. There Pepe was greeted at several market stalls and was given some of the finest fresh squid I have ever seen. It transpired that these individuals were Pepe's patients, who he was treating for dietary conditions. Although we had a splendid dinner with Pepe and his family, we never did get to taste the freshly prepared squid!

My summer was rounded off in August with an annual pilgrimage to Portugal, where my family and I have spent our summer holidays for the past 6 years. Later in November, with 'wanderlust' still in my blood, I set off for mainland China on behalf of the School of Biomedical Sciences and the Society. One of my objectives was to discuss joint degrees and exchange of postgraduates with senior colleagues at Tsinghua University and Peking University. On behalf of the International Sub-Committee of our Society, I met with the President and Meetings Secretary of the Chinese Association of Physiological Sciences to explore the possibility of a joint meeting in China in 2008. David Eisner, our International Secretary, is now liaising further with colleagues in China.

Giovanni E. Mann
Academic Department of Physiology and Cardiovascular Division, King's College London, UK

Above: Iguazu Falls, a natural boundary between Argentina and Brazil (with Pepe, M-Carmen and Chelo).

Below: Giovanni, Jose Viña (member of our International Sub-Committee, University of Valencia, Spain) and Guiseppe Poli (University of Torino, Italy) visiting the sights in Buenos Aires, Argentina.

Above: Katharina Mahn (Giovanni's PhD student and a now a postdoc with Rachel Tribe and Lucilla Poston), originally from the Humboldt Universität in Berlin, enjoys a beer or two with Tetsuro Ishii (Univ. Tsukuba, Japan) in the beautifully restored 'Gendarmenmarkt' in Berlin.

Below: Between travels abroad, I seem to find time to field calls from the Society's office and/or my daughters.

The Nobel Prize

Tim Jacob traces the route that Linda Buck and Richard Axel took to claim one of the major uncollected prizes in sensory science – the secrets of the olfactory system

This year's Nobel Prize for Medicine and Physiology was shared by Linda Buck (57) and Richard Axel (58) for their discovery of the olfactory receptor gene family.

In 1991, after about 8 years of research effort, they published their landmark paper in *Cell* in which they reported that they had succeeded in cloning 18 different members of an extremely large multigene family that, they said, 'may encode odorant receptors'. This family we now know is the largest so far discovered and occupies about 3% of the human genome. In order to achieve this breakthrough they made some educated guesses that narrowed the odds – in other words luck played a part.

Following publication they went their separate ways. Axel remained at Columbia where he has been since his undergraduate studies. Buck moved to Harvard for 10 years and then westward in 2002 to the Fred Hutchinson Cancer Research Center in her home town, Seattle. Although working separately, they both demonstrated, in different publications, that each olfactory receptor neuron (ORN) expressed only one type of olfactory receptor and that each ORN expressing the same receptor sent its axon to the same place in the olfactory bulb. Buck went on to publish the idea of a 'combinatorial code' that is the currently accepted view of how different odours are discriminated.

The secrets of the olfactory system had long been one of the major uncollected prizes in sensory science. Over the years there had been many theories attempting to explain how/why molecules smell including molecular vibration, piezo electric currents, membrane diffusion pores and molecular shape. Most of them were empirical and did not lend themselves to scientific test. It was the advent of molecular biology and, in particular,

Linda Buck (top) and Richard Axel

polymerase chain reaction (PCR) that finally unlocked the secrets of the olfactory system.

From 1982-1991 Linda Buck was a postdoctoral fellow in Richard Axel's lab. The Howard Hughes Medical Institute (HHMI) was supporting both of them during this period. To understand the olfactory system it was necessary to discover how the system responded to thousands of different molecules of different shapes and sizes. Did it achieve this with a restricted set of promiscuous receptors or a large number of relatively specific receptors? And second, how did the brain utilise these responses to discriminate between odours? In 1983, Kary Mullis at Cetus Corporation conceived of a way to start and stop a polymerase's action at specific points along a single strand of DNA. The result was PCR for which he was awarded the Nobel Prize for Chemistry in 1993. So, instead of hunting for the receptor proteins directly, Axel and Buck used PCR to look for genes that contained instructions for proteins found only in the olfactory epithelium. It was a technique in its infancy and at first their efforts came to nothing. Looking back Axel has commented that this was because of the large number of odorant receptors, each of which was only expressed at a very low level. Finally, Buck made the breakthrough by making three assumptions. The first was that the odorant receptors were likely to be members of the 7-transmembrane G-protein coupled receptor family. The second was that the odorant receptors themselves should exhibit significant diversity and belong to a multigene family and the third that their expression be limited to the olfactory epithelium. Homologues of the 7-TM domain superfamily were amplified from olfactory epithelial RNA. Using restriction enzymes to digest the PCR product they looked for fragments that consisted of a mixture of DNA sequences arguing that a multigene family would generate a set of DNA fragments whose molecular weight would be far greater than the original PCR product. The restriction digestion of a single species of DNA, on the other hand, would generate a set of fragments whose molecular weights would sum to that of the original PCR product.

Stuart Firestein, a colleague at Columbia and another major player in olfactory research has pointed out that this work would probably not have been possible without HHMI support: 'It would have been hard to do this if you were required to produce regular publications to support your next grant,' he said. Buck was a 44-year old postdoc at the time of the publication of their Cell paper with 10 papers to her credit – only three as first author. The HHMI has nurtured 13 Nobel Prize winners since it was established in 1984 and Columbia University itself has produced a steady stream of Nobel Laureates, 72 in all. Twenty-one of these are in Physiology and Medicine, including Eric Kandel (2000).

Tim Jacob
University of Cardiff, UK

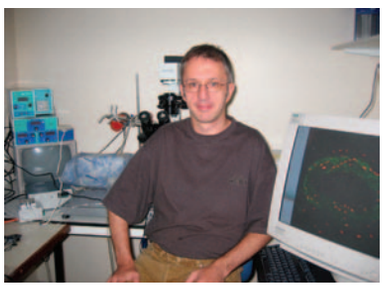
50 years of caveolae – a round-up

It is 50 years since the first microscopic observation of the tiny flask-shaped plasmalemmal invaginations termed caveolae. Only in the last decade, however, with the discovery of the family of caveolin proteins that are integral to these organelles, have we begun to unravel the possible physiological roles of these enigmatic structures

The decade following the second world war proved to be a prolific period for the application of electron microscopic techniques to the analyses of the ultrastructure of tissues and cells. Through such endeavours Pallade (1953) and Yamade (1955) became the first workers to describe an unusual feature of the plasma membrane of endothelial and epithelial cells: they found that the plasmalemma, far from being uniform, often gave the appearance of regular, Ω-shaped invaginations; Yamade termed these structures *'caveolae intracellulares'* (see Inset). Ever since, the physiological roles of these organelles has perplexed and fascinated in equal measure. What follows is a very brief round-up of this topic but for more extensive background the reader is directed to the reference list at the end of this article.

The early sightings

As caveolae were initially discovered in cells lining the lumenal surface of hollow organs, a role in macromolecular transport phenomena was postulated, including capillary permeability and transcytocis and the regulation of cellular free cholesterol flux. With regard to the latter, cholesterol sequestering agents have been known for many years to disrupt the appearance of caveolae. Subsequently, caveolae were found to be prominent, occupying approximately 25% of plasmalemmal surface area, in many other cell types including adipocytes, smooth muscle (Fig. 1) and cardiac cells (with a few notable exceptions being lymphocytes and some cell lines such as HepG2 cells). This wide distribution necessitated consideration of this idea that caveolae might be important for a number of functions. Regulation of transmembrane ion fluxes important for cellular excitability was one possible function ascribed to caveolae in smooth



Michael Taggart

muscle as early as the 1970's. The observations of a close appositioning of caveolae to elements of the sarcoplasmic reticulum (the major source of releasable organellar Ca^{2+}), and immunogold localisation of a Ca^{2+}-ATPase to caveolae, were instrumental in developing this idea. By and large, however, experimental evidence in support of these different roles of caveolae was observational and progress was hindered by the lack of a definitive molecular marker of caveolar structures.

'Endothelial cells ... possess ... a large number of vesicles concentrated immediately under the cell membranes facing both the capillary lumen and the precapillary spaces. The vesicles, sometimes tightly packed in layers, are speherical in shape and measure ~650A in diameter. Many of these appear to open at the surface of the cell membrane.'

Palade (1953)
J Appl Physics 24, 1424

'Some of these vesicles seem to communicate with the lumen through openings in the cell membrane covering the microvillus. These small cave-like indentations of the cell wall..... resemble similar structures described along the inner and outer cell membrane of capillary endothelial cells by Palade. It is here proposed to speak of such a recess or pocket as a '*caveolae intracellulares*'

Yamade (1955)
J Biophys Biochem Cytol 1, 445-458

The missing link identified

The discovery at the turn of the 1990s of a protein component of caveolae, termed caveolin, was to revolutionise the study of these organelles. Caveolin is actually a family of protein molecules of mass 21-24kDa with three main mammalian isoforms (imaginatively termed caveolin-1, -2 and –3). There are two and three isoforms, respectively, of caveolin-1 (α and β) and caveolin-2 (α, β, γ). Whereas these show a wide tissue distribution, caveolin-3 has a much more restricted appearance, being predominant in striated muscle cells. Crucially, transfection of non-caveolin-containing cells, which had no morphological appearance of caveolae, with caveolin-1 (or -3) induced the formation of Ω-shaped invaginations. Subsequently, an interaction of high molecular weight caveolin oligomeric complexes with cholesterol appeared to be key to the formation of caveolae.

Caveolins, however, quickly established themselves as something more than just plasma membranous structural components. Biochemical characterisation studies, including immunoprecipitation, began to highlight a multitude of signalling molecules co-localising with caveolin-1. Furthermore, a small 20 amino acid peptide derived from caveolin-1 was, in *in vitro* assays, found to bind to a whole host of signalling molecules that act downstream of receptor-coupled membrane effectors. In cardiovascular cells, for example, these included PKCα, rhoA, ERK, and nitric oxide synthase (NOS). Binding to this peptide, termed the caveolin scaffolding domain, even altered the enzymatic activity of these signalling molecules and, once introduced into live cells, altered functions as diverse as cytosol-membrane protein translocations, cardiac myocyte beating, flow-induced arterial dilation and eNOS activation.

Much attention focussed on the inhibitory interaction of caveolin and eNOS, regulated by Ca^{2+}-calmodulin and transcriptionally modulated by altering cholesterol levels, and this became something of a model system for understanding other caveolin-signalling molecular events.

Subsequently still more possible functions of caveolin emerged. In endothelial cells, agonist-dependent Ca^{2+} waves appeared to be initiated at caveolin-rich regions of the plasmalemma, whilst in smooth muscle cells, caveolae disruption with cholesterol-modifying agents altered the appearance of Ca^{2+} sparks. Both these scenarios supported the earlier suggestions of these organelles contributing to cellular excitability by regulating Ca^{2+} homeostasis.

Life after caveolae

Just as it seemed that caveolae and caveolins could be all things to all cell biologists and physiologists, a more sobering analysis was demanded following the publication of caveolin knockout mice that were both viable and fertile (cav-$1^{-/-}$, cav-$2^{-/-}$, cav-$3^{-/-}$ or cav-$1^{-/-}$/-$3^{-/-}$). Clearly, caveolins and caveolae were not essential for life. However, marked phenotypic changes were noticed in cav$^{-/-}$ mice that included elevated triglycerides, cardiomyopathy, changes in pulmonary extracellular matrix and enhanced endothelial-dependent relaxation of isolated arteries. Subsequently, the functional implications of caveolin gene depletion has become increasingly clear when the caveolin$^{-/-}$ mice, or cells derived from cav$^{-/-}$ mice, are physiologically challenged. For example, caveolin-$1^{-/-}$ mice have a lowered exercise tolerance (probably as a result of the lung histopathologies), a poor response to an insulin tolerance test, impaired angiogenesis, reduced lifespan (due to cardiac hypertrophy and/or pulmonary fibrosis), and aged knockout mice on a high fat diet develop hyperinsulinaemia. Thus the murine caveolin/caveolae ablations, although not lethal, are increasingly providing interesting phenotypic information with relevance to many human

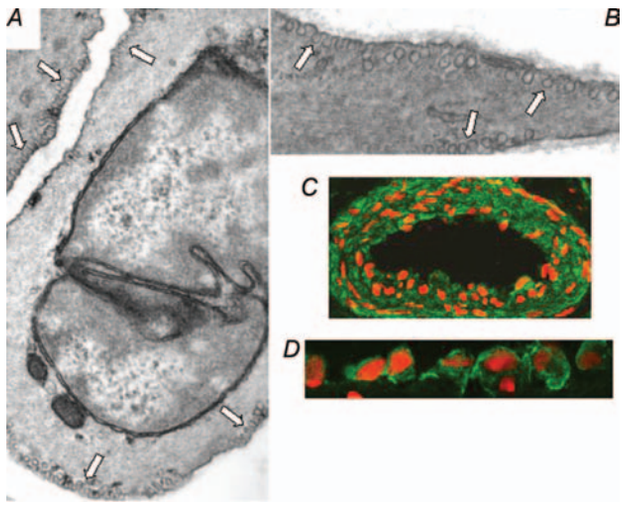


Figure 1. Caveolae and caveolin in human arteries. *A, B*: the plasma membrane of smooth muscle cells of arteries has an abundance of rows of caveolae (arrows). *C*: immunofluorescence studies indicate the appearance of caveolin-1 (green) in smooth muscle and endothelial cells of the artery wall. Red staining indictes nuclei. *D*: magnified view of caveolin 1 staining in arterial endothelial cells.

pathophysiologies. Indeed, altered caveolin or caveolae levels have now been associated with animal models of hypertension, diabetes, hypercholesterolaemia and heart failure.

Future perspectives

The discovery of caveolins as integral protein components of caveolae has had a huge impact upon the volume of research into these intriguing structures. As illustrated in Fig. 2, as many papers are now published *per annum* on this topic as in the near-forty years of caveolae research preceding the discovery of caveolin. It is remarkable that many of the initial roles ascribed to caveolae, largely based upon morphological data, have received support from recent molecular studies with caveolins. Yet after 50 years many questions still remain to be answered as to the physiological roles of caveolae - not least of which is the paradox whereby cavolins perform the dual function of being scaffolding molecules for cellular signal integration, but whose binding often exerts an inhibitory regulatory effect. Further consideration of the temporal and spatial dynamics of caveolin-regulated signalling will be required to elucidate this and many other puzzles still surrounding these membrane pockets.

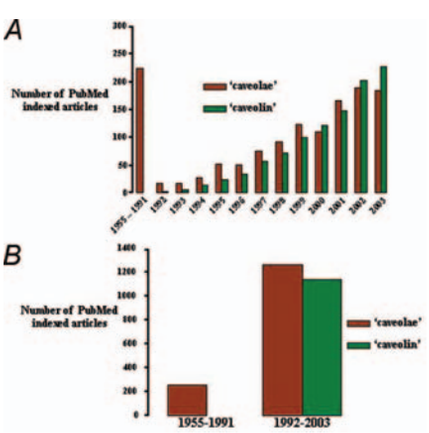


Figure 2. Caveolae publications from 1955 to 2003. The diagrams illustrate the number of articles listed following PubMed searches for the key words 'caveolae' and 'caveolin' in the title or abstracts. The earliest entry for 'caveolae' is in 1971 so the figures given for 1955-1991 will be slightly underestimated. Nontheless, the discovery of caveolins (the terminology coined in 1992) as molecular markers of caveolae has led to an enormous increase in research articles relevant to these plasma membranous invaginations.

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Obesity – why all the noise?

Paul Trayhurn

It is almost impossible to be unaware of the growing concern with obesity. Newspapers, radio and other media present a steady stream of stories, from the rising tide of the numbers of obese to breaking news of the latest potential targets for a 'cure.' Even politicians (the slimmer ones?) have entered the fray, with a recent enquiry from the House of Commons Health Committee calling for UK Government action to stem the rise in obesity. More relevantly, it is also a growing focus in biomedical research with *Science,* for example, publishing a special issue on the area in February 2003 with a series of articles, an Editorial (*The ironic politics of obesity*) and a cover featuring fat cells. But why all the attention?

There is no doubt that the incidence of obesity is rising rapidly and some have even described the situation as a 'pandemic'. The UK provides a stark illustration of the international trends. In the early 1980s just 6% of men and 8% of women in the UK were classified as obese, but the latest figures indicate that the incidence has increased 3-fold in the past 20 years - to 22 and 24% of men and women, respectively (Fig. 1). Obesity is customarily defined on the simple basis of body mass index (wt in kg/height in m^2), and a value of 30 or more equates to clinical obesity (a lower value is increasingly used in East Asia). There has also been a corresponding increase in overweight (BMI: 25-29.9). Although the UK has one of the highest obesity rates in Europe, the situation is worse in the United States. The focus has until recently been on adults, but there is now growing concern with the rapid rise in overweight and obesity in children.

How much does this really matter? The answer is greatly; being obese reduces life expectancy by on average 8 years, and there is an increased incidence of several major diseases, particularly type 2 diabetes, coronary heart disease and certain cancers (such as breast, colon). Proportionately, the greatest impact of obesity is on type 2 diabetes, the risks for which increase approximately 10-fold once the threshold of a BMI of 30 is reached – and the more obese the greater the risk. The consequences of the link between diabetes and obesity are considerable; the current figure of nearly 1.8 million diagnosed diabetics in the UK is predicted to rise to over 3 million within a few years, essentially as a result of the surge in obesity. In the case of cancer, in the UK being obese is now seen as important a risk factor as smoking.

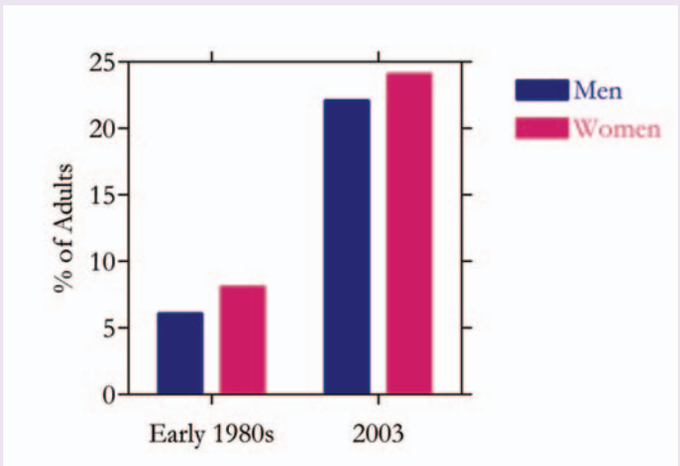

Figure 1. The rise in the incidence of obesity (BMI, 30 or more) in the U.K. over the past 20 years.

Treating obesity, and indeed reversing the rise in incidence, is in principle simple – either food intake should be reduced or energy expenditure increased. In other words, obesity is fundamentally an issue of energy balance, developing only when intake is in excess of expenditure (Trayhurn, 2005). However, public health messages encouraging dietary change and increased exercise, whether from scientists, clinicians, or Government agencies, have had little impact. Whether direct Government intervention, as increasingly advocated, will be helpful, or counter-productive as some fear, is a moot point. Drug-based approaches to treatment are being actively pursued, and pharmaceutical companies have extensive programmes for the development of new anti-obesity agents, and these are targeted particularly to the suppression of appetite.

The rapid increase in obesity is in practise a reflection of social and cultural changes, principally the now ready access to cheap and palatable high fat foods together with a sedentary lifestyle. What then is the role of biomedical research, and of physiologists in particular, in this area? The central challenge, as it has long been, lies in unravelling the fundamental mechanisms of the regulation of energy balance and body weight. There is an underlying genetic component to obesity, but it is not a genetic disease in the sense of resulting from single gene mutations (with rare exceptions). However, a number of specific gene polymorphisms are associated with weight gain and obesity. In essence, our genetically determined physiological mechanisms for body weight regulation have been overwhelmed by lifestyle changes.

Energy balance has traditionally been considered separately in terms of food

intake and the components of energy expenditure, the differences between which are buffered by changes in the storage of triacylglycerols in white adipose tissue. In recent years there have been major developments in our understanding of appetite control. New neuroendocrine factors which either inhibit or stimulate appetite, such as orexin B, cocaine- and amphetamine-regulated transcript, and the endogenous cannabinoid system have been identified, adding to established factors such as neuropeptide Y (Wilding, 2002; Trayhurn, 2005). Recently identified peripheral signals include leptin, released largely from adipose tissue, and ghrelin and peptide YY (3-36) from the gut. The challenge is to integrate the nexus of central neuroendocrine pathways and the various peripheral factors into a coherent view of the appetite system.

The main components of energy expenditure are the basal metabolic rate, adaptive thermogenesis (whether from cold, diet, drugs) and physical activity. A continuing theme has been the extent to which adaptations in expenditure leading to the dissipation of excess energy intake as heat are important in the regulation of energy balance and the development of obesity (Trayhurn, 2005). The issue gained resonance with the recognition of brown adipose tissue as the key site of non-shivering thermogenesis in rodents, the tissue generating heat by the controlled uncoupling of oxidative phosphorylation through the presence of the tissue-specific mitochondrial uncoupling protein-1 (UCP1). Contrary to initial expectations, the subsequent discovery of a family of mitochondrial 'uncoupling proteins' (UCP2, UCP3…) has not led to the identification of new loci for adaptive thermogenesis (Rousset *et al.* 2004). Perhaps the most interesting development in energy expenditure is the emergence of the concept of 'NEAT' (non-exercise activity thermogenesis) in which small movements (such as fidgeting) play a role in energy balance regulation (Levine *et al.* 1999).

Until recently, white fat was viewed simply as fuel reserve, passively buffering differences between intake and expenditure. However, it is now recognised as a key endocrine organ which plays a central role in energy balance through the secretion of leptin (Zhang *et al.* 1994). This hormone acts as a powerful satiety factor, interacting with multiple neuroendocrine systems in the hypothalamic control of appetite. In practise, leptin (a pleiotropic hormone) is one of the rapidly expanding list of protein signals secreted by white adipocytes. Indeed, adipocytes are veritable secretory powerhouses, releasing in excess of fifty different hormones and protein factors, termed adipokines (Trayhurn & Beattie, 2001; Trayhurn & Wood, 2004). These adipokines include adiponectin and resistin, which have been the focus of considerable attention because of their putative role in insulin resistance and glucose homeostasis.

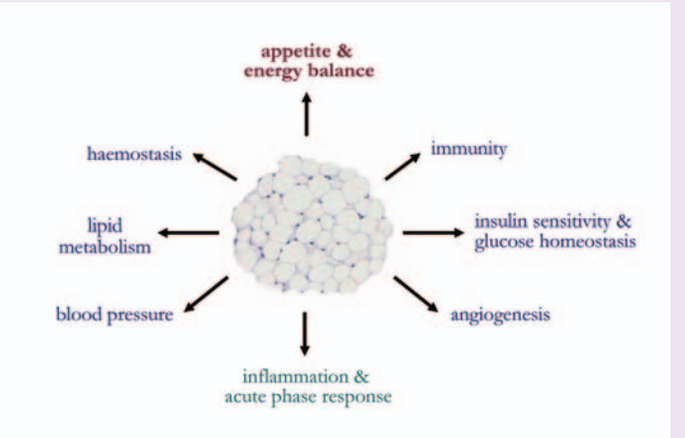

Figure 2. Physiological and metabolic processes with which adipose tissue is involved through the secretion of various adipokines (adapted from Trayhurn & Wood, 2004).

The diversity of adipokines is considerable, and their secretion indicates that white adipose tissue communicates extensively with other organs and is involved in a multiplicity of metabolic functions beyond lipid storage (Fig. 2). A number of adipokines are related to inflammation and the inflammatory response, including cytokines and acute phase proteins (Trayhurn & Wood, 2004), and the production of these is generally increased as adipose tissue mass expands in obesity. A key development is the recent recognition that obesity is characterised by chronic low grade inflammation, with adipose tissue being central to this (Trayhurn & Wood, 2004).

Changes in adipokine production in obesity are increasingly considered causal in the development of obesity-related diseases, particularly type 2 diabetes and the metabolic syndrome. Consequently, there is now the possibility that these associated diseases may be amenable to treatment, whether through pharmacological or nutritional intervention, by targeting specific adipokines. Indeed, there is more cause for optimism with this approach than with overcoming the social and cultural changes which have led to the tide of obesity itself.

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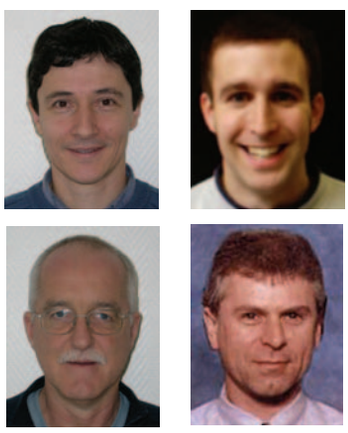
Metamorphosis from tadpole to frog: a tale of two networks

The transformation from tadpole to frog has long fascinated scientists and laymen alike, yet little is known about the neural basis of the switch in locomotory strategy from tail oscillations to limb kicking. Our new *in vitro* preparations herald unique opportunities to study neural plasticity accompanying metamorphosis



Top: Denis Combes (left) and Simon Merrywest
Above: John Simmers (left) and Keith Sillar

Within the vertebrates there are two principal modes of locomotion: limb-based propulsion (such as walking or flying) and axial body movements using the trunk muscles (such as swimming or side-winding). The phylogenetic position and developmental timetable of most species commits them to a body format predisposed for one or other type of movement.

For some amphibian species, however, a body format has evolved which allows for both locomotory modes to occur conjointly, at least at some stages of development. In urodeles (salamanders) this capacity is retained throughout adult life. In anurans (frogs and toads) a remarkable developmental transition, called metamorphosis occurs in which an axial swimming system in tadpoles is progressively superseded during metamorphosis by an adult limb-based locomotor strategy (Shi, 2000). In each case, the organism must possess neural circuitry within the spinal cord underpinning both behaviours simultaneously. The transition during metamorphosis must result from a set of developmental events including neurogenesis, apoptosis and synaptogenesis. Amazingly, all of these coordinated processes must be engaged whilst the organism continues to behave within its environment (in contrast to insect metamorphosis). Moreover, the entire palette of plastic changes occurring in the nervous system during metamorphosis is critically dependent on the presence of thyroid hormone and its subsequent impact on the genome. A detailed knowledge of the underlying neuronal mechanisms is thus of general interest and potential importance in understanding how hormones configure neural networks during development. However, a cellular and systems based neurobiological approach to understanding metamorphosis in a spinal motor system has thus far proven elusive.

To begin to address this issue of developmental neural plasticity, we have recently developed isolated preparations of the spinal cord of the frog *Xenopus laevis* at different metamorphic stages. These remain viable *in vitro,* expressing stage-specific motor patterns that would normally drive locomotion *in vivo* (Combes *et al*. 2004). Thus in isolated pre-metamorphic preparations, spinal ventral root motor output corresponds to typical fish-like undulatory swimming movements involving alternate bilateral contractions of axial muscles with a characteristic head-to-tail delay along the body (Roberts *et al.* 1998). Following tail resorption in post-metamorphic froglets, spinal motor output is now appropriate for rhythmic leg-kicks via slower and bilaterally-synchronous cycles of hindlimb extension and flexion. Thus, in a period of 2-3 weeks the organism's central locomotor circuitry, which is distributed along the larval spinal cord, is replaced by an adult hindlimb-kick network confined to the lumbar region of the cord.

At intermediate metamorphic stages the earliest movements of the emerging hindlimbs consist initially of bilateral extension movements that maintain the legs in a rearward position during propulsive undulatory swimming (Fig. 1).

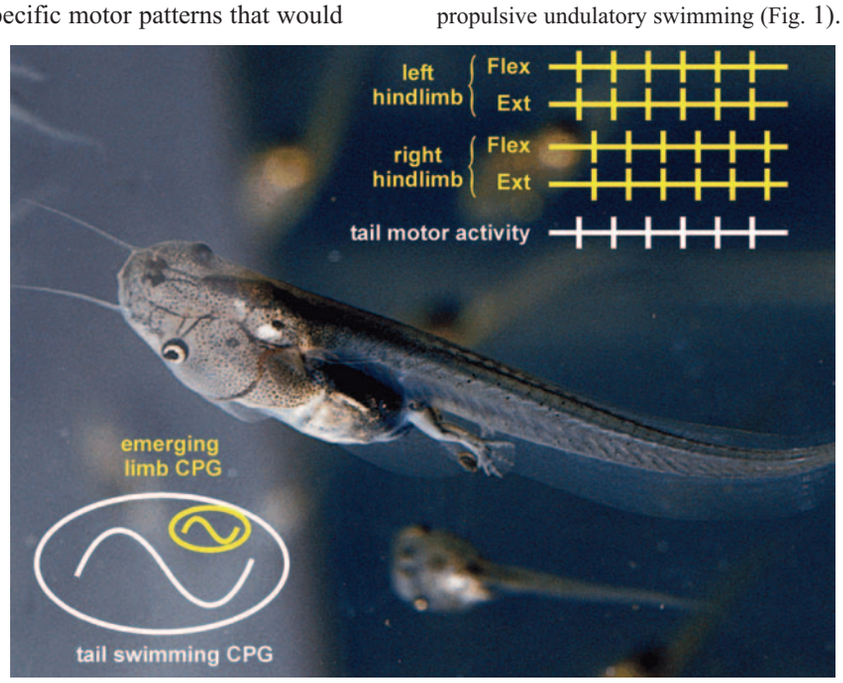


Figure 1. In early metamorphosing *Xenopus*, the hindlimbs are not yet sufficiently developed to contribute actively to locomotion. Swimming is performed by tail undulations while the emerging hindlimbs are held against the body. Spinal cord motor output to the tail and hindlimbs is tightly coordinated in a single rhythm (upper inset). At this stage, therefore, the future limb kick central pattern generator (CPG) remains embedded in the tail swimming CPG network (lower inset).

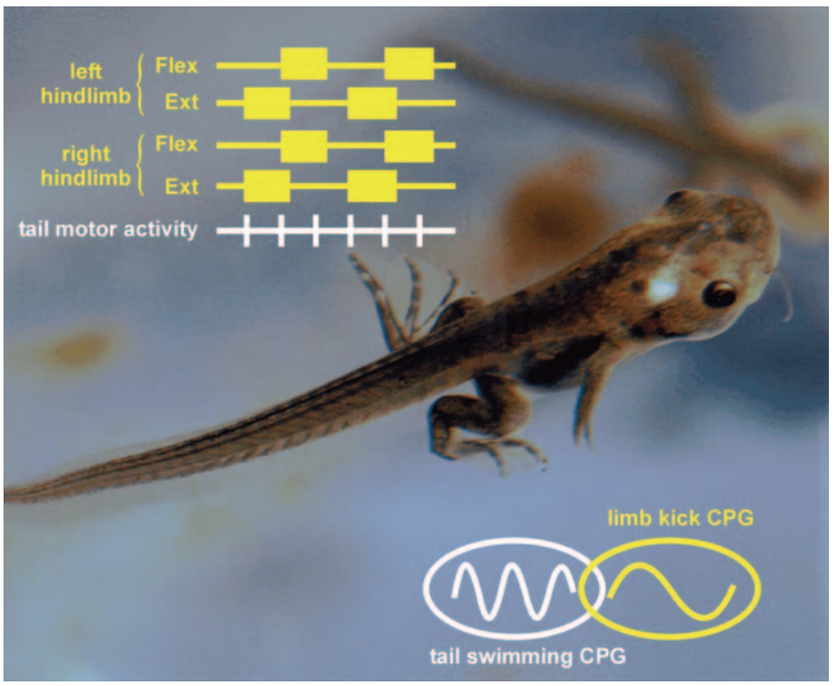


Figure 2. During the metamorphic climax, *Xenopus* can use both tail and limb-based movements for propulsion. In contrast to tail undulations, rhythmic hindlimb movements are slower and bilaterally synchronous, corresponding to kicks in which the flexor (flex) and extensor (ext) muscles of each limb are alternately active. At this developmental stage, therefore, the spinal cord can generate separate motor patterns appropriate for both locomotor modes (upper inset) suggesting the existence of two almost independent CPG networks (bottom inset).

However, the bursting pattern of lumbar motorneurons is tightly co-ordinated with the axial rhythm (Fig. 1 insets) suggesting that alternating lateral displacement of the hindlimbs may actively assist tail-based propulsion.

As the hindlimbs and their muscles continue to develop, this essentially auxiliary locomotor role is superseded by synchronous rhythmic leg movements now with their own independent frequency to provide supplementary propulsive force (Fig. 2). As in the freely-behaving animal, the motor patterns for both axial- and limb-based locomotion can be expressed independently or conjointly (albeit at very different frequencies), thereby confirming the co-existence of separate spinal rhythm generators. However, the temporal coincidence of hindlimb and axial motor rhythms in these transitional metamorphic preparations (Fig. 2 insets) suggests the existence of separate but still functionally-overlapping neural circuits.

Clearly, unravelling such developmental issues in *Xenopus* spinal locomotor networks now awaits detailed examination at the cellular and network levels. Moreover, our newly developed preparations offer opportunities to pursue this study through multiple approaches from molecular development and endocrinology via physiology, to the ontogeny of motor behaviour.

Acknowledgement

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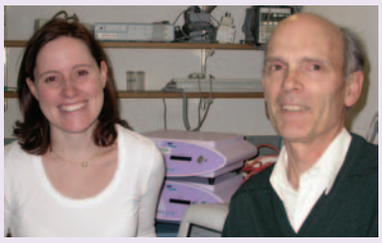
Impact of the intrauterine environment on respiratory health throughout life

The fetal environment, particularly oxygen and nutrient availability, is critical for organ development. Recent studies show that the lungs can be permanently altered by conditions that restrict fetal growth



From the left: Megan Cock, Richard Harding and Gert Maritz

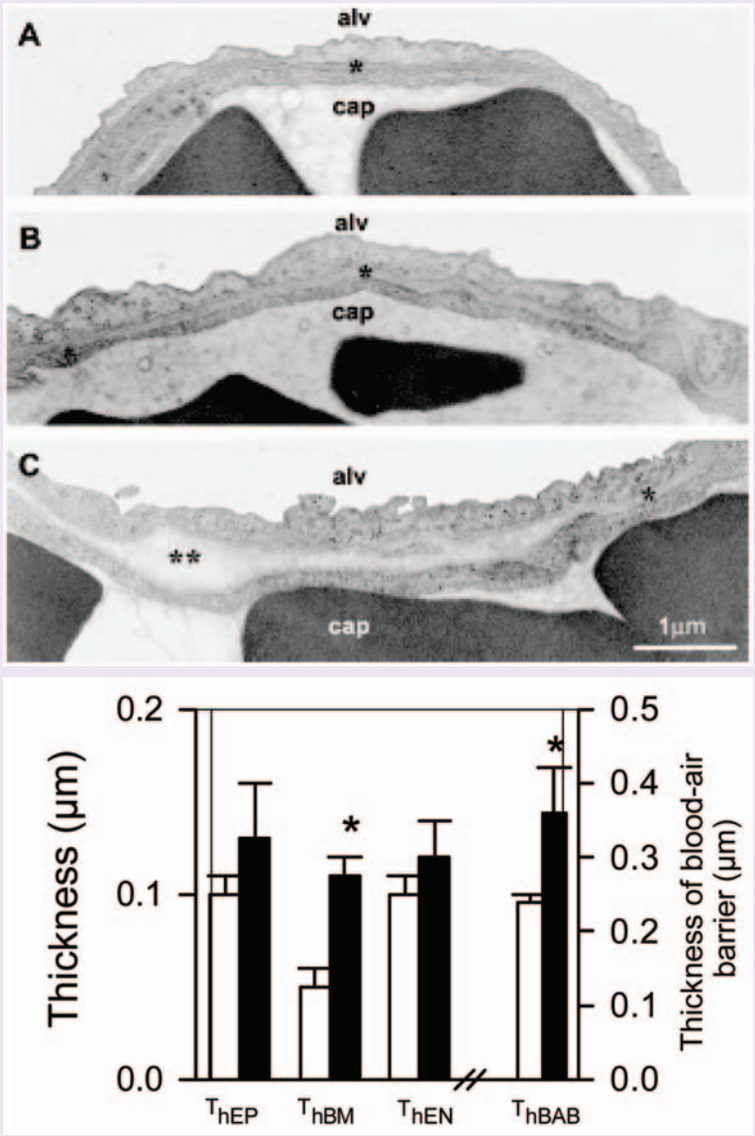


Figure 1. *Upper panel:* electron micrographs of the alveolar blood-air barrier of 2 year old control (*A*) and IUGR sheep (*B, C*). In controls (*A*), the basement membrane of the blood-air barrier (asterisk) is of even thickness; in IUGR sheep, however, the basement membrane was either (*B*) similar to that of controls, or (*C*) thicker, due to extracellular matrix between the epithelial and endothelial cells (**). alv: alveolar side of blood-air barrier lined by type 1 alveolar epithelial cells; cap: capillary side of the blood-air barrier lined by endothelial cells (parts of red blood cells are evident). Bar = 1.0 µm.
Lower panel: The total thickness of the blood-air barrier (T_{hBAB}) of IUGR sheep was significantly greater than that of controls; this was largely due to the greater thickness of the basement membrane (T_{hBM}) than in controls. The thicknesses of the alveolar epithelial cells (Th_{EP}) and capillary endothelial (Th_{EN}) cells were not affected. (Taken, with permission, from Maritz *et al.* 2004).

The concept that the intrauterine environment can have long-term or 'programming' effects on organ development, thereby increasing the risk of adult onset diseases, has grown in strength in the last decade. For example, epidemiological studies from a number of countries have shown that low birthweight resulting from intrauterine growth restriction (IUGR) increases the risk of metabolic disorders such as diabetes and obesity in later life. Important aspects of our prenatal environment that have been shown to affect later organ function and health include fetal oxygenation, nutrient availability, the endocrine environment (particularly corticosteroids), as well as exposure to common maternally-used drugs such as nicotine and alcohol. It is now apparent that these perturbations to the prenatal environment have the potential to permanently interfere with genetic programmes of organ development. Of particular interest to our Fetal and Neonatal Research Group at Monash University is the regulation of prenatal lung development and the impact of the intrauterine environment on pulmonary structure and function during postnatal life.

It is now established that the fetal lung is liquid filled and develops in an expanded state, with a low level of inherent recoil. In the fetus, during at least the last third of gestation, a high level of lung expansion is maintained by a combination of continuous, active secretion of 'lung liquid' by the pulmonary epithelium, the resistance of the upper airway (mainly the glottis) to the escape of this lung liquid, and by fetal breathing movements (which tend to oppose lung recoil and resist the escape of lung liquid into the fetal pharynx). We now recognise that this high level of lung expansion before birth is critical for normal growth and structural maturation of the lungs. When the degree of lung expansion is reduced for prolonged periods, such as

with oligohydramnios (lack of amniotic fluid) or diaphragmatic defects, lung growth is impaired and structural maturation of lung tissue retarded; if severe these can lead to respiratory insufficiency and death after birth. In survivors, the normal development of alveoli never occurs. Thus the physical environment of the fetal lung has a profound and lasting impact on its growth, architecture and functional capacity.

It is now evident that the metabolic and endocrine environment of the fetus can also have a substantial and persistent effect on lung development and postnatal lung structure. Epidemiological and clinical studies have shown that IUGR, which is associated with fetal hypoxaemia, hypoglycaemia and elevated corticosteroid levels, increases the risk of impaired airway function and respiratory illness in later life (Harding *et al.* 2004). However, the impact of restricted fetal growth on lung structural development is largely unknown. The problem is not insignificant as up to 10% of babies are considered to be growth restricted; that is, they do not reach their expected growth potential *in utero*. Using sheep, we have restricted fetal growth during the last third of gestation by experimentally inducing placental insufficiency. In this technique, microspheres are administered daily into the fetal arterial supply to the placenta. This embolisation technique induces chronic fetal hypoxaemia, hypoglycaemia and fetal endocrine changes which are similar to responses seen in human IUGR. We have found that restricting fetal growth by placental insufficiency leads to alterations in lung structure, some of which are present at birth, while others develop in the neonatal period (Maritz *et al.* 2001).

Of considerable interest is the finding that these changes persist at least until maturity at 2.3 years of age (Maritz et al. 2004). In particular, the lungs formed fewer alveoli and the alveoli were larger, resulting in a reduced surface area for gas exchange. In addition, the alveolar blood-air barrier was significantly thicker throughout

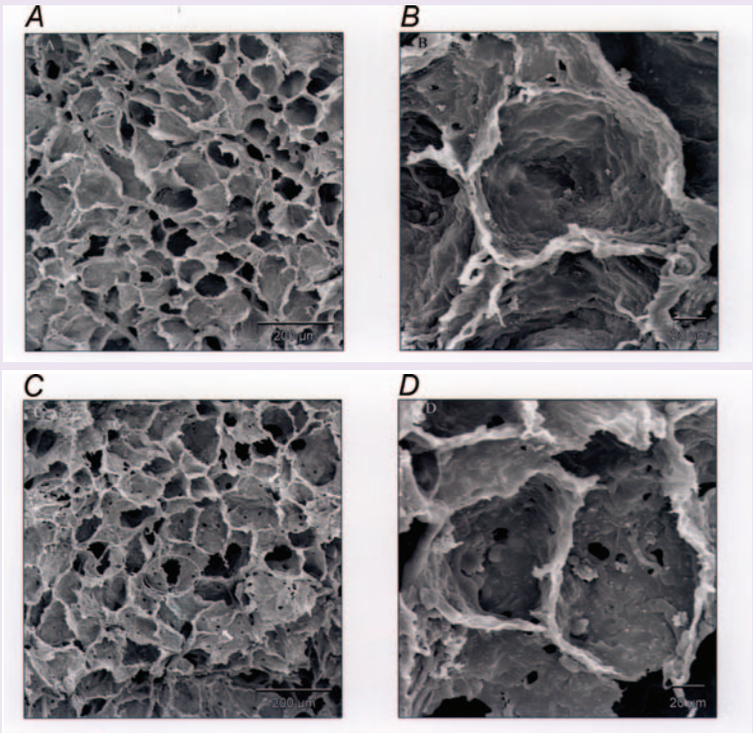


Figure 2. Scanning electron micrographs of the alveolar surface of lung tissue of adult control (*A,B*) and IUGR sheep (*C,D*). These are shown at low power (left panels) and high power (right panels). Alveolar fenestrations in IUGR sheep were more numerous than in controls. (Taken, with permission, from Maritz *et al.* 2004).

postnatal life as a result of a thicker basement membrane; together with a reduced alveolar surface area, this would be expected to impair gas transfer. Indeed we observed a reduction in the lung diffusing capacity for CO in the postnatal IUGR animals (Joyce *et al.* 2001). The alveolar walls were thicker after IUGR due to excessive accumulation of extracellular matrix, which may have contributed to increased lung stiffness in postnatal animals; this increased thickness persisted to maturity. In this regard, it is of interest that the expression of pulmonary surfactant proteins was not altered by IUGR. An unexpected finding was an increased presence of inter-alveolar pores, which is often taken as a sign of aging of the lungs; these pores are regarded as an early sign of emphysematous changes in the lung, as seen with aging or chronic exposure to tobacco smoke. Hence, in the parenchyma of the lung, there was evidence of both impaired development and premature aging. We also observed changes in the airways of these IUGR animals, notably an increased presence of epithelial secretory cells and transiently thinner airway walls (Wignarajah *et al.* 2002).

What could be the underlying processes leading to these persistent alterations in lung structure? As elastin is a long-lived structural protein that is intimately involved in lung development, including alveolar formation, we have examined the expression of tropoelastin and elastin content in the lungs after fetal growth restriction. Elastin synthesis is known to be metabolically regulated and hence it seemed reasonable to expect it to have been altered by IUGR; however, we found that this was not the case (Cock *et al.* 2004). At present, it seems likely that FGR leads to persistent alterations in pulmonary extracellular matrix synthesis or degradation in the lung parenchyma.

Maternal cigarette smoking during pregnancy is a major cause of low birthweight, and nicotine exposure has been shown to exert its own effects on the developing lung and airways. Infants and children who were exposed *in utero* to the effects of maternal smoking are known to be at increased risk of impaired airway function and respiratory illnesses such as asthma. It seems likely that at least part of this smoking-related problem is due to

IUGR, and that the effects remain to adulthood. However, this remains to be established.

In summary, our studies in sheep have shown that physical, metabolic and endocrine impairments in the intrauterine environment can alter lung development in the fetus, and that these changes can persist to maturity. Therefore, in fully understanding adult respiratory illness, prenatal environmental factors must be taken into account. It is also clear that to enable our progeny to have the best possible respiratory function throughout their lives, as parents we must ensure that they have the best possible intrauterine experience.

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This article is based on 'The lung from fetus to neonate: impact of the intrauterine environment' presented at the IUPS in 2001.

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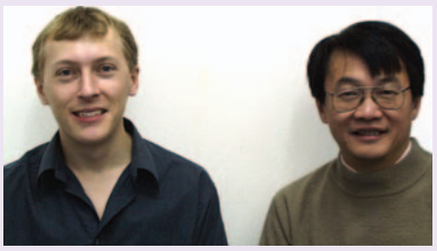
The interdependence of cell volume and resting membrane potential



James Fraser (left) with Chris Huang

A reader might justifiably believe that the mechanisms that determine the resting volumes (V_c) and membrane potentials (E_m) of animal cells were clarified long ago. Cell volume maintenance is understood to require sodium (Na^+) pump activity to exclude Na^+, which then balances the osmotic effect of intracellular proteins (Guyton & Hall, 2000). E_m at equilibrium may be calculated accurately, using Mullins and Noda's (1963) elegant modification of the Goldman-Hodgkin-Katz equation (Hodgkin & Katz, 1949). Numerous well-characterized processes alter V_c and E_m from their resting states. For example, depolarization of E_m occurs due to increased Na^+ permeability during action potentials, while most cell types show V_c regulation in response to volume changes and all must change their resting V_c during e.g. differentiation and mitosis (review: Lang *et al*. 1998).

So what remains to be understood? E_m and V_c are dependent on similar mechanisms, particularly Na^+ pump activity, and it is not clear how their *steady state* values are *determined*. For example, what mechanisms of control of Na^+ pump activity are necessary to achieve stable values of V_c and E_m? Furthermore, what mechanisms could *regulate* V_c and E_m independently in processes such as muscle hypertrophy, when V_c changes and most recognised mechanisms of V_c regulation necessarily alter the intracellular ion concentrations that determine E_m (Ferenczi *et al.* 2004)?

In *The Journal of Physiology*, we recently (Fraser & Huang, 2004) formulated a limiting relationship between steady state V_c and E_m (Box 1). However, full investigation of V_c and E_m determination required the development of a formal model. Its principal innovation was the calculation of E_m directly from the intracellular charge difference and membrane capacitance, thus avoiding the equilibrium assumptions implicit in Goldman-Hodgkin-Katz type equations. The influence of transmembrane ion fluxes and V_c changes upon E_m could then be modelled directly from the resultant changes in *precise* intracellular ion concentrations, allowing inclusion of essentially any quantifiable process in the model, including the activity of the Na^+ pump and its electrogenic influence (Hernandez & Chifflet, 2000).

BOX 1 Constraints upon steady state V_c and E_m in animal cells

(1) Intracellular and extracellular osmolarity are equal: $[Na^+]_i + [K^+]_i + [Cl^-]_i + [X^-]_i = \Pi_e$

(2) There is gross charge neutrality inside the cell: $[Na^+]_i + [K^+]_i - [Cl^-]_i + z_X[X^-]_i \approx 0$

(3) Cl^- is passively distributed across the cell membrane.

Thus steady-state V_c and E_m are related:

$$V_{c(t=\infty)} = \frac{(1 - z_X)(X_i^- / V_{c(t=0)})}{(\Pi_e - 2[Cl^-]_e e^{(E_m F / RT)})}$$

where: square brackets [ ] denote concentrations; subscripts e and i denote extracellular and intracellular respectively; t=0 denotes initial (disequilibrium) conditions; t=∞ denotes steady state conditions; V_c = cell volume; X^- membrane-impermeant anions; z_X mean charge valency of X^-; Π_e total extracellular osmolarity; E_m resting membrane potential; F Faraday's constant; R the gas constant; and T the absolute temperature.

Figure 1 demonstrates the principal conclusion of this work: V_c and E_m converge to unique set-points *without requiring* any explicitly V_c- or E_m-sensitive mechanisms. However, the existence of stable points of V_c and E_m *requires* the presence of membrane-impermeant intracellular ions (X^-_i) as well as a functional sodium pump. Given the constraints detailed in Box 1, consider the (physiological) situation where Cl^- is the major extracellular anion. X^-_i then prevents Cl^- from achieving chemical equilibrium ($[Cl^-]_i = [Cl^-]_e$) across the cell membrane. In the absence of sodium pump activity, the inward Cl^- gradient would result in an unopposed Cl^- influx, permitting a cation influx and cell swelling until X^-_i was infinitely diluted. Conversely, in the absence of X^-_i, Na^+ pump activity would cause cell shrinkage indefinitely. Each pump cycle decreases $[Na^+]_i$ and increases $[K^+]_i$, creating an outward K^+ gradient. Efflux of K^+ then results in hyperpolarization of the cell, thereby promoting Cl^- efflux which "short-circuits" the K^+ potential and shrinks the cell. When Cl^- is the only intracellular anion, $[Cl^-]_i$ must always be half the total intracellular ion concentration, despite such a reduction in its cellular *content*, so cell shrinkage could continue indefinitely and significant polarization of the membrane would be impossible. This would not occur in the presence of X^-_i: $[Cl^-]_i$ reduction is then possible as shrinkage increases $[X^-]_i$, so that eventually K^+ efflux cannot drive Cl^- efflux, and instead causes E_m polarization that then opposes further K^+ efflux. Together, then, the tendency of X^-_i to make the cell swell and the tendency of the sodium pump to make it shrink can, at one single point, reach a precise balance. It was thus shown that V_c was linearly related to X^-_i content (Fig. 1).

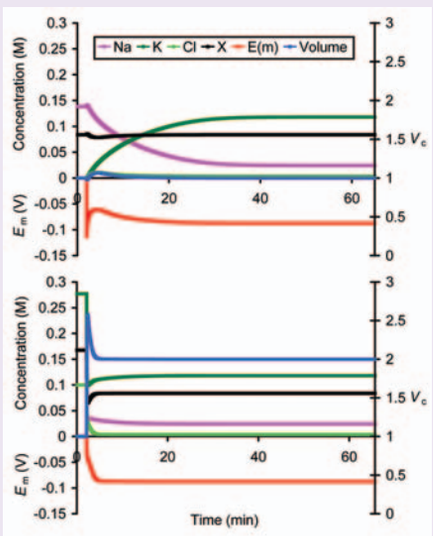


Figure 1. Cell volume (V_c) and membrane potential (E_m) converge to fixed set-points at steady state. The results of two simulations starting at Time = 2 min are shown. V_c denotes relative volume, and thus both simulations start with V_c = 1. The upper panel shows a simulation with $[X^-]_i$ initially at its normal resting value, while the lower panel starts with $[X^-]_i$ twice normal. Other starting ion concentrations were chosen semi-arbitrarily, although the net intracellular charge was initially zero in both cases. Note that despite these sharply divergent starting conditions, E_m and all intracellular ion concentrations eventually converge to identical steady state values, while steady-state V_c is directly proportional to the initial concentration of X^-_i.

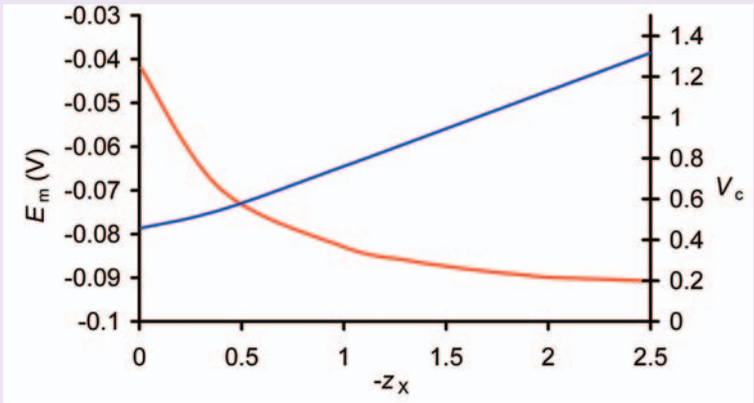


Figure 2. The influence of z_X upon E_m and V_c. E_m (red line) and V_c (blue line) are plotted against ($-z_X$). V_c denotes cell volume relative to that when ($-z_X$) = 1.65, close to its value in skeletal muscle. Increases in the magnitude of z_X result in cells which, at steady state, are larger for a given cellular X^- content and more polarized.

However, this linear relationship implies that the steady-state *concentration* of X^-, and hence the value of E_m, is then independent of X^-_i content. However, as shown in Fig. 2, the mean charge valency of X^- (z_X) does influence E_m as well as V_c. If $(-z_X) \ll 1$, $[X^-]_i$ must be higher than $[K^+]_i$ to achieve gross charge neutrality, whereas if $(-z_X) \gg 1$, $[K^+]_i$ could significantly exceed $[X^-]_i$. As intracellular and extracellular osmolarity must remain equal, greater z_X magnitudes are required for higher $[K^+]_i$ and hence more polarized E_m. Thus the previously overlooked parameter z_X is critical to determination of E_m and V_c.

This analysis (Fraser & Huang, 2004) thus identifies and characterizes the factors that determine V_c and E_m and the relationship between them. In excitable cells at least, Na^+ pump density above a critical value little influences either V_c or E_m as it operates close to its energetic limits at steady state. Instead, for given transmembrane ion permeabilities, steady-state V_c is determined by X^-_i content *and* z_X, while E_m is determined *solely* by z_X. Charge-difference modelling thus proved a powerful tool, permitting investigation of the many mechanisms that determine, maintain and regulate V_c and E_m.

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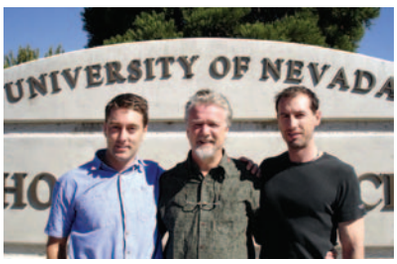
Mechanosensory transduction in the enteric nervous system

Two classes of sensory neuron within the myenteric plexus of the colon give complementary information regarding the tension of smooth muscle and its degree of stretch. Both sensory systems appear to be capable of generating a different pattern of motility



From the left: Nick Spencer, Terence Smith and Grant Hennig

Over the last few years the intriguing similarities and differences between the simple reflex behaviour of the somatic nervous system and the enteric nervous system (ENS) are gradually emerging. We have presented evidence that there are two distinct sensory systems in the ENS that underlie muscle movements of the gut wall that drive fecal pellet propulsion. Mucosally projecting AH neurons appear to register the tension (tone) of smooth muscle, whereas S interneurones register the length of smooth muscle or gut diameter. Functionally, these sensory modalities appear analogous to those in skeletal muscle where Golgi tendon organs and muscle spindles within the same muscle bundle give complementary information about changes in muscle force and length respectively.

The ENS lies within the intestinal wall and consists of two ganglionated neural networks – these are the myenteric and submucous plexuses, that mainly regulate motility and secretion respectively. Stretching of the gut wall or mucosal stimulation usually elicits simultaneous contraction of the longitudinal (LM) and circular (CM) smooth muscle orally and relaxation of both smooth muscles anally. These reflex responses underlie propulsion of gut contents or peristalsis (Bayliss & Starling, 1899).

The neurons involved in these reflex pathways lie within the myenteric plexus and have been classified into S/Type I and AH/Type II neurons (Hirst *et al.* 1974). S/Type I neurons receive extensive fast excitatory synaptic (S) input. They are slowly adapting neurons that comprise excitatory and inhibitory motor neurons and interneurons. In keeping with their function, S-neurons respond to distension or mucosal stimulation with bursts of fast excitatory postsynaptic potentials (fEPSPs) (Smith *et al.* 1992). AH/Type II neurons, on the other hand, are characterized by a prolonged after-hyperpolarization (AH-up to 20s) that follows a single action potential. They receive little fast synaptic input but can generate slow excitatory postsynaptic potentials (sEPSPs) in other AH neurons and S neurons.

AH-neurons, unlike S neurons, do not respond to reflex stimulation when it is applied some distance away from the recording site (Smith *et al*. 1992; Spencer & Smith, 2004). AH neurons are multipolar neurons with one or more processes projecting down into the intestinal mucosa. Unlike S neurons, they respond directly to chemical stimulants applied to the mucosa. AH-neurons also respond to stretch with an ongoing action potential discharge. Surprisingly, this discharge is dependent upon muscle tone/tension rather than stretch *per se*, since despite maintained stretch, their activity is abolished by drugs such as nicardipine (L-type Ca^{2+} channel antagonist) and isoprenaline (β-antagonist) that abolish smooth muscle tone (tone being the muscles capability of generating active tension to resist stretch) (Kunze *et al.* 1998).

As a result of these findings, it has been assumed until now that myenteric AH-neurons are the only intrinsic primary afferent neurons in the gut that are responsible for initiating the peristaltic reflex. However, our earlier studies suggested that enteric reflexes activated by mucosal stimulation and stretch are mediated by two different sensory neurons that converge onto common interneurons and motor neurons within the reflex pathways (Smith *et al.* 1992). Previously we have shown interactions between these two sensory systems; habituation of the response to repetitive stretch can be overcome, and even sensitized, by a preceding mucosal stimulus (Smith *et al*. 1991). Although it seems likely that mucosal reflexes are initiated by AH neurons, the intrinsic sensory neurons mediating stretch reflexes have only recently been identified (Spencer & Smith, 2004). We show below that these different sensory neurons can produce different motor behaviours, depending upon the stretch and tone of the smooth muscle.

Muscle tone dependent peristalsis

We investigated the relationship between smooth muscle tone and propulsion of fecal pellets in the guinea-pig distal colon (Smith *et al*. 2003). This was in part to determine whether smooth muscle tone-dependent enteric neurons may contribute to peristalsis. To do this we threaded a segment of distal colon through two partitions, which divided the bowel for pharmacological purposes into oral, stimulation and anal regions. An intraluminal balloon to mimic a fecal pellet was inserted between the partitions (stimulation chamber) and held in position. Maintained distension of the balloon produced rhythmic (~0.3/min), peristaltic-like waves of contraction that propagated down the colon. Each wave of contraction (duration ~40-60s) exerted considerable force on the balloon. These waves were neural in origin since they were blocked by hexamethonium. When a smooth muscle relaxant (isoproterenol, nicardipine or papavarine) was added selectively to the stimulation chamber the muscle relaxed and the peristaltic-like waves were abolished. Atropine, a muscarinic antagonist, added to the stimulation chamber also relaxed the

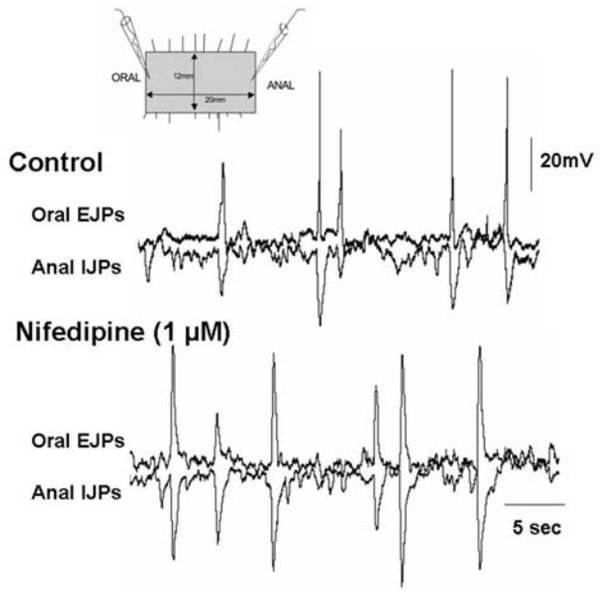


Figure 1. Muscle tone independent ongoing reflex activity. A simultaneous intracellular electrical recording from 2 CM cells at either end of a sheet (20 mm long) of guinea pig distal colon that was maintained under circumferential stretch. The mucosa and submucous plexus were removed. Control: EJPs and action potentials occur at the oral recording site. These occur at the same time as IJPs at the anal recording site. After muscle paralysis with nifedipine the same motor pattern was recorded, but muscle action potentials were abolished.

muscle and blocked peristaltic waves. This suggested that ongoing cholinergic excitatory motor nerve activity was largely responsible for generating smooth muscle tone around the balloon. Therefore, the enteric neural circuitry responsible for these waves was critically dependent upon smooth muscle tone. In addition, removing the mucosa around the balloon also abolished the rhythmic peristaltic waves. Thus it seems likely that smooth muscle tone dependent AH neurons may be involved in initiating these waves.

Ongoing stretch-activated, muscle tone-independent, reflex activity

We also made simultaneous intracellular electrical recordings from the CM or LM at either end of a sheet of guinea-pig distal colon that was maintained under circumferential stretch (Spencer *et al*. 2002, 2003). At the oral end of these stretched sheet perparations excitatory junction potentials (EJPs) occurred at the same time in both the LM and CM. If an oral EJP elicited an action potential it evoked a robust contraction that propagated anally. At the anal end of the tissue inhibitory junction potentials (IJPs) occurred synchronously in both muscle layers. Also, the rapidly firing (frequency of ~15/min) oral EJPs were synchronized in both time and amplitude with the anal IJPs recorded some 20mm away (Fig. 1). Unstretched tissues did not exhibit this activity. Unlike the muscle tone dependent peristaltic waves, ongoing reflex activity was unaffected by removal of the mucosa and the submucous plexus. This rhythmic motor pattern was also unaffected by abolishing smooth muscle tone in the stretched segment of distal colon with nifedipine (L-type channel antagonist that blocks smooth muscle action potentials).

The only way we could envisage the oral EJPs and anal IJPs to be 'locked' in both time and amplitude and to occur at the same time in both the LM and CM muscles (see Fig. 1) was if the excitatory and inhibitory motor neurons innervating both muscles at either end of the tissue were activated by common interneurons in ascending excitatory and descending inhibitory nerve pathways that communicate with one another (see Fig. 2). Taken together, these results suggested that muscle-tone dependent activity in AH neurons was unlikely to drive this ongoing reflex activity. It seemed more likely that only S neurons participated in this ongoing motor pattern.

Mechanosensitive interneurons and S motor neurons

We next attempted to determine whether S or AH neurons were involved in driving this muscle tone-independent, stretch-activated, ongoing reflex activity. To do this we made simultaneous intracellular electrical recordings from both myenteric neurons and adjacent CM cells in stretched sheets of distal colon (Spencer & Smith, 2004). AH neurons were found to be electrically silent despite ongoing junction potentials in the muscle. S motor neurons, on the other hand, showed phasic bursts of fEPSPs that just preceded an EJP or IJP in the muscle. Another class of S neurons exhibited a continuous high frequency burst of action potentials. This ongoing discharge was insensitive to synaptic blockade with low Ca^{2+}/high Mg^{2+} solution, which blocked the coordinated EJPs and IJPs in the muscle. The discharge of action potentials in these neurons could often be converted to proximal process potentials by membrane hyperpolarization.

We therefore assumed this activity was generated by a mechano-sensitive soma or stretch sensitive dendrites. This was confirmed since, even after synaptic blockade, stretching the adjacent CM with a fine probe produced an increased discharge of action potentials in these neurons. Dye injection revealed that these particular neurons had a filamentous soma and were ascending and descending interneurons since their long axon gave off collateral branches to other neurons as it passed through several myenteric ganglia. Interestingly, a dendrite could usually be traced to leave the underside of a ganglion and enter the CM where it ran parallel to the CM fibres. Dendrites from these neurons did not appear to enter the LM. Therefore, it appears that these dendritic processes within the CM are involved in stretch activation of these mechanosensitive interneurons. This was supported by the observation that removing the LM had no effect on the ongoing reflex activity. However, no activity was recorded in the LM of stretched sheets devoid of CM. It turns

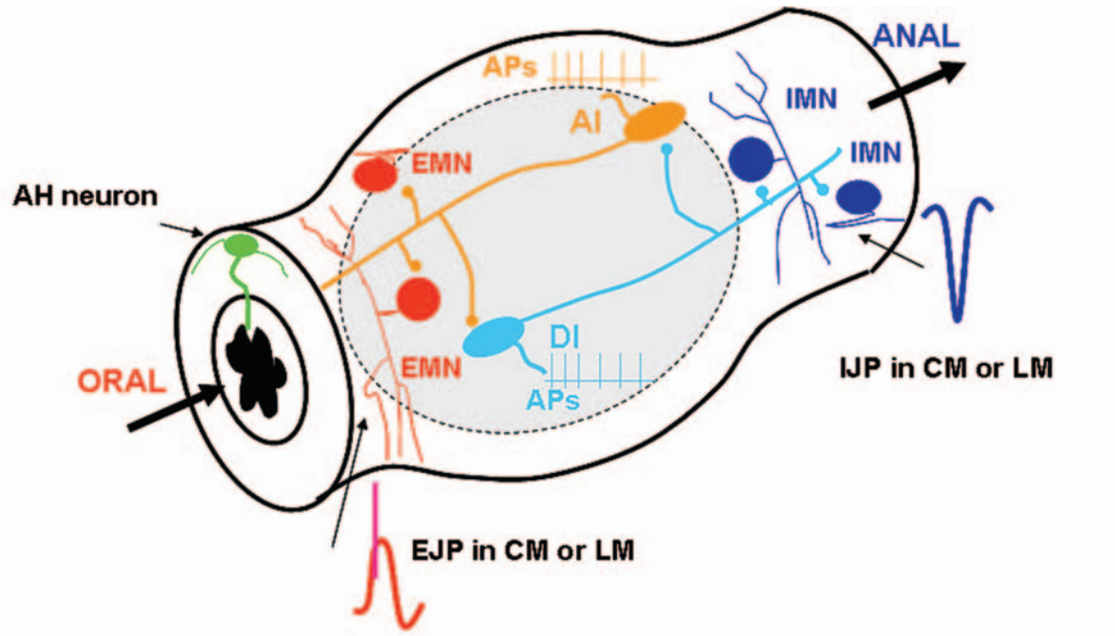


Figure 2. Schematic of stretch-dependent, muscle tone-independent neural circuitry underling fecal pellet propulsion. EJPs and IJPs occur at the same time in both muscles simultaneously at the oral and anal ends of the stretched segment respectively. The excitatory (EMNs) and inhibitory motor neurons (IMNs) innervating both muscles appear to be driven by common mechanosensory ascending (AI) and descending interneurons (DI). The stretch-sensitive dendrites of these interneurons are within the CM. APs action potentials. AH neurons that project into the mucosa did not contribute to this activity.

out that mechanosensory interneurons are not unusual since they have been identified in a variety of invertebrates (reviewed in Spencer & Smith, 2004).

Conclusions and future directions

We have found two different neurally-mediated motor behaviours in the guinea-pig distal colon that likely underlie fecal pellet propulsion: smooth muscle tone-dependent peristaltic waves and tone-independent, stretch-activated ongoing reflex activity. Stretch-sensitive S interneurons are the only sensory neuron needed to drive ongoing reflex activity. However, peristaltic waves, which require stretch, smooth muscle tone and mucosal stimulation for their activation, likely involve a complex interaction between AH sensory neurons and stretch-activated S interneurons. Presumably, there is a positive feedback when both sensory neurons are activated. Activity in AH neurons could increase the excitability of interneurons by inducing sEPSPs. Oral contraction activated by interneurons could further excite tone-dependent AH neurons.

Future directions will include determining how these two sensory systems interact to produce intestinal propulsion. By analogy with Golgi tendon organs and muscle spindles within the skeletal muscular system, we will also need to determine what in series and in parallel elements are responsible for transducing muscle tension and muscle stretch to AH and S interneurons.

A possibility is that the intramuscular interstitial cells of Cajal (ICC-IM), which run parallel to and within CM bundles, initiate stretch-dependent activity in the mechanosensitive dendrites of S interneurons. ICC-IM also mediate excitatory and inhibitory neuro-transmission from motor neurons to the muscle (Beckett *et al*. 2004).

Acknowledgements

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The fire within: fuel selection in shivering muscles

François Haman and colleagues are looking for essential clues on what limits human survival in the cold



From the left: François Haman, Stéphane Legault and Jean-Michel Weber

Keeping warm bodies in cool environments has been a critical challenge for endotherms since their origin on Earth. As furless mammals, humans are particularly vulnerable to cold, and have trouble coping with even slight decreases in ambient temperature. Without access to proper clothing or shelter, our survival is limited to a few hours during accidental cold exposure. When this happens, a lethal decrease in body temperature is prevented, at least temporarily, through a rapid increase in internal heat production. In adults, this process is mainly supported by shivering thermogenesis, whereby skeletal muscles become metabolic furnaces that generate heat from the oxidation of carbohydrates (CHO), lipids and proteins.

The relative contribution of these different fuels is the subject of heated(!) debate because fundamental questions about cold endurance remain unanswered: what selection mechanisms govern the mixture of fuels we use, and how does this choice affect our survival? From a practical perspective, designing new means to improve survival by manipulating fuel selection would clearly be useful. Even though complete answers to these questions are not available, important advances have been made recently in this field of human physiology.

Over the last decade, most studies of fuel metabolism in cold-exposed humans have focused on CHO (glycogen) as a possible limiting factor for shivering (this fuel only represents ~1% of total energy stores and is known to limit endurance exercise events such as marathon running). Therefore, in the absence of quantitative information on heat generation from fuels other than CHO, the role of lipids and proteins had been consistently underrated. Recent experiments during prolonged, low-intensity shivering show that lipids can produce more heat than all other fuels combined (Haman *et al.* 2002). In addition, it is now clear that heat production is **not** affected by depleting CHO reserves, either at low- or high-thermogenic rate, because lipid and protein oxidation are both stimulated to compensate for the reduced contribution from CHO (Young *et al.* 1989; Haman *et al.* 2004c). Contrary to what was previously thought, these results suggest that CHO may not be essential for shivering. More importantly, they demonstrate that heat production can be sustained for several hours, even when CHO reserves are depleted, because humans show remarkable flexibility in fuel selection.

Selecting a mixture of fuels can either be achieved by recruiting distinct muscle fibre populations specialized for different fuels or by mobilizing different metabolic pathways within the same fibres. Therefore, heat production depends critically on co-ordinating muscle fibre recruitment and oxidative fuel metabolism. Traditionally, research on shivering falls in two broad categories dealing either with muscle metabolism or with electrophysiological aspects of muscle recruitment. We reasoned that combining these complementary approaches would provide valuable insights. Detailed electromyographic analyses (EMG) by Meigal (2002) identified two shivering patterns associated with the recruitment of specific muscle fibers: continuous, low-intensity shivering (or thermogenic muscle tone) and burst shivering of high-intensity. While continuous, low-intensity shivering is linked to low-threshold fibres (type I, slow-oxidative, fatigue-resistant), high-intensity burst shivering is associated with high-threshold fibres (type II, fast-glycolytic, fatigable) (Fig. 1). Because these two fibre types are biochemically specialized for different fuels (type I: lipids; type II: CHO), we hypothesized that changing the relative importance of low-intensity shivering and burst shivering might be a key mechanism of fuel selection. During high-intensity

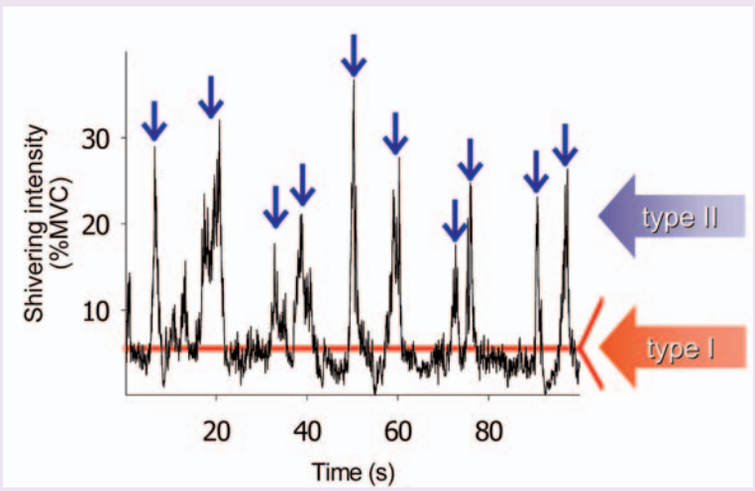

Figure 1. Typical EMG signal of shivering muscle. *Burst shivering* is indicated by blue arrows and *low intensity shivering* by a red horizontal line. (modified from Haman *et al.* 2004a)

shivering, our hypothesis was confirmed; we found that changes in fuel selection are achieved by recruiting different 'fuel specific' fibres (Fig. 2A) (Haman et al. 2004b). Even though this important mechanism of selection has been thought to play a key role in exercise, our shivering study is the first to provide direct evidence of its existence. Therefore, EMG signals contain quantitative information on fuel metabolism during high-intensity shivering. In contrast, during low-intensity shivering, the alternate mechanism of fuel selection is used: CHO-depleted and CHO-loaded individuals are able to sustain the same rate of heat production by oxidizing very different fuels within the same muscle fibres (Haman et al. 2004a) (Fig. 2B).

Where do we go from here? Results from these studies, together with our novel experimental approach, provide a new direction for shivering research. The physiological significance of the dual shivering pattern is puzzling and should be clearly characterized in relation to fuel selection and thermogenic rate. The detailed study of shivering bursts, as it relates to the average fibre composition of each individual, will provide essential clues on what limits human survival in the cold. One cannot investigate muscle physiology without marveling at the remarkable flexibility of this tissue: from well co-ordinated movements to intense heat production. So… if exercise physiology leaves you cold, turn to shivering.

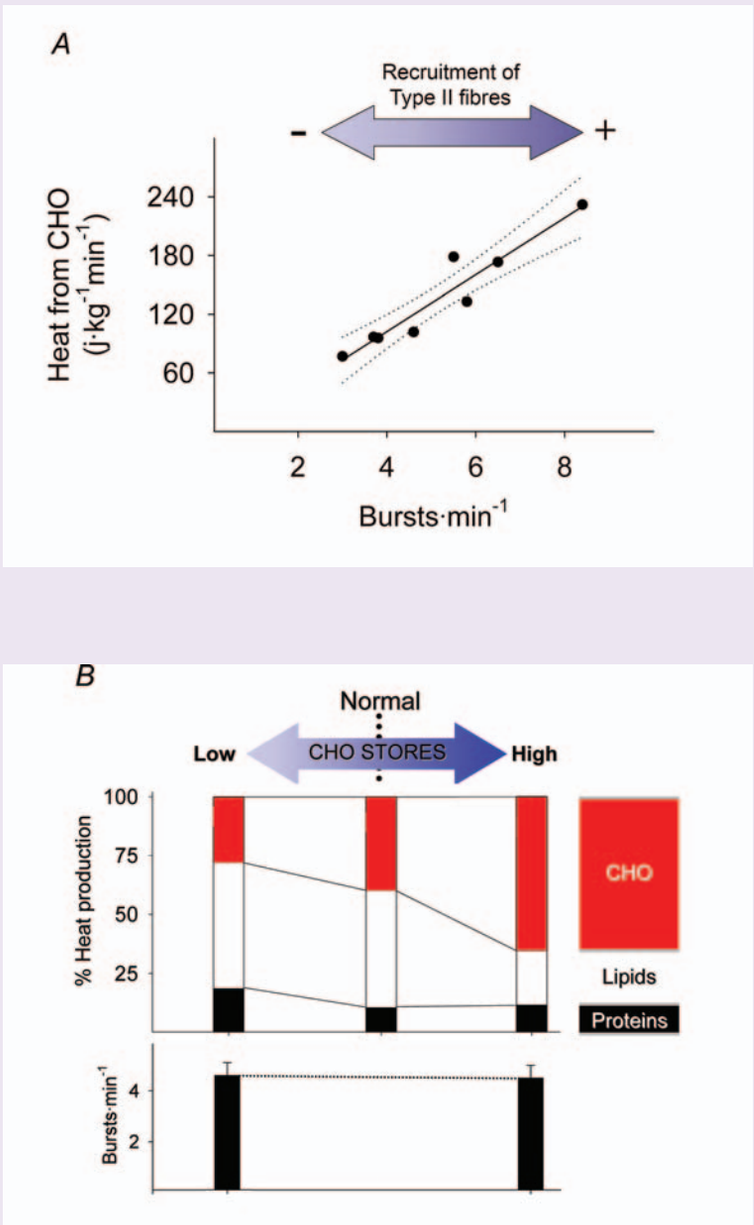

Figure 2. ***A.*** **High-intensity shivering**: Relationship between the rates of burst shivering and CHO utilization in adult men (modified from Haman *et al.* 2004b). ***B.*** **Low-intensity shivering**: Relative contribution of CHO, lipids and proteins to total heat production in adult men with low, normal and high glycogen reserves (upper panel). Burst shivering rate (whole-body average) in adult men with low and high glycogen reserves (lower panel) (modified from Haman *et al.* 2004a, 2004c).

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Differential screening of a subtractive cDNA library reveals that maternal undernutrition affects fetal heart gene expression

Maternal undernutrition during the first half of gestation induces differential transcription of genes in ovine fetal left ventricular heart. Several of the differentially expressed genes have been associated with hypertrophied adult heart tissue, while the remaining genes have been reported to inhibit hypertrophic growth in adults

Hyungchul Han (left) and Thomas Hansen

Offspring from under-nourished mothers have a predisposition to obesity, diabetes, and cardiovascular disease in adult life. Low weight or thinness at birth in human neonates is associated with increased risk of cardiovascular and metabolic disorders in later life (Barker, 1994). The process whereby the fetus compensates for a maternal insult (undernutrition, stress, etc.) at a sensitive or critical period of fetal development, with consequential long-term effects, has been termed fetal programming. This phenomenon is likely to reflect the benefits of developmental flexibility by the fetus, allowing for short-term survival. However, such adaptations that are beneficial for short-term fetal survival may be detrimental to health in later life.

A global 50% nutrient restriction during the first half of gestation in sheep resulted in lower fetal weight while both the left and right ventricles of the fetal heart showed compensatory growth by day 78 of gestation (Vonnahme *et al.* 2003). In order to follow up this observation, we generated a subtractive cDNA library that was enriched for fetal left ventricular heart cDNAs from nutrient-restricted ewes. Screening revealed differential transcription of 11 genes (caveolin, stathmin, cyclin G-1, α-actin, titin, cardiac ankyrin repeat protein, cardiac-specific RNA-helicase activated by MEF2C, endothelial and smooth muscle derived neuropilin, prostatic binding protein, NADH dehydrogenase subunit 2, and an unknown gene) in fetal left ventricle from the nutrient-restricted ewes when compared to control fed ewes (Han *et al.* 2004). The up-regulation of these genes during fetal development may induce hypertrophic growth in the fetal heart as a consequence of maternal undernutrition (Fig. 1).

Many of these up-regulated genes have been shown by others to be involved with cardiac hypertrophy in adults. Notably, the remaining genes have actually been reported to inhibit hypertrophic growth in adults. For example, cyclin G1 is up-regulated in nutrient-restricted fetal heart. Cyclin G1 facilitates entry into the cell cycle, thereby increasing cell numbers. In adult heart, cyclin G1 initiates protein synthesis to cause cardiac hypertrophy, rather than DNA synthesis through entry into the cell cycle (Nozato *et al.* 2000). Cyclin G1 also is up-regulated in growing heart that is still capable of continuing the cell cycle during mid-gestation.

After birth, heart tissues enter into a stage in which cell numbers do not increase, but size of cells can increase. Thus, genes responsible for hypertrophy may induce hypertrophic growth (increase in cell size) rather than hyperplasia (increase in cell number) in adult heart. Numbers of fetal heart cells increase significantly at mid-gestation. So in the present studies it was not clear if the increase in size of left ventricle was caused by hypertrophic or hyperplastic responses. Interestingly, right ventricular systolic pressure load caused both hyperplastic and hypertrophic growth of right ventricle in near term fetal sheep (Barbera et al. 2000). However, most fetal cardiac tissues near term have

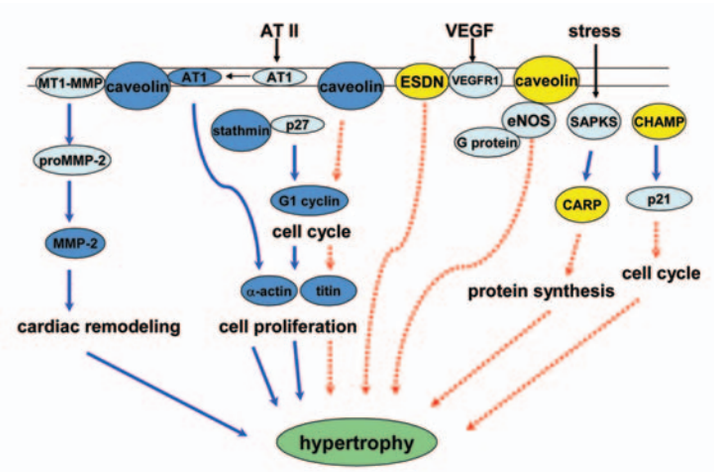

Figure 1 Proposed model describing up-regulation of fetal left ventricle mRNAs in response to hypertrophy induced by maternal undernutrition. Binding of MT1-MMP activates proMMP-2, which is then cleaved to form activated MMP-2. Caveolin is also required for the AT2 induced activation of AT1 to initiate signal transduction. Stathmin inhibits CDKI p27, which allows the cell cycle to proceed. These molecules are involved in inducing hypertrophy and mediate cell proliferation and cardiac remodeling. Cardiac α-actin and titin are up-regulated in response to these processes. Caveolin is also known to block G1 cyclin and binds to eNOS to inhibit its activity. CARP is activated by SAPKs in response to stress, which prevents protein synthesis. RNA helicase, also known as CHAMP prevents cell cycle by activation of CDKI p21. These molecules are up-regulated and have inhibitory effects during hypertrophy. It is proposed that hypertrophy of fetal LV in response to maternal undernutrition is a homeostatic response between stimulatory and inhibitory signal transduction pathways. The abbreviations used are: MT1-MMP, membrane type 1 matrix metalloproteinase; AT1, angiotensin II type 1 receptor; ESDN, endothelial and smooth muscle derived neuropilin; eNOS, endothelial NO synthase, SAPKs, stress activated protein kinases; CHAMP, cardiac-specific helicase activated by MEF2. Solid arrow denotes activation and dotted arrow denotes inhibition of signalling pathway. Adapted from Han *et al.* (2004).

already terminated cell division and have entered into a binuclear stage that is similar to adult heart. Future studies of cell size and number would help in interpreting function of fetal left ventricular gene expression in response to maternal undernutrition.

Cardiomyopathy is an important cause of death in the United States and claims more than 27,000 lives annually. Maternal undernutrition during the first half of gestation caused compensatory growth of the left ventricular heart by day 78 of gestation when compared to controls. Whether the changes in gene expression discussed in Fig. 1 are a cardio-protective response in the face of limited nutrient supply, a response to increased systemic vascular resistance and myocyte stretch, or a response to an altered endocrine milieu remains the focus of future investigation. More specifically, the encoded proteins need to be studied to determine if they function as a cause or a consequence of altered left ventricular heart growth and if they represent markers for cardiovascular disease.

Acknowledgements

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NMDA receptor kinetics are tuned for spike-timing dependent synaptic plasticity

Activation of NMDA receptors by action potentials underlies spike-timing dependent plasticity (STDP). New data indicates magnesium unblock of these receptors is not instantaneous, and contains a slow component dependent on the timing of depolarisations after glutamate binding. This property enhances the ability of NMDA receptors to act as coincidence detections during STDP

Björn Kampa (left) and Greg Stuart

Our current ideas suggest that memories are stored in the neural circuits of the brain via changes in the strength of their connections (Hebb, 1949). Long-term increases in synaptic strength are called long-term potentiation (LTP), whereas long-term decreases are called long-term depression (LTD). Interestingly, these two forms of plasticity depend on the precise timing of single action potentials in pre- and postsynaptic cells (Linden, 1999). Like many forms of synaptic plasticity, this so-called spike-timing dependent plasticity (STDP) is dependent on activation of N-methyl-D-aspartate (NMDA) receptors. These ionotropic glutamate receptors are blocked by external Mg^{2+} at resting membrane potentials, and require depolarisation to open (Mayer *et al.* 1984; Nowak *et al.* 1984). During STDP this depolarisation is thought to be supplied by postsynaptic action potentials that 'backpropagate' from the soma to the site of synaptic input in the dendritic tree.

Exactly how quickly action potentials can remove Mg^{2+} from NMDA receptor channels is unclear. Early studies investigating the kinetics of short

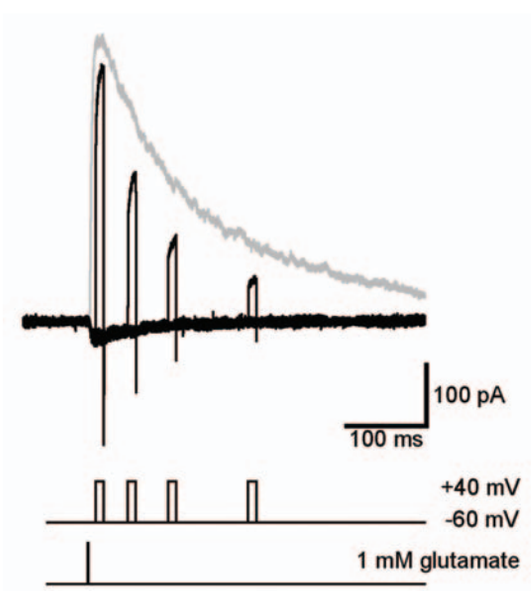

Figure 1. Dependence of Mg^{2+} unblock of NMDA receptors on timing. NMDA receptor currents were evoked by brief (1 ms) applications of glutamate to a nucleated patch from a cortical pyramidal neuron at a holding potential of –60 mV (black) or +40 mV (grey trace). Traces show superimposed responses to 10 ms voltage steps from –60 mV to +40 mV at different times after glutamate application. Note that currents evoked by voltage steps occurring later in time reach only a small fraction of the current measured at a holding potential of +40 mV. Modified from Kampa *et al.* (2004).

interruptions in single channel openings during steady state changes in membrane potential concluded that Mg^{2+} block and unblock of NMDA receptors was extremely rapid (sub-millisecond). Recent studies, however, have shown a slow component of Mg^{2+} unblock during depolarising voltage steps (Spruston *et al.* 1995; Vargas-Caballero & Robinson, 2003; Kampa *et al.* 2004; Vargas-Caballero & Robinson, 2004). In addition, we have found that the relative amplitude of fast and slow components of Mg^{2+} unblock depends on the timing of depolarising voltage steps relative to the onset of glutamate applications (Kampa *et al.* 2004). Fitting a kinetic model to this data indicates that Mg^{2+} binding increases desensitisation of NMDA receptors, and reduces both the open channel probability and affinity for glutamate. These findings are consistent with a recent study by Vargas-Caballero and Robinson (2004) who also report that binding of Mg^{2+} enhances the rate for NMDA channel closure. Our kinetic model may also explain the original observations of Nowak *et al.* (1984) that single channel burst duration, as well as frequency, are decreased at negative holding potentials by external Mg^{2+}.

As a result, Mg^{2+} unblock becomes slower the longer the NMDA receptor has been blocked by Mg^{2+} after glutamate has bound. The physiological consequence of this is that depolarising voltage steps, like action potentials, that occur later in time will have a smaller effect on NMDA receptor activation than depolarisations that occur just after the release of glutamate (Fig. 1).

This finding is likely to have important implications for STDP. To test this, we decided to have a closer look at what happens to Mg^{2+} unblock of NMDA receptors during STDP. As it is not possible to record directly from synaptic NMDA receptors, we used brief (1 ms) applications of glutamate to nucleated patches to mimic synaptic activation of NMDA receptors. Dendritic recordings of membrane potential during pairing of excitatory postsynaptic potentials (EPSPs) and backpropagating action potentials

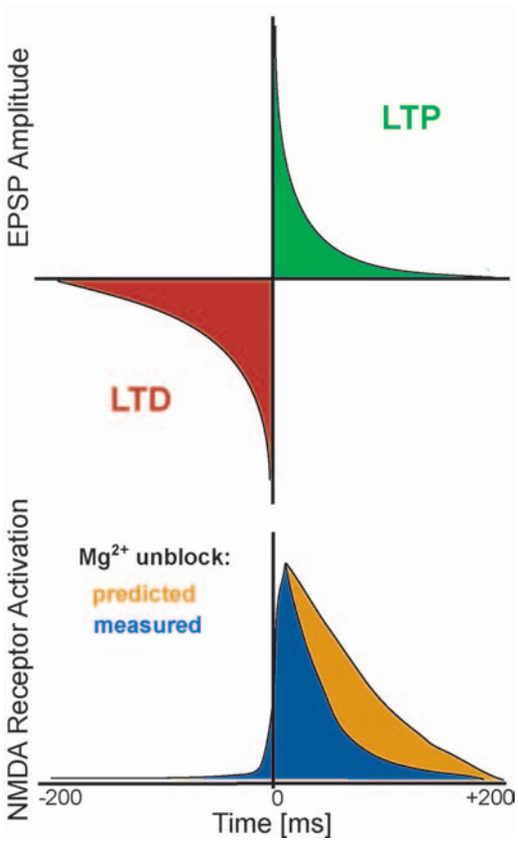

Figure 2. Kinetics of Mg^{2+} unblock of NMDA receptors is tuned for STDP. Top: STDP timing curve for induction of LTP and LTD. Bottom: Measured activation of NMDA receptors by realistic dendritic voltage waveforms during EPSP/action potential pairing (blue) compared to the predicted NMDA receptor activation assuming instantaneous Mg^{2+} unblock (orange).

provided realistic postsynaptic voltage waveforms. By combining the two, we were able to measure NMDA receptor currents similar to what would be expected to occur during STDP. During STDP-type protocols, we found that the time window for NMDA receptor activation by backpropagating action potentials was narrower than expected assuming Mg^{2+} unblock occurred instantaneously (Fig. 2). These results indicate that slow magnesium unblock of NMDA receptor channels increases the precision of the STDP timing window. This finding may help explain the short time window required for LTP induction (~10 ms) compared to the long time glutamate can stay bound to the NMDA receptor (~100 ms).

In summary, we have shown through the use of realistic dendritic voltage waveforms that backpropagating action potentials can deliver sufficient depolarisation to postsynaptic NMDA receptors to release the Mg^{2+} block inside the NMDA receptor channel.

Importantly, we find that the ability of backpropagating action potentials to activate NMDA receptors is increased if the timing of presynaptic glutamate release and postsynaptic firing is more synchronised.

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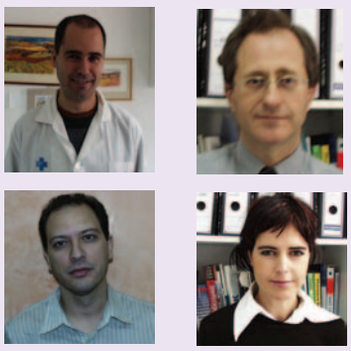
Myocardial connexin 43: gap junction-dependent and gap junction-independent effects on ischemia/reperfusion injury

Everyone knows the heart is a 'functional syncytium' with adjacent cells electrically coupled by connexin 43-formed intercellular channels (gap junctions). But these connexin 43 molecules may have more subtle roles in ischemia – reperfusion injury



Top: Antonio Rodriguez-Sinovas (left), David Garcia-Dorado; above: Alberto Cabestrero (left) and Marisol Ruiz-Meana

Connexin 43 (Cx43) is the main protein forming gap junctional channels in mammalian cardiomyocytes. Six Cx43 molecules form a hemi-channel (connexon) that docks to another hemi-channel in the plasma membrane of an adjacent cell to assemble a complete junctional channel. These channels allow cell-to-cell passage of molecules of less of 1 kDa, including ions and most second messengers. This results in electrical and chemical coupling of adjacent cardiomyocytes, essential for normal heart function. Altered electrical coupling through gap junction channels has been associated with arrhythmogenesis in different pathological conditions.

Previous studies demonstrated that after ischemia/reperfusion, dead, hypercontracted cells are not found scattered across the myocardium, but are connected to other dead myocytes within well-delimited areas of contraction band necrosis, a pattern that could be explained only by the existence of some kind of interaction between cells. The first evidence suggesting that this interaction could be chemical and mediated through gap junctions came from studies using heptanol, a gap junction uncoupler, that was able to reduce infarct size and LDH release in two different models of ischemia/reperfusion (Garcia-Dorado *et al.* 1997). However, the therapeutic potential of the protective effect of inhibition of gap junction communication against reperfusion injury is limited by the low specificity of heptanol and by the undesirable effects of such inhibition in normal myocardium. For these reasons, we have recently extended our studies to three other chemically unrelated gap junction uncouplers. We have correlated their protective effects on infarct size with their effects on the recovery of macroscopic electrical properties of the myocardium (i.e. tissue resistivity), an indirect marker of gap junction closure (Rodriguez-Sinovas *et al.* 2004). We found that gap junction uncoupling with heptanol, 18α-glycyrrhetinic acid, palmitoleic acid or halothane reduced reperfusion injury, as assessed by LDH release, in isolated rat hearts, and that these effects correlated consistently with an attenuation in the recovery of myocardial electrical resistivity during reperfusion. More importantly, these effects occurred at concentrations that lacked any measurable effect on myocardial electrical resistivity in normal hearts during normoxia. This opens the possibility of developing new therapeutic strategies that selectively interfere with gap junction mediated spread of necrosis in myocardium undergoing reperfusion, but which have minimal actions on macroscopic electrical properties in the myocardium at distance.

Propagation of cell injury through gap junction channels is not exclusive to the myocardium, and has been also described in other tissues such as astrocytes (Lin *et al.* 1998), and during chemical or physical treatment of tumour cells (Azzam *et al.* 2001). However, gap junctions play a complex role in cell death and their effects may vary depending on the conditions. In fact, it has been reported that they can reduce the susceptibility of rat neonatal

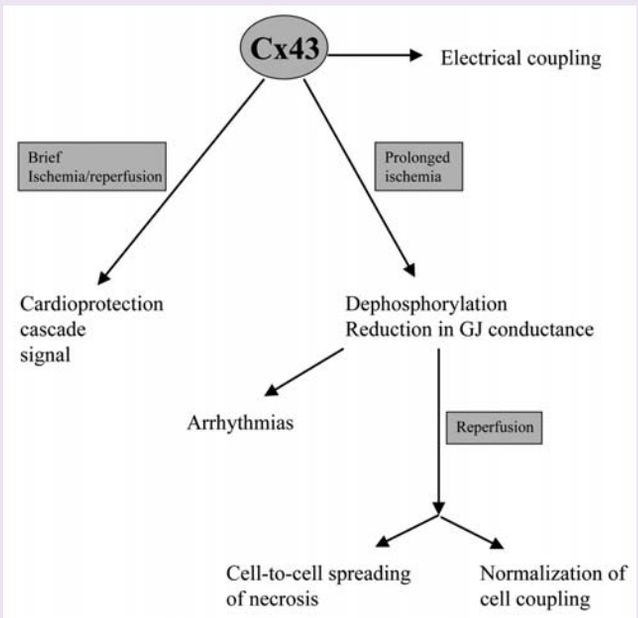


Figure 1. Diagram representing the role that connexin 43 (Cx43) can play in ischemia/reperfusion injury. Cx43 molecules, that in normal myocardium are essential for electrical and chemical coupling dephosphorylate during prolonged ischemia, which is in part responsible for a reduction in gap junction (GJ) coupling. This favours the appearance of ventricular arrhythmias. Upon reperfusion, there is a quick recovery in cell coupling, associated with cell-to-cell spreading of necrosis. When episodes of ischemia/reperfusion are brief, as during preconditioning ischemia, Cx43 may play a role in some endogenous cardioprotection signal cascades.

myocardial cells to potentially lethal insults by diluting them within a larger cell mass (Yasui *et al.* 2000).

An intriguing point is the role that Cx43 may play during ischemic preconditioning, a phenomenon by which brief episodes of ischemia/reperfusion protect the myocardium from the damage induced by a subsequent more prolongued ischemia. Heptanol administered before preconditioning ischemia attenuated the protective effect in isolated mouse hearts (Li *et al.* 2002), and underexpression of Cx43 in a transgenic mouse model completely abolished the preconditioning protection (Schwanke *et al.* 2002).

However, this effect seems to be independent of gap junctional communication, since it is maintained in isolated cardiomyocytes from heterozygous Cx43-deficient mice (Li *et al.* 2004). Gap junctional-independent effects of Cx43 have been described in other cell types, notably astrocytes, in which forced expression of this protein was protective against energy depletion despite physical separation of the cells (Lin *et al.* 2003).

The possibility that Cx43 may play a role ischemic preconditioning independently of gap junctional communication opens a new area of research in the field of cardiac protection.

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Zoltan Nusser wins the Lieben Prize

First endowed in 1862, abolished by Nazi Diktat in 1938, but now resurrected, the Lieben Prize for 2004 was awarded to Zoltan Nusser (pictured right) on 9 November in a ceremony at the Austrian Academy of Science, Vienna.

Now back in his native Hungary as Head of the Laboratory of Cellular Neurophysiology, Zoltan Nusser is known for his work on the precise subcellular distribution of GABA and glutamate receptors, some of which was done whilst he was at Oxford and University College London. So, his mentors and former colleagues in England will be delighted over the recognition Zoltan Nusser has now received.

When Ignaz L Lieben, a wealthy Jewish entrepreneur and banker in Vienna, founded a prize 'zur immerwährenden Förderung der wissenschaftlichen Forschung' ('the continuing promotion of scientific research'), Hungary and much else was part of the Hapsburg Empire. So when Alfred Bader, the single-handed working founder of the Aldrich Chemical Company, now trading as Aldrich-Sigma, donated generous funds for the restoration of the Lieben Prize, he stipulated that it be open to young scientists throughout the countries once united under the Hapsburgs and still today possessed of a similar cultural heritage. This produced in all 56 nominees for the Lieben Prize.

In the past, the judges for the Lieben Prize were shrewd enough to pick scientists who, like Otto Löwi, went on to win also Nobel Prizes – a younger foundation of 20th century origin. Time will tell whether the present judges are possessed of similar prescience.

Though they had lost much of their fortune in the inflation that gripped Austria after World War I, the descendants of Ignaz Lieben contrived to sustain the Lieben Prize until the 1938 Anschluss, when they were hounded out of Austria. Alfred Bader is not related to the Liebens, but he also had to flee Austria in 1938. It so happens that he and I were on the same Kindertransport train to England. But that is something we discovered only when we ran into each other years later.

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Endocrine granules

Exocytosis and endocytosis are not as separate as once thought, report David Perrais and colleagues

From the top: David Perrais, Justin Taraska and Wolfhard Almers

Endocrine cells release proteins and small molecules into the blood stream. It is well known that the release is controlled by regulating exocytosis, the fusion of secretory granules to the plasma membrane. As in presynaptic terminals, exocytosis is triggered by an increase in cytoplasmic Ca^{2+}. The classical view was that, once exocytosis has occurred, the membrane of the vesicle flattens into the plasma membrane and mixes with it, and that the material thus inserted into the plasma membrane is later retrieved by endocytosis. This view began to change when capacitance measurements could detect the exocytosis of single granules and, more recently, when the method was combined with amperometry to track exocytosis and catecholamine release simultaneously (Ales *et al*. 1999). At least occasionally, individual granules were seen to connect transiently with the plasma membrane, release their catecholamine and then re-seal. This transient exocytosis is sometimes called 'kiss and run' (Ales *et al*. 1999) or 'cavicapture', because the cavity of the granules is recaptured intact (Taraska & Almers, 2004). In small synaptic terminals that have only about a hundred synaptic vesicles, the benefits of kiss-and-run seem obvious, as this mechanism would allow cells to re-use synaptic vesicles rather than making new ones. Endocrine granules, however, are not generally believed to be re-used. Nor does cavicapture seem to influence how much catecholamine is released by granules. So why do endocrine cells perform cavicapture, and what difference does it make physiologically?

Endocrine cells also release peptides and proteins. When these are fused to green fluorescent protein (GFP), their release from single granules can be observed by evanescent field fluorescence microscopy (also called total internal reflection fluorescence, or TIRF). The evanescent field illuminates only a thin surface layer where the cell comes in close contact with the glass coverslip, and leaves deeper regions in the dark. Our group has used it to compare the release of two proteins from single granules, neuropeptide Y and the protease tissue plasminogen activator, or tPA, both normally contained in chromaffin granules (Perrais *et al*. 2004). NPY-GFP was lost from granules in fractions of a second while tPA-GFP remained there. About

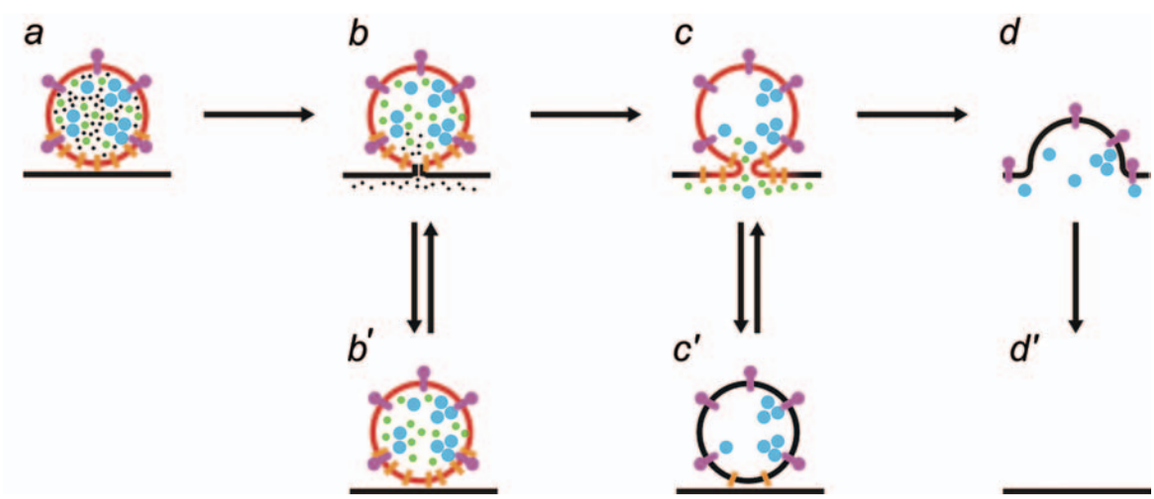

Figure 1. Exocytosis and endocytosis of granules. After a rise in cytosolic calcium, vesicles connect to the extracelluar space through a narrow fusion pore (b) releasing small molecules like protons and adrenalin (black dots). If this narrow pore closes, no protein or peptide can escape, and even the smallest and most mobile contents fail to escape completely (b'). If the pore expands instead, the graule releases first small peptides such as NPY (green) and then even larger molecules, such as tPA (blue). Membrane lipids (red) and certain membrane proteins like synaptobrevin-2 (orange) are free to escape as well. Others, like phogrin (purple), however, remain mostly trapped in the granule cavity. Partially empty granule cavities are then recaptured (c'). In many cases the fusion pore expands further and the granule collapses into and mixes with the plasma membrane (d').

one-third of the granules re-sealed before they could release all their tPA-GFP.

Related findings were made in cell lines derived from chromaffin cells (Taraska *et al*. 2003) and pancreatic β cells (Tsuboi *et al*. 2004). Thus, cavicapture keeps some proteins in granules after catecholamines, and in most cases NPY, are released completely. Surprisingly, some granules were seen to undergo exocytosis, then cavicapture, and then to release the remainder of their tPA in a second round of exocytosis. Related results were also obtained in PC12 cells (Holroyd *et al*. 2002). Apparently, granules are sometimes re-used after all. And perhaps cells regulate protein release not only by controlling exocytosis, but also by cavicapture. Other recent studies highlight further complexities of protein release from single granules (e.g. Barg *et al*. 2002).

Do granules get to keep their membrane components when they undergo cavicapture? They probably exchange most or all of their lipids with the plasma membrane (Taraska & Almers, 2004), but keep selected membrane proteins such as phogrin. Most granules also lose the majority of their synaptobrevin-2 and synaptotagmin-1 (Tsuboi *et al*. 2004), although one supposes that granules planning to undergo exocytosis a second time must retain enough of both.

Finally, which proteins are required for cavicapture? Some proteins participating in clathrin-mediated endocytosis, among them clathrin itself, never appear at sites of cavicapture, but dynamin does. Dynamin separates endocytic vesicles from the plasma membrane. When dynamin is blocked, then cavicapture is blocked as well, and phogrin and tPA are both rapidly lost from granules (Holroyd *et al.* 2002, Tsuboi *et al*. 2004).

Cavicapture implies that exocytosis and endocytosis are not as clearly separated as they are, e.g. in the recycling of transferrin receptors between endosomes and plasma membrane. Instead, there are multiple steps on a continuum (Fig. 1). When an exocytic fusion pore connects the inside of the vesicle to the outside of the cell, catecholamines are released within 100 ms, as judged by amperometry. However, the open cavity of many granules stays behind (Taraska *et al*. 2003), and may re-seal in seconds to minutes (Perrais *et al*. 2004). A fission machinery including dynamin is recruited. Such recruitment is probably more important for cavicapture than the size of the fusion pore, because during its life the pore can start out small enough to retard the escape of catecholamines, then dilate to allow partial escape of a relatively large protein such as tPA-GFP, and still close again.

It remains to be seen what mechanisms control how soon the pore closes, and how large it gets before it closes. Dysfunctions in such control mechanisms could alter the release of proteins and hormones from endocrine cells, and possibly lead to abnormal protein release.

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New Council Members

Seven new ordinary Council members were elected at the AGM last Autumn. Although their biographies and personal statements appeared in the voting papers, the 'turnout' (i.e. the number of members who actually voted, see p. 3) suggests these bios may not have been all that widely read! In the cause of introducing the membership to the new Council intake, we reprint highlights from four of their bios here.

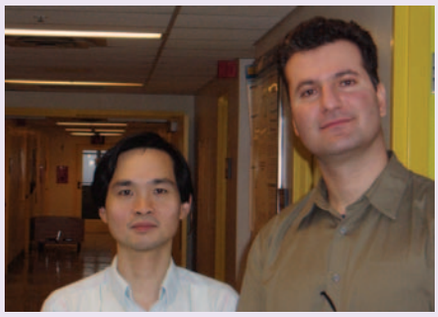
Firstly, for those of you that like executive summaries, the seven new members comprise two cardiovascular cellular physiologists (Clive Orchard and Ian McGrath), one of whom (Ian McGrath) admits to being at least as much a pharmacologist as a physiologist; a human physiologist (Paul Greenhaff); two neuroscientists (Ann King and Stafford Lightman); and two integrative physiologists (Patrick Harrison and James Jones). Several of them have had long-standing involvement with the Society's committees, journals and special interest groups. They include one clinical academic (Stafford Lightman) and are drawn from the Universities of Bristol (two), Cork, UC Dublin, Leeds, Nottingham and Glasgow. The eagle-eyed among you will note that this means the UK-based among them all hail from Russell Group 'civic' universities.

Clive Orchard has been Professor of Physiology and Head of the Department of Physiology at the University of Bristol since 1 February, after almost 20 years in Leeds. He is a cellular cardiac physiologist who works on cardiac excitation-contraction coupling and its regulation. Clive did his BSc and PhD at the University of London, and a first post-doc at UCL with David Allen before moving to Baltimore for 3 years (1983-6) as a research fellow at

(this article concludes on p. 52)

Exploring connections between the cerebellum and motor cortex in humans

Animal studies have demonstrated that the cerebellum influences both inhibitory and excitatory neurons in the motor cortex. Daskalakis and colleagues use transcranial magnetic stimulation to elucidate such connectivity in healthy human subjects



Robert Chen (left) and Jeff Daskalakis

It is well known that both the motor cortex and the cerebellum are important structures involved in motor control. Previous animal and human studies had shown that Purkinje cells, output neurons of the cerebellar cortex, form inhibitory connections with the deep cerebellar nuclei (DCN), which have a disynaptic excitatory pathway through the ventral thalamus to the motor cortex. Clarifying the interaction between cerebellum and the motor cortex in healthy human subjects is important not only for understanding motor control, but also to help advance the pathophysiology of neurological and psychiatric diseases. For example, essential tremor can be treated by lesioning or high frequency stimulation of the cerebellar thalamus (Schuurman *et al.* 2000) and dysfunction of cerebellar-cortical connectivity has been proposed as a mechanism mediating schizophrenia.

In the article by Daskalakis et al. (Daskalakis *et al.* 2004), a unique approach involving a combination of stimulation pulses was used to evaluate the connectivity between the cerebellum and the motor cortex in human subjects. This approach involves delivering two transcranial magnetic stimuli (TMS), known as conditioning stimuli (CS), one to a distant cortical site such as the cerebellum, and one to a local cortical site over the motor cortex, prior to a single test stimulus (TS) to the motor cortex. The local CS stimulus has been shown to activate local inhibitory and excitatory cortical interneurons and, when preceded by a CS applied to distant cortical sites, can test how distant brain regions interact with local cortical interneurons to modulate cortical pyramidal cell output.

Cerebellar activation was achieved through TMS applied to the cerebellum with a double-cone coil (110 mm mean diameter). The coil was centered over the right cerebellar hemisphere 3 cm lateral to the inion on the line joining the inion and the external auditory meatus. The double-cone coil provides stronger magnetic field that penetrates deeper into the brain than standard flat figure-of-eight coils and previous studies showed that it activates cerebellar inhibitory neurons (Ugawa *et al.* 1995). Local motor cortical activation was achieved through TMS of the left motor cortex with a 7 cm figure of eight coil.

Three separate experiments were conducted to evaluate the connectivity between the cerebellum and motor cortex in humans. The first involved a controlled manipulation of TS intensities on several inhibitory and excitatory TMS paradigms. These include cerebellar inhibition (CBI), short interval cortical inhibition (SICI), long interval cortical inhibition (LICI) and intracortical facilitation (ICF). If these paradigms share common mechanisms, their profiles of response under conditions of controlled manipulation should be similar. Second, connectivity can be explored by examining the impact of one inhibitory/excitatory phenomenon on the other by applying them together. Here, the interaction between CBI and SICI is tested when a cerebellar conditioning stimulus precedes a cortical conditioning stimulus by 3 ms which precedes a suprathreshold TS by 2 ms. In this way, the effect of cerebellar activation on cortical interneurons may be examined. Finally, the interaction between CBI and LICI is tested when a cortical conditioning stimulus precedes a cerebellar conditioning stimulus by 95 ms which precedes a suprathreshold TS by 5 ms. Here too, this triple stimulus approach allows one to test the interaction between these two inhibitory

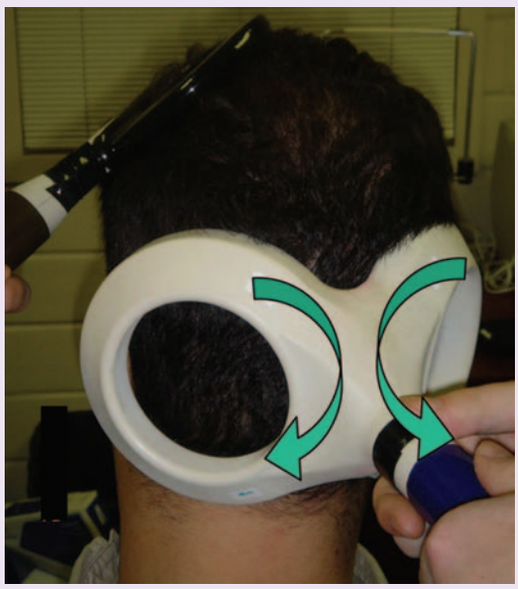


Figure 1. A figure demonstrating cerebellar and motor cortical stimulation through TMS. Cerebellar stimulation is delivered through a double-cone coil centered over the right cerebellar hemisphere 3 cm lateral to the inion on the line joining the inion and the external auditory meatus while motor cortical stimulation through TMS was delivered at the optimal position for eliciting MEPs from the right FDI muscle. Arrows indicate a downward flow of current through the coil which induced upward current in the cerebellar cortex

paradigms. Moreover, as it has been suggested previously that SICI is mediated primarily by inhibitory interneurons producing fast IPSPs due to $GABA_A$ receptors, whereas LICI is mediated primarily by inhibitory interneurons producing slow IPSPs due to $GABA_B$ receptors, this approach allows us to test the effects of cerebellar inhibition on these two different populations of inhibitory interneurons.

In experiment 1 we found that increasing TS intensities resulted in less LICI, CBI and ICF but greater SICI. In experiment 2, SICI was reduced and ICF was increased in the presence of CBI. It was speculated that CBI may decrease SICI through reduced thalamocortical facilitation of cortical inhibitory interneurons mediating SICI. This connectivity may be important for the dynamic focusing of motor output (Shinoda *et al.* 1993). In experiment 3, it appears that CBI and LICI interact to produce decreased inhibition in the motor cortex.

It was suggested that reduced inhibition was mediated by one of the following mechanisms:

• Disruption of the cerebellothalamocortical inhibitory pathway at the level of the motor thalamus. Animal studies have shown that cortical stimulation results in activation of reticular nuclei neurons and thalamic inhibitory neurons, which, in turn, inhibit the cerebellothalamocortical pathway (Ando *et al.* 1995) (Fig. 2).

• Motor cortex stimulation from the CS pulse influences the cerebellar cortex through activation of the mossy fibers that come from the pontine nuclei via the corticopontocerebellar pathway. Activation of this pathway may inhibit Purkinje cells through activation of inhibitory Golgi and basket cells in the cerebellar cortex. Delivery of the cerebellar CS in the presence of inhibited Purkinje cells would produce the loss of CBI seen in this experiment.

• Yet another possibility is that motor cortex stimulation results in decreased Purkinje cell inhibitory output through activation of the inferior olive (Schwarz & Welsh, 2001). Here, the collaterals of climbing fibers from the inferior olive also innervate the Golgi and basket cells leading to suppression of Purkinje cells.

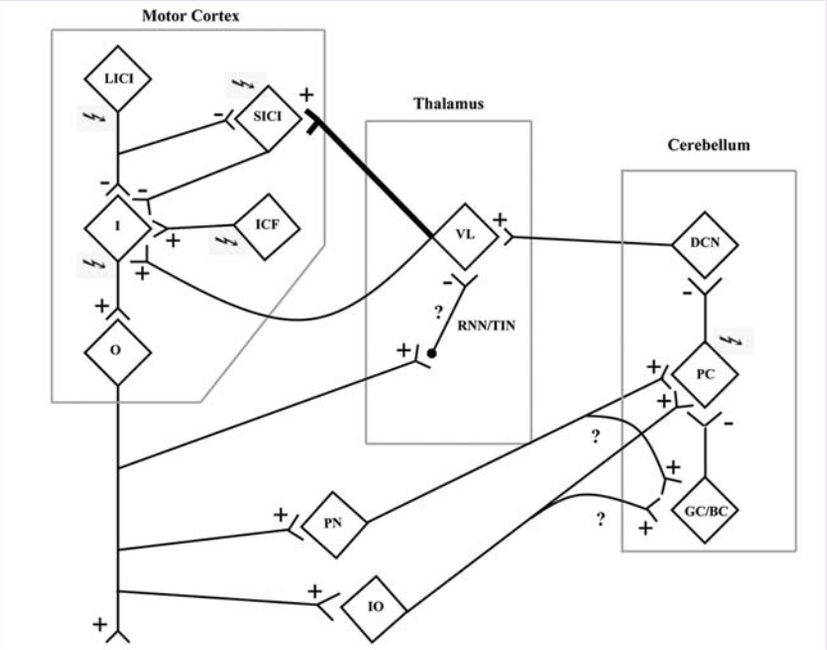


Figure 2. A possible model that may explain our experimental findings.
Each diamond schematically represents a population of neurons mediating either inhibitory or facilitatory processes (i.e., SICI, LICI, ICF) or an anatomic location (i.e. DCN, VLN, IOP, PC). The diamond labeled 'I' represents cells leading to descending I-waves and 'O' represents corticospinal output neurons. LICI is showed to inhibit SICI based on the result of a previous study (Sanger *et al.* 2001). 'Bolts' represent the presumed site of TMS stimulation. The question marks '?' indicate pathways that may explain some of our experimental findings but whether they are involved remain speculative. Lines in bold represent connections confirmed by these experimental findings. Our finding of reduced SICI in the presence of CBI can be explained by activation of the cerebellar Purkinje cell (PC) leading to suppression of excitatory output from deep cerebellar nuclei (DCN). This results in suppression of excitatory output from the ventrolateral nucleus of the thalamus (VL), leading to decreased excitatory drive to output neurons (causing decreased MEP amplitude) as well as inhibitory (SICI) interneurons (bold line). TMS-induced activation of corticospinal output neurons by the conditioning pulse for LICI may activate thalamic inhibitory neurons (TIN) or reticular nuclei neurons (RNN) that, in turn, inhibit thalamocortical neurons that may account for the finding of decreased CBI in the presence of LICI. Alternatively, activation of the mossy fibers that come from the pontine nuclei (PN) via the pontocerebellar pathway may inhibit Purkinje cells through activation of inhibitory Golgi cells (GC) and basket cells (BC). Another possibility is that a cortical projection activates the inferior olive (IO) and the collaterals of the climbing fibers also innervate the inhibitory GC and BC that may also lead to decreased PC output. It is important to note that while these pathways exist, their involvement in these experimental paradigms remains speculative.

Our findings suggest that cerebellar stimulation results in changes to both inhibitory and excitatory neurons in the human motor cortex, to our knowledge one of the first times that such connectivity has been demonstrated in healthy human subjects.

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Bilateral interactions between the upper limbs

Richard Carson and colleagues consider the neural origins of bimanual coordination, and the implications for movement rehabilitation and therapy

From the left: Richard Carson, Stephan Riek and Winston Byblow

In the course of our daily activities we routinely engage in tasks in which the two hands execute quite different actions. The apparent ease with which we unscrew the cap from a bottle, or thread a needle, belies the fact that there is a strong tendency for simultaneous movements of the upper limbs to be drawn towards one another. This predisposition is expressed clearly in a test of dexterity with which we are all familiar: rubbing your stomach and patting your head at the same time (if this seems easy at first, try swapping the role assigned to each hand). Mirror movements - involuntary muscular contractions during what are intended to be unilateral movements of the opposite limb, represent an extreme expression of this tendency. These are typically considered pathological, as they occur in association with specific disorders of the CNS. Yet they are also observed frequently in normally developing children, and bilateral motor irradiation – an increase in the excitability of the (opposite) homologous motor pathways when unilateral contractions are performed, is a robust feature of the mature motor system.

These phenomena are not simply of academic interest. The systematic nature of the interactions that occur between movements of the upper limbs has given rise to the expectation that functional improvements in the control of paretic muscles may be realised when bilateral movements are prescribed. Indeed, in both acute and chronic stroke survivors, bilateral movement training leads to improvements in unilateral actions performed subsequently by the hemiplegic arm (e.g. Whitall *et al.* 2000). It is clearly desirable that there are principled grounds upon which to develop programs of movement rehabilitation and therapy. Yet until recently there has been remarkably little consensus concerning the neural mechanisms that mediate bilateral interactions between the upper limbs.

Transcranial magnetic stimulation (TMS) affords a means of probing the excitability of corticospinal pathways with a degree of sensitivity beyond that which can be achieved by other non-invasive techniques. It is therefore being used with increasing frequency to examine the nature of bilateral motor irradiation. An initial finding that electromyographic (EMG) responses evoked by TMS were potentiated during forceful contractions of the opposite hand, in patients with agenesis of the corpus callosum, suggested that the interactions might occur below the level of the cortex (Meyer *et al.* 1995). Recent studies, however, challenge this view and reveal that in neurologically intact individuals, bilateral motor irradiation is mediated at least in part by interhemispheric interactions between cortical motor areas.

Hortobágyi *et al.* (2003) reported that during moderate to strong isometric contractions of the wrist flexors, potentials evoked in a homologous muscle of the opposite limb by TMS were potentiated. In contrast, those evoked by direct stimulation of the descending tracts at the level of the cervicomedullary junction (CMEPs)

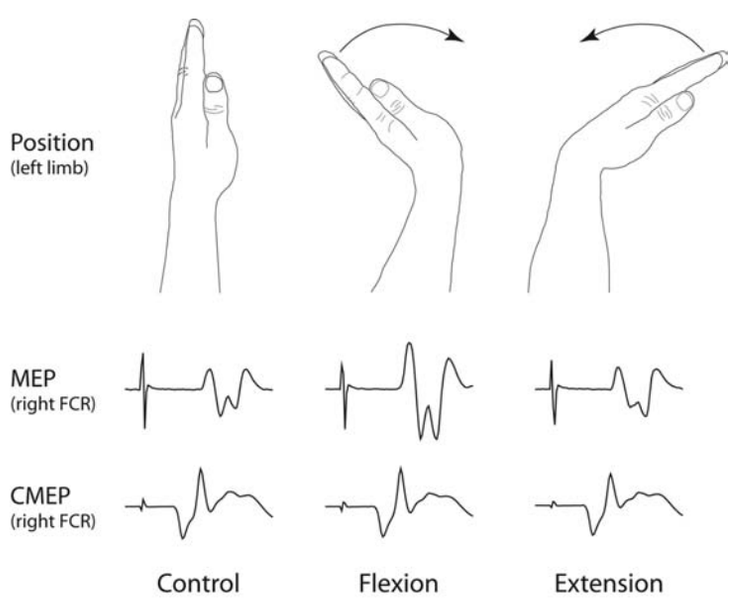

Figure 1. Mean compound muscle action potentials evoked in the relaxed right flexor carpi radialis (FCR) by magnetic (MEP) and cervicomedullary junction (CMEP) stimulation during flexion/extension movements of the left wrist. Flexion corresponds to the portion of the movement cycle following peak extension during which the left FCR muscle is activated strongly and the wrist begins to flex. Extension corresponds to the portion of the movement cycle following peak flexion during which the wrist begins to extend, and the left FCR is quiescent. The Control responses obtained when the left wrist is at rest are also shown. Adapted from Carson *et al.* (2004).

were unaffected by the contractions of the muscles of the opposite limb. This latter finding indicated that there was no change in the excitability of the spinal motoneurons. We have recently shown that during cyclic flexion and extension of the wrist, the largest responses to TMS are obtained during the phases of movement in which the corresponding muscle of the opposite limb is most strongly engaged (Fig. 1). Responses to cervicomedullary stimulation were unaffected by movement of the opposite limb (Carson *et al.* 2004). These studies indicate that the bilateral motor irradiation generated by both tonic and phasic contractions has a cortical component.

The hand and forearm representation in primary motor cortex (M1), the area most obviously implicated in movement execution, is relatively sparsely connected with its contralateral counterpart. Secondary motor areas such as the cingulate motor area (CMA), exhibit much denser connectivity via the corpus callosum. Indeed, it appears that the scope for direct inter-hemispheric interactions via callosal pathways decreases progressively along a functional gradient that culminates in those regions that have the most prominent role in generating motor output. Bilateral motor irradiation may arise first in the secondary motor areas of the hemisphere contralateral to the moving limb, spread through the callosal fibres to secondary motor areas in the opposite cortex, and subsequently to the primary motor cortex ipsilateral to the moving limb (Fig. 2).

The degree of crossed-facilitation may thus be contingent upon activity in motor centres "upstream" of M1, rather than upon the level of output from the primary motor cortex that is engaged to generate the movement. This conjecture is supported by recent studies in which it has been shown that the relationship between the motor output to the actively moving limb, and the degree of bilateral motor irradiation, is altered by the mechanical context in which the movements are performed (Carson & Riek, 2000), and when there is visual feedback of the moving limb (Carson *et al.* 2004).

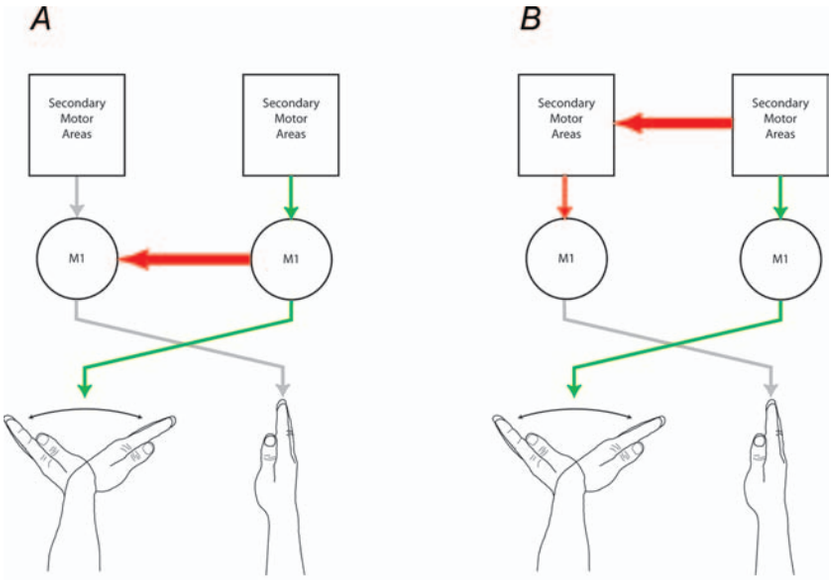

Figure 2. Panel *A* illustrates the possibility that the bilateral motor irradiation that is evident during the voluntary movement of a single limb may be attributable to direct interactions between the two primary motor cortices. Panel *B* depicts the possibility that the irradiation may arise first in the secondary motor areas of the hemisphere contralateral to the moving limb, spread via callosal fibres to secondary motor areas in the opposite cortex, and subsequently to the primary motor cortex ipsilateral to the moving limb. In each case the principal pathway mediating the irradiation is indicated in red. Motor pathways that project to the quiescent limb are otherwise shown in grey. Motor pathways engaged in generating the intended motor output are shown in green.

The conclusion that bilateral motor irradiation is mediated to a significant degree by interhemispheric interactions between cortical motor areas has important implications with respect to strategies for rehabilitation. In particular, it suggests that the efficacy of bilateral training may be enhanced by the conjoint use of techniques such as sensory-induced plasticity that promote the functional remodelling of cortical motor areas. The specific brain areas that might most appropriately be the targets for these techniques, however, remain to be resolved.

Acknowledgements

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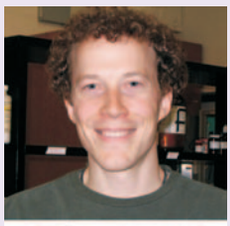
Fishing for O_2 chemoreceptors in vertebrates

Despite phylogenetic differences in modes of breathing, mammalian and aquatic vertebrates appear to utilize similar O_2-sensing pathways



Michael Jonz (top) and Colin Nurse

Maintenance of arterial O_2 tension by respiratory regulation is of fundamental importance for animal survival and adaptation to hypoxia (low O_2). Detection of hypoxia occurs at the cellular level by specialized O_2-sensitive cells that initiate local or centrally-mediated physiological responses, such as changes in ventilation and heart rate. In mammals, these include type I chemoreceptors of the carotid body (CB; the primary O_2-sensing organ), pulmonary neuroepithelial bodies (NEBs), adrenal chromaffin cells, and arterial smooth muscle cells. A common mechanism for detecting O_2 levels in these cells involves regulation of K^+ channel activity during chemotransduction (López-Barneo *et al*. 2001). In CB type I cells for example, hypoxia causes a receptor potential, due to inhibition of K^+ channels that are open at rest, leading to voltage-gated Ca^{2+} entry and release of neurotransmitters that activate sensory pathways. Despite the similar responses to hypoxia in all vertebrates, characterization of O_2- chemoreception at the cellular level has traditionally been confined to air-breathing mammals. Yet, it might be expected that the basic cellular mechanisms arose earlier, perhaps in water-breathing vertebrates that rely on gills for ventilation and regulation of gas exchange.

Indeed, decades of research have implicated the gills as the common O_2-chemoreceptive site in aquatic vertebrates, e.g. fish and larval amphibians (Burleson & Milsom, 2003). Interestingly, the gill or aortic arches in these animals share a common embryonic origin with O_2-sensitive carotid and aortic bodies of mammals. Moreover, the fish gill contains neuroepithelial cells (NECs) that have long been considered potential O_2 chemoreceptors (Zaccone *et al*. 1997), which store the neurotransmitter serotonin (5-HT) and are morphologically similar to mammalian CB type I cells and pulmonary NEBs. The morphology and innervation pattern of NECs were recently described in the zebrafish gill (Jonz & Nurse, 2003). Although CB type I cells occur in clusters, rather than in isolation as in gill NECs, both cell types receive sensory innervation from the glossopharyngeal (IX^{th}) nerve (Fig. 1A,B) and generate a receptor potential during exposure to acute hypoxia (Fig. 1C,D). The latter responses are attributable, at least in part, to inhibition of voltage-independent, quinidine-sensitive 'leak' K^+ channels with biophysical and pharmacological properties of the two-pore domain, background K^+ channel family (Buckler *et al*. 2000; Jonz *et al*. 2004). While the molecular identity of the O_2-sensitive background K^+ channel in zebrafish NECs awaits determination, in rat type I cells it appears to be related to the mammalian TASK-1 channel (Buckler *et al*. 2000). Thus, regulation of background K^+ channels by hypoxia appears to be a fundamental mechanism that has been relatively conserved. Additionally, the O_2-sensitivity of NECs (which are found on all gill arches) appears to confirm the hypothesis that throughout phylogenesis, and the later evolution of air-breathing, the distribution of peripheral O_2 chemoreceptors was reduced from multiple dispersed sites (i.e. gills) in fish to a single primary location (i.e. carotid body), as found in mammals (Burleson & Milsom, 2003).

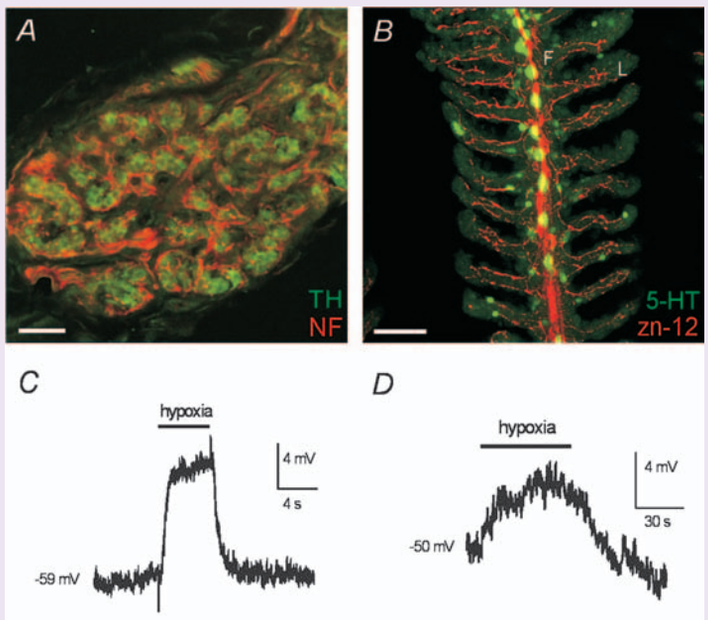


Figure 1. O_2-sensitive chemoreceptors of the rat carotid body and zebrafish gill. *A*, immunolabelling of a tissue section with antibodies against tyrosine hydroxylase (TH) and neurofilament (NF) showed clusters of type I cells (*green*) and innervating sensory nerve fibres (*red*) of the rat carotid body. *B*, confocal image of a whole gill filament from zebrafish. Solitary neuroepithelial cells (NECs, *green*) of the filament (F) and lamellar (L) epithelium were labelled with antibodies directed against the neurotransmitter serotonin (5-HT), while innervating sensory nerve fibres (*red*) were identified with a zebrafish-specific neuronal marker (zn-12). Scale bars 50 µm. Modified from Jonz & Nurse (2003). *C* and *D*, current-clamp electrophysiological recordings from an isolated rat carotid body type I cell (*C*) and a zebrafish gill NEC (*D*). In both preparations, application of hypoxic solution to the recording chamber resulted in a reversible depolarization of the membrane potential. Resting potentials are indicated to the left of each trace. Trace in *D* is modified from Jonz *et al*. (2004).

In spite of recent progress, the remaining steps in the cellular response to hypoxia, including the molecular identity of the O_2 sensor, are still controversial. Current models suggest that the O_2 sensor may be a plasma membrane or intracellular heme protein, capable of reversibly regulating ion channels directly or through a signalling cascade (López-Barneo *et al*. 2001; Williams *et al*. 2004). The popular redox hypothesis proposes that reactive oxygen species produced by NADPH oxidase or the mitochondrial electron transport chain regulate ion channel activity during hypoxia (López-Barneo *et al*. 2001). The recent identification of an O_2-sensing mechanism in NECs of a model vertebrate, i.e. zebrafish (Jonz *et al*. 2004), and subsequent characterization of mutations that perturb this function, may lead to the elucidation of a general O_2-sensing mechanism that arose early in vertebrate evolution.

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Funding boost for graduate training in animal research

AstraZeneca-GSK-Pfizer announce funding to enhance research and PhD training in *in vivo* mammalian physiology, pharmacology and toxicology

For several years, leaders of the pharmaceutical industry have expressed increasing concern about the shortage of graduates and postgraduates who are trained to carry out research on animals. There is no shortage of students who are keen to embark on a research career in this area. The main problem is the dwindling number of UK academics who are engaged in basic animal research and in a position to provide the necessary training. Now, the three largest pharmaceutical companies in the UK have sent a clear signal that something has to be done to reverse this trend.

AstraZeneca, GlaxoSmithKline and Pfizer, working with the British Pharmacological Society, have set up a joint fund to support high quality research, in UK universities, that is relevant to the discovery of new medicines. The Integrative Pharmacology Fund is targeted at *in vivo* science and will help to bridge the gap in our understanding of how the function of molecules, genes and cells affect whole animals. Its aim is to enhance research and training in integrative pharmacology and related disciplines (physiology, toxicology, pharmacokinetics) with the objective of promoting excellence in these disciplines and ensuring their long-term viability in the UK.

The companies are investing £1 million a year, for the next 4 years, to support the training of new and existing scientists in pharmacology, physiology and toxicology.

There are two currently active funding streams administered by the Biotechnology and Biological Sciences Research Council (BBSRC). One will offer a £6,000 per annum top-up, for a maximum of 3 years. This will help fund the costs of consumables associated with up to 15 BBSRC Quota or Strategic Research Studentships that are fully funded and provide significant training in mammalian *in vivo* techniques. These awards are competitive and applications should be submitted in June 2005. The second currently available stream will offer a financial contribution to research projects using *in vivo* techniques and so help researchers to apply for a BBSRC Industrial Partnership Award. Requests for a financial contribution from this stream can be made at any time. In both cases, grants will be offered to academic institutions with the greatest expertise in this area and with the highest standards of *in vivo* research and animal welfare.

Potential applicants under these funding streams should bear in mind that BBSRC does not fund studies of human diseases or clinical research and will not accept applications that address questions that are primarily of clinical relevance. The new scheme is consistent with this policy because it is intended to help researchers discover novel therapeutic targets that need to be studied in animals before any potential medicines can be tested in humans.

Usually, the funds to cover consumables for PhD studentships do not even begin to meet the true cost of the research. This is a particular problem for PhD projects using animals, which are now formidably expensive. This scheme will help to relieve this funding deficit and ensure that the skills and expertise that are vital for whole animal research prosper in UK universities. Doubtless, it will also entice scientists, who have previously worked only in cellular and molecular biomedical sciences, to venture into more integrated research.

In addition, the Fund has already committed support of up to £125,000, over 5 years, to each of eight Research Councils UK Academic Fellowships in *in vivo* physiology, pharmacology and toxicology. These Fellows will start work over the next 2 years, and will undertake teaching and some schools outreach work, as well as research, to fulfil the Fund's aims. The Fund plans to work wherever possible with other bodies to steer more resources in this direction. New funding streams will be announced from time to time, on the BPS web site (www.bps.ac.uk) and elsewhere.

The launch of this latest scheme will be applauded by all those trying to understand how mammalian systems are regulated *in vivo*. It will not solve the funding problem, but it will certainly invigorate the effort to ensure that UK universities continue to produce graduates who are adequately equipped to continue their research in the UK pharmaceutical industry.

Further information from the British Pharmacological Society (sjs@ bps.ac.uk). Information about BBSRC studentships and industrial Partnership Awards can be found on the BBSRC website.

Clare Stanford

British Pharmacological Society

This article was first published in *RDS News*, Autumn 2004, 4-5.

Transport mechanisms across cell membranes

David Brown reports on an international workshop for young physiologists in St Petersburg

Some of the workshop participants on the grand staircase of the Russian Academy of Sciences. Front row (from the left): Yulia Matskevich and David Brown (UK organisers), with Florian Lang (visiting speaker).

An international workshop for young physiologists was held in St Petersburg (Russia) from 13-17 October, 2004, hosted by Lev Magazanik. The theme of the workshop was *Transport mechanisms across cell membranes: channels and pumps*. The meeting itself was preceded by a Welcome Reception in the St Petersburg Scientific Centre in the Russian Academy Building on the north bank of the River Neva. On the subsequent four mornings talks were given in the Scientific Centre, followed by lunch in the nearby University cafeteria. On the first two afternoons everyone migrated up to the Sechenov Institute. There, student participants presented posters of their research, followed by a series of laboratory demonstrations. On Saturday afternoon participants were taken on a guided tour of the glorious (and huge) Hermitage museum followed by a well-lubricated banquet.

In addition to the welcome addresses, talks (see panel) and a short description of the Physiological Society's international activities, laboratory demonstrations were wide-ranging and mostly 'live', and included experiments on osmoregulating epithelia, molecular modelling of protein-ligand interaction, patch-clamping of isolated neurons and of neurons in brain slices, expression of recombinant receptors in oocytes, photolysis of rhodopsin, and suction-electrode recording from retinal rods.

The workshop was attended by 36 students. Most were from other parts of Russia, but they included seven students from Romania, two from the Ukraine, two from the Czech Republic, one each from Belarus, Kazakhstan, Hungary, Poland, Germany and Switzerland, and three from the UK. Students from St Petersburg also attended the workshop and took an active part in all the scientific events.

I would like to thank our host, Lev Magazanik, his St. Petersburg co-organizer Ludmila Japaradze at the St Petersburg Scientific Centre, and my UK co-organizer Yulia Matskevich from Edinburgh University, for the fantastic work they did, both scientifically and organizationally; and Denis Tikhonov, Konstantin Bolshakov and the many other staff and students in the Sechenov Institute for all the work they put in to the demonstrations, posters, coffee, web-site, AV, ad hoc taxi services and such like that were so essential to the success of the workshop. We were lucky with the weather - St Petersburg looked glorious in the October sunshine, and so far as I am aware, no one got lost (at least, not by accident).

David Brown
UK Organizer

The full programme of the workshop (with abstracts of talks and posters) is available at:
http://www.iephb.ru/conference/index.html

Lev Magazanik at coffee with Tatiana Kolesnikova and Nadejda Kalashnikova from Moscow

Programme

Welcome addresses

Lev Magazanik (Laboratory of Biophysics, Sechenov Institute of Evolutionary Physiology & Biochemistry, Russian Academy of Sciences)

Yuri Natochin (Laboratory of Kidney Physiology, Sechenov Institute)

Nikolay Vesselkin (Director, Sechenov Institute)

Speakers

David Brown (London, UK) *KCNQ potassium channels*

David Marples (Leeds, UK) *Aquaporin channels*

Denis Tikhonov (Sechenov Institute) *Ion channel structure and function*

Clive Ellory (Oxford, UK) *Cation-chloride co-transport*

Florian Lang (Tuebingen, Germany) *SGK1 transport-regulating kinase*

Richard Boyd (Oxford, UK) *PepT1 peptide transporter*

Anna Bogdanova (Zurich, Switzerland) *Na/K pump in neuronal cultures*

David Beech (Leeds, UK) *TRP channels*

Stuart Bevan (Novartis Institute, London, UK) *Trp channels and thermosensation*

Alan North (Manchester, UK) *P2X receptor channels*

Stuart Cull-Candy (London, UK) *Glutamate receptor subunits*

Pyotr Bregestovsky (Marseilles, France) *Glycinergic transmission*

Victor Govardevsky (Sechenov Institute) *Regulation of phototransduction*

Elena Kaznacheyeva (Institute of Cytology, Russian Academy of Sciences) *Store-operated calcium channels*

Alexander Vorotnikov (Russian Cardiology Centre) *Calcium and pathways of cell motility and contractility*

Myrtani Pieri, a participant at the workshop, writes:

I feel extremely fortunate to have been a young physiologist at the International Workshop in Cell Physiology. This workshop was focused on the molecular mechanisms of membrane transport and was of a high standard both academically and organizationally.

The participants had a chance of attending a number of lectures of excellent standard that were clear and easy to comprehend by both the native and non-native English audience. The lectures took place at the St Petersburg Scientific Centre, the historical core of the Russian Academy of Sciences and a building of astonishing architecture and great beauty. The atmosphere in the lecture room was unique, followed by the finest coffee-breaks in the company of the great Mendeleyev (below)!

In addition to the intense academic work, the St Petersburg workshop was characterised by an active social scene. The students were excellently accommodated at St Petersburg State University Students' House, where socialising was more than inevitable, since we were allocated to rooms of two, all close to each other. The location of the hotel also provided a good excuse for long walks to/from the centre of the city. Some of the brave ones even stayed in the centre till the early hours to watch the spectacular view of the opening of the bridges over the River Neva before returning home!

A special reference should be made to the well organised excursion to the Hermitage museum where we all travelled back in time, walking through the corridors and rooms of the Winter Palace to gain a small taste of the prosperous life of the Russian Tsars.

We also had the opportunity to attend and obtain hands-on experience at a number of interesting demonstrations. We all enjoyed the friendly environment under which these displays took place and the awareness and enthusiasm of the speakers. Moreover, the fact that we had the chance to directly discuss our concerns and ideas with the experts – whether they were postgraduate students or heads of laboratories – in these different fields was of great value to us all, as was obvious from the long discussions that ensued. At the same time, young physiologists were able to present their own work as a poster presentation in a friendly and enthusiastic environment. Students received very useful feedback from lecturers and fellow students, which gave the prospect of future interaction and collaboration between different laboratories.

Special thanks to the organisers for the last night banquet at the Europa ship restaurant, where amazing food, cheerful spirit, dancing and, most certainly, vodka and 'Selëdka' left some – if not all – of us with a wide smile!

On behalf of all students that participated, I would also like to say 'thank you' to the organisers, and all the other staff and researchers who worked with us. They made this trip exceptionally educational and inspiring for our future work and simultaneously provided us with the chance to see this important city in the most enjoyable way!

I think we all left St Petersburg saying 'Do skoroy vstryechee' (see you soon), rather than 'Do svidaniya' (goodbye)!

Myrtani Pieri

9th Annual Molecular Techniques Workshop Preliminary Announcement

A 10-day residential workshop for the training of physiologists in molecular biological techniques is to be held in the Department of Physiology at University College Cork, Ireland this summer. Provisional dates are 4-14 July, 2005.

The workshop, established to increase the use of molecular techniques by physiologists in UK/Ireland, is sponsored by the Physiological Society and the Wellcome Trust, and is based on practical experimental procedures in molecular physiology. Techniques include the handling of DNA and RNA, sub-cloning, restriction enzyme digests, siRNA-based technologies, western blots, RT-PCR, site-directed mutagenesis and transfection of cells in tissue culture.

The experimental work is complemented by a series of formal lectures and tutorials. The course is most appropriate for established PhD students or physiologists at the post-doctoral level who have little or no prior experience of molecular techniques and who intend to follow a career in the physiological sciences. The number of participants on the course will be limited to 16.

Full details will be announced in March when application forms will be available to download at:

www.ucc.ie/ucc/depts/physio/meetings-mtw2005.html

Patrick T Harrison
Course Director
p.harrison@ucc.ie

PPTR 2004

Participants at the First Integrated Symposium on the Physiology and Pharmacology of Thermal Biology and Temperature Regulation (PPTR 2004) held in Rhodes, Greece from 10-15 October, 2004 may like to visit the website (www.ortra.com/pptr) to view the symposium photo album.

When is a young physiologists' symposium NOT a young physiologists' symposium?

The answer is simple – when, on the day, it evolves into an exceptionally high standard satellite meeting with a consistent attendance of 100 people throughout the day and becomes a highlight of a major conference.

The King's College London YPS was, from the outset, always going to be slightly different from other YPS meetings that have been held by the Physiological Society, because this time students from the UK were going to be joined by students from Chile. That should have been the only difference – it was in concept supposed to be a small, informal meeting. Nothing extraordinary, nothing special, fairly easy to organize…

However, somewhere along the line (I think about June 2004), the concept mutated. Over the next 6 months it slowly evolved into something much bigger. By the end of October, the number of participants presenting at the symposium (either a poster or an oral communication) had hit 70. Not only that, but I had also received abstracts from Denmark, Spain and the Ukraine along with those from Chile and the UK. By the end of October I had had interest from students in South Africa and Australia. From an organizational point of view I was beginning to panic slightly. Was the room large enough? Was there going to be enough food? Where, oh where, was I going to have the coffee? If it wasn't for the help of Clive Daws and Stephen Franey before the meeting and on the day, things may have gone horribly wrong, but apart from a slight glitch first thing, the day went incredibly smoothly.

And what a day! Despite the 8.30 a.m. start, the room was full (we had seating for 100, and people were standing). Juan Bacigalupo (University of Chile) opened the meeting with a highly illustrated talk on sensory neurones, discussing the data he obtained from single-channel recordings to look at both the electrical response of the neurone and the metabolite changes within it. Mike Duchen (University College London) closed with a movie-animated seminar on mitochondria containing an abbreviated history as well as discussing their role in cells and their part in some pathologies. In between we had 18 excellent oral communications, each session chaired by a post-doc or student from both the UK and Chile. The diverse subjects on offer ranged from MAP kinases and signal transduction in the oxidative stress response, to the effect of altering maternal melatonin on foetal adrenal function to systemic oxygen delivery and uptake during exercise. The chairpersons handled every session superbly, thinking of questions for every talk and, more importantly, making sure that we kept to time. As a result we had longer for lunch and coffee, so more time was spent reading the posters and enjoying the sandwiches. After Mike Duchen's seminar we returned to the posters (this time accompanied by wine) before heading off to The River Bar at Tower Bridge to finish the day with a great meal.

Above: Some of the 100 participants who enjoyed a day of high quality talks and presentations at a symposium which became the highlight of a major Society conference

Below, left: Paola Casanello (Chilean organizer), far left, with Luis Sobrevia and symposium participants

(photos by Ling Gao)

My lasting memory of the day is of the high quality of all the talks and presentations. Above all, a feeling of pride endures – everyone put so much effort into their talks, their posters, and making sure the symposium ran smoothly, and for that I am truly grateful. For a symposium to become the highlight of a major conference you rely on your participants and your audience – organization plays only a small part. We had excellent presentations and a huge audience. To sum up, the Young Physiologist's Symposium at KCL was big, international, and a resounding success.

Charlotte Waters
King's College London

Affiliate members of the Physiological Society's Council are Helen Taylor and Patricia de Winter.

The *Dead Ringer* team clean up at Lastingham

On Saturday 30 October last, a group of devotees of Sydney Ringer from Leeds, Manchester and Glasgow gathered at Lastingham, North Yorkshire. There lies buried the man most properly credited with 'inventing' experimental physiological salines. Sydney Ringer has been known to the parishioners at Lastingham principally as the benefactor, in 1879, of the very substantial 'restoration' of their ancient church. That project (costing over £4,000 then – equivalent to well over £250K in today's terms) was to commemorate the tragic death of his elder daughter Annie at her own 7th birthday party. (Despite having an eminent physician and physiologist for a father, she choked on a plum stone. Of course, this was at a time before the simple, but highly effective, Heimlich manoeuvre that might well have saved her had become established as routine first-aid.)

The graveyard at St Mary's was in need of several person-days of labour. The day before our visit, the vicar, Rev Dr Alastair Ferguson, had had felled, or tree-surgically thinned, a large number of trees that excessively shaded the graves. The potential to build a bonfire to rival any in the UK last year couldn't be resisted by the Phys Soc pyromaniacs. However, despite free access to kerosene, matches and enough wood to build an armada, any guy atop the pyre would have suffered a very slow burn indeed. We held the previous week's moist weather to blame rather than Derek Steele for the disappointing 'inflammation' (see photo – DS with petrol can, but eyebrows intact; don't try this at home).

The volunteer group spent the fine autumn day working through the churchyard, clearing the tree-felling debris and generally tidying as best we could. A brief lunch break at the adjacent *Blacksmith's Arms* helped to see us through a long day. We finished up later in the vicarage as guests of Alastair Ferguson and his wife Denise.

Clockwise from above: The team was (left to right) David Eisner, David Miller, Clive Orchard, Mark Boyett, Stephen O'Neill, Matthew Lancaster (head only!), Derek Steele and Sandra Jones. (The railing at our feet surrounds Sydney and Ann Ringer's common grave and, with the cross over it, their daughter Annie's grave); Annie Ringer; Derek Steele; Clive Orchard, David Miller, Rev Alastair Ferguson and Matthew Lancaster proving that science and religion can't cut it … even with two saws; the tower and western end of St Mary's, seen from beside Ringer's grave *(photos by David Eisner)*

Parish meeting records that they have from Ringer's time provided some fascinating reading – he once seems to have upset fellow parishioners over a voting-rights dispute. Luckily for the *Dead Ringer's* group, the clocks went back on 30 October giving extended recovery time after a strenuous, but thoroughly enjoyable day.

The church itself was started in the year 801 on the still more ancient site of a monastery founded by St Cedd and St Chad 1,350 years ago (*i.e.* in 654). It has a crypt that is apparently unique for an English church, being entered down a stair from the centre of the nave. This access was part of Ringer's renovation, though the crypt has remained virtually unchanged since the time of William the Conqueror. It is still a site of pilgrimage and enjoys very large visitor numbers, perhaps over 20,000 *p.a.* This figure belies the tiny, secluded nature of Lastingham village itself, but is testament to its attractions.

Under the auspices of the Society, a plaque has been commissioned to commemorate Ringer within the church. David Miller and others are writing a booklet describing Ringer and his place in biological and medical science intended for the lay reader which will be made freely available to church visitors. We hope that by informing at least some of these visitors, both Ringer's work and physiology itself will become a little more familiar to the public.

The Dead Ringer Society

'Gilding the lily'

'Do you agree?' (*Physiology News* 2004, **57**, 3) asks, is it legitimate to 'gild the lily'. The answer is no, since the quotation is wrong. What Shakespeare wrote was 'to gild refined gold, to paint the lily, to throw a perfume on the violet … is wasteful and ridiculous excess'. He gives other examples in this beautiful passage – see King John, Act IV, Scene ii. And, of course, Shakespeare is correct.

Tim J Biscoe
Honorary Member

Starling improperly dressed?

In *Physiology News* recently (2003, **53**, 35), I was interested to see a photograph of Ernest Starling dressed in the uniform of the Royal Army Medical Corps and looking suitably regimental. However, it seemed to me that either Mr Starling was improperly dressed or the photograph was printed in reverse.

The observant reader will notice that the shoulder strap to his Sam Browne belt runs from left shoulder to right hip. As the shoulder strap is intended to brace a sword and scabbard and the assumption is always that the wearer is right-handed, this might seem to be definitive evidence for misprinting of the photograph. My military advisers tell me that this need not be so, as Starling could have been wearing his number two dress and have been permitted the use of side-arms, in which case the support might have been for a revolver and holster.

Readers will be pleased to know that I have the key to the problem. At the same time, I can show that a first degree in zoology from Sheffield, with the interminable focus on speciation that it then had, was indeed an asset, although I didn't realise it at the time. The key is in the RAMC 'collar-dog' on the lapel, which shows the serpent and the staff of the familiar motif. The first turn of the snake is to the left in your photograph, whereas in the

With apologies to Ernest Starling - now properly dressed

photograph printed here the snake first twists of the right. I think there is a case for one or more of your editorial staff to report to the Adjutant.

Michael Lucas
Gastrointestinal Physiology Group University of Glasgow

A hitherto undescribed autonomic reflex

Every two months for the past three years or so, I have had a 500 ml venesection performed on my right antecubital vein (the only accessible vein I've got!) for polycythaemia rubra vera. Six months ago (i.e.last venesection but two), while the needle was in my arm, I felt wetness on the right side of my face and neck (but NOT in the axilla or arm). I turned out to be dripping with sweat in these contiguous regions. The sweating stopped as soon as the needle was withdrawn. This has not occurred with previous or subsequent venesections.

I am normally oligohydrotic, and not subject to conscious sweating (and certainly not when at rest). I have not previously read or heard of such a reflex, especially one so precisely anatomically defined – presumably due to activation of the upper part of the stellate ganglion (only). However, I am sure that the phenomenon has occurred before, but simply not been reported. Can anyone provide information on similar cases?

David Bowsher
Department of Neurological Science, Pain Research Institute, University Hospital Aintree, Liverpool, UK

Graham Baker

I should like to express my appreciation of the sympathetic and detailed obituary notice for Graham Baker written by Drs Segal and Naftalin *(Physiology News* 2004, **55,** 49).

I was one of Graham`s colleagues for 20 years and found him to be loyal, conscientious and supportive. Graham was very popular with the students as he was so approachable and helpful in elucidating problems in physical chemistry, mathematics and electronic circuitry. In spite of a heavy teaching load, Graham developed his own research topic in using micro-electrode techniques to compare the ionic properties of human buccal epithelial cells from cases of cystic fibrosis with those from normal subjects.

At the same time he was involved in work with Wilfred Widdas and other colleagues, and was able to maintain this work during the very disruptive two years when the Department from Bedford College, operated on two different sites, 30 miles apart, following the merger with Royal Holloway College at Egham. Joint work with Widdas continued and their last paper is now 'in press' in *J Cell Mol Biol*.

The Department benefited enormously from Graham`s numerous practical skills. His ability to design and make electronic circuits and to identify and correct faults was invaluable. He was also generous to his colleagues in several ways, using his welding gear to repair their cars and supplying fruit and vegetables from his garden. He was a governor of his local school and regularly gave demonstrations with a microscope on the study of the inhabitants of pond water to stimulate the interest of the children.

George Darlow
Bedford and Royal Holloway College, London, UK

Profiting from Postgraduate Talent 2004

The meaning of the word 'postgraduate' has changed and is evolving into a very different species than was intended when it was first proposed by Von Humboldt back in 1809. Taken up in 1920 in the UK, its role was to develop and prepare students for academic appointments. And, of course, this is still the case for some postgraduates who are aiming to take up a lectureship and conduct their research within a university. However, increasingly postgraduate researchers will work beyond universities and go into business, industry, the public sector and other professions. A well-attended conference, organised by the UKGRAD Programme and held on 9 September 2004, addressed the changing role and potential of the postgraduate researcher within the context of the European and global higher education and employment markets, and looked at how this may be maximised for the benefit of all stakeholders. It asked specifically whether postgraduate training is compatible nowadays for all future career prospects, be it as a professional researcher or as a 'researching professional'.

From the employer's perspective it is vital to compete against global competition in order to stay on top. As technology speeds ahead there is an ever-growing need for companies to invest in research and development in order to stay ahead of the field. Within the context of a global environment the skills of the industrial researcher need to be specialised as well as generic so that they can adapt as the needs of the company change. In this respect employers rely on their PhD-trained researchers to keep up with cutting-edge technologies and to bridge the gap between academia and industry. Similarly, research institutes and universities have much higher expectations of their senior researchers requiring them to have the skills to forge collaborations with other international research groups and with industry, keeping at the forefront of breakthroughs and attracting funding.

British Council speaker Piera Gerrard

In this respect, the training of postgraduates in universities is changing to address these needs and to enhance their employability skills within a broader career sphere. They are also taking into account the changing needs of a more heterogeneous cohort of postgraduates, which include increasing international and part-time students amongst their number. The Joint Research Councils' Statement of Skills published in 2001, and the Roberts Review published in 2002, issued recommendations for the training of postgraduate students. These are being taken up by universities, and guidelines have also been revised by the Quality Assurance Assessment in line with the recommendations. This represents a challenge for universities, most of whom still require their researchers to achieve the highest results in the Research Assessment Exercise where publications remain the highest priority. It has led to the introduction of a range of measures including enhanced supervision, the appointment of postgraduate training professionals and/or the re-assignment of duties for some academics. Generic skills are being incorporated into postgraduate training programmes, including communication and management skills, computer and electronic equipment training, and workshops on ethics and career-related skills.

Most universities are aiming to provide postgraduates with a range of skills workshops from which to choose, as well as encouraging them to attend outside courses provided by organisations such as the UKGRAD Programme. Philosophies differ amongst universities such that some are making it a requirement that the recommended 2-weeks' per year training be undertaken before a PhD qualification is conferred upon a student. Others are taking a more flexible approach, considering the requirement as guidelines and allowing conference attendance to be included as a skills training exercise. Increasingly, however, it is being recognised that a 'learning contract', drawn up and agreed between a supervisor and their PhD student, will ensure that both parties' needs are met during the period of training.

The British Council has produced statistics which show that the number of international postgraduates in the UK is already out-numbering the number of 'home' students, in particular, among those embarked on masters courses. Projected figures show that countries such as Asia, Africa and the Middle East will increase demand for international student places in Higher Education by up to 7.8% over the next 16 years. The need to attract these students grows ever stronger as countries compete for the most talented students at a global level, and so the need for compatibility is necessary to accommodate a growing overseas cohort of students. This is being extended at the European level to include doctoral degrees; at the Berlin Summit in 2003 European ministers recognised the need to include the doctoral level as the 'third cycle' in the Bologna Process.* Differences such as the length and content of doctoral training need to be addressed in a move to develop a framework for PhD training programmes, in order to establish a European doctorate by 2010.

In summary, the conference drew out some clear points: globalisation is here to stay, and the future wealth of countries can be considered to be linked to the provision of high quality education to train and retain talented postgraduate students from home and overseas. Training, at the specialised and generic levels, will prepare students for a wide range of careers in a highly flexible, competitive and changing market, producing 'researching professionals' who may or may not become professional researchers.

Sarah Blackford
Society for Experimental Biology

*http://www.bologna-bergen2005.no/EN/BASIC/Pros-descr.HTM

G L Brown lecture

The Bristol 'leg' of this year's G L Brown Lecture by Michael Rennie (pictured above) proved to be a rewarding, if sometimes nerve-racking, experience! We knew that Mike was keen to encourage attendance from secondary schools, and a mailshot to local schools soon produced a potential audience of around 200 GCSE biology and physical education students - how could any self-respecting 14-year olds (or their teachers) fail to be interested in the prospect of a prize physiology lecture that included diet, exercise and body maintenance?

Because of impending building work in the School of Medical Sciences we booked a lecture theatre in a neighbouring building. We decided to film Mike's talk, for the benefit of schools unable to attend, so I arranged a site visit by a local production company. Unfortunately, they were not impressed by the lighting or acoustics in our proposed venue so we had to revert to using one of our own lecture theatres instead. Alas, by then our SRIF building work was in full swing, with the School of Medical Sciences shrouded in scaffolding, the road in front of the main entrance closed to traffic and the nearest coach drop-off point some distance away.

Problem – how to get 200 teenagers safely into the lecture theatre via a potentially hazardous building site. Answer – recruit some resourceful physiology undergraduates to act as guides, tempted by the promise of a small fee, attendance at a prize physiology lecture and the opportunity to wear one of our new customised 'Physiology at Bristol' polo shirts! There was no shortage of volunteers….

The day arrived – our guides were duly trained and attired, the film crew had been briefed and the weather was good. Surely all would now go smoothly? I arrived in the Department to find a message from Mike's secretary that his train had broken down at Derby!

Fortunately, Mike arrived in good time to give a very polished performance that included tips on exercise training regimes for all ages – for instance, optimal benefits in building muscle protein are not obtained if resistance (e.g. weight) training and endurance work are combined in the same session. Also, exercising above 60% maximal effort provides little additional benefit in terms of muscle building. There was interesting information about interaction between food intake and exercise (muscle protein synthesis is facilitated if you eat immediately after exercise) and advice for the students on what they should encourage their grandparents to eat for Christmas dinner - plenty of turkey but avoid the roast potatoes, as many elderly people have 'amino acid resistance' so need a larger proportion of their dietary energy to come from protein in order to reduce age-related muscle loss.

Some of the teenage audience displayed an impressive knowledge of physiology and biochemistry in answer to Mike's impromptu questions (I'm sure I couldn't have defined an essential amino acid when I was 14!) and they clearly enjoyed the opportunity to attend a physiology lecture in a university setting.

Several of the questions after the talk pursued the training theme and included requests for Mike to devise the 'ideal' training schedule – he could clearly become a successful personal trainer if physiology ever loses its appeal! Bridget Lumb rounded off the proceedings with a vote of thanks and the students were given Society and university promotional literature to further whet their appetites.

Our thanks go to Mike Rennie for a stimulating and thought-provoking talk, to the Physiological Society for sponsoring the event and contributing to the cost of filming, and to the University of Bristol for a Widening Participation Award that funded all additional local costs.

Judy Harris

The full G L Brown Lecture will be published in an early issue of *Experimental Physiology*

What it's like to be the G L Brown lecturer

When I was approached by the then Chairman of the Executive Committee of the Society Dafydd Walters for 'a quiet word' during coffee at a Council meeting, his serious mien suggested a ponderous subject, possibly to do with my chairmanship of the Audit Committee. It was therefore a great pleasure to be told I was to present the Society's G L Brown lecture for 2004 in 'six or so' venues. In fact my secretary, (somewhat enthusiastically and unilaterally), accepted 9 invitations – Glasgow, Sheffield, Loughborough, Oxford, Belfast, Aberdeen, King's College London, Coventry and Bristol (although the Glasgow gig was a double session – I couldn't refuse the next Chairman of the Executive Committee, Ian McGrath!). But it was an enjoyable, though at times scary, experience – leading up to the most sphincter-tightening of all in Bristol where Judy Harris arranged for me not only to deliver my talk before a large number of teenage schoolchildren, but also to be videoed for posterity.

Sir George Lindor Brown, FRS (pictured below) was a distinguished

The Royal Society

physiologist who had the wit to work with first rate mentors – A V Hill was his first professor as a medical student and physiology Master's student at the University of Manchester and he later worked with Sherrington, Eccles, Dale, Feldberg and Gaddum, mainly on neurophysiology, but particularly on chemical transmission between nerves for which he was elected FRS in 1946, the year I was born. He was also chairman of the wartime committee that dealt with diving physiology which resulted in the identification of safe partial pressures of hyperoxia in submarines. He was an enthusiastic teacher, always attempting to recruit young people into physiology and the main aim of the eponymous lectures is to widen the appreciation of physiology among prospective students. I stretched the concept a bit by attempting to persuade host departments to let me deliver the lecture, not only to early years undergraduates, but also to local schoolchildren between 12 and 15 who had not yet fixed their academic futures. Having completed my lecture series I am now much more appreciative of the skills needed to be a school science teacher!

The audiences were very varied. In Sheffield the lecture was given not in the University but in a local science specialist school, of which Mike Holley was a school governor – and in Oxford there were no schoolchildren at all, although the audience were certainly young in spirit. It was a real challenge to make my lecture as accessible as possible without dumbing down, but if the best popular science programmes on TV and radio could manage it, why shouldn't a professional university teacher? It is hard for me to tell how well I succeeded but I thoroughly enjoyed myself, and I had some wonderful questions.

I heartily recommend the whole experience and would encourage anyone who thinks they know someone willing to do so much travelling and partake of so many bibulous dinners within a short period to nominate a suitable candidate.

Mike Rennie
Graduate Entry Medical School, University of Nottingham, City Hospital Derby, UK

Benevolent Fund

Annual General Meeting

The Benevolent Fund AGM will be held on Friday, 22 April at 2.00 p.m. at the Society's Administration Office. All those who have donated to the Fund are welcome to attend.

Further details from Joanna Rattray (jrattray@physoc.org)

Raffle

Prize winners at the KCL Meeting were:

- Fang Lou (Imperial College) £15 book token (*Saturday*)
- John Harris (University of Nottingham) £20 Marks & Spencer voucher (*Sunday*)
- Joe Bruton (Karolinska Institute, Stockholm) £10 book token (*Monday*)

The total raised from the three raffles was £253.80. All prizes were donated, so every penny raised goes to the Benevolent Fund.

Deceased Members

The Society reports, with regret, the deaths of the following Members since the last issue of the magazine.

H M Adam (Edinburgh)
Elected Member 1951

Hugh McLennan (Vancouver, Canada)
Elected Member 1958

Autar S Paintal (Delhi, India)
Elected Member 1953
Elected Honorary Member 1988

Sir John Vane (London)
Elected Member 1953
Elected Honorary Member 1988
(An appreciation of Sir John's life and work will appear in the next issue of *Physiology News*.)

Where does my future lie?

In November 2004, the Life Science Careers Conferences that have been running for over 16 years, were, for the first time, organised by the Biosciences Federation.

The Physiological Society won the bid to carry out all the administration for the activities. This involved booking venues, catering, delegate bookings (around 250 delegates per venue), speaker and exhibitor liaison. I wouldn't recommend anyone to try organising these events single-handedly.

The format followed the same pattern as previous years: talks, lunch, cv clinic and an exhibition of potential employers of life science graduates. This year the exhibition was larger than in previous years, with many exhibitors interested in taking part every year.

The Life Science Careers' conferences during 2005 will be held at:

University of Bristol
5 November

University of Westminster
19 November

University of Newcastle
3 December

Please start advertising now, and if any departments would like the opportunity to highlight their PhD studentships or Masters courses please contact me at the London office.

Sai Pathmanathan

Biology in the real world

Last year, a group of life science societies (including the Physiological Society) and the research councils joined together to stage a programme of talks (designed as CPD for teachers) at the Association for Science Education AGM. It was so successful, we did it again. On 7 January, at the University of Leeds, we held a whole day event under the banner of *Biology in the real world: cure the world/feed the world*. This consisted of two parallel sessions: *Cure*, which covered human/animal biology and *Feed*, which covered plant biology. Karen Birch (University of Leeds and Society Member) gave an extremely interesting talk on the subject of *Female hormones, cardiovascular health and exercise*. Chris Pollard's

(AstraZeneca) enjoyable insight into *Fruit flies and fibrillation* was organised by the ABPI, but he is also a Society Member. Our two members attracted the largest audiences on the day, and Helen Garner helped man the Society stand at the exhibition –always good to have an extra pair of hands to publicise our resources. For further details of the talks and event as a whole, please contact Elizabeth Bell at (ebell@physoc.org).

Sai Pathmanathan

What have the Council been talking about?

The Council meeting on 25 November was an extended 'forward looking' meeting where Council members broke up into groups each charged with discussing a particular area of the Society's affairs. This year the broad areas covered were governance; communication; open access publishing; and education and external relations. What follows are some key points from each of these areas.

Under governance, most of the discussion centred on the complex question of the identity of the Society's Trustees, who are legally responsible for the running of the Society.

Following the major changes in the governance structure of the Society at the start of the milennium, the 20-plus member Council became the formal governing body of the Society, with all Council members being Trustees. However, this arrangement is unusual for societies that are charities, where the model that seems to be preferred (notably by the Charity Commission) is to have a small group of trustees, typically less than eight. In response to this a vote at the recent AGM instituted a new set-up in which only some Council members are Trustees.

The downside of this arrangement is that it effectively creates two different kinds of Council members; those who are Trustees and those who are not, with some potential for conflict. An alternative model, used by some charities and societies, is to have a small group of trustees drawn from outside the society's membership who are viewed as acting as disinterested 'guardians'. Although these Trustees, usually drawn from the ranks of the 'great and the good', have legal responsibility for sound management of a society, they are separate from the people who control the society's day-to-day and even year-to-year activities. The governance group, and subsequently the full Council, discussed these two alternatives but without a clear consensus emerging. In the end the decision was taken to set up a working group to review the changes in governance and report back to Council later in 2005.

The Communication group discussed communication both within the Society and between the Society and the wider world. Communication between the membership and the Council was highlighted and it was felt that Members should be encouraged to see Council members as their representatives, rather in the way an MP represents his or her constituents. The group suggested that Council members should perhaps be doing more to canvas the views and concerns of Members in their vicinity, but this is, as also discussed in the editorial in this issue (p. 3), a two-way street.

Under education and external affairs, there was considerable discussion of whether more efforts should be made to promote physiology, especially in schools, and a number of suggestions were made. There was also discussion of whether the Society should recruit undergraduate students as Student Members. It was generally felt that the Affiliate scheme worked well for getting PhD students involved with the Society, but there was a problem of the loss of a group of Affiliates who join as PhD students but then let their Affiliate status lapse when they take postdoctoral jobs outside the UK. Although these people can and do rejoin the Society later, especially if they return to the UK, some argued that more effort needed to be made to hold on to these Affiliate members through their postdoctoral years.

A further category of Society Member, or potential Member, highlighted with respect to promotion of physiology was people who become full Members during their postdoctoral years but ultimately leave research or academia for other jobs, for instance in teaching or in commercial science writing and editing. This group may be small, but an effort to encourage them to remain Members and keep up a connection with the research community would have benefits to both parties.

Last but not least, the hot topic of the Council meeting was Open Access Publishing. Major science funding bodies like the NIH and the Wellcome Trust appear committed to an 'open access' model of science publishing. They feel access to the results of work they have funded should be free, almost certainly online, and not dependent on buying subscriptions from commercial publishers.

Any move to open access will have major financial implications for the profits from scientific journals, and hence also for learned societies (like the Physiological Society) that derive income from journal profits.

Treasurer Jeremy Ward outlined several possible financial scenarios of this kind, ranging from the merely sobering to the frankly alarming. Put bluntly, if open access publishing comes, it seems certain to cost the Society money, since even imposing page charges is unlikely to recoup all of the loss of income. This would clearly have potential knock-on effects in other areas of the Society's activities. This looks likely to be an issue with major implications for the Society, and will hopefully be covered in more depth in a future article.

Members who have views on any of the issues highlighted above should make them known – this was one of the points made by the Communication group. Tell any Council members in your Department, or who you know, what you think. Or write in to the magazine – we exist partly to foster dialogue between the membership and the Council.

Austin Elliott
University of Manchester, UK, Council Member and Editor, Physiology News

Have the lunatics taken over the asylum?

Edmund Burke famously said something to the effect that evil triumphs when good men do nothing. Variations of this sentiment can be applied, with good effect, to contemporary university life.

My thesis is that we (the right thinking majority) are too passive and have let the zealots get away with whatever they want to.

Of course, this passivity is not restricted to university life. Militant Tendency allegedly took over the Liverpool Labour Party by holding meetings at antisocial times of the day (and night) to which only the zealots would come.

What, you may say, does this have to do with university life? I have two answers:

• problem-based learning

• research management

I don't claim to be an expert on education theory. Like many others, I have sat through dull lectures where no attempt was made to make the students think. Such perceived deficiencies in traditional, lecture-based courses are used to justify the brave new world of problem-based learning (PBL, known to its detractors as FOFO – 'f… off and find out').

However, even if we accept these arguments, does it necessarily follow that lecture-based courses must be replaced by courses that are almost entirely lecture free, and where students sit in rooms with facilitators who (in the most extreme versions of PBL) are not supposed to speak?

I suppose that the bright side of this is that being a PBL facilitator is warmer than selling *The Big Issue*.

How did we get such courses? I have no doubt that many of us could not be bothered to join the teaching committees that decided on them and, therefore, have only ourselves to blame.

A related issue has occurred in research. All universities have research committees, often at many levels from departmental via faculty to university. There are research deans and pro-vice chancellors for research. All these have been around for some time. A more recent phenomenon is that of research themes. Everyone, it is argued, must fit into a research theme. A friend who worked on ion channels in the kidney had to decide whether he was a member of the 'ion channel' or the 'renal' theme. While this sort of lunacy would amaze even Lewis Carroll, its proponents (with no sense of irony) also wholeheartedly embrace the idea of multidisciplinary research.

As scientists we are brought up to demand evidence for assertions. What is the evidence that this sort of research management improves quality? Did Watson and Crick dutifully attend their research committee meetings? How worried was Albert Einstein about whether he should be a member of the photoelectric or the theoretical theme? Are the most successful physiology departments in the UK those with the most aggressively organized research committees? Answers please?

The author is a UK-based professor of physiology, who prefers to remain anonymous

Long-term potentiation: enhancing neuroscience for 30 years

Edited by TVP Bliss, GL Collingridge and RGM Morris. 2004, Oxford University Press. 398 pp, £65.00. ISBN 0-19-853030-7 and Philosophical Transactions of the Royal Society 2003, 358, 603-842

This theme issue of *Philosophical Transactions* is a very good read. The editors are to be congratulated on a very well structured addition to the already abundant literature on LTP.

The volume is divided into sections on the history of LTP (7 chapters), its induction (3 chapters), its expression (7 chapters), its persistence (4 chapters) and its function (5 chapters, although no heading is given for this section in the contents list). These are followed by a further three chapters on new directions. Many more chapters could have been added, but this volume gives the feel of the excitement still palpable in the field 31 years after the original papers by Bliss and Lømo and Bliss and Gardner-Medwin were published in *The Journal of Physiology.*

In their introduction the editors engender their own excitement in the reader and point out that there are two themes that have dominated research in LTP:

• is it a neural model of memory formation, or is it the actual neural mechanism that is used by the brain to store at least some forms of acquired information?
• does it tell us something about the fundamental mechanisms of synaptic communication?

Obviously these two themes interact with one another throughout the publication and it is heartening to see how molecular biological techniques are being used to comprehend physiology.

It is very difficult to summarise such a wide-ranging volume, but all of us in neuroscience have questions about LTP and this well edited compilation answers many of them. It is a very useful volume to keep in the office or study for reference and reflection. The production is good, as one would expect from the Royal Society. Hopefully there will be a further edition to keep us up to date in a few years from now.

Bill Winlow

Textbook of endocrine physiology

5th Edition. Edited by James E Griffin & Sergio R Ojeda. 2004, Oxford University Press, 431 pp. ISBN 0-19-516565-9 (£35.99, hardback), ISBN 0-19-516566-7 (£18.99, paperback)

The first edition of this multi-author text book was launched in 1988 and I did indeed purchase a copy and subsequently placed it on my recommended reading list. It remains a solid text book of endocrinology written in a clear, no-nonsense style.

The first five chapters overview general aspects of endocrinology. These not only include hormone synthesis, hormone receptors and signalling pathways, immune-endocrine interactions and assessment of endocrine function but also a large chunk of molecular biology and associated techniques. The remaining 11 chapters follow the typical pattern of describing the anatomy, functions and control of specific endocrine glands.

Some of the text has been updated to encompass recent developments in the field of endocrinology and is commendable. That said, there is a paucity of illustrations (I am a visual person) and many of these remain the same as those in the first edition. This gives the book a somewhat 'dated' look and does not do justice to, or set off, a well written text.

The clinical aspects of endocrinology take less prominence than the basic science and at times there is a mismatch between the attention given to the relatively common endocrine disorders and the very rare and obscure endocrinopathies. For example, diabetes mellitus is dealt with in just under two pages and this is followed by a half page on Tangier disease, a very rare autosomal recessive disease that most training medics are unlikely ever to see. Whilst such examples may serve to illustrate some aspects of the science of endocrinology this could give a distorted perspective of clinical endocrinology. To be fair, this is not a clinically-lead book, nor was it intended to be, and thus I would consider that the book is more relevant to science students than medical students. If one can cope with relatively dense text, few illustrations and complete lack of colour, then this book provides a good overview of endocrine physiology.

Saffron Whitehead

Environmental physiology of animals

2nd edition. P Willmer, G Stone, I Johnson. 2005, Blackwell Publishing. 754 pp, £34.99. ISBN 1405107243

The new edition of this book is visually attractive and a great improvement on what was already a very good textbook. The use of two colour printing particularly enhances the diagrams and call out boxes. The addition of two new chapters, one on excitable tissues and the other on endocrine systems, considerably improves the scope of the book and should greatly increase its undergraduate audience. The new chapter on excitable cells is a particularly useful synopsis of the field and, at 117 pages, almost long enough to be a short textbook in its own right.

The book is divided into three sections:
- basic principles – 3 chapters dealing with environmental adaptation and the problems of size and scale;
- central issues in comparative physiology – 7 chapters dealing with basic physiological mechanisms;
- coping with the environment – 7 chapters demonstrating how animals cope physiologically with a wide variety of habitats.

The text is very well written and aimed at an undergraduate audience, although I am sure that it will find its way onto the bookshelves of many more senior comparative physiologists, as it provides a good basic reference source.

The book takes an evolutionary perspective to environmental adaptation and also provides a molecular biological basis for it wherever possible. As a comparative neuroscientist, I was particularly pleased to see so many well chosen invertebrate examples to illustrate physiological adaptability throughout the text. It is an excellent textbook and I thoroughly recommend it to everyone with an interest in environmental and comparative physiology.

Bill Winlow

Other books received. Reviews may be carried in future issues of *Physiology News*

Synthesia: perspectives from cognitive neuroscience. By Lynn C Robertson and Noam Sagiv.

Neuroglia. By Helmut Kettenmann and Bruce R Ransom.

Brain and visual perception. The story of a 25-year collaboration. By David H Hubel and Torsten N Wiesel.

Basic and clinical neurocardiology. By Andrew J Armour and Jeffrey L Ardell.

Free radicals: enzymology, signalling and disease. Edited by C Cooper and V Darley Usmar.

Electrical impedance tomography: methods, history and applications. By D S Holder (available for review from lrimmer@physoc.org)

New Council Members

(continued from p. 34)

the NIH and then a Research Assistant Professor at the University of Maryland. He was appointed to a lectureship in Leeds in 1986, getting a personal Chair in 1995 and serving as Head of the School of Biomedical Sciences from 1998-2001. Currently he is particularly interested in the role of the t-tubules in E-C coupling, and his lab has developed the 'detubulated single cardiac myocyte' to study this in depth. Clive has been an editor on Experimental Physiology, and served on the old Society Committee and numerous sub-committees between 1995 and 1999.

Paul Greenhaff is Professor of Muscle Metabolism and Director of the Centre for Integrated Systems Biology and Medicine at the University of Nottingham. The Centre (http://www.nottingham.ac.uk/cisbm/) champions the experimental application of integrative physiology. Paul has acted as Convenor for the Human Physiology Special Interest Group of the Society for the past four years and is currently a member of the Editorial Board of the Journal of Physiology. At present his laboratory is specifically concerned with the effects of dietary, exercise/ immobilisation and pharmacological interventions on the regulation of energy metabolism and anabolic/catabolic signalling pathways in human and rat skeletal muscle.

Stafford Lightman is Professor of Medicine at the University of Bristol and Director of the Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology. He first got interested in basic science as an intercalated BSc student and, after completing medical training, did a PhD with Les Iversen. Professor Lightman is a neuroendocrinologist whose research concerns the functional significance of the stress response and takes in basic molecular studies of the central nervous system response to stress, through animal models, to clinical studies. In particular, the preclinical programme defines neural pathways through which different stresses can alter hypothalamic function. The clinical programme has developed novel techniques to assess hypothalamic-pituitary-adrenal, sympathetic and parasympathetic nervous system activation in man and is using these to assess the role of dysfunctional stress responses in the development of metabolic, cardiovascular and psychiatric disease. Professor Lightman is an editor of more than half a dozen scientific journals.






From the top: New Council members Paul Greenhaff, Stafford Lightman, Ian McGrath, Patrick Harrison, James Jones and Ann King

Last, but not least, **Ian McGrath** is a smooth muscle pharmacologist and physiologist. Ian provided a bio so informative and entertaining that it would be difficult or impossible to improve upon, so it is reproduced here in full. Thanks Ian.

Austin Elliott

"Born Renfrewshire 1949; enthusiastic, but totally unskilled, footballer; converted from Rangers supporting by political awakening at about 14; entered Glasgow University to study Natural Philosophy at 17; emerged with two pharmacology degrees at 24; PhD started with quantitative microscopy but machine broke and converted to smooth muscle; against all logic, lectureship in physiology at 26; stopped counting age; showed anococcygeus NANC transmission was autonomic; failed over 2 years to reach statistical significance bioassaying NANC transmitter (how was I to know it was a bloody gas); throughout 1970s only person on planet to believe vas deferens had two transmitters; unable to drink wine from any country during this decade due to multiple boycotts; with Docherty and MacDonald discovered post-junctional alpha-2-adrenoceptor 1980; postulated alpha-1-adrenoceptor subtypes 1980 then recanted before mol biol showed initial thought was right; galvanized out of political complacency by formation of SDP (joined Labour Party); 2hr 50 marathon to assuage early mid-life crisis; sucked into Physoc stuff through being local organizer IUPS Glasgow 1988-1993; Regius Prof of Physiology 1991; disintegration of global old right allows resumption of varied wine selection; take up microscopy again; discover adrenoceptors are everywhere; briefly run short-lived heart failure inititiative in mid-90s; complete 13 years of head of this'n'that – sometimes even including word 'physiology' – Summer 2004. Vice-Chair Physoc now.**"**

Biographies of the remaining new Council members to follow in the next issue of *Physiology News*.

The Physiological Society Meetings 2005

University of Bristol
20-23 July (Wed-Sat)
International joint meeting of the Physiological Society and FEPS

University of Oxford
5-7 September (Mon-Wed)
Ion channels, genes and regulation in smooth muscle

For further details please visit the Society's website http://www.physoc.org

King's College London

The Physiological Society's joint Meeting with the Chilean Physiological Society at King's College London from 17-20 December, 2004

(photos by David Eisner)

Clockwise from right:
1 Francisco Sepulveda (Centro de Estudios Cientificos, Valdivia, Chile
2 Ron Jacob (King's College London) dispenses refreshment on the bus
3 Cláudio Ribeiro,Teresa Tiffert, David Eisner, Giovanni Mann, David Brown, Elain del Bel, Bridget Lumb and Nick Boross-Toby plan the Brazil meeting
4 Charlotte Walters, local organiser of the Young Physiologists' Symposium at KCL, with Society Vice-Chairman Ian McGrath
5 HoDs go Head to Head
6 Bayliss Starling lecturer Gerhard Giebisch (Yale University School of Medicine) (2nd left) with Jeremy Ward, Stan White and Malcolm Hunter
7 Giovanni Mann presents Ann Silver with her Society Dog to mark her longstanding service to the Society in many roles including Press Editor (*Experimental Physiology*), Editor (*The Journal of Physiology*) and Honorary Consultant in the Society's Publications Office
8 Robin Irvine (University of Cambridge) presents the Annual Review Lecture 'Inositide expansion – towards turtle domination?'