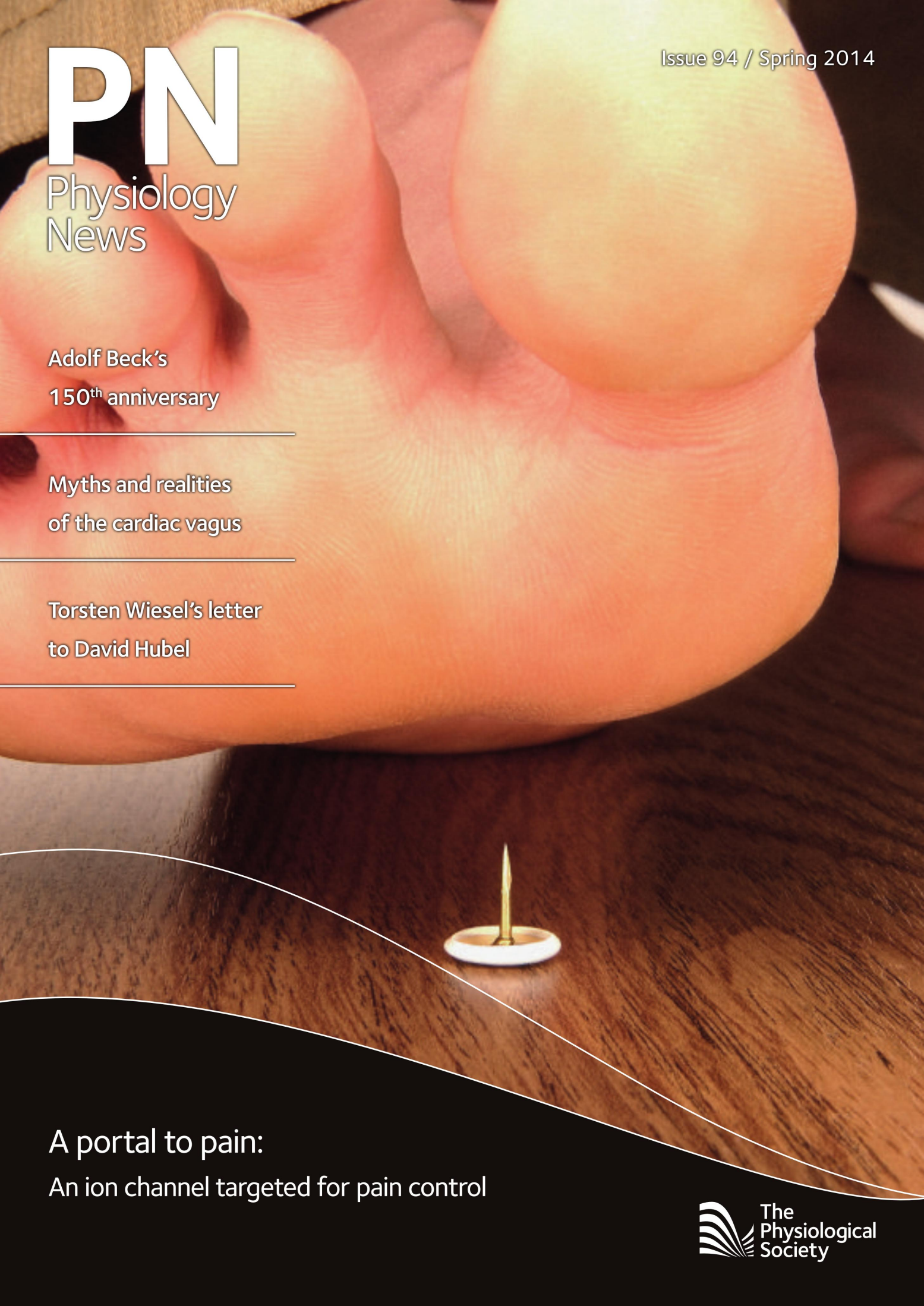
PN
Physiology News

Issue 94 / Spring 2014



Adolf Beck's 150th anniversary

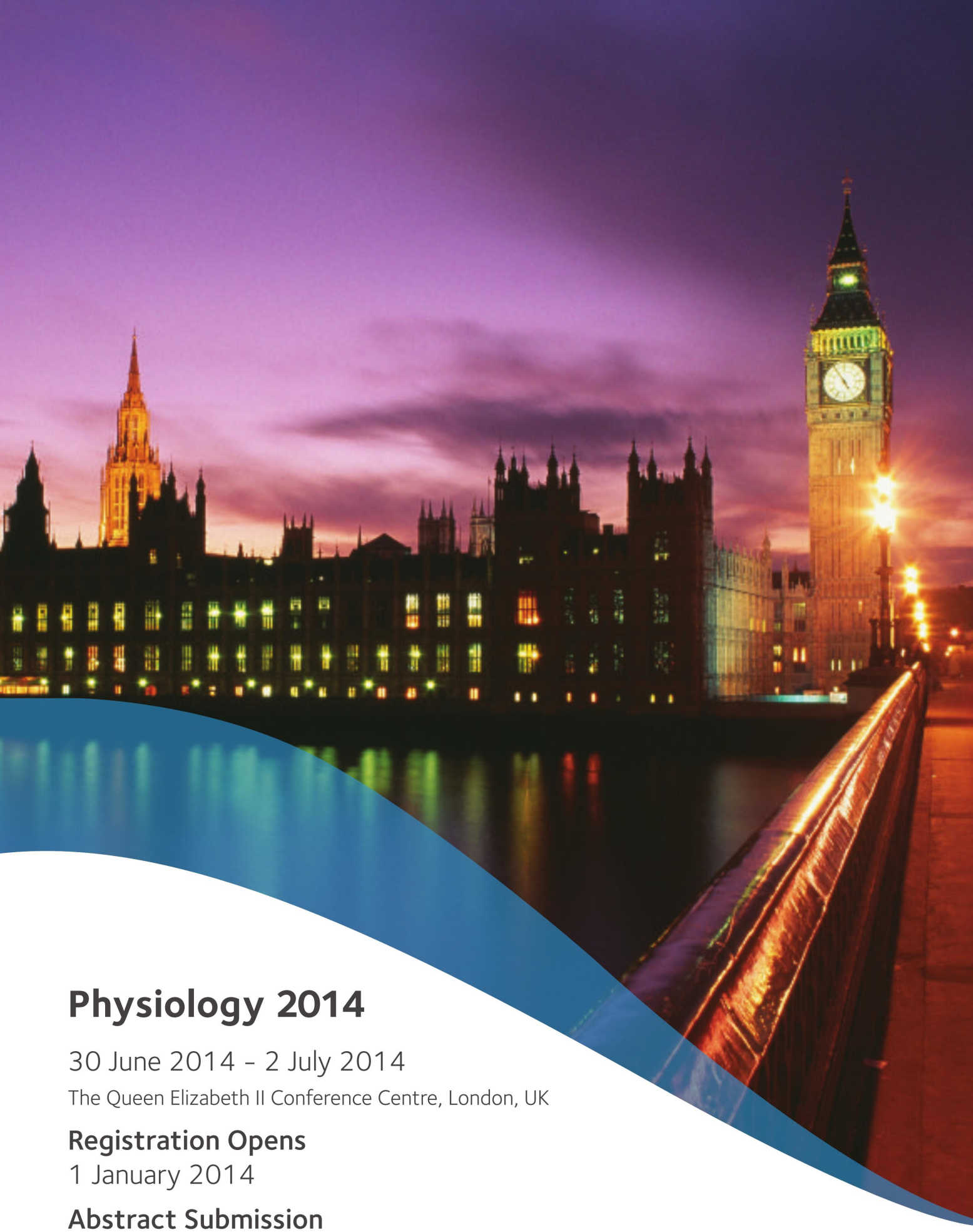
Myths and realities of the cardiac vagus

Torsten Wiesel's letter to David Hubel

A portal to pain:

An ion channel targeted for pain control

The Physiological Society



Physiology 2014

30 June 2014 – 2 July 2014

The Queen Elizabeth II Conference Centre, London, UK

Registration Opens
1 January 2014

Abstract Submission
1 March – 31 March 2014

www.physoc.org/p14

The Physiological Society

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Membership

Physiology News

We welcome feedback on our membership magazine, or letters and suggestions for articles for publication, including book reviews, from Physiological Society Members. Please email **magazine@physoc.org**

Physiology News is one of the benefits of membership of The Physiological Society, along with reduced registration rates for our high-profile events, free online access to The Physiological Society's leading journals, *The Journal of Physiology* and *Experimental Physiology*, and travel grants to attend scientific meetings. Membership of The Physiological Society offers you access to the largest network of physiologists in Europe.

Join now to support your career in physiology:
Visit **www.physoc.org/membership** or call **0207 269 5728.**

Membership Fees for 2014	**FEES**	
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Ordinary Retired Member	–	–
Affiliate	£16	£21
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Editorial

Jonathan Ashmore

President

Two years ago when I took over from Mike Spyer as the Society's President at the Edinburgh meeting in 2012 we were in the middle of planning how we wanted to organise The Society's office when we moved from Peer House. Now we occupy Hodgkin Huxley House (HHH) as though we have always been there. Officially opened in May 2013 by David Willetts MP, Minister for Universities and Science, we have it being used for our Council business as well as small meetings and lectures. If you have not yet been to see HHH, or even started to think of holding your meetings there yet, you should! It is there for your use.

Two years ago we were only thinking about starting a new open access journal. Now, together with the American Physiological Society, we have launched *Physiological Reports*. With Sue Wray as Editor-in-Chief, it has been up and running for nearly a year and has published 178 research papers in it's first year with a further 42 to the end of February. Is open access the way of the future? We don't know. Speak to any publisher and they will say that they are looking at a mixture of conventional and open access publishing. All of us have been pursued by requests to submit to all sorts of new journals (this may have died down a little, or maybe they have just given up on me). Some have been supported by institutions as powerful as the Wellcome Trust, some clearly are opportunistic ventures run from backrooms. It stirs up fierce emotions: Randy Shekman, on the morning of his Nobel acceptance speech, used the airtime for the advocacy of open access. Nevertheless, the unaddressed problem remains quality control – how does the reader know that the science does not have major flaws? *Caveat lector!*

So it seems to me that the strength of The Society's journals is precisely that – the quality of the papers and reviewing system that we provide. Papers submitted to *The Journal of Physiology* and *Experimental Physiology* seem to stand the test of time and remain cited for many years. Within the last two years we saw the 60th anniversary of the publication in *The Journal* of the Hodgkin–Huxley papers on the action potential. The papers really initiated modern neuroscience and remain essential reading, with an exponentially increasing citation rate. These papers do indeed stand the test of time and show how impact factors completely distort the essence and significance of scientific publishing. Indeed, 1952 was an *annus mirabilis*. The year also saw the publication of the papers by Fatt and Katz in which they used microelectrodes to show synaptic and miniature end-plate potentials. Also published, of course, by *The Journal of Physiology*. (An interview with Paul Fatt, who has just celebrated his 90th birthday, is available on *The Journal*'s website: **journals.physoc.org/site/misc/History/Oral_Histories/OH_Paul_Fatt.pdf**).

The other major event in this eventful couple of years has, of course, been the IUPS meeting held in Birmingham in July last year. This was only the fifth such congress ever held in the UK. When I last wrote for *PN*, IUPS 2013 was just getting up to speed. There was considerable enthusiasm and energy being put into the preparations by the organising team. But we did not know whether the Congress was going to be a success. I think everyone would now agree it was a great scientific and social success. It even attracted physiologists from North Korea and Burma – for the first time ever.

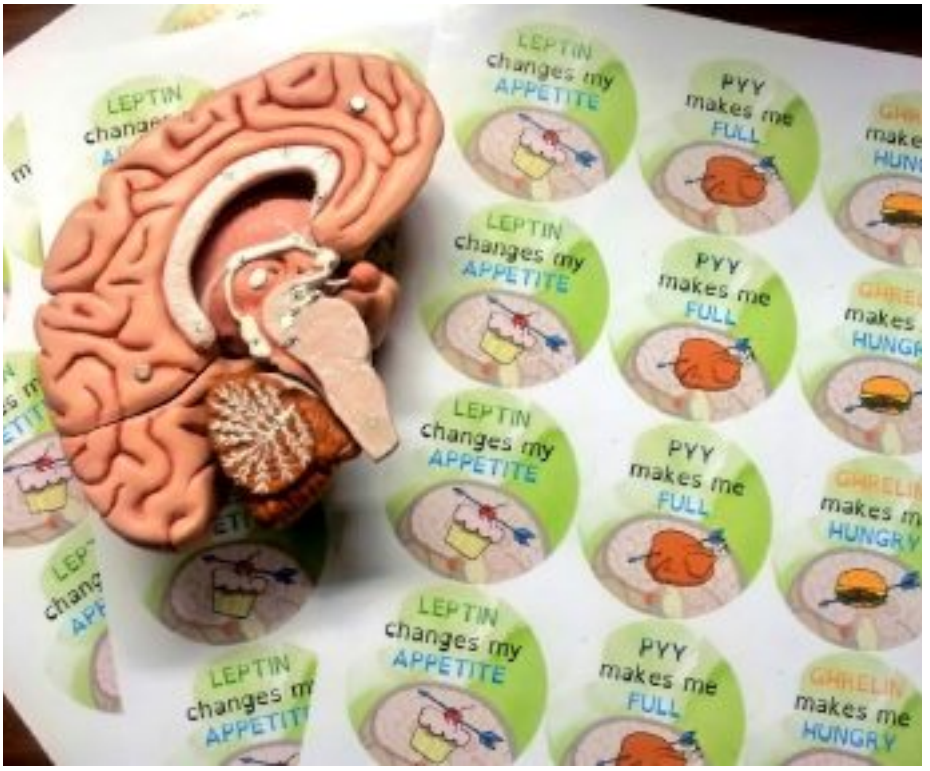
Such successes come at a cost, but The Society was, I am glad to say, committed to underwriting this congress from the instant we agreed to host it. The Society is a charity as well as providing the best services for its Members. As a charity we need be organised in such a way as to be able to fulfil our charitable objectives. What are they? It is worth thinking about and a topic to which Council frequently returns. We have obviously moved on from being a dining club, as it was conceived by The Society's founders. We now cover a whole range of activities, from organising meetings to influencing policy, from providing grants to Members to communicating physiology in schools and universities. We try to support the discipline at all levels. This is quite a brief.

My two years as President have gone by in a flash. The task has been immeasurably assisted by Philip Wright, The Society's Chief Executive, and his enthusiastic and able staff. When I step down at the AGM in July I will be passing on the baton to Richard Vaughan-Jones, and I know that The Society will be in excellent hands. He has been chairing the 'Health of Physiology' project which has been looking at who, what and where our Members are. Indeed, I often think that every researcher, every teacher and every student in the biomedical field should admit to being a physiologist. It does not take much learning to realise that physiology is the study of the *nature* of life, not simply its description – a distinction without which we cannot really profess to understand the complexity of living things. We live in an age when such an understanding is critical, and I hope we agree that The Society has an essential role to play in its pursuit.

Obesity Outreach

The Society has been busy over the last few months preparing for our festival season. We hit the ground running with our interactive stand 'The Hungry Games' at The Big Bang Fair in Birmingham, 13–16 March.

With barely any time to recover from a fantastic few days of hands-on fun with hundreds of 7 to 19 year olds, we are now hot-footing it up to Scotland for the Edinburgh International Science Festival. The Society will be holding an interactive discussion entitled 'Separating the Fat from the Fiction' on Saturday 5 April. Join us at 5.30pm in the National Museum of Scotland as our panel of experts look at the complex subject of obesity from a range of perspectives. We will be arming our audience with electronic voting remotes to find out their opinions on this multifaceted topic as our speakers, chaired by BBC Scotland's health correspondent Eleanor Bradford, present the facts on genes, exercise, diet and our body's basic physiology when it comes to food.



Speakers

Julian Mercer, Head of Division in Obesity and Metabolic Health, Rowett Institute of Nutrition and Health, University of Aberdeen

Tony Goldstone, Consultant Endocrinologist and Senior Lecturer, Imperial Centre for Endocrinology and Imperial College Healthcare NHS Trust, London

Naomi Brooks, Lecturer in Health and Exercise Sciences, University of Stirling

Colin Moran, Lecturer in Health and Exercise Sciences, University of Stirling

The Society will also be holding an event at Cheltenham Science Festival in June on the subject of BMI. To keep up-to-date with all our activities please visit **www.physoc.org / public-engagement**

We would like to thank Imperial College London, The Nutrition Society, University of Stirling, Biochemical Society, University of Essex, and Heriot Watt University for working with us to develop a public programme of events for our themed year of 'Understanding Obesity'.

Valuation of Teaching in Higher Education

The Academy of Medical Sciences, The Physiological Society, the Heads of University Biosciences, and the Society of Biology are working together to review the status and valuation of teaching in Higher Education (HE) biosciences three years following publication of the Academy's 2010 report 'Redressing the balance: the status and valuation of teaching in academic careers'.

A joint steering group was formed to: determine which, if any, of the recommendations continue to be of key relevance in the current policy context, and how these can be addressed; and raise awareness in order to share best practice, discuss barriers to progress, and catalyse activity to redress any identified imbalance across key stakeholders.

The steering group surveyed individuals across bioscience departments and medical schools in UK universities in the summer of 2013. Results from the survey indicate that there is still much to do to raise the status of teaching.

These survey results have helped to develop a workshop organised by the steering group that will be held in late March 2014. The workshop will be attended by representatives from across the HE sector, including Vice Chancellors, Pro Vice Chancellors of Education, Deans of Faculty, Heads of Bioscience, Mid/Early career researchers, Funders, Nationals bodies and Learned Societies. The aim is to raise awareness of the 2010 report, its recommendations and the extent of their implementation in 2013; and share best practice in, discuss barriers to, and catalyse activity toward implementing the 2010 recommendations. This workshop will initiate further work by learned societies on developing standardised metrics and frameworks for evaluating and appraising teaching experience and expertise.

2014 Honorary Members: Call for proposals

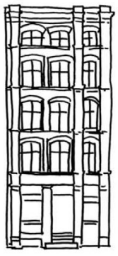
We are now seeking nominations for Honorary Membership of The Society. Honorary Membership may be awarded to any eminent physiologist, and the privilege is not just limited to current Members of The Society.

If you know of any physiologists who can be considered 'persons of distinction in science who have contributed to the advancement of physiology or to the work of The Society', please send us their name and your statement of support. Your proposals will be considered by the Nominations Committee who will advise Council on formal nomination.

The new Honorary Members will be announced at the 2014 Annual General Meeting.

Honorary Members have the same rights and benefits as Ordinary Members of The Society, but are not called upon to pay annual subscriptions. In addition, Honorary Members are also eligible to receive a print subscription to *The Journal of Physiology* free of charge as well as free attendance at Society meetings.

Please submit your proposals at **www.physoc.org/honorary-membership** by 4 April 2014.



H³ Symposium

Inaugural H³ symposium

To provide an opportunity for Members to host and run their own events at Hodgkin Huxley House (H³), The Society is launching the H³ symposium series. The first H³ symposium takes place on 4 April 2014 on the focused topic of 'Cellular approaches for cardiac repair: a physiological perspective'. In this symposium the view that stem cell-derived cardiac myocytes will provide a solution for the much needed supply of human cardiac cells for *in vitro* studies will be challenged. Registration for this event is open until 31 March.

The symposium will feature a session on 'Stem cells and the heart: where do the future therapies lie for cardiac regeneration?' The symposium will also present new, more indirect approaches for cardiac repair and consider which cell type represent an ideal target. Together with pluripotent stem cells, can existing progenitor cells in the adult heart be reawakened to promote cardiac repair? Can non-contractile cardiac fibroblasts become cardiac myocytes?

The content will appeal to both those involved in basic cardiac research and those involved in clinical cardiac regenerative therapies. We will discuss stem cells in culture and how they might be manipulated to aid regeneration, through to the transition from the bench to the bedside.

Run your own H³ symposium

Three grants of up to £5000 are available every year for Members who wish to host a small one day focused meeting at Hodgkin Huxley House (H³). There is a capacity of up to 70 participants, with an option for a further 30 in overflow, and a facility to live-stream your event on the day to a much wider audience. There is also space for up to 30 poster boards and there are catering areas.

Utilising the Bernard Katz Auditorium and a number of break-out rooms (including state-of-art audio visual equipment), potential organisers will have no venue or AV costs associated with their event.

H³ is located a mere 200 yards from Farringdon Station, providing easy access from most mainline stations and London airports. There are numerous hotels within walking distance and the vibrant area of Clerkenwell is our back-drop.

Do you have an idea for an H³ meeting? Why not make an application to organise one? We would love to hear from you. www.physoc.org/meetings-grants

Physiology Feed

Bringing you snippets of the latest intriguing research

Brain decoding: Reading minds

By scanning blobs of brain activity, scientists may be able to decode people's thoughts, their dreams and even their intentions.

DOI: 10.1038/502428a

Sleep clears brain of molecules associated with neurodegeneration

Using mice, researchers showed for the first time that the space between brain cells may increase during sleep, allowing the brain to flush out toxins that build up during waking hours. These results suggest a new role for sleep in health and disease.

DOI: 10.1126/science.1241224

Biological clock hidden in our DNA can identify ages of specific tissues

It is proposed that DNA methylation age measures the cumulative effect of an epigenetic maintenance system. This novel epigenetic clock can be used to address a host of questions in developmental biology, cancer and ageing research.

DOI: 10.1186/gb-2013-14-10-r115

The elusive transducer channel of hair cells

Two recent studies from the USA throw an intriguing light on the long searched for mechanotransducer channel of hair cells. They focus on the role of the transmembrane channel-like family of membrane proteins (TMC) on hair cell transduction using mouse mutants lacking one or both of TMC1 and TMC2. One study concludes that they are components of the channel, the other concludes that they are not the channel, but that the channel requires these proteins (and others) to function correctly.

DOI: 10.1085/jgp.201311111

Linking loud noise to hearing loss

Research investigating tinnitus has revealed new insights into the link between the exposure to loud sounds and hearing loss. The study helps to understand how damage to myelin alters the transmission of auditory signals occurring during hearing loss.

DOI: 10.1523/JNEUROSCI.3977-13.2014

continues overleaf

Physiology Feed

Bringing you snippets of the latest intriguing research

Autism connections

In many people with autism and other neurodevelopmental disorders, different parts of the brain don't communicate well. This study shows that microglia failing to trim connections between neurons can explain how this decreased functional connectivity can come about.

DOI: 10.1038/nn.3641

Combating muscle waste

The loss of skeletal muscle mass and function as we age can lead to the muscle-wasting condition sarcopenia. The findings of this study indicate that altering two particular cell-signalling pathways independently in aged mice enhances muscle stem cell renewal and improves muscle regeneration.

DOI: 10.1038/nm.3465

Tyrosine helps you stop faster

A driver who has recently eaten spinach or eggs will be better able to perform an emergency stop, according to this paper. This is the first-ever study to test whether the intake of tyrosine enhances our ability to stop an activity at lightning speed. The findings seem to indicate that this is the case.

In press: http://dx.doi.org/10.1016/j.neuropsychologia.2013.12.027

The hunger–smell connection

Until now, the brain mechanism governing the connection between hunger, sense of smell and appetite was unknown. This study – on mice – shows the type of endogenous cannabinoid involved in these processes, the place where it acts and the effect that is unleashed.

DOI: 10.1038/nn.3647

DNA PAINT

A new microscopy method could enable scientists to generate snapshots of dozens of different biomolecules at once in a single human cell. DNA-PAINT can create ultrasharp snapshots of up to three cellular workers at once by labelling them with different coloured dyes. Such images could shed light on complex cellular pathways.

DOI: 10.1038/nmeth.2835

If you spot some interesting research that you'd like to share with your fellow Members, please send it to us at **magazine@physoc.org**

Policy Corner

Engaging with Parliamentarians

The Policy Committee is delighted to announce the launch of a new flagship 'Engaging with Parliamentarians' programme. The programme will offer Members the opportunity to gain knowledge of the policy making process and training on how to best engage with MPs and policy makers. It aims to enable Members to impact on the UK policy environment and also to help advance The Society's key policy messages.

If you would like to further information on the programme or would like to apply please see **www.physoc.org/engaging-parliamentarians** or contact Ed Hayes on **policy@physoc.org**

Freedom of Information Act: Our lobbying activity

The Society, working alongside the Wellcome Trust, lobbied MPs over a proposed amendment to the Freedom of Information (FOI) Act. The intention of the proposed changes was to introduce greater clarity that pre-publication research was exempt from FOI requests.

However, the wording of the proposed bill left open the possibility that intellectual property conceived in the pre-experimental, planning phase of a research programme (including grant and/or license applications, etc.) would not be covered by this research exemption.

At the time of writing it remains unclear if our joint efforts will be successful. The Shadow Minister for Business Innovation and Skills, Iain Wright MP, raised our concerns at the parliamentary Public Bill committee stage. However, the amendments that we called for have yet to be adopted, with the minister David Willetts continuing to deflect concerns. We expect further debate over the suggested amendments to take place at the next parliamentary stage, and will continue to monitor developments.

Women in Physiology reception

Dame Julia Higgins

The Society hosted a vibrant reception at Hodgkin Huxley House to celebrate the women featured in the *Women in Physiology* booklet that was launched at IUPS. It also fired the starting gun ahead of 2015, when The Society will celebrate the centenary of the admission of female members. The key note address was delivered by Dame Julia Higgins, patron of Athena Swan and WISE, who provided attendees with a background of her involvement in women in STEM. The Society also welcomed Athena Swan, the Daphne Jackson Trust and Science Grrl as exhibitors at the event.

The Society is also pleased to announce that videos from the IUPS Women in Science sessions are now available online at **www.physoc.org/gallery/media/women-science-iups-2013**

Our leading policy maker scientist

Policy Committee member Max Headley was named as one of the 10 leading policy maker scientists in a recently published list of leading scientists published by the Science Council. He was recognised for his work on *in vivo* policy. Others also on the list included the Chief Medical Officer, Dame Sally Davies, and the Government Chief Scientific Advisor, Sir Mark Walport.

Max said, "The Science Council's selection came as a total surprise – and I was more than a little taken aback at being cast alongside such eminent policy makers. It is of course hugely rewarding to see that my input into this area has been appreciated on a broad front, but it's clearly also the case that the sector's input to national policies has been based on far more than my own contribution. Many colleagues right across the life science sector have contributed much, and I hope that the sector recognises the teamwork that has made for the successes achieved."

If you are interested in these or any other policy related issues please contact us at **policy@physoc.org**

Great textbooks of physiology, part 1

Ruch and Patton's *Physiology and Biophysics*, 19th edition, 1965

R L Maynard

Honorary Professor,
Birmingham University, UK

The age of great textbooks of physiology seems to have passed. Those splendid thousand-page volumes that used to inform and perhaps intimidate have, like battleships, disappeared. But anyone who studied physiology 40 years ago might regret their passing and those who are now studying the subject are deprived of a resource and, perhaps, a pleasure. I remember the step change from introductory textbooks for medical students to books for students of physiology *per se*: Davson's two volumes on *General Physiology*, Ruch and Patton, Mountcastle's two large volumes, Davson and Eggleton's 14th edition of *Starling's Principles of Human Physiology*, Bayliss's new edition in two volumes of his father's *General Physiology* and Best and Taylor's 1800 pages. Not one of these works remains in print but in an age when 'reading physiology' meant reading physiology they were well known. Of course our subject has moved on and these books are now regarded as out of date. This is not entirely true: much may still be learnt from their pages. In this series I shall discuss just a few of the 'greats' from 40 years ago.

Ruch and Patton (*Physiology and Biophysics*, 19th edition, published by W B Saunders in 1965) was a superb book: perhaps the best of the textbooks of the 1960-1975 period, perhaps the best of the 20th century. The 19th edition was dedicated to John F Fulton who had taken over the 15th edition of what had been in 1896, *An American Textbook of Physiology* edited by W H Howell. Fulton was joined by T C Ruch for the 18th edition and the word 'Biophysics' was added to the title. Two further editions, the 20th (in three volumes) and the 21st were produced and then it died. Copies of the great 19th are still available at very modest prices and are worth hunting out. What made it so good?

The answer was and is obvious: the distinction of the authors and the quality of their writing. J Walter Woodbury, his son Dixon M Woodbury, Harold Copp, TC Ruch, HD Patton, RF Rushmer, RL Riley, AM Scher: a roll call of leading physiologists all at the top of their form. The book was not an easy read: I remember reading in the Preface, "This is not an easy textbook for students, nor is physiology an easy subject lending itself to memorization. Students... may find it initially difficult, but with application, the know-how comes and with it the pleasures of following the quantitative pathway... ". Space forbids a lengthy review but two contributions are worth a little discussion.

J Walter Woodbury's chapters on electrophysiology (membrane potential and action potential) were outstanding and still read very well today. The author set out to explain, with quantitative rigour, what Hodgkin and Huxley had discovered: the excitement was tangible. Woodbury had been influential in recommending Hodgkin and Huxley for the Nobel Prize and understood their work so very well. His writing sparkles with intelligence and wit. An appendix "for use by readers whose physics is rusty" cost me a lot of paper and pencils: the problems are worth looking at today. An easy read? Hardly that, but the quality of the explanations was memorable: Figures 7, page 21, and 4, page 35, deserve to be embossed on the walls of physiology departments. And it was witty! There was no sign of the patronising approach one found in other books; everything was explained, step by step, with numbers and equations. Anybody who wishes to find a place to start in understanding electrophysiology and who is foxed by the difference between a capacitance current and an ionic current would be well advised to read Woodbury. His chapter 'Regulation of pH' was just as good: if one word sums it up that word is rigour. But the rigour again tempered by wit: pH? logarithms? Calculate your own! All you need to remember is 0.3010, 0.4771 and 0.8450 and you can work out the rest in your head!

Riley's chapter, 'Gas Exchange and Transportation', was equally good. Riley, Rahn, Otis, Fenn, Fahri and Cournand were the great men of respiratory physiology in the 1950s. In his chapter, Riley began at square one and wrote out a summary of work on gas exchange. A summary? Yes, the full account appeared in the great *American Handbook of Physiology*, but what a summary! The chapter bristled with equations, properly developed and derived, and with graphs that actually explained things. The development of the CO_2-O_2 diagram was so well explained that I remember the thrill I experienced when I realised, for the first time, how to combine the gas and blood R lines.

How much of this is worth reading today? I think a lot of it is worth reading: it provides a starting point for understanding what has happened since but, and more important, it provides such a good example of what physiology is actually about. Physiology is the explanation of biological phenomena in the terms of physics and physical chemistry. A quantitative approach is essential. Ruch and Patton took that approach and their book remains a landmark in the history of textbooks of physiology.

Editorial note by David Miller: The sentence in Bob's last paragraph; "Physiology is the explanation of biological phenomena in the terms of physics and physical chemistry" is very close to Davson's definition of *general* physiology as; "the study of those aspects of living material that show some immediate prospect of being described in the terms of the known laws of physics and chemistry". It is fascinating that this sentiment chimes well with the views of Sydney Ringer, no less. When he chaired the Society Dinner at the March 1891 meeting, a motion was passed stating "That in the opinion of this Society it is important that, as recommended by the General Medical Council, a large part if not the whole of the additional year which is to be added to the medical curriculum should be devoted to Elementary Physics, Chemistry, and Biology."

Keeping the UK a world leader in the field of bioscience

Tracey Jewitt
BBSRC, UK

Physiology research – from lab to lives

As a society we currently face major global challenges such as feeding nine billion people sustainably by 2050, developing renewable low carbon sources of energy, and increasing health span in line with lifespan.

In the coming decades bioscience will be at the heart of providing solutions and the Biotechnology and Biological Sciences Research Council (BBSRC) has a central role to play in ensuring the UK remains a world leader in the field and is at the forefront of providing sustainable solutions.

In 2012/13, BBSRC invested around £467M in world-class bioscience research and training on behalf of the UK public to further scientific knowledge, to promote economic growth, wealth and job creation, and to improve quality of life in the UK and beyond.

Funding streams

As well as a strong commitment to funding curiosity-led research across a broad base, at the core of our remit BBSRC has three strategic priority areas: agriculture and food security; industrial biotechnology and bioenergy; and bioscience for health.

Animal and plant physiology have an important role to play across these areas – as to find solutions we need a thorough understanding of the normal functioning of living organisms and their component parts.

BBSRC's main funding mechanism for all research, including animal physiology, is through responsive mode grants – whereby applications can be made to one of four research committees on any topic within BBSRC's portfolio, throughout the year. Within the responsive mode remit, BBSRC has a set of Council-wide research priorities, including animal health, ageing research, livestock production, welfare of managed animals and the replacement, refinement and reduction (3Rs) in research using animals.

It is important to note that BBSRC funds human physiology research relevant to understanding normal human function, but does not support work on specific human disease, disease process or abnormal conditions – these are areas funded by the Medical Research Council.

BBSRC also has special opportunities: for example, last year £1.4M was awarded to three projects looking specifically at athletes' vision and movements at a physiological level. These awards were made in collaboration with UK Sport and the Economic and Social Research Council as part of a 'High Performance Sports' call. The findings will not only help to improve sporting performance but also provide answers which will benefit our ageing population.

Another way BBSRC has been working with Research Organisations to ensure vital physiology skills are not lost is through Strategic Skills Awards. In partnership with the MRC, BBSRC introduced this scheme to ensure departments do not feel under financial pressure to keep students away from high-cost research training which is strategically important for the UK. Since their inception in 2010, over 35 have been awarded totalling nearly £900k.

BBSRC's Doctorial Training Partnerships (DTPs) also support physiology researchers. DTPs are BBSRC's mechanism for awarding universities and institutes funding for PhD students. DTP bids are invited to address strategically important niche skills within the BBSRC remit, including *in vivo* skills, where partners have the necessary expertise and facilities.

David McAllister, BBSRC Head of Skills and Careers, explains: "Maximising the impact of our science, socially and economically, is dependent on researchers having world-class skills as well as the ability to translate their research ideas and knowledge into technologies and therapeutics to meet the challenges we face. For example, with a growing, ageing population, the need has never been greater to understand the fundamental bioscience underpinning health and ageing."

Skills gap

In 2004, a British Pharmacological Society/ Physiological Society survey documented a significant decline in the number of university departments able to deliver *in vivo* teaching.

As a result BBSRC in partnership with the Higher Education Funding Council for England, the MRC, the Scottish Funding Council, the British Pharmacological Society's Integrative Pharmacology Fund and the Department for Business Innovation and Skills awarded £12.3M in 'Capacity Building Awards' to support four major projects to build capacity in integrative mammalian biology (IMB).

These four centres, which have come to the end of their awards, were Imperial College London, King's College London and through two consortia between the universities of Manchester and Liverpool and the Universities of Glasgow and Strathclyde. Over 150 PhD students and 600 undergraduates have benefited from training at the centres.

"Animal physiology is central to the development of new therapeutic approaches to human and animal diseases so BBSRC saw addressing the skills gap in advanced *in vivo* sciences through springboard funding as vital to the future development of safe and effective therapeutics.

"BBSRC has a crucial role to play in nurturing and developing scientists to ensure they have the skills and facilities to carry out world-class science and we will continue to do all we can to train and support highly skilled researchers in stringent economic times," says McAllister.

Wider training opportunities are also available to BBSRC funded researchers working in any area, including media and public engagement training as well as awards which support and encourage the movement of people between environments and commercialisation.

To find out more about the research and training opportunities offered by BBSRC, visit: **www.bbsrc.ac.uk**

Case study: Strategic Skills Award

Charlie Kwok is in her final year of a PhD looking at the neurobiology of pain, specifically looking at the development of endogenous pain signalling pathways during postnatal development at the University of Nottingham.

"I did my undergraduate degree in Neuroscience and one of the core modules was systems neuroscience, which included pain as a main topic. I came across a lot of research papers during my studies and physiological techniques were almost in all of them. At the time I had never performed any experiments like this and I was intrigued. In order to understand the research and interpret the data, I needed to understand the methodology, so I decided I wanted to learn more about physiology.

A BBSRC Doctoral Training Grant and a BBSRC Strategic Skills Award have enabled me to do a PhD in neurobiology of pain, which is what I wanted to do after I graduated. I was fortunate enough to be working in the Laboratory of Developmental Nociception, with very supportive, knowledgeable supervisors and fun lab members. I am now fully trained in a range of techniques, such as electrophysiology, immunohistochemistry and RT-PCR (a molecular biology technique to look at gene expression), and I have performed several studies using these techniques. BBSRC has also given me an opportunity to do a seven week placement at Unilever (research assistant in the ice-cream division), as part of BBSRC's Doctorial Training Partnership (DTP). Overall, the Strategic Skills Award has been really important to my training and career development."

Case study: Physiology spin-out

Following a BBSRC-RSE Enterprise Fellowship, Margaret Craig – a researcher in cardiovascular physiology – has added Chief Executive Officer of Clyde Biosciences to her CV, a company she hopes will become a world leader in drug toxicity innovation.

Craig explains: "After graduating from the University of Strathclyde with a degree in Immunology/Pharmacology I went on to complete a PhD at the University of Glasgow in the pathophysiology of cancer. Following this I became a research associate where I was involved in the development of biological assays and novel discovery platforms as well as cardiovascular physiology research.

In 2011 I was awarded a BBSRC/RSE enterprise fellowship which allowed me the time and money to spend one year validating our group's technologies, exploring the market potential and carrying out business training. During the course of the year, it became apparent that our technology had much commercial potential and we formed the spin-out company Clyde Biosciences.

Before this I never knew anything about business or thought it was something I'd find myself involved in. But I love it and I don't think I could do anything else now.

For more information about Enterprise Fellowships, visit:
www.bbsrc.ac.uk/enterprisefellowships

Case study: Responsive Mode Funding

Roxana Carere from the University of Southampton has recently been awarded £600K of responsive mode funding to study the physiology of perivascular drainage of the brain and how it is affected by age, over the next three years.

Carere explains: "Fluid and soluble waste drain from all organs of the body to regional lymph glands. For organs such as the lung and liver, there are clearly defined channels along which the fluid and waste products drain. However, there are no such well-defined channels to drain fluid and waste products from the brain; instead, the drainage pathways are very narrow and confined to the walls of the arteries that supply the brain. This drainage pathway for waste products from the brain has received little attention in the past but its importance is becoming increasingly recognised because of its potential role in the decline of mental and psychological health. There are many unknown factors concerned with the perivascular drainage pathways from the normal brain and they need to be resolved before measures can be taken to maintain normal mental health in the elderly."

Remembering the 150th anniversary of the birth of Adolf Beck (1863-1942)

Polish-born physiologist, co-developer of electroencephalography who suffered persecution in two world wars and committed suicide facing arrest by the Nazis

Oksana Zayachkivska

Department of Physiology,
Lviv National Medical University,
Lviv, Ukraine

Adolf Beck was the founder of the Physiology Department in the Medical Faculty, the National Medical University in Lviv (formerly known as Lemberg, 1772–1919, or Lwów, 1340–1772 and 1920–1939), western Ukraine. He was not merely a scholar, with first-rate credentials for having developed methods for the study of the cerebral cortex and neurophysiology, but also a man of great personal courage.

Beck was a pioneer in the development of electrophysiology and a co-developer of electroencephalography. He performed his influential work at his *alma mater*, the Jagiellonian University in Kracow, under the leadership of Napoleon Cybulski (1854-1919). In 1890, his article about the spontaneous and evoked electrical activity in the brain was published in the *Centralblatt für Physiologie*, then a leading European physiology journal. Beck accurately localised sensory modalities in the cerebral cortex by employing electrical and sensory stimulation whilst recording electrical activity. In doing this, Beck also discovered the spontaneous oscillations of brain potentials, just as Caton (1875) had done, and showed that these fluctuations were not related to heart and breathing rhythms, but had to be regarded as genuine electrical brain activity. Later, in the 1890s, Beck studied parts of the cerebral cortex that reacted upon stimulation with electro-negativity: the first recorded 'evoked potentials'. Moreover, Beck discovered a new element: a decrease in the amplitude of the potentials upon sensory stimulation. Thus, he was the first to describe the phenomenon now known as desynchronization of the EEG. Beck published that work as his doctoral thesis (in Polish). Many years later, MAB Brazier (1904–1995), the neuroscientist, international organizer and prominent expert in the history of neuroscience, translated the dissertation into English, placing Beck's eminence in the company of such scientists as Gustav Fritsch, Eduard Hitzig, David Ferrier, Emil du Bois-Reymond or Ivan Sechenov (Brazier, 1973).

In 1895, Adolf Beck became head of the Department of Physiology and an appointed Professor at the newly renovated Medical Faculty of the University Franz I in Lemberg, in Galicia (at that time under the Austro-Hungarian monarchy). With great energy and enthusiasm, Beck organised the Department in very similar style to that of his *alma mater* and other European universities equipped with modern scientific apparatus and laboratories for chemistry and morphology. He organized an operating and vivisection room, and care rooms for experimental animals that made it possible to carry out extensive research. In the same year, together with Cybulski, Beck produced a report for the Third International Physiological Congress in Bern on their extensive electrophysiological studies of brain potentials. He took part in the organisation of the Eighth International Congress of Physiology in Vienna (1910) where, with Gustaw Bikeles, he presented data on *The galvanometric study of the spreading reflex arc in the spinal cord*. His originality and creativity in research attracted attention from the whole international community.

It is important to note that Beck's research was not limited to neurophysiology. He also worked in fields of general physiology, such as visceral and sensory function and laboratory medicine. He also arranged a local physiological society and the Institute of Physiology of the university. He did not receive the Nobel Prize despite being nominated several times (as recently released records have revealed), but Beck's academic *oevre* remains remarkable. It comprises 180 texts, many published in the most influential European journals. Also amongst his works are textbooks on the physiology of the central nervous system, and a two-volume *Human Physiology* (two editions) popular among medical students for many years. Beck's teaching and pedagogical work merits special attention, as attested by the memoirs of his students.

He was reappointed Rector at Lemberg/Lviv in the difficult years of World War I. He manifested rare diplomatic skills under the extreme wartime conditions, using his diplomacy to make a convincing case for academic needs to the occupying authorities. He joined the efforts of those colleagues who remained in the city to protect the university's property. However, in 1915 he was arrested by the Russian commandant and exiled. After a

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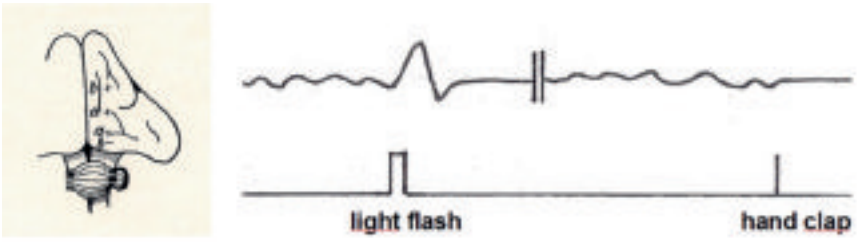


Figure 1. Right: the filtered and plotted reproduction of the experiment which Beck described in his doctoral thesis (from p33 of the English translation). The recording shows two essential elements: a visual evoked potential after a flash of light and the desynchronisation both after the visual stimulus and the hand clap. Left: the recording places on the occipital and parietal cortex of the rabbit brain. Due to the placement of electrodes the flash gives an evoked response and the clap only a desynchronisation (from Coenen *et al.* 2013).

few months, Beck was released from prison thanks to the efforts of Nobel laureate Ivan Pavlov, and of the Red Cross. In 1935, he authored a memoir on the adversities endured in World War I, which became a *sui generis* chronicle of events at the university. He had a memory that retained the smallest details of the war in Lviv and these enliven the book. Beck's persistence and tireless work ethic – he did not interrupt his research even in the difficult war and postwar days – were another element of his personality. Adolf Beck became a visionary in the development of societal relations. An ardent critic of Zionists, he founded and headed the 'Unity' organization, whose mission was to ensure equality among people of various ethnicities and religions, sentiments which resonates with the present day slogans of the European Union (Zayachkivska, 2013).

In the absence of a detailed personal memoire, truly understanding Adolf Beck, the man, remains a challenge. Did he sense danger in 1915 when he was imprisoned and deported to an evacuation camp in Russia? What emotions stirred in his breast in 1939, at the outbreak of World War II and the start of the 'new' Soviet era, or in 1941, when he was required to pin a Star of David to his garments and suffer Nazi persecution, or when the Janowska concentration camp was founded in Lwów? What were his final thoughts when, on the point of arrest by the Nazis, he took poison from his own son's hands in order to commit suicide? We do not know the answers to these questions – but it is said that 'each question contains part of an answer'. We can be confident that, under all the adversities he faced, Beck proved courageous, chose to do good and to honour cooperation. The sesquicentennial celebrations that took place at Beck's *alma mater* as part of the Neuronus 2013 International Brain Research Organization (IBRO) and International Research Universities Network (IRUN) (Coenen *et al.* 2013), as well as a presentation of his life-story at IUPS, Birmingham, 2013, confirm that Adolf Beck offers a fine example of noblemindedness for future generations, and a person worthy of remembrance in the 21st century.

Adolf Beck, 1939 (from the MAB Brazier collection, Department of Special Collections, Biomedical Library of University of California at Los Angeles, USA).

2014 *Forthcoming events*

29 April

JP Symposium:
Insights gleaned from pharmaco-genetic dissection and modelling of cardio-respiratory neural networks
San Diego Convention Center, San Diego, United States

30 April

EP Symposium:
Physiological and pathophysiological signalling between the gut and the kidney: role in diabetic kidney disease
San Diego Convention Center, San Diego, United States

30 Jun – 2 Jul

Physiology 2014
The Queen Elizabeth II Conference Centre, London, United Kingdom

10-12 Sept

Obesity: A Physiological Perspective
Newcastle Upon Tyne, United Kingdom

Meeting Preview

Obesity: A Physiological Perspective

10-12 September 2014
Newcastle United Football Club, Newcastle Upon Tyne, UK
www.physoc.org/topicobesity

The Society's Meetings Committee are excited to launch their new 'Topic Meetings' – a new format which aims to attract physiologists from diverse backgrounds to promote cross-fertilisation and integration.

The first Topic Meeting, a part of The Society's 2014 theme Understanding Obesity, is entitled *Obesity: A Physiological Perspective*, and will be held on 10-12 September 2014 at St James' Park – home of Newcastle United Football Club.

The programme will look at the hot topic of obesity from a physiological point of view, starting with an opening prize lecture from Steve Bloom (Imperial College London) on the consequences of obesity. Sessions on metabolic and cardiovascular consequences, and maternal obesity will follow.

Day two will look at the aetiology of obesity, with sessions focusing on the manipulation of appetite for clinical benefit and causal issues beyond appetite with an opening lecture from John Blundell (University of Leeds). The meeting will then conclude by looking at possible remedial interventions and the impact on society. Roy Taylor (Newcastle University) will open the day with a lecture entitled 'Reversing type 2 diabetes to normal: The impact of the personal fat threshold'. On the final day, The Society will be hosting outreach activities at Newcastle United, further information for which can be found at **www.physoc.org/obesity2014**

There will also be a Society Dinner taking place on Thursday 11 September, a great chance for delegates to network and have an enjoyable evening out on 'The Toon'.

Plenary lectures:

Steve Bloom (Imperial College London, UK)
Mark Walker (Newcastle University, UK)
John Blundell (University of Leeds, UK)
Roy Taylor (Newcastle University, UK)

Confirmed speakers include:

Marietta Charakida (Great Ormond Street Hospital for Children, UK)
Jennifer Logue (University of Glasgow, UK)
Frank Reimann (University of Cambridge, UK)
Alexander Miras (Imperial College London, UK)
Marco Bueter (University of Zurich, Switzerland)
Francesco Rubino (King's College London, UK)
John-Olov Jansson (University of Gothenburg, Sweden)
Jonathan Johnstone (University of Surrey, UK)
Grahame Hardie (University of Dundee, UK)
Mirko Trajkovski (University College London, UK)
Lucilla Poston (King's College London, UK)
Tony Lam (Toronto General Research Institute, Canada)
Amanda Daley (University of Birmingham, UK)
Susan Ozanne (University of Cambridge, UK)
Amandine Everard (Université catholique de Louvain, France)
Julian Mercer (University of Aberdeen, UK)
Isabelle Szmigin (University of Birmingham, UK)
Mike Lean (University of Glasgow, UK)
Amelia Lake (Durham University, UK)

Registration is now open, to register and for further information about the meeting please visit: **www.physoc.org/topicobesity**

Register before 11 August 2014 for reduced rates.

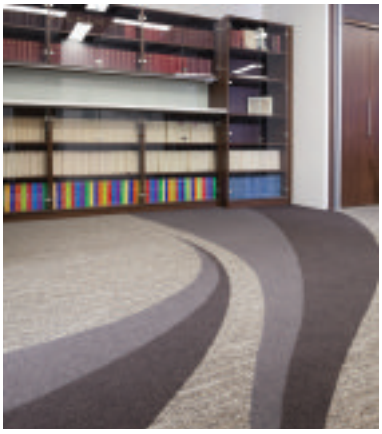
Abstract submission will open on 13 June and close on 11 July 2014, poster communications are welcome.

Call for 2015 Topic Meeting symposia proposals

We are calling for proposals for symposia for the 2015 Topic meeting on 'Ageing and Degeneration' The Society is running in partnership with *The Journal of Physiology*, please visit **www.physoc.org/suggest-symposium#Ageing** for further information and to submit your proposal (deadline 31 March 2014).





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Meeting Notes

Calcium signaling in Health and Disease

19-24 September 2013
Kiev, Ukraine

Ganna Tolstanova

Taras Shevchenko National University of Kiev

Taras Shevchenko National University of Kiev hosted the 2nd Annual Undergraduate International School in Biomedical Sciences, entitled 'Calcium signaling in Health and Disease'. This event was supported by The Physiological Society Representatives fund.

Students from Ukrainian universities had a great chance to listen to lectures delivered by prominent scientists from the UK, USA, Thailand and Ukraine. Students also took part in workshops and presented their data at a poster session. Three of the best physiology-related poster presentations were chosen for PhySoc prizes, with international lecturers acting as referees.

What was said...

"This is an unusual school for the medical community that I am in – talking about scientific challenges and education, especially with specialists from overseas universities. Lecturers discussed molecular principles of calcium signalling. Workshops on confocal microscopy and tips on scientific writing and talking were both intelligent and amusing. The poster session was the most pleasurable event, because of the absence of a sense of competition, despite of having a jury talking to you, asking questions, giving advice. It was a nice opportunity to talk with people who are interested in your work. I am very glad that such events are taking place and becoming a tradition in our scientific students' community thanks to PhySoc and the organizing committee."
Vlada Bokii, 1st prize in the poster competition (Bogomolets National Medical University, Kiev)

"The most impressive thing was the willingness of the students to engage in both asking and answering questions. This really energized the tutorial sessions, some of which had to be stopped as they were overrunning because of the students' enthusiasm to participate and learn..."
Graham McGeown, Queen's University Belfast, UK

From left to right: Jonathan Ashmore, Roddy Large (one of the organisers of the Early Career Physiologists Symposium), Noel McHale, Siobhan Hendrick (Winner of the Oral Communication Prize) and Brian Harvey

Meeting Notes

Epithelia and Smooth Muscle, Interactions in Health and Disease – Physiological Society Joint Themed Meeting

11–13 December 2013
Dublin Convention Centre, Republic of Ireland

Roddy Large

Dundalk Institute of Technology, Ireland

As the festive season got underway in Dublin, a group of physiologists descended on what would be a very enjoyable and informative few days. From 11 to 13 December, The Dublin Convention Centre was the venue for The Society's *Epithelia and Smooth Muscle, Interactions in Health and Disease* Joint Themed Meeting.

Preceding the meeting was an early career physiologists' symposium, held in the magnificent Royal College of Surgeons on Dublin's St Stephen's Green. This meeting was well attended, with around 50 young physiologists presenting some fascinating work on ion channel transport and its role in health and disease. Invited speakers, Olivier Soriani, Michael Gray and Thomas Jentsch, had the audience enthralled with talks covering cancer cell electrical activity, CFTR bicarbonate secretion and the roles of both Cl^- and K^+ in sensory functions. The standard of presentations was extremely high with James Reihill (Queens University Belfast) and Karen Hannigan (Dundalk Institute of Technology) sharing the oral communication prize sponsored by Andor Technology.

The meeting, organized by Brian Harvey (Royal College of Surgeons Ireland) and Noel McHale (Dundalk Institute of Technology), aimed to bring together those working in epithelia and membrane transport, and those focused on smooth muscle physiology. Over the three days we were treated to 14 superb oral communications and 41 poster presentations covering a wide range of topics. We heard the current research in bile acid regulation of epithelial cells, epithelial function in the GI tract, airway, smooth muscle and epithelial physiology, the roles of cation currents in a variety of tissue types and a lot more.

Again, as at the early career symposium, the standard of data on show was extremely high and congratulations must go to Siobhan Hendrick (Royal College of Surgeons Ireland) for Best Oral Communication and Arvind Kshatri (Dundalk Institute of Technology) for Best Poster Presentation.

Plenary Speakers for the meeting were Kim Barret (University of California San Diego) and Kent Sanders (University of Nevada). Kim gave us an insight into 'Epithelial function and dysfunction in the GI tract'. Kent's presentation was, for me, the highlight of the conference. Entitled 'Epithelial–smooth muscle interactions in the regulation of gastrointestinal motility', it was both entertaining and insightful. We were introduced to the concept of a tri-modal interaction between smooth muscle cells, ICC and PDGFRα+ cells, and the role these cellular interactions play in the regulation of GI motility.

I suppose I can't sign off my report without some mention of the Society dinner. I think I'm safe in saying that a great night was had by all. Dinner was held in the Old Jameson Distillery, where, upon arrival, delegates were treated to a tour of the distillery before being invited to try a glass (or three) of Jameson Irish Whiskey. A delicious dinner was followed by a night of entertainment. Delegates joined in a singsong of some classic Irish songs and traditional Irish dancing. For some the night ended here and for others it was only just the beginning.

In conclusion, the organizers should take a lot of credit for what was a really enjoyable meeting and I'm sure that it was a huge success in terms of their aims of stimulating and generating new research ideas and collaborations.

Meeting Notes

The AHA Scientific Sessions 2013

16–20 November 2013,
Dallas Convention Center, USA

Jonathan Goodchild
The Physiological Society

The American Heart Association's Scientific Sessions of 2013 were held in the Dallas Convention Center. That week in November marked the 50th anniversary of the death of JFK, and it was but a short walk to the white X in the road below the former Book Depository. On a cheerier note, 'Wild Bill' was in the exhibition hall itself to fit people out with cowboy hats; at the pub next to his downtown store they had wonderful smoked steak and black beer; and there was an exhibition of Edward Hopper's drawings at the Museum of Art.

The Physiological Society had a stand along the main aisle of the exhibition hall, and few could have missed *The Journal of Physiology* logo emblazoned on the backdrop. To publicize *The Journal* to cardiovascular physiologists, both the Editor-in-Chief, David Paterson, and Deputy Editor-in-Chief for Europe, Julian Paton, were there to talk to potential authors.

Especially for the meeting, the 1 September issue of *The Journal* was dedicated to the subject of cardiac arrhythmia (bit.ly/17azzJn), and featured a historical item on one of the pioneers, George Ralph Mines. We gave away a stack of them and when they'd gone we handed out leaflets about it. Leaflets also advertised an online-only collection of classic cardiovascular papers published in *The Journal* over the past century and a quarter (bit.ly/JPCARDIAC), and a historical display in a glass case featured volumes of *The Journal* open at three of them, by George Mines, Ernest Starling (the 'law of the heart' paper) and August Krogh (one of his Nobel Prize-winning series).

The Society's stand and the Editor-in-Chief and Deputy Editor-in-Chief for Europe with Wild Bill

The stand also had publicity material for The Society and its other two journals: on the first morning the delegates came in droves for the free notepads, pens and bags, and stripped it bare. With renewed stocks of pads and pens, from here The Society and its journals go on to EB2014 in San Diego in April.

Meeting Notes

Young Investigators Symposium, European Muscle Conference

21 September 2013,
Felix Meritis, Amsterdam,
The Netherlands

Josine de Winter & Rob Wüst
Department of Physiology,
VU University Medical Center,
Amsterdam, The Netherlands

Although the meeting was called the '*European* Muscle Conference', people from all corners of the world gathered in Amsterdam for an exciting meeting on muscle physiology. Together with the help of some travel grants, scientists from Brazil, Australia, South Africa, South Korea and the USA were able to present their work in a World Heritage Canal House: Felix Meritis – 'Happy through Merit'. The venue was constructed in the late 18th century to provide a meeting point between 'enlightened' scientists and artists. As such, the location perfectly matched the aims of the meeting.

Co-sponsored by The Physiological Society, a satellite Young Investigators Symposium was held on Saturday 21 September 2013. We were happy to welcome over 120 young (and more senior) scientists to this 'pilot event' before the start of the EMC conference. David Eisner started the afternoon with an entertaining presentation about how to become successful in science. He emphasised that science is fun and you should follow your own dream, but not become a hermit!

His presentation was followed by a moderated panel discussion with David Eisner, Karin Sipido, Jill Tardiff and Pieter de Tombe. Questions from the audience on topics like 'what to do after your PhD' and 'work–life balance' were vividly answered by the experienced panel. After this, three young investigators presented their work, followed by an interactive discussion in a friendly atmosphere.

During the subsequent four days of the European Muscle Conference, which had the theme 'moving into translation', many young investigators were given time to present their work in an oral presentation. The poster room, located in the old library room overlooking the canals, was the perfect location for lively and friendly discussions on the latest developments in muscle physiology. Oral prizes were awarded to Steve Hunter (UK), Benedetta Tosi (Italy), Arpad Kovacs (Hungary) and Claire Latroche (France). Poster prizes were awarded to Charles Jung (USA), Svitlana Pasteuning (Netherlands), Silva Bogaards (Netherlands) and William de Assis Silveira (Brazil). We are grateful to Springer and Digital Printing Partners for their sponsorship of these prizes.

Given the feedback from young and old participants, we can conclude that the 'pilot' of bringing young scientists into the core of the EMC conference has been very successful.

We are looking forward to seeing you all at the Young Investigators Symposium at the 2014 EMC conference in Salzburg, Austria!
www.emc2014.com

Teaching and research in physiology in Sub-Saharan Africa: achievements and challenges

Sub-Saharan Africa faces many challenges when it comes to teaching and research in physiology, but efforts are being made to play 'catch up'. A clear vision is in place to give assistance to Sub-Saharan Africa's physiologists, aiming to keep competent and willing researchers in the country so they can contribute meaningfully to global scientific enterprise.

Soga Sofola

University of Lagos, Nigeria

The history of teaching of physiology in Sub-Saharan Africa (SSA) is a fairly recent one, the earliest having been in the University of Cape Town (Republic of South Africa – RSA) in 1912, Pretoria (RSA) in 1943, Makerere (Uganda) in 1924, University College, Ibadan (Nigeria) in 1948, and Zimbabwe in 1952. There are about 168 Medical Schools in SSA with 26 in Nigeria and eight in the Republic of South Africa (Mullan *et al.* 2011).

Teaching of physiology has traditionally been domiciled in medical schools with the majority using the traditional face-to-face method due largely to limited resources. One notable exception is the Republic of South Africa, which we in Nigeria refer to as a 'European country located in Africa'. Our teaching methodology largely utilizes the white board and overhead/multimedia projectors. Many schools are beginning to incorporate some information and communications technology (ICT) components into their teaching, e.g. with use of videos, YouTube and electronic blackboard.

However, we can claim some achievements as several physiologists have been trained in SSA, despite limited resources, though many have 'brain drained' to developed countries. In addition, we have contributed to the training of many of the 145,000 doctors, as of 2011 (Mullan *et al.* 2011) as well as recording some modest achievements in training of PhDs that have helped to reinforce the system. The majority of faculty staff have obtained their PhD locally. Despite the constraints, many institutions are increasing student intake (Mullan *et al.* 2011). Many schools surveyed (personal questionnaire of 25 schools from 10 countries in geographical zones of west, central, east and southern African states) have student enrolment ranging from 20 to over 600 while the number of lecturers ranges between two and 18, to cope with a large workload, with over 50% having a PhD or MD degree. In the survey, post-graduate students enrolled for training in MSc/PhD programmes range from nil to about 30 while post-graduates produced cumulatively in the last 5 years range from nil to 20, per school, the larger numbers being from South Africa and the older universities in Nigeria.

The major constraint is funding. Most universities in SSA depend on government subsidies with little donor support. The issue is not helped by governments pegging tuition fees as well as poor staff salaries (Mullan *et al.* 2011). It is estimated that funding for tertiary education can be as low as $1000 per student in about 10% of countries (UNESCO, 2009), while the majority have per student funding in the range of $1800 to $4000 (Moyer, 2007). It is only recently that some universities have embarked on the use of Income Generating Units (IGUs) or charge high tuition fees so as to raise additional funds which can account for up to 56% in Uganda (UNESCO, 2009)

Other issues related to teaching challenges include but are not limited to the following:

- Limited number of PhD holders as lecturers. This is mainly due to low production rates,

A large group of students in Lagos in a practical class demonstration, with one item of equipment.

"Several physiologists have been trained in Sub-Saharan Africa, despite limited resources, though many have 'brain drained' to developed countries"

as a result of low number of supervisors/ advisors.

- Low lecturer:student ratio and large classes, resulting in non-ideal lecture rooms and facilities as well as poor supervision during practical classes. An example of a large practical class with few teachers and limited equipment is shown in the above image. Recently, there have been efforts to acquire digital, teaching/practical platforms such as ADI PowerLab and WPI DataQ instruments, though very few are available (only about one or two pieces).

- Outdated and inadequate textbooks due to unaffordable costs, e.g. the cost of an imported textbook is about the monthly living allowance of an average student in Nigeria. There is now the alternative of locally authored textbooks, which are affordable, but not necessarily current in content.

- Limited ICT/internet facilities for lecturers to engage students in out-of-class teaching. This is because access is poor and expensive. Many universities cannot afford the cost of internet bandwidth and students and staff often have recourse to internet cafes, at high cost.

- Outdated curriculum: this is rampant in many SSA universities, due to lack of exposure of lecturers to foreign science and hence the inability to update their course contents. However, some universities are now reviewing their curricula and embracing such approaches as Problem Based Learning, e.g. Ibadan (Nigeria) and Sudan.

- Poor and erratic power supplies are prevalent in majority of countries which make running classes difficult, especially for long duration projects.

As for research, with the exception of South Africa, the output from the region is very low, in terms of publication in indexed journals. It has been estimated that SSA contributes less than 0.9% to global published work, with South Africa contributing over half of that (UNESCO, 2009). In a report covering the decade 1995–2004, the top three publishing countries, in terms of output of published works, indexed in PubMed, from medical schools in SSA, are South Africa (41.5%), Nigeria (16.1%) and Kenya (6.8%) (Hofman *et al.* 2009). An analysis of university rankings bears this out as the highest ranked university from SSA is University of Cape Town at 113. Only five African universities are in the world's top 1000 (THE, 2013). This was not the case in the 1970s when some African universities featured among the topmost institutions in the world.

The obvious reason for the low research output is poor funding and thus fewer resources for acquiring appropriate equipment for research. There are hardly any grants for research except in South Africa and one or two other countries, e.g. Nigeria. where the Tertiary Education Trust Fund, which is contributed by the business community, is now being used to fund research grants and postgraduate

Sub-Saharan Africa is the land mass extending below the Sahara desert, and thus excluding countries in the north of Africa. This comprises 47 countries with a total population of about 886 million

"Efforts are being made to play 'catch up' "

An aged Grass Polygraph Model 7D recorder, with organ baths, which we use for our isolated aortic ring experiments.

training. The poor funding in SSA is reflected in the quality of articles, which lack mechanistic approaches with little or no cellular or subcellular mechanisms. This is in contrast to what appears in papers in journals from the developed world, e.g. *The Journal of Physiology*, where a considerable number of articles are largely biophysical, molecular and translational (Paterson *et al.* 2013).

However, efforts are being made to play 'catch up'. For example, our laboratory has been studying the effects of high salt diet on vascular mechanisms, using rat aortic rings. Our earlier results were later confirmed using the pressurized mesenteric artery preparation (Sofola *et al.* 2002) during the author's appointment as a British Heart Foundation Fellow at Leeds University. However, on return to Nigeria, such facilities were not available but we are still publishing using the ring preparation (Oloyo *et al.* 2012) although we have recently acquired digital recorders for research work with better results (unpublished). The image above shows our old faithful, the Model 7D Grass polygraph, which we are currently using. Our subsequent studies, however, have been carried out investigating the role of the renal epithelial sodium channel (ENaC) in normotensive and hypertensive Nigerians (S. O. Elias, PhD thesis, Lagos, 2012) while collaborating with foreign laboratories for DNA sequencing and identification of genetic mutations. We hope that this foray will open new grounds and attract more graduate students to genetic and molecular aspects of physiology as well as allow us to establish some laboratory space for such research.

Other challenges relating to research include:

- Heavy teaching load, mentioned earlier, with too many students and too few teachers and hence little or no time for research work.
- Outdated equipment and little availability of reagents and consumables for research projects due to very low budgets, which is very prominent in most universities in SSA with the possible exception of South Africa. This is compounded by low currency exchange rates in most of our countries as a result of devaluation, as well as political instability.
- Low PhD production, also exacerbated by in-breeding due to inability to send our students for exposure to foreign laboratories due to funding constraints.
- Lack of, or limited access to, journals, which is worsened by high costs as well as low access to free e-journals (except mostly back issues from Highwire Press–Stanford and Hinari). Availability of full text of current issues in PubMed apparently is less than 20%.

- Brain drain from SSA, as a large percentage, about 20–30%, of graduates are lost from the profession, with about 30% leaving the continent for better pay and better access to research facilities while others go to the ministry or the private sector (Mullan *et al.* 2011).

Appeal for Support

This brings up the point of how we in SSA (except perhaps South Africa) can leverage on the superb research facilities, more like those in the developed countries. It will also need to involve the exposure of our staff to research at cellular and subcellular levels including cell signalling as well as translational research in line with current trends.

Thus, an appeal is being made to the IUPS to come to the aid of SSA. As the way forward, some suggestions are:

- Provision of sabbaticals for nationals of SSA to laboratories in the developed countries where they can acquire requisite skills that are in demand.
- Provision of laboratory space for research training/mentoring and skills acquisition by our younger colleagues in order to increase their research capabilities.
- Initiation of technology transfer workshops by experts from the IUPS or its affiliates, from the developed world. In 1980, the IUPS organized such a workshop in Lagos, supervised by Profs Otto Hutter, Lawrence Smaje and John Patrick. This attracted lecturers from the West African subregion. In addition staff from institutions in SSA can go to developed countries for a duration of 6–12 months for hands on experience, on more frequent arrangements. A few of these initiatives exist which are limited or not widespread and more will be required.
- A mechanism for equipment transfer through donation of 'surplus to requirement' but useful equipment to universities in SSA. For example, establishing a 'warehouse' system in the IUPS and affiliates, for donation of equipment and transfer of such to interested laboratories in SSA.
- Funding/grants to be made available to identified research-active laboratories, doing some good work, so as to scale up their researches. This can be tagged on to the Association of African Physiological Sciences (AAPS), which can then initiate South–South research collaboration to increase the internal pool of active African researchers.

The theme of these and other suggestions is to give assistance to SSA physiologists to boost teaching and research capabilities and thereby improve on the present dismal situation. This should also serve to arrest the brain drain and make competent and willing researchers remain in their country and contribute meaningfully to global scientific enterprise.

In conclusion, it is hoped that this article will make us in Sub-Saharan Africa more visible on the world map of scientific enterprise in the subject of physiology.

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"Teaching of physiology has traditionally been domiciled in medical schools with the majority using the traditional face-to-face method due largely to limited resources."

Have the carotid chemoreceptors anything to do with the control of breathing during exercise in man?

In man, breathing matches (or exceeds) metabolic rate (the rate of oxygen consumption) from rest to maximum exercise. How the brain achieves this remains one of the biggest unanswered questions in physiology.

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The traditional belief is that breathing matching metabolic rate is somehow controlled by the carotid chemoreceptors in man. Yet since their discovery around 80 years ago, experimental evidence has consistently failed to support this. The carotid chemoreceptors are in the wrong anatomical location to detect metabolic rate, receive no known signal linking them to metabolic rate and their denervation has remarkably little effect on breathing matching metabolic rate. Intriguingly in 2014 we still remain unable to establish either that they control or that they do not control breathing matching metabolic rate during exercise in man.

"Might we make more progress over the next 80 years if we started to question this belief overtly, rather than just continuing to accept and to propagate it?"

The carotid chemoreceptors are located bilaterally at the bifurcation of the common carotid arteries and connected to the brain via a branch of the glossopharyngeal nerve (IX). Directly stimulating them causes an immediate increase in breathing. Their principal stimuli are arterial hypoxia, hypercapnia or acidaemia. Moreover they are thought to be the only chemoreceptors in man that can detect hypoxia to stimulate breathing (because patients without them fail to increase their breathing in hypoxia). Their discovery in dogs in around 1927 was believed to be so fundamental that it won Corneille Heymans the Nobel Prize in Physiology or Medicine in 1938. It was believed to be only a matter of time before their fundamental role in controlling breathing would be established in man. Yet such experimental evidence consistently fails to materialise.

It is reasonable to assume that one continuous process explains breathing matching metabolic rate from rest to maximum metabolic rate and the easiest way to establish that breathing is matching metabolic rate is from the stability of arterial blood gas levels. To establish if the carotid chemoreceptors have any role in this matching, classical scientific method (Stein & Stoodley, 2006; Parkes, 2013) would seek to obtain positive results with the following three key experimental approaches:

- stimulation (their stimulation at rest should be able to mimic the minute ventilation levels of maximum exercise)
- ablation (their destruction should abolish matching and prevent minute ventilation ever rising appropriately during exercise)
- recording (their afferent nerve discharge should always be proportional to metabolic rate – from rest to maximum exercise)

If carotid chemoreceptors are important, the effects of stimulation and ablation might be detectable at rest, but should be most obvious at the highest metabolic rates. Moreover their role should be particularly easy to see in humans. This is because it is easy to ask humans to exercise at maximum metabolic rate and because in humans only one set of peripheral chemoreceptors – the carotid chemoreceptors – mediate the hypoxic ventilatory response. In contrast, such experiments are much more difficult in other species, where measurements at high

metabolic rates are rarely attempted and the existence of multiple peripheral chemoreceptors mediating the hypoxic ventilatory response makes denervation experiments much harder to undertake and to interpret.

If the carotid chemoreceptors have no role in matching, the above experiments should show no effects (i.e. their results would be negative). Unfortunately, whereas appropriate positive results are essentially self-validating, it is much more difficult to validate negative results. Either the negative experiment was in some way inadequate (e.g. poorly controlled with insufficient numbers), or multiple control factors exist, or it is genuinely negative because the ablated factor has no role.

Since 1927, the difficulty has always been in how best to interpret the essentially negative results of the above three key experimental approaches with carotid chemoreceptors in man.

Recorded arterial blood gases fail to change appropriately during exercise

Figure 1 (Sun *et al.* 2001) shows no substantial rise in arterial P_{CO_2} (P_{aCO_2}) during exercise in man. Indeed it actually falls during more severe exercise. Similarly no consistent fall in P_{aO_2} has ever been measured at maximum exercise (and the occasional observed falls are insubstantial). So how can the carotid chemoreceptors ever 'know' what metabolic rate is? These facts have been known in outline since before the carotid chemoreceptors were discovered. Yet increasingly better recording experiments are still published in case something different might appear. Are these negative results definitive? Investigation of more subtle functions of P_{aCO_2} too has failed to reveal anything useful (CO_2 oscillations apparently disappear and CO_2 sensitivity fails to rise sufficiently – or at all – during exercise (Parkes, 2013)). Yet some new function of arterial blood gases, or some new arterial chemoreceptor stimulant might still be found (or not, if they do not exist!).

Figure 2 shows that carotid chemoreceptors in man are actually in completely the wrong location to measure metabolic rate. It has been known since the 1920s that it is systemic venous blood gas levels that change in proportion with metabolic rate (and see Fig. 1). But systemic venous chemoreceptors have not yet been found in man and the search for them seems to have been abandoned many years ago.

Carotid chemoreceptor 'stimulation' in man fails to achieve the breathing of maximum exercise

In man it remains impossible to stimulate carotid chemoreceptors directly, but hypoxia and hypercapnia are their well-known

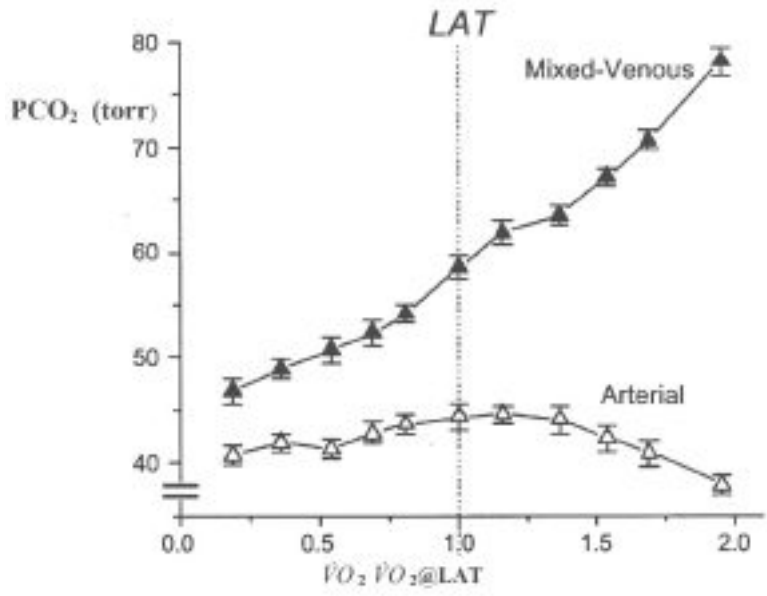

Figure 1. P_{aCO_2} fails to rise above the normal range during exercise (unlike P_{vCO_2}). Mean ± SEM P_{aCO_2} (brachial artery) and mixed venous P_{vCO_2} (pulmonary artery) during incremental exercise to maximum, normalized to their mean lactic acidosis threshold – LAT – of 2.0 ± 0.0 L O_2 min^{-1}. (0.7 kW) in 5 healthy subjects. From Sun *et al.* (2001).

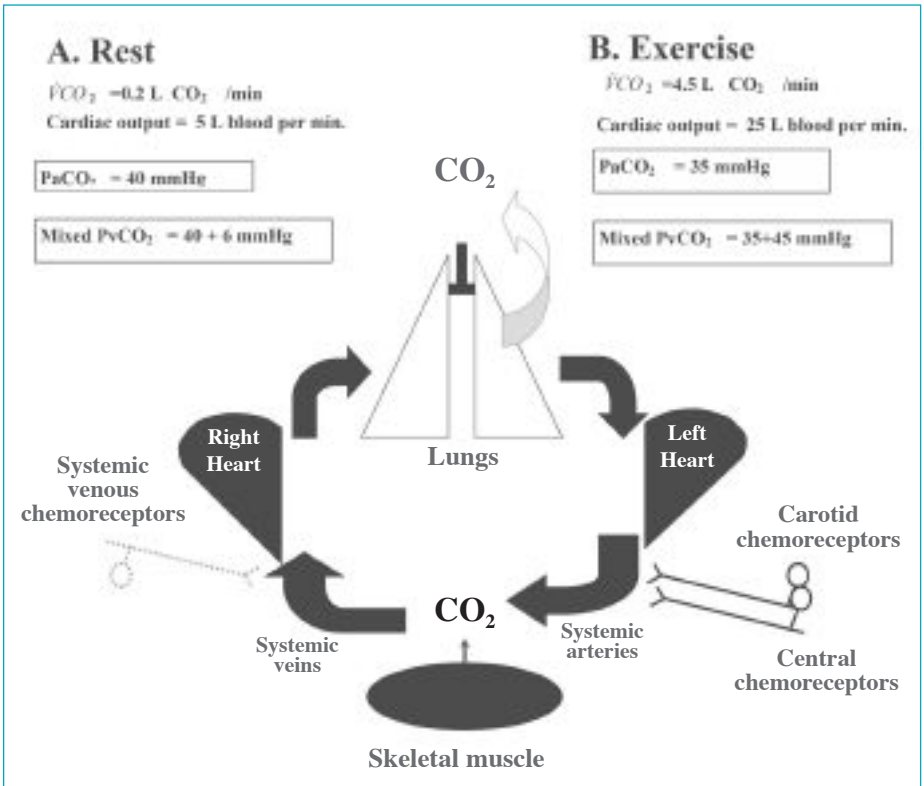

Figure 2. Systemic arterial chemoreceptors are anatomically in the wrong location to measure metabolic rate or metabolically produced CO_2. Diagram of typical values of systemic arterial P_{aCO_2} and mixed P_{vCO_2} at rest (*A*) and maximum exercise (*B*), with data from multiple sources. For clarity, the corresponding numbers for metabolic rate are omitted. Comparison of *A* and *B* shows that systemic arterial chemoreceptors are in the wrong place to measure metabolically produced CO_2, because metabolically produced CO_2 is carried via the systemic veins from muscle to air without P_{aCO_2} rising. Reproduced with permission from Parkes (2013).

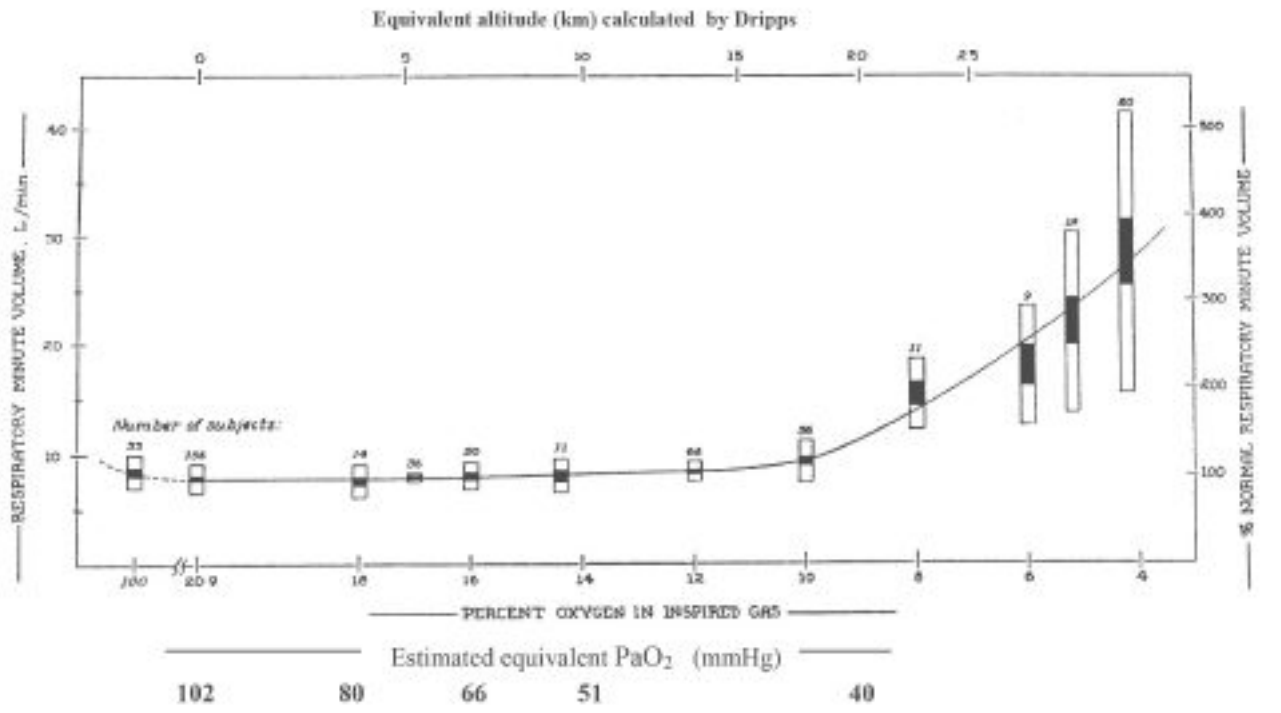

Figure 3A Relative insensitivity of breathing at rest to artificially lowering P_{O_2} in man. Minute ventilation (±SEM filled bars, ±SD open bars) in normal subjects as inspired oxygen is artificially lowered (strictly hypocapnic hypoxia exists once hyperventilation occurs). Equivalent P_{aO_2} points are aligned on the F_{IO_2} scale, with P_{aO_2} estimated before hyperventilation occurs using the alveolar gas equation (assuming 760 mmHg barometric pressure, RQ= 0.8, $P_{aO_2} = P_{AO_2}$ and $P_{aCO_2} = P_{ACO_2}$) and the point afterwards is estimated based on dynamic forcing experiments in isocapnia (courtesy of G.A. Balanos). From Dripps *et al.* (1947).

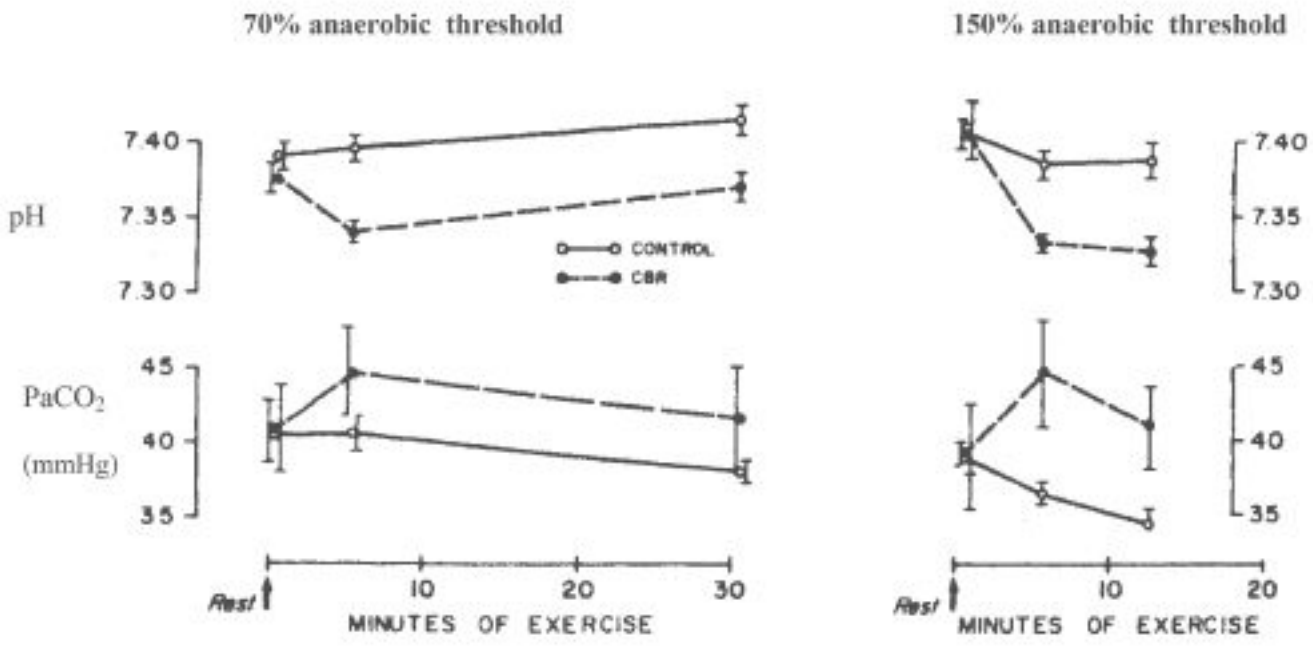

Figure 4. Breathing appears to match metabolic rate during exercise after carotid chemoreceptor denervation in man. Five to eleven controls at 70% (53 ± 7 Wew) or 150% (109 ±9 Wew) anaerobic (lactic acidosis) threshold and 5–6 carotid denervated subjects at 70% (52 ± 7 Wew) or 150% (98 ± 17 Wew) anaerobic threshold during constant load bicycle ergometry. Mean ±SEM pH and P_{aCO_2} in controls (open circle with continuous line) and denervated (filled circle with dashed line). Mean resting P_{aCO_2} in controls was 38 ±2 mmHg and in denervated was 39 ±3 mmHg. From Wasserman *et al.* (1975) with permission.

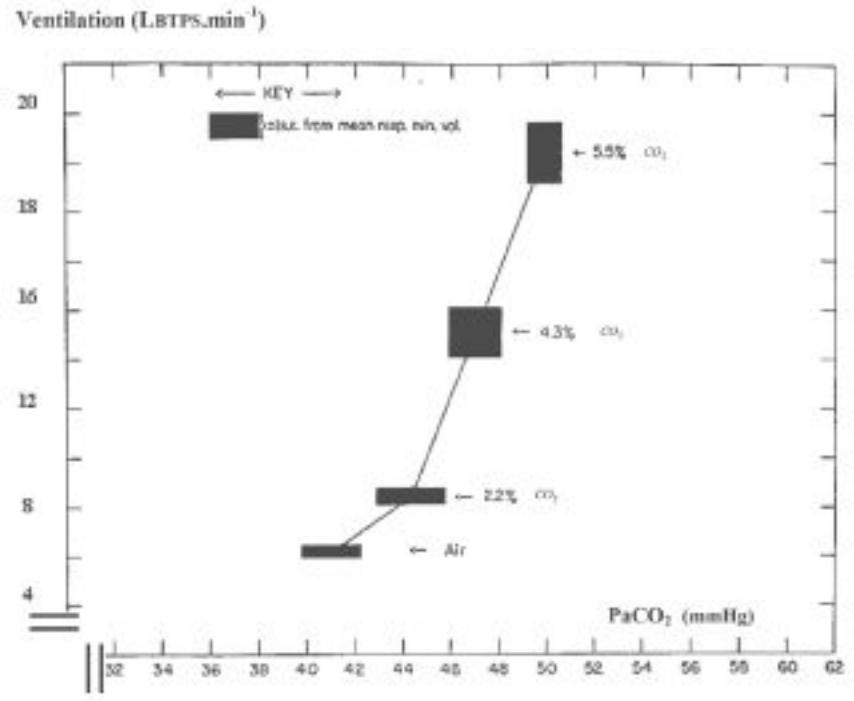

Figure 3B. Sensitivity of breathing at rest to artificially raising P_{aCO_2} in man. Minute ventilation, and P_{aCO_2} (femoral) in 8 healthy men while inhaling 0–6% CO_2 in air at atmospheric pressure (mean slope is 2.5 litres min^{-1} $mmHg^{-1}$ artificial P_{aCO_2} rise). From Lambertsen *et al.* (1953).

stimulants. Figure 3*A* and *B* (Dripps & Comroe, 1947; Lambertsen *et al.* 1953) shows how good these are at stimulating breathing to the levels seen at maximum exercise (100–150 litres (BTPS) of air per minute). Breathing ~6% oxygen achieves only ~20 litres (BTPS) of air per minute and with any more severe hypoxia, humans start to pass out. Similarly even breathing ~7% CO_2 achieves only ~40 litres (BTPS) of air per minute. It can be argued that by breathing more severely hypercapnic gases, or even by combining this with hypoxia (i.e. breathing asphyxiating gas mixtures), greater breathing levels could be achieved. But this seems pointless since such asphyxiating arterial blood gas levels do not occur during exercise.

Carotid chemoreceptor ablation barely changes matching during exercise

If the carotid chemoreceptors were solely responsible for matching in man, then it might be expected that ablating them bilaterally would have major effects on blood gas levels at rest and catastrophic effects during exercise. Breathing and hence blood gases might become so unstable that other responses might be triggered (Parkes, 2013), e.g. unconsciousness at P_{aO_2} levels below ~25 mmHg and/or P_{aCO_2} levels above about 90 mmHg, or hypocapnic tetany at P_{aCO_2} levels below 20 mmHg (hyperoxia being innocuous in the short term).

Figure 4 (Wasserman *et al.* 1975) shows how little the matching of breathing with metabolic rate is disturbed (i.e. how relatively stable is P_{aCO_2}) during exercise in patients with bilateral carotid chemoreceptor denervation. (Compare the P_{aCO_2} levels in Fig. 4 with those required to stimulate breathing in Fig. 3*B*). Even if the data in Fig. 4 are accepted as evidence that there is a small change in P_{aCO_2}, we still do not know whether this change was caused by their asthma or by the denervation (because the controls were different subjects, not the same patients before and after denervation).

Intriguingly this negative experiment (denervation making such a small difference) has never been accepted as evidence that carotid chemoreceptors have no role. This is despite the accompanying negative evidence from the above recording and stimulation experiments. This result has always been interpreted instead as showing that carotid chemoreceptors still do control breathing during exercise, but something else too is equally important and can immediately take over! In fact we cannot yet distinguish between these two interpretations, so the correct conclusion of this negative ablation experiment so far is 'inconclusive without further investigation'.

Conclusions

The unquestioned belief in Heymans's carotid chemoreceptors has always trumped the experimental evidence in man that has been obvious ever since. And intriguingly, because of the difficulty in validating negative results, neither can we establish definitively that this belief is wrong!

Suppose one day we might be able to record the afferent activity from the carotid chemoreceptors in man. If it fails to change in proportion to metabolic rate, then we know finally that this belief is incorrect. If it does increase with metabolic rate then we know that all the negative stimulation and ablation results to date are false.

Has this belief really served us so well over the last 80 years that it should continue to be propagated without question in some textbooks, reviews and scientific papers? It may well have done no harm in the sense that it may never have killed a patient nor helped anyone win (or lose) a race. But might it also be preventing recognition of inconveniently novel hypotheses? Might we make more progress over the next 80 years if we started to question this belief more overtly, rather than just continuing to accept and to propagate it?

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A portal to pain: the transient receptor potential (TRP) vanilloid 1 channel

With a role in several pathophysiological conditions and its location in sensory neurons that respond to harmful stimuli, the non-selective ion channel TRPV1 has become a target for the control of pain. It is important to determine what regulates the function of TRPV1 for the development of new pain therapies.

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Pain is an unpleasant physiological and emotional response that is commonly associated with tissue damage. Although the sensation of pain may be useful in avoiding re-injury, in general, people obviously want to avoid being in pain. Therefore research based on finding new therapeutic targets for the treatment of several diseases and the pain resulting from them has led to the discovery of various molecular regulators of ion channels that are found in neurons and whose activation will result in pain (reviewed in Julius & Basbaum, 2001). Among these channels are TRPV1, a member of the transient receptor potential (TRP) superfamily of ion channels. TRPV1 is a non-selective ion channel activated or modulated by diverse noxious stimuli such as high temperatures, changes in acidity, capsaicin, the pungent compound in chili peppers, and certain molecules released during tissue damage and inflammatory processes (Rosenbaum & Simon, 2007). Due to its role in several pathophysiological conditions (see below), TRPV1 has become a target for the control of pain. This is because it is found in sensory neurons (nociceptors) that respond to noxious or harmful stimuli. Below we outline several of the recently described endogenous small molecules that have been found to regulate the function of TRPV1 and therefore regulate the physiology of nociception or the way neurons process noxious stimuli.

TRP channels are gateways to our senses

TRP channels are found in organisms ranging from worms to humans. Their discovery has revealed them to be critical in the peripheral events in sensory physiology including osmotic regulation, calcium homeostasis, pain and inflammation, photoreception, taste, and thermosensation (reviewed in Nilius & Owsianik, 2011).

There are seven known TRP subfamilies and six of them are present in humans (reviewed in Palazzo *et al.* 2013): TRPC ('canonical'), TRPA ('ankyrin'), TRPM ('melastatin'), TRPML ('mucolipin'), TRPP ('polycystin') and TRPV ('vanilloid'). The TRPN ('no mechanoreceptor potential C') channels are found in *Xenopus laevis*, *Danio rerio* and *Drosophila melanogaster*, but not in mammals (reviewed in Palazzo *et al.* 2013).

All TRP channels are tetramers composed of subunits with six transmembranal domains (S1 to S6), intracellular N- and C-termini and a region between the S5 and S6 domains that gives rise to the conduction pathway or

Receptor	Temperature threshold for activation	Agonist
TRPV1	≥42°C	Capsaicin/Allicin/Ginerol/Eugenol/Camphor/THC/ Protons/Lipids Osmolality (hyper), stretch
TRPV2	≥52°C	2-APB Osmolality (hypo), stretch, shear stress
TRPV3	>33°C	Camphor/Gingerol/Zingerone/Carvacrol/Eugenol/ Thymol/2-APB/FPP
TRPV4	>25°C	Osmolality (hypo), shear stress
TRPM2	>35°C	ADPR/H_2O_2
TRPM3	~20-30°C	Osmolality (hypo)
TRPM4	~15-35°C	Ca^{+2}/Stretch
TRPM5	~15-35°C	Intracellular Ca^{+2}
TRPM8	~28°C	Menthol/Eucalyptol
TRPA1	<17°C	Allicin/Cinnamaldehyde/Allylisothiocyanate/Stretch

Table 1. Stimuli that regulate thermo-TRP channel activity. Activating stimuli are indicated for the different channel types. A variety of these compounds are found in plants. Some of these are menthol (a compound obtained from mint oils and eucalyptol); capsaicin (from chili pepers); allicin (from garlic); eugenol (from clove); gingerol and zingerone (from ginger); camphor (from camphor laurel); isothiocyanates (from mustard oil, wasabi and horseradish); cinnamaldehyde (from cinnamon); and carvacrol, eugenol and thymol (from oregano, camphor and thyme). Other agonists include ADPR (adenosine diphosphate ribose); 2-APB (2-aminoethoxydiphenyl borate); H_2O_2 (hydrogen peroxide) and THC (tetrahydrocannabinol from the marijuana plant).

"TRPV1 has been associated with several pathophysiological conditions such as the pain and inflammation generated as a result of ischaemia, angina pectoris, diabetic neuropathy, irritable bowel syndrome, and arthritis and cancer"

pore (Fig. 1A). TRPV1 is a non-selective cation-permeable channel that preferentially allows the entrance of Ca^{2+} into the cell. The currents generated by the opening of this ion channel are of an outwardly rectifying nature. That is, less current is evident at hyperpolarizing (negative) than at depolarizing (positive) voltages (Fig. 1B). TRPV1 has six ankyrin repeats in the N-terminus (green rectangles, Fig. 2) that contain sites for molecules that regulate its activity. Among them are phosphorylation sites and an ATP binding site (reviewed in Szolcsanyi & Sandor, 2012).

A recent structure for TRPV1 was solved using novel cryo-electron-microscopy and it was proposed that the gate (the region that controls the passage of ions through the ion channel when it is opened or closed) is located intracellularly (Liao *et al.* 2013). However, functional data previously obtained by other groups show that a residue located further up in the middle of the pore is the one that exhibits a conformational change during the opening of the pore that can allow (or hinder) the entrance of permeant ions (Salazar *et al.* 2009). Thus, to date, two possible gates have been proposed: one on the basis of a static structure (Liao *et al.* 2013) and another one on the basis of functional data (Salazar *et al.* 2009).

The TRP channel family contains a subpopulation, called 'thermo-TRPs', that respond to changes in temperature (reviewed in Tominaga, 2007). Their threshold temperatures range from 15°C (TRPA1) to 52°C (TRPV2) (Table 1). Importantly, their thermal sensitivity decreases during inflammation. For example, for TRPV1 the threshold temperature is 42°C and it can decrease to 35°C under inflammatory conditions (reviewed in Tominaga, 2007). However, TRPV1 is not the only channel to respond to compounds found in plants. TRP channels respond to a variety of spices some of which are in mustard oil, horseradish, ginger and cloves, as well as menthol and tetrahydrocannabinol (THC), the primary psychoactive constituent of the marijuana plant (*Cannabis*) and others (see Table 1). Thus, their activation of TRPs can cause different types of sensations such as a cooling (TRPM8 with menthol) or a burning sensation (TRPV1 with capsaicin) (reviewed in Tominaga, 2007). Moreover, some of these thermo-TRP channels

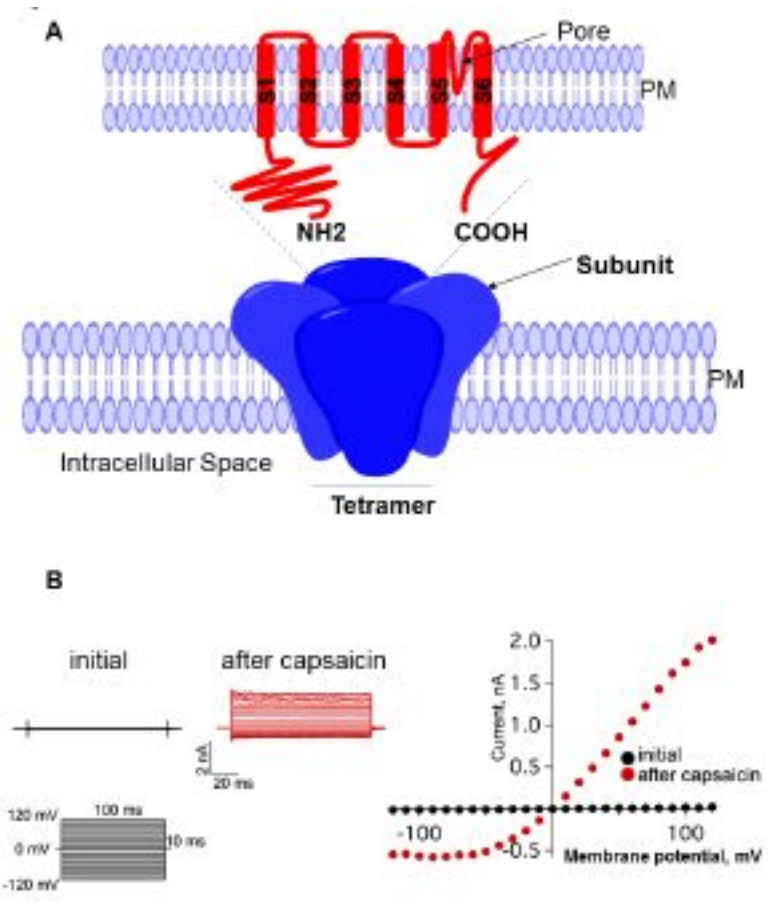


Figure 1. TRP channels are tetramers. A, TRP channels are formed by four subunits (top panel) each of which have six transmembranal domains (S1–S6), with intracellular N (NH_2)- and C (COOH)-termini and a region between S5 and S6 that forms the channel's pore. The union of the four subunits gives rise to the functional tetramer (bottom panel).
B, representative currents from excised-membrane patches from HEK293 cells expressing TRPV1 (left panel) before (black traces) and after the application of 4 μM capsaicin (red traces). The voltage protocol used for these experiments is shown below the traces. Briefly, the holding potential was 0 mV and the voltage was increased from −120 mV to 120 mV with 10 mV increments every 100 ms. The panel on the right shows the steady-state current–voltage relationship generated from the currents on the left illustrating the outwardly rectifying nature of the channel.

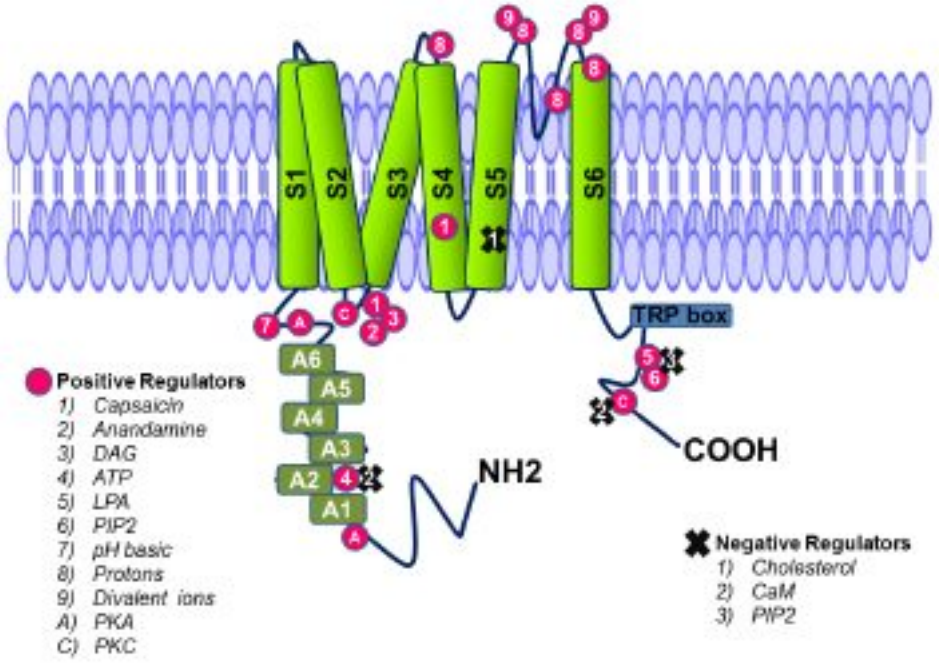


Figure 2. TRPV1: a polymodal ion channel. Shown are the interaction sites for several endogenously (naturally) produced molecules that regulate TRPV1's activity. These are indicated on the cartoon of TRPV1 where the six transmembranal subunits are shown as green cylinders. The code for the numbers and letters is indicated below together with the associated binding molecule. Molecules are characterized as positive and negative regulators of TRPV1 activity. Ankyrin repeats are marked as green rectangles. DAG (diacylglycerol); ATP (adenosine triphosphate); LPA (lysophosphatidic acid); PIP_2 (phosphatidylinositol 4,5-bisphosphate); PKA (protein kinase A); PKC (protein kinase C); CaM (calcium–calmodulin).

(TRPV1, TRPV2, TRPV4, TRPA1 and TRPM3) respond to changes in osmolality and to stretch and shear (frictional force produced by a fluid on a surface) stress (Table 1) (reviewed in Palazzo *et al.* 2013).

Characteristics of TRPV1

At present, the best-studied member of the 'thermo-TRP' group of channels is TRPV1. In the peripheral nervous system it is expressed mainly in small unmyelinated neurons from dorsal root (located throughout the body), nodose (in the viscera), and trigeminal (on the face) ganglia. TRPV1 has been associated with several pathophysiological conditions such as the pain and inflammation generated as a result of ischaemia, angina pectoris, diabetic neuropathy, irritable bowel syndrome, and arthritis and cancer (reviewed in Szolcsanyi & Sandor, 2012) and, consequently, has become a therapeutic target for the treatment of pain. TRPV1, like many ion channels, can exist in several states: closed, open and desensitized. In the closed state no ions can flow across the channel whereas they can in its open state. For TRPV1, the desensitized state arises from the increase in intracellular calcium that produces a conformation in which no ions flow across the channel. The activation of TRPV1 by its agonists (see Fig. 1) results in membrane depolarization of the sensory neurons due to the influx of Na^+ and Ca^{2+} into the cell giving rise to the generation of action potentials which, when they reach the cortex, are interpreted by the central nervous system as pain. In the continued presence of a TRPV1 agonist, an interesting phenomenon takes place: instead of pain being present as long as the agonist is present, what happens is that the nerve becomes less sensitive (harder to activate) as a consequence of the rise in intracellular Ca^{2+}, which causes TRPV1 to desensitize. This process is called neuronal 'defunctionalization' and is one of the reasons why TRPV1 is so intensively investigated for relieving pain (reviewed in Jara-Oseguera *et al.* 2008). This is also the reason that creams that contain capsaicin and sold over the counter are used to help subjects that experience certain types of pain.

Endogenous molecules that positively regulate TRPV1 function

Several molecules can regulate the activity of TRPV1 (see Fig. 2). Some of these are of an exogenous nature, such as the compounds found in plants mentioned above (Table 1). Others are endogenous molecules meaning that they are produced in our bodies.

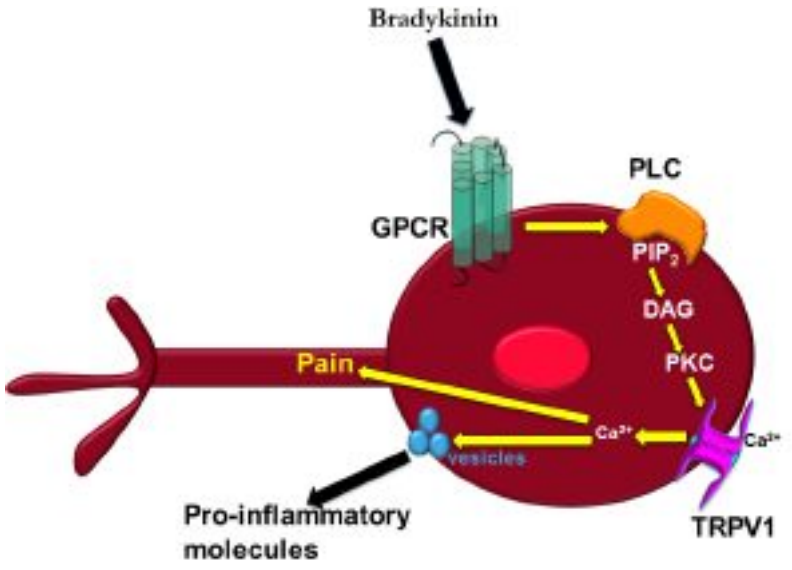
Among endogenous regulators of TRPV1 activity there are several compounds of a lipidic (fatty) nature. Two widely studied positive regulators of TRPV1 are phosphatidylinositol 4,5-bishosphate ($PI(4,5)P_2$ or PIP_2), which is localized to the cytosolic leaflet of plasma membranes and that positively regulates the activation of TRPV1 by capsaicin and diacylglycerol (DAG) (reviewed in Julius & Basbaum, 2001). Both of these molecules bind to intracellular regions of the channel (Fig. 2). DAG is produced as a result of the calcium-dependent activation of phospholipase C (PLC) that catalyses PIP_2, into DAG and inositol trishosphate (IP_3) (Fig. 3). Anandamide (*N*-arachidonoylethanolamine), an endogenous ligand of the CB1 cannabinoid receptor (reviewed in Szolcsanyi & Sandor, 2012), also activates TRPV1 by binding to the same site in the channel as capsaicin (Fig. 2). Thus, as would be expected, other *N*-acyl-ethanolamines (NAEs) such as *N*-oleoylethanolamine (18:1 NAE or OEA) are also positive effectors of TRPV1 activity (reviewed in Morales-Lazaro *et al.* 2013).

Other TRPV1 agonists include several compounds derived from arachidonic acid, which is a polyunsaturated omega-6 fatty acid. These compounds include 20-hydroxyeicosatetraenoic acid (20-HETE), and the lipoxygenase products as hydroperoxyeicosatetraenoic acids (HPETEs) and hepoxilins (HXA3, HXB3) (reviewed in Szolcsanyi & Sandor, 2012). These molecules exert their effects on TRPV1 through the activation of signalling pathways that regulate the channel's activity rather than directly interacting with it.

One endogenous molecule that positively regulates TRPV1 is adenosine triphosphate (ATP), which is released from tissues during inflammation and/or tissue damage and that sensitizes TRPV1 (i.e. makes it easier to activate) by directly binding to TRPV1 in a region between ankyrin repeats 1–3 of the channel (Fig. 2) (reviewed in Szolcsanyi & Sandor, 2012). Other endogenous agonists include protons (H_3O^+), ammonia (NH_3) and divalent cations. When the extracellular pH decreases to 6.4 (as may occur during ischaemia), this potentiates TRPV1's activity by decreasing the threshold to capsaicin and temperature. In addition, pH as low as 5.4 can, by itself, evoke TRPV1 currents (reviewed in Julius & Basbaum, 2001). Interestingly, protons regulate TRPV1 activity by binding to residues localized to the third extracellular loop, to the linker between the selectivity filter and the sixth transmembrane domain (reviewed in Jara-Oseguera *et al.* 2008), to the pore helix and to the linker between the S3 and S4 segments (see positive regulator 8 in Fig. 2). On the other hand, NH_3, a well known irritant found in household cleaners, diffuses across cell plasma membranes where it associates with

"This is a new and exciting area involving the regulation of pain and we are awaiting more and safer molecules to be discovered"

Figure 3. A signalling pathway associated in the activation of a GPCR results in TRPV1 sensitization. The binding of bradykinin to a G-protein-coupled receptor (GPCR) produces the activation of downstream signalling pathways by activation of phospholipase C (PLC). PIP_2 (phosphatidylinositol 4,5-bishosphate), DAG (diacylglycerol) and protein kinase C (PKC) are produced leading to activation of TRPV1 and the entry of calcium into the cell that produces the depolarization of the membrane resulting in the generation of action potentials which reach the central nervous system and are interpreted as pain. Also, pro-inflammatory molecules are released from vesicles into the innervated tissue resulting in inflammation of this area.



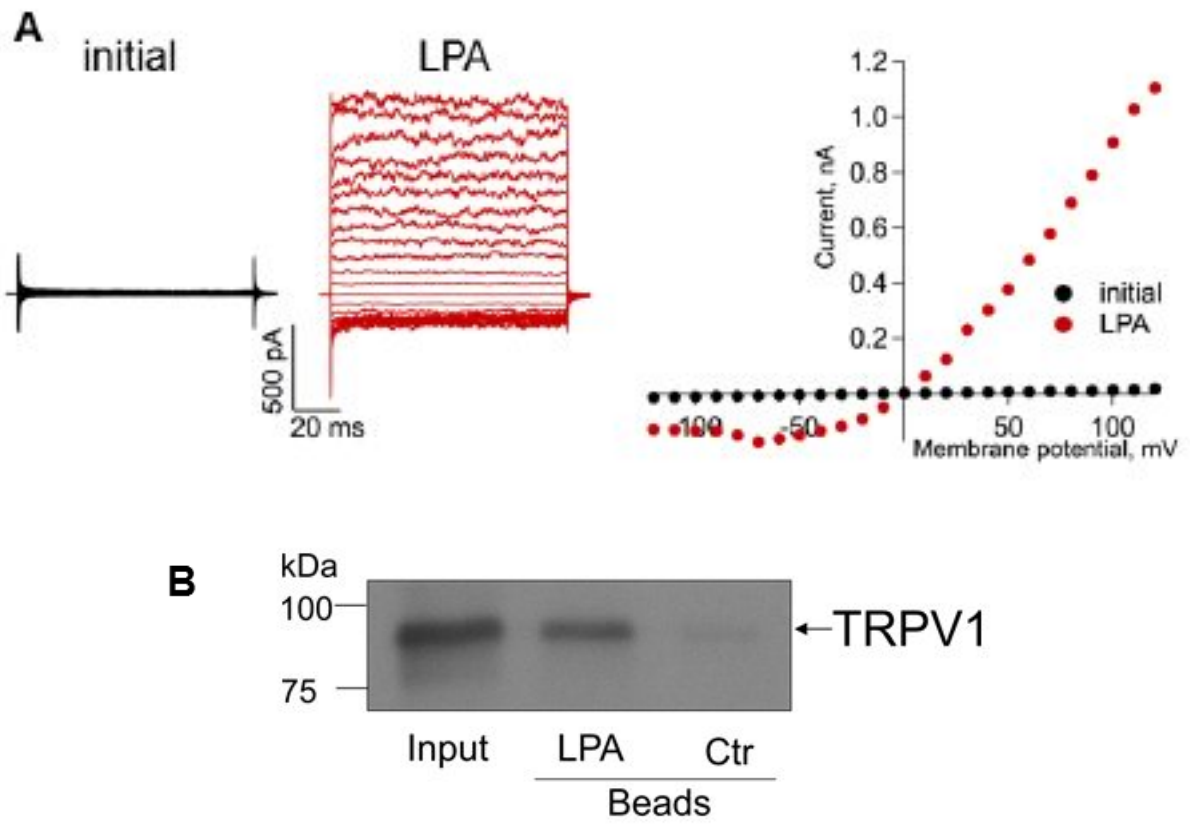


Figure 4. LPA is an endogenous agonist that directly binds to TRPV1. A, representative currents from excised-membrane patches of HEK293 cells expressing TRPV1 (left panel) before (black traces) and after the application of 5 μM LPA (red traces) with the same voltage protocol shown in Fig. 1B (from −120 mV to 120 mV). The panel on the right shows the outwardly rectifying current–voltage relationship generated from the currents on the left. B, interaction of TRPV1 with LPA-coated beads. Lane 1 is input or control (1 μg of total surface membrane protein added to the pull-down assay, no LPA-coated agarose beads added), lane 2 is TRPV1 bound to LPA-coated agarose beads, and lane 3 is a in the presence of agarose beads without LPA. When the TRPV1 channel is pulled down with beads that are coated with LPA, there is a clear signal indicating interaction of TRPV1 with LPA (lane 2). In contrast, when TRPV1 is pulled down with agarose beads without LPA, there is a lack of interaction of the channel with the beads indicating that the signal in lane 2 is specific for the protein–lipid interaction.

a proton leading to an increase in the pH of the cytoplasm that, in turn, will activate TRPV1 on the cytoplasmic surface through a mechanism involving a histidine residue (see positive regulator 7 in Fig. 2) (reviewed in Morales-Lazaro *et al.* 2013).

Finally, high concentrations of divalent cations such as Mg^{2+} and Ca^{2+} can directly activate TRPV1. Mg^{2+} and Ca^{2+} mediate their effects through extracellular residues in the channel's structure (reviewed in Morales-Lazaro *et al.* 2013) (Fig. 2), the same residues that interact with protons.

Negative regulators of TRPV1 activity

To date, adenosine and cholesterol are among the very few endogenous negative regulators of TRPV1. Adenosine, a purine nucleoside, has been shown to promote analgesic effects in animals through its interaction with adenosine receptors. However, adenosine can negatively regulate TRPV1 by binding to the same region where capsaicin binds (between S2 and S3, see Fig. 2), thus leading to a decrease in the efficacy of capsaicin to activate the channel (reviewed in Morales-Lazaro *et al.* 2013).

Another compound that has been recently shown to modulate a variety of ion channels is cholesterol (Picazo-Juarez *et al.* 2011). We have shown that cholesterol down-regulates the TRPV1 activity by binding to a cholesterol recognition amino acid consensus (CRAC) motif in the S5 transmembrane domain of the channel (see negative regulator 1 in Fig. 2; Picazo-Juarez *et al.* 2011). Other compounds of a steroidal nature, such as 17-β-oestradiol, also have been shown to regulate the sensitivity of the nerves where TRPV1 is expressed by putatively modifying the expression levels of TRPV1 (Wu *et al.* 2010).

Finally, although they are not strictly endogenous molecules, resolvins, which are derived from polyunsaturated fatty acids (PUFAs) that are found in certain types of foods such as walnuts, sunflower seeds, peanuts and olive oil, have been shown to inhibit TRPV1. Resolvin E1 (RvE1) and resolvin D2 (RvD2) inhibit TRPV1 currents through a mechanism mediated by the activation of G-protein-coupled receptors (Park *et al.* 2011). In mice these resolvins reduce the pain associated to the activation of TRPV1 (Park *et al.* 2011) and thus have the potential to become useful analgesic drugs.

Molecules that activate G-protein coupled receptors also activate TRPV1

As mentioned above, some molecules are capable of regulating the activity of TRPV1 indirectly (without binding to a region in its structure). One of the molecules known to indirectly regulate TRPV1's activity is bradykinin (BK), a nine amino acid peptide generated in inflammatory conditions. The activation of GPCRs by bradykinin results in the production of DAG, which in turn activates protein kinase C (PKC), which sensitizes TRPV1 (reviewed in Nilius & Owsianik, 2011) leading to an increase in intracellular calcium and resulting in the generation of pain and in the release of pro-inflammatory molecules (Fig. 3). In this manner, such nociceptors display an afferent response via the generation of action potentials that will ultimately lead to pain and an efferent response that will cause an inflammatory response.

Additionally, it was recently found that lysophosphatidic acid (LPA), another GPCR agonist, also directly activates TRPV1. This lysophospholipid is involved in several important cellular processes such as neurite retraction, apoptosis and calcium mobilization (reviewed in Ueda *et al.* 2013). Previously, LPA's actions were thought to be solely mediated by its interaction with specific G-protein-coupled receptors (LPA_{1-6}) to produce neuropathic pain (reviewed in Ueda *et al.* 2013).

However, our group recently showed that LPA can produce acute pain by a novel mechanism which involves its direct interaction with TRPV1 (Nieto-Posadas *et al.* 2012). We found that the injection of LPA into the paws of mice produced an increase in the time the animals spent licking their paws as compared to the time spent licking after saline injection. The difference in these times is used as a measure of the pain the animal experiences. We demonstrated using electrophysiological and biochemical measurements that LPA directly activates TRPV1 and that this behaviour does not arise from the activation of the LPA receptors (Fig. 4). Moreover, we found that it binds to the proximal region of the C-terminus of the channel where it competes with PIP_2 for a binding site (see positive regulator 5 in Fig. 2).

In summary, several physical and chemical stimuli have been shown to modulate the activity of TRPV1. This is a new and exciting area involving the regulation of pain and we are awaiting more and safer molecules to be discovered.

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The Wanderer returns: myths and realities of the cardiac vagus

For years, most textbooks have overlooked the cardiac nerve fibres in the vagus, leaving their actions almost unnoticed. But unravelling their anatomy and physiology is a key component in understanding heart dysfunction, particularly related to brain damage or disease.

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For more than a century the established idea was that the cardiac ventricles were devoid of a parasympathetic innervation. Early anatomical studies were unclear on this assertion. Here, I briefly cover the anatomical and physiological evidence showing that parasympathetic nerves, like sympathetic nerve fibres, innervate all chambers of the heart. New anatomical studies identify many cholinergic fibres distributed to both ventricles. Data show there is a complex organisation of the cardiac parasympathetic supply with a cardiotopic projection within the heart extending to the arrangement of cardiac preganglionic neurones in the medulla. Functional studies show that parasympathetic nerve excitation interacts with the sympathetic actions in the ventricle both presynaptically and postsynaptically indicating that parasympathetic terminals must extend into these chambers. Several actions of the parasympathetic nerves are described and attention is drawn to the most recent discoveries regarding an ability of vagal activity to quell life threatening ventricular arrhythmias. Evidence that this action of parasympathetic nerve fibres on the ventricles is postganglionic and due to a release of nitric oxide from non-cholinergic nerves is briefly described.

It is that which we do know which is a great hindrance to our learning that which we do not know. (Claude Bernard)

This quote reported to be from a lecture by Claude Bernard was a reference to Joseph Priestley's discovery of the life sustaining gas in air that he referred to as dephlogisticated air. Bernard implied that Priestley missed specifically identifying oxygen because he clung to the established idea that a constituent of all combustible substances was *released* on burning, leaving phlogisticated air. Such a conclusion is amazing when we realize that Priestley had shown that such substances gained weight on burning in air and that the resultant compound lost weight when burned, and the released gas (oxygen) supported a flame and life. Similarly in my opinion, attachment to established opinion has resulted in many physiologists and cardiologists believing that the vagus nerve does not innervate the ventricles of the heart.

Since Willis (1664) first recognised that vagus nerve fibres supply the heart, the trademark action of this parasympathetic nerve has been a bradycardia. We now know that it does much more than just slow heart rate and mainly influence the atria. The cardiac parasympathetic nerves slow atrio-ventricular conduction, but in the ventricle they also decrease force of contraction, change action potential duration and refractory period, and are antifibrillatory.

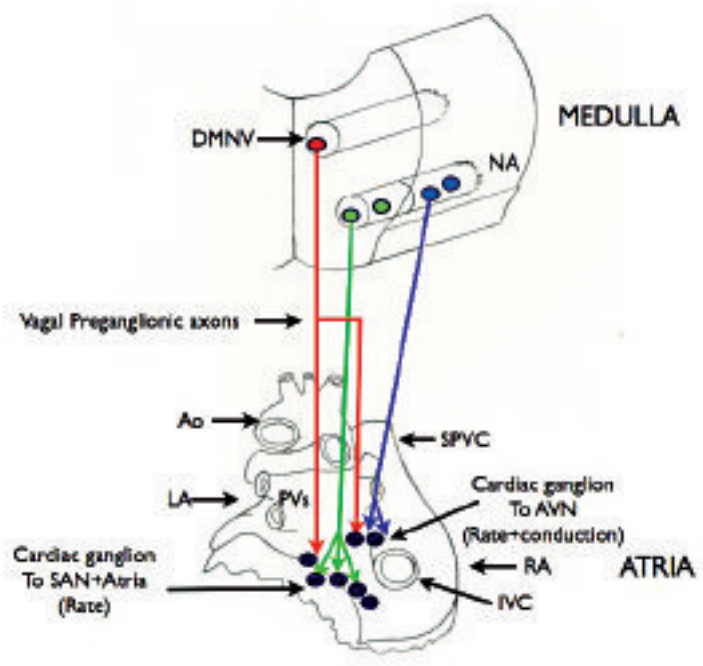

Figure 1. Origin of cardiac vagal preganglionic neurones. Schematic illustration of cardiotopic arrangement of vagal preganglionic neurones in the brain. Neurones in the nucleus ambiguus (NA) of the medulla project from caudal (green) or more rostral regions (blue) to innervate different cardiac ganglia in the atria (filled circles). These cardiac ganglia influence different cardiac regions. A third group of preganglionic neurones (red) with smaller axons arise from the dorsal motor nucleus of the vagus (DMNV) in the medulla and project to either similar or different ganglia. A posterior view of the human atria is depicted. Ao, aorta; SPVC, superior vena cava; RA, right atrium; IVC, inferior vena cava; LA, left atrium; PVs, pulmonary veins; AVN, atrioventricular node; SAN sinoatrial node. Based on various authors (see Coote, 2013).

"Attachment to established opinion has resulted in many physiologists and cardiologists believing that the vagus nerve does not innervate the ventricles of the heart"

For more than a century the cardiac vagus nerve fibres have been portrayed as limited to the atria and nodal tissue of the heart with virtually no projection to the ventricles. It seems somewhat strange that the major pumping chambers of the heart were thought to be devoid of parasympathetic nerves, whilst the atria that provide only an assist to filling of the ventricles (although nonetheless important) were densely innervated.

Frustrated by negative reviewing of many studies of the extensive actions of the vagus on the heart by our group, I decided to take a thorough look at the publications on which many early misconceptions were based. A detailed account of my examination was recently published in *The Journal of Physiology* (Coote, 2013). It is now clear that the vagal motor system's influence on the heart is more complex than thought hitherto. Not only do parasympathetic nerves supply all chambers of the heart, but there is also an arrangement of the terminal projections within the heart suggesting a selective influence on different regions of the heart (cardiotopic targeting). Furthermore this topographical functional organisation of the cardiac ganglia is reflected in the grouping of preganglionic cardiac vagal neurones within the hindbrain (Fig. 1).

The cardiac vagal origins

Cardiac vagal preganglionic neurones lie in two nuclei, the dorsal motor nucleus of the vagus (DMNV) and the more ventral nucleus ambiguus (NAmb), on each side of the caudal medulla oblongata. This location was first elegantly defined by Mike Spyer and his colleagues (McAllen & Spyer, 1976). The cardiac preganglionic neurones fall into two groups, a larger group (80%) with small myelinated axons (B fibres) located in the NAmb and a smaller group with unmyelinated axons found in the DMNV and intermediate region. Each group has different discharge characteristics and their axons different conduction velocities. The preganglionic axons project in the right and left cervical vagal nerve bundles as far as the heart, where they synapse on principle postganglionic parasympathetic neurones in ganglia that affect different regions of the heart and influence different aspects of cardiac function (Fig. 1). Of course the cervical vagus nerves also contain many other parasympathetic efferents that supply the thorax and abdominal organs and it also contains postganglionic sympathetic efferent fibres. Consequently a contentious issue related to heart function has been that stimulation of the cervical vagus may also activate cardiac

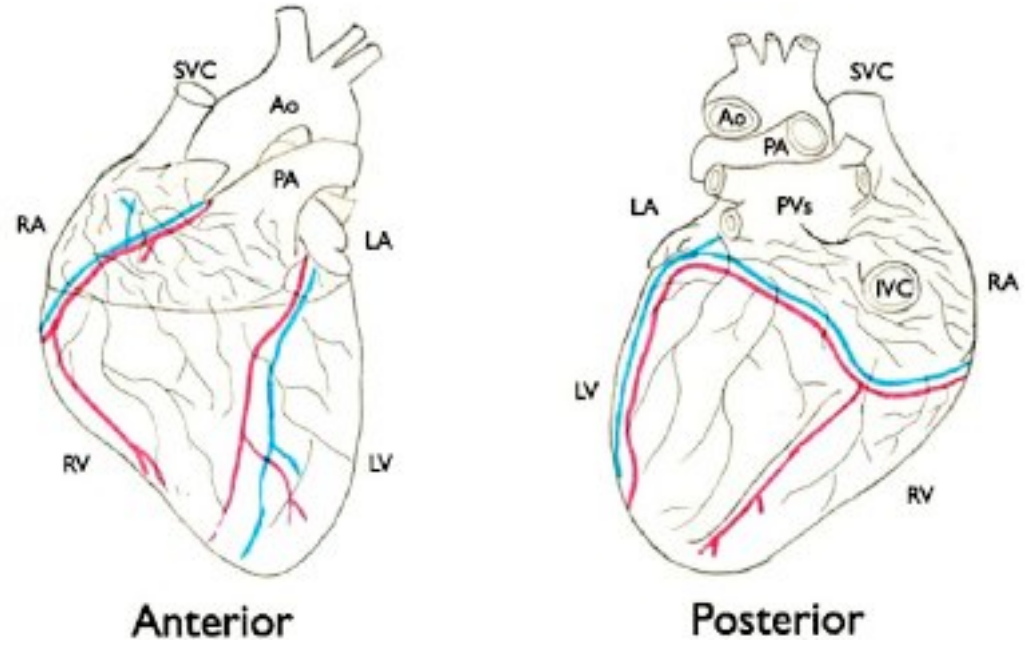

Figure 2. Distribution of cardiac parasympathetic postganglionic nerves. Hand drawing from original images of posterior and anterior views of the human heart with the anticholinesterase or choline acetylase stained fibres traced (fine lines) over the surface of the atria and ventricles. Coronary vessels outlined in red and blue. Ao, aorta; SPVC, superior venal cava; RA, right atrium; IVC, inferior vena cava; RV, right ventricle; LV, left ventricle; LAa, left atrial appendage; LA, left atrium; PVs, pulmonary veins; PA, pulmonary artery. Based on various authors (see Coote, 2013).

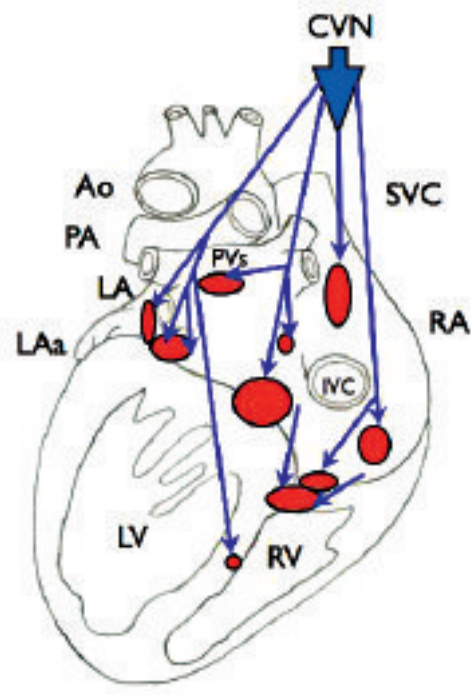

Figure 3. Cardiac vagal ganglia. Posterior view of the human heart showing principle sites of ganglia (red) which receive vagal preganglionic terminals (blue). Most sites are supraventricular but note the ganglion present in the interventricular septum. Abbreviations same as in Fig. 2. Based on various authors (see Coote, 2013).

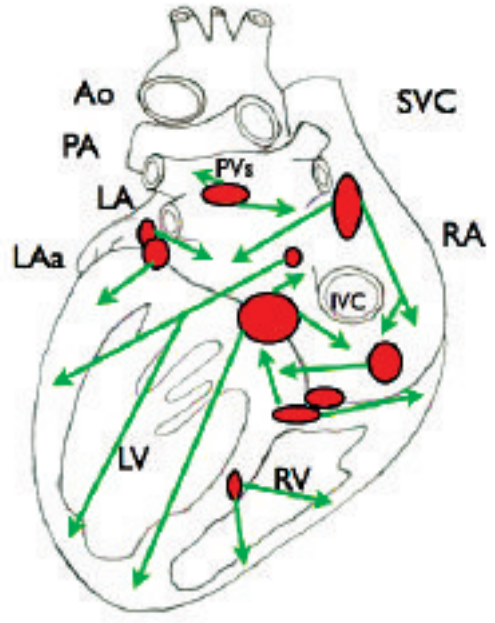

Figure 4. Cardiac parasympathetic postganglionic nerves. Posterior view of the human heart illustrating the apparent widespread projection of parasympathetic postganglionic fibres (green) based on anatomical identification and physiological observations of cardiac effects. Abbreviations as in Fig. 2. Summary from various authors (see Coote, 2013).

sympathetic fibres. However, a classical series of papers robustly demonstrated that the postganglionic sympathetic fibres coursing throughout the length of the cervical vagus nerves were not cardiac but supplied the bronchial and pulmonary blood vessels (see Coote, 2013). Cardiac sympathetic fibres from the stellate ganglion do join the vagus, but low in the neck. Stimulating these can be avoided by placing electrodes somewhere on the upper two-thirds of the cervical vagi as in the present clinical trials concerning the benefit of implanted vagal electrodes to increase cardiac vagal tone in patients with heart failure (INOVATE trial 2013).

Vagal nerve supply to cardiac chambers

A cardiac vagal influence extending into the ventricles had been viewed with scepticism because early anatomical studies appeared not to clearly demonstrate parasympathetic terminals amongst ventricular myocytes. For example Sarnoff and collaborators (1960) in an exquisite series of experiments on the action of autonomic nerves on cardiac function ignored possible actions of vagal stimulation largely due to a stated belief that parasympathetic fibres projecting so far were sparse. Perhaps as a consequence research into the actions of the cardiac vagal fibres has lagged behind that on the sympathetic influences.

Early in my career I was working with heart failure patients and I was struck by the physiological and physical benefits to these patients of regular aerobic exercise. Several mechanisms are likely to account for the cardiovascular improvements. However, an easily observable characteristic for me was a reduction in heart rate, which we now know is largely due to an increase in cardiac vagal tone. So how can an increase in vagal tone benefit a failing heart? It would not seem unreasonable to believe that in these patients the changes in vagal activity were also influencing the cardiac ventricles. This has since been implied by the physiological results of Levy and others that have clearly shown parasympathetic effects on the ventricles similar to those on the atria. Yet the area was haunted by the continued belief that the parasympathetic nerves did not project throughout the ventricles.

A more careful look at the anatomical and functional evidence shows it was not as negative as had been thought. We now understand that cardiac parasympathetic nerves do have an influence on all chambers of the heart and some actions are quite surprising.

An oft-quoted source for the absence of parasympathetic fibres in the ventricles actually concluded that fine heavily silver-impregnated fibres in autonomically decentralised young dog and cat hearts were parasympathetic (Nonidez, 1939). Support for this conclusion later came from several other groups and most substantially from studies using the thiocholine method to identify acetylcholinesterase (AChE), the enzyme responsible for hydrolysing acetylcholine (ACh). More recently renewed interest in the parasympathetic innervation of the heart prompted several studies using similar methodology. These have revealed a remarkably dense distribution of AChE stained fibres throughout all the chambers of the heart of mouse, guinea pig, rat, cat, dog, pig, sheep and human (Fig. 2; Coote, 2013). Hence it appeared reasonable to conclude that cholinergic nerves richly innervate the epicardial and endocardial surfaces of the ventricles as well as the atria. Although the evidence favours this interpretation, essential confirmation has come from recent studies using choline acetyltransferase (CHAT) immunohistochemistry. CHAT is the enzyme that catalyses the final step in the synthesis of ACh and hence is a more definitive marker of ACh nerve fibres (see Coote, 2013). These studies have successfully demonstrated a significant presence of cholinergic fibres in the ventricles (Fig. 2).

In summary, present knowledge is that the cardiac vagal preganglionic nerves pass close to the cardiopulmonary vessels and superior vena cava to synapse on ganglia located in several epicardial fat pads on the dorsum of the atria close to the site of entry of the major veins and surface of the ventricles as well as the interventricular groove and the interatrial and interventricular septa (Fig. 3; Singh *et al.* 1996; Coote, 2013). These ganglia are now considered the principle sites of vagal preganglionic termination and their number varies across species. However, the description is still a little confused because of the dense network of neurones that form the cardiac plexuses of an intrinsic nervous system of the heart chambers (Armour, 2008). To my mind, despite the exquisite studies of Bob Wurster and colleagues (for example Singh *et al.* 1996, 2009), a more comprehensive identification to reveal both pre- and postganglionic projections and location of the parasympathetic ganglia is needed.

Armed with this knowledge of a widespread cholinergic innervation of the heart it has become possible to understand why there are many studies showing a dense distribution of muscarinic receptors throughout the heart that includes both right and left ventricles. These findings are supported by convincing evidence showing that ACh is released from various postganglionic sites in the ventricles that is dependent on the strength and frequency of preganglionic vagal stimulation (Coote, 2013).

In conclusion the anatomy and pharmacological data indicate that the cardiac parasympathetic nerves not only innervate

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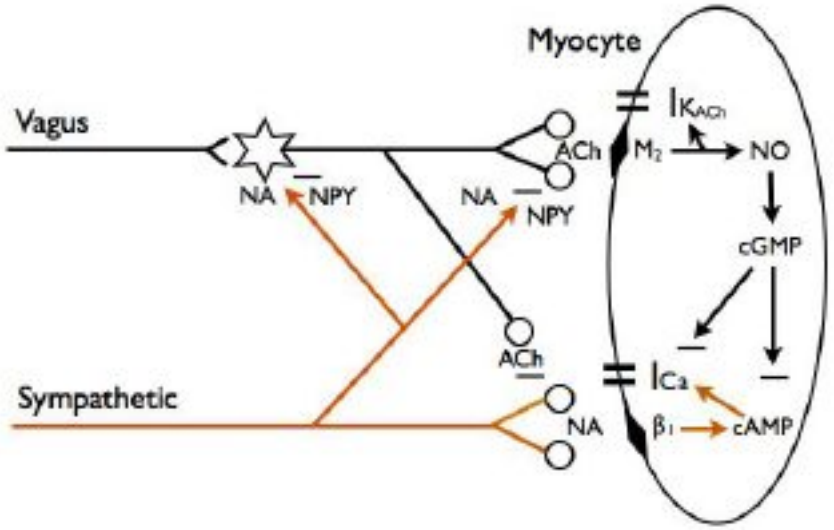

Figure 5. Parasympathetic–sympathetic interaction. Diagram illustrating accentuated antagonism between the two divisions of the cardiac nerve supply that occurs in the atria and the ventricles. Sympathetic nerves in red. The chemical transmitters released at each site are indicated; ACh, acetylcholine; NA, noradrenaline; NPY, neuropeptide Y. Inhibitory actions are indicated by minus sign; all other sites are excitatory.

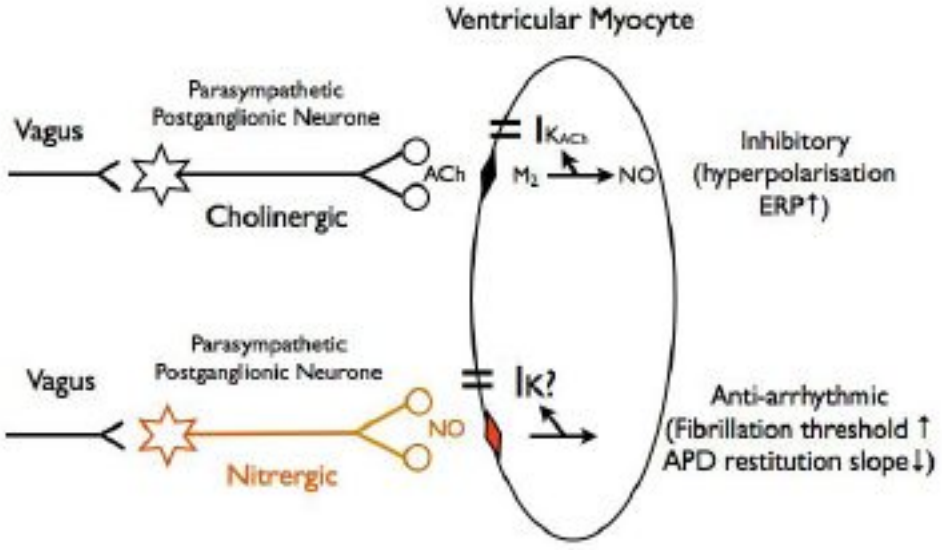

Figure 6. Antifibrillatory nitrergic parasympathetic postganglionic nerves in the ventricles. Diagram interpreting the experimental results on rabbit hearts (e.g. Brack *et al.* 2007) that suggest there are two chemical phenotypes of parasympathetic postganglionic fibres ending on ventricular myocytes and with different postsynaptic effects on the myocyte.

the atria, nodal and conducting tissue but also both ventricles as indicated in Fig. 4. This is further supported by functional studies.

Physiological evidence of vagal control of the cardiac ventricles

There has been considerable evidence from studies over the last 40 years that stimulation of the vagus nerve changes ventricular muscle electrophysiology and force of contraction. Despite this, even up to quite recently textbooks still depict the cardiac parasympathetic nerve supply only projecting as far as the conducting tissue. There is now substantial and robust physiological data from studies showing interaction between parasympathetic and sympathetic activity on myocardiac performance (Fig. 5).

For example the effects of vagal stimulation on reducing rate of ventricular contraction and its force, and lengthening atrial–ventricular conduction time are enhanced in the presence of sympathetic activity. Thus, in the presence of sympathetic tone, muscarinic receptor activation by parasympathetic nerve-released ACh suppresses the action of sympathetic nerves on the ventricular myocardium (Coote, 2013). Much evidence suggests this is partly a pre-junctional effect whereby ACh released from parasympathetic postganglionic terminals reduces the amount of catecholamine released from sympathetic nerves (Levy, 1977). The cardiac effect of the pre-junctional actions is enhanced by a post-junctional cholinergic receptor-dependent intracellular elevation of cGMP that then inhibits cAMP so reducing the sympathetic adrenergic-activated currents. These parasympathetic–sympathetic interactions known as accentuated

antagonism have been elegantly confirmed and extended to the cellular level in Paterson's lab (for example Dawson *et al.* 2008).

Additionally, there is robust evidence that parasympathetic postganglionic nerve fibres have direct effects on ventricular myocardial cells independent of sympathetic activity.

In intact animals and in an isolated innervated heart preparation vagal stimulation has been shown to lengthen the duration of ventricle monophasic action potentials and the refractory period, in the absence of sympathetic activity (Brack *et al.* 2007; Coote, 2013). Negative inotropic actions of the vagus after removal of sympathetic influence have also been shown in several studies. These indicate that in anaesthetised animals and humans, after beta-adrenoreceptor blockade, vagal nerve stimulation has a small but significant negative inotropic action on the ventricles (Coote, 2013). Such results have not gone unchallenged but it seems to me that a direct parasympathetic influence on ventricular muscle force would be at least as functionally important as the established negative inotropic action on atrial muscle.

Vagal modulation of ventricular rhythm

One influence of the cardiac parasympathetic activity on the ventricles that is overlooked but is well documented is a protective effect on the vulnerability for ventricular fibrillation (Coote, 2013). Part of this action may be due to accentuated antagonism of sympathetic action via parasympathetic cholinergic nerves (Fig. 5).

However, there is now convincing evidence supporting a direct non-cholinergic anti-arrhythmic action of vagal stimulation which has been demonstrated in the isolated innervated rabbit heart preparation in the absence of sympathetic activity (Brack *et al.* 2007, 2009, 2011). In confirmation of many early reports in intact animals, stimulation of the vagus nerves either prevented or increased the threshold for a stimulus to cause fibrillation. These authors also measured the vagus nerve effect on action potential duration restitution (APDR), a characteristic that reflects the probability of an electrical wave front breaking up into multiple wavelets that result in desynchronised spread of electrical activity and uncoordinated myocyte contraction. We can liken this to a sea wave breaking onto the shoreline where the slope of the beach, the wavelength and the velocity of the wave determine wave break-up. In the case of the heart, diastolic interval (slope of beach) determines the action potential duration (wavelength) and APDR measures this relationship with a higher value facilitating fibrillation. Vagus nerve stimulation decreased APDR so confirming the fibrillation threshold results. A real surprise, though, was that the raised ventricular threshold to fibrillation was unaffected by atropine but selectively blocked by a neuronal nitric oxide synthase antagonist suggesting it is mediated via NO release and is independent of ACh acting at muscarinic post-junctional receptors. In further experiments NO release was directly measured and demonstrated to be independent of ACh release. Whilst there are several possible explanations for these results, the most plausible is that the anti-arrhythmic action on the ventricle of parasympathetic terminals is exerted by a select population of postganglionic nitrergic fibres (Fig. 6). There are anatomical data from several studies showing postganglionic nitrergic nerve fibres supplying the heart chambers. For example Singh *et al.* (2009) calculated that 37% of human cardiac ganglion neurones contain NO synthase.

Up to quite recently we have always assumed that the cardiac parasympathetic postganglionic nerve fibres are cholinergic and are phenotypically homogeneous. However, parasympathetic fibres to the gastrointestinal tract and to the lower urinary tract and vas deferens consist of both cholinergic and nitrergic fibres (see Coote, 2013).

Therefore, the cardiac parasympathetic innervation is most unlike the common picture that is presented in textbooks. It is heterogeneous in terms of both anatomical location and projection of preganglionic and postganglionic neurones (for example Sampaio *et al.* 2003) and in neuronal size as well as in neurochemistry and physiology.

Interaction with intrinsic nerve plexuses

It is common to interpret neural effects on the heart as being due to the actions of the extrinsic autonomic nerves. However, the heart, like the gastrointestinal tract, also has an extensive intrinsic network of neurones that are postulated to be a 'little brain' (Randall *et al.* 1996) that is capable of powerfully modulating regional and whole heart function (Armour, 2008). The presence of the ganglion plexuses that have connections throughout all cardiac chambers adds to the complexity of the innervation of the heart. A few studies have examined the interaction of intrinsic and extrinsic nerve systems, but such participation has not so far featured strongly in interpretation of the actions of extrinsic autonomic nerves on the heart.

Conclusion

For many years most textbooks have neglected the cardiac nerve fibres in the vagus and so their many actions have gone almost unnoticed. This has to change. A full knowledge of the anatomy and physiology of the cardiac parasympathetic nerves is essential if we are to understand heart dysfunction and in particular how brain damage or disease can have serious adverse cardiac effects.

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Our hyper-polarizing story: understanding ATP-mediated vasodilatation in humans

Negative results, cynicism, the piecing together of puzzles and integrating physiology with experimental approaches. It's all part of the inspiring and meandering journey on the path to understand ATP-mediated vasodilatation.

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While it is satisfying to be 'right' as scientists, we know sometimes the most important progress occurs when data are surprising or contrary to our original hypothesis. The pursuit of explanations for unexpected findings often leads to the best advancements. The story of how our laboratory came to investigate the underlying vasodilator pathways of adenosine triphosphate (ATP) (Crecelius *et al.* 2012) is an example of such a path to our current understanding.

Regulation of vascular tone and the endothelium

Since the early 20th century, physiologists have been interested in skeletal muscle blood flow regulation, particularly during occasions of stress to the body, such as muscle contraction (exercise) or changes in gravitational force (standing). Eventually it was realized the endothelium, a monolayer of epithelial cells separating the lumen of the vessel from the smooth muscle cells, was an important mediator of vascular tone and capable of releasing factors that elicited vasodilatation. Robert F. Furchgott first posed the idea of an 'endothelium-derived relaxing factor' (EDRF) (Furchgott & Zawadzki, 1980), later identified by Furchgott and Louis J. Ignarro as the gaseous nitric oxide (NO).

In 1998, a Nobel Prize was awarded for the discoveries concerning NO as a cardiovascular signalling molecule. We and others were aware of the potential relationship between NO and cardiovascular health, particularly as it related to ageing. Initially, we focused on the impact of age and regular aerobic exercise training on large artery structure and function, conduit and resistance vessel endothelial function, and peripheral blood flow under resting conditions. Many of these studies did not address NO specifically; however, bioavailability of this molecule, either attenuated with age or improved with exercise, was a proposed mechanism to a number of our observations.

Eventually, we used intra-arterial pharmacology to address mechanisms of local regulation of vascular tone and performed a variety of studies, many to determine the role of NO by utilizing exogenous L-arginine analogues (the precursor for endothelial nitric oxide synthase (NOS)-derived NO) to inhibit NO synthesis. We also possessed the ability to directly stimulate and inhibit the action of the sympathetic nervous system with specific receptor agonist and antagonists, fuelling our rapid growth of understanding how the nervous system influences skeletal muscle blood flow.

As the new millennium was ushered in, the phenomenon of 'functional sympatholysis' (see box), first proposed by Remensmyder in the early 1960s (Remensnyder *et al.* 1962), was observable in both human and animal studies in a variety of preparations. Regarding underlying mechanisms of this response, Thomas and colleagues demonstrated that functional sympatholysis in the contracting rat hindlimb was impaired in the presence of NOS inhibition (Thomas & Victor, 1998). However, when we attempted to translate these findings of a significant role for NO in functional sympatholysis to our human studies, we were

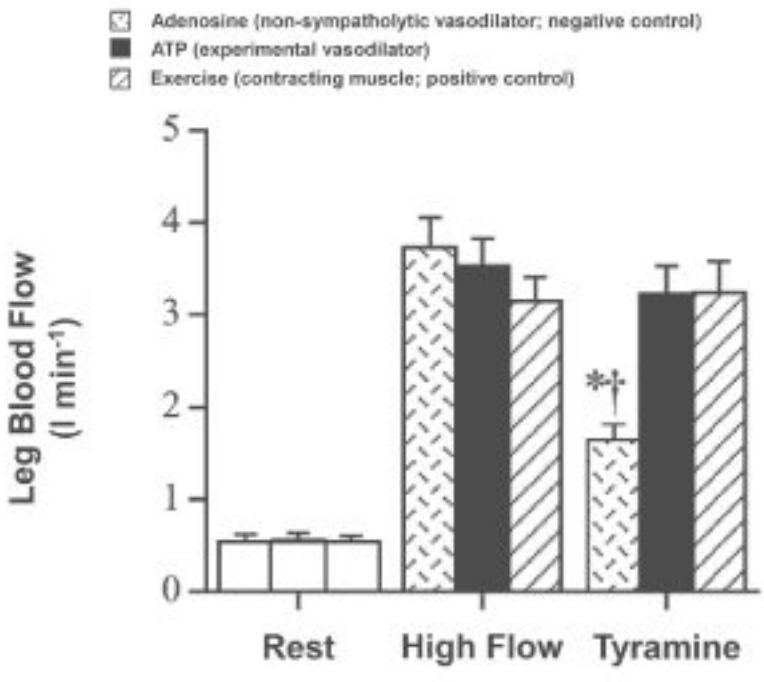

Figure 1. ATP is sympatholytic in the human leg. In young healthy humans, leg blood flow was measured at rest, during a hyperaemic steady-state and with femoral artery infusion of tyramine to elicit endogenous noradrenaline release and therefore sympathetically mediated vasoconstriction. Adenosine (cross-hatched bar) is used to cause significant vasodilatation and increase blood flow to inactive tissue. Tyramine infusion results in significant sympathetically mediated vasoconstriction during adenosine infusion but not during exogenous ATP infusion (filled bars) or single leg-extension exercise (hatched bars). Data are means ± SEM for 8 subjects. *$P < 0.05$ *vs.* high flow; †$P < 0.05$ *vs.* both combined ATP and tyramine and exercise and tyramine. Modified from Rosenmeier *et al.* (2004) with permission.

unable to do so. We took a variety of approaches, but continually failed to observe a significant ability for NO to blunt sympathetically mediated vasoconstriction when given directly as sodium nitroprusside, as well as observed intact functional sympatholysis in the presence of NOS inhibition (Dinenno & Joyner, 2003). Additionally, NO did not appear to be obligatory for vasodilatation during muscle contractions and combined inhibition of NO and other endothelial-derived vasodilators such as prostaglandins (PGs) resulted in a modest decline (~25%) in exercise hyperaemia when inhibition occurred during muscle contractions (Schrage *et al.* 2004). Taken together, while evidence was strong for the vasoprotective properties of NO in humans, data from our laboratory and others indicated that vascular regulation during muscle contractions appeared to be somewhat independent of this endothelial-derived vasorelaxant.

Interestingly, the lack of an obligatory role for NO in both exercise hyperaemia and functional sympatholysis in humans was somewhat perplexing given our findings demonstrating impaired vasodilatation and functional sympatholysis in healthy, sedentary older individuals during exercise, a group well-characterized by decreased NO bioavailability (Kirby *et al.* 2010, 2011). Had we observed that NO was obligatory in these cases, a logical theory of impaired blood flow control during exercise in older adults would have existed. This was not the case, and it would take us several more years of both basic science and clinical studies before we formed an overall hypothesis for what molecule other than NO might explain these collective findings.

Extracellular ATP: unique vascular capabilities

Early studies appreciated the diverse function of purines in cardiovascular regulation, but it was not until the late 1990s that investigators began to develop a hypothesis regarding the role of erythrocyte-released extracellular ATP as a mediator of the matching of muscle perfusion to oxygen demand (Ellsworth *et al.* 2009). Building upon this idea, in 2004 Rosenmeier and colleagues demonstrated that circulating ATP was capable of overriding sympathetic vasoconstriction in the leg evoked by the infusion of tyramine, a drug that elicits endogenous noradrenaline (NA) release (Fig. 1) (Rosenmeier *et al.* 2004). The finding of an exogenous substance capable of being 'sympatholytic' was rather surprising as over the years we had tested many substances in this regard, none of which mimicked what occurred in contracting skeletal muscle.

What is 'functional sympatholysis'?

- Activation of the sympathetic nervous system elicits vasoconstriction via noradrenaline (NA) binding to post-junctional α-adrenergic receptors on vascular smooth muscle cells.
- Functional sympatholysis describes the ability of muscle contractions to blunt the magnitude of vasoconstriction that a given sympathetic stimulus elicits, relative to what occurs in inactive tissue.
- This mechanism of vascular control during exercise is thought to allow for a balance between increased local blood flow and therefore oxygen delivery to active tissue, while the ability to cause some sympathetically mediated vasoconstriction can occur to prevent unopposed declines in systemic resistance and therefore maintain mean arterial blood pressure.

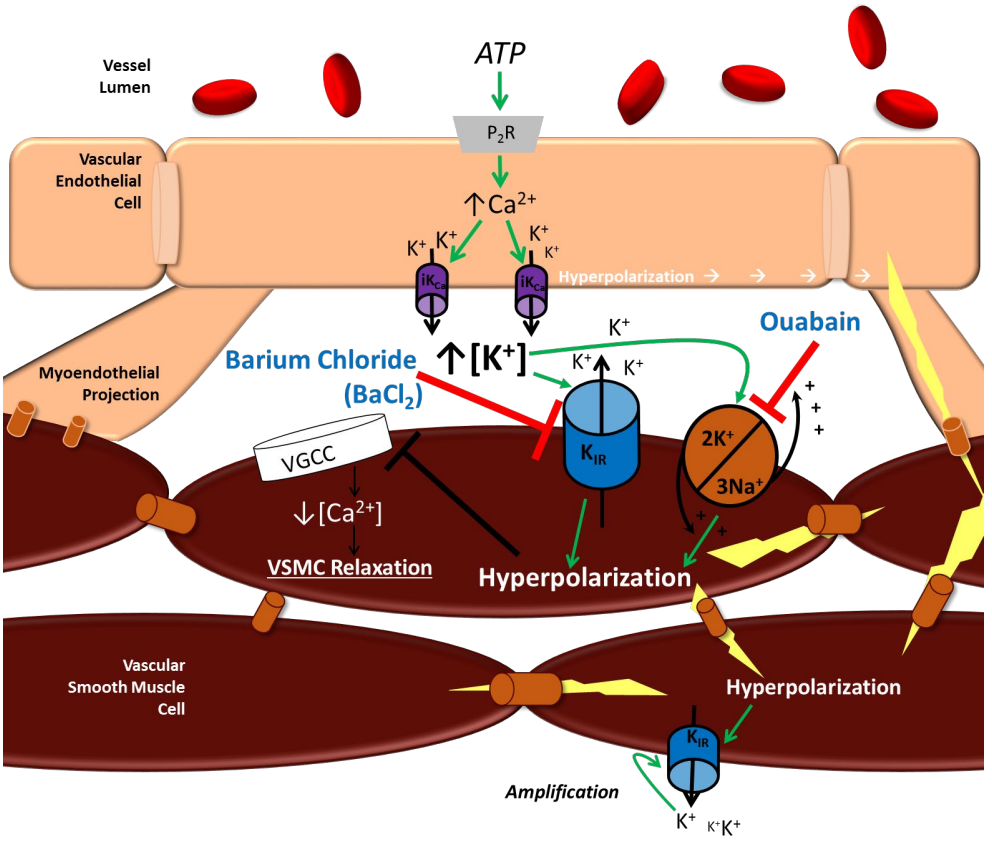

Figure 2. Summary of endothelial-derived hyperpolarization and pharmacological inhibition of inwardly rectifying potassium channels (K_{IR}) and Na^+/K^+-ATPase. ATP binds to purinergic type 2 receptors (P_2R) causing endothelial intracellular [Ca^{2+}] to increase, stimulating calcium-activated potassium channels of small (sK_{Ca}) and intermediate (iK_{Ca}) conductance as well as hyperpolarization of endothelial cells. K^+ efflux from the K_{Ca} channels stimulates inwardly rectifying potassium (K_{IR}) channels and the Na^+/K^+-ATPase pump, both of which lead to membrane potential hyperpolarization and relaxation of the vascular smooth muscle cells (VSMCs). Barium chloride ($BaCl_2$) and ouabain can be used to inhibit K_{IR} channels and Na^+/K^+-ATPase, respectively. K_{IR} channels are also activated directly by VSMC hyperpolarization and are thus thought to contribute to the amplification (Jantzi *et al.* 2006) and spread of hyperpolarizing stimuli throughout the VSMC. VGCC, voltage-gated Ca^{2+} channel.

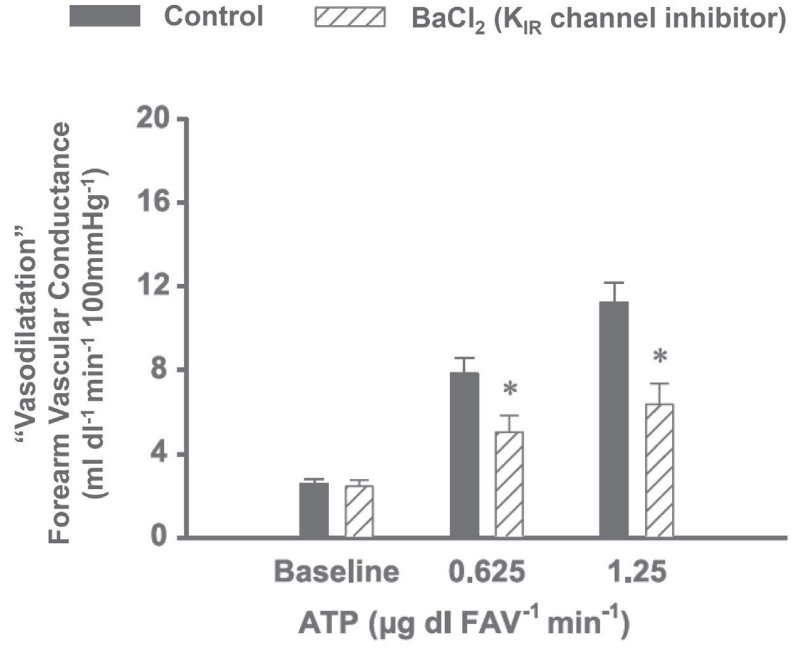

Figure 3. ATP-mediated vasodilatation occurs through activation of K_{IR} channels. In young healthy humans, forearm blood flow was determined and forearm vascular conductance (FVC) was calculated (index of vascular tone) at rest and during increasing doses of exogenous ATP infusions (brachial artery) in control conditions (filled bars) and with coinfusion of $BaCl_2$ (cross-hatched bars) to inhibit K_{IR} channel activation. The increase in FVC was attenuated ~50% at both doses of ATP. Data are means ± SEM for 6 subjects. *$P < 0.05$ *vs.* Control. Modified from Crecelius *et al.* (2012).

In truth, we were quite sceptical of these intriguing findings, and thus we designed a study in the forearm to confirm ATP was capable of overriding sympathetically mediated vasoconstriction and specifically address whether this occurred post-junctionally, as is the case during muscle contractions. The synaptic level of modulation was unable to be determined from the findings of Rosenmeier and colleagues given their experimental approach of tyramine-induced vasoconstriction. To our surprise, we built upon the results from the Scandinavian group and showed ATP is clearly capable of post-junctional modulation of sympathetically mediated vasoconstriction and importantly, that this occurs in a graded manner such that a low dose of exogenous ATP is not sympatholytic, whereas higher doses are (Kirby *et al.* 2008). The graded nature of the sympatholytic ability of ATP parallels the graded effect of exercise intensity on functional sympatholysis. We were then convinced that in addition to being a potent vasodilator, ATP possesses unique signalling properties that merit additional study.

At this time our interest in ageing began to merge with our developing knowledge of vasoactive ATP. Animal-based experiments indicated that ATP-mediated vasodilatation was dependent on an intact endothelium and this led us to pursue whether ATP could be used as a test of endothelial function in older adults, similar to how the muscarinic agonist acetylcholine was used by our group and others. However, contrary to our hypothesis, ATP-mediated vasodilatation was not impaired in older individuals, despite these subjects demonstrating 'endothelial dysfunction' as characterized by impaired dilator responses to acetylcholine (Kirby *et al.* 2010). This 'incorrect' hypothesis would be critical in the development of our future research that tried to explain this unanticipated finding. Firstly, what endothelial-derived vasodilators was ATP stimulating? Secondly, whatever this mechanism might be, could it lend important insight into the unexplained aspects of vascular regulation during exercise?

Several lines of evidence suggested that what was termed 'endothelial dysfunction' at that point could be more specifically termed 'decreased NO bioavailability'. Given ATP seemed to be dissociated from NO bioavailability based on our dilatory study in older adults (Kirby *et al.* 2010) and the studies on sympatholysis in younger adults (Kirby *et al.* 2008), we pursued what vasodilator pathways were stimulated by exogenous ATP. Initially, we investigated the role of the endothelial-derived vasodilators NO and PGs, as the existing literature was equivocal in this regard. No matter the manner in which we tested the idea, at varied doses and timing of inhibition and multiple measurement techniques of muscle blood flow, we were unable to inhibit ATP-mediated vasodilatation more than ~20–30% (Crecelius *et al.* 2011). We were left to consider the non-NO, non-PG mechanisms of endothelium-dependent vasodilatation.

Endothelial-derived hyperpolarization: factoring it in

Upon closer examination of the literature from animal models and isolated vessel preparations, we began to appreciate that non-NO, non-PG mechanisms of vasodilatation were likely to be critical for vascular control at rest and in response to stimulation. However, similar to the original unknown nature of NO and generalized name of EDRF, these pathways were not well described and generally termed endothelial-derived hyperpolarizing factors (EDHFs); a response dependent on the endothelium that caused a characteristic hyperpolarization (decrease in membrane potential) of endothelial and vascular smooth muscle cells leading to vasodilatation (Feletou & Vanhoutte, 2007). One hypothesis proposed potassium (K^+) could be an EDHF given its potential release from endothelial cells and ability to stimulate the Na^+/K^+-ATPase pump and inwardly rectifying potassium channels (K_{IR}) on vascular smooth muscles causing membrane potential hyperpolarization and vasorelaxation (Edwards *et al.* 1998). An important aspect of the proposed mechanism for K^+ was its efflux through calcium-activated K^+ channels (K_{Ca}). Taken together with data that demonstrated inhibition of small- and intermediate-conductance K_{Ca} channels essentially abolished vasodilatation to luminal ATP application in the rat mesentery (Edwards *et al.* 1998), we had even more motivation to try and address hyperpolarizing mechanisms of vasodilatation in our human model as it might lend insight to our previous findings regarding ATP.

To date, investigators interested in inhibiting vascular hyperpolarization in humans were somewhat limited in the pharmacology that could be safely administered to do so. The toxins and venoms often used in isolated vessel preparations to inhibit small- and intermediated-conductance K_{Ca} channels posed safety risks. Enzymatic inhibition of specific proposed stimuli of hyperpolarization (e.g. cytochrome p450, H_2O_2, etc.) left readers questioning efficacy since directly challenging these inhibitors was difficult. We were excited to find that barium chloride ($BaCl_2$) and ouabain could be given intra-arterially in low doses to inhibit K_{IR} channels and Na^+/K^+-ATPase, respectively (Dawes *et al.* 2002). Importantly, low doses of KCl could be given intra-brachially to cause hyperpolarization and directly challenge inhibitor efficacy (Fig. 2). We saw an exciting opportunity to try and translate the isolated vessel experiments that supported a role for hyperpolarization in ATP-mediated vasodilatation (Winter & Dora, 2007) by inhibiting downstream mechanisms of VSMC hyperpolarization (Edwards *et al.* 1998).

"It is often challenging to translate mechanistic findings from animal models and in vitro studies to our human model, given our concerns for human safety."

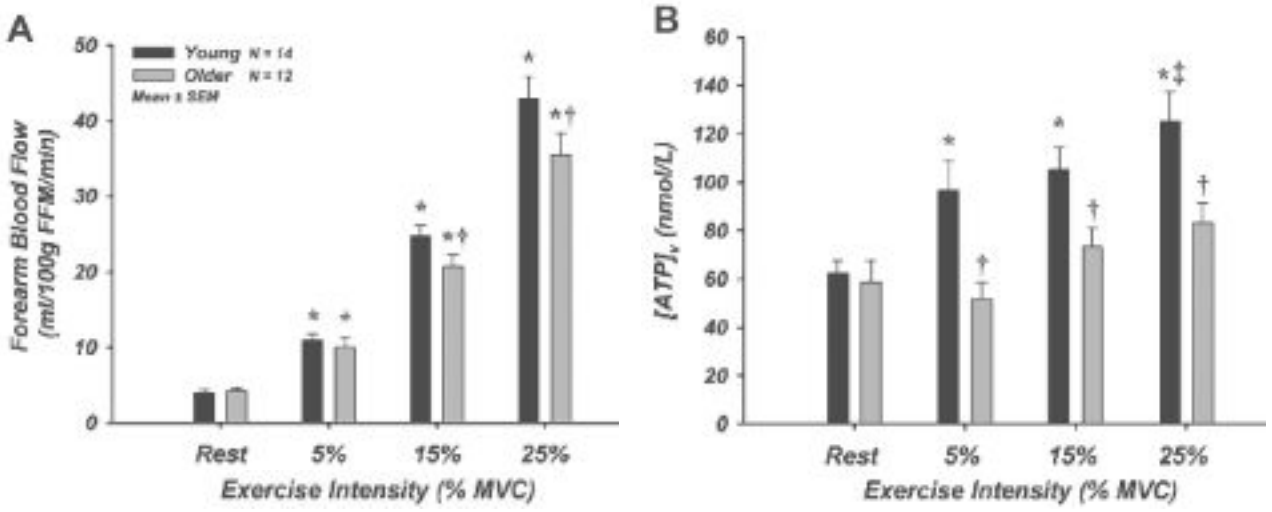

Figure 4. Older adults fail to increase plasma [ATP] during handgrip exercise. Young (dark bars; 18–35 years) and older (light bars; 60–85 years) healthy individuals performed rhythmic handgrip exercise for 5 min at each increasing intensity (percent of individual maximal voluntary contraction (MVC)). Forearm blood flow (FBF) was measured and venous plasma [ATP] was determined via luciferin–luciferase assay of samples obtained from a retrograde antecubital catheter in the exercising arm. *A*, FBF was attenuated in older adults at 15% and 25% MVC. *B*, young individuals significantly increased $[ATP]_v$ at all exercise intensities, whereas older individuals failed to increase $[ATP]_v$ during exercise. At all intensities, $[ATP]_v$ was lower in older individuals than the young adults. $*P < 0.05$ *vs.* rest; $\dagger P < 0.05$ *vs.* young adults. $\ddagger P < 0.05$ *vs.* 5% and 15% MVC within young adults. FFM, fat-free mass. Modified from Kirby *et al.* (2012).

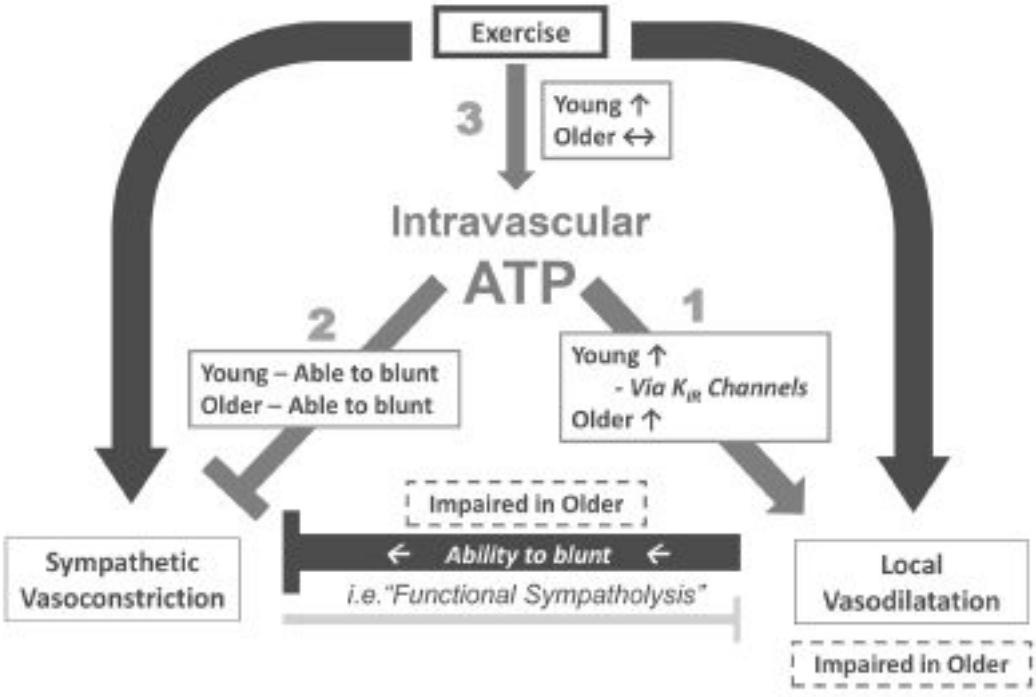

Figure 5. Relationship of ATP, ageing and the regulation of vascular tone during exercise in humans. Exercise stimulates significant local vasodilatation and at sufficient intensity can activate the sympathetic nervous system to cause sympathetic vasoconstriction. The blunting of sympathetically mediated vasoconstriction that occurs in active skeletal muscle during exercise is known as 'functional sympatholysis'. Older individuals display attenuated exercise vasodilatation and impaired functional sympatholysis (Dinenno *et al.* 2005; Kirby *et al.* 2011), yet the underlying mechanisms are not well understood. We have recently shown that ATP signals vasodilatation (1) primarily through K_{IR} channel activation (Crecelius *et al.* 2012) and unlike other exogenous vasodilators, ATP is capable of modulating sympathetic vasoconstriction (2) and this occurs in a graded fashion, similar to during exercise (Kirby *et al.* 2008). Interestingly, the dilatory responsiveness to ATP (1) as well as the sympatholytic ability of this purine (2) is preserved in older individuals. Exercise elicits significant increases in venous plasma [ATP] in young individuals (3); however, this does not occur in older adults (Kirby *et al.* 2012). Thus, we propose impaired functional sympatholysis in this population may be due in part to the inability to release sufficient concentrations of ATP to signal endothelium-dependent hyperpolarization.

The 'wow' moment

It was necessary to first establish our ability to sufficiently inhibit a hyperpolarizing stimulus (exogenous KCl) with the combination of $BaCl_2$ and ouabain, as had previously been described (Dawes *et al.* 2002). With these control experiments completed (in fairly profound fashion as we essentially eliminated any K^+-mediated vasodilatation), we began our first experiments to test the impact of inhibition of K_{IR} channels and Na^+/K^+-ATPase on ATP-mediated vasodilatation (Crecelius *et al.* 2012). These first studies were some of the more exciting in the laboratory to date. Given our data are collected in real-time, we were able to immediately estimate the changes in muscle blood flow following inhibition. From the first subject forward, it was clear these inhibitors were more 'powerful' than those we had used before and a large portion of ATP-mediated vasodilatation was explained by these pathways. After a number of experimental approaches, we determined the primary mechanism of ATP-mediated vasodilatation is vascular hyperpolarization via activation of K_{IR} channels (Fig. 3) (Crecelius *et al.* 2012).

Putting it all together

As we were working to understand the basic signalling mechanisms of ATP, we were concurrently studying the potential role for ATP in the control of vascular tone during exercise in young and older adults, given the finding in young subjects that in sufficient concentration, it was sympatholytic (Rosenmeier *et al.* 2004; Kirby *et al.* 2008). Interestingly, although not completely surprising given our emerging overall working hypothesis, we demonstrated ATP was capable of blunting direct sympathetically mediated vasoconstriction in older individuals, despite these individuals having impaired exercise-induced functional sympatholysis (Kirby *et al.* 2011). Had we dissociated ATP and sympatholysis with these findings? Or, was it possible ATP retained the same vascular signalling capabilities in older adults, but this population failed to increase ATP during exercise to the same concentration as young individuals? We had begun to make plasma measures of ATP in the laboratory and pursued this hypothesis to tie our multiple studies together. This time, our ageing hypothesis was 'correct' as we showed older individuals failed to increase plasma ATP during incremental handgrip exercise in contrast to the significant increase observed in younger individuals (Fig. 4) (Kirby *et al.* 2012). Thus, while we admittedly have not been able to directly inhibit the purinergic receptors to which ATP binds, as no pharmacology has been established that is capable of doing so, our findings of the mechanisms for ATP-mediated vasodilatation and our ageing data continue to support our overall hypothesis regarding a role for ATP in muscle blood flow regulation during exercise (Fig. 5).

Along the way

The ability to inhibit K_{IR} channels and Na^+/K^+-ATPase has provided the laboratory with a powerful pharmacological tool that we continue to use to address a number of hypotheses. Armstrong and colleagues had demonstrated a role of K^+-mediated vasodilatation in rapid vasodilatation following a single muscle contraction in the hamster

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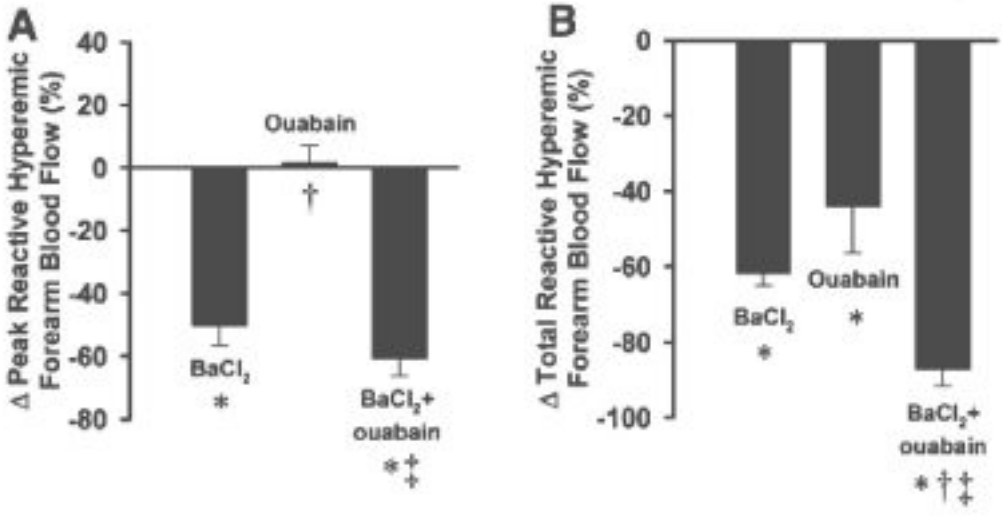

Figure 6. Reactive hyperaemia occurs via activation of K_{IR} channels and Na^+/K^+-ATPase. In young healthy humans, inhibition of K_{IR} channels via barium chloride ($BaCl_2$) significantly attenuates both the peak (*A*) and total (area under 150 s curve) (*B*) reactive hyperaemia (RH) following 5 min of forearm ischaemia (via upper arm cuff arterial occlusion). Inhibition of Na^+/K^+-ATPase via ouabain has no impact on peak RH (*A*) whereas results in a significant attenuation of total RH (*B*) and when combined with $BaCl_2$, nearly abolishes the response. Data are means ± SEM for 8 and 16 subjects ($BaCl_2$ or ouabain and $BaCl_2$+ouabain, respectively). **P* < 0.05 *vs.* zero; †*P* < 0.05 *vs.* $BaCl_2$. ‡*P* < 0.05 *vs.* ouabain. Modified from Crecelius *et al.* (2013*b*).

cremaster (Armstrong *et al.* 2007) using $BaCl_2$ and ouabain along with a pharmacological inhibitor of K^+ efflux from skeletal muscle. Given our interest in rapid vasodilatation and the minimal number of mechanistic studies on the topic (Kirby *et al.* 2007), attempting to translate the findings of Armstrong and colleagues seemed prudent. In general, in line with the findings in the animal model, we demonstrated a significant role for K^+ in mediating a portion of rapid vasodilatation in response to a single muscle contraction at a variety of intensities (Crecelius *et al.* 2013*a*).

Of perhaps greater clinical relevance, we recently determined whether reactive hyperaemia (RH), the large increase in blood flow following release of temporary ischaemia of skeletal muscle, was mediated by K_{IR} channels and Na^+/K^+-ATPase. Although RH is a useful test of microvascular function and has clinical value in assessing risk of cardiovascular health (Anderson *et al.* 2011), prior to our work the underlying signalling mechanisms were largely undetermined. Impressively, nearly all (~90%) of the total (area under the curve) RH can be explained by combined activation of K_{IR} channels and Na^+/K^+-ATPase and ~50% of the peak response is due to K_{IR} channel activation (Fig. 6) (Crecelius *et al.* 2013*b*). This magnitude of inhibition is by far the most profound that has been observed to date.

Moving forward

We continue to pursue our ideas regarding muscle blood flow regulation, specifically during exercise and the unique role ATP may have in modulating sympathetic vasoconstriction. It is often challenging to translate mechanistic findings from animal models and *in vitro* studies to our human model, given our concerns for human safety. Part of what we find inspiring from this story is the integration of physiology and experimental approaches that was required to reach the point we find ourselves at. We drew from findings in older individuals to guide our basic science studies as well as applying our findings from young healthy humans to older individuals. While we probably would not have pursued many of these ideas without the initial findings and discoveries related to NO, we have developed a cautious attitude towards 'endothelial function' as we have seen first-hand this monolayer is far more involved in vascular regulation than simply being a source of NO. Similarly, mechanistic studies *in vitro* and in animal models continue to stimulate ideas and provide rationale; yet, we observe important differences when translating some of these approaches to humans. Importantly, we acknowledge that scepticism, negative findings and unsupported hypotheses have provided us important directions we have excitedly followed.

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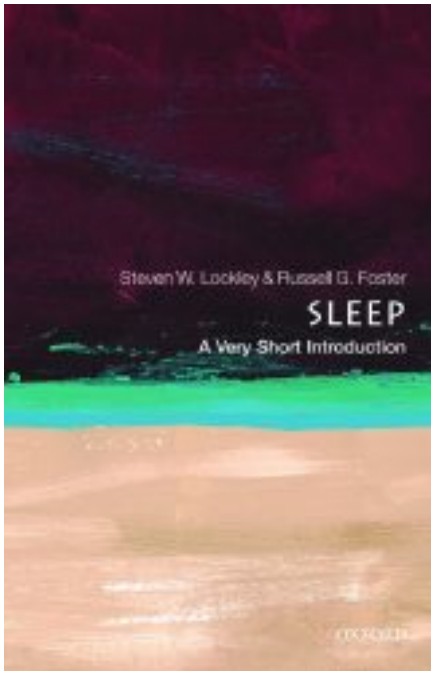
Book review:
Sleep: A Very Short Introduction
By Steven Lockley and Russell Foster

Keith Siew & Yasmin

University of Cambridge



Oxford University Press

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Humans, like many species, live a dual existence divided between the waking world and the realm of dream-filled slumber. Yet, despite spending almost a quarter of our lives asleep, this significant portion of our being still remains one of the greatest physiological mysteries. Why do we sleep? What are its evolutionary origins? What are the consequences of losing sleep?

Russell Foster and Steven Lockley, world leaders in circadian rhythm and sleep, are perhaps the best equipped transatlantic double act capable of addressing these fundamental questions. Throughout the nine chapters of the pocket-sized, 152 page *Sleep: A Very Short Introduction* they weave a captivating tale intertwining the science of sleep with its history and sociological and pathophysiological implications.

You may have always known that not getting enough sleep was ill advised, though with the many pressures of work and social life, sleep often took a back seat to other "more important" things. Having read the litany of severe health and safety consequences attributable to sleep deprivation, one must re-evaluate priorities. Alarmingly, shift workers with prolonged sleep-loss are at 50% higher risk of cancers. Merely, losing an hour's sleep during daylight savings increases heart attacks by 5% for the three weeks after and road accidents by 20%. These startling facts raised by Foster and Lockley cannot simply be ignored! Their concept of 'second-hand sleepiness' is an intriguing one: why is it acceptable for sleepy drivers or healthcare workers to endanger others? For example, changing doctors' shift hours from 24 to 16 reduces attentional failures at night by half and medical errors by 36%. Not so long ago you would hear little rebuke for drink-driving or smoking in public; perhaps the radical societal shifts in attitude towards sleep they propose are truly needed for all our health and well-being. After all, how did we survive before the 24/7 society?

Apart from the portents of sleep-deprivation, the reader will garner insights into why we are either an 'early bird' or 'night owl', cheating jet lag and the dos and don'ts for a good night's sleep. In particular, parents may appreciate the reasons why their teenage son or daughter is zombie-like to a morning class. As the authors state '...teenagers are essentially living in another time zone, so having teenagers get up for school at 7am is like asking adults to wake up at 4am...'

For a very short introduction, this book is an enlightening and fascinating exploration of the neurological enigma. Perhaps 'Chapter 5 - The Seven Ages of Sleep' will have the most impact on readers. For the first-time parents, an understanding of their newborn's ultradian rhythms (<24 hours) can help to develop strategies to minimise parental sleep loss. On the other end of the spectrum, for an estimated 44.4 million people worldwide who suffer with dementia, making changes in care homes, such as increasing indoor brightness during daylight hours, will stabilise the circadian clock improving sleep quality and reducing cognitive decline.

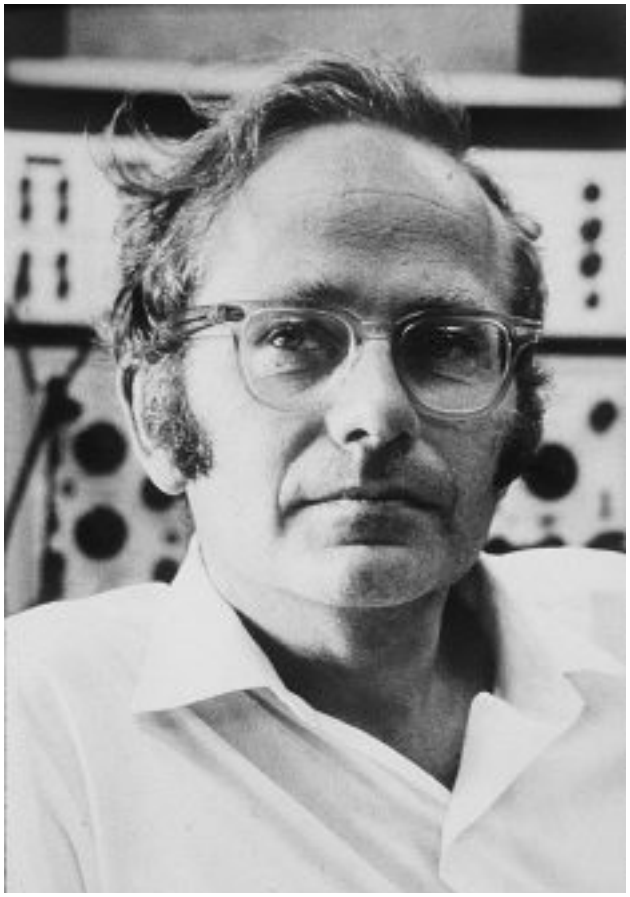
While most of the book is accessible to a non-expert audience, those without a background in neurophysiology may find 'Chapter 3 – The Sleeping Brain' challenging (the authors break the "fourth wall" to warn us and advise a cup to coffee before diving in!). A revised edition would be most welcome to correct some typos and clarify the more technical sections for the lay person, although the book would benefit most from a glossary of terms for the non-sleep/neurophysiology expert.

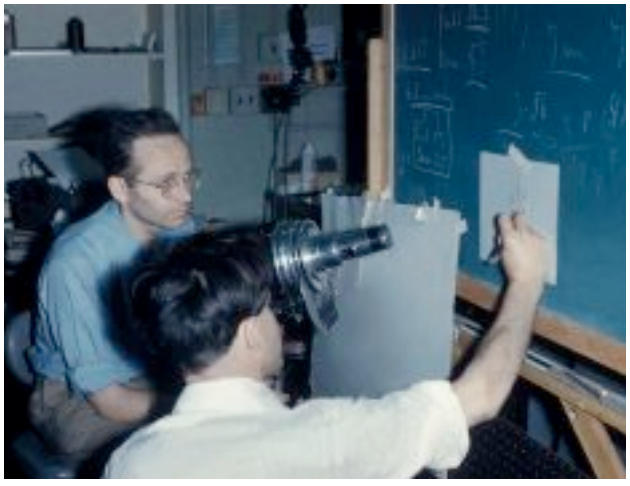
We highly recommend *Sleep: A Very Short Introduction* as a must have for each shelf. You'll be astounded by the difference a good night's sleep can make!

Would you like to submit a book review to *Physiology News*? Please get in touch with us on **magazine@physoc.org**

Letter to David Hubel

To mark the death of the Nobel Prize winner and Society Honorary Member, we here present a tribute to David Hubel by his scientific partner, Torsten Wiesel. This was presented at a memorial event at Harvard University, USA, 16 November 2013.





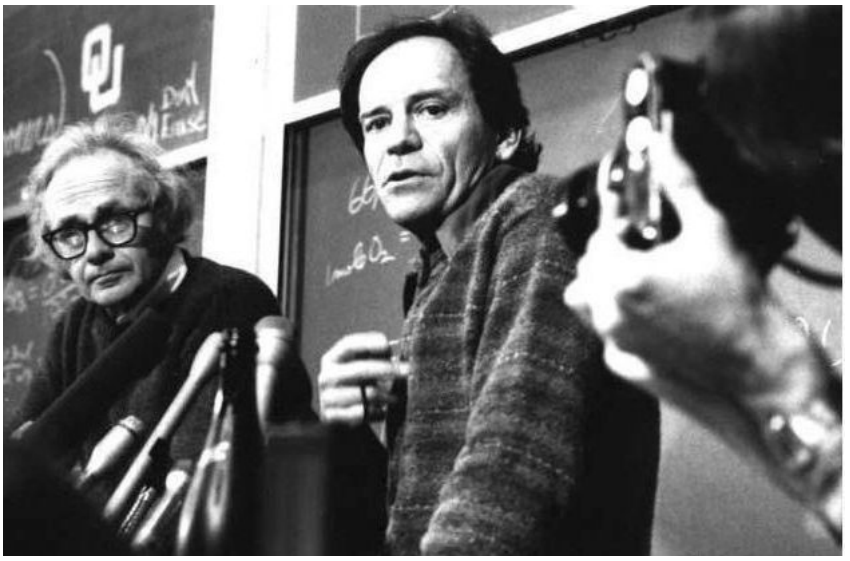
Dear David,

I am writing these words not to say farewell but to point out that you will always remain in my heart and mind as one of the best things that ever happened to me. Even more amazing is that our 20 years working together happened completely by chance. As you well remember, your move to the department of physiology at Johns Hopkins University School of Medicine was delayed because of lab renovations and that Vernon Mountcastle asked Stephen Kuffler at the Wilmer Institute in ophthalmology, where I was a postdoc, if you could be with his group for a year. Steve was delighted and the three of us met. None of us would have guessed how much that lunch meeting would change everything for us, as you and I over many cups of coffee that day began to carve out our future scientific course.

For inexperienced me, having just arrived from Sweden, you were as a gift from heaven coming with your famous tungsten microelectrode, which you had successfully used to record single visual neurons in the awake cat, made possible by elegant chambers machined on your lathe and mounted on the animal's head (a method subsequently copied by colleagues from all over the world). Of course, more than all these technical and inventive skills you came with a brilliant and creative mind.

Our real bonding was probably established while still at Hopkins when at dawn we would go down through dark tunnels to the animal quarters to pick up a cat or monkey to be anaesthetized and later prepared for the experiment. You often like to tell the story when a spider monkey, to our amazement, skillfully used its long tail to pull the syringe with the anesthetic out of my hand as I tried to make the injection in its abdomen. You were also amused when in late night experiments I resorted to speaking Swedish.

These often more than 24 hour experiments were indeed tiring, but the long hours gave us time to get to know each other well and, above all, to explore ideas for future experiments and approaches. We were lucky to, over and over again, get exciting leads from our experiments, which in turn led to new questions and answers. Looking back on the years at Hopkins and Harvard, experiments felt like great adventures, with you rushing down the corridors screaming 'Come and look at this amazing cortical cell responding only to a contour of a given orientation!', and again when we found binocular cells and discovered the columnar organization of the visual cortex. We no doubt will always treasure those days and moments, which nothing can ever match. You must agree that those were the 'golden days'. You used to say that it was like rolling yarn into a big, beautiful ball.



Your ability to write so eloquently is without question that of a true master. This is in part due to your love of the English language – Fowler's Modern English Usage and other books on writing were always on your desk. You will remember the press conference after the announcement of the Nobel Prize, when I emphasized that from the very beginning your writing was critical for the understanding and acceptance of our papers.

You were always the messenger and your talks and lectures about our work are still famous for their clarity and brilliance. I must have heard your presentations of our work countless times and I still enjoyed them time after time.

You also had an amazing talent and passion to communicate, not only about our work, but the many other wonders of nature. You may remember when we visited a small sea resort outside Tokyo in the seventies when 20 or so students came around and you completely charmed them by speaking English and some broken Japanese. Actually, after a fierce effort, you became proficient enough to give a lecture in Japanese. Your passion for engaging with young students kept you yourself youthful. Many Harvard college students over the years have had the joy to listen and talk with you about science and many other interests.

For so many years we experienced the absolute wonder and excitement of discovering something that nobody else knew. Now we must leave it to the next generation, to probe into the secrets of nature yet to be revealed.

Looking back on our years together you will always remain my much admired and beloved scientific brother.

Thank you,

Torsten

(Clockwise from bottom left) David and Torsten at the Wilmer Institute in 1958; David Hubel, 1970s; Meeting the press upon receiving news of their receipt of Nobel Prize in Medicine or Physiology in 1981; One of David's many creative passions was weaving. Pictured here in the spring of 2008 at his home in Newton, Massachusetts, David demonstrates how his loom works; Torsten visiting David at his home in Lincoln, Massachusetts, in 2012

Outreach report: Promoting physiology and related careers in schools

In 2012, The Physiological Society piloted its Public Engagement Grant Scheme, offering up to £5000 to run a public engagement activity discussing physiology. Shelia Amici-Dargan, the first recipient of a grant, reports on how the money has been used.

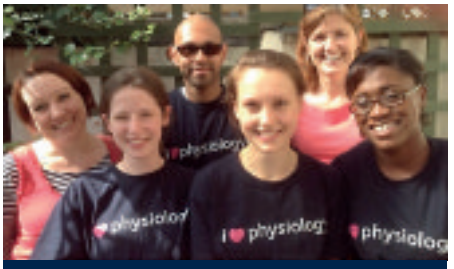
Sheila Amici-Dargan

School of Biosciences,
Cardiff University

The Physiological Society Public Engagement Grant enabled us to develop and deliver a programme of interactive physiology workshops for secondary schools and create online copyright-free resources that can be shared freely amongst Members of The Physiological Society and educators to promote physiology.

In the summer of 2012, two high-achieving undergraduate physiology students, Lucy Olukogbon (funded by The Society) and Lydia Parsons (funded by the Cardiff Undergraduate Research Opportunities Programme, CUROP) worked to design resource packs for secondary school teachers on the following topics: 'breathing and asthma', 'healthy hearts and exercise' and 'muscles and movement'. A variety of interactive resources were developed and piloted in local schools and colleges to make sure the activities were pitched appropriately and could be easily adapted for different age groups. After running these pilot tests, two biology pupils (AS and A2 level) were recruited for three weeks to test our resources, give feedback on their suitability and help make them more engaging to pupils. This opportunity helped the students work towards and achieve their Gold CREST award, a nationally recognised award recognising personal achievements in STEM (science technology, engineering and maths) subjects.

The resource packs contain session plans, a short PowerPoint presentation on the physiology topic and links to useful career resources. The packs also contain simple hands-on activities, quizzes and promotional bookmarks with QR codes and weblinks to The Physiological Society's 'Understanding Life' website and 'CUBE' (see box). Workshop objectives are concisely mapped onto current school curricula (WJEC, AQA, QCR and Edexcel) to help teachers integrate them into their teaching and to give researchers and students a guide to pupils' understanding.



Physiology education and engagement team – Sheila Amici-Dargan, Ruth Jones, Sumit Mistry, Lydia Parsons, Sarah Hall and Lucy Olukogbon

Alongside these resources, we used the funding to run some advanced physiological experiments (ECG, EEG and EMG) using ADI kits in Cardiff, Merthyr Tidfil and Abergavenny. We had some excellent feedback, with one teacher from St David's College commenting, "The students thought it was applicable to the syllabus and enjoyed the style in which it was taught – fun and interactive – but most importantly educational."

To increase the impact of our project and reach wider audiences, we ran sessions at other venues (e.g. Techni-quest 'adult night', teachers' panel day, Foster Carers' event, Cardiff Science Festival, Penylan library and Green Man Festival). We have also just initiated a public engagement training programme for undergraduate bioscience students and researchers to equip them to run workshops with schools and community groups. This will enable us to get out to more schools to promote physiology and related bioscience disciplines, whilst also increasing awareness of the need for current physiological research amongst the general public.

Acknowledgements: Academic staff and students in Cardiff Schools of Biosciences and Psychology (especially Sarah Hall and Fiona Willey, and those who contributed videos/profiles); secondary school pupils and teachers; IT team at Cardiff University; CUROP and Physiological Society funding.

C.U.B.E: Free online resources for physiologists, biomedical scientists and teachers

Ruth Jones, an undergraduate summer student (funded by CUROP) designed a website which we have recently launched called C.U.B.E: Collaborative University Bioscience Engagement. We have started to populate this with resources and will continue to do so. We are building up a collection of short videos of students and researchers to expose pupils to degree schemes, to opportunities at university and to scientific careers. The "CUPID" (Collaborative University Physiology Interactive Demonstrations) section contains examples of simple hands-on activities that are cheap to run and have proved popular with schools and local community groups. We are also creating 'Loan Boxes' which can be borrowed by teachers or researchers to run practical activities.

More recently, we have started creating biomedical research-based activities to expose 'more able and talented' (MAT) pupils to laboratory techniques and to help develop literacy and numeracy skills. Sumit Mistry, an undergraduate summer student (funded by The Physiological Society and CUROP) has been instrumental in developing MAT activities and piloting them in schools across Wales, including Whitchurch High School in Cardiff and Afon Taf High School in Merthyr Tydfil. To date these activities have been well received by pupils (average enjoyment score 4/5 on Likert Scale, $n = 70$) and teachers are keen for us to develop more activities on different research topics. The resources on this website are currently Cardiff-focused, but we are keen to collaborate with other institutions to expand this resource, so please get in touch if you are interested in getting involved: DarganSL@cf.ac.uk

Outreach report: Arnold Hill Academy pupils visit the University of Nottingham

Phillip Rhodes, teacher at Arnold Hill Academy, describes the day his pupils had the opportunity to see where and how physiologists work in a modern academic institution.

Phillip Rhodes

Arnold Hill Academy,
Nottingham, UK

In 2013, David Gardner was awarded an outreach grant from The Society to support a visit to the University of Nottingham's School of Biosciences and School of Veterinary Medicine and Science for pupils of Arnold Hill Academy, Nottingham. On 17 October, 16– and 17– year-old pupils from the Academy were welcomed for a full day of activities. Throughout the day, they were given opportunities to observe and use the fantastic facilities available at the university, which they would be unable to experience in school.

The day began with experiments in the Rob Clarke Teaching Lab within the School of Biosciences. These involved investigating the effect of exercise on oxygen consumption and exhaled gas composition using some very impressive exercise bikes and face masks. Carl Stevenson was the academic lead for the practical, which resulted in many red-faced pupils pushing themselves to the limit (well, to 150 W anyway!).

The pupils were then given the chance to perform electromyography (EMG) on their gastrocnemius, with John Harris and Alan Waterfall as academic leads. They conducted a 'before and after' experiment on themselves, exploring antagonistic pairs of muscles, nerve conduction and various reflex responses. It was at this point that some pupils took great enjoyment in firmly striking one another with a reflex hammer – naturally all in the name of science!

Pupils investigate the effect of exercise on oxygen consumption and exhaled gas composition

After lunch, the pupils were split into three groups. One group was given a tour of the fantastic teaching facilities within the School of Veterinary Medicine and Science (including a dissection room, small group teaching room and lecture theatre) in order to experience the varied environments in which veterinary medicine is taught. Another group looked at the school's veterinary models and specimens in the museum. The remaining group participated in an open discussion and demonstration of cardiac anatomy and physiology delivered by David Gardner – a highlight of which was the plastinated cow and horse hearts.

The pupils found the whole day inspiring. It opened many discussions with lecturers about future careers, physiology and veterinary medicine degree courses and the university application process.

Thank you to The Physiological Society for funding this great opportunity, as well as to David and his colleagues for organising and hosting such a fabulous event.

Feel inspired?

If you'd like to host a similar event at your lab or pursue another way of communicating the excitement of physiology to young people and the wider community, please get in touch: **outreach@physoc.org**.

The Outreach grant scheme can offer funding of up to £1000 for such activities and is open to all Ordinary Members, Affiliates and Associates of The Society.

Colin Ingram

1960 – 2013

Colin Ingram

Colin David Ingram, Director of the Institute of Neuroscience at Newcastle University, passed away suddenly at home on 15 December 2013 aged 53, leaving a wife, Christine, and children Alex, Rachael and Miles.

Colin was an outstanding neuroscientist; his focus throughout his career was on the neuroendocrine systems that regulate stress and reproduction, and his work encompassed studies of the secretion of growth hormone, prolactin, oxytocin, vasopressin and ACTH employing a diverse array of techniques. Lately, his focus was on the psychobiology of stress, anxiety and depression, and this led him to studies of the factors regulating serotonin neurones in the dorsal raphe nucleus, especially the interaction with adrenal steroids, and the possibility that modulation of either corticosteroid levels or their effect might have therapeutic potential for the treatment of affective disorders. He also developed a strong interest in how data may be analysed and shared using developments in the computing grid (cyberinfrastructure) and in this capacity he led the CARMEN e-science project.

I first met Colin when he, then an undergraduate student at The University of Bath, came to the Babraham Institute as a sandwich student to undertake a 6-month research project with John Bicknell and me. We were then interested in stimulus–secretion coupling in the neurohypophysis, and Colin worked with an *in vitro* perifusion system to study oxytocin and vasopressin release from the rat pituitary in response to electrical stimulation. That project led to his first paper, and deservedly he was the first author (Ingram CD *et al.* 1982, *Neuroendocrinology* 35, 424-8). His success marked him out as an exceptional talent, and after graduating from Bath (with first class Honours, in 1982) he returned to Babraham for his PhD, where he made pioneering studies of the electrical activity of lactotrophs. With his PhD behind him, in 1986 he went to Bristol as an MRC Training Fellow, where he worked with Jon Wakerley on the control of the milk-ejection reflex and where he forged a key collaboration with Francoise Moos, then in Strasbourg. In 1988, he won a Royal Society University Research Fellowship, and in 1996, was appointed a reader at Bristol. This period saw Colin develop a key collaboration with Stafford Lightman, studying the hypothalamo-pituitary-adrenal stress axis. That collaboration continued throughout his career, long surviving his own move to Newcastle University in 2000. The 26th paper from that productive collaboration appeared last year in *Endocrinology*.

Colin's work for the broader scientific community won him enormous respect and affection internationally, and he forged close links with scientists from Romania to Australia. He was a stalwart (and one of the founding members) of the British Society for Neuroendocrinology, and with Stafford Lightman was an organiser of the International Congress of Neuroendocrinology at Bristol in 2002. He became very active in the British Neuroscience Association and at the time of his death was their Honorary Secretary.

Colin's talents as a communicator and teacher were well known, and are well displayed in a video of his keynote lecture at Kobe in 2004 'Working in the clouds: creating an e-science collaborative environment for neurophysiology' youtu.be/hdR10_A-vR0

Gareth Leng

The Society also regrets to announce the death of:

Helen Duke

who became a Member in 1950 and published in respiratory physiology while at the Royal Free Hospital School of Medicine and the Middlesex Hospital Medical School.

Roger Wadsworth

who was elected a Member in 1990 and was Professor of Cardiovascular Pharmacology at the University of Strathclyde.

Notices and full obituaries can be found The Society website at www.physoc.org/obituary-notices

New Director of Publications: Simon Rallison

Apart from a brief postgraduate spell as a theoretical ecologist, Simon is a career-long science publisher, previously working at Blackwell (where in 2002 his team bid successfully for The Society's journal contract), Springer and the sustainability publisher Earthscan. Until recently he was a Visiting Lecturer at UCL, teaching the journals module of UCL's MA course in publishing.

In his spare time Simon puts his knowledge of aquatic foodwebs to practical use, fly fishing in Scotland..

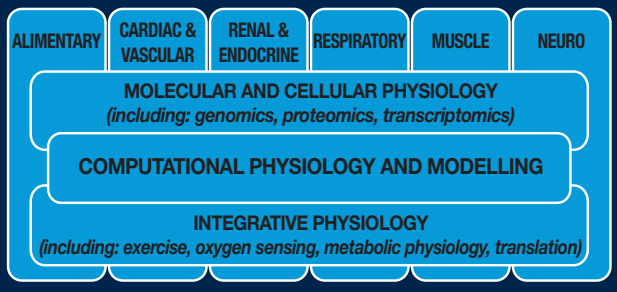
The Journal of Physiology

2013: Another Year of Progress

After another busy and fruitful year for *The Journal of Physiology*, we continue our mission to promote excellence in the communication of physiology. In 2013 full-text downloads exceeded 5.7 million, highlighting the need for us to maintain our loyal readership by promoting *The Journal* and its content in new and engaging ways online.

Focusing scope

The pictogram below aims to visually define our scope for the benefit of authors. We welcome submissions across the range of tissues and systems (vertical bands), and also papers that cut across these systems (horizontal bands). Computational Physiology and Modelling could cover any of the categories and is all-encompassing in its breadth of coverage.



Editorial Board changes and achievements

In the 2014 New Year Honours list, Peter Ratcliffe FRS, one of our Consulting Editors, was awarded a knighthood for his services to clinical medicine. Simon Gandevia and Ole Paulsen have been selected to join our team of Senior Editors.

Plans for the future

In 2014, we will target the European Society of Cardiology's annual meeting in Barcelona, Spain, with the aim of attracting submissions from the cardiovascular community closer to home.

We will be publishing a special issue devoted to the integration of evolutionary biology with physiological science which is being spearheaded by Consulting Editor Denis Noble in collaboration with former Reviewing Editor Mike Joyner and others.

Experimental Physiology

Sponsored symposium at Experimental Biology

The Physiological Society and *Experimental Physiology* are sponsoring the symposium 'Physiological and pathophysiological signalling between the gut and the kidney: role in diabetic kidney disease' (30 April 14.30–16.30, San Diego Convention Center, USA – organised by Carel le Roux, Dublin). Reports from the symposium will be published in *Experimental Physiology*.

An 'Editor's Choice 2014' virtual issue will be freely available to delegates at the meeting, containing examples of the integrative and translational research recently published in *Experimental Physiology*.

New Editor

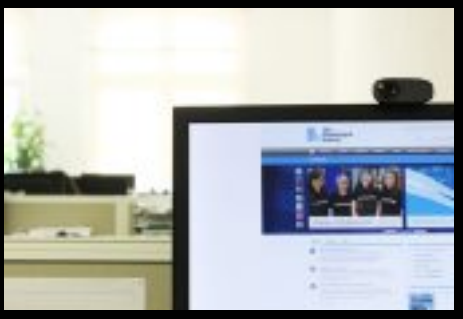
The Editorial Board are pleased to welcome Kate Denton, Senior Research Fellow of the National Health and Medical Research Council of Australia and Head, Cardiovascular and Renal Physiology, Monash University, Melbourne, Australia. Kate's goal is to improve cardiovascular health for men and women across their lifespan by building a strong interdisciplinary and translational research program around the integrative control of arterial pressure, with a strong emphasis on the contribution of the kidney.

Physiological Reports

At the end of its launch year, we are pleased to report that *Physiological Reports* had published 178 research articles. The Editorial Board has 102 members in addition to the Editor-in-Chief, Deputy Editor-in-Chief and four Associate Editors, as well as six Consulting Editors.

Editor-in-Chief Sue Wray says, "I am delighted with the success of *Physiological Reports* since its launch and all the signs are that 2014 will be even more successful. At the end of the year we had had over 300 submissions, demonstrating the need for a journal that accepts papers over the whole range of physiology and is open access. Importantly submissions have remained robust after our initial fee waiver period expired. Our author survey results came back so glowing that it will be hard to improve on them – with 100% of authors marking their experience 'great' (78%) or good. Finally I am particularly pleased to report that our robust publication schedule has allowed us to already be featured on PubMed, which was one of our key objectives for this new journal. Please take a look at our website to see the range of interesting papers we have published and to be abreast of the exciting developments we have planned."

Re-launch for physoc.org



A 'refreshed' www.physoc.org launched in March, as part of a programme to make The Society's online offering more attractive and more usable.

In 2013, a group of Members was convened to advise on certain issues around the site, and the new-look and simplified navigation represent delivery on their initial recommendations. An improved homepage design aims to offer our various audiences quicker access to what they need. The homepage is also designed to be usable from mobile devices. Throughout 2014, work based on the further advice of the Website Working Group will continue on the sections of the site to make each more conducive to the aims of The Society and the needs of the user.

Website Working Group member, Fiona Hatch, said: "The website has previously been a frustration for me, and I'm sure it was for others. But now it has been modernised and revamped as part of The Society's ongoing efforts to make the site clearer and more inviting for the public and Members alike."

Our thanks to the Working Group (Richard Vaughan-Jones, David Eisner, David Miller, Fiona Hatch, Pavel Demidov and Victor Owoyele) for their invaluable contribution to this work.

Benevolent Fund

The Benevolent Fund of The Physiological Society is an unincorporated charity established in 1976 'for the purpose of assisting Members of The Physiological Society and staff and former staff (who by the nature of their employment can be considered to have contributed to the advancement of physiology) employed at teaching, research and industrial establishments who are in necessitous circumstances and their dependents'.

Help can be given in the following ways:

- Health and carer support including assistance towards specialist wheelchairs, home adaptations, mobility equipment and respite care (including welfare breaks)
- Short-term financial assistance in the form of grants and donations in exceptional financial difficulties including funeral arrangements, medical treatment, grants for re-training and childcare arrangements

The Fund now has its own dedicated website which can be accessed at **www.physoc.org/benfund**

100 leading UK scientists

Society Members featured prominently in a list of 100 leading scientists published by the Science Council in an effort to challenge the prevalent, narrow concept of scientists as purely academics.

Deputy Chair of the Education and Outreach Committee, Judy Harris, earns her listing under 'Teacher Scientist' for championing higher education teaching as a profession through international collaborative projects and workshops. Judy said: "It's wonderful that the Science Council have included the category of the 'teacher scientist'. I hope that this will send a really positive signal to all teacher scientists both within and outside higher education, and to the organisations within which they work. Many colleagues right across the life science sector have contributed much, and I hope that the sector recognises the teamwork that has made for the successes achieved."

Other Society Members on the list include Colin Blakemore, Dame Kay Davies, Sir Paul Nurse, Alison McConnell, Dame Nancy Rothwell and Max Headley.

See the full 100 leading UK practising scientists list: **www.sciencecouncil.org/content/100-leading-uk-practising-scientists**

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