The enzyme 11β-hydroxysteroid dehydrogenase type 2 (hsd11b2) confers mineralocorticoid specificity to the mineralocorticoid receptor (MR) by converting the potent agonist cortisol to inactive cortisone. Inactivating mutations in HSD11B2 cause Apparent Mineralocorticoid Excess (AME), resulting in severe hypertension and hypokalemia. AME is rare, but polymorphisms within the general population have been linked to Na⁺ sensitive hypertension (1, 2). We assessed the effect of a high Na⁺ diet on blood pressure (BP) and renal function in hsd11b2+/- mice, which have a 50% reduction in enzyme activity.

Two protocols were used to measure BP and renal Na⁺ handling. In the first, male hsd11b2+/-(n=6) and hsd11b2+/+(n=5) mice were housed in metabolic cages with daily Na⁺ excretion measured. Mice were fed control diet (0.25% Na⁺) for 3 days, followed by high Na⁺ diet (2.5% Na⁺) for 7 days. After this period, systolic BP (SBP) was recorded by tail plethysmography. In the second protocol, hsd11b2+/- and hsd11b2+/+ mice (both n=7) were maintained on a high Na⁺ diet before being anaesthetised (Inactin, 100mg/kg IP) and prepared for renal function experiments as described (3). After a control collection of urine, the ENaC antagonist amiloride (2mg/kg IV) was administered, and a second collection made. Arterial BP was measured throughout. Data are mean ± SE; statistical comparisons were made using either t-test or ANOVA, as appropriate.

On control diet SBP was similar in hsd11b2+/- and hsd11b2+/+ mice display blunted natriuresis, increased blood pressure and impaired ENaC regulation on a high Na⁺ diet

E. Craigie and M. Bailey

Centre for Cardiovascular Sciences, The University of Edinburgh, Edinburgh, UK

The natriuretic response can therefore be induced by the infusion of γ-MSH and is one method of regulating osmolality and plasma sodium concentration in rats chronically fed a high salt diet. This system may be an important target to modulate in those with salt-sensitive hypertension.

Authors have confirmed where relevant, that experiments on animals and man were conducted in accordance with national and/or local ethical requirements.
Renal sodium handling in a mouse model of Cushing’s Syndrome

M.A. Bailey, N. Wrobel, J.J. Mullins and C.J. Kenyon

Centre for Cardiovascular Science, The University of Edinburgh, Edinburgh, UK

Cushing’s Syndrome can be caused by ACTH secretion from pituitary adenomas or from ectopic tumours and is characterized by glucocorticoid excess, central obesity, altered metabolism of glucose and hypertension. Hypertension is an important predictor of outcome in Cushing’s Syndrome and although the causes are not fully known, renal sodium reabsorption may be a contributory factor (Ferrari, 2003). Cushing’s has been modeled experimentally in rats but this is not ideal as ACTH excess causes a profound weight loss, rather than the central obesity seen in humans. Our previous studies indicate that ACTH infusion in the C57BL6 mouse causes hypertension without the catabolic effects seen in rats (Kenyon et al, 2007). In the present study, we have investigated the effect of ACTH infusion on renal sodium handling.

Male C57BL6 mice (~25g) were infused via osmotic minipump (under halothane anaesthesia (2% with oxygen by inhalation)) with ACTH (n=7. Synacthen; 3μg/day) or saline (n=7) for two weeks before being anaesthetized (Inactin; 100mg/kg IP) and prepared surgically for renal function experiments as described (Bailey et al, 2008). Mice were infused IV with a saline solution (0.2ml/h/10g) containing FITC-inulin for the measurement of glomerular filtration rate (GFR). After a control urine collection, amiloride (2mg/kg; IV) was injected and a second urine collection was made. At the end of the experiments, mice were killed with an overdose of anaesthetic and the kidneys removed for extraction of RNA. The expression of mRNA encoding subunits with ACTH (n=7. Synacthen; 3μg/day) or saline (n=7) for two weeks before being anaesthetized (Inactin; 100mg/kg IP) and prepared surgically for renal function experiments as described (Bailey et al, 2008). Mice were infused IV with a saline solution (0.2ml/h/10g) containing FITC-inulin for the measurement of glomerular filtration rate (GFR). After a control urine collection, amiloride (2mg/kg; IV) was injected and a second urine collection was made. At the end of the experiments, mice were killed with an overdose of anaesthetic and the kidneys removed for extraction of RNA. The expression of mRNA encoding subunits of the epithelial sodium channel (ENaC) and the Na-K-2Cl cotransporter (NKCC2) were measured by quantitative RT-PCR.

Authors have confirmed where relevant, that experiments on animals and man were conducted in accordance with national and/or local ethical requirements.

Role of the N-terminal in the targeting of the mouse urea transporter mUT-A3

V.M. Collins and G. Cooper

Biomedical Science, University of Sheffield, Sheffield, UK

The efficient handling of urea by the kidney is crucial for the development of maximally concentrated urine. The inner medullary collecting duct (IMCD) plays an important role in urea reabsorption. The transport of urea across the IMCD is governed by the UT-A family of urea transporters, with UT-A3 providing a pathway across the basolateral membrane. In the current study we have investigated the role of the N-terminal of UT-A3 on membrane targeting.

All clones were N-terminally tagged with eGFP. N-terminal truncations were created by standard PCR protocols, verified by sequencing and subcloned into the eGFP expression plasmid pEGFP-C2. The MDCK II cells were grown on permeable filters and transiently transfected with 1μg of cDNA. Cells were fixed and the localisation of each construct determined by immunofluorescence and confocal microscopy. The apical membrane was labelled with TRITC-conjugated peanut agglutinin and the basolateral membrane was labelled using a primary antibody against β-catenin and a Cy-5 conjugated secondary antibody. Transfections were replicated 3 times for each construct.

When expressed in MDCK II cells, mUT-A3 is delivered to the basolateral membrane of the cell (Stewart et al., 2004). We have shown previously (Cooper and Collins, 2006) that removing the initial 55 residues of UT-A3 (M55-start) does not affect urea-transporting ability. However when expressed in MDCK II cells, M55-start targets to the apical membrane. When we removed the initial 25 residues (S25-start) we found that targeting was once again basolateral. When expressed in LLC-PK1 cells mUT-A3 targeted to the apical membrane. LLC-PK1 cells lack the μ1B subunit of the adaptor protein 1 complex (AP1-μ1B). The μ1B subunit has been implicated in basolateral targeting of a number of proteins (Folsch et al., 1999). We expressed mUT-A3 and M55start in LLC-PK1 cells stably transfected with AP1-μ1B. Although mUT-A3 was now targeted to the basolateral membrane, the M55-start clone was still resident in the apical membrane. Our results indicate that a region between residues 25
TASK-3 potassium channels: gating at the cytoplasmic mouth of the channel  

P.R. Stanfield¹, I. Ashmole¹, P.J. Stansfeld² and M.J. Sutcliffe³

¹Biological Sciences, University of Warwick, Coventry, UK, ²Biochemistry, University of Oxford, Oxford, UK and ³Manchester Interdisciplinary Biocentre, University of Manchester, Manchester, UK.

We have used patch- and two electrode voltage-clamp recording, site directed mutagenesis and molecular model building to ask whether the tandem pore potassium channel TASK-3 is gated at the ’helix bundle crossing’. Although tandem pore channels are described as constitutively open, the P(open) of wild type TASK-3 channels, heterologously expressed in CHO cells, was only 0.023 ± 0.0004 (mean ± sem, n=6) at -80mV (140mM-K). P(open) increased with depolarisation, but with a low gating charge (z′=0.16). We have used this voltage dependence to examine effects of mutations on gating.

Replacement with threonine of an alanine residue, A237, close to the cytoplasmic end of membrane helix M4, raised P(open) to 0.205 ± 0.031 (n=3) in the same conditions. The voltage dependence of P(open) is shifted more negative potentials without change in gating charge. The shift gives an energy difference of ~1.2kcal/mol, consistent with the mutant channel being held open by a H-bond (or bonds). Contrary to our previous report, we can find no change in the response of A237T to acidification (measured in channels expressed in Xenopus oocytes) (Ashmole et al., 2005). Gating in response to acidification occurs at the selectivity filter (Yuill et al., 2007).

Modelling TASK-1 (which has strong identity with TASK-3) using KvAP (jiang et al, 2003) as template suggests a H-bond between Thr in position 237 and Asn 133, at the cytoplasmic end of M2. However, N133A also has a raised P(open), as does the dual mutant N133A/A237T. Neither mutant form of the channel has an altered response to acidification.

Gating at the bundle crossing of helices M2 and M4 is expected to occur around hinge glycines. Such residues are conserved through the tandem pore family, in TASK-3 at positions 117 (M2) and 231 (M4). In G117A and G231A; P(open) is reduced to 0.0021 ± 0.0003 (n=3) and 0.0039 ± 0.0013 (n=4) respectively. The voltage dependence is shifted positive, again without change in gating charge. In spite of a low P(open), macroscopic currents can be recorded from G117A and G231A (oocyte expression). The pH-sensitivity of these currents is again unaltered from wild type. Voltage dependence is weak and its physiological importance is uncertain. But this voltage dependence appears to involve gating by movements of M2 and M4 similar to those found in other potassium channels. It is likely that modulation of TASK-3 by hormones, neurotransmitters and inhalational anaesthetics (Kim, 2005) occurs by gating at this part of the channel.


We thank the Wellcome Trust for support.

Authors have confirmed where relevant, that experiments on animals and man were conducted in accordance with national and/or local ethical requirements.

CAMP-initiated but PKA-independent regulation of vascular ATP-sensitive K⁺ channels: The role of exchange proteins directly activated by cAMP

G.I. Purves¹, T. Kamishima², L.M. Davies¹, J.M. Quayle² and C. Dart¹

¹Biological Sciences, University of Liverpool, Liverpool, UK and ²Department of Human Anatomy and Cell Biology, University of Liverpool, Liverpool, UK

The exchange proteins directly activated by cyclic AMP (Epac or cAMP-GEF) are a family of cAMP-regulated guanine nucleotide exchange factors (GEF) [1]. Binding of cAMP to Epac activates the GEF activity thus stimulating the exchange of GTP for GDP on the monomeric G proteins Rap1/2 [1]. The discovery of the Epac proteins (Epac1/2) has raised the possibility of novel signalling pathways for cAMP that are independent of its traditional target, protein kinase A (PKA). It has previously been reported using yeast two-hybrid screening that Epac interacts with sulphonyleurea receptors (SUR) [2], the regulatory subunits of ATP-sensitive potassium (K₅ATP) channels. This suggests that Epac may play a role in the regulation of K₅ATP channel activity. Indeed, we found that antibodies directed against Epac1 co-immunoprecipitate SUR2B, the dominant SUR subtype found in vascular smooth muscle, from rat aortic homogenates. Also, using the Epac-specific cAMP analogue 8-pCPT-2'-O-Me-cAMP at concentrations that activate Epac but not PKA, we show cAMP-mediated but PKA-independent modulation of vascular K₅ATP channels. Application of 8-pCPT-2'-O-Me-cAMP (5 μM) caused a 41.6 ± 4.7 % inhibition (mean±SEM; n=7) of pinacidil-evoked whole-cell K₅ATP currents recorded in isolated rat aortic
(Simán et al 2001). Medium was collected daily for analysis of hCG (ELISA: mIU/h/mg protein) and lactate dehydrogenase (LDH), a marker of cellular integrity, (Cytotoxicity Detection Kit: absorbance units/h/mg protein), and extracts treated daily with K+ channel modulators, or medium alone, on days 3-6. Data are presented as mean±SE, with n=5 placentas and analysed by 2 way ANOVA with Bonferroni post tests.

hCG secretion increased from day 3 of culture, rising from 1.13±0.14 to 3.63±0.69 at day 6, while LDH release was stable at 0.071±0.02 and 0.065±0.01 respectively, coincident with syncytiotrophoblast regeneration previously reported (Simán et al 2001). Tetraethylammonium (TEA: blocker of voltage-gated (KV) and calcium-activated (KCa) K+ channels) prevented the increase in hCG secretion over days 4-6, significantly reducing hCG secretion at 5mM (1.61±0.24) and 10mM (1.1±0.28) on day 6 compared with control (p<0.05). 4-aminopyridine (4-AP: blocker of KV channels) did not alter hCG secretion at 1mM on day 6 compared with control (p<0.05). In contrast, the K+ channel opener cromakalim (10μM) was without effect (3.41±0.63 at day 6, n=4). None of the K+ channel modulators altered LDH release, indicating that the inhibition of hCG secretion by TEA and 4-AP was not caused by loss of tissue integrity.

We conclude that KCa and/or KV channels, sensitive to TEA and 4-AP, modulate hCG secretion by placental trophoblast. Modulation may occur either directly, by altering the secretory mechanism, or indirectly, by influencing the cellular turnover required for syncytiotrophoblast renewal.


Supported by Tommy’s, the baby charity.

**Authors have confirmed where relevant, that experiments on animals and man were conducted in accordance with national and/or local ethical requirements.**

**PC40**

Placental materno-fetal transfer of amino acids by exchangers

J.K. Cleal, K.M. Godfrey, M.A. Hanson and R.M. Lewis

The University of Southampton, Southampton, UK

Objectives: The mechanisms mediating amino acid transport across the basal membrane of placental syncytiotrophoblast and into the fetal circulation are not well understood. Our previous data indicate that amino acid exchangers mediate serine (ser) and leucine (leu) transport into the fetoplacental circulation in exchange for specific amino acids (Cleal JK et al., (2007)) Physiol 582, 871-882). This study characterises amino acid stimulation of alanine (ala), phenylalanine (phe), tyrosine (tyr), isoleucine (iso), lysine (lys), threonine (thr), and glutamine (gln) transfer into the fetoplacental circulation. Methods: Human placentas (n = 5 per amino acid) were collected within 30 minutes of delivery and an intact cotyledon was perfused with a modified Earl’s bicarbonate buffer. The maternal arterial circulation was perfused with 50 μmol/l of amino acid plus radio-labelled tracer amino acid and 1.8 mM creatinine to determine the rate of paracellular diffusion. Amino acid [12.5 μmol] boluses were administered to the fetal side inflow perfusate. 14C- and 3H-labelled amino acids were measured in maternal and fetal (indicating transport) venous samples by liquid scintillation counting. Data (mean ± SEM) were expressed as area under the curve and analysed by one-way ANOVA.

Results: Following fetal arterial boluses of specific amino acids transfer of ala, phe, tyr, iso, lys, thr, and gln increased, indicating that transport by exchange was taking place (Table 1).

**Conclusion:** This study demonstrates that in the perfused human placenta amino acids are transported into the fetal circulation by exchange mechanisms. The data indicates activity of the exchangers ASC, LAT1 and y’LAT between the placenta and fetal circulation. This provides an important mechanism by which maternal amino acids can be transported to the fetus and thus be available for fetal growth and development.

Table 1: Amino acid exchange between the placenta and feto-placental circulation

<table>
<thead>
<tr>
<th>Fetal bolus</th>
<th>Maternal amino acid (mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ala</td>
</tr>
<tr>
<td>glu</td>
<td>0.1±0.7</td>
</tr>
<tr>
<td>ala</td>
<td>174±56*</td>
</tr>
<tr>
<td>the</td>
<td>83±13*</td>
</tr>
<tr>
<td>ser</td>
<td>86±25*</td>
</tr>
<tr>
<td>gln</td>
<td>69±15</td>
</tr>
<tr>
<td>lys</td>
<td>7±4</td>
</tr>
<tr>
<td>leu</td>
<td>20±3</td>
</tr>
<tr>
<td>trp</td>
<td>197±30*</td>
</tr>
<tr>
<td>bch</td>
<td>5±3</td>
</tr>
</tbody>
</table>

*P<0.05, significantly different to glutamate (glu), 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid (bch), glycine (gly), tryptophan (trp).

This work was supported by The Henry Smiths Charity.

**Authors have confirmed where relevant, that experiments on animals and man were conducted in accordance with national and/or local ethical requirements.**

**PC41**

Renal actions of urotensin II in anaesthetised young rats

E.J. Forty and N. Ashton

Faculty of Life Sciences, The University of Manchester, Manchester, UK

Urotensin II (UII) has been implicated in transepithelial sodium transport in fish [1] and in mammalian renal function [2]. We have shown that infusion of exogenous rat UII in the adult Sprague-Dawley (SD) rat, at a dose with minimal effect on the renal vasculature, decreased renal tubular sodium reabsorption [3]. As urinary concentrating ability develops over the first few post-natal weeks in the rat, the aim of this study was to
determine the renal actions of UII in young SD rats. Inactin anaesthetised (10mg. 100g bwt⁻¹, i.p.) 4-week-old male SD rats (n = 5 per group) were infused i.v. with 0.154M NaCl containing ³²H inulin (0.3μCi h⁻¹) and para-aminohippuric acid (3mg h⁻¹) as markers of glomerular filtration rate (GFR) and effective renal blood flow (ERBF), respectively, at a rate of 40μl min⁻¹ for 2.5h. Animals then received either vehicle or rat UII at 0.6 or 6 pmol.min⁻¹.100g bwt⁻¹ for 1h. Urine was collected from a bladder catheter every 15 mins, two blood samples (0.4ml) were taken via a carotid artery catheter. Animals were killed humanely at the end of the experiment. Rat UII at either dose had no effect on mean arterial blood pressure (vehicle 92±5 vs rUII at 6pmol 108±7mmHg) or ERBF (Table 1). Compared with the vehicle-infused group, rUII at 6pmol induced an initial 30% reduction in GFR after 15 mins (vehicle 0.6±0.1 vs rUII 0.4±0.1 ml.min⁻¹.100g bwt⁻¹) which returned to control levels after 45 mins. Rat UII also induced a 50% reduction in urine flow (UV) and sodium excretion rates (UNaV) which returned to control levels after 45 mins. The antidiuretic hormone arginine vasopressin (AVP) mediates the calmodulin-dependent increase in urea permeability in the rat inner medullary collecting duct (IMCD) [2, 3]. It is therefore likely that one, or both, of these proteins is involved in the calmodulin-dependent increase in urea permeability in this portion of the renal tubule.

In this study, the effect of the calmodulin inhibitor W-7 on transepithelial urea flux by monolayers of Madin-Darby canine kidney (MDCK) cells stably expressing rat UT-A1 was investigated. In the absence of AVP, transepithelial urea flux was 1.64 ± 0.34 (mean ± S.D.) nmoles/cm²/min (n = 4). Under these control conditions DMU-sensitive urea flux was 0.80 ± 0.22 nmoles/cm²/min (n = 4). In the presence of 100nM AVP transepithelial urea flux increased to 4.41 ± 0.66 nmoles/cm²/min (P<0.01; ANOVA; n = 4) and DMU-sensitive flux was 3.01 ± 0.25 nmoles/cm²/min (n = 4). In the presence of the calmodulin inhibitor W-7, AVP-stimulated DMU-sensitive urea flux was reduced significantly to 1.14 ± 1.00 nmoles/cm²/min (P<0.01; ANOVA; n = 4). In contrast, the presence of Calphostin-C (PKC inhibitor), CKII (Casein kinase II inhibitor) or H-89 (PKA inhibitor) had no effect on AVP-stimulated, DMU-sensitive urea flux (P>0.05; ANOVA; n = 4). These data suggest AVP regulation of the UT-A1 urea transporter is dependent on calmodulin, supporting a role for UT-A1 in the calmodulin-dependent regulation of urea permeability in the rat inner medullary collecting duct. However, further studies are required to confirm this and to elucidate the molecular mechanisms involved.


This work was funded by Kidney Research UK.

Authors have confirmed where relevant, that experiments on animals and man were conducted in accordance with national and/or local ethical requirements.
in CaR$_{TP88}$ phosphorylation (160kDa mature, membrane-localised receptor; P<0.001 by ANOVA, N=6). However, following 10 min treatment with higher Ca$^{2+}$o concentrations (3-5mM), CaR$_{TP88}$ phosphorylation was not elevated. The effect of 2mM Ca$^{2+}$o treatment (which also elicited oscillatory Ca$^{2+}$i mobilisation) on CaR$_{TP88}$ phosphorylation was sustained for at least 20mins. However, 5mM Ca$^{2+}$o (associated with sustained Ca$^{2+}$i mobilisation) did increase CaR$_{TP88}$ phosphorylation briefly, but with levels returning to baseline within 2mins suggesting that increased CaR activation might induce subsequent CaR$_{TP88}$ dephosphorylation. To test this, CaR$_{TP88}$ phosphorylation was first induced by phorbol ester treatment (1μM PMA, 10 mins) with the cells then incubated for 30secs in buffer containing either 1.2, 2.2 or 5mM Ca$^{2+}$o, or 1.2mM Ca$^{2+}$o plus the CaR positive allosteric modulator L-Phe (10mM) [3]. Increasing [Ca$^{2+}$]o stimulated subsequent CaR$_{TP88}$ dephosphorylation (1.2mM, 33±14%; 2.2mM, 52±9%; 5mM, 78±5%, P<0.05 vs 1.2 by ANOVA; N=8) whereas L-Phe was without additional effect (31±9%). Therefore, orthosteric CaR activation elicits CaR$_{TP88}$ dephosphorylation perhaps contributing to the high frequency oscillatory and sustained Ca$^{2+}$i mobilisation responses to Ca$^{2+}$o. In contrast, the failure of L-Phe to stimulate CaR$_{TP88}$ dephosphorylation may explain why this CaR modulator elicits low frequency Ca$^{2+}$i oscillations. Therefore, CaR$_{TP88}$ is subject to agonist-specific phosphorylation and dephosphorylation in CaR-HEK cells. Such receptor-elicited dephosphorylation of this protein kinase C consensus site could help explain the control of signal oscillation frequency observed in this and other type III G protein-coupled receptors.


Authors have confirmed where relevant, that experiments on animals and man were conducted in accordance with national and/or local ethical requirements.

Renal haemodynamics in healthy volunteers and type 2 diabetic persons after endotoxin injection

A. Andreasen 1,2, T. Pedersen-Skovsgaard 1,2, H. Gutte 3, R.M. Berg 1,2, A. Kjær 3, B. Feldt-Rasmussen 4 and K. Møller 1,2

1Centre of Inflammation and Metabolism M7641, Rigshospitalet, Copenhagen, Denmark, 2Intensive Care Unit 4131, Rigshospitalet, Copenhagen, Denmark, 3Department of Clinical Physiology, Rigshospitalet, Copenhagen, Denmark and 4Department of Nephrology, Rigshospitalet, Copenhagen, Denmark

BACKGROUND: Acute kidney injury develops in 20-50% of patients with sepsis and septic shock (1), the risk being increased in patients with type 2 diabetes (2). To which extent, if any, changes in renal haemodynamics during sepsis contribute to the pathogenesis of AKI, remains controversial. The aim of this study was to measure renal plasma flow (RPF) and glomerular filtration rate (GFR) in healthy volunteers and persons with type 2 diabetes, respectively, using an intravenous injection of Escherichia coli endotoxin as a model of systemic inflammation during early sepsis.

METHODS: After ethical approval, a thorough physical examination and informed consent, RPF and GFR were measured with DTPA renography in 16 healthy men and 16 men with type 2 diabetes at baseline as well as 1.5 hours and 6.5 hours after endotoxin injection (0.3 ng/kg). Noninvasive blood pressure and heart rate were measured every 15 minutes. Filtration fraction (FF) was calculated as GFR / RPF. Repeated measurements analysis of RPF, GFR and FF were performed using SAS Mixed Models with the model TIME GROUP TIME*GROUP and SUBJEC as a random factor. Significant changes from baseline were analysed post hoc with paired t-tests.

RESULTS: Data are presented in the Figure “Renal Haemodynamics” and Table 1. A mixed model analysis showed no interaction between time and group (healthy vs. diabetics). Time, but not group, had a significant effect on RPF (P<0.001), GFR (P<0.01) and FF (P<0.05). Mean arterial pressure and heart rate were unchanged. A systemic inflammatory response with leucocytosis, temperature rise and malaise was seen but resolved within 6 hours. CONCLUSION: RPF, GFR and FF are reversible reduced during early systemic inflammation triggered by an injection of Escherichia coli endotoxin. The presence of type 2 diabetes did not affect these changes. The results suggest a role for renal haemodynamic alterations in sepsis-induced acute kidney injury. In contrast, the significance of these changes for the increased risk in diabetic patients of developing acute kidney injury during sepsis is less clear.

Table 1. Renal Haemodynamics - Healthy / Diabetics

<table>
<thead>
<tr>
<th>Hours post Endotoxin</th>
<th>0 (Baseline)</th>
<th>1.5</th>
<th>6.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Observations</td>
<td>16 / 16</td>
<td>16 / 16</td>
<td>16 / 15</td>
</tr>
<tr>
<td>RPF (ml/min) - Mean (SEM)</td>
<td>742 (64) / 701 (74)</td>
<td>662 (58) / 534 (78)</td>
<td>905 (97) / 704 (52)</td>
</tr>
<tr>
<td>RPF (ml/min) - Mean change from baseline (SEM)</td>
<td>-79 (36) / -167 (66)</td>
<td>164 (68) / 24 (70)</td>
<td></td>
</tr>
<tr>
<td>GFR (ml/min) - Mean (SEM)</td>
<td>110 (6) / 111 (7)</td>
<td>102 (4) / 82 (10)</td>
<td>110 (7) / 110 (7)</td>
</tr>
<tr>
<td>GFR (ml/min) - Mean change from baseline (SEM)</td>
<td>-8 (5) / -29 (12)</td>
<td>0.8 (6) / -14 (7)</td>
<td></td>
</tr>
</tbody>
</table>

FF - Mean (SEM) | 0.17 (0.002) / 0.18 (0.002) | 0.17 (0.001) / 0.19 (0.003) | 0.14 (0.001) / 0.15 (0.003) |

FF - Mean change from baseline (SEM) | 0 (0.01) / 0.02 (0.02) | -0.03 (0.01) / -0.03 (0.02) |

The Centre of Inflammation and Metabolism is supported by a grant from the Danish National Research Foundation (#02-512-55). This study was further supported by grants from private funding organisations.

Authors have confirmed where relevant, that experiments on animals and man were conducted in accordance with national and/or local ethical requirements.

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PC45

Using a human patient simulator to demonstrate the autonomic control of the cardiovascular system

P.D. Maskell, K. Brandom, E. Lloyd and E.J. Robinson

Department of Physiology and Pharmacology, University of Bristol, Bristol, UK

The METI Human Patient Simulator (HPS) is a state-of-the-art, life-sized, high fidelity mannequin linked to a computer through a host of electro-mechanical equipment. This integration of software-driven electro-mechanics allows the modelling of a wide range of physiological and pharmacological states. The data from the HPS is projected in the format of a clinical monitoring system. Drugs can ‘interact’ with the underlying HPS model via predefined pharmacokinetic and pharmacodynamic parameters.

In this study we describe the development of an HPS session integrating pharmacology and physiology in order to demonstrate sympathetic and parasympathetic control of the cardiovascular system.

A 30 minute HPS scenario for around 20 students is integrated into the existing first year MBChB and second year BSc practical classes in cardiovascular pharmacology. The students, using their knowledge of the cardiovascular system have to predict the effects of various drugs (phenylephrine, propranolol, atropine and dobutamine) that act to influence the parasympathetic and sympathetic nervous system on heart rate, blood pressure and systemic vascular resistance. The students then give i.v. administrations by ‘injecting’ the drugs into the HPS using a drug recognition system that detects different drugs using a barcode reader. Under the guidance of a member of staff the students discuss the responses obtained from the HPS. The students also learn about the autonomic control of the heart by the autonomic nervous system via chemical denervation using atropine and propranolol.

The effects of the drug dosages ‘given’ to the HPS on the cardiovascular parameters correlate well with published human data (Atropine and propranolol for intrinsic heart rate, phenylephrine, atropine, propranolol, and dobutamine). The session was rated highly by students with 85% (n = 164) scoring the value at 4 or above (scale of 1-5, 5 being very well), when responding to the question how well did the HPS session help you understand the control of blood pressure? The students also thought the session helped improve their understanding of the clinical relevance of drugs acting on the CVS with 78% of students (n = 164) scoring the value of this session at 4 or above (scale of 1-5, 5 being very well).

We conclude that this HPS session enhances the current physiology and pharmacology student learning experience and gives accurate qualitative physiological changes to the drugs administered.

Jose AD (1966) Am J Cardiol 18, 476-478.


HEFCE funding established and supports the Applied and Integrated Medical Sciences Centre for Excellence in Teaching and Learning (AIMS CETL).

Authors have confirmed where relevant, that experiments on animals and man were conducted in accordance with national and/or local ethical requirements.

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PC46

The response to hypoxia: a comparison of the Human Patient Simulator (HPS) with human data

R. Helyer1, A. Coombs1,2, A. Cousins1,2, H. Dee1,2, E. Kermode1, C. Rogers1,2 and E. Lloyd1

1Department of Physiology & Pharmacology and AIMS Centre For Excellence in Teaching & Learning, University of Bristol, Bristol, UK and 2Intercalating MB ChB students, University of Bristol, Bristol, UK

The Human Patient Simulator (HPS 337; METI, Sarasota, Florida) has a computer driven mechanical lung and gas exchange mechanism, designed to model the human respiratory system. We have previously demonstrated that the HPS is a useful tool for illustrating physiological principles but requires adjustments to the modelling software in order to improve the fidelity of the quantitative response to perturbations such as simulated hypovolaemia [1]. The aim of this study was to compare the response of the HPS to hypoxia with available human data in order to determine the accuracy of the HPS response and the utility of the HPS for teaching high altitude human physiology. Data can be obtained from the HPS for a range of respiratory variables including breathing rate, tidal volume, simulated alveolar and arterial partial pressures of oxygen and carbon dioxide, and arterial oxygen saturation. The simulator was intubated and baseline measurements were made of the respiratory variables including the partial pressures of oxygen and carbon dioxide in alveolar (PAO2 and PACO2) gas whilst “breathing” atmospheric air at ambient pressure. The responses were then determined to breathing hypoxic gas mixtures (range = 19-5% O2) applied using Douglas bags and a three-way valve system to separate inspired and expired gases. The data were used to construct an Oxygen-Carbon Dioxide diagram for comparison with published human data [2,3,4].

In response to hypoxia the HPS showed a linear relationship between PAO2 and PACO2 over the entire range investigated (PAO2 = 25-110 mmHg; n = 6). Published human data for acclimatised individuals shows a linear relationship between PAO2 and PACO2 over a PAO2 range of 60-100 mmHg but below this...