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Contents

Editorial

Welcome to the April 2006 issue of *The* Bulletin!

In the review article for this issue, Dr Ian Fearon (University of Manchester) presents the mechanisms underlying cardiovascular oxygen sensing. Dr Fearon elegantly illustrates the processes by which cells of the cardiovascular system are able to detect a low oxygen level and adapt appropriately to promote their survival under hypoxic conditions. The review concludes by highlighting the potential for therapeutic targeting of the oxygen-sensing pathways to treat cardiac pathologies.

In this issue, we are pleased to announce the winners of the Young Investigator Awards at the successful BSCR meeting which took place recently at the Wellcome Trust Sanger Institute, Cambridge. Also, Xiaoke Yin, who was awarded the *Clinical Science* Young Investigator prize at the Autumn Meeting, and colleagues at St George's provide a brief overview of their work for this issue. Fascinatingly, their proteomic study reveals an increase in oxidate stress upon differentiation of embryonic stem cell-derived smooth muscle cells.

We have been delighted to see that the incentive of a £300 travel grant has prompted an increased number of travel reports for *The* Bulletin and we would be glad to see this trend continue. If you plan to travel to an appropriate Cardiovascular meeting and would like to share your experience with readers of *The* Bulletin, please contact us.

As is our tradition, we include details of the latest grants awarded to researchers in the Cardiovascular field, by the British Heart Foundation and the Wellcome Trust.

Helen Maddock and Nicola Smart

Acute hypoxia, ion channels and the cardiovascular system: the quest for the O_2 sensor

by Dr Ian M. Fearon,

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Cellular responses to acute hypoxia are pivotal to cardiovascular and respiratory adaptations which maintain arterial O_2 homeostasis and support the adequate delivery of oxygenated blood to respiring tissues. While hypoxic regulation of plasmalemmal ion channels has long been identified as a key step in acute hypoxic chemotransduction, our understanding of the cellular biochemical and molecular mechanisms underlying O_2-dependent signalling is incomplete. Recent studies have utilised powerful molecular techniques to shed new light on issues surrounding O_2 chemoreception, providing novel answers to long-standing questions surrounding physiological regulation of the cardiovascular and respiratory systems during acute hypoxia.

Introduction

Cell survival is critically dependent on the delivery of oxygenated blood commensurate to its metabolic needs, due to the essential role of oxygen in mitochondrial ATP production via oxidative phosphorylation. Even transient, localised perturbations in oxygen delivery can have detrimental effects on cell function, and are intimately involved in human pathologies such as stroke and myocardial infarction. The adequate supply of oxygen is a constant physiological challenge and occurs in the face of ever-changing demand, availability and utilisation. In the preceding issue of *The* Bulletin, Sarah Welsh and Christopher Pugh provided an excellent and informative review of the transcriptional responses within the cardiovascular system which promote cardiovascular adaptations, such as angiogenesis and erythropoiesis, in response to *prolonged* hypoxic episodes. Here, I provide an account of the *short-term* cardiovascular and respiratory changes which occur during exposure to an acute hypoxic stimulus, and discuss the regulation of ion channels as a means by which this stimulus is transduced into a cellular signal capable of rapidly altering cardiorespiratory function.

The carotid body – a classical O_2-sensing organ

Located bilaterally in the carotid bifurcation, a major branch point of the common carotid artery into the external and internal carotid arteries, the carotid body (CB) is the principal mammalian peripheral O_2 chemoreceptor. As well as possessing the ability to detect and signal reductions in arterial O_2 levels (hypoxia), this polymodal organ is also stimulated by hypercapnia, acidosis and hypoglycaemia.[31, 63, 68] While there is perhaps not a complete consensus concerning the structural components of O_2-sensing,[74] it is widely accepted that glomus or type I cells are the primary transducers of chemosensory information. In response to low O_2, these electrically-excitable cells,[19] release neurotransmitters onto chemosensory afferent nerve endings of the carotid sinus nerve (CSN), which are apposed to clusters of type I cells.[31] The ensuing increase in discharge of these neurons signals the alteration in blood chemical composition to brainstem respiratory areas from where reflex, compensatory changes in ventilation are initiated.[31] The seminal biophysical change within type I cells during hypoxia is the inhibition of O_2-sensitive K^+ channels situated within the plasma membrane.[51] Such inhibition facilitates membrane depolarisation, causing the entry of Ca^{2+} through depolarisation-activated channels, eliciting the Ca^{2+}-dependent release of vesicular neurotransmitters onto sensory neurons[7, 31, 99] (Figure 1).

The first demonstration of hypoxic inhibition of a

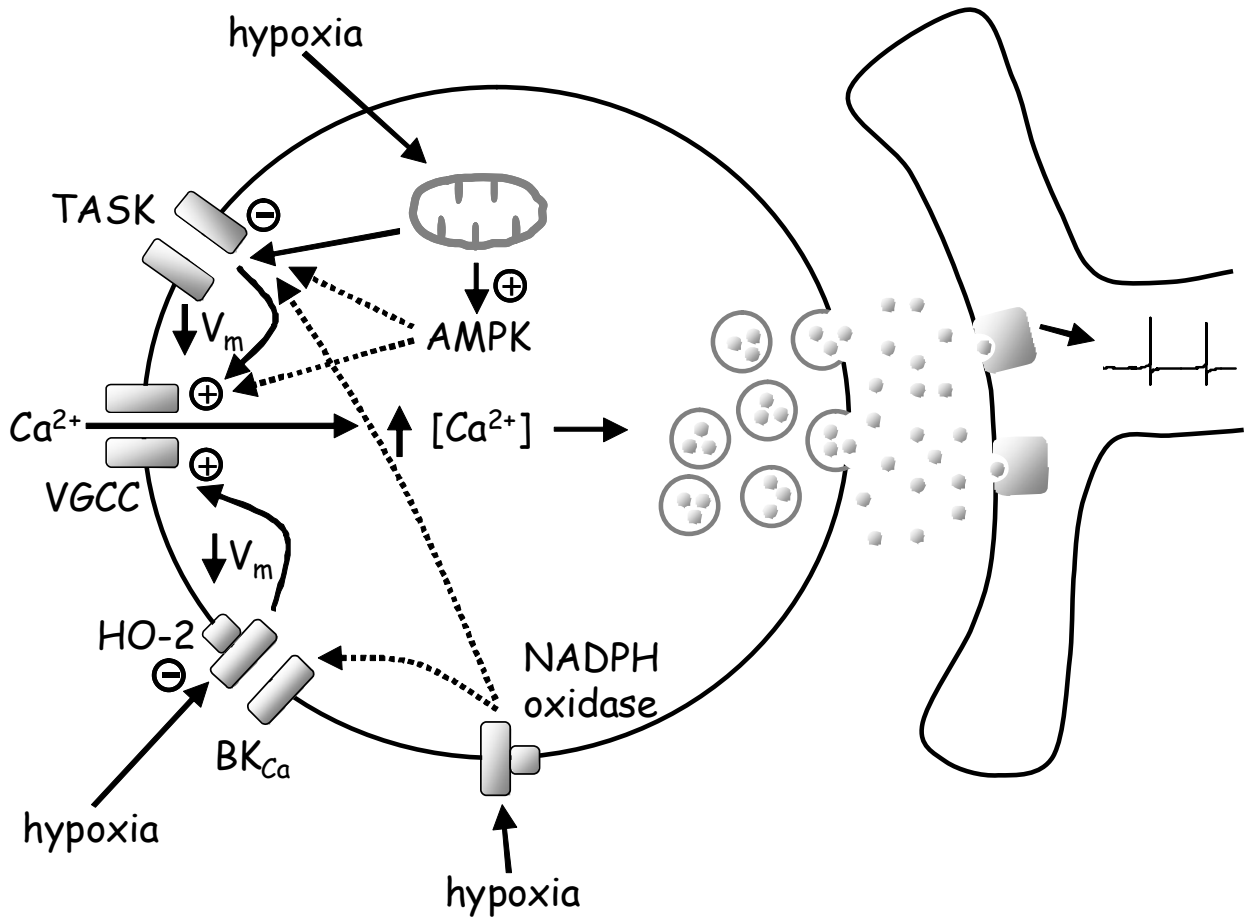

Figure 1. Proposed mechanisms underlying carotid body O_2 chemoreception. Hypoxia elicits the Ca^{2+}-dependent release of excitatory neurotransmitters from chemosensory type I (or glomus) cells onto adjacent sensory nerve endings. Depicted are putative mechanisms by which hypoxia regulates the activity of K^+ channels in the type I cell membrane, causing depolarisation, activation of voltage-dependent Ca^{2+} entry and elevation of intracellular Ca^{2+} levels. The involvement of mitochondrial regulation of TASK-like channels[9] and heme oxygenase-dependent regulation of BK_{Ca} channels[112] is described in the text. AMPK activation during hypoxia elevates Ca^{2+} levels by activating transmembrane Ca^{2+} influx;[21] the precise mechanism is yet to be described. NADPH oxidase activation during hypoxia may play a regulatory role by activating K^+ channels.[37] HO-2, heme oxygenase 2; BK_{Ca}, large-conductance Ca^{2+}-activated K^+ channel; TASK, tandem-pore domain acid-sensitive K^+ channel; VGCC, voltage-gated Ca^{2+} channel; V_m, membrane potential; AMPK, AMP-activated protein kinase.

K^+ current in type I cells was made by Lopez-Barneo in 1988, in cells isolated from the rabbit CB.[51] Subsequently the particular type of K^+ channel inhibited by hypoxia has been demonstrated to show both species and environmental variation,[52] with candidate channels including large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels,[70, 53] background ('leak') K^+ channels of the tandem-pore domain family,[9] voltage-gated (K_v) channels[82] and potentially a human ether-a-go-go-related gene- (hERG)-like channel.[67] While the dogma of K^+ channel involvement in chemoreception is widely accepted, what is far less apparent is the molecular basis of the signal transduction mechanism involved in O_2-sensing. That is to say while several hypotheses have evolved, there is not yet a clear, definitive answer to the question, how is an altered O_2 level translated into a change in current flow through a particular K^+ channel.

How does the CB sense hypoxia?

Mitochondria have long been thought to be a critical organelle in carotid body O_2 sensing, particularly since mitochondrial inhibitors are powerful stimulants of carotid body activity.[47] This 'mitochondrial

hypothesis' was previously reliant on the hypoxia- and mitochondrial inhibitor-mediated elevation of intracellular Ca^{2+} due to release of Ca^{2+} from mitochondria and other intracellular stores.[18] However, subsequent work concerning the membrane hypothesis of hypoxic chemotransduction (described above) suggested the necessity of voltage-gated Ca^{2+} entry, and not release from an internal store, in hypoxic elevation of intracellular Ca^{2+}.[7, 31, 99] With this apparent lack of a role for mitochondria in hypoxic Ca^{2+} elevation, the mitochondrial hypothesis appeared unfavourable. Recently however this hypothesis has come back to the fore, supported by the resurgence of interest in cell redox status as a mediator of O_2-sensitivity in other organs and tissues.[50] The complexes of the mitochondrial electron transport chain (ETC) drive the production of a trans-innermitochondrial membrane proton gradient which drives ATP production by the ATP synthase (Figure 2). It is now considered that inefficiencies in electron transfer cause the loss of electrons from ETC complexes, which reduce molecular O_2 to produce highly-reactive free radicals termed reactive oxygen species (ROS).[98] Radicals react with cell proteins and regulate their function, providing a transduction mechanism by which altered ROS production during hypoxia can alter ion channel activity. While this schema may be attractive in other tissues such as the lung vasculature (see below), and despite several demonstrations of redox agents modulating K^+ channel activity,[52, 81, 100] specific lines of evidence suggest that mitochondria and cell redox status do not mediate CB O_2 sensing. For example, indices of cell redox status were unaltered in whole CBs during hypoxia, while the antioxidant N-acetylcysteine (NAC) neither activated the CB nor regulated its O_2-sensitivity.[84] Furthermore, other chemoreceptive cells retain their O_2-sensitivity following pharmacological and genetic ablation of the ETC.[46]

Several recent studies have focussed interest onto mitochondria as CB O_2 sensors, not due to their ability to produce ROS but owing to their central role in controlling cellular metabolic status. In isolated CB type I cells, mitochondrial uncouplers inhibited TASK-like background K^+ channels, depolarised the membrane and promoted Ca^{2+} entry.[8] Similarly, not only did several inhibitors of the mitochondrial ETC acting at diverse sites mimic hypoxia by inhibiting background K^+ channels and elevating Ca^{2+}, they also ablated the hypoxic modulation of these channels.[114] One proposal put forth by the authors is that ETC inhibitors and hypoxia reduce ATP production, causing inhibition of ATP-activated background K^+ channels.[111] In contrast to this direct role of ATP in O_2-sensing, they also propose that the role of altered mitochondrial metabolism during hypoxia may be an indirect one, feeding ATP into a further signalling event/cascade. An attractive candidate for this proposed transducer is the AMP-activated protein kinase (AMPK), a ubiquitous sensor of metabolic stress. Thus, during hypoxia inhibition of oxidative phosphorylation would elevate the cell AMP/ATP ratio, activate AMPK and initiate downstream Ca^{2+} signalling events.[21] Supporting evidence for this proposal comes from the stimulation of transmembrane entry of Ca^{2+} into type I cells, and of *in vitro* CB afferent discharge, by the selective AMPK agonist, AICAR.[21] The complete mechanism underlying AMPK-stimulated Ca^{2+} entry in type I cells, and the role of altered membrane excitability in this process remains to be elucidated.

NADPH oxidase, a cellular enzyme commonly found in neutrophils but also found in type I cells of various species,[48, 115] has been proposed as a sensor for molecular O_2. This enzyme produces superoxide, which is dismutated to H_2O_2. It is proposed that during hypoxia the production of these ROS is altered, such that subsequent alteration in cGMP levels or cell redox status modulates ion channel activity.[3, 113] In support of this, Cross *et al*[13] demonstrated the presence of a diphenyleneiodonium- (DPI)-sensitive oxidase in the CB, inhibition of which blocked chemoreceptor responses to hypoxia. O_2-sensitivity of other systems, including lung neuroepithelial bodies (NEBs; see below) and the pulmonary vasculature[91, 116] is also DPI-sensitive. However, unlike that of NEBs[28] (see below) the O_2-sensitivity of K^+ currents and intracellular Ca^{2+} levels in isolated type I cells was unaltered in a mouse model in which NADPH oxidase deficiency was induced by knockout of the catalytic ($gp91^{phox}$) subunit.[36, 80] In the same model, *in vitro* CSN responses and whole-animal ventilatory responses to hypoxia were observed.[36, 80] Similarly, pharmacological abrogation of the oxidase did not interfere with hypoxic signal transduction in isolated rat and rabbit type I cells.[64] Perhaps the O_2 sensor lies away from the $gp91^{phox}$ subunit? Deletion of a further component of NADPH oxidase, $p47^{phox}$, enhanced basal CSN activity and ventilation, and also potentiated hypoxic ventilatory and chemoreceptor responses.[83] A recent paper from the same group[37] supports the notion that the enhanced basal activity occurs due to reduced background ROS production by the oxidase. However, fluorescence measurements of ROS production in type I cells clearly show increased

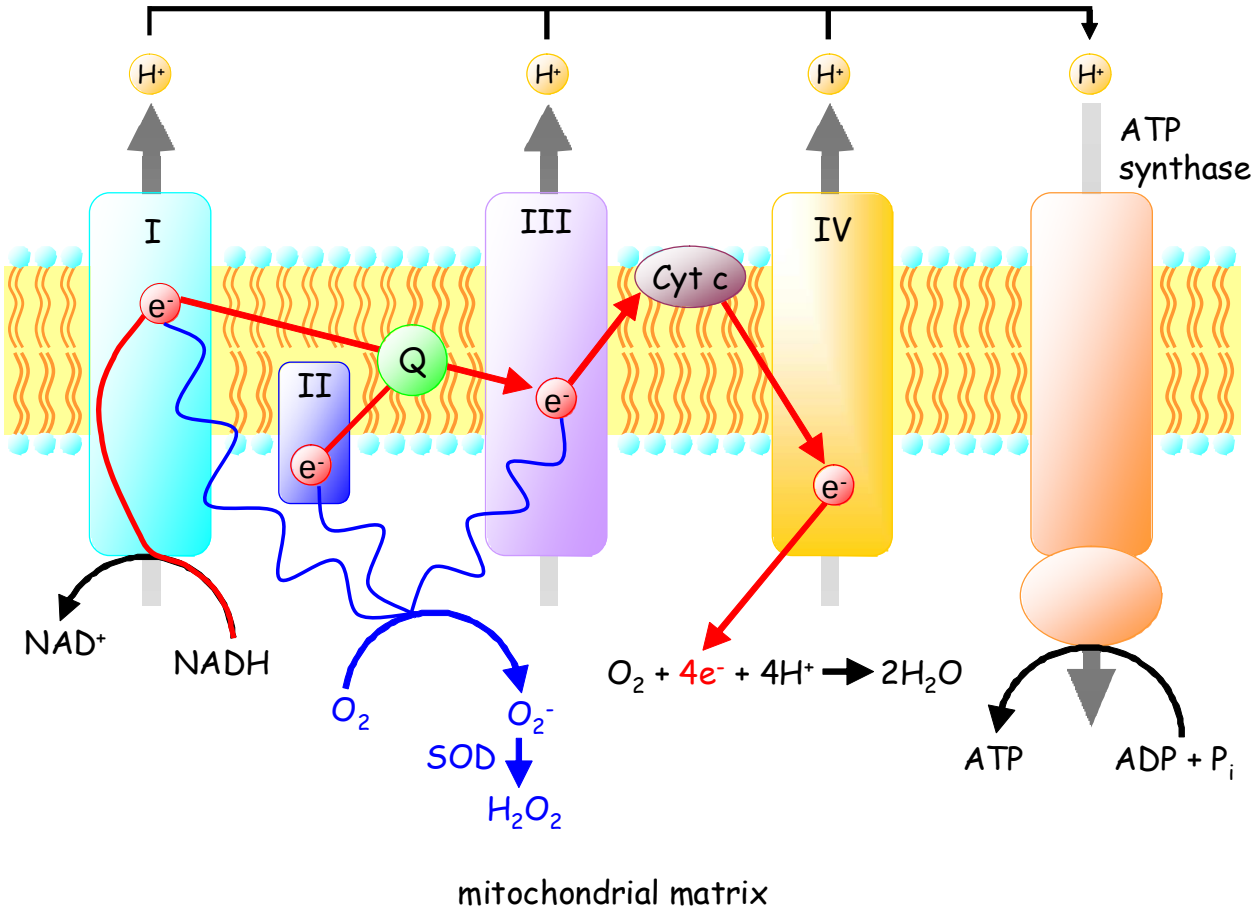

Figure 2. Electron transport in the mitochondrial respiratory complexes. ETC complexes (labelled I to IV) span the inner mitochondrial membrane. Energy release due to sequential shuttling of electrons though the complexes creates a proton gradient across the inner mitochondrial membrane, which is used to drive the ATP synthase. Due to inefficiencies within the ETC, several complexes may 'leak' electrons to O_2, producing the superoxide anion (O_2^-).[98] This is the precursor to many types of free radicals (or reactive oxygen species; ROS) which react with cellular proteins, including ion channels. Changes in free radical production during hypoxia are proposed to mediate signal transduction, for example in hypoxic pulmonary vasoconstriction (HPV). Mechanisms to account for observed decreases and increases in ROS production in hypoxia are discussed.[62, 86, 98, 107]

oxidant production during hypoxia,[37] suggesting the mechanism is not simply one of deficient oxidase substrate (O_2) during hypoxia causing a decrease in ROS production.[3, 113] A more complex mechanism involving (both direct and indirect) activation of the oxidase causing elevated superoxide and H_2O_2 levels and regulation of plasmalemmal K^+ channel activity is suggested.[37] Perhaps in this sense, the role of the oxidase is as a modulator, and not a mediator, of hypoxic signal transduction.

Carotid body O_2-sensing - a *complex* mechanism

The most recent proposal of a mechanism which underlies hypoxic regulation of a carotid body K^+ channel arose following the utilisation of powerful proteomic and molecular techniques to describe a direct interaction between a putative O_2 sensor and the BK_{Ca} channel.[112] This hypothesis proposed the carbon monoxide- (CO)-generating enzyme, heme-oxygenase 2 (HO-2), as a protein partner which forms an intimate and direct interaction with the BK_{Ca} channel complex. Under normoxic conditions, constitutive activity of HO-2 generates CO which promotes channel activity. During hypoxia the reduced availability of O_2, a HO-2 substrate, abrogates CO production. The ensuing fall in CO-induced channel activation causes inhibition of channel activity, initiating downstream depolarisation–evoked chemotransmission events. This hypothesis is

supported by the biochemical studies immunoprecipitating HO-2 with BK_{Ca} performed alongside studies showing ablation of O_2-sensitivity when HO-2 was knocked-down by RNA silencing.[112] This work was also in accordance with earlier studies suggesting a role for HO-2 in CB chemosensing which identified the presence of HO-2 in type I cells of different species,[76] and with that indicating that BK_{Ca} O_2-sensitivity in the carotid body was membrane-delimited[29] and reversed by CO.[78] Furthermore in HO-2 knockout mice, ventilatory responses to hypoxia were diminished.[4]

Clearly, the CB possesses an abundance of potential O_2 sensors, transduction systems and mechanisms by which membrane excitability can be altered and intracellular Ca^{2+} levels elevated during hypoxia. What is the requirement for this in terms of O_2 sensing? One suggestion is that the range of Po_2 levels over which the CB operates and reacts, along with the rapidity of the hypoxic response, requires contributions from several independent signalling systems.[75]

K^+ channels and O_2 sensing in other chemosensitive organs

The general schema described above concerning the dependence of O_2-sensing on hypoxic regulation of plasmalemmal K^+ channels appears conserved in other chemosensory organs. A prominent example are the innervated *neuroepithelial bodies (NEB) of the lung* which secrete amines in response to airways hypoxia, a mechanism of suggested importance in respiratory control, particularly in neonates.[27] Similar to type I cells, hypoxia inhibits K^+ currents in NEBs and depolarises the cell membrane, giving rise to voltage-gated Ca^{2+} influx and neurotransmitter secretion.[14, 116] Candidate O_2-sensitive K^+ currents in the native cells may be mediated by both Ca^{2+}-dependent and -independent channels.[14] Use of the small cell carcinoma of the lung (H146) cell line, derived from NEB precursors, has suggested the importance of a TASK-like background K^+ conductance in O_2 sensing.[65] Since the O_2-sensitivity of native NEB is DPI-sensitive and ablated in the $gp91^{phox}$ mouse knockout model, NADPH oxidase has been proposed as a signal transducer.[28, 116] While this has been corroborated in H146 other transduction systems, excluding the mitochondrial ETC, may co-transduce the hypoxic signal.[46]

Derived from the same sympathoadrenal branch of the neural crest as CB type I cells, *adrenomedullary chromaffin (AMC) cells* secrete catecholamines into the bloodstream as part of the classic 'fight or flight' response. Prior to sympathetic innervation of the adrenal medulla, which develops during the first week of postnatal life, stressors such as acute hypoxia cause catecholamine secretion from AMC.[85] This 'non-neurogenic' response is critical to early postnatal cardiovascular and respiratory adaptation and development, and enables neonates to cope with hypoxic (and other) stresses; interference with this response causes mortality.[85] In isolated neonatal rat AMC, hypoxia inhibited a K^+ current, depolarised the cell membrane and evoked catecholamine secretion[93] The entities responsible for O_2-sensitive K^+ currents in AMC have been proposed as BK_{Ca}, SK_{Ca} and K_v channels, findings made in studies on both isolated native[44, 94] and immortalised AMC (MAH cells)[24] Intriguingly, while a TASK-like channel proposed to be O_2-sensitive in both CB type I and NEB cells is expressed in MAH cells, it does not appear to possess O_2-sensitivity.[41] This highlights the ability of cells to couple discrete signalling systems to individual channel types, and further implies that the effect of hypoxia on TASK channels is not a direct one and requires an intracellular mediator. Regarding possible signal transducers in AMC, NADPH oxidase appears not to play a role since AMC sense hypoxia in the $gp91^{phox}$ knockout mouse model.[92] While mitochondrial function has also attracted attention as a potential O_2 sensor,[61] a role for the ETC has yet to be fully defined. Interestingly, a recent finding demonstrates that, similar to type I cell O_2 sensitivity,[66] hypoxic inhibition of SK_{Ca} channels in ovine AMC is rotenone-sensitive,[43] highlighting the potential similarity in O_2-sensing pathways in these cell types. Whether this sensitivity involves ETC blockade or participation of a distinct rotenone-inhibitable site[66] remains unresolved.

Hypoxic control of pulmonary arterial conductance

Occurring primarily in small diameter resistance pulmonary arteries,[109] hypoxic pulmonary vasoconstriction (HPV) is a physiological contractile response critical to maintaining a high pulmonary vascular resistance in the foetus, enabling blood to be diverted through the ductus arteriosus and away from the unventilated lungs.[109] Postnatally, HPV remains important due to its role in reducing blood flow to those areas of the lung which are poorly perfused and thus assisting in maintaining the matching of perfusion to ventilation. Biphasic in nature, an initial transient constriction (phase 1) gives way to a slow tonic constriction (phase 2).[20, 62] As for O_2-sensing in

chemosensory organs, many hypotheses concerning the transduction and effector mechanisms underlying both phases of HPV prevail.

Regulation of the sensitivity of the contractile apparatus to Ca^{2+} may be involved in HPV,[20, 33, 79, 102-104] particularly in phase 2. At least in phase 1, a critical event in HPV is the elevation of intracellular Ca^{2+} in pulmonary myocytes, which stimulates contraction. Many ion channel-independent signalling pathways leading to Ca^{2+} elevation have been described, including the release of Ca^{2+} from intracellular stores,[17, 20] possibly via AMPK-activated cyclic ADP-ribose--dependent Ca^{2+} mobilisation.[21] Capacitative Ca^{2+} entry may also play a role in hypoxic Ca^{2+} elevation.[105] Variably, HPV is endothelium-dependent,[1, 2, 17, 38, 62, 118] with the presence of the endothelium commonly needed for the phase 2 constriction.[103] Similar to that in neurosecretory organs though and in contrast to the Ca^{2+} regulation mechanisms described above, a major body of evidence suggests the involvement of ion channels located in the cell membrane of pulmonary smooth muscle cells in HPV.

The membrane hypothesis of HPV utilises the O_2-dependent regulation of plasmalemmal K^+ channels in pulmonary arterial myocytes to describe how hypoxic membrane depolarisation and Ca^{2+} entry through voltage-gated channels elicits Ca^{2+}-dependent myocyte contraction.[108] Subsequent to the initial demonstration of a hypoxia-sensitive K^+ current in isolated pulmonary arterial myocytes,[73] the expression of numerous K^+ channels in these cells has been demonstrated, given candidacy to each channel in mediating O_2 sensitivity. This multiplicity of channels includes subtypes of both homomeric and heteromultimeric K_v channels,[12, 33, 60, 62, 88, 89] calcium-activated (K_{Ca}) channels,[69] and the background K^+ channel, TASK-1.[34, 35] Evidence of roles for these channels is derived from a vast amount of experimental data obtained using pharmacological and molecular tools to both isolate potential channel sensors and abrogate cellular and tissue sensitivity to hypoxia.

What is the transduction mechanism which signals a lack of O_2 to K^+ channels in pulmonary myocytes? Initially proposed by Archer and colleagues in 1986,[6] cell redox status has received much attention as a hypoxia signalling mechanism. This theory proposes that ROS are produced by the proximal mitochondrial ETC (Figure 2) in direct proportionality to available O_2. That is to say, that tonic ROS production in normoxia is inhibited in hypoxia.[62] This hypothesis is supported at least by direct measurement of ROS levels using several different methods, which detected decreased ROS levels during hypoxia and in the presence of pharmacological inhibitors of the proximal, but not the distal, ETC.[57] This was concurrent with both hypoxia- and rotenone-induced inhibition of K^+ currents in isolated pulmonary myocytes and relaxation of aortic rings.[57] Other, similar measurements of ROS in other preparations further support this hypothesis.[62] Despite this evidence, some have questioned the *initiating* role of K^+ channels in HPV,[106, 107] and conversely, several groups have demonstrated an increase in ROS production during hypoxia.[49, 106] Although difficult to reconcile,[98] this model suggests that ROS production within mitochondrial complex III increases during hypoxia, triggering Ca^{2+} signalling pathways with culminate in contraction.[106, 107] An explanation offered for the regulation of K_v channels in hypoxia proposes that the rise in intracellular Ca^{2+} inhibits these channels,[72] making the observed membrane depolarisation secondary to the initial signalling event.

A further possible source of ROS, NADPH oxidase, is a putative HPV O_2 sensor. Hypoxia activates a superoxide-generating, DPI-inhibitable pulmonary oxidase,[56] while DPI and other inhibitors abrogate HPV in isolated arteries and intact lungs.[42, 110] However, HPV still persists in the $gp91^{phox}$ knockout mouse model.[5]

The reasons for the disparities evident in the mitochondrial / NADPH / ROS / membrane depolarisation schemata are not clear They may reside within differences between the many different preparations used to examine signal transduction, the different endpoints measured, and the different methodologies used to measure ROS levels and the inherent technical and interpretational difficulties arising from the use of these dyes.[62, 86, 98] These aside though, mitochondrial ROS are clearly of great importance and certainly, addressing these issues thoroughly will yield vital clues as to the role of the ETC in HPV. Particularly, the development of more specific assays for ROS will add fuel to the debate concerning the specific, directional nature of the hypoxia-induced alteration in ROS production.

Far from being a mere conveyor of Ca^{2+} across the membrane in response to K^+ channel-mediated depolarisation as described above, voltage-gated Ca^{2+} channels may also play a more direct role in HPV. In a sub-population of distal pulmonary myocytes, hypoxia enhanced an L-type Ca^{2+} current and regulated cytosolic Ca^{2+} oscillations.[52] The significance of this is unclear, though it has been suggested that the localisation of myocytes whose L-type channels responds to low

Po_2 in this way provides a localised hypoxic response.

Hypoxic *dilation* in the systemic vasculature

In direct contrast to the contraction elicited by hypoxia in resistance pulmonary arteries, hypoxia dilates systemic arterial vessels.[101] Thus in response to a local decrease in Po_2, systemic arterial vasodilation, particularly in the cerebral and coronary vasculature, favours the perfusion of those tissues deprived of O_2 and promotes oxygenation.[50] Hypoxic activation of K_{ATP} channels[15, 16] was initially thought to underlie hypoxic vasodilation, by hyperpolarising the cell membrane and subsequently reducing Ca^{2+} entry through voltage-gated channels. Contradictory to this proposal are, at least, the recent studies demonstrating hypoxic dilation in the presence of the K_{ATP} channel inhibitor glibenclamide in coronary arteries exhibiting spontaneous myogenic tone,[54, 55] despite the functional expression of the channel in these vessels. This lack of involvement of K_{ATP} channels may be a consequence of ATP depletion-evoked channel activation requiring prolonged exposure to low Po_2 levels.[15] Moreover, hypoxic effects occur over a range of Po_2 levels that is physiologic for most vessels, and may not involve restricted energy metabolism and so occurs without a fall in $[ATP]_i$.[10] In the search for a more acutely-acting systemic sensor, K_{Ca} channels have received attention,[30] as they have in the foetal lung vasculature.[71] A role for K_v channels has also been examined, for instance since the lack of hypoxic dilation in an organ culture preparation correlated with a loss of K_v channel expression,[95] However, other evidence suggests that K^+ currents were unaffected by hypoxia in isolated myocytes.[117] Like the pulmonary circulation the endothelium has been shown, variably, to play a role in hypoxic systemic vasodilation.[55, 87] The use of different vessels from, in some instances, different species makes for difficult interpretation of many of the contrasting findings described above. The differing preparations used to investigate mechanisms of dilation, for instance pharmacologically pre-contracted vessels versus those exhibiting spontaneous myogenic tone, may further be a source of inconsistency between experimental observations from different groups.

Systemic hypoxic relaxation may be a response to altered Ca^{2+} sensitivity of the contractile apparatus[32] or modulation of Ca^{2+} handling by internal stores.[96] A direct effect of hypoxia on a major transmembrane Ca^{2+} influx pathway, the voltage-gated Ca^{2+} channel, has also been proposed.[50] In support of this proposal, hypoxia inhibited L-type channels in isolated myocytes from numerous vascular beds.[25, 26, 87] Arising from this work, the first identification of a recombinant O_2-sensitive ion channel confirmed the O_2-sensitivity of the L-type channel.[22] Numerous transduction pathways have been examined for their role in regulating Ca^{2+} channel activity during hypoxia and, once again, altered cell redox potential may be important.[23] While NADPH oxidase as an O_2 sensor for the Ca^{2+} channel has been ruled out,[40] a finding confirmed for the native channel in isolated cardiac myocytes,[39] ROS production within the mitochondrial ETC may yet again receive attention as a regulator of ion channel activity during hypoxia.[39]

The ductus arteriosus and O_2-dependent adaptation to extrauterine life

In the foetus, the ductus arteriosus (DA) allows blood to bypass the unventilated lungs. Shortly after birth this vessel closes in response to the relatively hyperoxic extra-uterine environment, a physiological phenomenon which critically enables the transition of the newborn from foetal to air-breathing life.[11] The initial phase of this closure is thought to be an acute vasoconstrictor effect due to the increased Po_2. While recent data propose that the source of Ca^{2+} which gives rise to muscle constriction is an IP_3-sensitive intracellular store,[45] other data suggest that transmembrane Ca^{2+} influx is critical, secondary to normoxic inhibition of membrane K_v channels.[58, 97] In support of this, the DA from pre-term animals failed to constrict to O_2 leading to a persistent ('patent') vessel. This was associated with a loss of K_v channel expression,[90] and gene transfer of K_v channels into these vessels restored their O_2 sensitivity.[90] Akin to the pulmonary vasculature enhanced ROS production, specifically of H_2O_2, in the mitochondrial ETC is a potential regulator of channel activity on exposure to normoxia.[59, 77] The quandary here however is that the same group propose decreased ROS production causes hypoxic inhibition of K_v channels in the pulmonary vasculature[57, 60, 62]. Differential sensitivity of K_v channel variants is proposed to explain this paradox.[59]

Conclusions

Cardiorespiratory responses to hypoxia are critical to ensure adequate delivery of O_2 to respiring tissues; failure may lead to significant human pathologies. The scope for treatment of these disorders would be considerably enhanced by the targeting, pharmacologically, genetically or otherwise, of treatments to components of O_2-sensing pathways in organs and vessels. Since the first demonstration of an

O_2-inhibited ion channel in 1988,[51] many groups have made great strides in identifying roles for numerous types and subtypes of ion channels in mediating the rapid cardiorespiratory responses necessary to maintain arterial O_2 homeostasis under conditions of altered O_2 availability and/or utilisation. While technical limitations have hindered the measurement of putative messengers of the hypoxic signal, and the vast array of responses, messengers and pathways involved has clouded our interpretation and understanding of experimental findings, the utilisation of powerful molecular, proteomic and genetic techniques has provided, and will continue to provide, fresh and innovative insight into one of the most fundamental questions of cardiorespiratory physiology – how does a cell sense changes in the partial pressure of O_2? The quest for the O_2 sensor(s) continues.

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Secretary's Column

The Spring meeting of the BSCR has just taken place, in the delightful parkland setting of the Wellcome Trust Genome Campus at Hinxton, not far from Cambridge. Andrew Grace and colleagues, Jane Rogers and Willem Ouwehand, delivered a fine programme of cardiovascular science, focusing on genotypes-phenotypes and the application of high-throughput technologies. The social time was informal and relaxed, with drinks taken in the poster area followed by dinner in the highly commended restaurant on site. In my last column, I emphasized again the Society's interest in promoting student membership and participation, so it was somewhat disappointing to see a relatively small grouping of student presentations. Nevertheless, competition for the Young Investigator prizes was strong and the winners, announced elsewhere in this issue, gave admirable performances.

So, what's new regarding BSCR committee matters? Firstly, five new members assumed office on 1 January, namely Barbara Casadei, Andrew Grace, Cathy Holt, Nicola King and Chris Newman (BAS representative), and David Eisner took up the position of Chairman. So discussion at the recent meeting of the committee in Hinxton Hall was lively and varied, dealing with day to day business such as contributions to NICE appraisals but mostly concerned with planning and organization of future research symposia and our main meetings.

At the annual scientific meeting of the British Cardiac Society held in Glasgow towards the end of April, the BSCR teamed up with a number of other groupings to provide sessions to interface basic science with clinical problems. Along with Heart Rhythm UK, a 'Teach-In' was held on Trainees' day (Monday 24th) on 'The humble ECG' and on CPD day (Tuesday 25th), the BSCR supported a symposium 'Update on lipids: from LDL to HDL' organized by the British Atherosclerosis Society (BAS). Later that day, BSCR / BAS in conjunction with the British Cardiovascular Intervention Society put on a plenary session 'The use of troponin in defining acute myocardial infarction'. Thinking ahead to BCS 2007, the BSCR committee has just discussed creating opportunity for the general membership to contribute ideas for plenary and other sessions. So a notice will be Emailed later in the year, and will appear in the July issue of this Bulletin, inviting members to put forward suggestions.

In keeping with this trend for joint ventures, the BSCR and BAS will merge their autumn events this year, creating a full two-day meeting, which will be held in Cambridge on 21-22 September. First advertisement of this meeting can be found on the back page and look out for further information which will appear on websites soon. To finish, I'll say what a great job Chris Jackson has done in updating and developing the BSCR website, recently adding a number of features including 'Other Cardiovascular Meetings' and 'Post Advertisements'. And, by the way, profiles of committee members now appear there too.

Barbara McDermott

PRIZES AWARDED AT THE SPRING 2006 MEETING

Young Investigator Prizes:

The ***Clinical Science*** **Prize** was awarded to Rizwan Sarwar (Imperial College London), for an oral presentation entitled "A combined linkage and expression study of rat heart to identify primary drivers of cardiac hypertrophy".

The **BSCR Prize** was also awarded for an excellent oral presentation to Malathi Raman (National Heart and Lung Institute), "Yeast one hybrid cloning of factors which bind a critical CACC/SP1 element in the human cardiac troponin I gene".

Proteomic Analysis Reveals Increased Oxidative Stress in Embryonic Stem Cell-Derived Smooth Muscle Cells

Xiaoke Yin, Qingzhong Xiao, Ursula Mayr, Manuel Mayr and Qingbo Xu.

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* Xiaoke Yin was the recipient of the *Clinical Science Prize* for the Best Oral Presentation at the Autumn 2005 BSCR Meeting held at St Thomas' Hospital, London.

Embryonic stem cells are the pluripotent derivatives of the inner cell mass of blastocysts. They have the capacity for unlimited growth and self-renewal and the ability to differentiate into all types of mature tissue cells including germ cells. Over the last several years, accumulating evidence indicates that stem cells can differentiate into smooth muscle cells [1]. Stem cell-derived smooth muscle cells could be an important source for tissue engineering and for vessel repair. However, no data exist whether stem cell-derived smooth muscle differs from mature smooth muscle cells from adult vessels. Moreover, it is unclear how much similarity both cell types share at the protein level. In the present study, we differentiated murine embryonic stem cells into smooth muscle and compared their protein expression to aortic SMCs.

Mouse embryomic stem cells were cultured according to manufacturer's instruction from ATCC. Stage specific embryonic antigen-1 expression was verified by immunofluorescence staining and FACS analysis. For differentiation, stem cells were cultivated on collagen IV-coated dishes without leukaemia inhibitory factor. After 3 days, stem cell antigen-1 positive (Sca-1$^+$) cells were isolated with high purity by magnetic cell sorting. After PDGF-BB (10ng/ml) treatment for 3 passages, 95% of cells expressed SMC markers (data not shown). Protein extracts of stem cells, Sca-1$^+$ progenitor cells and aortic SMCs were separated by two-dimensional gel electrophoresis as described previously [2-4]. Over 300 protein species of each cell line were analyzed by tandem mass spectrometry (MS/MS) or MALDI-ToF MS. Protein maps are

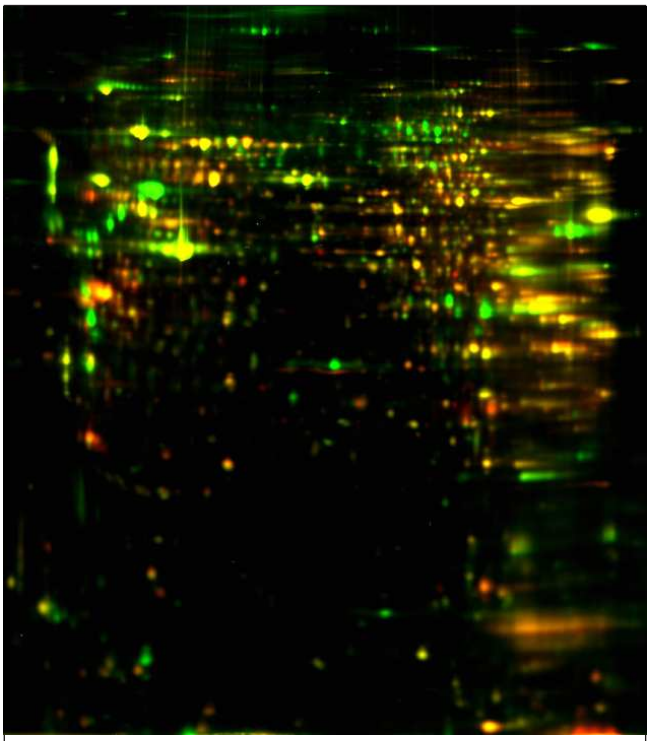

Figure 1. Proteomic comparison of stem cell-derived SMCs and aortic SMCs. Red and green spots indicate higher abundance in aortic and stem cell-derived SMCs, respectively. Yellow spots indicate similar expression in both cell lines. A colour version of this figure can be viewed online in the April 2006 Bulletin pdf (www.bscr.org).

available on our website http://www.vascular-proteomics.com [5, 6].

To allow accurate comparisons of protein expression between esSMCs and aortic SMCs, we employed the difference in-gel electrophoresis approach (DIGE) [7]: in brief, proteins were labelled with Cy3 or Cy5 and co-separated by two-dimensional electrophoresis using a broad range pH gradient (pH 3-10 NL) and large format 12% SDS gels (Figure 1). After normalization to a pooled internal standard labelled with Cy2, 146 spots showed a significant 2 fold change in the biological variation analysis module of the Decyder software (GE healthcare). Proteins of interest were picked for identification by mass spectrometry.

Among the differentially expressed proteins were several antioxidant proteins and subsequent immunoblotting confirmed a reduction in mitochondrial but a compensatory increase in cytosolic antioxidants in esSMCs. Despite a 3-fold rise in glutathione reductase activity, esSMCs showed lower levels of reduced glutathione and increased oxidation of redox-sensitive proteins. Moreover, depletion of glutathione by diethylmaleate or inhibition of glutathione reductase by carmustine resulted in a pronounced loss of cell viability compared to aortic SMCs. Their increased susceptibility to oxidative stress was due to elevated levels of mitochondrial-derived reactive oxygen species paired with a reduction in cellular ATP.

Thus, we present the first protein profiles of murine aortic SMCs, stem cell-derived SMCs and their progenitors. Our comparison revealed that differentiation of stem cells to SMCs is associated with mitochondrial dysfunction and increased oxidative stress. Consequently, stem cell-derived SMCs require additional antioxidant protection for survival and treatment with anti-oxidants could be beneficial for stem cell-based tissue repair.

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Cardiovascular Related Meetings

The XXVI ISHR European Section Meeting will be held **14-17 June 2006**, at the University of Manchester, Manchester, UK. **Enquiries:** Mrs R Poulton, Scientific Secretariat, The University of Manchester, Room 1.302, Stopford Building, Oxford Road, Manchester, M13 9PI, United Kingdom. Tel: +44 161 2751628, E-mail: rpoulton@fs1.scg.man.ac.uk or The University of Manchester, ConferCare, Meeting Secretariat, Barnes Wallis Building, Sackville Street, Manchester M60 1QD. Tel: +44 161 3065068, Email: mcc.reg@umist.ac.uk, Website: www.meeting.co.uk/confercare/ishr2006.

The XXVIIIth Annual Meeting of the ISHR - North American Section will be held **June 13-16, 2006** at the Westin Harbour Castle in Toronto, Canada. **Enquiries:** Dr. Peter Liu, Heart & Stroke/Richard Lewar Centre of Excellence, University of Toronto, Rm 78 A, 150 College Street, FitzGerald Building, Toronto, Ontariou M5S 3E2. Tel: 416-946-8543, Fax: 416-946-7545, Email: hsrlcentre.excellence@utoronto.ca, Website: www.ishr2006.com.

Heart Failure 2006, 17th-20th June. This year's meeting will be held in Helsinki, Finland. Contact information: HFsecretariat@escardio.org

The Annual Symposium of the **American Heart Association Council on Basic Cardiovascular Sciences**, "Translation of Basic Insights into Clinical Practice", will be held July 31-August 3, 2006 at the Keystone Conference Center, Keystone, Colorado. Abstracts will be accepted January 23 - March 31, 2006.Enquiries: http://www.americanheart.org

The XXXth Annual Meeting of the ISHR -Australasian Section will be held in conjuction with the Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand on August 4-7, 2006 at the National Convention Centre, Canberra, Australia. Abstract submission 27 February to 27 March, 2006. Enquiries: Dr. Lea Delbridge, Dept. of Physiology, University of Melbourne, Parkville, 3010. Tel: 61-3-8344-5853, Fax: 61-3-8344-5897, Email: lmd@unimelb.edu.au, Website: http://www.csanz.edu.au/.

World Congress of Cardiology 2006: Joint Congress of the European Society of Cardiology and the World Heart Federation. 2nd - 6th September 2006. Barcelona, Spain. Further information can be obtained from: EUROECHO Secretariat: ESC, 2035 route des Colles, Les Templiers - BP 179, 06903 Sophia Antipolis Cedex, France. Tel: +33 (0) 4 92 94 76 00; Fax: +33 (0) 4 92 94 76 01; E-mail:webmaster@escardio.org; Website: www.escardio.org

4th Annual Meeting of the Society for Heart and Vascular Metabolism, "Cardiac Energy Metabolism in Heart Failure: From Concepts to Therapies", will be held on September 6-9, 2006 at the Semiahmoo Resort near Seattle, Washington. Enquiries: Organizer: Dr. William Stanley, Dept. of Physiology & Biophysics, Case Western Reserve Univ., 10900 Euclid Ave., Cleveland, OH 44106-4970, Tel: 216-368-5585, Fax: 216-368-3952, Email: wcs4@case.edu, Website: www.heartmetabolism.org.

Scientific Sessions of the American Heart Association, Chicago, Illinois, **12-15th November, 2006.** For further information, please refer to the AHA website: www. americanheart.org

XIX ISHR World Congress in Bologna, Italy **22-26 June 2007**. Organizers Roberto Ferrari and Luigi Tavazzi. **Enquiries:** Prof. Roberto Ferrari, Chief of Cardiology, University Hospital of Ferrara, Corso Giovecca 203, 44100 Ferrara, Italy. E-mail: info@ishr-italy2007.org, Website www.ishr-italy2007.org

Travel Reports for *The* Bulletin

The Bulletin editors look forward to publishing travel reports written by BSCR members. These can be on any conference, course or laboratory visit of interest to other members and could perhaps contain photographs. If you are planning to travel to a cardiovascular-related meeting and would like to write a report for the Bulletin, please contact the editors. A bursary of **£300** is available towards the cost of your visit, and this will be provided on receipt of the report. *Bon voyage!*

British Heart Foundation Grants

PROJECT GRANTS COMMITTEE NOVEMBER 2005

DEFERRED APPLICATIONS AWARDED

Dr J E Schneider et al, John Radcliffe Hospital, Oxford. "Development of proton magnetic resonance spectroscopy in human at 3 tesla" heart 3 years £141,964.

Dr N J Brand. Harefield Hospital, Middx. "Cloning and characterisation of cardiac determinants of glucose transporter 4 (GLUT4) expression in myocardium" 3 years £147,766

Dr A Afzal et al, St George's Hospital Medical School. "Study of stress genes and their effects on vascular inflammatory markers in a large twin cohort" 2 years £202,365

NEW APPLICATIONS AWARDED

Dr A Stephanou & Prof D S Latchman, Institute of Child Health, University College London. "Role of autophagy in the ischaemic myocardium" 2 years £106,904

Dr D A Middleton, University of Manchester. "Further studies on the structure of sarcolipin, an atrial-specific regulator of calcium cycling in cardiac cells" 1 year £47,093

Dr C M N Terracciano & Prof S Harding, Harefield Hospital, Middlesex. "Regulation of Na^+/Ca^{2+} - exchanger activity by the α_2- adrenoceptor in normal and failing heart" 2 years £130,781

Prof C H Orchard & Dr F Brette, University of Bristol. "Cardiac t-tubule function in health and disease" 3 years £181,528

Dr D A Slatter & Dr R W Farndale, University of Cambridge. "Characterisation of platelet binding to collagen IV using synthetic peptides" 2 years £125,041

Dr D P Ramji, Cardiff University. "Intracellular signalling pathways activated by agonists of liver-X- receptors in macrophages" 3 years £130,426

Dr S Ponnambalam et al, University of Leeds. "The role of VEGF receptor 2/KDR trafficking, recycling and proteolysis in the regulation of VEGF-A signalling and endothelial function" 3 years £130,903

Mr R S Bonser et al, Queen Elizabeth Hosp, Birmingham. "Application of remote ischaemic pre-conditioning to human coronary artery bypass surgery (CABG)" 2.5 years £131,152

Dr J E Cartwright & Prof G S Whitley, St Georges, University of London. "The role of soluble HLA-G in induction of endothelial apoptosis and uterine vascular remodelling in early pregnancy" 3 years £199,833.

Dr A P Davenport, Addenbrooke's Hospital, Cambridge. "Characterisation and function of the novel trace amine receptor, TA1 and its ligand tyramine in the human cardiovascular system" 3 years £189,994

Dr A M Evans et al, University of St Andrews. "Nicotinic acid adenine dinucleotide phosphate and cyclic adenosine diphosphate-ribose: do these synergistic, convergent Ca^{2+} signaling pathways underpin hypoxic pulmonary vasoconstriction?" 3 years £142,856

Dr T F K Antonios et al, St Georges, University of London. "The role of capillary rarefaction in the pathogenesis of essential hypertension and pre-eclampsia: insights from studies in pre-eclamptic women" 2 years £111,595

Dr C Loughrey & Prof G L Smith, University of Glasgow. "Cellular basis for arrhythmias: the inter-relationship between calcium transients and calcium waves in cardiac muscle" 3 years £173,954

Prof A Tinker, University College London. "The mechanism of abnormal trafficking of potassium channels in the pathogenesis of the hereditary long QT syndromes" 3 years £143,410

Dr A M Randi & Dr J C Mason, Hammersmith Hospital, London. "Regulation of angiogenesis by the adhesion molecule ICAM-2" 2 years £163,609

Prof T M Griffith & Dr D H Edwards, Cardiff University. "Analysis of the inhibitory effects of nitric oxide and cGMP on gap junctional communication and the EDHF phenomenon" 3 years £161,598

Prof S P Watson et al, University of Birmingham. "Studies on three novel platelet membrane signalling proteins" 3 years £152,258

Dr P M Elliott et al, Great Ormond Street Hospital, University College London. "Prevalence of sarcomeric protein gene mutations in children with unexplained left ventricular hypertrophy" 2 years £126,252

Dr F M Marelli-Berg et al, Hammersmith Hospital, London. "The role of CD31 (PECAM-1)-mediated

interactions in antigen- driven T cell-mediated inflammation and transplant rejection" 3 years £179,068

Prof P M W Bath & Prof D Auer, Queen's Medical Centre, Nottingham. "Effect of an angiotensin receptor antagonist on cerebral blood flow, cerebral perfusion pressure and systemic and peripheral haemodynamics in patients with recent cerebrovascular disease" 2.5 years £144,072

Prof A M Shah et al, King's College Hospital, London. "Investigation of the effects of neuronal nitric oxide synthase on human cardiac function in vivo" 2 years £126,719

Dr K M O'Shaughnessy & Dr I B Wilkinson, Addenbrooke's Hospital, Cambridge. "Investigation into the molecular genetics of large artery stiffening: a candidate gene based approach" 2 years £135,156

Prof J C McGrath & Dr C J Daly, University of Glasgow. "Isolation and analysis of each of the three vascular α_1-adrenoceptor subtypes using double α_1-adrenoceptor knockout mice" 3 years £156,660

Dr N J Alp & Prof K M Channon, John Radcliffe Hospital, Oxford. "Mechanisms of intracellular tetrahydrobiopterin generation and oxidation in the regulation of endothelial nitric oxide synthase activity" 3 years £175,053

Dr R M A Sitsapesan & Dr K Ventkateswarlu, University of Bristol. "Investigating the impact of SR load and phosphorylation on ryanodine receptor mutations associated with arrhythmias and sudden death" 3 years £149,243

Dr A F James & Prof J C Hancox, University of Bristol. "Atrial remodelling in spontaneously hypertensive rats: effects of angiotensin receptor blockade" 3 years £187,394

FELLOWSHIPS COMMITTEE JANUARY 2006

DEFERRED APPLICATIONS AWARDED

Intermediate Research Fellowships

Dr J O Turner Imperial College London. "Regulation of inflammatory signalling by adiponectin in obesity and the metabolic syndrome" 3 years £321,061

PhD Studentships

Ms P Campagnola (prev Mr S Sanna), Bristol Royal Infirmary. "Vascular progenitor cells contribute to angiogenesis from adult human vessels in organ culture and to neovascularization of ischaemic limbs" 3 years £74,643

Unnamed and Dr P M Taylor, Harefield Hospital, Middlesex. "Factors influencing mesenchymal stem cell diferentiation and function in tissue engineering heart valves" 3 years £84,555

NEW APPLICATIONS AWARDED

Intermediate Research Fellowships

Dr J T B Crawley, Hammersmith Hospital, London. "Proteolytic specificity of the ADAMTS13 metalloprotease domain" 3 years £156,706

Dr G A Knock, King's College London. "Functional and molecular investigations into the role of $pp60^{c\text{-}src}$ in the responses of the pulmonary vasculature to hypoxia and agonists" 3 years £167,907

Dr K B Abbitt, Northern General Hospital, Sheffield. "The effects of disturbed flow on ULVWF and platelet and leukocyte recruitment" 3 years £127,697

Dr C M McEniery, Addenbrooke's Hospital, Cambridge. "Mechanisms underlying hypertension in young adults" 3 years £177,566

Dr A Cheong, University of Leeds. "The control of REST expression in vascular smooth muscle cells: transcriptional regulation and vascular proliferation" 3 years £142,374

Dr L M Work, University of Glasgow. "A combined approach to target reactive oxygen species and neuronal death in stroke" 3 years £149,954

Junior Research Fellowships

Dr R M Dewberry, University of Sheffield. "Notch and endothelial progenitor cells: death, division or differentiation?" 2 years £78,345

Dr M Marciniak, St Georges, University of London. "Effect of potassium bicarbonate and potassium chloride on blood pressure, endothelial function and markers of target organ damage in hypertensive patients" 2 years £95,003

Mr S D Patel, King's College London. "The role of vascular progenitor cells in restenosis following arterial injury" 2 years £100,848

Clinical PhD Studentships

Mr A Wadoodi, King's College London. " The role of bone marrow in thrombus resolution" 3 years £163,442

Dr S Daga, Royal Infirmary, Edinburgh. "Platelet activation in the pathogenesis of infective endocarditis" 3 years £146,196

PhD Studentships

Unnamed and Dr A S Izzard, Manchester Royal Infirmary. "The myogenic response and predisposition to hypertension-induced cerebral haemorrhage" 3 years £77,676

Unnamed and Prof P Talmud, University College London. "Impact of alpha-1 antitripsin on coronary heart disease: in vivo and in vitro studies" 3 years £83,848

Miss S Pitkin, Addenbrooke's Hospital, Cambridge. "In vitro characterisation of the function of the apelin family of peptides in man and their role in cardiovascular disease" 3 years £84,955

Miss H R Watson, University of Southampton. "Identifying the motifs responsible for maintaining cardiac calcium pumps in the sarcoplasmic reticulum: a search for targeting and retrieval signals" 3 years £75,129

Mrs C Matute, University College London. "Mechanisms mediating functions of neuropilins 1 and 2 in endothelial cells" 3 years £83,848

Mrs J Brewin, Institute of Child Health. "Adoptive immunotherapy with EBV-specific CTL for lymphoproliferative disease post-solid organ transplantations" 3 years £85,368

Unnamed and Dr C Longstaff, NIBSC, Herts. "Modelling the kinetics of plasminogen activation in fibrin clots" 3 years £81,623

Mr P Andrikopoulos, Imperial College London. "A novel mechanism controlling calcium signalling in human endothelial cells: voltage-gated sodium channel activity and its functional consequences" 3 years £83,623

PROJECT GRANTS COMMITTEE JANUARY 2006

DEFERRED APPLICATIONS AWARDED

Prof V A Zammit, University of Warwick. "Role of DGAT 1 and 2 expression in cardiac muscle triglyceride synthesis and secretion" 3 years £164,815

Prof S B J Ebrahim et al, London Sch of Hygiene & Trop Med. "British Women's Heart and Health Study: the causes and consequences of cardiovascular disease in older women" 1 year £84,805 (Jointly funded by BHF and Department of Health)

Prof P H Whincup et al, St George's, University of London. "Contributions of physical activity and fitness to emerging ethnic differences in cardiovascular disease risk: a study in children" 2.5 years £70,722

Dr A Zhou et al, University of Cambridge. "Vitronectin and the regulation of fibrinolysis and coagulation" 2 years £91,021

NEW APPLICATIONS AWARDED

Dr M E Diaz & Dr A C Elliott, University of Edinburgh, "Characterisation of the effects of myocardial iron toxicity at the cellular level" 3 years £139,896

Dr L A Tskhovrebova & Prof J A Trinick, University of Leeds. "Structure of titin molecule - spatial conformation of the eleven-domain super-repeat" 3 years £150,786

Dr D Hauton, University of Birmingham. "Metabolism and the hypertrophied heart: The role of fatty acids and triacylglycerol in cardiac metabolism and dysfunction" 3 years £135,367

Prof S E Harding et al, NHLI, London. "Sarcoplasmic reticulum Ca^{2+} - release channel phosphorylation state and function in the failing heart" 2 years £103,514

Miss M Jahangiri et al, St George's, University of London. "Ventricular function in valve disease - when does the ventricle fail irreversibly, can this be detected by non invasive imaging using strain rate echocardiography?" 2 years £73,924

Dr P K Luther, Imperial College, London. "Electron tomography of the sarcomere in cardiac muscle: 3D organisation of myosin binding protein C and role in cardiac disease" 2 years £205,461.

Dr I C Wood & Prof D J Beech, University of Leeds. "Regulation of gene expression and smooth muscle function by repressor element 1-silencing transcription factor" 2 year £115,903

Dr N A Turner & Dr K E Porter, et al University of Leeds. "Expression, regulation and function of p38 MAP kinase subtypes in human cardiac myofibroblasts" 3 years £133,155

Dr A C Brewer & Prof A M Shah, King's College London. "Transcriptional regulation of NADPH oxidase isoforms in the vasculature" 2 years £92,091

Dr A B Mackenzie, University of Bath. "The functional expression of N-methyl D-aspartate glutamate-type receptors by megakaryocytes" 3 years £169,072

Prof J S Owen, Royal Free Campus, University College London. "Low-toxicity oligonucleotides and delivery vehicles to optimize gene editing technology and create the natural atheroprotective phenotype, ApoAI-Milano" 2 years £97,524

Dr J G McCarron, University of Glasgow. "Ca^{2+} store organisation, luminal regulation and IP_3 receptor-evoked Ca^{2+} release in vascular smooth muscle" 2 years £107,077

Dr R J Evans, University of Leicester. "The contribution of lipid rafts to the regulation of P2Y receptors in the cardiovascular system" 2 years £75,922

Dr M I Mackness & Dr B Mackness, Manchester Royal Infirmary. "Antiatherogenic properties of paraoxonases 2 and 3" 1.5 years £41,543

Dr B J Wojciak-Stothard, University College London. "Role of Rho GTPases in nitric oxide-mediated cytoskeletal remodelling and barrier function in pulmonary endothelial cells in vitro" 3 years £196,750

Dr J Selvanayagam and Prof S Neubauer, John Radcliffe Hospital, Oxford. "A comparison of myocardial perfusion imaging with cardiovascular magnetic resonance at 1.5T and 3T" 2 years £147,363

Dr S Loughna & Prof J D Brook, University of Nottingham. "Rapid knockdown of developmentally important cardiac genes" 3 years £188,935

Dr M Falasca & Prof I C Zachary, University College London. "Role of class II phosphoinositide 3-kinase in endothelial cell functions" 3 years £216,063

Prof G Murphy & Dr C H J Roghi, University of Cambridge. "Post-ischaemic endothelial repair: The roles of aminopeptidase N and membrane type 1 (MT1) MMP and their interactions in angiogenesis" 3 years £145,724

Prof M R Bennett & Dr T D Littlewood, University of Cambridge. "Selective vascular smooth muscle cell death in atherosclerosis" 3 years £160,383

Prof S B Marston et al, NHLI, London. "Development and functional investigation of transgenic mouse models of dilated and hypertrophic cardiomyopathy" 3 years £267,921

Dr J C Mason et al Imperial College, London. "The role of heme oxygenase-1 in the cytoprotective and anti-inflammatory effects of statins on the vascular endothelium" 3 years £175,152

Prof S B Marston, Imperial College London. "Contractile protein phosphorylation and dephosphorylation in HOCM and end-stage failing human heart" 3 years £136,976

Dr M P Mahaut-Smith University of Cambridge. "Molecular identification and activation mechanisms of cation-permeable channels in the platelet and megakaryocyte" 3 years £125,001

Dr X Y Luo, University of Glasgow. "Towards a better understanding and design of mitral bioprosthesis" 2 years £63,001

Prof S D BrainKing's College London. "Mechanisms involved in TRPV1 receptor-dependent vascular reactivity" 3 years £157,287

Prof D J Webb et al, University of Edinburgh. "Investigation of endothelin-1-mediated regulation of blood pressure and renal haemodynamics through cell type-specific knockout of endothelin B receptors" 3 years £182,261

Submission Deadlines for *The* Bulletin:

Volume	*Date*	*Deadline*
19 (3)	***July 2006***	*1st June*
19(4)	***October 2006***	*1st Sept*
20 (1)	***January 2007***	*1st Dec*
20 (2)	***April 2007***	*1st March*

Articles for *The* Bulletin

Would you like to write a Review or Laboratory Profile for the BSCR Bulletin? These articles provide an excellent opportunity to let BSCR members know about your research activities and also provide an insight into your research field.

We are keen to hear from anyone in cardiovascular research who would be willing to write for *The* Bulletin. If you are interested, please contact the Bulletin editors with your ideas:

Helen (h.maddock@coventry.ac.uk) or Nicola (N.Smart@ich.ucl.ac.uk)

Cardiovascular Related Wellcome Trust Grants

November to December 2005

Project Grant

Professor Sian E Harding. Department Of Cardiac Medicine, Imperial College School Of Medicine, National Heart And Lung Institute London Role Of Protein Kinase A-Dependent G-Protein Switching Of The Beta2-Adrenoreceptor In Depression Of Cardiac Contraction. 24 Months, £127,870

Dr Michael Khan. Biomedical Research Unit, Department Of Biological Sciences, University Of Warwick Coventry. Use Of Unique Animal Models To Study Reversible Effects Of Hyperglycaemia On The Arterial Edothelium In Vivo. 24 Months, £177,335

Dr P W Flatman. Centre For Integrative Physiology, School Of Biomedical And Clinical Laboratory Science, University Of Edinburgh, Scotland. Identification Of The Kinases And Phosphatases That Regulate Phosphorylation And Activity Of The Na-K-2cl Cotransporter In Response To Environmental Change. 36 Months, £286,216

Professor Gerard B Nash. Department Of Physiology, The Medical School, University Of Birmingham. Mechanisms By Which Fibroblasts From Different Origins Modify The Transendothelial Recruitment Of T-Cells And Their Retention In Inflammed Tissue. 36 Months, £199,177

Dr Edward White. Department Of Physiology, School Of Biomedical Sciences, University Of Leeds, Leeds. Do Adaptive Changes In ECG, In Response To Voluntary Exercise Training, Reflect Changes In Myocardial Ion Channel Gene Expression And Single Myocyte Electrophysiology? 24 Months, £150,564

Dr John G Mccarron. Department Of Physiology And Pharmacology, University Of Strathclyde, Glasgow Scotland. The Contribution Of The Sarcoplasmic Reticulum And Mitochondria To Local Ca2+ Signalling In Smooth Muscle. 36 Months, £592,769

Professor Jeremy P T Ward. Department Of Asthma, Allergy And Resp Science, Guy's Hospital Campus, King's College London. Modulation Of Vasomotor Tone By Hypoxia In The Pulmonary Circulation. 36 Months, £498,929

Professor Nishi Chaturvedi. Department Of Clinical Pharmacology, National Heart And Lung Institute, Imperial College London At St Mary's, London. Hepatitis C Infection And Clearance: Associations With Atherosclerosis And The Metabolic Syndrome. 24 Months, £284,356

Professor Andrew H Baker, Glasgow Cardiovascular Research Centre, Division Of Cardiovascular And Medical Science, University Of Glasgow, Glasgow Scotland. The Effect Of Cadherin Dysregulation In The Heart. 18 Months, £93,393

Professor N Cameron. Department Of Human Sciences, Loughborough University, Loughborough Childhood Determinants Of Adolescent Risk Factors For Later Morbidity. 12 Months, £70,040

Research Career Development Fellowship

Dr R S Scotland. William Harvey Research Institute, Queen Mary, University Of London. The Influence Of Gender And Sex Hormones On Vascular Inflammation And Cardiovascular Disease: Role Of Specific Chemokines. 48 Months, £335,130

Dr Matthew A Bailey. Molecular Physiology Laboratory, Wilkie Building, University Of Edinburgh Medical School, Edinburgh Scotland. Paracrine Control Of Renal Function: Extracellular Nucleotides And Sodium Reabsorption. 24 Months, £171,774

Intermediate Clinical Fellowship

Dr S Plein. Institute For Cardiovascular Research, Leeds General Infirmary, University Of Leeds, Leeds K-T Accelerated Cardiac Magnetic Resonance Myocardial Perfusion Imagaing. 48 Months, £545,352

Dr David R Mole. Henry Wellcome Building For, Molecular Physiology, University Of Oxford. Non-Hypoxic Regulation Of Hif Hydroxylation. 48 Months, £518,164

BSCR Autumn Meeting 2006

A joint meeting with the

British Atherosclerosis Society

"BIOMECHANICAL SIGNALLING IN ATHEROSCLEROSIS"

Dates: Thursday 21st and Friday 22nd September, 2006
Venue: Queens' College, University of Cambridge, UK
Organisers: Professor Dorian Haskard, Dr Peter Weinberg and Professor Qingbo Xu

Objectives: Biomechanical stimulation of cell signalling pathways makes a major contribution to cellular physiology in the healthy arterial wall and, conversely, mechanical disturbances are increasingly thought to underlie the development of arterial pathology. This symposium will cover current and emerging concepts regarding the molecular and cellular mechanisms whereby biomechanical factors influence atherosclerosis.

Programme: The programme will consist of state-of-the-art presentations by leaders in the field. Speakers include: Shu Chien (La Jolla, US), Rob Krams (Rotterdam), Justin Mason (London), Martin Schwartz (Charlottesville, US), Alain Tedgui (Paris), Peter Weinberg (London), Qingbo Xu (London).

Free Communications: Part of the programme will be devoted to oral presentation of selected abstracts and posters. There are two prizes of £250 each: the Clinical Science Young Investigator Award and the BSCR Young Investigator Award.

Travel & Accommodation: Queens' College within the University of Cambridge is easily accessible by train and bus or taxi. En suite accommodation will be available within the College, or delegates can make their own arrangements with local hotels. Visit www.visitcambridge.org for information on places to stay. Logistics for the meeting will be handled by Natasha Dougall of Wheldon Events and Conferences (+44 (0)1922 457 984, natashadougall@wheldonevents.freeserve.co.uk)

Registration Fee: Free to BSCR members, £40 for non-members.

Student Bursaries: The Society will consider awarding travel grants of up to £200 to BSCR members who are *bona fide* students and application forms are available from the BSCR website **(www.bscr.org)**

The full programme, abstract pro-forma and meeting registration / accommodation forms will be available for downloading from the website by the end of April 2006.

Deadlines: Submission of abstracts - Friday 14th July. Registration and application for student bursaries - Friday 8th September.

Further enquiries: Enquiries about the programme should be directed to Dr Peter Weinberg, Physiological Flow Studies Group, Department of Bioengineering, Imperial College, London SW7 2AZ, UK, Tel +44 (0)20 7594 1517; p.weinberg@imperial.ac.uk. Enquiries about registration and accommodation should be directed to Natasha Dougall of Wheldon Events and Conferences (contact details above).