9th International Symposium on Resistance Arteries (ISRA)

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Shaun L. Sandow^a Christopher R. Triggle^b Michael A. Hill^c

^aDepartment of Pharmacology, University of New South Wales, Sydney, N.S.W., Australia;

^bMedical Education, Weill Cornell Medical College in Qatar, Education City, Doha, Qatar;

^cDalton Cardiovascular Research Center and Department of Medical Pharmacology and Physiology, University of Missouri, Columbia, Mo., USA

The 9th International Symposium on Resistance Arteries (ISRA) was held between the 17th and 21st February, 2008 on Hamilton Island, Australia. Hamilton Island is a Great Barrier Reef Island situated within the Whitsunday Islands off the north east coast of Australia. The meeting, as had been the case for previous ISRAs, brought together a truly international group of scientists with either a direct focus on the resistance vasculature or with areas of interest applicable to resistance artery research. Ten thematic symposia covered areas including cellular communication, ion channels and the regulation of resistance vessel function, mechanotransduction, rhythmicity, vascular dysfunction (diabetes, oxidative stress, vascular remodeling) and the influence of the fetal environment. Aspects of the meeting are briefly described below, while a full listing of abstracts are available through the *Journal of Vascular Research* (www.karger.com/doi/10.1159/000113929). The complete meeting report is available at www.karger.com/doi/10.1159/000243970.

Fundamental to the behavior of resistance arteries is the communication that occurs between endothelial cells and the underlying vascular smooth muscle (VSM). This interaction occurs through direct physical contact such as provided by myoendothelial gap junctions (MEGJs) or via chemical mediators. In relation to MEGJs an important question relates to whether these structures provide low resistance pathways for electrotonic spread of signals or whether they also provide a pathway for transfer of chemical mediators. Beny [1] reviewed passive and regenerated elements of propagated signals with an emphasis on the roles of chemically and electrically coupled pathways. Beny further emphasized the likelihood that VSM membrane potential (E_m) likely influences the underlying endothelial cell layer. In contrast, endothelial cell E_m would only impact on VSM in arterioles and decrease in importance as vessel diameter increases with a greater number of smooth muscle layers. De Wit [2] described the roles of various connexins (Cx37, Cx40, Cx43 and Cx45) in communication along the vessel

wall. Using genetically manipulated mouse models differing connexins were shown to provide distinct pathways for conduction. For example, the Cx40 deficient mouse exhibits impaired conducted responses to acetylcholine and bradykinin while the conducted response to adenosine was not altered by the lack of the particular connexin. Further specificity was shown by Cx45 knock-in on the Cx40 knock out background not being able to rescue the impaired ACh conduction response [3].

Ledoux [4] introduced a novel spatially-restricted Ca^{2+} signaling event termed the ‘ Ca^{2+} pulsar’. Important for these studies was the availability of the endothelial-specific GCaMP2 Ca^{2+} indicator expressing mouse [5]. The kinetics and pharmacology (inhibited by the non-specific blocker xestospongine C, but not ryanodine) of these events showed them to be separate to other localized Ca^{2+} release phenomena such as sparks. These IP_3 -mediated localized events appear important in modulating endothelial function particularly as relates to Ca^{2+} -activated K^+ channels localized in the vicinity of myoendothelial junctions [6], which corresponds to the spatial localization of IP_3 receptors at such sites [7]. In a related presentation, Isakson described an *in vitro* vascular co-culture system using murine microvascular endothelial and VSM to image Ca^{2+} dynamics at the myoendothelial junction [8].

A particular focus of the meeting related to signaling mechanisms underlying the myogenic response of small arteries. Although vasoconstriction to the mechanical forces exerted by intraluminal pressure has been recognized for over 100 years (Bayliss, 1901) the membrane events involved in sensing a change in pressure have largely remained obscure. Brayden [9] presented evidence for the involvement of non selective cation channels involving TRP proteins (TRPC3 and TRPC6) as upstream mediators of pressure-induced membrane depolarization [10], which is believed to precede opening of voltage-gated Ca^{2+} channels and an increase in global cytosolic Ca^{2+} . In addition to being candidate mechanosensors Brayden highlighted other

mechanisms by which TRP proteins modulate myogenic tone. In cerebral VSM, TRPV4 channels, for example, allow entry of extracellular Ca^{2+} which stimulates Ca^{2+} sparks and STOCs (resulting from increased BK_{Ca} activity) leading to hyperpolarization and inhibition of myogenic tone. Adding to the significance of these channels in vivo suppression of TRPM4 with antisense oligonucleotides impairs both cerebral vessel myogenic responsiveness and autoregulation [11]. Scholfield et al [12] similarly demonstrated that Ca^{2+} sparks in retinal arteriolar smooth muscle underlie activation of BK_{Ca} channels. This may, however, not occur in all vascular beds as Jackson [13] suggested that in VSM from skeletal muscle sparks are absent and BK_{Ca} is not regulated by ryanodine-sensitive Ca^{2+} release. Supporting this, it was suggested that differences may exist in the subunit composition of BK_{Ca} channels across vascular beds [14].

In related studies the role of integrins in arteriolar myogenic reactivity [15] were considered. Using atomic force microscopy Hill et al [10] described studies showing that myogenic-like activity could be elicited at the single smooth muscle level by application of force through a specific matrix protein-integrin interaction. Specific emphasis was placed on the role of fibronectin in arteriolar smooth muscle mechanotransduction and the concept that distinct mechanoreceptor complexes may be formed by different matrix protein – integrin interactions [16].

Stefan Bolz [17] provided further details of the possible involvement of a novel pathway in the myogenic response, namely that involving sphingosine-1-phosphate (S1P). An increase in transmural pressure leads to translocation of sphingosine kinase to the plasma membrane, phosphorylation of sphingosine and generation of the mediator S1P. S1P then participates in the activation of Ca^{2+} dependent (Ca^{2+} -calmodulin) and Ca^{2+} independent (Rho kinase modulation of myosin phosphatase). Adding to this picture Bolz described the phosphatase involved in inactivating S1P, namely S1P phosphohydrolase. Interestingly, access to extracellular S1P by

S1PP was suggested to be dependent on the transport function of the cystic fibrosis transporter (CFTR). By transporting S1P across the membrane CFTR decreases availability of the phosphorylated messenger to its receptor and targets it towards the phosphatase for inactivation. Collectively these data suggest an intriguing interaction between SPP1 and CFTR in the regulation of arteriolar tone [18].

A number of presentations centered on the role of various ion channels in resistance vessel function. Aalkjaer's group presented an interesting paper describing a siRNA approach for the in vivo down regulation of the L-type Ca^{2+} channel in small mesenteric arteries of the rat [19]. This transient transfection procedure showed a down regulation of mRNA for Cav1.2 by $93 \pm 2\%$ after three days and was paralleled by decreased protein expression as shown by immunohistochemistry. Jaggar [20] challenged the conventional view that IP_3 -mediated vasoconstriction occurs solely through SR Ca^{2+} release. Specifically, in cerebral artery vascular smooth muscle IP_3 was shown to activate a plasma membrane cation channel which led to depolarization, opening of voltage-gated Ca^{2+} channels, and constriction. shRNA approaches indicated a role for TRPC₃ both in isolated cells and pressurized arteries [21]. Leblanc similarly prevented evidence for a novel ion channel-based mechanism in pulmonary arterial smooth muscle cells [22]. Specifically, it was shown that Ca^{2+} -activated Cl^- currents could be activated in parallel with a store-operated non-selective cation current (I_{SOC}).

Another dominant theme of the meeting related to sub-cellular Ca^{2+} handling and rhythmicity, or frequency-dependent events, in arterial smooth muscle. While not in resistance vessels, Imiataz and van Helden [23] presented a detailed model of pacemaking in lymphatic smooth muscle which will no doubt provide clues for the resistance artery field particularly with regard to arterial vasomotion. Lymphatic pacemaking was shown to utilize inositol-1,4,5-triphosphate (IP_3) receptor-coupled Ca^{2+} stores synchronized as coupled oscillators [24].

Coupling of stores along the lymphatic vessel involved membrane depolarization and L-type Ca^{2+} channels. Interestingly, blockade of L-type Ca^{2+} channels with nifedipine, while blocking vasomotion, does not prevent asynchronous Ca^{2+} waves in either lymphatics [23] or arteriolar smooth muscle [25]. Further developing the vasomotion theme Terui (JVR citation) and Matchkov [26] presented novel evidence that vasomotion enhances tissue-capillary fluid exchange and that ICl_2/cGMP is mediated by bestrophin-4 and which may be important for vasomotion, respectively. Using elegant imaging and caged-compound approaches in single smooth muscle cells, McCarron [27] highlighted the complexity of the intracellular Ca^{2+} stores. A model was introduced where the SR exists as a luminously-continuous Ca^{2+} store rather than a series of discrete compartments. However, functional diversity arises from the distribution of IP_3 and ryanodine receptors and their regulation by luminal $[\text{Ca}^{2+}]$ [28].

The contribution of oxidative stress to inflammation and vascular dysfunction was covered by a number of speakers throughout the ISRA meeting. In the session dedicated to the subject Clark [29] stressed the importance of BOXes (Bilirubin Oxidation products) as important contributors to cerebral vasospasm in patients following hemorrhagic strokes. Kennedy [30] focused on the protease activated receptor-2 (PAR-2) and its contribution to neointima formation, which was much reduced in vascular injury studies with the PAR-1 knockout mouse. Zhang [31] stressed the importance of NF κ B and TNF signaling in amplifying diabetes-associated endothelial dysfunction. Thomas [32] described the potentially important role that the leukocyte enzyme, myeloperoxidase (MPO) has, when associated with the endothelial cell, in inducing oxidative stress and endothelial dysfunction. Thus, blocking MPO sequestration into the endothelium is a potential target for protecting endothelial function. von der Weid extended the focus on inflammation to show that in a model of inflammatory bowel disease that lymphatic

contractile activity was impaired [33]. The inhibition of lymphatic pumping was attenuated by cyclooxygenase inhibition suggesting a role for prostaglandins.

The role of the resistance vasculature in vascular disease was further considered in sessions relating to diabetes and hypertension. Jenkins [34], Triggle [34], Vanhoutte [35], Plane [36], focused on the effects of type 1 and type 2 diabetes on microvascular function with data presented from both human and animal studies. Jenkins emphasized the importance of the measurement of biomarkers as indicators of the impact of diabetes on cardiovascular function in humans as well as the efficacy of lifestyle and therapeutic interventions [34]. Complication-prone patients have comparatively higher levels of inflammation, oxidative stress, insulin resistance and tissue Advanced Glycation End-products (AGEs) burden as well as levels of the nitric oxide inhibitor, asymmetric dimethyl L-arginine (ADMA). Interestingly, comparable data is seen in animal models of type 1 diabetes thus supporting the argument that clinical and animal-based laboratory observations will facilitate the development of new approaches to the treatment as well as the prevention of diabetes-linked vascular disease. Triggle stressed the link between hyperglycaemia and, notably, the effects of acute changes in blood glucose (postprandial) on endothelial function with data indicating that elevated glucose resulted in a rapid “uncoupling” of eNOS that was possibly related to the oxidation of tetrahydrobiopterin [37]. Based on data from a cell culture assay with mouse microvascular endothelial cells exposure to elevated glucose also resulted in changes in expression of p22phox, eNOS, SOD1 and SOD3 indicating that the continued exposure of the endothelium to abnormal levels of glucose created a pro-oxidative stress environment that could be corrected by the provision of sepiapterin, a precursor of tetrahydrobiopterin. The effects of severe dyslipidaemia on the eNOS pathway, and cognitive function, were also stressed in a poster presentation by Drouin et al [38]. Triggle also noted that changes in the relative contributions of endothelium-derived nitric oxide versus the contribution

and/or 'nature' of the endothelium-derived hyperpolarizing factor, EDHF, pathway also contributes to endothelial dysfunction [37]. Several presentations (Luksha et al., [39], Bansal et al., [40], Yang et al [41]) also provided evidence that alterations in the cellular processes contributing to EDHF are altered in cardiovascular disease. Vanhoutte focused on the link between vascular disease and endothelium-dependent increases in vascular tone that could be attributed to the release of Endothelium-Derived Contracting Factors – EDCFs [35]. The contribution of EDCFs to vascular disease has been noted in both animal and human studies and the resultant elevated vascular tone may result from a combination of the loss in the bioavailability of endothelium-derived nitric oxide as well as increases in the synthesis of EDCFs – angiotensin II, endothelin-1 as well as oxygen-derived free radicals and vasoconstrictor derivatives of arachidonic acid. Of importance was the argument that selective antagonists of prostanoid TP-receptors prevented endothelium-dependent contractions thus indicating the potential for such drugs in the treatment of endothelial dysfunction in not only diabetes but also hypertension. The poster presentation from Wong et al [42] also emphasized the contribution of COX-2-dependent EDCFs to acetylcholine-induced contractions in the hamster aorta. Plane presented data from streptozotocin (STZ)-induced diabetic rats that deficits in endothelium-dependent relaxation to acetylcholine in small mesenteric arteries and basilar arteries from the diabetic rat may be related to a dysfunction in the activation of endothelial intermediate conductance K_{Ca} (IK_{Ca}) channels [36]. The provision of the activator of IK_{Ca} channels, 1-ethyl-2-benzimidazolinone (1-EBIO), restored acetylcholine-induced NO-dependent and –independent relaxations in vessels from diabetic rats, but quantitative RT-PCR showed no differences in the expression of either IK_{Ca} or the small-conductance SK_{Ca1-3} channels. Thus, targeting the IK_{Ca} may prove to be a novel target for treating diabetes-related vascular disease. Presentations from Haddock et al [43] and Brondrum et al [44] also supported the argument that changes in the

regulation or distribution of IK_{Ca} may be altered in vascular disease. Thorin [45] provided data from studies with both animal and human endothelial cells that linked endothelial cell senescence with cardiovascular disease and also linked smoking with a loss of antioxidant reserve and stress-induced senescence (SIS). Endothelial senescence was associated with a rise in markers of oxidative stress, such as HNE (4-hydroxy-2-nonenal), caveolin-1 expression as well as telomere shortening. These data indicated the importance of the redox environment and that an un-buffered bursts of free radical release results in accumulated damage. Of interest to was data from dyslipidemic mice that indicated that indicated that dyslipidemia hastened endothelial senescence and dysfunction and that chronic treatment with the antioxidant polyphenol catechin slowed progression of the indices of endothelial dysfunction.

Plasticity of the resistance vasculature was considered in the context of remodeling events which occur during physiological and pathophysiological conditions. Osol [46] described the physiological remodeling of the rat uterine circulation during pregnancy and then considered the added effects of NO inhibition (via L-NAME treatment) and increased perfusion pressure per se. While pregnancy caused marked effects on both axial remodeling (lengthening of the uterine artery and its branches) and circumferential remodeling of radial arteries, hypertension exerted a negative effect on only the circumferential changes. Van Bavel [47] described arteriolar organ culture studies underlying eutrophic remodeling responses to increased pressure and flow reduction. A sequence of events was proposed involving an initial inflammatory response and subsequent action of transglutaminase enzymes which modify the vessel wall by amino acid cross-linking reactions. Involvement of multiple members of this family of enzymes was suggested by data obtained in a transglutaminase 2 knockout model. Providing a link between mechanical forces and remodeling of the vessel wall, Pohl [48] presented studies showing that endothelial shear stress leads to elastase-mediated modification of the extracellular matrix,

activation of $\alpha_v \beta_3$ integrins and release of basic fibroblast growth factor.

A topic new to the ISRA program was the impact of the fetal environment on vascular (dys)function in later life. Considerable interest has developed over recent years in the concept of ‘fetal programming’ contributing to adult vascular disease including hypertension (for recent reviews see Poston [49] and Nuyt [50]). Davidge described animal model studies linking intrauterine hypoxia to endothelial dysfunction in adult offspring along with decreased cardiac tolerance to an ischemia/reperfusion event [51]. Leading on from this presentation several papers examined the effects of factors often found in the gestational environment, including alcohol [52], nicotine [53] and glucocorticoids [54], on vascular function of the offspring. Parkington reported that fetuses exposed to alcohol showed marked increases in arterial stiffness with extrapolations to large vessels thus suggesting that children with fetal alcohol syndrome would be more susceptible to atherosclerosis [52]. Similarly Tare concluded that prenatal glucocorticoid exposure resulted in endothelial dysfunction and pro-vasoconstrictor thus predisposing the offspring to lifelong cardiovascular dysfunction [54]. Lee described the detrimental effects of nicotine exposure in the fetus and neonate on perivascular adipose tissue (PVAT) function that resulted in a reduction in blood pressure lowering contribution of PVAT [53].

A vital part of the 9th ISRA was sessions dedicated to Young Investigators. Outstanding oral presentations were made by Jonathan Ledoux, University of Vermont, Rebecca Haddock, University of New South Wales and Henrik Kold-Petersen, University of Aarhus. Ledoux (briefly mentioned above), demonstrated an association of calcium ‘pulsar’ release at internal elastic lamina hole sites, which are a prerequisite for myoendothelial gap junctions and correspond to sites of IK_{Ca} and IP_3R localization [4,6,55] [7]. Such results support a novel mechanism of IP_3 -calcium signaling which is likely critical for vascular heterocellular signalling.

Haddock highlighted changes in vasodilator function in disease, with a focus on diet-induced obesity [43]. Endothelium-dependent hyperpolarization (EDH) being due to activation of small and intermediate conductance calcium-activated potassium channels (S/IK_{Ca}) in normal rat mesenteric artery, and IK_{Ca} alone in obese rat. Extending this theme, Kold-Petersen presented data examining the influence of S/IK_{Ca} activation with NS309 on the impaired EDH response of small arteries from the Zucker diabetic fatty rat (model of Type 2 diabetes) [44]. The K⁺ channel activator was found to improve EDH-dependent dilation independently of an effect on intracellular Ca²⁺. Additional studies performed with apamin and TRAM-34 suggested that the improvement occurred largely at the level of IK_{Ca}.

While the meeting began under monsoon conditions the science shone through and eventually perfect weather followed. After successful completion of the 9th ISRA plans have begun for the 10th ISRA to be held in Denmark in 2011. As a sad footnote to the meeting the ISRA community would like to acknowledge the immense contributions of Dr William Halpern (1923 - 2008). He was an 'ISRA Founder' and a vital contributor both through his science and support through generous sponsorship provided by his company. Bill will be missed.

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