

**New Frontiers in Basic
Cardiovascular Research 2012**

dependent on COX-2/PGI₂ pathway, endogenous MNA, may play an important role in the homeostasis of cardiovascular system. Finally, treatment with nicotinic acid provides robust activation of MNA-dependent mechanisms. In conclusion, our findings may foster the development of novel vasoprotective agents based on exogenous stimulators of MNA/COX-2/PGI₂ pathway.

[1] K. Bryniarski et al., Eur. J. Pharmacol. 578, 332-338 (2008), [2] S. Chlopicki et al., Br. J. Pharmacol. 152, 230-239 (2007), [3] M. Bartus et al., Pharmacol. Rep. 60, 127-138 (2008), [4] C. Watala et al., Pharmacol. Rep. 61, 86-98 (2009), [5] L. Mateuszuk, et al., Pharmacol. Rep. 61, 76-85 (2009), [6] M. Sternak et al., Pharmacol. Rep. 62, 483-493 (2010).

Emerging roles for transient receptor potential channels in vascular biology

Ágnes Czikora¹, Ibolya Rutkai¹, Tamás Csipő¹, Gábor Fülöp¹, Viktória Csató¹, István Édes¹, Zoltán Papp¹, Attila Tóth¹

¹*Division of Clinical Physiology, Institute of Cardiology, University of Debrecen, Debrecen, Hungary*

Transient receptor potential channels (TRPs) are being recognized as a major type of cation channels expressed in various cell types, including vascular smooth muscle and endothelial cells. We have started to characterize the vascular biological role of some members of this group, such as TRPA1, TRPV1, TRPM4 and TRPM8. The first channel being characterized in detail was the capsaicin receptor (TRPV1). TRPV1 is well known to be expressed in sensory neurons, where it plays a major role in inflammatory thermal hyperalgesia. We found that TRPV1 is expressed in various blood vessels, including skeletal muscle arteries. In accordance, TRPV1 stimulation results in a vasoconstriction in some arteries. Moreover, it was found that TRPV1 stimulation results in an increase in intracellular Ca²⁺ concentrations. This effect was partly dependent on voltage gated Ca²⁺ channels, suggesting a role for membrane depolarizations. Another studied TRP was the melastatin 4 (TRPM4). It was reported that TRPM4 may contribute to the stretch induced contractile response (myogenic tone) in intracranial arteries. We have also tested the involvement of this channel in agonist evoked constrictions, such as evoked by high extracellular K⁺ or norepinephrine in various arteriolar beds. TRPM4 inhibition significantly antagonized the contractile responses, suggesting a major role for this channel in smooth muscle constriction. TRPA1 (AITC) and TRPM8 (menthol) stimulation resulted in a dilation, suggesting an unknown role for these channels. Our data suggest that TRP channels may have a significant impact in vascular biology. They may be involved in physiological responses, such as myogenic response and endothelium mediated hyperpolarization.

Lung radical stress in the pathogenesis of hypoxic pulmonary hypertension

Jan Herget¹

¹*Department of Physiology, 2nd Faculty of Medicine, Charles University in Prague, Prague, Czech Republic*

Secondary pulmonary hypertension is a serious complication of lung and heart diseases with respiratory or cardiac insufficiency. Pathogenesis is linked to chronic hypoxia - induced injury to the walls of prealveolar pulmonary blood vessels, hypoxic pulmonary hypertension (HPH). Therapy of HPH is still not based on the knowledge of primary pathogenetic mechanisms and stands mostly on pharmacological vasodilatory therapy of variable effectiveness and specificity. In the last decade evidence accumulated that the important mechanism of hypoxia-induced injury of pulmonary vasculature is the radical stress of lung tissue. Rationale of this hypothesis is as follows: 1. Exposure to chronic hypoxia stimulates oxygen radical (ROS) production in the lung. 2. The ROS production is highest in early phase of sojourn in hypoxia. 3. HPH is accompanied with the expression and activation of NO synthases which are the source of NO and also superoxide (uncoupled NO synthase). 4. The increased NO and superoxide production results in formation of peroxynitrite. 5. Radical stress of lung tissue recruits and activates lung mast cells which are clearly linked with the mechanism of hypoxia - induced remodeling of prealveolar vessels. 6. Administration of antioxidants at the onset of hypoxic exposure prevents development HPH.

IL-1beta-induced inflammatory response in vascular smooth muscle cells is enhanced by amyloid-peptide 1-40 through activation of NF-kB and PI3K/AKT pathways

Régis Blaise¹, Amélie Vromman¹, Clotilde Rouxel¹, Isabelle Limon¹

¹*Paris 6 Pierre et Marie Curie University, UR4, Stress, Vieillesse et Inflammation, Paris, France*

Cerebral amyloid angiopathy (CAA) is a common pathology in the elderly characterized by the deposition of amyloid proteins within the leptomeningeal and cortical arteries. Recently, coexisting inflammations in CAA patients have been recognized as CAA-related inflammation, which might contribute to disease pathogenesis. In this study, we demonstrated that wild-type (WT) Aβ₁₋₄₀ peptide (the main amyloid peptide accumulated in CAA sporadic forms) alone did not induce an inflammatory response in vascular smooth muscle cells (VSMC). However, expression of IL-1β-induced inflammatory markers -such as MMP-9, Cox-2, PGE₂- are strongly enhanced when VSMC are pretreated with WT-Aβ₁₋₄₀. We demonstrated that the increase of IL1β-induced inflammatory response by WT-Aβ₁₋₄₀ is due in part to a WT-Aβ₁₋₄₀-dependent increase of IL-1β receptor, through activation of NF-kB and PI₃K/AKT pathways. Inhibition of these pathways during WT-Aβ₁₋₄₀ treatment completely suppressed the enhanced IL1β-induced inflammatory response. We next evaluated whether the inflammatory signal could be provided by endothelial cells (EC) exposed to WT-Aβ₁₋₄₀. By treating VSMC previously exposed to WT-Aβ₁₋₄₀ with conditioned media from EC treated with WT-Aβ₁₋₄₀, we obtained the same enhanced inflammatory response as the one obtained with IL-1β. Furthermore, treating