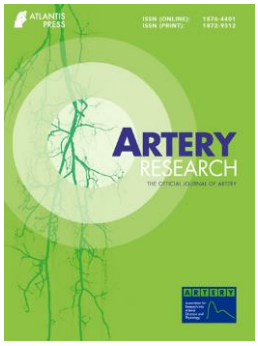

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P10.03: ENDOTHELIUM-SPECIFIC CALCIUM-ACTIVATED POTASSIUM CHANNELS: TARGETS FOR ALDOSTERONE

V. Griol-Charhbili, A. Nguyen Dinh Cat, G. Palais, L. Loufrani, D. Henrion, N. Farman, F. Jaisser

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Poster Presentation Abstracts
Animal Studies

P10.01
INVOLVEMENT OF CALCIUM-CALMODULIN DEPENDENT PROTEIN KINASE II ON ENDOTHELIN RECEPTOR EXPRESSION IN CEREBRAL ARTERIES OF RAT

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Background. Experimental cerebral ischemia and organ culture of cerebral arteries result in enhanced expression of endothelin ET_B receptors in smooth muscle cells. The present study was designed to evaluate the involvement of calcium-calmodulin dependent protein kinase (CAMK) on the expression of endothelin receptors.
Methods. Rat basilar arteries were incubated for 24 hours with and without the CAMK inhibitor, KN93, or the ERK1/2 inhibitor, U0126. The contractile responses to endothelin-1 (ET-1; ET_A and ET_B receptor agonist) and sarafotoxin 6c (S6c; ET_B receptor agonist) were studied using a sensitive myograph. The mRNA levels of ET_A and ET_B receptors, and of CAMKII were determined with real-time polymerase chain reaction (PCR) while the protein level was evaluated by immunohistochemistry and western blot.
Results. The mRNA levels of CAMKII and of the ET_B receptor were increased during organ culture but not for ET_A receptor. This effect was abolished by co-incubation with KN93 or U0126. In functional studies, both inhibitors attenuated the S6c and potassium induced contractions, and KN93 decreased the ET-1 induced response. This was confirmed at the protein level by immunohistochemistry where the endothelin receptors were found co-localised with CAMKII. Phosphorylated extracellular signal-regulated kinase p-ERK1/2 and CAMKII was measured by immunohistochemistry and western blot. Incubation of arteries with KN93 decreased the protein levels of p-ERK1/2 and CAMKII while U0126 has no effect on CAMKII.
Conclusion. Our results show that the CAMK II is involved in the endothelin receptor regulation and interacts with the MEK/ERK1/2 pathway, resulting in enhanced receptors expression in rat cerebral arteries.

P10.02
EFFECT OF INTEGRIN-EXTRACELLULAR MATRIX INTERACTIONS ON SMALL ARTERY STRUCTURE AND MECHANICS DURING HYPERTENSION AND AGING

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An age-related increase in systolic blood pressure and similarities in the consequences of hypertension and aging on arterial structure/mechanics have been reported, particularly in larger arteries. As the structural/mechanical properties of smaller resistance vessels in the context of advancing physiological age and the mechanisms underlying these parameters are less well defined, we studied the effect of disintegrin-treatment (kistrin, or echistatin), *ex-vivo*, on mesenteric artery structure and mechanics, using wire-myography, in 8 week-old (young), 15 week-old (adult) and >1 year-old (old) Spontaneously Hypertensive (SHRs) and Wistar-Kyoto rats (WKYs). Vascular integrin αV and α5 expression were also quantified. Initial narrowing of the lumen by inward eutrophic remodelling, in arteries from young and adult SHRs, was superseded by expansion of the lumen as a result of outward hypertrophic remodelling in old SHRs. Vascular stiffness was increased in young SHRs versus WKYs but was similar in adult and old SHRs versus WKYs, despite increased integrin αV and α5 expression in these latter two groups. Disintegrin-treatment of arteries did not alter structure or mechanics in SHRs. Aging in WKYs was associated with hypertrophic remodelling of mesenteric arteries which was independent of integrin expression and associated with no change in vascular stiffness. In WKYs at all ages, vascular structure remained unaltered by disintegrin-treatment; however, stiffness was significantly reduced with echistatin-treatment ($P<0.05$), suggesting that integrin-ECM interactions contribute towards passive stiffness of WKY arteries. Further insight into the influence of integrin-ECM interactions on vascular structure/mechanics will contribute towards a better understanding of hypertension and age-related cardiovascular complications.

P10.03
ENDOTHELIUM-SPECIFIC CALCIUM-ACTIVATED POTASSIUM CHANNELS: TARGETS FOR ALDOSTERONE

V. Griol-Charhbili [1], A. Nguyen Dinh Cat [1], G. Palais [1], L. Loufrani [2], D. Henrion [2], N. Farman [1], F. Jaisser [1].
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To define the vascular role of the mineralocorticoid receptor (MR) in cardiovascular pathophysiology, we generated a conditional transgenic mouse model with MR overexpression in the endothelium.
We previously described increase sensitivity to several vasoconstrictors in mesenteric arteries such as in aorta of mice over-expressing the MR in the endothelium (MR-EC) in presence of a normal relaxation to vasodilatators. *In vivo*, blood pressure (BP) was increased in awaked MR-EC mice, as compared to the controls (CT) (tail-cuff method).
We have investigated the role of the small (SK_{Ca}), and the intermediate (IK_{Ca}) and the big (BK_{Ca}) conductance potassium channels in vascular function. In infra-renal aorta, endothelial SK_{Ca} and IK_{Ca} channel blockade (Apamin 1 μM + TRAM-34 1 μM) unmasked an impaired relaxation to acetylcholine in MR-EC mice as compared to controls. Inhibition of the smooth muscle specific BK_{Ca} channel with Iberiotoxin (0.1 μM) blunted the higher phenylephrin-induced contractile response observed in MR-EC as compared to CT. These pharmacological data suggest that endothelial MR overexpression is associated with an increased activity of EDHF-mediating endothelial Ca-activated K channels and a functional decrease of the smooth-muscle BK_{Ca} channel activity. Western-blot analyses of the protein expression levels of these channel subunits were performed. None of them showed significant modulation, suggesting that channel activity, rather than expression level, is affected in this model.
MR activation specifically in endothelial cells is therefore associated with increased BP and altered vascular reactivity, in absence of renal collecting duct mediated MR effects. This may be related to ion channels remodeling.

P10.04
INFLUENCE OF 1,25(OH)2D3 (VITAMIN D) ON RESISTANCE ARTERY CONTRACTILITY

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Low serum vitamin D is linked with higher vascular risk. It is unclear how.