Changes in resistance arteries expression of extracellular nucleotides signaling partners during arterial hypertension.

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Cardiovascular diseases are the leading cause of mortality in industrialized countries and their prevalence increases with aging populations. Small arteries constitute the main site of peripheral vascular resistance and play a key role in the regulation of blood pressure. Vascular tone is exacerbated in hypertension (HBP) and accompanied by a hypertrophy of the arterial wall. Although signaling by extracellular nucleotides is important in vascular homeostasis its contribution to vascular pathologies affecting small arteries remains poorly understood. We evaluated here the expression pattern of nucleotides signaling pathway in resistance arteries vs aorta in mice. Genes of interest including P2 receptors, ectonucleotidases (CD39, CD73) and hemic channels (connexins, pannexins) were investigated by quantitative RT-PCR. Their expression in resistance arteries was assessed in Angiotensin II-treated mice, spontaneously hypertensive rats (SHR) and, since HBP is related to age, in 24-month old mice. Our results showed that several genes are more expressed in aorta (P2y2 and connxin 43) while others are expressed specifically (P2x1, connxin 37) or preferentially (P2ry6) in small arteries. The latest might be involved in pathologies affecting the small arteries. With HBP, we observed a decreased connxin 37 and 40 expression level in Angiotensin II-treated mice and in SHR respectively and both decreased with aging. Interestingly, CD39 (tone regulator) decreased in the two models of HBP and with aging. Such decrease in nucleotidase activity may enhance P2 receptors activation and increase vascular contractility/tone. This is especially true considering P2y6 (tone promoter) that increased with aging. Further studies may allow us to evaluate the contribution of these mediators in the development of small arteries defect in aging associated or not with HBP. Signaling by extracellular nucleotides may constitute new therapeutic targets in the treatment of HBP.

Deficiency in nitric oxide decreases the microcirculation reactivity in mouse resistance arteries

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Endothelial dysfunction is associated with cardiovascular diseases and can be evaluated in clinical setting for risk stratification in patients. Flow mediated dilation (FMD) or local acetylcholine (ACh) administration are used to assess endothelial dysfunction in arteries but also in microcirculation (MC) using Laser Doppler Flowmetry (LDF). In our study, we aim to investigate the role of nitric oxide (NO) in the endothelial response of microcirculation in vivo in mice. Two strains of mice (C57BL6 and BALBc mice; 20 weeks old) were treated with NO synthase inhibitor (L-NAME) in drinking water (1 g/L) and in SHR respectively and both decreased with aging. Interestingly, CD39 (tone regulator) decreased in the two models of HBP and with aging. Such decrease in nucleotidase activity may enhance P2 receptors activation and increase vascular contractility/tone. This is especially true considering P2y6 (tone promoter) that increased with aging. Further studies may allow us to evaluate the contribution of these mediators in the development of small arteries defect in aging associated or not with HBP. Signaling by extracellular nucleotides may constitute new therapeutic targets in the treatment of HBP.

Role of kinins in diabetic wound healing

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The diabetic foot is associated with pain, decrease in patient’s quality of life, considerable costs, and amputation. In this study, we determined the role of KKS, via activation of bradykinin receptors (B1R or B2R), in a mouse model of diabetic wound healing. Diabetic or non-diabetic mice are wounded with an 8-mm punch biopsy and then are treated or not with specific B1R or B2R agonists (720nmol/kg,d’) and/or B2R antagonist (Icatibant, 500µg/kg,d’). The wound healing surface was daily followed up. At 11 days, the scar was analysed by histology (Masson’s trichrome staining) and B1R and B2R expression were assessed (RT-qPCR). Effects of the agonists on cells (fibroblasts and keratinocytes) migration and proliferation were also analysed. In diabetic condition, mRNA of B1R and B2R was increased in skin (p<0.01). B1R activation had no effect on wound closure in our model. In contrast, B2R activation dramatically delayed wound healing in diabetic (p<0.001) or non-diabetic (p<0.01) mice. Histological analysis of scar showed significant skin disorganization and epidermis thickening with B2R agonist (p<0.05). In vitro, B2R agonist induced an increase of keratinocyte proliferation (+46% after 48h, p<0.01) and a stimulation of keratinocyte migration (+30% after 24h, p<0.05). These effects was associated with ERK phosphorylation which occurs downstream of EGFR activation (p<0.05). B2R agonist had no effect on fibroblast migration but decreased fibroblast proliferation (~33% after 48h, p<0.05). Co-treatment with Icatibant abrogated in vivo and in vitro effects observed with B2R agonist. Moreover, Icatibant alone hasted wound healing and decrease the epidermis thickening induced by diabetes. In conclusion, KKS, through the B2R but not the B1R, plays a critical role in proliferation and remodeling phases of skin wound healing in mice. While more studies are needed, Icatibant could be used to correct the diabetic wound healing defect.