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NEW DRUG TARGETS FOR SLOWING VASCULAR AGEING: SIRT1, SIRT5, JUND AND P66SCH

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THE REGULATORY ROLE OF COAGULATION FACTORS ON ARTERIAL FUNCTION

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The coagulation takes place in the physiological system of hemostasis. Hemostasis is known to be disturbed in many diseases leading to hemorrhages or thrombosis. Despite the role of coagulation in hemostasis, recent evidence suggest that coagulation factors are involved in other physiological as well as pathological processes related to vascular function such as blood pressure regulation, arterial stiffness or atherosclerosis. Many direct (through protease activated receptors; PARs) or indirect effects of several coagulation factors are now well described.

We are studying the interplay between the vascular phenotype at a physiological and a cellular level with coagulation factors. Previous work in the laboratory showed that coagulation factors such as tissue factor pathway inhibitor (TFPI) are related to modulations of arterial function. TFPI expression by vascular smooth muscle cells (VSMCs), is modulated by cyclic stretch. A 10% mechanic stretch at 1 Hz leads to increased synthesis of TFPI. This relation between TFPI and increased pulse pressure and aortic stiffness was present in a cohort of postmenopausal woman. The importance of elevated blood pressure was also studied in spontaneously hypertensive rats (SHR). In these rats thrombus formation was accelerated in carotid artery and could be reversed by an inhibitor the thrombin receptor PAR-1. Thrombus formation was accelerated due to the ability of VSMCs to support greater thrombin generation with an increased exposure of negatively charged phospholipids (1). Similarly, in obese Zucker rats mimicking the metabolic syndrome thrombin generation was increase at the surface of VSMCs. Circulating fibrinogen was increase in the Zucker rats and is also a marker of inflammation and vascular inflammation was increase in these rats. Indeed gelatinase activity which represent metalloproteinase-2 (MMP-2) and MMP-9 was elevated in the aortic wall. We found in this work that the prothrombotic phenotype of the blood compartment was reinforced by procoagulant properties of dedifferentiated and inflammatory VSMCs (2). Thrombin is the pivotal protease of coagulation and coagulation factor XI (FXI) is important for its amplification. In hypertension the thrombin driven FXI feedback activation was found to mediate the vascular inflammation and dysfunction. We found that FXI receptor glycoprotein Ibalpha on platelet support the increased thrombin generation increasing both platelets and leukocytes activation. This localised thrombin generated because of FXI triggers endothelial dysfunction and monocytes infiltration which are known to participate in the development of arterial hypertension. Moreover inhibition of FXI in angiotensin II infused mice and rats limit blood pressure increase and adverse effect of hypertension (3).

Coagulation factors are not only important for hemostasis. Studying their role in vascular function regulation is novel and important function now starts to be revealed. A number of important questions remains, concerning the ability of many cell types to synthesize coagulation factors that could have localized cellular effects in vascular or circulating immune cells. More work is also necessary to understand how circulating coagulation factors could move from the blood to the vascular wall (and inversely) and how this movement is modulated under pathological conditions as well as how cellular effects of coagulation factors could play a role in the vascular regulation of these pathologies.

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Invited lecture

NEW DRUG TARGETS FOR SLOWING VASCULAR AGEING: SIRT1, SIRT5, JUND AND P66SCH

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Western societies are aging due to an increasing life span, decreased birth rates, and improving social and health conditions. On the other hand, the prevalence of cardiovascular (CV) and cerebrovascular (CBV) diseases rises with age. Thus, in view of the ongoing aging pandemic, it is appropriate to better understand the molecular pathways of aging as well as age-associated CV and CBV diseases. Oxidative stress contributes to aging of organs and the whole body by an accumulation of reactive oxygen species promoting oxidative damage. Indeed, increased oxidative stress produced in the mitochondria and cytosol of heart and brain is a common denominator to almost all CV and CBV diseases. Accordingly, different aging/longevity genes have been described as potential drug targets being involved in lifespan determination, oxidative stress modulation and CV disease pathophysiology. Among those, the mitochondrial adaptor protein p66(Shc) is deeply involved in age-related CV dysfunction by mediating reactive oxygen species production and translating oxidative stress into apoptotic signals. Furthermore, p66(Shc) was shown to be a potential target to blunt post-ischemic damage in both myocardial infarction and ischemic stroke. Also, the family of deacetylase enzymes, the sirtuins, regulates the aging process, determine lifespan of many species and are involved in oxidative stress modulation and CV diseases. Similarly, the longevity gene JunD, by enhancing antioxidant pathways and reducing the inflammatory response was reported as a critical modulator of ischemia/reperfusion in brain and heart.

Joint session with latam artery, north American artery, pulse of Asia

GREATER AORTIC STIFFNESS IS ASSOCIATED WITH LOWER HIPPOCAMPAL CEREBROVASCULAR RESERVE BUT NOT CEREBRAL BLOOD FLOW OR AMYLOID IN MIDDLE-AGED AND OLDER ADULTS

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Background: Recent studies suggests cerebrovascular dysfunction precedes amyloid deposition and cognitive impairment in Alzheimer's disease (AD). However, if functional impairments in the hippocampus, as evidenced by reduced hippocampal cerebral blood flow (CBF) during memory stimulation and cerebrovascular reserve (CVR), are associated with aortic stiffness is unknown. Therefore, we tested the hypothesis that elevated aortic stiffness would be associated with 1) lower hippocampal CBF during memory stimulation; 2) reduced hippocampal CVR; and 3) greater hippocampal amyloid burden in middle-aged/older adults (MA/O).

Methods/Results: Twenty-four MA/O adults (range: 55–87 years; mean ± SE: 70.0 ± 2.0 years) were recruited to undergo measures of aortic stiffness (carotid-femoral pulse wave velocity, cfPWV) and global and regional CBF using quantitative [¹⁵O]water PET imaging. Regional hippocampal CBF (mL/min/100mL) was measured during memory recall of a learned word list. Hippocampal CVR was calculated as the percent (%) change in CBF in response to the pharmacological vasodilator, acetazolamide. Hippocampal amyloid burden was quantified using distribution volume ratio (DVR) from [¹¹C]PIB PET imaging. The following correlations were adjusted for age, MAP (cfPWV only) and education (% word recall only). Elevated cfPWV was associated with reduced hippocampal CVR ($r = -0.59$, $p = 0.005$) but not hippocampal CBF ($p = 0.126$) or amyloid deposition ($p = 0.232$). Lower successful word recall trended to be associated with elevated cfPWV ($r = -0.38$, $p = 0.097$) and reduced hippocampal CVR ($r = 0.38$, $p = 0.087$) in the present cohort.

Conclusion: Elevated aortic stiffness may impair the ability of the hippocampal cerebrovasculature to augment CBF independent of basal CBF.

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