to obtain membrane-specific loss of function (iii) mice lacking the AF2 ligand-dependent-transcriptional function domain of ERα (AF2°) and (iv) wild type (WT) mice. Hypertension was induced using Angiotensin II (Alzet minipumps) and blood pressure measured using tail cuff. After 28 days vascular structure and function were measured in vitro. Angiotensin II-induced hypertension was greater in ERα°- and in AF2° mice than in WT and C451A-ERα mice. These data suggest that the protective effect of ERα against elevated blood pressure involved nuclear AF2-mediated transcriptional functions rather than MISS-mediated function. Changes in pressure were associated with proportional changes in endothelium-dependent dilation and wall thickness. Thanks to this work, we hope to better understand how ERα is able to mediate the protective effects of estrogen against hypertension.

0343

Essential role of P2Y6 UDP receptor in Angiotensin-II dependent arterial hypertension

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Extracellular nucleotides are responsible for pleiotropic effects in the vasculature. Uracil nucleotides are vasoactive and trophic agents and promote vascular wall remodeling. The participation of specific P2 receptors in these effects remains undefined and their potential contribution in arterial hypertension is unknown. Objective: To evaluate the contribution of the UDP receptor P2Y6 in hypertension in mouse. Methods: Arterial contraction was evaluated using a wire myograph. Blood pressure was measured following nucleotides infusion and experimental hypertension was induced either by Angiotensin-II (Ang-II 1mg/kg/j) or DOCA-salt (1%) in uninephrectomized mice. Histological approaches, immunofluorescence and RTqPCR were used to evaluate the nature of vascular remodeling. Results: P2Y6 displayed the highest arterial expression level among P2Y receptors. Contraction of conductance (thoracic aorta) and resistance (mesenteric) arteries was abrogated in P2y6°/- mice in response to UDP and UTP while other vasoconstrictor induced normal responses. P2Y6 receptor triggered a moderate intracellular calcium increase while RhoA (calcium facilitating pathway) activation was abrogated in P2y6°/- mice. Both genetic deletion and pharmacological blockade of P2Y6 receptor abolished Ang-II-induced blood pressure increase (40 mmHg in wild type mice). By contrast, hypertensive response in DOCA-salt was equivalent in P2y6°/- mice, a model of the human Pseudoxanthoma Elasticum (PXE). Conclusions: The hypothesis that hypertension confers a hypercoagulable state arises from the complications associated with hypertension, stroke and myocardial infarction. Our objective was to determine whether spontaneous hypertension causes changes in the thrombin generating capacity of the vascular wall.

0356

Disseminated arterial calcification and enhanced myogenic response are associated with Abcc6 deficiency in a mouse model of pseudoxanthoma elasticus

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OCBA has been previously shown to provide a model for the human disorder pseudoxanthoma elasticum (PXE), characterized by arterial hypertension and enhanced arterial calcification. In PXE, the ABC transporter ABCC6 is involved in the transport of urate from urine. Our objective was to study the role of ABCM6 in arterial structure and function. Wild type and ABCM6 heterozygous and knock out mice were used. These mice were subjected to an arterial pressure increase induced by Angiotensin II or DOCA-salt. Cardiac hypertrophy was also evaluated. Arterial structure and function were measured in vitro. Uracil nucleotides were infused in the aortic arch of the mice to evaluate vascular tone. Results: ABCM6 knock out mice presented an arterial pressure increase that was equivalent to wild type mice while cardiac hypertrophy was not modified in ABCM6 knock out mice. By contrast, arterial calcification was significantly increased in ABCM6 knock out mice. Conclusions: The ABCM6 transporter is involved in the development and regression of arterial calcification in the context of hypertension. The enhancement of arterial calcification by the absence of ABCM6 is associated with changes in blood pressure and is not due to changes in vascular parameters.

0416

Vascular smooth muscle cells are responsible for a prothrombotic phenotype of spontaneously hypertensive rat arteries

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Objective: The hypothesis that hypertension confers a hypercoagulable state arises from the complications associated with hypertension, stroke and myocardial infarction. Our objective was to determine whether spontaneous hypertension causes changes in the thrombin generating capacity of the vascular wall.

Approach and Results: We used spontaneously hypertensive rats (SHR) compared with Wistar rats. The addition of thoracic aorta rings of SHR to a Wistar or SHR plasma pool resulted in a greater increase in thrombin generation compared to the addition of equivalent rings from Wistar. Comparison of 5 week-old and 12 week-old rats indicate that established hypertension is required to induce increased thrombin generation within the vessel wall. Whereas no difference was observed for endothelial cells, thrombin formation was higher at the surface of cultured aortic smooth muscle cells (SMCs) from SHR than from Wistar. Exposure of negatively-charged phospholipids was higher on SHR than on Wistar aortic rings as well as on SMCs. Tissue factor activity was higher in SHR SMCs. Twelve week-old SHR exhibited accelerated EC50-induced thrombus formation in carotid arteries and the resulting occlusive thrombi were disaggregated by blockade of glycoprotein Ibα-von Willebrand factor interactions. SHR SMCs were more sensitive to thrombin-induced proliferation than Wistar SMCs. This cellular effect was totally abolished by a protease-activated receptor 1 inhibitor.

Conclusions: The prothrombotic phenotype of the SHR vessel wall was due to the ability of SMCs to support greater thrombin generation and resulted in accelerated occlusive thrombus formation after arterial injury, which is sensitive to glycoprotein Ibα-von Willebrand factor inhibitors.

0194

Angiotensin II type 2 receptor reduces metabolic and vascular effects of type 1 diabetes in the mouse

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The renin-angiotensin system has a key role in cardiovascular homeostasis, mainly through activation of angiotensin II type 1 (AT1R) and type 2 (AT2R)