P29.394 VASCULAR FUNCTION MODIFICATION IN THE MODEL OF LONG-TERM CONTINUOUS LIGHT-INDUCED HYPERTENSION OF RATS

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Objective: Exposure of rats to continuous light results in hypertension development. There is shortage of data on peripheral blood vessels function in this particular model of hypertension. We investigated whether 6-week exposure of Wistar rats to continuous 24/7day light can deteriorate vascular function with the focus on potential influence on mesenteric vessels.

Method: Experiments were performed on male adult normotensive Wistar rats divided into five groups: (a) control Wistar rats – exposed to normal light/dark cycle (12/12h day, 12/12h dark); (b) rats exposed to continuous light (24/24h); (c) rats with Nω-nitro-L-arginine methyl ester (L-NAME); (d) Wistar rats exposed to continuous light + L-NAME; (e) Wistar rats exposed to continuous light + L-NAME + captopril. Blood pressure was measured weekly by tail-cuff technique. Rings of isolated thoracic aortas were suspended in organ baths containing modified Krebs solution and connected to a force-displacement transducer for the recording of isometric tension.

Results: The prolonged exposure of Wistar rats to continuous light for 6 weeks, beginning at 12 weeks of age, induced elevation of blood pressure from 124±1 mmHg (controls) to 151±1 mmHg. In controls, L-NAME treatment increased blood pressure to 173±1 mmHg, and in rats with continuous light even to 183±1 mmHg. Simultaneous treatment with angiotensin-converting enzyme inhibitor, captopril, normalized blood pressure despite continuous light exposure. Continuous light application induced deterioration of endothelium-dependent relaxation in isolated rings of the thoracic aorta. Also L-NAME administration alone or in combination with continuous light decreased endothelium-dependent relaxation. This inhibitory effect was partially reversed by the simultaneous captopril administration. Moreover, continuous light exposure, as well as L-NAME treatment or their concomitant action, increased sensitivity of aortic smooth muscle to exogenous noradrenaline.

Conclusions: The results indicate that long lasting exposure of Wistar rats to continuous light results in elevation of blood pressure and modification of vascular responses to vasoactive drugs. This effect could be, at least in part, mediated by diminution of nitric oxide production.

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P29.395 PIOGLITAZONE ALTERS THE PARTICIPATION OF CYCLOOXYGENASE-2 PRODUCTS AND REACTIVE OXYGEN SPECIES ON VASCULAR REACTIVITY IN HYPERTENSIVE RATS

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The nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ) is expressed in all major vascular cells, where it may play an important role in vascular diseases. Thus, the PPARγ agonists, glitazones, exert depressor action in both hypertensive subjects and various animal models, improve endothelium-dependent vasodilation, and reduce vascular contractility in response to different vasoconstrictors. In addition, glitazones have anti-inflammatory actions associated to interference with redox-sensitive transcription factors, such as NF-κB, involved in the transcription of several genes including COX-2.

Objective: To analyze the effect of chronic pioglitazone treatment on the vascular reactivity of mesenteric resistance arteries from spontaneously hypertensive rats (SHR) to phenylephrine, as well as the role of prostanooids and reactive oxygen species in such effect.

Methods: Mesenteric resistance arteries from 6- month old SHR rats untreated or treated with the PPARγ-activator pioglitazone (2.5mg/kg/day for 28 days) were used. Vascular reactivity was studied with wire myography and protein expression by western blot.

Results: Pioglitazone did not lower blood pressure of SHR (control: 198±9;3 mmHg; pioglitazone: 200±2.2 mmHg; p<0.05). Concentration-response curve to phenylephrine (0.1-30 μM) was similar in segments from untreated and pioglitazone-treated rats. Indomethacin (10 μM), the selective COX-2 inhibitor NS 398 (1 μM), the TxA2 receptor antagonist SQ 29,548 (1 μM) and the EP2 receptor antagonist CG 208,399 (10 μM) reduced the response to phenylephrine only in segments from treated rats, while the TXA2 synthase inhibitor furafylline (1 μM) did not modify this response in both treated and untreated rats. In addition, COX-2 expression was higher in mesenteric arteries from treated than untreated rats. Pioglitazone treatment abolished the inhibitory effect of the respective inhibitors of NADPH oxidase and xanthine oxidase, apocynin (0.3 mM) and allopurinol (0.3 mM) on vasoconstrictor responses to phenylephrine.

Conclusions: Chronic pioglitazone treatment of hypertensive rats increases mesenteric COX-2 expression, associated with increased participation of contractile prostanoids from COX-2 in vasoconstrictor responses to phenylephrine. On the other hand, the observed reduction of involvement of NADPH oxidase and xanthine oxidase-derived reactive oxygen species in the contraction elicited by phenylephrine can explain the similar vasoconstrictor response to this agonist found in resistance arteries. If pioglitazone regulates reactive oxygen species production needs to be elucidated. Supported by URJC-CM-2007-BIO-1423, Fundación Mutua Madrileña, Red RECAVA (RD06/0014/101) and DICYT SAF2006-02378.

P29.396 BETA-ADRENERGIC VASODILATATION OF ISOPRENAINE IS LARGELY PREVENTED BY ENDGENOUS NITRIC OXIDE IN CONSCIOUS WISTAR BUT NOT IN SHR RATS

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Objective: High blood pressure (BP) in spontaneously hypertensive rats (SHR) is generally attributed to the increased activity of sympathetic nervous system (SNS) and/or impaired vasodilator action of endothelial-derived NO system. Our previous studies have shown no differences in the dose-response curves to noradrenaline in conscious normotensive Wistar (WIS) and SHR. Thus, high dependence of BP on SNS in SHR could result from excessive noradrenaline release from nerve endings and/or the imbalance between vasodilator alpha-adrenergic and vasodilator beta-adrenergic action. We focused our attention on the contribution of NO-dependent or beta-adrenergic vasodilatation to BP regulation in WIS and SHR rats.

Design and Methods: The effect of beta-adrenergic stimulation was measured using continuous infusion of isoprenaline (ISO, 100 ng/kg/min i.v.) with or without previous inhibition of NO formation by L-NAME (30 ng/kg i.v.) in SHR rats. The effect of NO donor sodium nitroprusside (SNP, 20 μg/kg i.v.) was studied under the conditions of acute NO deficiency.

Results: Isoprenaline infusion without previous inhibition of NO formation by L-NAME decreased BP more in SHR than in WIS rats. Following acute inhibition of NO formation, which caused the same BP increase in both rat strains, this L-NAME effect was completely abolished by subsequent isoprenaline infusion in both WIS and SHR rats (isoprenaline effects being completely reversed by beta-adrenergic blockade with propranolol, 1 mg/kg i.v.). Exogenous NO (delivered by SNP injection under the conditions of acute NO deficiency) significantly decreased BP in WIS rats, which was not observed in SHR rats.

Conclusions: Our results suggest that the difference in the cardiovascular response to beta-adrenergic stimulation between SHR and WIS rats is likely to be partly related to differences in the activity of the SNS and NO system, which could determine the regulation of vascular resistance in these two rat strains.

P29.397 HYPERTENSION AND VASCULAR INFLAMMATION: CONTEXT FOR A NEW PATHWAY OF ENDOGENOUS NITRIC OXIDE PRODUCTION

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Objective: Hypertension is associated with up-regulated expression of inflammatory genes, such as those encoding the endothelial cell adherence molecules. These molecules are involved in the recruitment and activation of inflammatory cells, which leads to increased vascular stiffness and impaired vasodilatation.

Methods: We used a rat model of hypertension induced by chronic renal artery stenosis (RAS) to study the expression of inflammatory genes in the thoracic aorta and the effect of NO donors on their expression.

Results: In RAS rats, the expression of the genes encoding E-selectin and ICAM-1 was significantly increased compared to control rats. Treatment with NO donors significantly decreased the expression of these genes, indicating a potential role for NO in the modulation of vascular inflammation.

Conclusions: These findings suggest that NO may play a role in the regulation of vascular inflammation in hypertension, and provide a new pathway for the treatment of hypertension.

P29.398 FREE RADICALS AND HYPERTENSION: AN INTERACTIONS WITH INFLAMMATION

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Objective: Free radicals are involved in the pathogenesis of hypertension, and their role is often associated with inflammation. We aimed to study the interaction between free radicals and inflammation in the context of hypertension.

Methods: We used a rat model of hypertension induced by chronic renal artery stenosis (RAS) to study the effect of free radicals on inflammation.

Results: In RAS rats, the levels of inflammatory markers, such as TNF-α and IL-6, were significantly increased compared to control rats. Treatment with antioxidants significantly decreased the levels of these markers, indicating a potential role for free radicals in the modulation of inflammation.

Conclusions: These findings suggest that free radicals may play a role in the regulation of inflammation in hypertension, and provide a new pathway for the treatment of hypertension.