I023

MODULATION DE LA DYSFONCTION ENDOTHELIUM DEPENDENTE PAR LA MALADIE ARTÉRIELLE LIÉE AUX PATHOLOGIES ASSOCIÉES CHEZ L'HÉMODIALYSÉ

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Objectifs — La fonction endothéliale (vasodilatation flux dépendante, FMD) est réduite chez l'hémodialysé. Nous avons étudié le rôle des atteintes artérielles reflétant les pathologies cardiovasculaires associées, dans l'altération de la FMD en fonction de la contrainte de cisaillement mesurée localement.

Méthodologie — Chez 35 patients avec insuffisance rénale dialysés (ESRD), 16 avec un antécédent de maladie cardio-vasculaire (CV+), 19 indemnes (CV-) et chez 22 contrôles appariés, nous avons évalué la géométrie de l'artère humérale (diamètre : D et épaisseur : IMT, Wall Track System) et ses changements (FMD) en réponse aux modifications du taux de cisaillement et de la contrainte de cisaillement (SS), calculée avec mesure de viscosité sanguine (viscosimètre Brookfield), pendant une hyperhémie induite par chauffage de la main dans un bain thermostaté (paliers de 35 à 44 °C). Les comparaisons multiples ont été faites par ANOVA et analyses post Hoc par test de Bonferonni.

Résultats — ESRD CV+ étaient plus agés avec pressions systolique et pulsée, D, IMT et module élastique plus élevés alors que SS étaient significativement réduit en baseline versus les deux autres groupes. Avec chauffage, les ESRD CV- et contrôles avaient une augmentation similaire de la pente D vs SS pour les températures faibles mais la pente devenait significativement plus faible pour ESRD à 44°. Les ESRD CV+ ont présenté une altération de la relation D vs SS pour toute la gamme de température. La réponse à la TNT était réduite pour ESRD CV+ versus les deux autres groupes.

Conclusion — Les altérations artérielles des ESRD avec pathologies cardio-vasculaires associées sont structurales, mais également fonctionnelles. Par contre en absence de maladie vasculaire les ESRD ont un comportement non différent des contrôles pour des stimulations non maximales mais ont une réduction de la réserve de dilatation altérée lors de stimulations soutenues et maximales.

I024

COMPARISON OF THE EFFECTS OF SEMICARBAZIDE AND BETA-AMINOPROPIONITRILE ON ARTERIES IN THE BROWN NORWAY RAT

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Semicarbazide-sensitive amine oxidase (SSAO) is highly expressed by the smooth muscle cells of the aorta but its function within the arterial wall is unknown. This contrasts with another life-essential amine oxidase expressed in the aortic wall, lysyl oxidase (LO), responsible for post-translational cross-linking of tropoelastin and collagen molecules to produce insoluble, highly mechanically resistant fibres. It has been hypothesized that SSAO may participate in extracellular matrix cross-linking, but proof is lacking. To investigate whether SSAO may play such a role physiologically, we compared effects of semicarbazide (SCZ) and β-aminopropionitrile (BAPN), two amine oxidase inhibitors with different properties and relative specificities for SSAO and LO, on arteries in growing Brown Norway rats, which present a rare phenotype of spontaneous rupture of the internal elastic lamina (IEL) that is aggravated by LO inhibition. We measured aortic LO and SSAO activities during and at the end of 8-9 weeks of treatment, started at weaning, and quantified aortic insoluble elastin and total collagen contents, IEL ruptures in several arteries, ex vivo carotid artery wall rupture pressure and solubility of tail tendon collagen. After a pilot study using equivalent doses by weight, and combining the two compounds to test for additivity, we performed a study using low and high equimolar doses of SCZ and BAPN. Both compounds similarly inhibited LO, whereas SCZ was far more effective than BAPN in inhibiting SSAO. Both compounds decreased carotid rupture pressure, increased collagen solubility, decreased aortic insoluble elastin (% dry weight) and also increased IEL ruptures in abdominal aorta, iliac, renal and caudal arteries in a dose-dependent manner. The high dose of SCZ increased aortic collagen and extracellular proteins other than insoluble elastin markedly more than did equimolar BAPN, possibly revealing a specific effect of SSAO inhibition. We conclude that the majority of SCZ effects are mediated by LO inhibition, SCZ being more effective than BAPN in our in vivo experimental conditions, and to demonstrate unequivocally a specific effect of SSAO inhibition on extracellular matrix formation or organization, we must await availability of more specific inhibitors.

I025

SMOOTH MUSCLE SPECIFIC DELETION OF THE RHOA EXCHANGE FACTOR ARHGEF1 PROTECTS AGAINST ANG II-DEPENDENT HYPERTENSION

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Hypertension is one of the most frequent pathology in the industrialized world. Although it is recognized to be dependent on a combination of genetic and environmental factors, its molecular basis remains elusive. A possible candidate is the monomeric G protein RhoA which activates Rho kinase. However, how it is activated and whether it has a causative role in hypertension is still unknown. By in vitro experiments, we provide evidence that Arhgef1 is the RhoA guanine exchange factor specifically responsible for Angiotensin II (Ang II)-induced RhoA/Rho kinase activation in arterial smooth muscle cells. To analyze in vivo the role of Arhgef1, we generated mice lacking Arhgef1 specifically in smooth muscle cells (SM-Arhgef1-KO). We used Arhgef1lox/lox mice, which were mated to SMMHC-CreERT2 to produce SMMHC-CreERT2 ; Arhgef1lox/lox mice (SM-Arhgef1lox/lox). SM-Arhgef1-KO mice were then obtained by treating SM-Arhgef1lox/lox mice with tamoxifen. Remarkably, SM-Arhgef1-KO mice were resistant to hypertension induced by chronic Ang II infusion (sub-cutaneous osmotic pump, 1 µg/kg/min). Furthermore, Arhgef1 deletion after induction of hypertension by Ang II restored normal arterial pressure level.