(tubuloglomerular feedback), et l'angiotensine II (AII), (iii) elle est accueillie par l'activité sympathique rénale.

Results — Après 7 J de régime hypo, normo et hypersodé (48, 144 et 432 mmol/j) : PAM = 96, 100 et 110 mmHg; PRA = 18, 16 et 13 pM/min. Sous régime hyposodé, l'inhibition de EC (δPAM=8 mmHg) réduit AII (2 pM) et accroît PRA et rénine (x30). L'inhibition de la rénine (δPAM=5 mmHg) réduit Ang II (2 pM) et augmente la rénine du même facteur. Comparaison à un jet de données cliniques : Nussberger et al., 2001, volontaires sains, apport normosodé, inhibition de la rénine (90%, avec Aliskiren©). Les 3 premières heures sont reproduites : écart moyen 0,3 pM/min et 2,3 pM, pour PRA et rénine resp. (n = 3); entre 4 et 24 h, le modèle dévie (rms = 7 pM/min et 5 pM, n = 3), tout en restant semi-quantitatif. Nous avons simulé deux types d'hypertension : (i) masse rénale réduite (2/3) et apport sodé (500 mmol/j), (ii) hyperlodasténorome primaire (aldo x10). Dans les deux cas : PAM augmente de ~40 mmHg en ~8j; PRA diminue à ~6 pM/min; à l'aide d'un diurétique (natriurèse x3) réduit PAM de ~20 mmHg en ~4j (PRA partiellement normalisée, de 20 et 50%, resp.).

Conclusion — Notre modèle manifeste un comportement réaliste (temps et amplitudes) en réponse aux manœuvres de contrôle de la PA. L'ajustement quantitatif des paramètres du modèle, la mise–à–jour continue des modules, et son encadrement par des pathologies définites (hypertensions primaires,...) permettra de simuler des patients hypertendus et les variabilités associées (polymorphismes génétiques, réponse thérapeutique,...).

K004

ORALLY ACTIVE AMINOPEPTIDASE A INHIBITORS REDUCE BLOOD PRESSURE BY BLOCKING THE BRAIN RENIN-ANGIOTENSIN SYSTEM ACTIVITY: A NEW STRATEGY FOR THE TREATMENT OF HYPERTENSION

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Overactivity of the brain renin-angiotensin system (RAS) has been involved in the development of hypertension (HTA) in several animal models, such as DOCA-salt rats, a hypertension salt-dependent model. We previously reported that in the murine brain, Ang I is converted to Ang II by aminopeptidase A (APA). We also showed that Ang II is one of the main effector peptides of the central RAS in the control of blood pressure (BP). Therefore, the inhibition of brain APA, but not peripheral APA, with EC33, a specific and selective APA inhibitor normalizes BP. Thus APA represents a potential candidate target for the treatment of HTA. If APA inhibitors are to be used as central antihypertensive agents, they must be able, after oral administration, to block brain APA activity. This was achieved with RB150, an orally active prodrug obtained by dimerization of EC33 through a disulfide bond. Thus, RB150 po administered in conscious DOCA-salt rats, crossed intestinal, hepatic and blood-brain barriers and inhibited brain APA activity until a value similar to that measured in the brain of normotensive rats. This resulted in DOCA-salt rats but not in normotensive rats in a marked dose-dependent reduction in BP (ED50: 0,5 mg/kg) in less than two hours for up to several hours, without changing heart rate. In addition, this treatment decreases plasma vasopressin levels inducing increased diuresis, which by limiting the fluid compartment, contributes to decrease BP. Thus, RB150 could constitute the prototype of a new class of central antihypertensive agents.

K005

ESTRADIOL ACCELERATES REENDOTHELIALIZATION THROUGH A COOPERATIVE EFFECT BETWEEN BONE MARROW AND ENDOTHELIAL CELLS EXPRESSING ESTROGEN RECEPTOR ALPHA

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Objectives — Drug-eluting stents releasing antimitotic drugs are frequently used in patients undergoing percutaneous coronary interventions. Although these stents inhibit proliferation of vascular smooth muscle cells and thus reduce rates of early stenosis, they also impair proliferation of endothelial cells. The resulting delayed arterial healing increases the risk of thrombosis and leads to higher late stent restenosis. Optimization of endothelium repair is then necessary to prevent intimal thickening and in-stent restenosis.

Methods — Using a mouse model of carotid injury, we previously demonstrated that 17βestradiol (E2) accelerates endothelium regeneration through estrogen receptor ERα but not ERβ (1) and involvement of FGF-2 (2). However, the molecular and cellular mechanisms underlying this beneficial effect still remain poorly understood, mainly due to the lack of appropriate models and tools to visualize endothelium. Here, we employed en face confocal microscopy to follow endothelium repair in longitudinally opened and flattened mouse carotid arteries.

Results — We showed that E2 accelerates both migration and proliferation of endothelial cells and increased the recruitment of cells in an uninjured adjacent retrograde zone, leading to enlarged reendothelialized area (3).

Many studies suggest that circulating bone marrow (BM) derived cells are involved in arterial healing. Thus, we generated chimeric mice by grafting wild type mice with ERα−/− or ERα++/+ BM and vice versa. The beneficial effect of E2 was abolished when the ERα was absent either in donor or in receiver mice, demonstrating that both BM and non-BM ERα-expressing cells cooperate to mediate E2 regenerative effects. Using a cell-specific inactivation mouse model of ERα, by the loxP/Cre recombination system, we showed that endothelial ERα is absolutely required in the accelerative effect of E2 on reendothelialization. To precise which BM derived cells are involved in the E2 effect, the implication of ERα-expressing macrophages is now under investigation.

Conclusion — These results might help us to propose new strategy to optimize post-angioplasty and in-stent reendothelialization.