the implication of the Epac–induced small G proteins and theirs networks.

In cardiomyocyte primary culture, we show that Epac activates the small G protein Ras, Rac and Rap. The Epac-induced hypertrophic effect is mediated by Ras and Rac activation. This Epac-induced activation of Ras is not influenced by Rac or Rap and is due to a Ca2+ release in response to phospholipase C and IP3 receptor activation. Moreover, we show that Ras mediates the Epac-induced activation of the pro-hypertrophic CaMKII/MEF2 and calcineurin/ NFAT signalling pathways which are both necessary for hypertrophy. Epac has been initially identified as a GEF for the small G proteins Rap. Surprisingly, the Epac hypertrophic effect is independent of its classical effector Rap. The Epac-induced Rap1 signalling cascade involves PKCε translocation, which is a key actor of multiple cellular phosphorylations. This finding is in agreement with other Rap functions reported in the literature such as cell to cell communication and adhesion.


Vendredi 3 avril 2009, de 11 h00 à 12 h30
K – HORMONES, SYSTEME RENINE-ANGIOTENSINE

K001
IS PRIMARY ALDOSTERONISM A CHANNELOPATHY?
S. TAREEN 1, C. SIMIAN 2, S. BENDAHOU 3, J. BARHANIN 3, X. JELINEMATRE 1, M. C. ZENNARO 1
1 Inserm U772, Collège de France, Paris, France
2 Département de Génétique, Hôpital Européen Georges Pompidou, Paris, France
3 Institut de Pharmacologie Moléculaire et Cellulaire, Valbonne, France

In mouse models the genetic deletion of TWIK-related acid-sensitive K (TASK)-1 and TASK-3 channels removes an important background of mutated channel function by heterologous expression, however, revealed the missense mutations detected were non-functional. As somatic mutations may be involved in some cases of sporadic PAL, sequencing 90 patients for tumoral DNA sequence variants is underway. We are also investigating expression of TASK 1 and TASK 3 by in-situ hybridization and immunohistochemistry on adrenal tissue sections of 150 PAL patients who have undergone surgery.

K002
ENDOTHELIAL ESTROGEN RECEPTOR ALPHA MEDIATES THE Atherosprotective ACTION OF ESTRADIOL IN LDLR DEFICIENT MICE
A. BILLON-GALES 1, C. FONTAINE 1, V. DOUIN-ECHINARD 1, L. DELPY 2, H. BERGES 1, H. LAUREL 1, J.-C. GUYER 3, P. GOURDY 1, J.-F. ARNAL 1
1 Inserm U858; CHU et Université de Toulouse, Toulouse, France
2 CNRS UMR6101; Faculté de Médecine, Limoges, France
3 Inserm U563; Centre de Physiopathologie de Toulouse Purpan, Toulouse, France

Background — Although estrogen administration to hysterectomized menopausal women did not prevent the occurrence of myocardial infarction in a randomized controlled trial (WHI 2004), epidemiological studies suggest and experimental results clearly demonstrate a major atherosprotective action of estrogens. The goal of the present study was to identify the cellular target(s) accounting for the estradiol (E2) beneficial action on fatty streak development.

Methods and Results — We first confirmed the key role of estrogen receptor α (ERα) in atheroprotective effect of E2 as this action was completely abolished in mice deficient both in Low Density Lipoprotein receptor (LDLr) and in ERα. Comparison of LDLr— mice transplanted with either ERα+/+ or ERα—/— bone marrow showed that functional ERα in the hematopoietic lineage is not required for E2 atheroprotection. We then showed that ERα floxed mice (ERαfox/flox) bred with the Tie2-Cre mice on the LDLr— background had a complete inactivation of ERα both in bone marrow and in endothelial cells. Remarkably, in this mouse model, the E2 atheroprotective action was completely abolished.

Conclusions — Altogether, this is the first in vivo demonstration that endothelial ERα represents a key target of the atheroprotective effect of E2, whereas the hematopoietic ERα is dispensable for the protective action. Selective estrogen receptor modulators that mimic this endothelial action of E2 should now be considered in hormonal treatment as well as in atheroprotection.

K003
MODELISATION PHYSIOLOGIQUE INTEGRATIVE DE LA REGULATION DE LA PRESSION ARTERIELLE ET DU SYSTEME RENINE-ANGIOTENSINE CIRCULANT
F. GUILLAUD 1, P. HANNAERT 1
1 Inserm U927 — CHU La Milétrie, Poitiers, France


Modélisation — Le modèle est implémenté sous Simulink© (Mathworks). Hypothèses : (i) la rénine est produite par l’appareil juxtaglomérulaire (JGA) et l’artériole afférente; (ii) la production de rénine est inhibée par la pression de perfusion, le signal TGF