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GRAFICA TADDEO – Charrúa 3480 – Buenos Aires – Tel: 4918.6300 l 4918.1675 l 4918.0482
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on the ligand. The stimulation of both CRHR1 and CRHR2α led to an increase of intracellular cAMP measured with FRET biosensors. We compared similarities and differences of the activation of CREB, ERK1/2 and AKT by western blot. We have previously reported that CRH-dependent ERK1/2 activation downstream of CRHR1 is biphasic, being dependent on G protein and receptor endocytosis mechanisms. Remarkably, the same pattern was observed when UCN1 was used as a CRHR1 ligand. However, the kinetics of ERK1/2 activation downstream of CRHR2α were different, either when CRH or UCNs were used for stimulation.

Keywords: CRHRs, UCNs, signal transduction, cAMP.

(579) **CHRONIC ADMINISTRATION OF AN AT2R SYNTHETIC AGONIST INCREASES INSULIN SENSITIVITY IN MICE**

Diego T. Quiroga (1), Carolina Gil (1), Ibán A. Cerviño (1), Jorge E. Toblli (2), Marina C. Muñoz (1), Fernando P. Dominici 1)

(1) Department of Biological Chemistry, School of Pharmacy and Biochemistry University of Buenos Aires IQUIFIB-CONICET. (2) Laboratory of Experimental Medicine, Hospital Alemán, School of Medicine, University of Buenos Aires.

Abstract:The renin-angiotensin system modulates insulin action. Angiotensin type 1 receptor exerts a deleterious effect, while the angiotensin type 2 receptor (AT2R) appears to have beneficial effects providing protection against insulin resistance and type 2 diabetes. In this study, we explored the role of AT2R in the control of insulin action. To that end, C57Bl/6 mice were administered the non-peptidic AT2R agonist C21 for 12 weeks (1 mg/kg per day; i.p. injection; n=12); vehicle treated animals were used as control (n=12). One week before to the sacrifice, glucose and insulin tolerance tests were performed, which showed increased glucose tolerance and insulin sensitivity in C21 mice (n=8; p <0.05). At the end of the treatment, a supraphysiological dose of insulin via cava vein (10 IU/kg) was administered, to investigate the *in vivo* status of the insulin signaling pathway. Baseline levels were studied in animals that were injected saline solution.The effect of the C21 on visceral adipose tissue was characterized by analysis of adipocyte size on hematoxylin-eosin-stained sections. A statistically significant decrease in adipocyte area was detected in C21-treated mice (n=4; p <0,05). Surprisingly, liver from animals treated with C21 showed increased basal Akt phosphorylation in Threonine 308 and Serine 473 residues and only a slight increase in insulin-induced Akt phosphorylation was observed in C21-treated animals when compared with control mice (n=4; p <0,05). In conclusion, chronic administration of an AT2R agonist to C57BL/6 mice, increased insulin sensitivity and reduce basal glycemia. Such change was associated with decreased adipocyte size in visceral adipose tissue and increased basal activation of hepatic Akt. To understand the effects at the metabolic level of AT2 agonist treatment would be necessary to analyze the status of the insulin pathway in muscle and adipose tissue and the inflammatory state of adipose tissue.

Keywords: Insulin receptor, angiotensin type 2 receptor, type 2 diabetes.

(98) **COX-2 REGULATION BY 1α,25(OH)$_2$D$_3$-VDR LIGAND IN ENDOTHELIAL CELLS EXPRESSING vGPCR**

Cinthya Tapia (1), Alejandra Suares (1), Gabriela Alejandra Salvador (2), Veronica Gonzalez Pardo (1)

(1) INBIOSUR-DBByF-Universidad Nacional del Sur. (2) INIBIBB-Universidad Nacional del Sur.

The Kaposi's Sarcoma-associated Herpes virus G Protein-Coupled Receptor (vGPCR) is a key molecule in the pathogenesis of Kaposi Sarcoma. 1α,25(OH)$_2$D$_3$ anti-proliferative impact in vGPCR cells occur in part by NF-κB pathway negative modulation, family of conserved transcription factors critical during the inflammatory response. In this work, we studied if COX-2 modulation by 1α,25(OH)$_2$D$_3$ in vGPCR cells contributes to the anti-inflammatory action. As we have previously reported vGPCR cell proliferation is inhibited by 1α,25(OH)$_2$D$_3$ (10 nM, 48 h) due to a reduction on cell number. The blockage of arachidonic acid release by ATK (cPLA2 inhibitor) or the COX-2 inhibition (Celecoxib) decreased vGPCR cell number in a dose dependent manner (10-20 μM), similarly to 1α,25(OH)$_2$D$_3$. These changes were accompanied by morphological modifications observed at the microscope. qRT-PCR analysis of COX-2 gene expression revealed a mRNA increase within 20 min of 1α,25(OH)$_2$D$_3$ treatment and remains increased at least for 72 h. Moreover, ATK (20 μM) could not counteract COX-2 mRNA induced by 1α,25(OH)$_2$D$_3$ (10 nM, 24 h). Finally, COX-2 VDR dependence was evaluated using the stable VDR knock-down cell line vGPCR-shVDR where COX-2 mRNA rise by 1**α**,25(OH)$_2$D$_3$ was found impaired. Significant differences of the data between control (vehicle) and treated conditions were analyzed by one way-ANOVA followed by Bonferroni test ($p< 0.05$) or t-test (*$p< 0.05$, **$p<0.01$). All together, these results suggest that 1α,25(OH)$_2$D$_3$ enhances endothelial inflammation initiation through COX-2 upregulation and contributes to its timely resolution through the antineoplastic action. This shows a possible dual effect as both a promoter and attenuator of inflammation.

Keywords: COX-2, vGPCR cells, Vitamin D, antineoplastic effects

(450) **H1 AND H2 HISTAMINE RECEPTORS CROSS-DESENSITIZATION AFFECTS ANTIHISTAMINE RESPONSE**

Antonela Diaz Nebreda (1), Daniel Zappia (2), Angela Rodriguez (1), Federico Monczor (2), Natalia Fernandez (3), Carina Shayo (1)

(1) Laboratorio de Patología y Farmacología molecular; IBY-ME-CONICET. (2) Laboratorio de Farmacología de Receptores; ININFA-UBA-CONICET. (3) Laboratorio de Transducción de Señales y Diseño de Fármacos; ININFA-UBA-CONICET.

Histamine exerts its effects by binding to four G protein-coupled receptors (H1R-H4R) and modulates numerous physiopathological processes through H1R and H2R, including allergy and inflammation. These receptors are effectively targeted by drugs belonging to the top twenty-used-drug-classes. We have previously described the cross-desensitization (CDS) between both receptors induced by Cetirizine, an H1R antihistamine (AH), on H2R agonist response. The aim of this work is to study the CDS between H1R and H2R caused by others AH and their influence on the regulation of the inflammatory process. In promonocytic U937 cells (endogenously expressing H1R and H2R) and HEK293 (HEK) cells transfected with H1R and H2R, pretreatment with the AHs mepyramine, trans-triprolidine, chlorpheniramine and diphenhydramine significantly decreased the cAMP production following amthamine (AM, an H2R agonist) stimulation, whereas the cAMP response through another Gs-coupled receptor (PGE2) was unaffected. Likewise, the pretreatment with the same AHs in HEK cells transfected only with H2R, did not alter AM response, showing specificity of CDS. On the other hand, we evaluated the AM effect on the inflammatory response of AH. The regulation of COX-2 and IL-8 expression was evaluated by qPCR in *U937 cells treated with PMA*. The pretreatment with AM reverted the inhibitory effects of the AH on the expression of both genes. The same effect was observed for the IL6 promoter activity in HEK cells transfected with both receptors in a reporter gene assay. As expected, the pretreatment with AM did not modify the AH anti-inflammatory response in HEK cells transfected only with H1R. These results show that there is a specific cross-desensitization between H1R and H2R induced by different AHs used in the clinic. Given the wide use of these drugs and the interest in drug repositioning, it is crucial to understand the regulation between the intracellular signaling cascades triggered by them.

Keywords: Histamine Receptors; Antihistamine; Cross-Desensitization

(1800) **MODULATION OF THE SENESCENCE ASSOCIATED SECRETORY PHENOTYPE IN RETINAL PIGMENT EPITHELIUM CELLS**

Mariela Marazita, Bárbara Weil, Pablo Tate, Melisa Marquioni-Ramella, Angela Suburo

IIMT-AUSTRAL-CONICET

Cellular senescence triggers the expression of a wide variety of inflammatory factors named the senescence associated secretory