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people worldwide are VD deficient. VD receptor (VDR) knock-out mice develop 50% more LCH. The histamine receptor H4 (HRH4) is considered a promising target for cancer therapy. Previously, we reported that VUF8430 (HRH4 agonist) inhibits proliferation and steroidogenesis in MA-10 and R2C tumor LC. Likewise, calcitriol (VD's active form) inhibits R2C proliferation and steroidogenesis, while it promotes HRH4 expression. Accordingly, we detected VDR and HRH4 in LCT.Objectives:To analyze the concomitant expression of VDR and HRH4 in LCH and xenograft murine models.To evaluate a possible synergism between calcitriol and VUF8430 in vitro, in tumor LC.Methods:R2C were treated with: calcitriol(10-9M), VUF8430(10-5M), or calcitriol(10-9M)+VUF8430(10-5M). Cell proliferation was assessed using sulforhodamine B assay. Aromatase activity was measured using a tritiated water-release assay. Tumor xenograft models were developed in athymic mice (R2C) and C57 mice (MA-10). Plasma steroids were measured by chemiluminescence. Formalin-fixed, paraffin-embedded (human and murine) sample sections were evaluated for VDR and HRH4 expression using immunohistochemistry.Results:Calcitriol-, VUF8430- or calcitriol+VUF8430-treated R2C showed diminished proliferation ($p<0.05$). Aromatase activity was only lowered by calcitriol+VUF8430 treatment ($p<0.05$).Athymic mice inoculated with R2C had elevated sex steroids levels ($p<0.001$) and normal VD level. Both murine tumors expressed VDR and HRH4. AIS samples exhibited different staining intensity, but in all cases, when VDR expression was weaker, HRH4 also was.Conclusion: These results suggest that targeting HRH4, in combination with VD treatment, may represent a novel therapeutic approach against LCH and LCT.

145. (437) **PITIUTARY RELEASE OF LH IS MODULATED BY PRL IN A TIME EXPOSURE-DEPENDENT MANNER IN LAGOSTOMUS MAXIMUS**

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The progressive decline of circulating progesterone (P4) during the first half of gestation elicits surges og GnRH and LH, followed by an ovulatory event that leads to the development of numerous accessory corpora lutea (CL). The naturally calcified and steroidogenically poor placenta strongly points to CL as the main source of P4 during pregnancy. For other rodents, an essential role of prolactin (PRL) in CL maintenance and P4 production has been clearly established. To investigate PRL relevance over the hypothalamus-hypophysis-ovarian axis performance, we analyzed PRL effect over LH release in vizcachas under two experimental conditions: 1) LH release of pituitary after one week in vivo treatment with Sulpiride 20mg/kg i.m. twice a day (PRL Chronic treatment, CRtx); 2) 6 h-culture of pituitary explants with serum of animals before/after CRtrxt animals (PRL Acute treatment, ACtx). Success of Sulpiride treatment in inducing a hyperprolactinemic condition was corroborated by the increase of both PRL transcription and immunoexpression compared to that of control pituitaries ($p<0.05$, n=5). LH released significant decreased in CRtx vs control pituitaries, while ACtx explants released significantly more LH than that of controls ($p<0.05$, n=5). CRtx and control ovaries showed similar number of primordial, primaries and CLs, but slightly higher of secondaries and pre-antral follicles. Circulating estradiol (E2) was higher in CRtx animals ($p<0.05$, n=5), yet no differences were detected in the P4. Immunoexpressions of both PRL-receptor and LH-receptor showed similar levels in CRtx and controls ovaries. We conclude that LH release is indeed modulated by PRL in a time exposure manner: initially PRL induces LH release however a sustained exposition of the pituitary to PRL diminishes LH release. Our results suggest that at ovarian level, PRL has a more predominant role over the follicular maturation rather than at luteal activity. Grants: PIP 110/14, PICT 1281/2014, Fundación Científica Felipe Fiorellino.

146. (321) **ACTIVATION OF MEMBRANE PROGESTERONE RECEPTORS (MPRS) REPRESENTS A NOVEL TOOL FOR PROLACTIN INHIBITION IN ANIMAL MODELS OF PROLACTINOMAS**

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Membrane progesterone receptors (mPRs) are known to mediate rapid non-genomic progesterone (P4) effects in different cell types. We recently demonstrated that mPRα is highly expressed in the rat pituitary, being primarily localized in lactotrophs and mPRα/β activation leads to a decrease in prolactin (PRL) secretion. The role of P4 in prolactinoma development remains unclear. In the present work, pituitary expression of mPRs was studied in a well-known model of prolactinoma, transgenic D2 dopamine receptor-deficient mice (Drd2 KO). Expression of mPRs and the classical P4 receptor (nPR) was found significantly decreased in female Drd2 KO pituitaries compared to their WT counterparts. However, the relative proportion of mPRα and mPRβ was increased (about 60% of total pituitary PRs) in tumoral pituitaries. This elevated proportion of mPR to total PR was also observed in other two animal models of prolactinoma. We also found gender differences: male pituitaries express higher levels of mPRs than females, without genotype differences. Males do not develop prolactinoma, even in the absence of dopaminergic inhibition. Finally, as P4 also regulates PRL secretion indirectly by acting on dopaminergic neurons, we studied mPR expression in hypothalamus. We found that the hypothalamus has high expression of mPRs, representing about 80% of total PRs, without genotype or gender differences. Interestingly, the mPR agonist increased dopamine release in hypothalamic explants. Taken together these findings suggest mPRα/β activation could represent a potential tool for hyperprolactinemic patients, especially those that present resistance to dopaminergic drugs.

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147. (450) **ANGIOTENSIN II: KEY ROL IN MAMMARY GLAND INVOLUTION AND MAMMARY TUMOURS.**

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Angiotensin (Ang) II, the main effector peptide of the renin-angiotensin system, has been implicated in multiple aspects of cancer progression such as proliferation, migration, invasion, angiogenesis and metastasis. Our previous studies have shown that AngII through AT1 receptor induces STAT3 activation, epithelial apoptosis and MMP-9 activation during mammary gland involution. The lack of AT1 receptor caused a delay in mammary involution. In this study, we show that AngII through AT1 receptor has a key role as tumour promoter on breast cancer cell lines. We found that AngII induced cell invasion (2 fold change $p<0.01$), MMP-9 activity and VEGF expression (2,5 fold change $p<0.001$) on MDA-MB231 breast cancer cells. In addition, migration induced by AngII was inhibited with the treatment of cells with an anti-angiogenic VEGF antibody (bevacizumab) (2 fold change $p<0.05$). On the other hand, AngII induced activation of Rac1 (a small Rho-GTPase involved in migration, proliferation, tumorigenesis and metastasis) on T47D breast cancer cells. We have performed an analysis on public databases TCGA (The Cancer Genome Atlas) that contains information of numerous samples of patients with different human mammary tumor subtypes. We found that AT1 receptor expression is increased in women with estrogen receptor positive (ER+) breast cancer tumors. Together, these results suggest that AngII could be involved in breast tumorigenesis with a preferential rol on ER+ tumors.

148. (456) **INVOLVEMENT OF PHOSPHO-SRC AND TGF-B TYPE I RECEPTOR IN THE ENHANCEMENT OF MESENCHYMAL FEATURES INDUCED IN BREAST CANCER CELLS BY CONDITIONED MEDIA FROM NORMAL MAM-**