electrolyte exchange and fluid balance are required. GR and MR act as ligand-activated transcription factors which, following interaction with co-regulators and DNA responsive elements, either promote or repress gene transcription. The affinity for the same ligands, structural homology, and binding to the same DNA regions suggest GR and MR can compensate for each other's actions. Yet, there are specific glucocorticoid and mineralocorticoid-mediated responses indicating GR-MR functional diversity. To investigate this interplay, we developed U-2 OS (human osteosarcoma) cell lines stably expressing GR, MR, and both GR and MR (GRMR). Immunofluorescence analysis showed that treatment of these cell lines with 1 nM of the synthetic glucocorticoid dexamethasone (Dex) induced nuclear traslocation of GR and MR. Conversely, treatment with 1 nM of aldosterone (Aldo) promoted nuclear translocation of the MR only. Moreover, Proximity Ligation Assay revealed that, in the absence of ligand, GR associated with MR in the cytoplasm and, upon 1 nM Dex exposure, GR-MR dimers were detected in the nucleus of GRMR cells. Surprisingly, nuclear GR-MR dimers were also detected in the presence of Aldo, suggesting that it is necessary to activate at least one receptor to induce nuclear traslocation of the heterocomplex. To decipher the functional contribution of GR-MR dimers in the transcriptional response of GR to Dex and MR to Aldo, we performed RNA-seq in GR, MR, and GRMR cells treated with 1 nM of Dex or Aldo. Transcriptome analysis revealed that Dex-activated GR regulated the transcription of 6180 genes. Co-expression of MR resulted in a blunted Dex-mediated gene response which affected only 1608 genes, suggesting a functional antagonism of MR. Aldo-activated MR regulated the transcription of 1660 genes. However, co-expression of GR expanded the Aldo-mediated gene response to 3150 genes. Strikingly, 74% of these genes were also regulated by Dex via GR, suggesting that GR-MR dimers in the presence of aldosterone are able to mimic the glucocorticod transcriptional response. Our data suggest that the role of distinct GR and MR homo- and hetero-dimers is relevant for regulating gene expression. Dissecting the mechanism and investigating the cross-talk between GR and MR may be useful to understanding these two receptors in heath and disease.

Neuroendocrinology and Pituitary

PITUITARY TUMORS I

Beta-Arrestin 2 Is Required for Dopamine Receptor Type 2 Inhibitory Effects on Akt Phosphorylation and Cell Proliferation in Pituitary Tumors

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β-Arrestin 2 is Required for Dopamine Receptor Type 2 Inhibitory Effects on AKT Phosphorylation and Cell Proliferation in Pituitary Tumors

Dopamine receptor type 2 (DRD2) agonists are the first-choice treatment for PRL-secreting pituitary tumors but are poorly effective in non-functioning pituitary neuroendocrine tumors (NF-PitNETs). DRD2 reduces AKT phosphorylation in lactotrophs, but no data are available in NF-PitNETs. DRD2 effects on AKT are mediated by a β-arrestin 2-dependent mechanism in mouse striatum.
The aim of this study was to investigate DRD2 effects on AKT phosphorylation and cell proliferation in human primary cultured NF-PitNET cells and in rat tumoral lactotroph cells MMQ, and to test β-arrestin 2 involvement.
We found that DRD2 agonist BIM53097 induced a reduction of p- AKT /total-AKT ratio in MMQ (-32.8±17.6%, p<0.001 vs basal) and in a subset (n=15/41,36.6%) of NF-PitNETs (subgroup 1). In the remaining NF-PitNETs (subgroup 2), BIM53097 induced an increase of p- AKT. The ability of BIM53097 to reduce p-AKT correlated to its antimitotic effect, since the majority of subgroup 1 NF-PitNETs was responsive to BIM53097 and nearly all subgroup 2 NF-PitNETs were resistant. β-arrestin2 was expressed in MMQ and in 80% of subgroup 1 NF-PitNETs, whereas it was undetectable in 77% of subgroup 2 NF-PitNETs.
In MMQ, β-arrestin 2 silencing prevented DRD2 inhibitory effects on p-AKT and cell proliferation. Accordingly, β-arrestin 2 transfection in subgroup 2 NF-PitNETs conferred to BIM53097 the ability to inhibit both p-AKT and cell growth.
In conclusion, we demonstrated that β-arrestin 2 is required for DRD2 inhibitory effects on AKT phosphorylation and cell proliferation in MMQ and NF-PitNETs, paving the way for a potential role of β-arrestin 2 as a biomarker predicting NF-PitNETs responsiveness to treatment with dopamine agonists.

Pediatric Endocrinology

UNDERSTANDING AND TREATING PEDIATRIC GROWTH DISORDERS

Interpretation of Insulin-like Growth Factor-1 (IGF-1) Levels Following Administration of Somatrogon (a Long-acting Human Growth Hormone - hGH-CTP)

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IGF-1 is often used as a biomarker to evaluate the efficacy and safety of hGH replacement therapy. Typically, the mean IGF-1 SDS level during the dosing interval, rather than the peak value, guides clinical decision-making: sustained mean values > +2 may require hGH dose modifications. With long-acting formulations (administered weekly), the IGF-1 evaluation paradigm needs to take into account when the sample was obtained relative to the last administered dose. Previous studies with OPKO's once weekly Somatrogon (hGH-CTP), demonstrated that IGF-1 SDS peaked ~ 48 hours post-dose and that values at ~ 96 hours best approximated the mean IGF-1 SDS throughout the dosing interval [1]. Data from the pivotal Phase 3 non-inferiority study comparing treatment with Somatrogon to