adipose-specific LXRβ-/- mice (AdβKO). Dex-dependent increases in lipolysis in gonadal WAT and plasma free fatty acids (FFA) were also attenuated by GSK co-treatment. With GSK co-treatment, Dex-induced liver steatosis was diminished suggesting that LXRβ antagonism attenuated FFA shuttling to the liver. The lipolytic and lipotoxic effects of Dex in AT and liver were largely abrogated in AdβKO along with improved systemic insulin sensitivity. Overall, our data suggest that LXRβ antagonism prevents disruption of BAT and WAT (and indirectly liver) function caused by GC treatment in an *in vivo* model, highlighting the potential role of LXRβ antagonists in combating the negative effects of excessive GC exposure on the development of diabetes and obesity. The identification of this novel mechanism of interrupting GC adipose tissue action suggests therapeutic targeting of LXRβ with an antagonist could improve the health of patients currently taking GCs to control inflammation but suffer the detrimental side effects of drug treatment.

Steroid Hormones and Receptors

STEROID RECEPTORS IN DEVELOPMENT AND DISEASE

LBD Dimerization of the Androgen Receptor but Not N/C Interaction Is Crucial for Normal Male Development in Mice

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The androgen receptor (AR) is a nuclear receptor with a main role in the development and maintenance of the male phenotype. To execute its role as transcription factor, the AR forms homodimers. Three dimerization modes have been described for the AR: one via the DNA binding domain, a second via the ligand binding domain (LBD) and a third via interactions between the LBD and the aminoterminus of the AR (N/C). Based exclusively on *in vitro* data, all three dimerization modes seem to contribute to full AR activity, albeit to a different extent. The *in vivo* role of the dimerization modes, however, remains unknown. To study the physiological relevance, we generated two mouse models using a CRISPR/Cas9 approach, in which either the N/C interaction (AR^{NoC}) or LBD dimerization (AR^{Lmon}) was disrupted. Surprisingly, the male AR^{NoC} mice have a normal phenotype, indicating that the N/C interaction is not crucial for male development. In contrast, AR^{Lmon} males have an external female phenotype with cryptorchid testes and high levels of circulating testosterone (T), androstenedione and luteinizing hormone (LH) (6-, 13- and 45-fold higher, respectively). They have no prostate, seminal vesicles or epididymis, illustrating the importance of LBD dimerization during male development. Phenotyping the AR^{Lmon} model furthermore provided evidence of a crucial role for the AR in bone homeostasis as well as steroidogenesis. The AR^{Lmon} males display a severe bone phenotype, similar to that of complete AR knockout (ARKO) mice. The bone phenotype of ARKO was postulated to be mainly due to lower estrogen levels. However, in contrast to ARKO mice, AR^{Lmon} mice have high circulating levels of T, which can still function as prohormone for estradiol and support bone function via the ERα. Immunohistological analysis of AR^{Lmon} testes showed hyperplasia of the Leydig cells and residual spermatogenesis. Analysis of the steroidogenic pathway revealed that while the expression of most genes is increased, the expression of *Hsd17b3*, encoding the enzyme responsible for conversion of androstenedione into T, is low in AR^{Lmon} testis. Reporter assays confirmed that the promotor of this gene is indeed upregulated by the AR itself. In conclusion, our work uncovers the physiological role of the N/C interaction and LBD dimerization of the AR. It furthermore demonstrates a direct role for AR in male bone development independent of T aromatization into estrogens. Finally, we show that the AR controls the final step in the synthesis of its own ligand. In contrast to the *in vitro* data, N/C interaction is not crucial for male development *in vivo*. The AR^{Lmon} model illustrates that LBD dimerization could be an excellent new therapeutic target for inhibiting AR activity for example in advanced prostate cancer that has developed resistance to the current AR-targeting therapies.

Steroid Hormones and Receptors

STEROID RECEPTORS IN DEVELOPMENT AND DISEASE

Mapping of Corticosteroids in Murine Kidneys Using Mass Spectrometry Imaging

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Renal sodium reabsorption is important for blood pressure homeostasis and is physiologically regulated by aldosterone; glucocorticoids may also contribute. Abnormal steroid hormone activity within the kidney contributes to hypertension but the mechanisms are not fully defined. Molecular profiling of receptors and metabolising enzymes indicates that steroid hormone action is compartmentalised within the kidney. Ambient steroid concentrations are a critical factor governing bioactivity at a cellular level, but this is largely unknown, and the kidney remains a "black box". Mass spectrometry imaging (MSI) was applied recently to localise steroids in brain and testes, and here is applied to kidney. Image reconstruction permits characterisation and co-registration of kidney histological regions based on regional markers detectable by MSI. Our aim was to map and quantify glucocorticoids and aldosterone in different histological zones (cortex, medulla) of murine kidneys, using an optimised MSI method. This approach has the potential to map steroids within functional zones of the kidney, providing fundamental new information relevant to hormone action in health and in disease. Cryosections of male C57BL6 mouse kidneys (age 12 weeks, n=6) were subject to MSI following derivatisation using Girard T reagent and α-cyano-4-hydroxycinnamic acid matrix application. Images were reconstructed, and methods optimised to enhance signal and limit diffusion of analytes of interest. Matrix assisted laser desorption/ionisation (MALDI) was used as a sampling method, coupled to Fourier Transform Ion cyclotron mass spectrometry. Ions with m/z 458.3010,