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SUN-012

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, and is characterized by hyperandrogenism, oligo/anovulation, and/or polycystic ovaries. Many women with PCOS also suffer from adverse metabolic phenotypes, including central adiposity, insulin resistance, and glucose intolerance, which can exacerbate reproductive dysfunction. Androgens can act upon androgen receptors (AR), which are expressed in many reproductive and metabolic tissues, and contribute to the pathogenesis of PCOS. AR are highly expressed in the neuroendocrine hypothalamus in areas which regulate the hypothalamic-pituitary-gonadal axis and contribute to the central regulation of metabolism. Many phenotypes of PCOS can be modelled in rodents by administration of the non-aromatizable androgen dihydrotestosterone (DHT) during critical periods of development. Neuronal AR is key in the development of PCOS, as female mice with neuronal AR deletion who are exposed to androgen excess are protected against development of anovulation, polycystic ovaries, and metabolic abnormalities. Yet it is not known which populations of neurons confers this protection. We hypothesize that leptin-receptor (LepR) neurons participate in the pathogenesis of PCOS, as sub-populations of LepR neurons co-express AR in the hypothalamus, and LepR neurons are critical in the central regulation of energy homeostasis, and exert permissive actions on puberty and fertility. We have pre-natally androgenized (PNA) a mouse model of AR deletion specifically in LepR cells ($LepR^{\Delta AR}$) and are conducting reproductive and metabolic phenotyping. As previously demonstrated, control PNA females show long periods of acyclicity, whereas $LepR^{\Delta AR}$ PNA female mice show a similar number of days in each stage of the estrous cycle, number of cycles, and cycle length as vehicle treated $LepR^{\Delta AR}$ females. Our findings indicate that a subpopulation of AR/LepR cells mediate the effects of prenatal androgen excess on female estrous cycles in a mouse model of PCOS-like phenotype.

Pediatric Endocrinology

PEDIATRIC OBESITY, THYROID, AND CANCER

Mathematical Modeling of Residual Endogenous FT4 Synthesis and Exogenous L-Thyroxine Administration over the First 2 Years of Life in Infants with Congenital Hypothyroidism

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MON-081

L-Thyroxine (L-T4) is the treatment of choice of congenital hypothyroidism (CH). Longitudinal measurements of free T4 (FT4) serum concentrations were collected over the first two years of life with oral L-T4 treatment in infants with CH. Purpose of this study was to develop an integrated mathematical model to characterize the kinetics of exogenous L-Thyroxine (L-T4) after multiple dosing in infants with CH, and the dynamics of residual endogenous FT4 synthesis under treatment in the context of severe, moderate and mild disease.

A total of 200 FT4 concentrations from 30 patients were available for analysis. At start of treatment, mean (standard deviation [SD]) postnatal age and weight of the population were 11 (8) days and 3.9 (1.3) kg. Mean (SD) pretreatment FT4 concentration was 11.3 (7.4) pmol/L. Measured FT4 concentrations were modelled as sum of residual endogenous FT4 and exogenously administered FT4 (L-T4). The integrated mathematical model consists of an absorption compartment for the exogenous FT4 administration, and a central compartment for measured FT4 with linear elimination. Hence, for residual endogenous and exogenous FT4 the same elimination rate constant was assumed. For the residual endogenous synthesis, different approaches were tested: a constant production and typical time-dependent production functions. FT4 data were analyzed using non-linear mixed-effects modeling.

The integrated mathematical model with a time-dependent non-linear Emax function describing a decreasing residual endogenous FT4 synthesis for increasing time provided the best data fit in terms of Akaike value and various goodness-of-fit plots. This is in line with the expected progressive suppression of the thyroid stimulating hormone by the exogenous FT4, and the subsequent decrease of residual FT4 endogenous synthesis. The developed mathematical model allows simulation of FT4 pharmacokinetic profiles for different disease severities and different dosing regimens.

Cardiovascular Endocrinology

FROM BEDSIDE TO BENCH AND BACK AGAIN: LIPID METABOLISM & VASCULAR DISEASE

Hypospadias Is a Predictor of Adverse Cardiometabolic Risk in Adulthood - a Case-Control Study

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OR17-05

Introduction: Abnormal development of the genital tract during the first trimester can lead to hypospadias. This stage coincides with the programming window during which androgens are required for normal masculinisation of the genital tract. Since fetal development may also be associated with long-term effects on cardiometabolic outcome and testosterone is itself an important vascular hormone, we questioned whether adults with a history of hypospadias are at increased risk of long-term cardiovascular and metabolic disease. Aim: This retrospective study determined if hypospadias is associated with increased risk of cardiometabolic disease later in life. Methods: Cardiovascular and diabetes admissions data were extracted through record linkage for all males with a history of hypospadias (ICD10 Q54)

from 1981 to 2019 through the NHS Scotland Information Services Division after ethics approval. Controls were matched for age, birthweight, gestation and deprivation index. Incident admissions for angina, arrhythmia, diabetes, heart failure, ischaemic heart disease, myocardial infarction, peripheral arterial disease, renal failure and stroke were obtained for each individual. Case control analysis was performed using Chi square test using R. Results: Admission data on 13,481 men with hypospadias and 9,615 matched controls were reviewed. Men with hypospadias had a 10- fold higher risk of diabetes (9.7 [8.4-11.2], p<0.0001); 9- fold higher risk of ischaemic heart disease (OR [95% CI] 9.1[8.1-10.2], p<0.0001); 8- fold higher risk of renal failure (7.9 [6.9-9.1], p<0.0001); 6- fold higher risk of stroke (6.2 [5.2-7.2], p<0.0001); 6- fold higher risk of myocardial infarction (6.4 [5.6-7.3], p<0.0001); 6-fold higher risk of angina (5.9 [5.3;6.8], p<0.0001); 5-fold higher risk of arrhythmia (4.8 [4.2-5.4], p<0.0001) 5- fold higher risk of peripheral arterial disease (4.8 [3.7-6.1], p<0.0001) and 4- fold higher risk of heart failure (3.6 [3.1-4.1], p<0.0001). Conclusions: Men with a history of hypospadias are at significantly increased risk of admission for treatment for cardiovascular and metabolic conditions, especially ischaemic heart disease, diabetes and renal failure. The mechanisms underlying this observed increase are unclear and merit further evaluation.

Thyroid

THYROID HORMONE ACTION AND SIGNALING

Long-Term Efficacy of T3 Analogue Triac in MCT8 Deficiency

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OR01-05

Background: MCT8 deficiency is a severe disorder caused by mutations in the thyroid hormone transporter MCT8. MCT8 deficiency is characterized by severe intellectual and motor disability and high serum T3 concentrations that result in thyrotoxic symptoms in peripheral tissues. This predisposes to substantial morbidity and mortality. Preclinical studies showed that the T3 analogue Triac can bypass defective MCT8 at the cellular level. Recently, we reported the results of an international multicenter trial, in which biochemical and clinical outcomes improved in patients with MCT8 deficiency who were treated with Triac for 12 months (1). However, long-term follow-up data of patients with MCT8 deficiency treated with Triac are lacking, particularly in young children. Therefore, we aimed to investigate the long-term efficacy of Triac therapy in a worldwide cohort of patients with MCT8 deficiency.
Methods: We investigated the efficacy of oral Triac treatment in pediatric (n=78) and adult (n=5) patients with MCT8 deficiency in 20 countries. Triac dose was titrated according a predefined dose-escalation scheme aiming to normalize serum T3 concentrations (target 1.4-2.5 nmol/L). Thyroid function tests and biochemical markers of thyroid hormone action in peripheral tissues (SHBG, creatine kinase, creatinine) were measured at baseline and during control visits.
Findings: In total, 83 patients with a median baseline age of 5 years (range 6 months – 66 years) were treated, including 24 patients aged 0-2.5 years and 17 patients aged 2.5-5 years. They were treated with Triac during 144 patient years, of whom the follow-up time was >5 years in 9 patients and 2-5 years in 22 patients. Mean dose was 45 µg/kg/day (range 11-107 µg/kg/day). Once a stable dose was achieved, no further dose adjustments were needed.
Mean serum T3 concentrations decreased from 5.02 to 1.94 nmol/L (normal 1.4 – 2.5 nmol/L). SHBG concentrations improved from 238 to 204 nmol/L (normal 40-140 nmol/L). Mean creatine kinase and creatinine concentrations improved from 113 to 140 U/L (normal <230 U/L) and from 32 to 38 µmol/L (normal 31-68 µmol/L), respectively. No drug-related severe adverse events were reported.
Interpretation: Triac is a safe treatment that results in sustainable improvements of the severe thyrotoxic state in pediatric and adult patients with MCT8 deficiency.
References: 1. Groeneweg S, Peeters RP, Moran C, Stoupa A, Auriol F, Tonduti D, et al. Effectiveness and safety of the tri-iodothyronine analogue Triac in children and adults with MCT8 deficiency: an international, single-arm, open-label, phase 2 trial. Lancet Diabetes Endocrinol. 2019;7(9):695-706.

Steroid Hormones and Receptors

STEROID AND NUCLEAR RECEPTORS

Steroid Hormone Metabolism Mediated Racial Disparity in Men with Benign Prostatic Hyperplasia

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SUN-747

Introduction and Objective: Racial disparity in prostate cancer has been well established, with African American (AA) men having higher rates of diagnoses and death from the disease compared to Caucasian American (CA) men. AA men also have a high incidence of benign prostatic hyperplasia (BPH), a disease associated with lower urinary tract symptoms (LUTS) that affect >210 million men worldwide. Furthermore, AA men with BPH have an increased incidence of non-surgical treatment failure, larger prostates at time of surgery, and surgery occurring at a younger age. The use of selective estrogen receptor modulators (SERMs) in the treatment of BPH has been proposed, as an increase in ERα has been associated with disease progression. AA men have higher levels of circulating estrogens as compared to CA leading to an increased prenatal exposure to estrogens. Estrogen exposure has been shown to alter the epigenetic landscape of genes, and this prenatal exposure to estrogens could sensitize the AA men to altered steroid homeostasis leading to an increase susceptibility to BPH and an altered response to treatment. In this study, we examine the prostate expression and localization changes in estrogen receptors (ERα, ERβ) as well as steroid metabolism genes