Ziekenhuis Lueven, Leuven, Belgium.

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

Stéphanie LEROUX, MD, PhD[1], Pfister Marc, MD[1], Tatjana Welzel, MD[1], Pascal Gächter, MS[1], Daniel Konrad, MD, PhD[2], Dagmar L'Allemand, MD[3], Gabor Szinnai, MD, PhD[1], Gilbert Koch, PhD[1].

[1]University Children's Hospital Basel, Basel, Switzerland, [2]University Children's Hospital of Zuerich, Zuerich, Switzerland, [3]Children's Hospital of Eastern Switzerland, St.Gallen, Switzerland.

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

Angela K. Lucas-Herald, MRCPCH[1], Sandosh Padmanabhan, FRCP[1], Katriona Brooksbank, PhD[1], Linsay McCallum, MRCP[1], Augusto C. Montezano, PhD[1], Rhian M. Touyz, FRCP[1], S Faisal Ahmed, FRCPCH[2].

[1]University of Glasgow, Glasgow, United Kingdom, [2]University of Glasgow, Glasgow, Scotland, United Kingdom.

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)