

IN THE NEWS

Highlights from SfE BES 2021

In November 2021, the Society for Endocrinology's annual meeting (SfE BES 2021) was held in Edinburgh, UK. This was a very special meeting for two reasons: it celebrated 75 years of the Society of Endocrinology and it was the first large in-person meeting since the beginning of the COVID-19 pandemic for many attendees. Over 900 delegates (wearing masks unless presenting) gathered at the venue to view a mixture of live and recorded presentations, and to experience in-person networking opportunities.

The meeting opened with Inês Cebola (Imperial College London, UK) outlining some exciting new developments in basic endocrinology research, such as adipose tissue being mapped with spatial transcriptomics and single-cell chromatin accessibility being assessed in pancreatic islets. Maralyn Druce (Barts Health NHS Trust, UK) also highlighted clinical developments; for example, new therapies for hot flushes in menopause and the wider use of GLP1 receptor agonists for adults without type 2 diabetes mellitus, but with overweight or obesity.

After this, Jeffery Friedman (Rockefeller University, USA) gave the SfE BES 75th Anniversary Lecture, discussing the discovery of leptin and its roles in appetite and obesity. Friedman outlined the neurocircuits that are regulated by leptin and how leptin resistance might be targeted in obesity. Following this theme, Sadaf Farooqi (MRC Institute of Metabolic Science, UK) discussed the biology of weight regulation in her excellent Society for Endocrinology Dale Medal Lecture. Farooqi discussed the heritability of obesity and the relevance of melanocortin 4 receptor signalling, before considering how hypothalamic circuits might integrate appetite with other behaviours.

On the second day, Wiebke Arlt (University of Birmingham, UK) delivered an illuminating talk on advances in diagnostics for adrenocortical carcinoma (ACC), using multi-omics technologies. Arlt discussed the validation of a new triple test for ACC, which incorporates tumour size, imaging characteristics and the steroid metabolome profile. Also on the adrenal theme, Alessandro Prete (University of Birmingham, UK) gave the clinical Early Career Prize Lecture, on benign adrenocortical tumours, which are an understudied contributor to cardiometabolic health.

Two plenary talks on the final day covered potential therapies for patients with iatrogenic Cushing syndrome, caused by exogenous glucocorticoid treatment. First, Márta Korbonits (St Bartholomew's Hospital, UK) considered the use of metformin to reduce symptom severity in patients without diabetes mellitus on glucocorticoids. Jeremy Tomlinson (University of Oxford, UK) then discussed targeting glucocorticoid metabolism upstream of the glucocorticoid receptor. The approach has shown promise in preclinical and early human investigations.

I very much enjoyed SfE BES 2021 and I look forward to the conference in 2022.

Shimona Starling

GROWTH AND DEVELOPMENT

MC3R controls growth and puberty onset

Nutritional availability is known to have a large effect on growth and the onset of puberty; however, the mechanism linking these factors was unclear. Now, a new study in *Nature* identifies the melanocortin receptor

MC3R as a key mediator of pubertal timing, childhood growth and body composition.

"MC3R is expressed mainly in the brain, so it seemed likely it was having an important role in the brain's signalling of nutrition. But exactly what this role entailed wasn't clear," says corresponding author Stephen O'Rahilly. The authors used genotyping data from approximately 500,000 individuals and whole-exome sequencing data from approximately 200,000 individuals to identify an association between deleterious *MC3R* genetic variants and delays in puberty, shorter stature, reduced circulating levels of insulin-like growth factor 1 and decreased total body lean mass.

The researchers used human embryonic kidney cells to test the ability of three of these deleterious variants to produce cAMP in vitro. They found that the *MC3R* variants with the most pronounced deficiency in cAMP signalling also resulted in a greater delay in puberty and shorter stature in both women and men. The striking discovery of an individual with complete loss of function of *MC3R* who was of extremely short stature and who did not start puberty until his early 20s confirmed this 'dose-response' relationship between *MC3R* functionality and the control of growth and puberty onset.

The researchers then investigated whether this association between *MC3R* activity and pubertal timing was conserved in mice. They found that mice lacking *Mc3r* had a notable delay in the onset of



Credit: Leontura

sexual maturity and that female mice had a statistically significantly longer oestrous cycle than wild-type mice. After an overnight fast, wild-type mice had a statistically significantly extended oestrous cycle, whereas fasting had no effect on cycle length in *Mc3r*-deficient mice. This finding confirmed that MC3R is involved in mediating the influence of nutritional state on sex hormone activity.

The researchers found that *MC3R* expression was enriched in two neuronal populations within the hypothalamus of both mice and humans. "MC3R is highly expressed in neurons expressing GHRH (the main central orchestrator of growth) and in neurons expressing kisspeptin (a major control of the reproductive hormone axis)," says O'Rahilly.

The authors plan to further investigate the neuronal populations through which *MC3R* regulates growth, reproduction and levels of lean mass. Additionally, they believe this discovery will have important clinical implications. "We need to know if activating the *MC3R* in adult humans can drive calories into lean mass more than fat mass. If so, this could be of great relevance to helping people with muscle wasting and frailty associated with a wide range of chronic diseases," O'Rahilly concludes.

Olivia Tysoe

ORIGINAL ARTICLE Lam, B. Y. H. et al. *MC3R* links nutritional state to childhood growth and the timing of puberty. *Nature* **599**, 436–441 (2021)