

# Neuroendo Celebrate!

*Celebrating our anniversary,  
nurturing our future*

Early career researcher symposium

## Abstract booklet

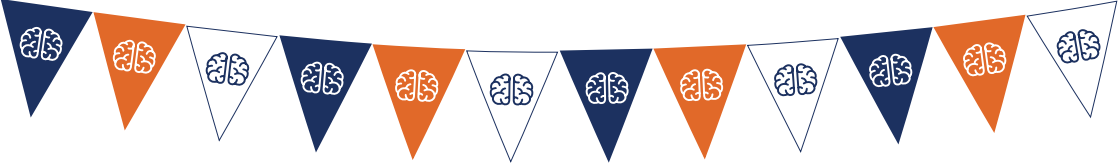
9 December 2019 | The Lighthouse, Glasgow | #JNE30

Hosted by the British Society for Neuroendocrinology  
in honour of Journal of Neuroendocrinology's 30th anniversary

CELEBRATING  
**30** years  
JOURNAL OF  
NEUROENDOCRINOLOGY

**BSN**  
British  
Society for  
Neuroendocrinology

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# Neuroendo Celebrate! Early Career Researcher Symposium Programme

9 December 2019 | Orangebox Gallery, The Lighthouse, Glasgow

10:30 Registration, tea and coffee

## 11:00 Session: Energy homeostasis (p4)

**Co-chairs:** Jo Lewis, BSN ECR Representative 2018-2019, Helen Christian, BSN Journals Secretary

- **Plenary:** Kate Ellacott, University of Exeter
- **ECR Talk:** Pablo Martinez de Morentin, University of Aberdeen
- **ECR Talk:** Alice Adrianensens, University of Cambridge
- **ECR Talk:** Aldara Martin Alonso, Imperial College London

## 12:30 Poster session (p16) and lunch

## 14:00 Session: Biological Timing (p8)

**Co-chairs:** Rebecca Dumbell, BSN ECR Deputy Representative 2019-, Stafford Lightman, JNE's first Editor-In-Chief 1989-1996

- **Plenary:** Fran Ebling, University of Nottingham
- **ECR Talk:** Ashleigh Wilcox, University of Bristol
- **ECR Talk:** Vincent van der Vinne, University of Oxford
- **ECR Talk:** Deyana Ivanova, Kings College London

15:30 Break, tea and coffee

## 16:00 Session: Neuroendocrinology in Health and Disease (p12)

**Co-chairs:** Ashleigh Wilcox, BSN ECR Deputy Representative 2019-, Julia Buckingham, JNE Editor-In-Chief 2004-2008

- **Plenary:** Dave Grattan, University of Otago, New Zealand
- **ECR Talk:** Chioma Izzi-Engbeaya, Imperial College London
- **ECR Talk:** Ben Jones, Imperial College London
- **ECR Talk:** Leonie Ruddick-Collins, University of Aberdeen

17:30 Closing remarks

## 19:00 30th anniversary dinner

Hutchesons City Grill, Glasgow

Ticket holders only



**#JNE30**

# British Society for Neuroendocrinology Early Career Researcher Representatives

*“The BSN is a welcoming and nurturing community for early career researchers. The symposium is a great opportunity to meet the great and the good in neuroendocrinology as well as peers.”*

- Rebecca Dumbell, BSN's ECR Representative



## Rebecca Dumbell, BSN ECR Representative 2019-

I am a postdoc currently working at MRC Harwell Institute, Oxfordshire, where I work on genetic regulators of body fat distribution, appetite and energy balance. My previous work was at the University of Luebeck, Germany, on the regulation of adrenal and glucocorticoid circadian rhythms and my PhD focussed on photoperiod and exercise stimulated growth and energy balance in the Siberian hamster. I've been involved with the BSN since 2011, both organising events and benefiting from funding grants, and find it an inclusive and welcoming community. This is something I try to encourage and hope comes across in the symposium today.



## Ashleigh Wilcox, BSN Deputy ECR Representative 2019-

I'm a Postdoctoral researcher at the University of Bristol, working in the lab of Prof. Hugh Piggins. Here my work focusses on circadian physiology in mammals, namely the role of central and peripheral oscillators in entrainment and how this is altered during ageing. This work builds on research interests that I developed during my DPhil in Dr Pat Nolan's group at MRC Harwell, where I worked on the genetic control of adult circadian rhythms and the master pacemaker of the circadian system – the Suprachiasmatic Nucleus.



## Jo Lewis, BSN ECR Representative 2018-2019

My primary area of interest is metabolic syndrome, which developed during my PhD and post-doc in the Neuroendocrinology Research Group with Dr Preeti Jethwa and Prof Fran Ebling at the University of Nottingham. In 2018, I joined the Institute of Metabolic Science at the University of Cambridge. Here I investigate the gut-brain axis, as a post-doc, with Prof Frank Reimann and Prof Fiona Gribble.

# Energy Homeostasis

Chairs: Jo Lewis and Helen Christian  
11.00-12.30



**Plenary: Kate Ellacott**  
University of Exeter, UK

## Astrocytes and the regulation of feeding behaviour

Precise control of energy homeostasis, the balance between food intake and energy expenditure, is essential for human and animal health. The regulation of energy homeostasis is a fascinatingly complex systemic process that functionally interacts with other neuroendocrine axes. The brain co-ordinates feeding behaviour by integrating information transmitted via hormonal, nutrient, and neural inputs from the periphery. The hypothalamus is the brain's main integratory hub controlling long-term energy homeostasis. Direct neuronal projections connect the hypothalamus to the brainstem and in turn, the vagus nerve bi-directionally connects the brainstem to the digestive tract. Pharmacological and genetic studies in rodents have begun to unravel the neuronal circuits regulating energy homeostasis. Our group has contributed to broader understanding of these networks by focusing on how non-neuronal cells in both the hypothalamus and brainstem contribute to the regulation of energy homeostasis. This talk will summarise evidence for a role of glial cells in the regulation of feeding behaviour and the pathology of obesity.



## Pablo Martinez de Morentin

The Rowett Institute, University of Aberdeen, UK

### Brainstem regulation of energy balance

Our bodies require energy to run, the physiological process underpinning energy expenditure has not been fully defined. Here we aimed to decode components of post-prandial thermogenesis by examining a brain-brown adipose tissue (BAT) axis. Following the ingestion of food, energy expenditure is increased to promote digestion, transport and the storage of nutrients and for heat production. BAT is a key tissue coordinating thermogenesis via the uncoupling of oxidative metabolism carried out by the uncoupling protein 1 (UCP1). Despite evidence illustrating the brain regulation of energy homeostasis, the neuronal elements mediating BAT thermogenesis are not fully understood. Here we examined the contribution of the distinct subpopulations of neurotransmitter serotonin to post-prandial thermogenesis. Taking advantage of chemogenetics and a genetic knockdown approach, we uncovered a specific subpopulation of serotonergic neurons modulating the post-prandial energy expenditure and increasing UCP1 in BAT. We report that serotonin-producing cells in the Raphe pallidus (RPa<sup>5-HT</sup>) are necessary for the thermogenic program following the ingestion of food. Clarifying the underpinnings of energy expenditure is essential to design new therapies to combat diseases where an impairment in energy balance is a threat to health, such as obesity.

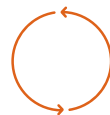


## Alice Adrianensens

University of Cambridge, UK

The identification and characterisation of glucose-dependent insulinotropic polypeptide receptor-expressing cells in the hypothalamus

Ambiguity regarding the role of glucose-dependent insulinotropic polypeptide (GIP) in obesity arises from conflicting reports asserting that both GIP receptor (GIPR) agonism and antagonism are effective strategies for inhibiting weight gain. To enable identification and manipulation of *Gipr*-expressing (*Gipr*) cells we created *Gipr*-Cre knock-in mice. As GIPR-agonists have recently been reported to suppress food intake we aimed to identify central mediators of this effect. *Gipr* cells were identified in the arcuate, dorsomedial, and paraventricular nuclei of the hypothalamus, as confirmed by RNAscope in mouse and human. Single cell RNAseq identified clusters of hypothalamic *Gipr* cells exhibiting transcriptomic signatures for vascular, glial and neuronal cells, the latter expressing somatostatin, but little proopiomelanocortin or agouti-related peptide. Activation of Gq-DREADDs in hypothalamic *Gipr* cells suppressed food intake *in vivo*, which was not obviously additive with concomitant GLP1R activation. These data identify hypothalamic GIPR as a target for the regulation of energy balance.



Aldara Martin Alonso  
Imperial College London, UK

## The role of vagal Y2R in PYY<sub>3-36</sub>-mediated appetite suppression

Peptide YY 3-36 (PYY<sub>3-36</sub>) is an appetite-suppressing gut hormone normally secreted postprandially. Peripherally administered PYY<sub>3-36</sub> is potentially anorexic in rodents and humans and has therefore emerged as a potential anti-obesity treatment. PYY<sub>3-36</sub> is thought to signal satiety via the Y2-receptor (Y2R) in the arcuate nucleus (ARC), but this receptor is also expressed in the vagus nerve, the main gut-brain neural link, where its role in satiety is poorly understood. We hypothesised that PYY<sub>3-36</sub> reduces food intake (FI) by activating vagal Y2R without activating central appetite pathways.

Adult Y2R<sup>loxP/loxP</sup> mice were bilaterally injected in the nodose ganglion (NG) of the vagus nerve with a Cre-expressing adenoassociated virus (AAV-Cre). This novel afferent vagus nerve-specific Y2R knockdown (KD) mouse (NG-Y2R-KD) was compared with Y2R<sup>loxP/loxP</sup> mice bilaterally injected with AAV-Cre in the ARC (ARC-Y2R-KD). AAV-GFP-injected littermates were used as controls.

Y2R mRNA quantification in NG, which contains only the cell bodies of vagal afferents, demonstrated >70% KD of Y2R in NG-Y2R-KD animals vs non-injected controls. This is, to our knowledge, the first example of selective Y2R vagal deafferentation. Low-dose peripheral PYY<sub>3-36</sub> decreased FI in control groups, but this effect was abrogated in NG-Y2R-KD. High-dose peripheral PYY<sub>3-36</sub> resulted in appetite suppression in all experimental groups, including ARC-Y2R-KD. High resolution FI analysis revealed a significant difference in meal patterning rather than total FI in the NG-Y2R-KD group. These results suggest that the afferent vagus nerve contributes to mediate the physiological effects of PYY<sub>3-36</sub> but that alternative pathways might be more important in mediating its pharmacological effects.

*This work was supported by Diabetes UK, the Wellcome Trust and the British Society for Neuroendocrinology.*

# Biological Timing

Chairs: Rebecca Dumbell and Stafford Lightman  
14.00-15.30



Plenary: Fran Ebling  
University of Nottingham, UK

Biological rhythms 1989-2019

Biological rhythmicity over different time scales is a fundamental feature of life on earth. My presentation will focus on the enormous advances made in understanding the mechanisms underlying seasonal rhythmicity in mammals since the inception of the *Journal of Neuroendocrinology* in 1989. There are a myriad of seasonal rhythms that all reflect profound changes in neuroendocrine and hypothalamic function, for example in reproduction, fat deposition, appetite, thermoregulation, hibernation, coat growth/moulting, and antler growth. We now understand that these rhythms arise through a combination of innate circannual timers and perception and response to changing environmental cues, the most important of which is the annual change in daylength. Since 1989, advances in our understanding of core processes include: 1 the unexpected role of retinal ganglion cells in photoreception, 2 the critical role of melatonin as a neurochemical index of night length in mammals, 3 the pars tuberalis (pituitary stalk) as a major site of melatonin action, 4 TSH as a retrograde signal of season from the pars tuberalis to the hypothalamus, 5 glial cells lining the hypothalamic third ventricle (tanycytes) as the key target of this changing TSH signal, and 6 changes in deiodinase gene expression in tanycytes determining local availability of thyroid hormone in the hypothalamus as a key determinant of seasonal changes in reproductive function and of energy metabolism.





Ashleigh G Wilcox

University of Bristol, UK

Entrainment and the master clock: are all oscillators born equal?

Previous work revealed the transcription factor ZFH3 as a key regulator of circadian rhythms throughout the lifespan in mice. Here, we employed a conditional mutagenesis approach to study *Zfhx3*'s role in the development of the key circadian pacemaker in mammals – the suprachiasmatic nucleus (SCN), and subsequent effects on circadian function in the whole animal.

Using the SCN-enriched *Six3*-Cre line, *Zfhx3* was deleted specifically in developing anterior hypothalamus. The resulting homozygous mutants displayed a dramatic circadian phenotype; complete behavioural arrhythmia in all lighting conditions and an inability to entrain to a light-dark cycle. Histological examination revealed that the SCN in these mutants fails to mature, as validated by loss of a histological definition and lack of expression of key circadian related genes *Vip*, *Avp* and *Rora*.

This mutant provided a unique opportunity for us to study the limits of entrainment of the mammalian circadian system in animals that have never possessed a master pacemaker. When examining responses to Zeitgebers other than light, entrainment to both social cues of cagemates and feeding times appears to be intact in these mutants. Therefore, it appears that peripheral circadian oscillators can persist and facilitate entrainment despite these mice being behaviourally arrhythmic throughout their lifetime and crucially in the absence of an SCN during development.



## Vincent van der Vinne

University of Oxford, UK

### Metabolic consequences of disrupting a system of hierarchical clocks

Disruption of the circadian regulation of physiology (e.g. shiftwork, jetlag, light at night) is associated with adverse health outcomes but the mechanisms underlying these effects are unknown. In order to identify these mechanisms, my recent work has aimed to describe how the hierarchical circadian system of mammals responds to disruption of environmental rhythms (chronic jetlag). For this, the behaviour of both central and peripheral clocks was assessed using behavioural and *in vivo* Luciferase imaging approaches. This identified internal misalignment, external misalignment and peripheral amplitude depression as consequences of chronic jetlag. To test the isolated effects of these changes in circadian organisation, I used temporally chimeric mouse lines in which the characteristics of the central clock in the suprachiasmatic nuclei can be altered while leaving clocks in the rest of the body effectively wildtype (*Vgat-Cre<sup>+</sup> CK1-d<sup>fl/fl</sup> -e<sup>fl/+</sup>*; *Vgat-Cre<sup>+</sup> Bmal1<sup>fl/fl</sup>*). When housed in constant darkness throughout their life, these mice provided an excellent model to test the metabolic effects of internal misalignment and peripheral amplitude depression in isolation. Surprisingly, neither of these disruptions to the organisation of the hierarchical clock system resulted in mice becoming obese and/or glucose intolerant.



## Deyana Ivanova

King's College London, UK

### Stress and altered pubertal timing: Is the limbic brain the key?

Post-traumatic stress (PTSD) is associated with altered pubertal timing and predator odour exposure (POE) is a classical rodent PTSD model. Kisspeptin neurones in the posterodorsal sub-nucleus of the medial amygdala (MePD) are thought to modulate pubertal timing and anxiety. We test the hypothesis that psychosocial stress, processed by the MePD, is relayed to the GnRH pulse generator to delay puberty. Female mice were exposed to predator odour, 2,4,5-Trimethylthiazole (TMT), for 14 days from postnatal day (pnd) 21 and pubertal onset was monitored. Anxiety was tested using the Elevated Plus Maze (EPM), Light/Dark Box (LDB) and social interaction (SI). The effect of TMT on luteinizing hormone (LH) pulses was measured, on pnd 26 and 29. Additionally, kisspeptin-cre mice were bilaterally injected with hM3Dq-DREADD AAV in the MePD at pnd 13. From pnd 21, CNO was administered via drinking water for 14 days and pubertal onset was monitored. The TMT-mice showed a significant delay of first estrous (FE;  $p < 0.001$ ) without affecting body weight (BW). TMT-mice spent less time exploring the open arm of the EPM and in the light compartment of the LDB, while engaging less in SI during TMT-exposure compared to controls. The TMT group exhibited a reduction in LH pulse frequency on pnd 26 and 29. DREADD activation of kisspeptin neurones in the MePD advances FE ( $p < 0.05$ ) without affecting BW. POE delays puberty in female mice, reduces GnRH pulse generator frequency and enhances anxiety-like behaviour, while selective chemogenetic activation of kisspeptin neurones in the MePD advances puberty.

*PhD funded by the Medical Research Council, which has supported this work.*

# Neuroendocrinology in Health and Disease

Chairs: Ashleigh Wilcox and Julia Buckingham  
16.00-17.30



## Plenary: David Grattan University of Otago, New Zealand

### Beyond lactation: what does prolactin do in the maternal brain?

The anterior pituitary hormone prolactin is critical for the process of lactation. Prolactin receptors are widespread in the body, however, including in the brain, and multiple additional functions of prolactin have been described. Just why a single hormone would have so many different functions, however, remains an open question. Here, I will present evidence supporting the hypothesis that elevated prolactin during pregnancy, together with its pregnancy-specific homologue placental lactogen, have an important role in coordinating a wide range of physiological adaptations in the maternal brain. Collectively, these adaptive changes help the mother prepare for the demands of her new physiological state, and promote successful outcome of the pregnancy. Examples of adaptive changes that involve prolactin action include metabolic changes and weight gain, suppression of the stress response, inhibition of fertility, and induction of maternal behaviour. Evaluating the role of prolactin in these apparently disparate functions during pregnancy provides novel insights into the evolutionary history of this hormone, including the question as to why do males have prolactin, when they don't lactate?



## Chioma Izzi-Engbeaya

Imperial College London, UK

### The role of kisspeptin in insulin secretion and metabolism

Reproduction and metabolic systems are closely linked. For example, type 2 diabetes and obesity are associated with hypogonadotropic hypogonadism. Conversely, hypogonadism results in higher weight gain, impaired insulin secretion and higher insulin resistance. However, the mediators of the interactions between reproductive and metabolic systems have not been fully characterised.

Kisspeptin, and its receptor, are expressed in the brain and in metabolically active tissues. Acting centrally, kisspeptin potently stimulates the hypothalamic-pituitary-gonadal axis by stimulating the release of gonadotrophin-releasing hormone with downstream secretion of luteinising hormone and follicle-stimulating hormone from the pituitary gland and sex steroids from the gonads. The actions of kisspeptin within the reproductive system have been well-established in rodents and humans (including healthy men and women, women with hypothalamic amenorrhea and obese men with type 2 diabetes and hypogonadism).

Recent evidence from animal studies has suggested that kisspeptin may have additional important roles outside reproduction. However, there is currently no consensus in the literature, with conflicting published reports of the effects of kisspeptin on glucose-stimulated insulin, food intake, energy expenditure and body weight.

As kisspeptin-based therapies are being developed to treat reproductive disorders and up to 40% of men with obesity and/or type 2 diabetes have hypogonadism, it is important to determine if kisspeptin plays a significant role in metabolic processes in humans. Data from the first interventional human study investigating the effect of kisspeptin on insulin secretion and food intake in humans will be presented and implications for the findings will be discussed.



**Ben Jones**  
Imperial College London, UK

Insights into the mechanisms underpinning the physiological effects of biased GLP-1 receptor agonists

*This work was funded by an MRC project grant, the British Society for Neuroendocrinology, Society for Endocrinology and the Academy of Medical Sciences. The Section of Endocrinology and Investigative Medicine is also funded by grants from the MRC, BBSRC, NIHR, an Integrative Mammalian Biology (IMB) Capacity Building Award, an FP7- HEALTH- 2009-241592 EuroCHIP grant and is supported by the NIHR Biomedical Research Centre Funding Scheme.*

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are an effective group of treatments for type 2 diabetes and obesity. We recently described “biased” peptide GLP-1RAs modelled on exendin-4 that uncouple the pronounced endocytosis that usually accompanies GLP-1R activation, leading to prolongation of intracellular signalling responses.

Here, we show that the metabolic consequences of biased GLP-1R activation *in vivo* are dominated by improvements in blood glucose, without concomitant increases in their anorectic properties (40-fold relative preference for glycaemic versus anorectic effects). As GLP-1R-mediated endocytosis has been proposed as a potential entry point to the central nervous system (CNS), e.g. via hypothalamic tanycytes, we hypothesised that this physiological divergence could result from reduced access of biased GLP-1RAs to anorectic CNS neurons due to diminished transport across the blood-brain-barrier (BBB). However, deep tissue imaging of optically cleared intact mouse brain and pancreas specimens showed that biased GLP-1RAs conjugated to the near-infrared fluorophore VT-750 had equal access to protected brain regions. Instead, their distinct physiological effects appear to be due to “tissue bias”, wherein the manifestations of biased signalling are influenced by cell-specific factors such as expression levels of target receptors and/or downstream effectors.

These findings argue against a GLP-1R-mediated transcytotic route of CNS entry for GLP-1RAs, and highlight tissue bias as a determinant of the therapeutic characteristics of biased ligands.



## Leonie Ruddick-Collins

The Rowett Institute, University of Aberdeen, UK

### The impact of breakfast composition on appetite, energy balance and gut health: a randomised controlled trial in overweight adults

There is accumulating evidence supporting morning predominant calorie consumption as a mechanism for improved weight loss, theoretically through influencing circadian synchrony. However, whether the composition of a morning predominant diet has a role in energy balance is not well established. Provision of a high protein (HP) or high fibre (HF) breakfast meal may support timely secretion of specific gut hormones and rhythms in gut microbiota, which could reinforce circadian rhythmicity and subsequently improve satiety and energy metabolism. The aim of this study was to compare HP versus HF big breakfast diets on mechanisms of energy balance (weight, energy expenditure (EE) and appetite). Nineteen overweight volunteers underwent a randomised crossover trial to compare 2 x 4-week weight loss diets (HP: 30% protein, 35% fat and 35% carbohydrate, 15 g fibre, and HF: 50% carbohydrate, 35% fat and 15% protein, 30 g fibre) with a 1-week washout in between. Diets were fed to resting metabolic rate and calorie distribution was 45%, 35%, 20% at breakfast: lunch: dinner respectively. Body composition, appetite and EE were assessed at the end of baseline, HP and HF diets. There were no differences in weight loss between the diets, however the subjective appetite AUC score was significantly lower ( $P = 0.003$ ) and fullness was significantly higher ( $P = 0.013$ ) following the HP versus HF breakfast meal. Both HP and HF big breakfast diets can adequately support weight loss, however HP may have the additional benefit of suppressing appetite and lead to greater reductions of energy intake on an *ad libitum* diet.

*The research leading to these results has received funding from the Scottish Government as part of the Strategic Research Programme at the Rowett Institute (2016-2021)*

# Poster abstracts

Lunchtime 12.30 - 14.00

1. Joyce Chan, Yi Ren, Helen Christian  
University of Oxford, UK

Anterior Pituitary ultrastructure in a novel hypogonadal mouse model with *Patched1* deletion

The Shh pathway is critical in regulating pituitary development but little is known of its role in the adult pituitary. It has been implicated in regulating reproduction as adult onset hypogonadotropic hypogonadism has been reported in transgenic mice in which the *Ptch1* gene, encoding for the *Patched1* receptor for Shh, has been selectively ablated from folliculostellate (FS) cells using S100A4 promoterdriven Cre recombinase. These anatomical changes were also accompanied by decreases in gonadotrophin expression. The aim of this study was to elucidate whether the dysregulation of the Shh pathway in FS cells leads to altered local, paracrine control of gonadotrophs, resulting in these manifestations downstream. This was investigated by use of electron microscopy to study the morphology and regulated secretion pathway ultrastructure of gonadotrophs and FS cells. In *Ptch1*<sup>-/-</sup> females a statistically significant reduction ( $P < 0.05$ ) in cell and cytoplasmic area compared to controls was found. No significant differences in these parameters were seen in the *Ptch1*<sup>-/-</sup> males although an increase in the proportion of FSH-positive “halo” granules and a small but significant paradoxical increase in rough endoplasmic reticulum (rER)/Golgi dilation was measured. FS cells in *Ptch1*<sup>-/-</sup> males and females were found in clusters with a more rounded compared to their stellate appearance in control mice. Overall linking the infertile phenotype to gonadotroph ultrastructure, the findings are consistent with reduced gonadotroph size reflecting reduced synthetic and secretory function in females but in males increased rough ER counters this. This might be explained by gender differences in the consequences of local FS-derived paracrine signalling.





## 2. Philippa Gleave<sup>1,2</sup>, Dr Nora Bourbia<sup>1</sup>, Dr Kerry A Broom<sup>1</sup>, Professor Daniel C Anthony<sup>2</sup>

<sup>1</sup>Public Health England, Centre for Radiation, Chemical and Environmental Hazards, UK; <sup>2</sup>University of Oxford, UK

### The effect of extremely low frequency electromagnetic field exposure on circadian rhythm control

We are constantly exposed to extremely low frequency electromagnetic fields (ELF-EMF), including from power lines and electrical mains. The long-term impact of this exposure on the health of the population is not fully known. One way that magnetic field exposure could affect health may be through the alteration of circadian rhythms. Circadian rhythms are biological rhythms that occur within a periodicity of 24 hours, generated by an endogenous self-sustained oscillator and entrained by the environment. Environmental disruption of circadian rhythms is associated with an increased risk of multiple health problems.

The impact of ELF-EMF on circadian rhythm control was examined using a mouse model. 14-week-old male C57BL/6J mice were exposed at ZT14 for 18 hours to a 50Hz electromagnetic field at 580 $\mu$ T using a pair of Helmholtz coils with a 30-minute blue light shock at 700 lux, at ZT14 and ZT8. 30 minutes after ELF-EMF exposure, memory and locomotor activity was assessed before tissue collection for downstream gene expression analysis.

Post-exposure behavioural analysis revealed no significant differences in memory or locomotor activity between the ELF-EMF exposure and sham exposure groups. Gene expression analyses showed that ELF-EMF had a significant suppressive effect on *Clock* and *Bmal1* expression in the liver, and *Clock* in the adrenals. The interaction between light and ELF-EMF had a significant suppressive effect on *Per1* in the liver and the adrenals, and on *Per2* in the hippocampus.

Further work is required to verify these initial gene expression results and to understand the biological impact of the changes.

*Funding  
acknowledgement  
PHE PhD studentship*



### 3. Peter J. Duncan, Paul Le Tissier & Michael J. Shipston University of Edinburgh, UK

#### Remodelling of the Corticotroph Ion Channel Landscape in Chronic Stress

Chronic stress (CS) represents a huge burden on health and society. In the UK, stress-related illness accounts for ~40% of work-related absence and costs the economy an estimated £6.5 billion per year. Following acute stress, glucocorticoids are beneficial. However, CS is associated with both desensitization of the HPA axis to glucocorticoid negative feedback, as well as hypersensitivity to novel stressors.

Corticotrophs of the anterior pituitary are electrically excitable and stimulation with hypothalamic neuropeptides CRH and AVP results in a characteristic a transition from spiking to bursting activity. Bursting is more efficient in raising intracellular calcium activity and is proposed to drive secretagogue-evoked ACTH secretion.

To investigate the effects of CS, mice were subjected to a 14 day CS paradigm using a daily restraint stress. We reveal that both CRH- and CRH/AVP-evoked secretion is enhanced in corticotrophs isolated from chronically stressed male mice compared to their non-stressed controls. These effects are independent of ACTH content, suggesting that hypersensitivity is at the level of secretagogue-evoked stimulus-secretion coupling.

CS induces significant changes in patterns of corticotroph excitability, including an increase in both basal and CRH-induced bursting activity. We reveal that CS induces significant up- or down-regulation of mRNAs for a variety of voltage-gated ion channel pore-forming and regulatory subunits, which likely explains the changes in electrical activity. Taken together, we predict that hypersensitivity in CS is, in part, due to enhanced corticotroph excitability and that specific ion channels may represent a target for pharmacological intervention to alleviate the effects of chronic stress.

*Work is generously supported by grant from the MRC to MJS and PLeT.*



#### 4. Nicola Romanò, Peter Duncan, Oscar Nolan, Paul Le Tissier, Mike Shipston, Thomas Chambers University of Edinburgh, UK

### Modelling glucocorticoid-induced HPA axis suppression in mice

Glucocorticoids are prescribed for >3 months to 1% of the UK population. 10-50% of glucocorticoid treated patients develop (potentially fatal) persistent HPA axis suppression. Understanding mechanisms which result in persistent HPA axis suppression may inform treatment strategies. Thus, we developed a mouse model of glucocorticoid-induced HPA axis dysfunction.

**Experiment 1:** 36 C57BL/6 adult male mice received Dexamethasone (DEX, ~10µg/day) or vehicle (CTL) via drinking water for 28 days, following which treatment was stopped and tissues were harvested at 0, 7 and 28 days. DEX suppressed serum corticosterone at week 0, which recovered by day 7, but caused persistent adrenal atrophy. DEX had no effect on whole pituitary *pomc*, *nr3c1* or *crhr1*, or on hypothalamic *avp* or *crh* expression. In the adrenal, *hsd3b2* and *cyp11a1* expression was reduced at time 0; normalising by 28 days.

**Experiment 2:** 24 POMC-GFP male mice were treated as above. Tissues were collected at day 0 (n=6), 7 (n=3) and 10 (n=3) following withdrawal. Corticotrophs were sorted by FACS and RNA extracted for qPCR. DEX reduced corticotroph *pomc* expression at time 0 (x20), with x5 suppression at day 7 and which recovered with evidence of compensation by day 10. DEX increased expression of *avpr1b* but not *crhr1*.

**Conclusion:** 28 days dexamethasone treatment in mice suppresses the HPA axis. Whilst basal corticosterone levels recover by 7 days, there is evidence of persisting HPA axis suppression in the adrenal and corticotroph population. This model may be helpful to determine mechanisms for delays in HPA axis recovery.

Work funded by  
generous support from  
the Medical Research  
Council



## 5. Erika Harno<sup>1</sup>, Alison Davies<sup>1</sup>, Tiffany-Jayne Allen<sup>1</sup>, Charlotte Sefton<sup>1</sup>, Jonathan R Wray<sup>1</sup>, Anthony P Coll<sup>2</sup>, Anne White<sup>1</sup>

<sup>1</sup>University of Manchester, UK; <sup>2</sup>University of Cambridge, UK

Glucocorticoid-induced insulin resistance is mediated in part by glucocorticoids acting on AgRP neurons

Glucocorticoids (Gcs) are used to treat inflammatory disorders, but long-term use can cause metabolic side-effects including obesity and diabetes. We have shown that Gc treatment in mice causes metabolic abnormalities and increases hypothalamic *Agrp*. Since AgRP neurons regulate peripheral metabolism and express Gc receptors (GR), we aimed to determine the role of these neurons in Gc-induced metabolic side-effects. We therefore generated mice lacking GR in AgRP neurons (GR/AgRP KO) and characterised their response to corticosterone (Cort).

After 3 weeks Cort treatment, GR/AgRP KO and control mice had similarly increased body weight and adiposity. With Cort, GR/AgRP KO and control mice developed hyperphagia, despite the elevated *Agrp* observed in control mice being absent in GR/AgRP KO mice. After 10 days, Cort-treated GR/AgRP KO mice had improved fasting hyperinsulinaemia (10-fold vs. 30-fold increase over vehicle-treated), reduced glucose stimulated insulin release and lower HOMA-IR, indicative of improved insulin resistance. Additionally, GR/AgRP KO mice had lower glucose excursion than control mice when both were Cort-treated. Cort treatment increased plasma triglycerides in control, but GR/AgRP KO mice were protected. Additionally, there was a trend towards reduced hepatic triglycerides accompanied by reduced hepatic lipid accumulation in Cort-treated GR/AgRP KO mice. Hepatic expression of the fatty acid transporter, Cd36, was increased with Cort but not in GR/AgRP KO mice.

In conclusion, loss of GR in AgRP neurons decreased Cort-induced hepatic steatosis and circulating triglycerides, and improved markers of insulin resistance. These data suggest AgRP neurons have a role in mediating Gc-induced hyperinsulinemia and insulin resistance.



## 6. Alasdair Pollock

Royal Alexandra Hospital, Paisley, UK

Case study on 60 year old man diagnosed with metastatic ileocaecal neuroendocrine tumour after negative qFIT

Mr S, 60 years old, presented to his GP with anorexia, diarrhoea, abdominal pain and significant weight loss. He did not have iron deficiency anaemia and had a negative qFIT test. He was referred to gastroenterology who organised multiple investigations including CT thorax, abdomen and pelvis and colonoscopy. He was found to have metastatic neuroendocrine tumours from an ileocaecal primary. Mr S was unsuitable for surgical intervention due to poor functional status and was started on Lanreotide for potential symptomatic relief of his diarrhoea.

### Discussion

Qualitative faecal immunochemical test (qFIT) has a negative predictive value of 99.7% in Mr S's population cohort using a threshold of <10 ug Hb/g. Lower thresholds for a 'negative' result do have fewer false negative results but also show increased false positive results. Limited service provision for colonoscopy make a lower threshold unfeasible therefore a small number of cancers will be missed using this investigation. Neuroendocrine tumours may be less likely to have a positive qFIT given their tendency to be situated deep in the mucosa or submucosa.

### Conclusion

qFIT is a very useful test in stratifying risk of serious bowel disease in symptomatic patients. There will however be missed cancers and referral to gastroenterology should be done for anybody with red flag symptoms.



## 7. Sophie Buller, Clemence Blouet

University of Cambridge, UK

Oligodendrocytes of the hypothalamic median eminence are highly plastic and regulated by nutritional stimuli

Although the majority of oligodendrocytes (OLs) are born in early postnatal life, OLs are generated from oligodendrocyte progenitor cells (OPCs) in adulthood in response to specific stimuli such as learning a new motor skill. Adult-born OLs add to the pre-existing OL population and produce myelin, which either ensheathes previously unmyelinated axons or modifies existing myelin structures. Emerging evidence suggests that hypothalamic oligodendrocytes (OLs) may play a role in the regulation of energy metabolism. OPCs constitute the main proliferative cell type within the hypothalamus, however the proliferation, differentiation and maturation of this population of OLs has not been previously characterised. Focussing our study on OLs of the median eminence (ME), a hypothalamic region devoid of a complete blood-brain-barrier that undergoes structural remodelling in response to changes in peripheral energy availability, we show that 1) OPCs of the ME are highly proliferative, 2) newly-formed OLs are continuously and rapidly generated in the adult ME, 3) the OL population here remains stable over time, 4) OLs of the ME rapidly turnover and 5) plasticity of the ME OL population is modulated peripheral energy availability. However, the functional significance of the unique dynamics of OL lineage cells in the adult ME is yet to be fully elucidated.

*This work was supported by a Wellcome Trust 4-year PhD Studentship (ref 108926/Z/15/Z).*



## 8. DeAsia Davis, Ruby Vajaria, Nandini Vasudevan, Evangelos Delivopoulos

University of Reading, UK

### Localisation of oestrogen receptors in stem cell derived neurons and astrocytes.

Steroid hormones act as first messengers that modulate physiology and multiple aspects of social and sexual behaviour. Oestrogen is generally thought to be produced by ovaries, however locally produced neuro oestrogens such as  $17\beta$ -estradiol ( $17\beta$ - E ) has been shown to regulate reproductive and social behaviours by binding to nuclear oestrogen receptors ER $\alpha$  and a putative membrane ER (mER) called GPER1. Recently, oestrogen stimulation has been shown to exert rapid behaviour effects via binding to mERs that activates multiple protein kinase pathways and regulates intracellular calcium concentrations. The presence of GPER1 and ER $\alpha$  at the plasma membrane has been identified in breast cancer cells; however there is still considerable debate about whether GPER1 is localized at the membrane or other organelles within the cell with ER $\alpha$ . Based on past literature that suggest that GPER1 activation phosphorylates ER $\alpha$  in the male mouse hippocampus, we hypothesize that there is colocalisation of these two receptors on the plasma membrane and other organelles. To address the hypothesis:

(a) Determine the localisation of ER $\alpha$  and GPER1 within the cell by confirming the presence of ERs within the cell and identifying where ERs are distributed within the cell using nuclear, Golgi apparatus and Endoplasmic reticulum markers in neurons and astrocytes derived from mouse embryonic stem cells.

(b) Determine the colocalisation of ER $\alpha$  and GPER1 on the membrane and within the cell.

(c) To characterise the distribution of ERs in stem cell derived neurons and astrocytes in order to develop an alternative to primary neuronal cultures.



9. Maria V. Carreira<sup>1,2\*</sup>, Isadora C. Furigo<sup>1\*</sup>, Lucas C. Pantaleão<sup>1</sup>, Juliana Faria<sup>1</sup>, Laura Dearden<sup>1</sup>, Susan E. Ozanne<sup>1</sup>

<sup>1</sup>University of Cambridge, UK; <sup>2</sup>University College London, UK

\* These authors contributed equally to this work

Investigating the role of hypothalamic miRNAs in the programming of obesity by maternal diet-induced obesity

Obesity is strongly associated with a variety of adverse health outcomes. Currently, more than half of pregnant women in the U.K. are either overweight or obese. This is concerning as the offspring of obese mothers have a higher susceptibility to develop obesity themselves as a result of exposure to an obese intrauterine environment. Animal models have shown that offspring obesity is preceded by hyperphagia, however the underlying epigenetic factors mediating this programmed change in feeding behavior remain elusive. In the present study we used a mouse model of maternal diet-induced obesity to identify programmed miRNAs by small RNA sequencing. We then used pulsed SILAC technology to identify targets of dysregulated miRNAs. Our results showed miR-505-5p was up-regulated in the hypothalamic paraventricular and arcuate nucleus of young adult offspring and then confirmed this difference was also present in hypothalami of fetuses exposed to maternal obesity. The expression of miR-505-5p was increased *in vitro* in neuroendocrine cells exposed for 24h to stearic acid treatments, mimicking the obesogenic intrauterine environment. Furthermore, pulsed SILAC experiments in neuronal cells overexpressing miR-505-5p revealed that its protein targets are involved in lipid metabolism, highlighting the interplay between fatty acid metabolism and miR-505-5p abundance in the hypothalamus. Our findings demonstrate maternal obesity directly programmes hypothalamic miRNAs. This provides novel insight into how maternal obesity may programme permanent changes in offspring food intake and thus provide insight into mechanisms and potential therapeutic targets to stop the development of obesity.

*This work was funded by the British Society for Neuroendocrinology Undergraduate Student Laboratory Experience Grant, and by São Paulo Research Foundation: FAPESP (#2019/06313-7).*





## 10. Erin Brown\*, Neil Evans, Michelle Bellingham University of Glasgow, UK

Is the Kisspeptin/ GnRH neuroendocrine system a target through which environmental chemicals can alter reproductive function?

Mammalian reproduction is tightly controlled by the hypothalamo-pituitary-gonadal (HPG) axis, which is highly sensitive to both endogenous and exogenous inputs. We have previously shown that maternal grazing of pastures fertilized with human biosolids, which contains a complex low-level mixture of environmental chemicals (ECs), disrupts mRNA expression of regulatory genes in the fetal HPG axis. This study examined the effects of maternal exposure to biosolids during pregnancy, on mRNA expression of key hypothalamic genes, in 1 day old lambs of both sexes.

Hypothalami were harvested from lambs (within 24 hours of birth) from mothers maintained on either fields fertilised with biosolids (n=8 male/female) or inorganic fertiliser (n=9 male/female). 1mm<sup>2</sup> hypothalamic tissue punches were taken from the preoptic area (POA) and arcuate nucleus (ARC) regions, and stored at -80°C prior to RNA extraction and reverse transcription to cDNA. qRT-PCR was used to quantify mRNA expression of genes of interest (*KISS1*, *ERα*, and *GnRH*) relative to house-keeping genes. Data was analysed using a general linear model ( $P < 0.05$  = significant).

*GnRH* mRNA expression was significantly increased in the POA of biosolids-exposed, compared to control males, but was not affected in females. *KISS1* mRNA expression was significantly increased in the ARC but not the POA of biosolids exposed compared to control males, whereas female *KISS1* expression was not significantly affected by exposure in either hypothalamic region. *ERα* mRNA expression was significantly higher in the POA of biosolids exposed compared to control females but the opposite effect was observed in exposed relative to control males. These results differed to previous expression patterns observed in fetal fetal animals which may indicate dynamic changes in regulatory systems or reflect differences in EDC exposure.

*\*Recipient of a  
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Neuroendocrinology  
Student Laboratory  
Experience Grant*

Fourth Joint Meeting  
Bordeaux, France

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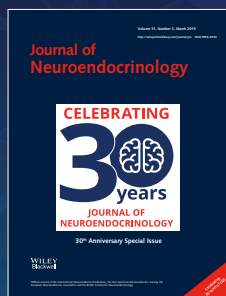
Winners will get a £300 bursary towards attending our next annual meeting in Bordeaux, screening at the AGM in Bordeaux and have their video uploaded onto the BSN website.

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<b>Academic Support Fund</b>	For new academic staff within 10y of obtaining their PhD and/or established academics with no current funding	£10,000



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# Travel and accommodation

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## Travel

### By air

Take the 15 minute journey on the 500 Airport Express from Glasgow Airport to Waterloo Lane which is a five minute walk to the symposium venue.

### By train

The symposium venue is a five minute walk from Glasgow Central Station. The dinner venue is a 10 minute walk from Glasgow Central Station.

## Travel grant

All ECRs attending the event can apply for a travel bursary of up to £150 to attend Neuroendo Celebrate! Postgraduate students and post-doctoral research fellows within 10 years of gaining their PhD who have also been BSN members for at least 6 months are eligible to apply. You do not need to have submitted an abstract to apply for a travel grant.

## Map

The accommodation at Motel One, symposium venue (The Lighthouse) and dinner venue (Hutchesons City Grill) are all within a 10-15 minute walk to each other.



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## Share your experience on Twitter

Use #JNE30 to share your thoughts and photos of the Neuroendo Celebrate symposium and dinner. Remember to tag us @bsneuroendo.