

## SA17

**The role of sleep in metabolism and obesity**

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Sleep is a complex behaviour whose precise physiological functions are unknown. Traditionally, it was believed that sleep is only for the brain, but increasingly, the role of sleep in other organs has been recognized. Recently the role of sleep duration and sleep disorders in the regulation of metabolism is increasingly appreciated. The hypothalamus, which is a major regulator for homeostatic regulatory mechanisms, is also a major regulator of sleep and wakefulness allowing integration of sleep, appetite, and metabolism. In particular, the lateral hypothalamic orexin (hypocretin) neurons have been shown to play a key role in wakefulness, appetite regulation, glucose sensing, locomotor activity and energy expenditure. The importance of hypothalamic integration of sleep and metabolism has been shown in both animals and also humans who suffer from the sleep disorder, narcolepsy. Narcolepsy is a profound neurological sleep disorder that results in excessive daytime sleepiness, but is also associated with obesity and insulin resistance. Patients with narcolepsy have undetectable orexin (hypocretin) neuropeptide levels in their cerebrospinal fluid and post-mortem studies have shown that orexin (hypocretin) mRNA expression is absent in hypothalami from patients with narcolepsy.

Data from large population studies show that both long and short sleep duration are associated with obesity, the metabolic syndrome, diabetes, cardiovascular disease and mortality. These studies have been carried out across all age groups, and in several countries and ethnic groups. In a study of over 1000 individuals, short sleep duration was shown to be associated with greater body mass index but lower levels of the adipocytokine hormone leptin and higher levels of the stomach-derived hormone ghrelin. Low leptin and high ghrelin levels are a powerful appetite stimulatory signal. Data from other population studies suggest a relationship between sleep duration and physical activity. Human sleep laboratory studies have shown that both short sleep duration and sleep disruption are associated with metabolic derangements that are associated with the metabolic syndrome and diabetes. These studies also report associations between shorter sleep and energy expenditure. The objective of the presentation will be to discuss data available regarding the relation between sleep, metabolism and obesity including potential neurohormonal mechanisms.

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*Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.*

## SA18

**Brain serotonergic pathways regulating body weight**

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The central serotonin (5-hydroxytryptamine, 5-HT) system is an established modulator of ingestive behaviour. Pharmacological and genetic research implicates the serotonin 2C receptor (5-HT<sub>2C</sub>R) specifically in these effects. New selective 5-HT<sub>2C</sub>R agonists are currently being pursued for the treatment of human obesity. We sought to clarify how serotonin in general and the 5-HT<sub>2C</sub>R in particular modulate ingestive behaviour. The hypothalamus is a key brain region coordinating endocrine, autonomic, and behavioral responses to changes in energy availability. Through a combination of functional neuroanatomy, feeding, and electrophysiology studies in rodents, we report that 5-HT<sub>2C</sub>R agonists require functional melanocortin pathways to exert their effects on food intake. Specifically, we observed that anorectic serotonin drugs activate proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus. We provide evidence that the 5-HT<sub>2C</sub>R is expressed on POMC neurons and contributes to this effect. Finally, we report that serotonin drug-induced hypophagia is attenuated by genetic inactivation of downstream melanocortin 4, but not melanocortin 3 receptors. A model is presented in which activation of the melanocortin system is downstream of serotonin and is necessary to produce the complete anorectic effect of serotonergic compounds and 5-HT<sub>2C</sub>R agonists.

The Wellcome Trust, The National Institute of Diabetes and Digestive and Kidney Diseases, and American Diabetes Association.

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## SA19

**The role of PYY in appetite regulation and obesity**

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Adequate food intake and body fat stores are essential for survival. As a consequence complex systems regulating feeding behaviour have developed. An increased understanding of how peripheral energy signals act upon these circuits to regulate food intake is essential for effective treatment of the current obesity crisis.

In recent years it has become apparent that hormones released from the gut play crucial roles in the regulation of hunger and body weight. Peptide YY (PYY), synthesised by gut-endocrine L-cells, predominantly as an N-terminally truncated form PYY<sub>3-36</sub>, is one such hormone. Exogenous administration of PYY<sub>3-36</sub> reduces food intake in obese humans and rodents.

Moreover, new lines of evidence support a role for endogenous PYY3-36 in regulating energy homeostasis.

The NPY-Y2 receptor mediates the anorectic actions of PYY3-36 with rodent studies implicating the hypothalamus, vagus and brainstem as key target sites. Functional imaging in humans has confirmed that PYY3-36 activates brainstem and hypothalamic regions. The greatest effects, however, were observed within the orbitofrontal cortex, a polymodal brain region involved in reward processing. Further evidence for a hedonic role for PYY3-36 is supported by rodent studies showing that PYY3-36 decreases the motivation to seek high-fat food. These emerging hedonic effects of PYY3-36 together with the weight-reducing effects observed in obese rodents suggest that targeting the PYY system may offer a therapeutic strategy for obesity.

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SA20

#### **Genetic basis of obesity**

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The recent and rapid increase in the prevalence of obesity in most developed and developing countries has correctly focused attention on environmental determinants of that secular trend. However, a fuller understanding of the factors determining any individual person's adiposity requires appropriate considera-

tion of inheritance. Studies of twins, adoptees and adopted twins provide incontrovertible evidence that heritable factors play a major, perhaps even the major factor, in determining a person's fatness. Until recently, the precise mechanisms whereby such genes might influence fatness were obscure. However, in the past decade we have witnessed an explosion of information regarding the molecular mechanisms underlying the control of mammalian energy balance. That information, much of it originating from animal models, is beginning to demonstrate its clear relevance to human energy balance. Thus, defects in several individual genes have now been demonstrated to result in human obesity. One of these (MC4R deficiency) is not uncommon, being responsible for up to 5% of severe obesity in childhood, and one rare form (congenital leptin deficiency) is amenable to life-saving treatment. Importantly, the vast majority of single gene defects causing human obesity do so through the impairment of satiety. Evidence is accumulating that more subtle genetic variants affecting these pathways underlie susceptibility and resistance to common forms of obesity in the general population. Far from encouraging a mood of deterministic nihilism, the more precise knowledge of biological pathways that genetic information provides should assist the prevention and treatment of human obesity by allowing the design of better therapies and improving the focus and precision of behavioural strategies for treatment and prevention.

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