

SA1

Coactivating CREB - coactivating central regulation of energy balance?R.G. Lerner¹, G.A. Rutter² and N. Balthasar¹¹Physiology and Pharmacology, University of Bristol, Bristol, UK and ²Cell Biology, Imperial College London, London, UK

A critical role for the novel CREB coactivator CRTC2 (CREB-regulated transcription coactivator, a.k.a TORC2 (transducer of regulated CREB activity)) in maintaining glucose homeostasis was previously demonstrated in liver, where hormonal and energy-sensing signals mediate their effects on gluconeogenic gene transcription via regulation of CRTC2 phosphorylation. Here, we report CRTC2 expression in neurons of several hypothalamic areas of the mouse, showing alterations in CRTC2's subcellular localisation and thus activity in response to fasting. Important questions arise: Which metabolic signals regulate hypothalamic CRTC2 activity? Which hypothalamic genes does CRTC2 regulate? What is the physiological role of CRTC2 in the hypothalamus?

Using a range of in vitro, in vivo and imaging studies, we identified glucose as one of the metabolic stimuli regulating hypothalamic CRTC2 activity. More specifically, glucose levels regulate hypothalamic CRTC2 subcellular localisation via AMP Kinase-mediated phosphorylation of CRTC2, thereby controlling CRTC2's occupancy of the insulin receptor substrate 2 (IRS2) promoter. We thus uncover CRTC2 as a novel hypothalamic AMPK target and highlight a role for CRTC2 in linking hypothalamic metabolic sensing pathways with CRE-gene regulation.

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SA2

AMP-activated protein kinase: part of the glucose-sensing machinery linked to K_{ATP} channels

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AMP-activated protein kinase (AMPK) is an integral part of the system in cells that allows them to sense and respond to metabolic stress and the consequent threat of lowered ATP levels. AMPK responds to various stresses, through sensing a raised cellular AMP/ATP ratio, resulting in increased kinase activity. This initiates multiple cellular outcomes predicated to oppose loss of high-energy phosphates by stimulating ATP producing processes and inhibiting non-essential ATP consuming processes. In single celled eukaryotes AMPK subunit homologs are required for their response to glucose starvation. Some mammalian cells are also capable of sensing alterations in the physiological levels of glucose. The best-known examples of such specialized cells are pancreatic beta cells and certain hypothalamic neurons, with their ability to sense changes in local glucose concentration coupled to the regulation of insulin secretion and to changes in feeding behaviour, respectively.

The archetypal glucose-responsive cell is the pancreatic beta cell, where GLUT2, glucokinase (GK; also called hexokinase IV) and ATP-sensitive K⁺ (K_{ATP}) channels combine to act as regulators of glucose sensing. In addition, certain glucose-responsive central neurons may use the same molecular mechanisms to recognize and respond to changes in extracellular glucose. In both cases, alteration of physiological glucose levels results in changes in cellular excitability, driven mainly through variation in the activity of K_{ATP} channels. We have attempted to address the question whether AMPK contributes to this glucose sensing and transduction system (i.e through alteration of K_{ATP} channel opening) in these cells. To that end, we have utilized two main approaches: genetic deletion of the AMPK α 2 subunit, and pharmacological activation of AMPK activity. The results of deletion of the AMPK α 2 subunit from defined hypothalamic neurons and pancreatic beta cells will be presented, showing that their glucose-sensing mechanisms utilize AMPK activity to link glucose metabolism with changes in excitability. We are currently investigating the effects of AMPK activation on the electrical activity of an insulin secreting cell line (CRI-G1). Preliminary data indicate that manipulations designed to increase AMPK activity can alter glucose sensing in these cells, but in a rather unexpected manner.

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SA3

Glucose sensing and metabolic regulation of neuronal excitability in the vagal complex

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A large number of studies have implicated the lower brainstem, and particularly the vagal complex of the medulla oblongata, in the central control of blood glucose levels and in the glucoprivic regulation of feeding. Within the vagal complex the nucleus of the solitary tract which is a major relay station for ascending visceral and cardiovascular homeostatic signals, and the dorsal vagal motor nucleus, which is the source of the vagal efferent fibers projecting to most visceral organs, including liver and pancreas, are of particular interest. Like several hypothalamic nuclei, these structures within the dorsal vagal complex contain glucose-inhibited and glucose-excited neurons. However, relatively little is known about the molecular components involved in glucose sensing and in generating the electrical signal.

Utilizing primarily rodent *in vitro* brain slice preparations we investigate whether specific brainstem cell populations are intrinsically sensitive to physiological changes in glucose availability. We explore which molecular and electrical pathways are responsible for this sensitivity and how it relates to their general metabolic sensitivity. This involves the combination

of patch-clamp electrophysiology with single-cell RT-PCR and immunocytochemistry. Our results indicate that brainstem responses to hypoglycemia are elicited at higher glucose levels than in hypothalamic nuclei. They also demonstrate the involvement of glucokinase and the activation of ATP-sensitive K^+ channels in the hypoglycemia response of glucose-excited neurons and suggest a variety of different mechanisms, including, but not limited to, inhibition of 2-pore-domain K^+ channels, in glucose-inhibited cells. We are using transgenic mouse models to ascertain the involvement of specific ion channels and to characterize the responses of specific cell populations.

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SA4

Arousal reward and metabolism: the hypocretin connection

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The hypothalamus encompasses multiple neuronal circuits regulating arousal, energy homeostasis and goal-oriented behaviors. Recent observations have linked sleep perturbances with leptin and ghrelin pathways and subsequent metabolic imbalances. Thus, hypothalamic circuits sharing both sleep and metabolic functions, such as the Hypocretin (Hcrt) and Melanin-Concentrating Hormone (MCH) systems, are strong candidates for mediating these imbalances. Hcrt containing neurons receive significant input from NPY and POMC neurons in the arcuate nucleus, are regulated by leptin and hyperpolarized by glucose; hence Hcrt neurons provide a powerful sensor of metabolism that is integrated into stable wakefulness. Optogenetic manipulation of Hcrt neurons is sufficient to induce sleep-to-wake behavioral transitions. Activation of Hcrt neurons can reinstate drug and food seeking behavior in extinguished animals, demonstrating a role for this peptidergic system in motivation and goal-oriented behaviors. Here, we propose new roles for these peptidergic systems as sensors and effectors of arousal state, and discuss their implications in the plasticity of complex hypothalamic networks regulating sleep and energy balance. Finally, we suggest that new tools for remote control of neuronal circuit activity provide an effective way of testing related questions by interrogation of these circuits with unprecedented specificity and temporal resolutions.

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SA5

Sugar sensing by arousal and appetite neurons

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Hypocretin/orexin neurons of the hypothalamus are essential for normal wakefulness, feeding behaviour, and reward seeking. Their electrical activity is directly silenced by glucose, providing a potentially important link between energy state and behavioural coordination. However, the cellular mechanisms underlying this electrical silencing are not well understood. Our new experiments show that the orexin/hypocretin glucosensors display a novel sugar selectivity, detecting mannose, D-glucose, and 2-deoxyglucose, but not galactose, L-glucose, fructose or alpha-methyl-D-glucoside.

Furthermore, conventional glucose metabolism does not appear critical for orexin cell glucosensing: the effects of extracellular glucose on orexin cells are not mimicked by intracellular glucose or lactate, and are not affected by glucokinase inhibitors. We also show that orexin cell glucosensing also exhibits an unusual temporal profile.

About 70% of orexin neurons are inhibited by glucose only transiently, self-restoring their firing despite high sugar levels. The remaining 30% of cells display sustained inhibition that follows the time-course of glucose application. The transient and sustained glucosensor cells display significant differences in their ion channel expression. The implications of these findings for the control of feeding and cognitive arousal will be discussed.

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Leptin and the biological basis of obesity

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The cloning of the ob gene and its gene product leptin has led to the elucidation of a robust physiological system that maintains fat stores at a relatively constant level. Leptin is a peptide hormone secreted by adipose tissue in proportion to its mass. Recessive mutations in the leptin gene are associated with massive obesity in mice and some humans establishing a genetic basis for obesity. Leptin circulates in blood and acts on the brain to regulate food intake and energy expenditure. When fat mass falls, plasma leptin levels fall stimulating appetite and suppressing energy expenditure until fat mass is restored. When fat mass increases, leptin levels increase, suppressing appetite until weight is lost. This system maintains homeostatic control of adipose tissue mass.

The cloning of the ob gene and hormone leptin has led to several new insights. The identification of leptin has uncovered a new endocrine system regulating body weight. This system

provides a means by which changes in nutritional state regulate other physiological systems. There are a number of leptin deficiency syndromes that are treatable with leptin replacement. The majority of obese subjects are leptin resistant establishing that obesity is the result of hormone resistance. Leptin treatment results in weight loss in a subset of obese patients and can also synergize with other anti-obesity agents. Leptin also has metabolic effects that are independent of its effects on food intake and body weight, findings which provide insights into the mechanisms by which the CNS controls fat and glucose metabolism. Leptin provides an entry point for studying a complex human behavior. Finally, there is a powerful biological basis for obesity, a fact that is (correctly) changing public perception about this medical condition.

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SA7

Metabolic control of pancreatic glucagon and somatostatin secretion

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Whereas the metabolic regulation of insulin secretion from the β -cell is fairly well understood, the processes that control hormone release from the non- β -cells of the islets (which include the glucagon-producing α -cell and the somatostatin-secreting δ -cell) are less well established.

Pancreatic α -cells exhibit many similarities with the β -cells. Like β -cells, α -cells contain ATP-regulated K-channels (KATP-channels) and the metabolic rate as well as ATP production are similarly affected by an elevation of the extracellular glucose concentration in both cell types. Yet, insulin and glucagon secretion are reciprocally regulated by glucose. In β -cells, closure of the KATP-channels leads to membrane depolarization, initiation of electrical activity, opening of voltage-gated Ca-channels and insulin secretion. Work on KATP knockout mice indicates that KATP-channels are involved in the regulation of glucagon secretion by glucose but precisely how these channels participate in the control of glucagon secretion is not unknown. Experiments using increasing concentrations of tolbutamide (a blocker) and diazoxide (an activator) to "titrate" KATP-channel activity in α -cells in intact mouse, rat and human islets suggest that there is a bell-shaped relationship between KATP-channel activity and secretion. Glucagon secretion is only possible within a narrow window of KATP-channel activity and both increases and decreases in channel activity lead to inhibition of secretion (MacDonald et al., 2007). These effects can be dissociated from any concomitant changes in insulin and somatostatin release and are therefore likely to reflect mechanisms intrinsic to the α -cell rather than involving paracrine processes (exerted by factors released from the neighbouring β - and δ -cells). Pharmacological suppression of KATP-channel activity (with high concentrations of tolbu-

tamide) inhibits glucagon secretion as strongly as glucose and the sugar has no further inhibitory action on glucagon secretion in islets already inhibited by tolbutamide. Addition of tolbutamide is associated with membrane depolarization to ~ -35 mV. All voltage-gated ion channels involved in α -cell action potential firing (TTX-sensitive Na-channels, A-type K-channels and N- and T-type Ca-channels) undergo voltage-dependent inactivation. Electrophysiological experiments have established that inactivation of these currents is complete at the membrane potential attained in the presence of tolbutamide. It remains unclear whether glucose inhibits glucagon secretion by exerting a tolbutamide-like effect mediated by inhibition of KATP-channels and changes in membrane potential or if it acts by direct modulation of, for example, the N-type Ca-channels that are tightly linked to exocytosis of the glucagon-containing granules.

In contrast to the strong effects of the KATP-channel modulators on glucagon secretion, the release of somatostatin is only weakly influenced by these compounds and downstream processes appear quantitatively more important. Among these, Ca-induced Ca-release (CICR) is of particular significance (Zhang et al., 2007). Pancreatic δ -cells express RyR3 at levels comparable to those found in the CNS, whereas RyR1 and RyR2 are present at very low levels in both δ -cell and the other islet cells. CICR is triggered by Ca-influx through R-type (but not L-type) Ca-channels and occurs with a delay as short as <10 ms. Glucose-induced somatostatin secretion is strongly inhibited by ryanodine, dantrolene and thapsigargin and depends on glucose metabolism as suggested by its sensitivity to the glucokinase inhibitor mannoheptulose. The effect of glucose is mediated by elevation of intracellular cAMP with resultant activation of PKA. In capacitance measurements of exocytosis in δ -cell in intact mouse islets, the stimulatory effect of glucose can be mimicked by a low concentration of forskolin ($2 \mu\text{M}$). Forskolin at this concentration lacked effects when added to cells already exposed to glucose. The involvement of the cAMP/PKA pathway in the control of δ -cell secretion was confirmed by the demonstration that glucose-stimulated somatostatin release was inhibited by the PKA inhibitor 8-Br-Rp-cAMPS. Glucose and/or cAMP stimulate(s) exocytosis of somatostatin-containing secretory granules via a dramatic increase in the amplitude of the cytoplasmic Ca-transient that can be evoked by membrane depolarization or intracellular Ca mobilization. Collectively, these data demonstrate that glucose-sensing involves rather different mechanisms in the three major islet cell types.

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in intracellular adenine nucleotides: ATP closes the channel by binding to Kir6.2, whereas interaction of Mg-nucleotides (MgATP, MgADP) with the nucleotide-binding domains of SUR1 stimulates channel activity and reverses channel inhibition by ATP. Channel activity thus reflects the balance between these excitatory and inhibitory effects.

K_{ATP} channels are found in numerous tissues. In neurones they regulate electrical activity in response to glucose, neuropeptides and ischemia; in heart they are important for ischemic preconditioning and the stress response; in smooth muscle they regulate vascular tone and in endocrine cells they mediate hormonal secretion. Our studies focus on their role in insulin secretion. At rest, K_{ATP} channels are open, hyperpolarizing the pancreatic beta cell membrane and inhibiting insulin release. When plasma glucose levels rise, K_{ATP} channels close, depolarizing the beta-cell and opening voltage-gated Ca²⁺ channels. The resulting Ca²⁺ influx triggers insulin release. The sulphonylurea drugs used to treat type 2 diabetes stimulate insulin secretion by binding to, and closing the K_{ATP} channel.

Gain-of-function mutations in the genes encoding both Kir6.2 (KCNJ11) and SUR1 (ABCC8) can cause neonatal diabetes. Some mutations produce a severe clinical phenotype, characterized by developmental delay, epilepsy, muscle weakness and neonatal diabetes (DEND syndrome). In many patients, sulphonylureas can successfully be used to treat their diabetes, and in some individuals the neurological symptoms can also be alleviated. This lecture will discuss the mechanisms by which nucleotides modulate K_{ATP} channel activity, how mutations causing human disease alter K_{ATP} channel function, how alterations in K_{ATP} channel activity cause the disease phenotype in man and mouse, and why some mutations are susceptible to sulphonylurea therapy and others are not.

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The role of circadian dysregulation and sleep loss in obesity and metabolic dysfunction

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The discovery just a few years ago that only a few days of partial sleep restriction, in otherwise healthy young men, can induce changes in glucose regulation that are indicative of a trajectory toward insulin resistance and diabetes, introduced a new era of sleep medicine and a new found interest in sleep and metabolism. Indeed, there is now considerable evidence from experimental and epidemiological studies that sleep loss and obesity are “interacting epidemics”. Similarly, the recent discovery that mice carrying a mutation in a canonical circadian clock gene show alterations not just in the timing of sleep and wake, but also in the amount of sleep and sleep architec-

ture, as well as changes in metabolism, has opened up a new era for thinking about how the circadian clock, sleep-wake and energy regulatory systems are integrated at the molecular, genetic and behavioral levels. Further support for the integration of these systems at many levels comes from studies showing that genetic and environmentally induced changes in metabolism can influence sleep and circadian rhythms.

The fact that the core molecular circadian clock machinery is found in most of the cells and tissues of the CNS and periphery and regulates the diurnal timing of expression of hundreds of “clock controlled genes”, and that core molecular circadian genes and proteins are also part of key energy metabolic pathways, has opened up new frontiers for investigating the importance of rhythmicity for mental and physical health. These lines of research are only in their infancy, but nevertheless, have provided a conceptual and experimental framework that potentially has great importance for developing a deeper understanding of complex behavioral and physiological processes. This lecture will review this new and rapidly evolving frontier of neuroscience.

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SA15

Developmental origins of metabolic syndrome

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The ‘metabolic syndrome’ develops when an individual makes inappropriate responses to their environment, predisposing to obesity, dyslipidaemia, Type 2 diabetes and vascular endothelial dysfunction. Whilst there is debate about the definition of the syndrome and its usefulness as a descriptor, it is associated with increased risk of coronary heart disease. Much research has focused on potential genetic determinants of the phenotypic components of the syndrome on one hand and lifestyle and nutritional factors on the other. There is however a third component of how individual risk is created, namely the interaction between genotype and environment during development. Such developmental origins of health and disease (DOHaD) accounts for a substantial fraction of risk. This is part of a broader picture in mammals, in which developmental plasticity sets many phenotypic traits during prenatal and infant life based on cues about the environment, transduced by the mother and transmitted to her offspring across the placenta or in her milk. Developmental plasticity is also utilised to produce polyphenisms in many other species too. In humans, mismatch between predicted and eventual environment can arise through unbalanced maternal diet or disease and migration or socio-economic development (1). This pathway is involved in the dramatic increases in metabolic syndrome between generations in both developing and developed societies. The effects are also exacerbated by demographic changes in reproductive behaviour,

such as the tendency for women to have children at the extremes of their reproductive age and for more primiparous pregnancies. A second set of developmental pathways also exists, by which fetal or infant overnutrition affects development, to become manifest later as metabolic syndrome in the offspring. Such overnutrition may originate as maternal diabetes, maternal obesity or infant overfeeding (2). Thus the risk which starts with mismatch can be perpetuated into new cycles of risk in successive generations. Low socioeconomic status and educational attainment underpin many aspects of these cycles.

The processes underlying these developmental effects involve various components of non-genomic inheritance. Particular interest concerns epigenetic processes, involving DNA methylation, histone structure and small non-coding RNAs (3). Other processes relate to parental physiology, for example maternal adaptations to pregnancy, or behaviour such as suckling and grooming of offspring (4, 5). In addition recent animal data reveal that the changes induced by dietary change or endocrine challenges in pregnancy can be passed to the grand-offspring (F2) without additional challenge in the F1 generation, and can affect a range of cardiovascular, endocrine and metabolic functions (e.g. 6). We have now shown that these effects may be due in part to epigenetic changes (7). Current emphasis on the metabolic syndrome is focused on screening and interventions in adults. We believe that understanding the epigenetic and other processes which operate early in life to determine risk holds greater hope for future detection of those individuals and population groups most susceptible and for design of appropriate interventions.

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II diabetes and stroke. Some of these obesity-related complications (e.g. type II diabetes) have been linked to changes in inflammation, as obesity is characterised by chronic low-grade inflammation (1). Obesity is also associated with an increase in the prevalence and severity of infections. Genetic animal models of obesity, such as leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice display altered centrally-mediated sickness behaviour in response to acute systemic infections (2-4). Although obese ob/ob and db/db mice are useful models of obesity, genetic mutations leading to leptin or leptin receptor deficiency have been only identified in a small subset of the obese population in humans, and to date diet-induced obese (DIO) rodents remain the most relevant model for human obesity. We have shown recently that DIO mice display a heightened and prolonged response to infection caused by lipopolysaccharide (LPS), and these observations maybe due to changes in the inflammatory response.

Growing evidence suggests that inflammation modulates the response to acute brain injury (5). Peripheral inflammatory stimuli, such as infection, increase the risk of stroke and are associated with poorer outcome (6,7). As obesity is a risk factor for stroke, and is associated with changes in the inflammatory response, we determined the effects of obesity on the outcome of stroke, and if changes in inflammation maybe involved. Ischaemic damage was exacerbated in obese ob/ob mice compared to lean controls 24h after experimental stroke and this effect was independent of leptin. This enhancement in damage was accompanied by an increased susceptibility of haemorrhagic transformation in ob/ob mice. We also observed changes in the number of inflammatory cells in the obese mice. These data demonstrate that obesity is detrimental to the outcome of stroke, and is associated with an increased risk of haemorrhagic transformation. Furthermore, the altered inflammatory state associated with obesity maybe involved in the detrimental affect this condition has on neuronal injury.

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SA16

Effects of obesity on the brain-mediated inflammatory response and recovery from neuronal injury

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Obesity is a major cause of morbidity and mortality and is a risk factor for many diseases such as cardiovascular disorders, type

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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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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_{2C}R) specifically in these effects. New selective 5-HT_{2C}R agonists are currently being pursued for the treatment of human obesity. We sought to clarify how serotonin in general and the 5-HT_{2C}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_{2C}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_{2C}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_{2C}R agonists.

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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 PYY₃₋₃₆, is one such hormone. Exogenous administration of PYY₃₋₃₆ 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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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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