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.

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

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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 tolbutamide) 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 tis 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 estblished 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-induces 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 μM). 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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Supported by the Wellcome Trust and Diabetes UK.

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response to hypoxia, the *de novo* production of CB glomus cells mainly depends on a population of stem cells, which form multipotent and self-renewing colonies *in vitro*. Cell fate mapping experiments *in vivo* indicate that, unexpectedly, CB stem cells are the glia-like sustentacular cells (Pardal *et al*. 2007). CB stem cells can be identified using glial markers such as the glial fibrillary acidic protein. Quite remarkably, the newly formed glomus cells have the same complex chemosensory properties as mature glomus cells in situ. They contain voltage-gated $Ca^{2+}$ and $K^+$ channels, are highly dopaminergic, and secrete neurotransmitters on exposure to acute hypoxia and hypoglycemia. These cells are also producers of glial cell line-derived neurotrophic factor (Pardal *et al*. 2007). Induction of CB growth in sustained hypoxia seems to depend, at least in part, on factors possibly produced by glomus cells and the neighbouring vascular tissue.

These observations suggest that CB glomus cells are polymodal chemoreceptors with an important role in oxygen and glucose homeostasis. They also indicate that the mammalian CB is a neurogenic niche with a recognizable physiological function in adult life. CB stem cells may explain the origin of some tumours in humans (e.g. paragangliomas) and they could also be potentially useful for antiparkinsonian cell therapy.

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SA12

**Matching ventilation to systemic metabolism: a role for peripheral chemoreceptors?**

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Elevations in systemic metabolism brought about by exercise will raise the venous partial pressure of $CO_2$ and decrease venous $Po_2$ and pH. Despite these changes in venous blood composition, steady state arterial blood gas tensions and pH are retained at normal, 'resting' levels by a proportional increase in alveolar ventilation, thus demonstrating the sensitivity and functional importance of the respiratory system to changes in blood chemistry. The means by which metabolic rate is 'sensed' to initiate the appropriate hyperpnoea is, however, not known with certainty and a number of mechanisms have been implicated. These include both neural and humoural mechanisms, implicate both feedforward and feedback mechanisms and even include the possibility that exercise hyperpnoea is a learnt phenomenon. Additionally, a degree of redundancy may occur in the system with each proposed mechanism apparently able to account for most, if not all, of the ventilatory responses observed.

We have raised metabolic rate in anaesthetised rats by means of insulin infusion and have shown that such a manoeuvre can raise ventilation without alteration in arterial blood gas tensions via alteration in carotid body $CO_2$[1,2]. In the absence of carotid bodies, elevations in metabolic rate led to excessively high falls in blood pH. Additional experiments we performed on in vitro carotid body preparations showed that this organ was not sensitive to a fall in glucose concentration and afferent chemodischarge was not elevated, but could even be decreased by severe hypoglycaemia. We subsequently suggested that circulating adrenaline might act to augment rat carotid body sensitivity and other studies have revealed that a number of other hormones may account for the response seen in humans[3]. Elevations in ventilation and $CO_2$ sensitivity may be observed even with the relatively small increase in post-prandial metabolism. However, in contrast, to our findings, there are other reports to show that the rat carotid body has an *in vitro* sensitivity to falls in glucose concentration and it has been suggested that it may act as a peripheral glucosensor[4], although the mechanism for sensing glucose appears to involve carotid body type 1 cell membrane channel activation rather than the inactivation known to occur during hypoxia. The reasons for the discrepancies are not known, but it has been suggested that an interaction between $Po_2$ and glucose may be important[5] or that the particular preparation used can influence the findings.

Whilst evidence to date regarding some role for the carotid body in mediating exercise hyperpnoea appears strong, more studies are warranted to establish precisely how metabolism is sensed so precisely.

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SA13

**ATP-sensitive potassium channels and neonatal diabetes: a treatable channelopathy**

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ATP-sensitive potassium ($K_{ATP}$) channels are metabolic sensors that couple the metabolic state of the cell to the electrical activity of the plasma membrane. They consist of pore-forming Kir6.2 and regulatory sulphonylurea receptor (SUR) subunits. Metabolic regulation of channel activity is mediated by changes

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 $Ca^{2+}$ channels. The resulting $Ca^{2+}$ 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.

Supported by the Wellcome Trust and the Royal Society.

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SA14

**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 architecture, 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, dyslipideamia, 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,