SA7

Metabolic control of pancreatic glucagon and somatostatin secretion

P. Rorsman

University of Oxford, Oxford, UK

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 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 slow 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 glucose-inase inhibitor mannheptulose. 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 B-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.


Supported by the Wellcome Trust and Diabetes UK.

Where applicable, the authors confirm that the experiments described here conform with The Physiological Society ethical requirements.
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 Ca2+ 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 neighboring 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.

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

SA12

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

P. Kumar

Department of Physiology, The Medical School, University of Birmingham, Birmingham, UK

Elevations in systemic metabolism brought about by exercise will raise the venous partial pressure of CO2 and decrease venous PO2 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 humoral 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 CO2 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 humans3. Elevations in ventilation and CO2 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 glucosensor4, 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 PO2 and glucose may be important5 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.


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

SA13

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

F.M. Ashcroft

University of Oxford, Oxford, UK

ATP-sensitive potassium (KATP) 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
mutations produce a severe clinical phenotype, characterized by hyperglycemia and ketosis, and why some mutations are susceptible to sulphonylurea therapy. The resulting Ca^{2+} influx triggers insulin release. The sulpholurea 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, sulpholureas 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 sulpholurea therapy and others are not.

Supported by the Wellcome Trust and the Royal Society.

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

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

F.W. Turek

Center for Sleep and Circadian Biology, Evanston, IL, USA

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 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.

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

Developmental origins of metabolic syndrome

M. Hanson1, P.D. Gluckman2, G. Burdge1, K. Lillycrop1 and K. Godfrey1

1Developmental Origins of Health and Disease Division, University of Southampton, Southampton, UK and 2Liggins Institute, University of Auckland, Auckland, New Zealand

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 phenomena 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,