PERSPECTIVES

The Yin and Yang of the K_{ATP} channel

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Whether you indulge in a few bars of chocolate or run a marathon, the pancreatic islets of Langerhans ensure that the swings in your blood sugar level are not large. Each islet consists of a central core of insulin-secreting β-cells, surrounded by an outer mantle of cells that secrete glucagon (α-cells), somatostatin (δ-cells) or pancreatic polypeptide (PP-cells). A rise in the plasma glucose level stimulates insulin and somatostatin secretion, but inhibits glucagon secretion; these hormonal changes serve to return the blood glucose to its resting level.

The β-cells compose more than 60% of the islet volume, so it is perhaps not surprising that the mechanism by which glucose stimulates insulin secretion is now well established (Ashcroft & Rorsman, 1989). Insulin exocytosis is produced by elevation of intracellular calcium, which results from Ca^{2+} influx through voltage-gated (L-type) Ca^{2+} channels. In the resting β-cell, the membrane is kept at a hyperpolarized level through the activity of ATP-sensitive potassium (K_{ATP}) channels. Glucose uptake and metabolism lead to the closure of the K_{ATP} channels, triggering a membrane depolarization that activates the L-type Ca^{2+} channels and electrical activity. Metabolic regulation of K_{ATP} channel activity is thought to be mediated by changes in the intracellular concentrations of ATP and ADP, which inhibit and activate the channel, respectively.

Much less is known of how glucose stimulates somatostatin secretion and inhibits glucagon release. Two papers by Göpel and colleagues in this issue of *The Journal of Physiology* remedy this lacuna (Göpel *et al.* 2000*a*,*b*). In the first of these, they show that, as in β-cells, glucose-dependent somatostatin release from δ-cells is triggered by closure of K_{ATP} channels, membrane depolarization and initiation of electrical activity (Göpel *et al.* 2000*a*). Their studies involved the use of a novel method that enables patch-clamp measurements of membrane currents from cells within intact islets. This technique is, in itself, a valuable addition to our range of tools for studying islet cells because several studies have shown that chemically dispersed cells do not always exhibit the properties of cells within the intact islet.

As in β- and δ-cells, a rise in intracellular calcium, brought about by Ca^{2+} influx through voltage-gated Ca^{2+} channels, also triggers glucagon secretion from α-cells. The mechanism by which glucose produces inhibition of α-cell electrical activity, $[Ca^{2+}]_i$ influx and glucagon secretion has, however, remained obscure. One particularly puzzling finding is that α-cells also possess K_{ATP} channels (Bokvist *et al.* 1999). Yet if both α- and β-cells possess K_{ATP} channels with similar properties how can they respond to glucose in opposite ways? In a seminal paper in this issue, Göpel and colleagues propose a new model of glucagon release (Göpel *et al.* 2000*b*).

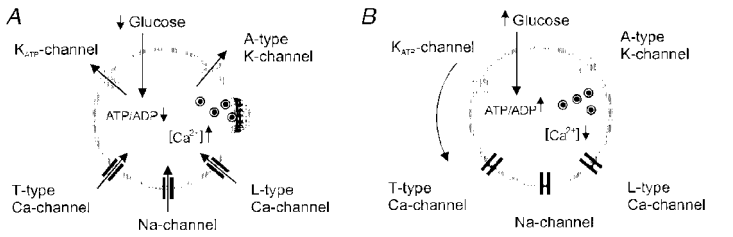

Figure 1

They argue that the α-cell membrane potential is partially depolarized in the absence of glucose, because α-cells contain fewer functional K_{ATP} channels than β-cells. This depolarization leads to activation of voltage-gated Na^+ channels, electrical activity and glucagon secretion (Fig. 1*A*). Göpel *et al.* further speculate that, as in the β-cell, glucose metabolism causes closure of K_{ATP} channels in the α-cell membrane, leading to further depolarization. This leads to the inactivation of three types of voltage-gated channels that support α-cell electrical activity: Na^+ channels, T-type Ca^{2+} channels and A-type K^+ channels. Consequently, K_{ATP} channel closure leads to a depolarization block of electrical activity (Fig. 1*B*). This does not happen in β-cells because electrical activity is not Na^+ dependent (indeed, β-cell Na^+ channels are almost completely inactivated at the resting potential of the cell) and L-type Ca^{2+} channels are sufficient to support electrical activity.

The model Göpel *et al.* propose thus suggests that the K_{ATP} channel in all three types of islet cells serves a similar function – the regulation of electrical activity in response to cell metabolism. It is the very different voltage-gated ion channels that the cells express that produces the opposite effects of glucose on electrical activity and secretion. The model also makes some interesting predictions. Thus, for example, in addition to stimulating insulin release, the sulphonylurea tolbutamide (which blocks K_{ATP} channels) should block glucagon release. Because glucagon secretion is often elevated in diabetes this might constitute part of the therapeutic effect of sulphonylureas. Second, low concentrations of the K_{ATP} channel opener diazoxide, which do not fully depolarize the α-cell, should actually stimulate glucagon secretion because they do not induce depolarization block of voltage-gated currents. Importantly, both of these predictions were confirmed experimentally.

Precisely how metabolism regulates K_{ATP} channels in α-cells remains unclear. Although the glucose uptake transporter differs in α-cells (GLUT1) and β-cells (GLUT2), glucokinase appears to serve as the rate-limiting step for glucose metabolism in both cell types (Heimberg *et al.* 1995). However, because changes in cytosolic ATP and ADP levels are not detected in response to glucose in α-cells, the mechanism of coupling metabolism to K_{ATP} channel activity in α-cells may differ from that of β-cells.

In conclusion, K_{ATP} channel closure produces activation or inhibition of electrical activity in α-cells, depending on the degree of channel inhibition and the resulting magnitude of the depolarization. Why does this not happen in β-cells? One reason may be that the L-type Ca^{2+} channel (unlike the Na^+ channel) does not exhibit voltage-dependent inactivation, but is inactivated by Ca^{2+}. Another is that the β-cell shows a bursting pattern of electrical activity over the physiological glucose range, so that the membrane is not permanently depolarized and recovery from inactivation can occur during the interburst hyperpolarizations.

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