PERSPECTIVES

Gap junctional communication between β- and δ-cells: another player for suppression of glucagon release

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Islets of Langerhans have the characteristic of precisely sensing changes in blood glucose concentration and transferring this signal to adequate secretion of pancreatic hormones. Insulin, which is produced by pancreatic β-cells, is responsible for lowering blood glucose, whereas glucagon, the hormone of pancreatic α-cells, antagonizes most of the effects of insulin. A third hormone, secreted by δ-cells of pancreatic islets, is somatostatin. Besides their endocrine function, insulin, glucagon and somatostatin influence each other by para- and/or autocrine mechanisms. On the level of single cells, the sequences of events leading to exocytosis of insulin or glucagon have been extensively characterized whereas there is less knowledge about mechanisms regulating somatostatin release. Electrical excitability is a key feature of all three cell types (Drews *et al.* 2010). Glucose stimulation of β-cells induces electrical activity and the intensity of membrane depolarization strictly depends on the concentration of the nutrient stimulus. With respect to glucagon the predominant role of this hormone is to counteract situations of hypoglycaemia. Consequently, rising concentrations of blood glucose and hyperglycaemia are accompanied by suppression of glucagon secretion. This feedback is disturbed in patients suffering from diabetes mellitus type 2. An excess of glucagon together with insufficient insulin secretion and insulin resistance are the basis of the imbalance between glucose-lowering and glucose-elevating mechanisms.

Glucose, as well as stimulating β-cells, changes the activity of α-cells. Induction of electrical activity and subsequent Ca^{2+} influx are features shared by α- and β-cells with regard to initiation of hormone release. But although both cell types are equipped with ATP-dependent K^+ channels, which are closed by increased substrate metabolism, the net effect in response to elevated plasma glucose concentration is contrarious. This indicates a completely different function of these channels in α-cells with respect to their regulatory role for glucose dependence of exocytosis (Zhang *et al.* 2013; Gylfe, 2016). Besides intrinsic factors, paracrine mediators (e.g. somatostatin, γ-aminobutyric acid, insulin and Zn^{2+}) have been suggested to contribute to the regulation of α-cells. Currently, the impact of these different pathways and whether they act in parallel or are arranged in a hierarchy remain to be elucidated.

The best method to investigate paracrine pathways in the complex network of α-, β- and δ-cells is to monitor cellular activity within their natural environment, i.e. in the intact islet. This is very difficult and requires reliable activation and monitoring of one single cell type in this mini-organ. In a study published in this issue of *The Journal of Physiology*, Briant and colleagues (2018) use an elegant and sophisticated approach addressing this challenge by optogenetics. This technique takes advantage of light-activated proteins, channelrhodopsins, allowing cells to be 'switched on and off' not by their physiological regulators but just by light (Nagel *et al.* 2003). Optogenetic methods have turned out to be a valuable tool for investigation and manipulation of neuronal circuits. This approach is now successfully used to investigate electrical coupling in islets of Langerhans. β-Cell-specific expression of channelrhodopsin-2 enabled exclusive light-induced membrane depolarization of the insulin-producing cells. Concomitant recording of δ- and α-cells localized in the same islet revealed rapid induction of action potentials in δ-cells within a few milliseconds, whereas α-cells were hyperpolarized with a clear delay of ∼10 s. Based on the fast transfer of the signal, the authors hypothesize β- to δ-cell communication via gap junctions, which has already been demonstrated for β- to β-cell coupling. This assumption was supported by detection of Ca^{2+} waves quickly spreading from one single light-activated β-cell to the neighbouring δ-cells and by a glucose-induced inward current in patch-clamped δ-cells, which was sensitive to the connexin and pannexin blocker carbenoxolone. But how is this signal transferred to α-cells? The missing link is provided by somatostatin. Applying a light-pulse to activate β-cells only hyperpolarized α-cells if somatostatin receptor subtype 2 (SSTR2) was functional. When SSTR2 was blocked pharmacologically, action potential firing of the α-cells continued. The data presented in the study of Briant *et al.* add this novel pathway, triggered by β-cell-dependent activation of somatostatin secretion via gap junctions, to the known regulatory mechanisms determining glucagon release.

Do these results obtained with mouse islets play a role for human islets? At present, this is not known. Seeking relevance in humans, Briant *et al.* combined their physiological studies with mathematical modelling. Based on morphological datasets illustrating spatial distribution of α-, β- and δ-cells generated from a few islets of a human donor (Hoang *et al.* 2014), the authors developed a computational model of electrical activity for each of these islets. Simulations testing the effect of glucose in this model showed that varying the degree of gap junctional conductance was indeed sufficient to suppress glucagon release. In good agreement with the experimental data, approximately one-fifth of glucose-induced suppression of glucagon release might be mediated by the newly described gap junction-dependent pathway in humans. Taken together, exclusive targeting of β-cells in their natural environment by optogenetic manipulation was successfully consolidated with mathematical modelling.

Certainly, every approach has its limitations. Confidence in computational models of biological systems must be provided by experimental data that either support or refute the findings. For example, the optogenetic approach could be repeated in human islets with lentiviral expression of channelrhodopsin-2 in β-cells, as was recently described for human brain slices (Andersson *et al.* 2016). Changes in islet architecture and thus also in gap junctional connections may contribute to islet dysfunction observed during progression of diabetes mellitus type 2. Future studies will reveal whether impaired

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β- to δ-cell communication is a key player for loss of adequate suppression of the pancreatic α-cell in these patients.

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Additional information

Competing interests

None declared.