

Regulating Glucagon Secretion: Somatostatin in the Spotlight

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The regulation of islet hormone secretion in vivo is likely to involve a complex interplay between circulating nutrients, hormones, and neurotransmitters (1). A new study by Hauge-Evans et al. (2) in this issue provides interesting new insights into the contribution of an intraislet paracrine role for somatostatin in the control of insulin, and more especially glucagon, release.

Glucagon is the principal counterregulatory hormone that opposes the anabolic effects of insulin, notably on the liver (3), and a relative excess of glucagon is a hallmark of all forms of diabetes. However, failure to secrete adequate quantities of glucagon in response to insulin-induced hypoglycemia characterizes longstanding type 1 diabetes (4) and is an important contributor to mortality in this disease, accounting for 2–4% of all deaths (5).

Glucagon is stored alongside insulin in the islet, albeit in a discrete cellular compartment, the pancreatic α -cell. Just as the metabolic actions of glucagon oppose those of insulin, the regulators of insulin's release (1) tend to exert opposing effects on glucagon secretion (6). Thus, elevated concentrations of glucose suppress glucagon release, while catecholamines stimulate the secretion of this hormone. Acting independently of these mechanisms, neuronal inputs into the islet exert a further important level of control over glucagon release (7).

Despite being a subject under investigation for more than 35 years (6), just how the effects of glucose are achieved at the level of individual α -cells is still disputed and has become an area of vigorous research in recent times (Figure 1). As yet, however, a consensus has not been reached. Several laboratories (e.g., 8), including the author's (9), have concluded that glucose acts directly on isolated mouse α -cells to suppress oscillations in intracellular free Ca^{2+} concentration in the absence of paracrine influences from β -cells (the latter parameter is usually taken in these excitable cells as an adequate surrogate for electrical and secretory activity). The Ca^{2+} changes were associated with increases in intracellular free ATP concentration (9), which might be "decoded" via 1) the partial closure of ATP-sensitive K^+ channels (K_{ATP}), resulting in the inactivation of N-type Ca^{2+} and voltage-gated Na^+ channels, suppression of electrical activity, and Ca^{2+} influx through L-type Ca^{2+} channels (1,10); 2) through the

activation of Ca^{2+} uptake by the endoplasmic reticulum, the consequent inactivation of a store-operated current that results in plasma membrane hyperpolarization, and decreased Ca^{2+} influx through voltage-gated Ca^{2+} channels (11); and 3) through changes in the activity of nutrient-regulated protein kinases including AMP kinase (12).

An alternative model has become known as the "intraislet" or "switch off" hypothesis. Informed by the strikingly "anti-parallel" regulation of insulin and glucagon secretion, this posits that factors released from the β -cell as glucose levels rise, including insulin itself (13) and cosecreted species such as γ -aminobutyric acid (GABA) (14–16) and Zn^{2+} ions (1,17,18), suppress the release of glucagon in a paracrine manner. This idea is supported by the fact that the intraislet circulation appears to be from β - to α -cell (19) and by the clinical observation that treatment of type 1 diabetic subjects with insulin usually lowers glucagon levels. Finally, purified rat α -cells have been reported to respond to elevated glucose concentrations with enhanced glucagon secretion (20) (though the impact of the fluorescence-activated cell sorting on the functional integrity of these preparations is uncertain). However, the "switch off" hypothesis has been challenged (8,9) on the grounds that the concentrations of glucose that almost fully inhibit glucagon release from isolated rodent (8) and human islets (3–4 mmol/l) are significantly below those that elicit detectable depolarization of the β -cell or the release of insulin and costored regulators (5.5–6 mmol/l). The existence of highly local "microdomains" of the regulators in the interstitial space between local β - and α -cells must therefore be invoked to sustain this hypothesis.

The release of an inhibitor of glucagon release over a range of glucose concentrations that more closely match that which regulates glucagon secretion would potentially provide a more attractive means of controlling α -cell activity. Enter somatostatin. Stored in pancreatic δ -cells, release of somatostatin is controlled similarly to that of insulin, but with the crucial difference that the secretion of somatostatin is already substantially stimulated by glucose concentrations as low as 3 mmol/l (half-maximal effects are observed at \sim 6 mmol/l) (8). Existing evidence that somatostatin may be involved in controlling the release of glucagon in response to changes in glucose concentration is mixed. Supporting this view, exogenously added somatostatin potently inhibits glucagon release from the pancreas (21), while anti-somatostatin antibodies activate glucagon release from isolated islets (22). However, studies with the isolated perfused pancreas have argued both for (23) and against (24) a role for locally acting somatostatin on glucagon release. Finally, the selective somatostatin receptor type 2 (SSTR2) antagonist DC-41-33 only weakly enhanced glucagon secretion from the perfused rat

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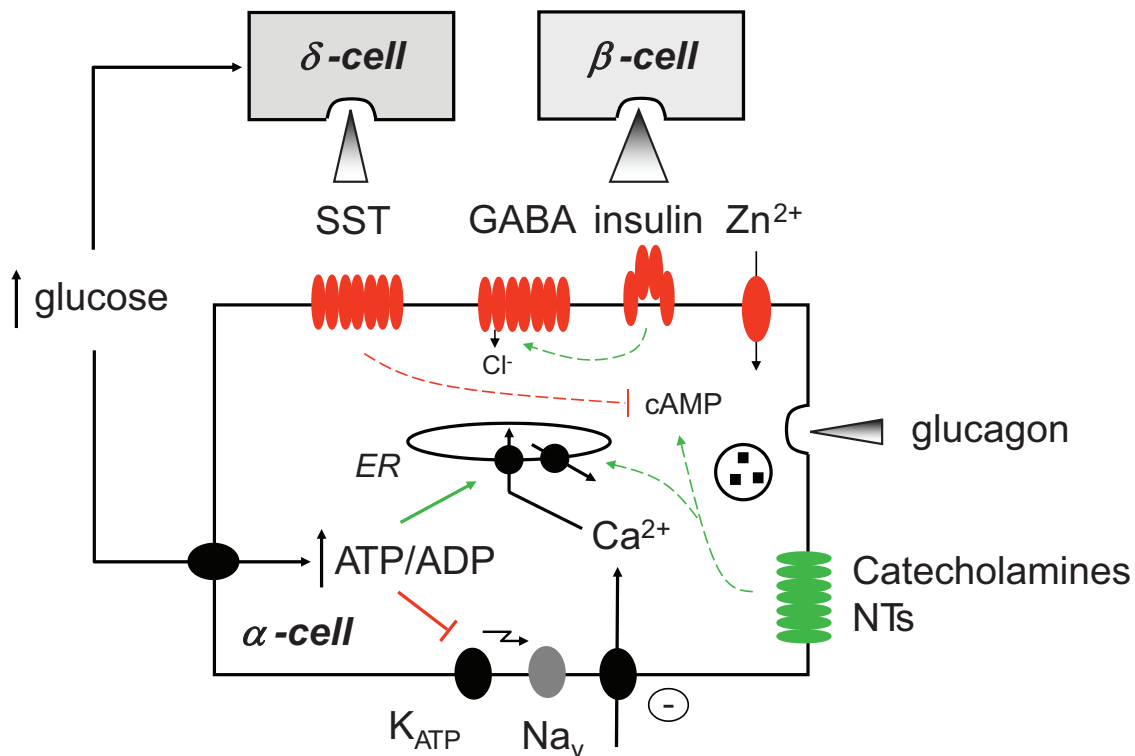


FIG. 1. Multiple mechanisms of control of glucagon secretion. For details, see the text. ER, endoplasmic reticulum; Na_v , Ca_v , voltage-gated Na^+ and Ca^{2+} channels, respectively; NTs, neurotransmitters.

pancreas in the presence of 3.3 mmol/l glucose while strongly potentiating the response to arginine (25).

The important new study by Hauge-Evans et al. (2) provides a key step forward by exploring the effects on glucagon and insulin release of the deletion, through homologous recombination, of the somatostatin gene in mice. $\text{SST}^{-/-}$ mice have previously been described to show a relatively modest phenotype including changes in the release of pituitary hormones (26). The new study shows first that arginine-induced release of insulin and glucagon is markedly stimulated *in vivo* when somatostatin is absent. Moreover, in islets isolated from $\text{SST}^{-/-}$ mice, the normal inhibition of glucagon release by glucose was eliminated, while the stimulation of insulin release by the sugar was enhanced. On the other hand, the rapid inhibition of insulin secretion upon glucose lowering was unaltered in $\text{SST}^{-/-}$ mice, questioning a role for somatostatin in this process.

These studies thus further emphasize the contribution of somatostatin as a tonic inhibitor of glucagon release during stimulation by low glucose concentrations or after challenge with arginine. The work also provides a powerful adjunct to earlier studies using pharmacological approaches, as well as those using $\text{SSTR2}^{-/-}$ mice (27). However, there remain uncertainties: SST was deleted unconditionally throughout the body in the present studies, providing the possibility for an indirect developmental effect on the regulation of glucagon secretion by other mechanisms (Figure 1); microarray profiling of islets from $\text{SST}^{-/-}$ mice may be informative to explore whether other changes occur in the expression of key genes in either β - or α -cells to limit the ability of glucose to control glucagon release normally.

The studies raise several important new questions: 1) Is the whole panoply of putative regulatory mechanisms (Figure 1) really important *in vivo*, and if so, under what

conditions? 2) Do they same mechanisms play a role(s) in humans as well as rodents? 3) Given the effects of somatostatin deletion to enhance insulin and glucagon secretion, respectively, might somatostatin receptor antagonists prove useful to treat hyperglycemia in type 2 diabetes and hypoglycemia in type 1 diabetes? Imaginative new approaches seem likely to be needed to address these points: studies of $\text{SST}^{-/-}$ mice under hypoglycemic clamp may be particularly informative to confirm or refute the importance of a decrease in somatostatin release to the activation of glucagon secretion *in vivo*. Additionally, a more detailed molecular exploration of other proposed mechanisms, for example, by α -cell-specific deletion of insulin or GABA receptors, or the islet-specific Zn^{2+} transporter, ZnT8 (28), in mice is also needed.

Although understanding of the regulation of glucagon release still remains incomplete, the new insights about the importance of somatostatin provided by Hauge-Evans et al. (2) may allow the more rational design and use of drugs to modulate glucagon (and insulin) release in all forms of diabetes.

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