

## CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor***Type 2 Diabetes, SGLT2 Inhibitors, and Glucose Secretion**

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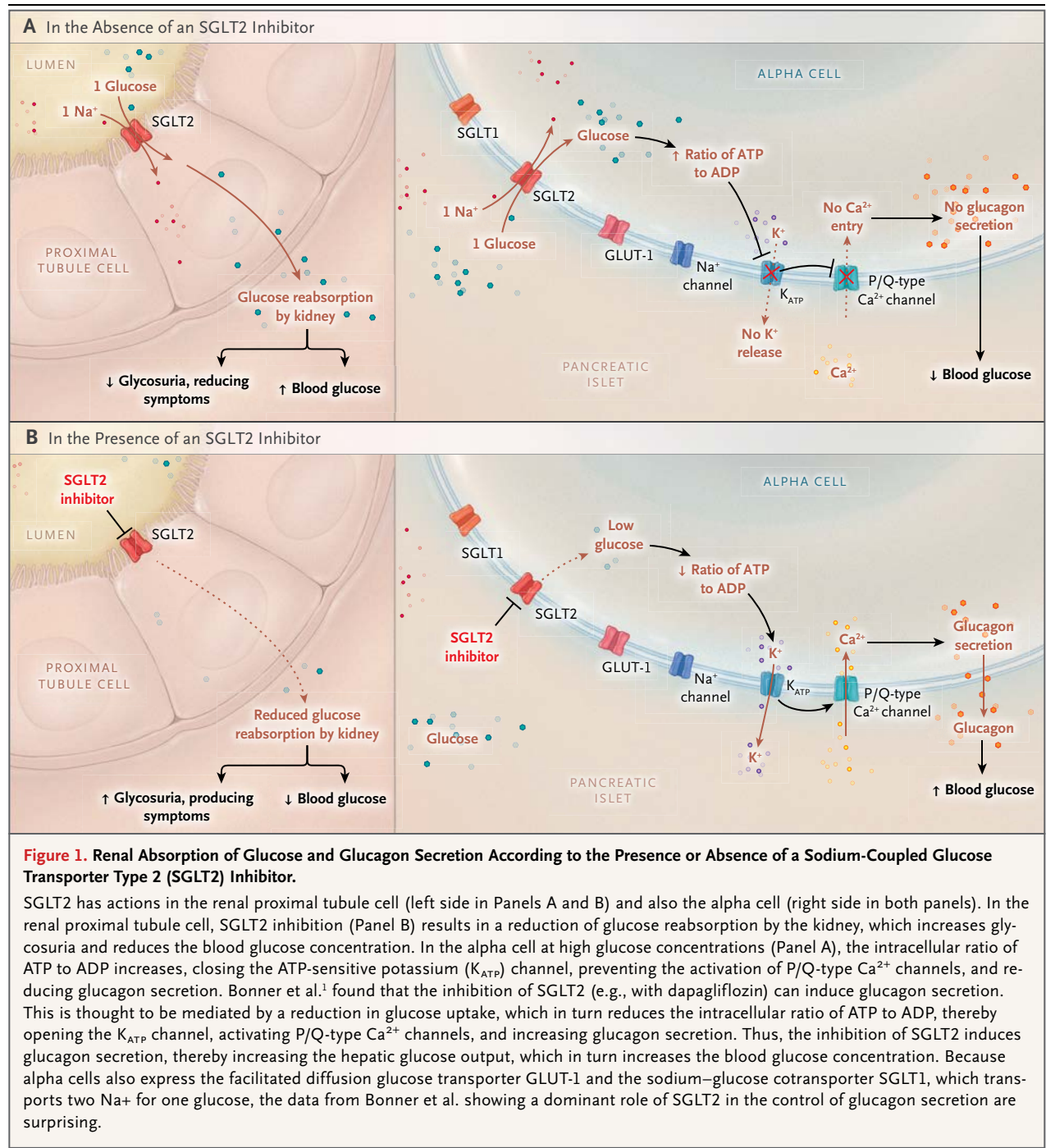
Type 2 diabetes is a major health problem in the 21st century, with increasing rates of obesity both driving up the number of patients affected and reducing the age at diagnosis. Drugs that lower the blood glucose level in patients with type 2 diabetes reduce symptoms and the risk of long-term complications. The progressive nature of the hyperglycemia and the failure of drugs to alter the rate of this progression mean that, with time, increasing numbers of agents are usually required to maintain glycemic control. Recently, a plethora of glucose-lowering agents have become available. These drugs have different mechanisms, and for each there exists a balance between their desired effect — lowering the blood glucose level — and their undesired side effects.

One recently approved class of glucose-lowering drugs inhibits the low-affinity (high  $K_M$ ), sodium-coupled glucose transporter type 2 (SGLT2) in the renal proximal tubule and hence reduces the renal reabsorption of filtered glucose, resulting in substantial glycosuria. The loss of glucose in the urine both lowers the blood glucose level and results in weight loss owing to caloric loss. The major side effects reflect increased glycosuria, with increased incidence of genitourinary infections (especially candida infection) and polyuria and an increased risk of dehydration. A recent study by Bonner and colleagues<sup>1</sup> suggests that SGLT2 inhibitors also increase the secretion of glucagon by means of a direct effect on the alpha cell.

Glucagon is a peptide hormone, produced by alpha cells of the pancreatic islet, that raises the blood glucose level and opposes the glucose-lowering action of insulin, which is secreted by the neighboring beta cells. Glucagon secretion is induced by hypoglycemia to stimulate hepatic glucose production and restore normoglycemia. In persons with type 2 diabetes, fasting glucagon secretion is abnormally increased, leading to elevated hepatic glucose production and contributing to fasting hyperglycemia.

The control of glucagon secretion is complex and still incompletely understood. It involves alpha-cell glucose-signaling mechanisms, islet paracrine regulation by insulin, and autonomic nervous control.<sup>2</sup> Alpha-cell glucose sensing depends on glucose uptake and metabolism, changes in the ratio of intracellular ATP to ADP, and the control of the activity of the sulfonylurea-sensitive ATP-sensitive potassium ( $K_{ATP}$ ) channel. In the presence of low levels of glucose, the activity of the  $K_{ATP}$  channel is low, which allows  $Ca^{2+}$  entry through P/Q-type channels, resulting in glucagon secretion. At high glucose concentrations, the activity of the  $K_{ATP}$  channel is fully suppressed, preventing the activation of P/Q-type  $Ca^{2+}$  channels and thereby reducing glucagon secretion. Glucose uptake by alpha cells is therefore the first and critical step in glucose signaling and, until the report by Bonner and colleagues, was thought to be solely controlled by the glucose transporter GLUT-1 (Fig. 1).<sup>3</sup>

Bonner et al. also found that alpha cells express the sodium-glucose cotransporters SGLT1 and SGLT2, and they propose that the inhibition of SGLT2 results in increased secretion of glucagon. Their study results are supported by the observations that the treatment of patients with type 2 diabetes with SGLT2 inhibitors unexpectedly increases hepatic glucose production and plasma glucagon levels.<sup>4,5</sup> Bonner et al. found that the SGLT2 inhibitor dapagliflozin can indeed induce glucagon secretion by isolated human and mouse islets and that when dapagliflozin was administered to mice, their plasma glucagon levels rapidly increased. Thus, the inhibition of SGLT2 induces glucagon secretion. They further found that SGLT2 expression is reduced and



glucagon expression increased in the islet in patients with type 2 diabetes and in islets from persons without diabetes who had exposure to chronic hyperglycemia.

The article by Bonner et al. raises as many questions as it answers, and it emphasizes how poorly we understand the regulation of glucagon

secretion in the alpha cell. In addition to SGLT2, alpha cells also express the alternative glucose transporters GLUT-1 and SGLT1, which should allow glucose transport when SGLT2 is inhibited. Why would a cotransport system that concentrates glucose be used to control glucagon secretion, which is important in the response to

hypoglycemia, when the concentrating action of these transporters may lead to intracellular glucose concentrations that do not reflect the extracellular ones?

What does this mean for the clinician considering an SGLT2 inhibitor to treat a patient with type 2 diabetes? The increased glucagon secretion that results from SGLT2 acting as an  $\alpha$ -cell secretagogue will mean that the glucose level will fall less than would be anticipated given the degree of urinary glucose loss.<sup>4,5</sup> This reduced fall in the blood glucose level for the degree of glycosuria matters because it is glycosuria that results in most of the symptoms of diabetes — polyuria, polydipsia, weight loss, and genitourinary infection. So, with SGLT2 inhibitors, a reduction in a patient's glucose level needs to be balanced against the increase in severity of their diabetes-related symptoms, whereas with other agents the reduction in the patient's glucose level is associated with a reduction in the severity of their diabetes-related symptoms.

Can other therapy counteract the increased glucagon secretion? The hypoglycemic effect of sulfonylureas and glucagon-like peptide 1 (GLP-1)–receptor agonists depends in part on their ability to reduce glucagon secretion. Interestingly, dapagliflozin-induced glucagon secretion can be suppressed by low levels of tolbutamide, which further supports the hypothesis that each of these

drugs counters the effect of the other with regard to glucagon secretion, at different steps of the glucose-signaling pathway (which regulates glucagon secretion). Coprescribing of low-dose sulfonylureas with GLP-1–receptor agonists in order to prevent the rise in glucagon secretion could result in a marked reduction in glycemia but at the risk of increased hypoglycemia. This therapeutic option needs direct investigation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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1. Bonner C, Kerr-Conte J, Gmyr V, et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic  $\alpha$  cells triggers glucagon secretion. *Nat Med* 2015;21:512-7.
2. Campbell JE, Drucker DJ. Islet  $\alpha$  cells and glucagon — critical regulators of energy homeostasis. *Nat Rev Endocrinol* 2015; 11:329-38.
3. Heimberg H, De Vos A, Pipeleers D, Thorens B, Schuit F. Differences in glucose transporter gene expression between rat pancreatic  $\alpha$ - and  $\beta$ -cells are correlated to differences in glucose transport but not in glucose utilization. *J Biol Chem* 1995;270:8971-5.
4. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest* 2014;124:509-14.
5. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest* 2014;124:499-508.

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