The Brains Behind SGLT2 Inhibition

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Diabetes Care 2022;45:273–275 | https://doi.org/10.2337/dci21-0050

Control of the central nervous regulation of eating behavior and further body functions by administration of drugs is a long-lasting dream in clinical research (1). In their study, Kullmann et al. (2) investigated whether the beneficial effects of empagliflozin from the new class of sodium–glucose transport protein 2 (SGLT2) inhibitors may in part be mediated by central nervous action. Drugs of the SGLT2 class recently yielded an unprecedented series of clinical trial results, which very quickly led to changes of guidelines in diabetology and cardiology. However, mechanisms of how these drugs work are not yet fully understood, and even initially believed concepts are now in doubt (3). This makes it even more important to gain further insight into SGLT2 action in the human body, especially exploring new mechanistic pathways not yet considered. In their study, the authors hypothesized that the SGLT2 inhibitor molecule would help restore insulin action in the brain (Table 1) and consequently induce favorable effects in the periphery. This is an intriguing assumption, as the focus of most studies investigating SGLT2 inhibitor action so far has been the renal effects, with the drug class's main property being reducing the body's glucose and fluid load (5).

The investigation of insulin action in the brain by intranasal application has been a fascinating field of research for the last two decades (6,7). By intranasal application, intracerebral insulin concentrations increase without the necessity of intravenous, i.e., systemic application. This gives the unique opportunity to study central nervous insulin effects without the undesirable experimental interferences of low blood glucose, which would disrupt any experiment assessing brain function. Intranasal application is possible because certain peptide hormones supposedly can bypass the blood-brain barrier through extracellular/paracellular olfactory and trigeminal pathways. This transports the molecules from the nasal mucosa to the subarachnoid space. From there, molecules are carried via perivascular channels to their central nervous target sites (8), probably preferably to brain areas near the administration site (9). Using this technique with insulin, a distinct assessment of the peptide's effects in the brain is possible.

In this study, patients with BMI 25–40 kg/m^2 and prediabetes were treated with the SGLT2 inhibitor empagliflozin or placebo for 8 weeks; group sizes were 19 and 21 patients. Functional MRI (fMRI) was performed without a task (i.e., in resting state) twice on each study day, once without and once with prior intranasal insulin administration. In addition to neuroimaging, thorough metabolic assessments were made for insulin secretion and sensitivity, intrahepatic fat content, resting energy expenditure by indirect calorimetry, and subjective feelings of hunger by visual analog scales, and further metabolic parameters were measured. All assessments were performed before and after the 8 weeks of drug treatment.

In patients with empagliflozin treatment, intranasal insulin administration decreased cerebral blood flow in the hypothalamic region. Before treatment in both groups, and after treatment in the placebo group, this effect could not be found. Metabolic assessments also showed treatment effects: liver fat content decreased slightly in the verum group, which was significantly different from the slight increase found in the placebo group. Furthermore, empagliflozin treatment reduced fasting blood glucose but not glucose after an oral glucose tolerance test, hemoglobin A_{1c}, or whole-body insulin sensitivity. Additionally, patients treated with empagliflozin reported decreased hunger feelings after 8 weeks of treatment. Eating behavior, energy expenditure, and body weight did not change through treatment.

The authors concluded that 8 weeks of empagliflozin intake restored hypothalamic insulin sensitivity. They stated that signals from the hypothalamus to the liver potentially lead to reduction of fat content. In their proposed model, a centrally controlled reduction in gluconeogenesis might have been responsible for the reduced fasting blood glucose concentrations (Fig. 1).

With their very well-designed study, Kullmann et al. (2) were able to investigate a potential difference in insulin action on the hypothalamus between 8 weeks of empagliflozin versus placebo in participants with overweight and obesity with impaired glucose control. The authors chose an appropriate

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Table 1—Most important suggested effects mediated by intracerebral insulin action

Central nervous effect of insulin	Direction of effect
Hippocampal memory processes	↑
Gluconeogenesis liver	↓
Pancreatic insulin secretion	↑
Peripheral insulin sensitivity	↑
Hunger	↓
Body weight	↓

Data as reviewed by Kullman et al. (4).

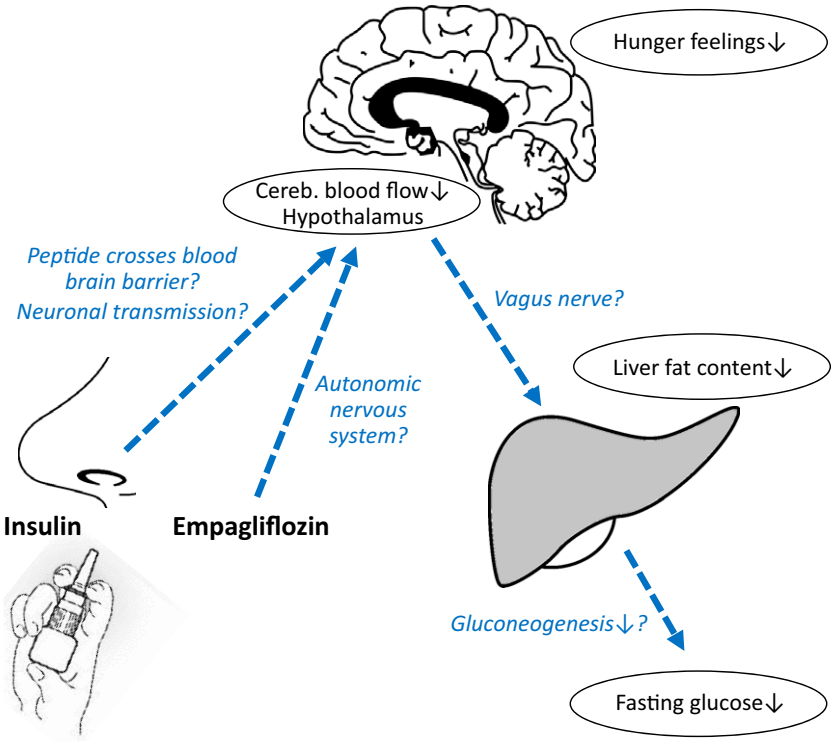

Figure 1—Hypothesized central nervous effects of intranasal insulin on patients with overweight or obesity and prediabetes after 8 weeks of empagliflozin treatment. Major findings of the study are circled; hypothesized mechanisms leading to observed results are in blue. Cereb., cerebral.

population, as in patients with prediabetes primary pathologies of diabetes, like insulin resistance, already exist, but assessments are not yet obscured by the detrimental alterations seen with chronic diabetes. Using this design, Kullmann et al. (2) report, for the first time, effects in the central nervous system after 8 weeks of SGLT2 inhibitor treatment compared with placebo in humans.

The authors readily concede that the proposed explanatory model is not sufficiently supported by data to draw conclusions related to causality. In general, fMRI is a scientific method susceptible to false-positive results (10). Nevertheless, it is still the best possibility we have to investigate acute changes in deep brain areas in humans. In their study, the authors link acute changes of hypothalamic blood flow after a single intranasal insulin application with body changes over 8 weeks of drug treatment. An event-related design with a correlation of acute fMRI findings with acute behavioral data, e.g., by further investigating the observed reduction in hunger feelings, would have helped to strengthen the results. Additionally, a lean control group with intact glucose tolerance would have been useful to demonstrate that observed changes are "towards normal."

Despite reduced hunger, no changes in body weight were seen, but these cannot really be expected after 8 weeks. In larger studies, weight loss during SGLT2 inhibitor treatment also is very moderate. Weight loss under treatment with SGLT2 inhibitors is most prominent in the first weeks of treatment, and in a recent meta-analysis, mean weight reduction was 1.9 kg over 6 months (11). Weight-reducing effects of SGLT2 inhibitors seem to near a plateau after 1 year of treatment (12). Body fat loss is usually primarily attributed to lipolysis with associated ketogenesis. It has been suggested that this weight loss can even be attenuated by a compensatory hyperphagia possibly induced by urinary glucose excretion (13). Suppression of hunger through hypothalamic circuits, as known from other antidiabetes drugs like the glucagon-like peptide 1 analogs (14), is not known for SGLT2 inhibitors. Further insights into mechanisms of the hypothalamic contribution to these changes in body weight known from larger and longer studies are clearly needed.

Another key finding of the study was the reduction in liver fat content compared with placebo, which was previously reported for SGLT2 inhibitor therapy in patients with type 2 diabetes and nonalcoholic fatty liver disease. Improvement of insulin resistance, decreased inflammation and oxidative stress, increased fatty acid oxidation, and effects of glucagon or ketones have been discussed as possible mechanisms (15). Several of these pathways were assessed in the study by Kullmann et al. (2), but no clear hint of any such mechanism could be identified.

Despite these exciting novel findings, further studies are needed to uncover mechanisms by which SGLT2 inhibitors act on the brain and how they improve insulin sensitivity of the hypothalamus. This would be a large step toward understanding more about a fascinating new drug class, which will increasingly shape therapy in both diabetology and cardiology in future years.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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