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**Commentary**

# Spotlight on the Human Brain: Central Actions of SGLT2 Inhibitors?

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**Abbreviations:** GLP-1RA, GLP-1 receptor agonist; SGLT2i, SGLT2 inhibitor.

SGLT2 inhibitors (SGLT2is) have been developed to lower blood glucose. They were subsequently found to be beneficial in other conditions that lead to the recent implementation in respective guidelines outside of diabetes (eg, heart failure). This drug class was initially thought to act exclusively in the kidneys, where it promotes urinary glucose loss. However, more recently, pleiotropic mechanisms were suspected to underlie their clinical benefits (1).

Despite continuous urinary energy loss in patients taking SGLT2is, their body weight stabilizes after a few weeks of initial weight loss (1). The other class of antidiabetic drugs with profound weight-lowering properties, GLP-1 receptor agonists (GLP-1RAs), induce an even stronger initial weight reduction also followed by a weight plateau (2). Of note, SGLT2is and GLP-1RAs seem to show opposing effects on appetite, at least acutely (3).

The maintenance of body weight is primarily regulated by the brain. Hence, SGLT2is and GLP-1RAs might act in the central nervous system to contribute to their weight-lowering mechanisms.

This possibility was recently addressed in an excellent and highly controlled investigator-initiated trial by van Ruiten and colleagues (3). In patients with obesity and type 2 diabetes, they compared the SGLT2i dapagliflozin, the GLP-1RA exenatide, their combination, and placebo. In this randomized, placebo-controlled trial, the neural response to food cues was assessed by functional magnetic resonance imaging in reward and satiety areas of the brain. Although this approach cannot fully uncover all aspects of appetite and eating behavior, it is used in a variety of high-class research projects and results have shown to be predictive for further weight course. After 10 days, dapagliflozin increased food responsivity in the putamen, whereas exenatide showed opposite effects. However, after 16 weeks, this effect was no longer detectable, but at least the combination therapy decreased food response in the amygdala. Both the putamen and amygdala are important reward-processing areas that show exaggerated activation in response to food cues in persons with obesity (4). Activation in these areas is predictive for the success of weight loss programs (4); thus, drug effects in these regions likely contribute to further weight course.

Nevertheless, effects of SGLT2is and GLP-1RAs on body weight regulation in the brain appear to be dynamic and involve a complex interplay of different reward-related brain areas. Although SGLT2 inhibition might even stimulate appetite acutely, the later synergistic effects of both substances detected by van Ruiten and colleagues (3) could support weight maintenance. Clearly, more clinical and mechanistic research is needed to disentangle underlying major regulatory pathways.

Central nervous effects of GLP-1RAs have been investigated quite extensively (for review see eg, Drucker (2)). However, the current study of van Ruiten et al (3) is among the first to demonstrate effects of SGLT2is and combined effects with GLP1-RAs in the human brain.

There are different possible mechanisms how SGLT2is could influence brain functions (5). These drugs appear to be transported across the blood–brain barrier into brain parenchyma. Of note, *SGLT2* is not exclusively expressed in the kidney but is also present in brain areas crucial for body weight, whole-body glucose homeostasis, and cognition (5), where these drugs could act directly. Furthermore, SGLT2is were found to also inhibit acetylcholinesterase (5), a major enzyme for neurotransmitter degradation in the synaptic cleft. However, dapagliflozin, which was studied by van Ruiten and

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colleagues (3), is less potent in this regard than some other SGLT2i inhibitors (5).

Besides the central nervous system, acetylcholinesterase is also crucial for the parasympathetic branch of the autonomic nervous system. SGLT2is were found to shift the autonomic tone from the sympathetic toward the parasympathetic branch (1). Although the brain communicates via the autonomic nervous system to the periphery, this system is also a major projection back to the brain. It is possible that SGLT2 inhibition in peripheral organs like the kidneys underlie effects on autonomic tone and thereby signal to the brain via autonomic afferences.

A third possibility is that glucose-lowering or other metabolic changes in response to drug treatment (1) are sensed by brain cells that respond with altered activity.

Potential brain effects of SGLT2is and GLP-1RAs recently gained interest also in neurological research (2, 5) because patients with diabetes are at increased risk for neurodegenerative diseases (6). Shared pathomechanisms likely contribute to this coincidence, including insulin resistance in periphery and brain (6). Given the close connection between diabetes and neurodegeneration, antidiabetic drugs are under extensive discussion in this regard (5, 6). Indeed, retrospective analyses of register data suggest differences in dementia risk between classes of antidiabetic medication (7). In these epidemiological studies, patients treated with SGLT2is or GLP-1RAs had the lowest risk to develop dementia (5, 7).

Potential underlying mechanisms for neuroprotective and appetite-regulating effects of SGLT2i and GLP-1RA are under intense investigation by a number of research groups. Exiting findings include an SGLT2i's ability to stimulate secretion of neurotrophic factors, revert mitochondrial dysfunction, and ameliorate neuroinflammation (5). Potential beneficial effects of SGLT2is include improved brain insulin resistance, which was linked, in obese rats, to improved cognition (5).

We recently translated this finding into a clinical setting and detected reversed insulin resistance in the hypothalamus upon treatment with the SGLT2i empagliflozin (8). In this randomized controlled trial, restored insulin action in the brain mediated improvement in fasting glucose and liver fat content in persons with obesity and prediabetes (8). Thus, brain effects of SGLT2i might not only help to prevent or eventually treat neurocognitive decline but could contribute to the beneficial metabolic effects of this substance class.

The study by van Ruiten and colleagues (3) and further accumulating results (5, 8) position SGLT2is as a promising pharmacological approach, which may improve brain functions related to metabolism and appetite control in patients with obesity and diabetes. The full potential of this substance class in the prevention or treatment of diabetes-associated brain diseases beyond current indications will hopefully become clear in the coming years.

## Disclosure Statement

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## Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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