Letter

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Altered Metabolic Phenotypes and Hypothalamic Neuronal Activity Triggered by Sodium-Glucose Cotransporter 2 Inhibition (*Diabetes Metab J* 2023;47:784-95)

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Sodium-glucose cotransporter-2 (SGLT2) inhibitors play a crucial role in cardiovascular, kidney, and metabolic health. Originally developed as antidiabetic medications, these drugs are now recognized for their ability to prevent kidney failure and exhibit cardioprotective effects, particularly in reducing heart failure-related hospitalizations and cardiovascular mortality [1]. SGLT2 inhibitors exhibit cardiovascular and kidney protection through various physiological mechanisms, including a negative caloric balance that reduces total body fat mass and body weight [2]. However, SGLT2 inhibitors result in less weight loss than initially expected [3]. This could be attributed to alterations induced by SGLT2 inhibitors in central reward and satiety circuits, leading to an increase in appetite and food intake [4,5]. However, there is much to be elucidated regarding the more specific mechanisms or pathways underlying this phenomenon.

In this study, Lee et al. [6] investigated the involvement of the hypothalamic circuit in the development of compensatory metabolic phenotypes triggered by treatment with SGLT2 inhibitors. To accomplish this, the authors assessed the metabolic phenotypes of mice treated with dapagliflozin, an SGLT2 inhibitor, using indirect calorimetry and feeding monitor systems. Additionally, they examined patterns of neuronal activity in various hypothalamic nuclei responsible for regulating appetite and energy expenditure. They also explored the projection of agouti-related peptide neurons into the paraventricular nucleus of the hypothalamus. Through these investigations, they demonstrated the role of the hypothalamus in the compensatory behavioral outcomes observed during prolonged treatment with SGLT2 inhibitors.

Despite the intriguing findings, there are several aspects related to this study that warrant further discussion. First, the metabolic characteristics of mice, especially those subjected to a high-fat diet, were not clearly delineated. While the authors provided information about changes in body weight, caloric intake, and energy expenditure, important details regarding parameters, such as glycemic status and insulin resistance, were notably absent in the paper. Medications affecting the central nervous system (CNS), like glucagon-like peptide-1 (GLP-1) receptor agonists, can produce diverse effects on different brain regions, contingent upon the metabolic state and specific conditions of drug administration. This consideration becomes particularly pertinent in the context of metabolic traits such as obesity or type 2 diabetes mellitus [7]. In a randomized, double-blind, placebo-controlled, phase 2 trial involving individuals with a body mass index of 25 to 40 kg/m^2 and prediabetes, 8 weeks of empagliflozin treatment restored hypothalamic insulin sensitivity in humans. Additionally, despite a significant decrease in hunger, no changes in body weight were observed. These effects were demonstrated through resting-state functional magnetic resonance imaging (MRI) and intranasal insulin administration [8]. Overall, these findings align with the results of the current study. However, given the consideration of

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interspecies differences in drug response, it is crucial to gather more comprehensive information on metabolic characteristics to accurately interpret the results for mice subjected to both a standard diet and a high-fat diet.

The second concern pertains to the study's inability to clarify whether the observed results are a direct consequence of dapagliflozin or if they represent an indirect effect influenced by changes in peripheral insulin sensitivity, fuel energetics, or other neurotransmitters. In this study, mice subjected to a high-fat diet demonstrated increase in food intake and meal size, accompanied by a reduction in energy expenditure due to overeating. However, there were no significant changes in body weight. The paper does not offer further explanation for this observation. The response of individuals to SGLT2 inhibitors in terms of weight varies. In real-world clinical scenarios, these differences are influenced by multiple factors, encompassing not only the drug itself, but also concurrent use of other medications. In a randomized clinical trial involving obese individuals with type 2 diabetes mellitus, functional MRI scans indicated that the combination of dapagliflozin and exenatide, a GLP-1 receptor agonist, significantly alleviated the heightened activation of the CNS observed during dapagliflozin administration alone [4,5]. This indicates that the combination of dapagliflozin and the GLP-1 receptor agonist is beneficial for weight loss irrespective of the precise mechanisms by which dapagliflozin affects the CNS. Consequently, elucidation of these mechanisms may not be imperative from a clinical perspective. However, to precisely comprehend the interindividual variability in weight changes attributed to SGLT2 inhibitors, to determine the conditions for optimizing the weight-related benefits of SGLT2 inhibitors, and to identify the most suitable combinations, including GLP-1 receptor agonists, additional research is needed. These studies should strive to unveil the mechanisms through which SGLT2 inhibitors influence the brain and enhance insulin sensitivity in the hypothalamus.

In conclusion, findings from these studies and ongoing research in the era of precision medicine will enhance our comprehension of the roles of antidiabetic medications in ameliorating metabolic disorders beyond glycemic control, revealing their pleiotropic effects in diverse patient populations.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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