Hypertension Research (2024) 47:571–572
https://doi.org/10.1038/s41440-023-01522-5

COMMENT

Inhibiting SGLTs diminishes sympathetic output by reducing rostral ventrolateral medulla (RVLM) neuron activity

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Keywords SGLT2/SGLT1 inhibitor · Blood pressure · RVLM neurons · Sympathetic nerve activity · Cardiovascular effects

Received: 12 October 2023 / Revised: 27 October 2023 / Accepted: 28 October 2023 / Published online: 22 November 2023

Hyperactivity of the sympathetic nervous system contributes greatly to the development of hypertension and heart failure, which are frequently associated with type 2 diabetes [1]. Importantly, the rostral ventrolateral medulla (RVLM), also known as the pressor area of the medulla in the brain, controls basal and reflex regulation of sympathetic nerve activity (SNA) and blood pressure (BP) [2]. Moreover, impulses from hyperactive RVLM neurons are received by the intermediolateral cell column (IML) at each level of the spinal cord. These stimuli subsequently activate sympathetic nerves that travel to peripheral tissues, such as the heart, arterioles, and kidneys, in turn raising BP, and eventually leading to heart failure [2].

The sodium glucose cotransporters (SGLTs), specifically SGLT2 and SGLT1, are mostly responsible for glucose reabsorption in the body [3]. SGLT2 expression has been reported mainly in the kidneys, but also in the brain. In contrast, SGLT1 has been identified in the intestine, heart, and brain. However, the precise role of SGLTs in the brain is still unknown. Recent reports have shown that SGLT2 inhibitors have a marked effect on reducing BP and on cardiovascular outcomes in patients with or without diabetes [4]. These noteworthy benefits, which appear to be independent of reducing glucose, have prompted the development of several translational hypotheses underlying the fundamental mechanistic insights of SGLT2 inhibitors. Despite prior research demonstrating several mechanisms underlying the cardioprotective benefits of SGLTs inhibition, which mechanism(s) are primarily responsible remain unknown. In this context, we reported that SGLT2 inhibitors induced inhibitory effects on SNA in metabolic syndrome [5] and in salt-loaded obese Otsuka Long-Evans Tokushima Fatty (OLETF) rats [6], and thereby reduced BP. Consistent with our preclinical data, Balcıoğlu et al. [7] also reported that treatment with an SGLT2 inhibitor caused sympathoinhibitory effects in patients with diabetes. In contrast, because of a moderate inhibitory effect of SGLT2 inhibitors on SGLT1, improved cardiovascular outcomes may occur through SGLT1 inhibition in the heart, as SGLT1 expression is much higher in cardiomyocytes. Moreover, the combination of SGLT2 and SGLT1 inhibitors causes a greater reduction in BP than an SGLT2 inhibitor alone, and reduces the risk of cardiac failure, and myocardial and cerebral infarction, indicating that dual blockade improves organ protection [8]. Taken together, previous reports have conclusively demonstrated the antihypertensive and cardioprotective benefits of SGLT2 and/or SGLT1 inhibitors, which are at least in a part attributable to an inhibitory effect on SNA. However, how SGLT2 and/or SGLT1 blockade affects SNA remains unclear.

A recently published study by Oshima et al. [9] demonstrated the suppressive effects of SGLT2 and SGLT1 inhibitors on the activity of RVLM neurons. Using the whole-cell patch-clamp approach in isolated brainstem spinal cord, this study showed that superfusion of bulbospinal RVLM neurons with an SGLT2 inhibitor, empagliflozin, reduced the frequency of action potentials and induced hyperpolarization of the membrane potentials. Intriguingly, previous reports have shown that SGLT2 inhibitors have potential neuroprotective effects by attenuating motor dysfunction [10]. In contrast, Oshima et al. [9] also observed a reduction in bulbospinal RVLM neuron activity after superfusion with the SGLT1 inhibitor, mizagliflozin. Furthermore, microsuperfusion of the RVLM area with empagliflozin and mizagliflozin also affected the membrane potential of the IML neuron, suggesting that both inhibitors alter impulse transmission from the RVLM to the IML. RVLM neurons regulate SNA at the basal and reflex levels [2]. Therefore,

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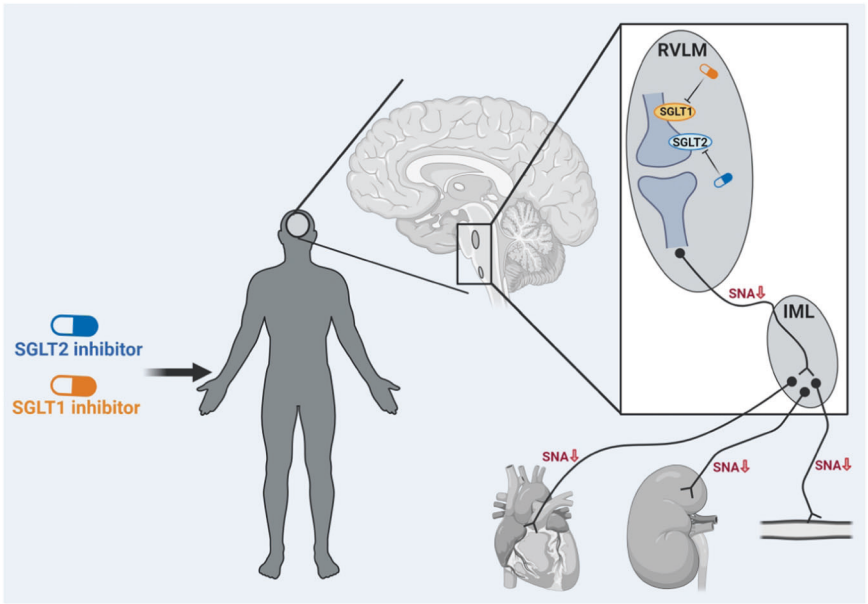

Fig. 1 A potential possible mechanism of sympathoinhibition caused by SGLT2 and/or SGLT1 inhibitors in the improvement of cardiorenal outcomes. SGLT2 and SGLT1 inhibitors could block SGLT2 and SGLT1, which are colocalized in the bulbospinal rostral ventrolateral medulla (RVLM) neuron and thus hyperpolarized membrane potential, and then transmit reduced sympathetic nerve activity (SNA) through intermediolateral cell column (IML) to the peripheral tissues including heart, kidneys, and arterioles, eventually improving cardiorenal outcomes

SGLT2 and SGLT1 inhibitors may reduce SNA in the peripheral tissues via the IML. Furthermore, Oshima et al. [9] showed for the first time that SGLT2 and SGLT1 were co-localized in RVLM neurons, despite previous findings showing SGLT2 and SGLT1 expression in the brain. Numerous mechanisms underlying the beneficial effects of SGLT2 inhibitors and dual blockade of SGLT1 and SGLT2 have been identified. However, suppressive effects on the activity of RVLM neurons are particularly important because this mechanism is connected to SNA, which has a significant impact on understanding the novel molecular insight in terms of clinical outcomes. Based on the findings of the recently published preclinical study by Oshima et al. [9], SGLT2 and/or SGLT1 inhibitors could block SGLTs in bulbospinal RVLM neurons, reducing RVLM neuron activity and thus causing a lower level of nerve impulse transmission to the IML. This could lead to a reduction in SNA in the peripheral tissues, and eventually improve BP and cardiorenal outcomes in patients with or without diabetes (Fig. 1). However, further in vivo studies using diabetic and non-diabetic animal models are required to corroborate the proposed mechanism specifically through which SGLT2 and/or SGLT1 blockade reduces the activity of RVLM neurons.

Acknowledgements We thank Ellen Knapp, PhD, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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