The Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Sympathetic Nervous Activity

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The EMPA-REG OUTCOME study revealed that a sodium-glucose cotransporter 2 (SGLT2) inhibitor, empagliflozin, can remarkably reduce cardiovascular (CV) mortality and heart failure in patients with high-risk type 2 diabetes. Recently, the CANVAS program also showed that canagliflozin, another SGLT2 inhibitor, induces a lower risk of CV events. However, the precise mechanism by which an SGLT2 inhibitor elicits CV protective effects is still unclear. Possible sympathoinhibitory effects of SGLT2 inhibitor have been suggested, as significant blood pressure (BP) reduction, following treatment with an SGLT2 inhibitor, did not induce compensatory changes in heart rate (HR). We have begun to characterize the effects of SGLT2 inhibitor on BP and sympathetic nervous activity (SNA) in salt-treated obese and metabolic syndrome rats, who develop hypertension with an abnormal circadian rhythm of BP, a non-dipper type of hypertension, and do not exhibit a circadian rhythm of SNA. Treatment with SGLT2 inhibitors significantly decreased BP and normalized circadian rhythms of both BP and SNA, but did not change HR; this treatment was also associated with an increase in urinary sodium excretion. Taken together, these data suggest that an SGLT2 inhibitor decreases BP by normalizing the circadian rhythms of BP and SNA, which may be the source of its beneficial effects on CV outcome in high-risk patients with type 2 diabetes. In this review, we briefly summarize the effects of SGLT2 inhibitors on BP and HR, with a special emphasis on SNA.

Keywords: sodium-glucose cotransporter 2 (SGLT2) inhibitor, EMPA-REG OUTCOME trial, CANVAS program, blood pressure, heart rate, sympathetic nervous activity

INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) is located at the S1 and S2 segments of the proximal tubule epithelium, which reabsorbs approximately 90% of filtered glucose (1). SGLT2 inhibitors induce glycosuria (2) and are widely used as antihyperglycemic agents in patients with type 2 diabetes (3). Recently, the EMPA-REG OUTCOME study demonstrated that treatment with empagliflozin, an SGLT2 inhibitor, significantly decreased the primary composite outcome of cardiovascular (CV) events, thereby reducing CV mortality by 38% (4). Further studies have shown that empagliflozin reduced heart failure hospitalization and CV death, with a consistent benefit in patients with and without baseline heart failure (5). The CANVAS program has also shown that canagliflozin, another SGLT2 inhibitor, lowers the risk of CV events by providing renal protection in type 2 diabetes patients (6). Moreover, in the large, multinational CVD-REAL study, treatment...
| Authors          | Study design | Treatment period | Drugs and doses | SBP (mmHg) | DBP (mmHg) | HR (bpm) |
|------------------|--------------|------------------|----------------|------------|-----------|----------|
|                  |              |                  |                | Baseline   | Change    | Baseline | Change    | Baseline | Change    | Baseline | Change    |
| Cherney et al.   | Clinical studies | 8 weeks | Empagliflozin 25 mg | 112.1 (8.9) | −1.5 | 66.2 (8.3) | −1.4 | 72.0 (11.0) | −1.2 |
| Häring et al.    | Clinical studies | 24 weeks | Empagliflozin 10 mg | 128.7 | −4.1 | 78.4 | −2.1 | NR | −0.8 |
| Chilton et al.   | Clinical studies | 12 weeks | Empagliflozin | NR | −3.9 | NR | −3.6 | NR | −0.6 |
| Kovacs et al.    | Clinical studies | 24 weeks | Empagliflozin 25 mg | 126.0 | −4.0 | 77.2 | −2.1 | NR | −0.8 |
| Nishimura et al. | Clinical studies | 4 weeks | Empagliflozin 10 mg | 119.1 (15.8) | −4.9 | 70.7 (10.7) | −1.3 | 65.3 (8.7) | 0.2 (4.8) |
| Tikkanen et al.  | Clinical studies | 24 weeks | Empagliflozin 10 mg | 129.6 | −4.5 (0.7) | 79.6 | −2.0 (0.5) | NR | −0.7 (7.0) |
| Rosenstock et al.| Clinical studies | 12 weeks | Empagliflozin 10 mg | 131.4 | −2.95 | 75.13 | −1.04 | NR | −0.17 (7.0) |
| Rosenstock et al.| Clinical studies | 78 weeks | Empagliflozin 10 mg | 132.8 | −4.1 | 78.4 | −2.9 | NR | −0.7 (8.6) |
| Rosenstock et al.| Clinical studies | 52 weeks | Empagliflozin 10 mg | 134.2 (16.4) | −3.4 | 79.5 (8.5) | −1.2 | NR | −0.3 (7.0) |
| Ferramini et al. | Clinical studies | 78 weeks | Empagliflozin 10 mg | 131.6 | 0.1 | 79.5 | −1.6 | NR | −0.3 (7.0) |
| Wölding et al.   | Clinical studies | 104 weeks | Dapagliflozin 5–10 mg | 131.9 | −1.7 | 80.2 | −2.2 | NR | −0.3 (7.0) |
| Nauck et al.     | Clinical studies | 52 weeks | Dapagliflozin 2.5–10 mg | 133.9 | −3.3 | 80.7 | −0.9 | NR | −0.3 (7.0) |
| List et al.      | Clinical studies | 12 weeks | Dapagliflozin 2.5 mg | 127 (14) | −3.1 (10.7) | 78.8 | 0.8 (6.4) | 71 (10) | −1.4 (8.0) |
| Sjöström et al.  | Clinical studies | 24 weeks | Dapagliflozin 10 mg | 149.9 (7.8) | −3.6 | 89.5 (9.1) | −1.2 | NR | −0.5 |
| Wölding et al.   | Clinical studies | 48 weeks | Dapagliflozin 2.5 mg | 139.6 (17.7) | −5.30 | 79.5 (10.1) | −2.96 | 75.4 (11.9) | −1.44 |
| Cefalu et al.    | Clinical studies | 52 weeks | Canagliflozin 100 mg | 130.0 (12.4) | −3.3 | 78.7 (8.5) | −1.8 | 74.2 | −1.1 (8.5) |
| Devi et al.      | Clinical studies | 4 weeks | Canagliflozin 100 mg | 130.0 (13.8) | −4.6 | 79.2 (8.4) | −2.5 | 74.8 | −1.2 (8.7) |
| Rosenstock et al.| Clinical studies | 12 weeks | Canagliflozin 50 mg | 126.8 | −1.3 | 76.9 | −0.1 | 69.9 | −0.2 |
| Leiter et al.    | Clinical studies | 104 weeks | Canagliflozin 100 mg | 130.0 (12.4) | −2.0 | 78.7 (8.0) | −1.3 | NR | −0.1 |

(Continued)
TABLE 1 | Continued

| Authors | Study design | Treatment period | Drugs and doses | SBP (mmHg) | DBP (mmHg) | HR (bpm) |
|---------|-------------|------------------|----------------|------------|------------|----------|
| Wan et al. (2) | SGLT2 Inhibitors and Sympathetic Nervous Activity | 2 weeks | L-González et al. | 74.4 (6.8) | 125.6 (17.7) | 77.7 (6.8) |
| Sha et al. (3) | Clinical studies | 52 weeks | Canagliflozin 100 mg | 126.7 (12.5) | 128.5 (12.7) | 77.7 (6.8) |
| Stenlöf et al. (4) | Clinical studies | 52 weeks | Canagliflozin 100 mg | 128.0 (12.7) | 128.7 (13.0) | 77.7 (6.8) |
| Wilding et al. (5) | Clinical studies | 52 weeks | Canagliflozin 100 mg | 130.4 (12.9) | 130.8 (10.4) | 77.7 (6.8) |
| Schernthaner et al. (6) | Clinical studies | 52 weeks | Canagliflozin 100 mg | 130.3 (14.6) | 130.6 (13.0) | 77.7 (6.8) |
| Rahman et al. (7) | Clinical studies | 52 weeks | Canagliflozin 100 mg | 130.3 (14.6) | 130.6 (13.0) | 77.7 (6.8) |

with an SGLT2 inhibitor was associated with lower rates of hospitalization for heart failure and death, compared with other glucose lowering drugs, implying CV benefits from SGLT2 inhibitor usage (7). The underlying mechanism by which an SGLT2 inhibitor improves CV disease is not clear; however, which the mechanism may not be limited to effects on metabolic parameters, body weight, and blood pressure (BP) (4).

There were close links and interactions between sympathetic nervous activity (SNA) and metabolic syndrome (8). And patients with obesity, hypertension, or diabetes exhibit high CV risk, which is associated with an inappropriate augmentation of SNA (9). A systematic meta-analysis revealed that SGLT2 inhibitors decrease systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline (−4.0 mmHg, and −1.6 mmHg, respectively) (2). However, clinical trials have failed to show notable changes or compensatory increases in heart rate (HR), following the administration of SGLT2 inhibitors (2, 10). These data suggest a possible sympathoinhibitory effect from an SGLT2 inhibitor, which may contribute in part to the cardioprotective effects of SGLT2 inhibitor therapy. In this review, we briefly summarize the effects of SGLT2 inhibitors on BP and HR in patients with type 2 diabetes. We also discuss the hypothesis that SGLT2 inhibitors elicit SNA inhibition.

**EFFECTS OF SGLT2 INHIBITORS ON BP**

Most clinical studies have shown that treatment with SGLT2 inhibitors, either as mono- or add-on therapies, significantly decreases both SBP and DBP in patients with type 2 diabetes (Table 1); however, some studies have shown no notable change in DBP (3, 23). Meta-analyses have revealed that SGLT2 inhibitors induce statistically significant reductions in SBP and DBP (2, 39). And Reed et al. (10) showed reasonable explanation of BP-lowering effects of SGLT2 inhibitors in type 2 diabetes. Interestingly, the extent of antihypertensive efficacy for each SGLT2 inhibitor differs according to patient background. For example, in a study of 1,031 type 2 diabetic patients who were divided into 5 groups based on body mass index (BMI, kg/m²) level [low-to-medium (<22.5, n = 222); medium (22.5–24.9, n = 270); high-level 1 (25–27.4, n = 262); high-level 2 (27.5–29.9, n = 142); and very-high (≥30, n = 135)], treatment with luseogliflozin significantly decreased SBP and DBP, relative to baseline, in all groups. However, reductions in SBP and DBP were greater in groups with higher BMI levels (40), suggesting that an SGLT2 inhibitor effectively decreases BP in high BMI, type 2 diabetic patients. Another clinical trial with ipragliflozin (50 mg/day for 24 weeks) showed no significant change in BP in 50 patients with type 2 diabetes. However, in 23 patients with poorly controlled BP (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg), treatment with ipragliflozin significantly reduced SBP and DBP (−6.6 mmHg and, −3.0 mmHg, respectively) (41). Similarly, treatment with empagliflozin for 12 weeks resulted in a greater BP reduction in hypertensive patients with type 2 diabetic who exhibited higher baseline BP (17). Taken together, these results suggest that SGLT2 inhibitors are effective for BP reduction in poorly controlled hypertensive patients with type 2 diabetes.
The restoration and maintaining a normal circadian rhythm is crucial to CV health (42). Diminished nocturnal decline in BP has been established as an important determinant for CV risk, independent of overall BP during a 24-h period (43). We have recently shown that SGLT2 inhibitors improve disrupted circadian rhythms of BP in metabolic syndrome rats [SHR/Ndmc-cp(+/-) rats; SHRcp] (37) and salt-treated obese Otsuka Long Evans Tokushima Fatty (OLETF) rats (44), both of which show non-dipper type of hypertension. Rahman et al. (37) showed a significant BP-lowering effect from luseogliflozin therapy in SHRcp rats. Interestingly, significant differences in BP levels appeared between dark and light periods, following treatment with an SGLT2 inhibitor, suggesting that the SGLT2 inhibitor altered the circadian rhythm of BP, from a non-dipper type to a dipper type. Similar effects were reported by Takeshige et al. (44) in salt-treated obese OLETF rats, following use of another SGLT2 inhibitor, empagliflozin. In these obese animals, high salt treatment increased BP and abolished differences in BP between dark and light periods, suggesting a non-dipper type of hypertension. Treatment with empagliflozin prevented the development of salt-induced hypertension and reversed their circadian rhythm of BP, from a non-dipper pattern to a dipper pattern. In SHRcp (37) and salt-treated obese rats (44), SGLT2 inhibitor-induced normalization of disrupted circadian rhythm of BP was associated with increased urinary excretion of sodium. Overall, these data suggest that an SGLT2 inhibitor induces natriuresis, which plays an important role in the improvement of the circadian rhythm of BP in type 2 diabetes (45).

Recently, a clinical case study examined the effect of dapagliflozin (5 mg/day) in patients with type 2 diabetes who exhibited a non-dipper type (sleep-time mean SBP > 90% of awake-time mean) of hypertension. Administration of dapagliflozin significantly decreased BP and altered the circadian dipping pattern of BP, from a non-dipper type to a dipper type (sleep-time mean SBP ≤ 90% of awake-time mean) (46). Another empagliflozin clinical trial also revealed that the reduction in BP was greater during sleep-time than during wake-time, in type 2 diabetes patients with non-dipper hypertension (47). These data indicate that BP reduction by an SGLT2 inhibitor is associated with restoration of a disrupted circadian rhythm of BP, from a non-dipper pattern to a dipper pattern, in hypertensive patients with type 2 diabetes.
FIGURE 2 | Effects of empagliflozin treatment on low frequency (LF) of systolic blood pressure (SBP), and on circadian rhythm of LF of SBP in Otsuka Long Evans Tokushima Fatty (OLETF) rats. (A) 24-h LF of SBP. (B) Average of 24-h LF of SBP. (C) LF of SBP in dark and light period. (D) Differences between dark and light period in LF of SBP. OLETF rats were treated with vehicle (vehicle, \( n = 7 \)), 1% NaCl drinking water (high-salt, \( n = 5 \)), or 1% NaCl drinking water and empagliflozin (high-salt + empagliflozin, \( n = 8 \)), for 5 weeks. Values are mean ± SEM. \( \dagger P < 0.001 \) vs. high-salt + empagliflozin dark period (2-way analysis), \( \# P < 0.001 \) vs. high-salt light period (t-test), * \( P < 0.05 \) vs. vehicle (one-way analysis of variance followed by Tukey’s multiple comparison test).

EFFECTS OF SGLT2 INHIBITORS ON HR

As shown in Table 1, many clinical studies have investigated the effects of SGLT2 inhibitors on BP and HR in patients with type 2 diabetes. Many clinical trials have shown that SGLT2 inhibitors significantly decrease BP in patients with type 2 diabetes; however, no study has reported any meaningful change or compensatory increase in HR. We have also recently monitored BP and HR, using a telemetry system, in hypertensive animals. We found that luseogliflozin significantly decreased BP, but did not change HR, in SHRcp rats (37). Recently, Sano et al. (48) reviewed clinical data regarding luseogliflozin treatment in Japanese patients with type 2 diabetes; their report showed that luseogliflozin significantly decreased HR in patients with high baseline HR levels (≥ 70/min before treatment). The authors of that study hypothesize that reduction in HR, by treatment with an SGLT2 inhibitor, is induced by the sympathoinhibitory effect of an SGLT2 inhibitor, in these patients.

EFFECTS OF SGLT2 INHIBITORS ON SNA

As discussed above, both clinical and animal studies indicate that SGLT2 inhibitors decrease BP without changing HR. The absence of HR changes, along with the reduction in BP, supports the notion that SGLT2 inhibitors elicit inhibitory effects on SNA; importantly, SNA strongly correlates with CV mortality (49). Previous studies have revealed that an SGLT2 inhibitor decreases SNA: Chiba et al. (50) showed that acute administration of dapagliflozin significantly suppressed norepinephrine turnover in brown adipose tissue of mice, which reflects SNA in brown adipose tissue. Further, Yoshikawa et al. (51) assessed the effects of ipragliflozin on arterial pressure and low frequency (LF, 0.04–0.60 Hz) of systolic arterial pressure, which reflects the level of sympathetic vasoconstrictor activity, in diabetes mellitus rats; their study demonstrated that inhibition of SGLT2 attenuated the arterial pressure lability associated with sympathoinhibition during the working period. Matthews et al. (52) concluded that SNA was upregulated in obesity and type 2 diabetes, and showed that dapagliflozin reduced SNA markers, such as tyrosine hydroxylase and noradrenaline, in the kidney and heart of C57BL6/J mice; these markers were routinely elevated by high-fat diet treatment. A rising in muscle SNA is usual during hypovolemia, like diuretic effects (53). Jordan et al. (54) demonstrated that there was no significant changes in muscle SNA despite increases in urine volume after short-term treatment of empagliflozin in
Recent studies have suggested that SGLT2 inhibitors elicit a reduction in SNA by decreasing insulin, leptin (55, 60) and blood glucose levels; and by improving insulin resistance and hyperinsulinemia, which could reduce the activation of carotid body (CB) (57); as well as by reducing sodium volume, which inhibits the activation of organum vasculosum laminae terminalis (OVLT) (59). Importantly, there are likely to be other mechanisms that have not been described.}

**FIGURE 3 |** Possible mechanisms for reducing sympathetic nervous activity (SNA) through use of sodium-glucose cotransporter 2 (SGLT2) inhibitors. Recent studies have suggested that SGLT2 inhibitors elicit a reduction in SNA by decreasing insulin, leptin (55, 60) and blood glucose levels; and by improving insulin resistance and hyperinsulinemia, which could reduce the activation of carotid body (CB) (57); as well as by reducing sodium volume, which inhibits the activation of organum vasculosum laminae terminalis (OVLT) (59). Importantly, there are likely to be other mechanisms that have not been described.

CONCLUSIONS

Here, we have summarized clinical data regarding the effects of SGLT2 inhibitors on BP and HR in patients with type 2 diabetes. During treatment with an SGLT2 inhibitor, BP reduction is not accompanied by compensatory increases or notable changes in HR. Further, SGLT2 inhibitors exhibit beneficial influences on the circadian rhythms of BP and SNA. Thus, these effects of SGLT2 inhibitors may be important in their CV protective effects, as shown in the EMPA-REG OUTCOME and CANVAS programs (4–6). The precise mechanism by which an SGLT2 inhibitor normalizes disrupted circadian rhythms of BP and SNA is not clear; however, multiple processes may be involved, including reduction of blood glucose level and body weight, improvement of insulin resistance, and initiation of natriuresis (8, 56–60) (Figure 3). Further studies are necessary to determine the mechanism responsible for the effects of SGLT2 inhibitors on SNA.

**AUTHOR CONTRIBUTIONS**

NW and AN analyzed previous clinical data. NW and AR performed the animal experiments and analyzed all experimental data. NW, HH, and AN wrote the manuscript. AN and HH supervised the study and revised the manuscript. All authors have read and approved the final manuscript.

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