Does SGLT2 Inhibition Affect Sympathetic Nerve Activity in Type 2 Diabetes?

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ABSTRACT

SGLT2 inhibitors increase renal glucose excretion and thus decrease both fasting and postprandial plasma glucose levels. The effects of SGLT2 inhibition outweigh those on glycemic control and are also associated with the induction of hemodynamic changes that improve cardiovascular and renal function in people with type 2 diabetes. The exact mechanisms have not yet been completely clarified. This review is focused on the potential relationship between SGLT2 inhibition and sympathetic nerve activity. There is accumulating evidence for a suppressive effect of SGLT2 inhibitors on the sympathetic nerve tone, which might be a putative mechanism for cardiovascular protection in subjects with type 2 diabetes.

The Role of the Kidney in Diabetes and its Chronic Complications

The kidneys play a key role in glucose homeostasis. They use glucose as a metabolic fuel, produce about 25 % of endogenous glucose, and reabsorb filtered glucose by the sodium-glucose co-transporters SGLT1 and mainly SGLT2 located in the early proximal tubules. The SGLT2 transporter is characterized by low affinity and high capacity. The maximum renal capacity for glucose reabsorption and the renal threshold for glucose are elevated in the diabetes population and, therefore, represent essential mechanisms in the pathogenesis of hyperglycemia. SGLT2 inhibitors counteract these mechanisms, thus, increasing glucose excretion and decreasing both fasting and postprandial plasma glucose levels. Although these effects are insulin independent, they lead to improved insulin secretion and insulin action. The beneficial effects of SGLT2 inhibition outweigh those on glycemic control. Accumulating data have demonstrated that suppressed renal glucose reabsorption results in decline in arterial blood pressure, decrease in the deleterious effect of glucotoxicity and induction of hemodynamic changes that improve cardiovascular and renal function in subjects with type 2 diabetes [1].

Type 2 diabetes is a cardio-metabolic disease leading to the development of micro- and macrovascular complications. While hyperglycemia is a proven major risk factor for microvascular complications such as nephropathy, retinopathy, neuropathy [2, 3], the elevated glucose levels are one of the relatively weaker risk factors for macrovascular complications – myocardial infarction, stroke, and peripheral vascular disease [2]. Dyslipidemia, hypertension, obesity, insulin resistance, and prothrombotic state have been recognized as more potent risk factors for macroangiopathy. By 2015, research data had shown that neither antihyperglycemic medications [4–6] nor lifestyle changes [7] had the potential to reduce cardiovascular risk in people with type 2 diabetes. In recent years, cardiovascular benefits associated with the use of two classes of antihyperglycemic drugs – SGLT2 inhibitors and GLP-1 receptor agonists in patients with type 2 diabetes, have been demonstrated and have changed the overall concept of the choice of antihyperglycemic therapy in type 2 diabetes [8, 9].

Putative Cardio-protective Mechanisms of SGLT2 Inhibition

The exact mechanisms underlying the cardio-protective role of SGLT2 inhibition is still debatable [10]. Even the landmark CVOT of empagliflozin – EMPA-REG OUTCOME has not explored the specific mechanisms responsible for cardiovascular benefits achieved with the administration of SGLT2 inhibitors.

The hemodynamic effects, such as reduction of arterial blood pressure and arterial stiffness, are due to the potential diuretic effect of SGLT2 inhibition. This is associated with improvement of left ventricular function, by reducing intra- and extracellular volume. Therefore, natriuresis and osmotic diuresis are potential factors that probably contribute to cardiovascular protection. These data have been proven in patients with type 2 diabetes and normal kidney function or the presence of chronic kidney disease stages 1 through 3a [11–22]. However, the osmotic diuresis hypothesis could not explain blood pressure lowering effects of SGLT2 inhibition across the whole spectrum of kidney function deterioration. More recent data from meta-analyses, including studies of patients with more advanced chronic kidney disease stages 3b–4, have demonstrated similar reduction of blood pressure, despite the decline in glycosuria in the diabetic population with advanced-stage chronic kidney disease [23]. Although dapagliflozin does not affect HbA1c level in patients with type 2 diabetes and chronic kidney disease stages 3b–4, it significantly decreases blood pressure and weight in the studied cohort [24]. Therefore, alternate pathways might be considered in the underlying mechanisms, which include the integrated effects of both hemodynamic and metabolic components [23]. One of the involved metabolic factors probably is weight loss, which could account for about 40 % of the change in blood pressure due to SGLT2 inhibition [25, 26].

The ketone hypothesis is also of scientific interest. The transition from glucose to fatty oxidation in the liver increases the plasma concentrations of ketones and they preferentially begin to be used as a fuel in the myocardium. This is considered to be related to improvement of cardiac metabolism and bioenergy [27–30]. The ketogenic hypothesis not only tries to explain the benefits of SGLT2 inhibitors for heart failure risk, but also may partially explain the class antihypertensive effect. Recent data implicate the potential for increased ketones, in particular β-hydroxybutyrate, associated with SGLT2 inhibition contributing to blood pressure lowering in a murine model [31]. Contrary to the above, some recent data propose the concept that circulating ketone bodies increased by SGLT2 inhibitors ameliorate the inflammatory process thus decreasing CV risk in diabetic patients rather than exert a direct effect on the heart [32]. In line with the above are data from hemodynamic and cardiac function measurements and myocardial uptake of glucose, lactate, free fatty acids or ketones, obtained during regional myocardial ischemia injury followed by reperfusion in healthy swines, which demonstrate the preserving cardiac contractile function independently of myocardial substrate utilization [33]. Since the decrease in HbA1c in EMPA-REG OUTCOME trial was about 0.25 %, this improvement in glycemic control could not explain the cardio-protective effect of empagliflozin [1, 8]. Moreover, the beneficial effect of good glycemic control on cardiovascular risk is expected after many years [34, 35], while a decrease in cardiovascular mortality and hospitalizations for heart failure following administration of empagliflozin have been observed within the first three months. Another potential mechanism is thought to be the expected weight loss and especially the decrease of visceral fat area, which is tightly related to increased insulin sensitivity, but these effects are also unlikely to occur within the first 3 months. Other potential mechanisms that may explain the cardio-protective effect of empagliflozin are the decreased serum uric acid levels, low-grade inflammation, oxidative stress and albuminuria, as well as the activation of angiotensin AT2 receptors, increased glucagon secretion, improved lipid profile, and changes in plasma electrolyte concentration [1, 8, 10]. Convincing evidence in support of these mechanisms is lacking. Moreover, SGLT2 inhibitors have been found to reduce the levels of troponin and the N-terminal fragment of the brain natriuretic peptide prohormone in adults with type 2 diabetes [36]. A direct effect of SGLT2 inhibition on the myocardium has been suggested. SGLT2 inhibitors suppress the myocardial Na^+/H^+ transporter, leading to a decrease in cytosolic sodium and vasodilation [37–39]. SGLT2 inhibitors have also been shown to play a role in the production of cytokines and in the decrease of epicardial fat volume [40–42], which is associated with a beneficial effect on myocardial inflammation, necrosis and fibrosis in subjects with type 2 diabetes and visceral obesity [36, 43, 44]. These data require further exploration to determine whether the observed changes are directly related to the cardiovascular benefits in subjects using these drugs [45].

Blood pressure lowering effect of SGLT2 inhibitors seems to be a cornerstone in their cardiovascular protection. SGLT2 inhibitors reduce systolic and diastolic blood pressure and improve its circadian rhythm without any change in heart rate, which is suggested to be based on probable direct suppression of sympathetic nerve activity [1, 10]. In addition to the negative calorie balance, weight loss and osmotic diuresis, they also suppress sodium–hydrogen antiporter 3, cause proximal tubule osmotic imbalance independently of glycemia, which results in increased tubular Na^+ secretion.

Since sympathetic hyperactivity is a consequence of insulin resistance and is a typical characteristic of patients with type 2 diabetes, the potential inhibitory effect of these drugs on sympathetic tone might contribute to a reduction in blood pressure and restoration of the normal circadian rhythm and thus play a pivotal role in the reduction of cardiovascular risk [46].

Main Features of Cardiac Autonomic Neuropathy in Diabetes

Cardiac autonomic neuropathy in subjects with diabetes presents as a sympatho-vagal imbalance with a predominance of sympathetic nerve activity and clinical evidence of decreased heart rate variability, tachycardia at rest, orthostatic hypotension, and increased risk of sudden cardiac death [47]. Tight glycemic control is not sufficient to reduce the risk of cardiac autonomic neuropathy in people with type 2 diabetes. A multifactorial interventions targeting not only glycemia, but other cardiovascular risk factors as well, have been shown to reduce the risk of cardiac autonomic neuropathy by up to 60 % of subjects with type 2 diabetes [48].

Cardiac autonomic neuropathy is an independent risk factor for cardiovascular mortality [49]. The ACCORD study in 8000 patients with type 2 diabetes has provided evidence for a 2.14-fold higher risk of overall and cardiovascular mortality in individuals with diabetes and cardiac autonomic neuropathy, after adjusting for traditional cardiovascular risks factors including the use of different classes of medications [50]. Data from other two large studies involving more than 31 000 subjects with cardiovascular disease and/or diabetes, followed for an average of 5 years have demonstrated that heart rate, as an indirect marker of cardiac autonomic function, analyzed as a categorical variable (resting heart rate < 70 bpm and resting heart rate > 70 bpm), is associated with a significant increase in cardiovascular morbidity and overall mortality [51], and the restoration of autonomic balance is of great importance in decreasing cardiovascular events, heart failure, and early mortality in subjects with diabetes. One of the central mechanisms for the development of cardiac autonomic neuropathy is the impaired hypothalamic regulation due to a dopamine deficiency, which leads to sympathetic dominance, increased insulin resistance and manifestation of the metabolic syndrome. It is considered that some of the newer antihyperglycemic drug classes, namely SGLT2 inhibitors, have the potential to improve autonomic function by reducing sympathetic nerve activity and should be considered when choosing therapy in patients with both diabetes and overt cardiac autonomic neuropathy [52].

Data from Clinical and Animal Studies for the Relation between SGLT2 Inhibition and Sympathetic Nerve Activity

EMPA-REG OUTCOME study data support the putative suppressive effect of SGLT2 inhibition on sympathetic hyperactivity. This trial has shown no reflex tachycardia despite the reported decrease in vascular volume and significant decline in blood pressure by 2–5 mmHg. These findings might be due to a relative reduction of sympathetic nerve activity, nevertheless other neurohormonal factors may also play an important role [8, 53–55]. ▶ **Tables 1–3** present available data from clinical studies regarding the effects of empagliflozin (▶ **Table 1**), dapagliflozin (▶ **Table 2**), canagliflozin (▶ **Table 3**), and ipragliflozin (▶ **Table 3**) on blood pressure and heart rate. A subanalysis of the studies with luseogliflozin in subjects with type 2 diabetes has not shown any change in heart rate in those with resting heart rate < 70 bpm. However, the administration of the drug has been associated with a decrease in heart rate in those with higher resting heart rate > 70 bpm, suggesting that SGLT2 inhibitors probably cause a decrease in sympathetic tone only in people with both type 2 diabetes and sympathetic hyperactivity [81, 82].

Data from experimental models are in line with the above mentioned findings in humans. The effect of SGLT2 inhibitors on blood pressure and sympathetic nerve activity has been investigated in animal models with obesity and/or metabolic syndrome and arterial hypertension with impaired circadian rhythm of blood pressure and sympathetic nerve activity. It has been shown that treatment with SGLT2 inhibitors significantly decreases blood pressure and normalizes its circadian rhythm without any change in heart rate. Therefore, it is considered that the inhibition of SGLT2 transporters might probably improve the circadian rhythm of sympathetic tone through suppression of sympathetic activity mainly during the night [83–85]. Norepinephrine is a major sympathetic neurotransmitter, which up-regulates SGLT2 protein expression in proximal tubule cells and its translocation to the cell surface in humans. Administration of dapagliflozin has been reported to exert a suppressive effect on the norepinephrine turnover in the brown adipose tissue of mice [86]. Moreover, SGLT2 inhibition leads to a decrease in tyrosine hydroxylase and norepinephrine levels in the kidney and heart of murine models, again demonstrating sympathetic nerve inhibitory potential of SGLT2 inhibitors [87, 88]. A direct tubular effect was observed after intraperitoneal injection of luseogliflozin in experimental models without diabetes, regardless of the change in plasma glucose levels and in the absence of hemodynamic renal effects. This is in support of the notion that the mechanism of tubulo-glomerular feedback is unlikely to be triggered [89]. These data provide evidence for an important cross-talk between sympathetic nervous system regulation and SGLT2 inhibition.

SGLT2 Inhibition Counteracts Sympathetic Nerve Hyperactivity – Pros

In the diabetic population, sympathetic nerve activity is primarily determined by afferent signals from the kidneys, which are richly innervated by chemoreceptors and baroreceptors that send signals to the brain [90]. It is highly likely that the excessive glucose resorption in the proximal renal tubules is involved in the activation of the renal autonomic nerves resulting in central sympathetic hyperactivity. This overstimulation of the sympathetic nervous system might be exacerbated by disruption of the negative feedback mechanism due to the decreased sensitivity of baroreceptor reflexes, which, in turn, increases the efferent sympathetic response to the heart, blood vessels and kidneys [91–94]. The change in the hemodynamics and homeostasis of fluid balance - a major risk factor for heart failure in type 2 diabetes, also contributes to the sympathetic overactivity [82].

It has been suggested that SGLT2 inhibitors decline sympathetic nerve tone through a decrease in the renal afferent nerve activity and suppression of the central reflex mechanisms, which is at the basis of the generalized sympathetic hyperactivity [95], thus exerting a beneficial effect on the hemodynamics of fluid balance. There is significant volume loading in subjects with type 2 diabetes and SGLT2 inhibitor administration leading to subsequent transient osmotic diuresis, which correct it. This phenomenon might be explained by the decrease in the sympathetic nerve outflow to the kidneys. This means that the renal pressure-natriuresis curve shifts to the left [95]. SGLT2 inhibition also corrects hypoxia at the level of the proximal renal tubules, thereby reducing hemodynamic congestion by decreasing sympathetic hyperactivity [82] (▶ **Table 4**).

Assuming that after the administration of an SGLT2 inhibitor the load on the heart is reduced by lowering blood pressure, improving its variability, and optimizing fluid volume by improving the renal pressure-diuresis curve; and afterload is diminished due to a

▶ **Table 1** Available data from clinical studies in type 2 diabetes regarding the effects of empagliflozin on arterial blood pressure and heart rate.

Study	Duration	Dose	Change in SBP (mmHg)	Change in DBP (mmHg)	Change in HR (bpm)
Cherney et al. [57]*	8 weeks	25 mg	−1.5	−1.4	−1.2
Häring et al. [58]	24 weeks	10 mg 25 mg	−4.1 −3.5	−2.1 −2.2	No change
Chilton et al. [20]	12 weeks 24 weeks	10/25 mg	−3.9 −1.5	−3.6 −1.3	−0.6 −0.8
Kovacs et al. [59]	24 weeks	10 mg 25 mg	−3.14 −4.00	−1.49 −2.21	No change
Nishimura et al. [60]	4 weeks	10 mg 25 mg	−4.9 −5.9	−1.3 −5.4	0.2 −1.7
Häring et al. [61]	24 weeks	10 mg 25 mg	−4.5 −5.2	−2.0 −1.6	No change
Tikkanen et al. [53]	12 weeks	10 mg 25 mg	−2.95 −3.68	−1.04 −1.40	−0.17 −0.74
Rosenstock et al. [62]	78 weeks	10 mg 25 mg	−4.1 −2.4	−2.9 −1.5	No change
Rosenstock et al. [63]	52 weeks	10 mg 25 mg	−3.4 −3.8	−1.2 −2.5	No change
Ferrannini et al. [64]	78 weeks	10 mg 25 mg	0.1 −1.7	−0.16 −2.2	No change

Adapted from Wan N et al. 2018 [56]. *The studied population is with type 1 diabetes. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate.

▶ **Table 2** Available data from clinical studies in type 2 diabetes regarding the effects of dapagliflozin on arterial blood pressure and heart rate.

Study	Duration	Dose	Change in SBP (mmHg)	Change in DBP (mmHg)	Change in HR (bpm)
Wilding et al. [65]	104 weeks	5 – 10 mg 10 mg	−2.6 −2.9	−7.5 −4.0	−1.3 −1.2
Nauck et al. [66]	52 weeks	2.5 – 10 mg	−4.3	−1.6	−0.1
List et al. [67]	12 weeks	2.5 mg 5 mg 10 mg 20 mg 50 mg	−3.1 −2.9 −6.4 −4.3 −2.6	0.8 −0.3 −2.6 −0.5 0.1	−1.4 −1.0 −0.03 1.9 −2.3
Sjöström et al. [25] with AH without AH	24 weeks	10 mg	 −3.6 −2.6	 −1.2 −1.2	 −0.5 0.1
Wilding et al. [68]	48 weeks	2.5 mg 5 mg 10 mg	−5.30 −4.33 −4.09	−2.96 −2.64 −2.85	−1.44 −1.25 −0.84

Adapted from Wan N et al. 2018 [56]. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; AH: Arterial hypertension.

moderate vasodilatation and a lack of compensatory tachycardia, the data on decreased incidence of hospitalizations for heart failure and cardiovascular mortality in subjects with type 2 diabetes are not surprising.

More recent data shift the focus from osmotic diuresis to the hypothesis that SGLT2 inhibitors might act like denervation agents in the kidney. It has been shown that renal denervation reduces blood pressure and improves glycemic control in humans [96].

▶ **Table 3** Available data from clinical studies in type 2 diabetes regarding the effects of canagliflozin and ipragliflozin on arterial blood pressure and heart rate.

Study	Duration	Dose	Change in SBP (mmHg)	Change in DBP (mmHg)	Change in HR (bpm)
Cefalu et al. [69]	52 weeks	100 mg 300 mg	−3.3 −4.6	−1.8 −2.5	−1.1 −1.2
Devineni et al. [70]	4 weeks	100 mg 300 mg	−10.7 −8.8	−7.1 −3.3	No change
Rosenstock et al. [71]	12 weeks	50 mg 100 mg 200 mg 300 mg 2 × 300 mg	−1.3 1.0 −2.1 −4.9 −3.6	−0.1 −0.2 −1.7 −2.1 −2.4	−0.2 −0.2 0.6 −1.7 0.2
Leiter et al. [72]	104 weeks	100 mg 300 mg	−2.0 −3.1	−1.3 −2.2	−0.1 −0.2
Sha et al. [73]	2 weeks	30 mg 100 mg 200 mg 400 mg 2 × 300 mg	−10.9 −4.7 −11.5 −9.4 −9.8	−3.9 0.2 −4.5 −3.4 −2.9	−7.1 −9.7 −5.1 −4.9 −5.5
Lavalle-González et al. [74]	52 weeks	100 mg 300 mg	−3.5 −4.7	−1.8 −1.8	−1.3 −1.9
Stenlöf et al. [75]	26 weeks	100 mg 300 mg	−3.3 −5.0	−1.7 −2.1	−1.6 −0.5
Wilding et al. [76]	52 weeks	100 mg 300 mg	−3.1 −2.9	−2.2 −1.7	−1.2 −0.4
Schernthaner et al. [77]	52 weeks	300 mg	−5.1	−3.0	−0.1
Forst et al. [78]	26 weeks 52 weeks	100 mg 300 mg 100 mg 300 mg	−5.3 −4.7 −3.4 −3.7	−3.3 −3.5 −2.5 −2.7	−0.3 −1.3 0.5 −1.0
Yale et al. [79]	26 weeks	100 mg 300 mg	−6.1 −6.4	−2.6 −3.5	−1.9 −1.1
Maegawa et al. [80] *	12 weeks	25–100 mg	−4.1	−2.2	−0.9

Adapted from Wan N et al. 2018 [56]. * The only study with ipragliflozin. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate.

Based on these findings, it has been hypothesized that norepinephrine increases SGLT2 expression and thus elevates blood pressure and impairs glucose homeostasis. A more recent study, exploring the direct interaction between sympathetic hyperactivity and SGLT2 regulation in a neurogenic hypertensive mouse model, have reported that downregulation of the renal sympathetic tone via either denervation or SGLT2 inhibition lowers SGLT2 expression and blood pressure. Dapagliflozin decreases tyrosine hydroxylase in heart tissue and norepinephrine content in the kidney without affecting plasma renin levels, indicating a reduced sympathetic nerve function due to SGLT2 inhibition [88].

Other recent studies indicate that some of the potential mechanisms associated with the reduction of sympathetic nerve activity after the administration of an SGLT2 inhibitor are the decreased insulin and leptin levels [97, 98], improved insulin sensitivity and decreased hyperinsulinemia, which suppress carotid body activation [99]. Reducing the sodium content that inhibits the activation of organum vasculosum laminae terminalis seems to be another possible mechanism [100] (▶ **Table 4**).

The putative effect of SGLT2 inhibitors on sympathetic nerve activity is what distinguish them from other diuretics. The main differences with loop and thiazide diuretics are: 1) SGLT2 inhibitors do not lead to reflex activation of the sympathetic nervous system, as there is no increase in heart rate in the presence of a significant decrease in arterial blood pressure; 2) thiazide diuretics exert their effects at the level of the distal renal tubules, whereas SGLT2 inhibitors act at the level of the proximal renal tubules, proximally to macula densa, and cause increased natriuresis to the juxtaglomerular apparatus [101, 102]; and thiazide and loop diuretics cause hyperglycemia and hyperuricemia, whereas SGLT2 inhibitors decrease plasma glucose and uric acid levels. It has been assumed that SGLT2 inhibitors restore tubular-glomerular feedback, which leads to va-

▶ **Table 4** The putative mechanisms, which determine the effects of SGLT2 inhibition on the sympathetic nervous system.

Central nervous system	Kidney	Heart	Vessels
ketosis ↓ hyperinsulinemia + ↓ hyperleptinemia ↓ ↓ activity of the carotid body ↓ activity of the afferent renal nerves + ↓ activity of OVLT ↓ ↓ sympathetic impulse to the heart + ↓ sympathetic impulse to the vessels + ↓ sympathetic impulse to the kidney	↓ tubular glucose reabsorption + ↓ Na + ↓ tubulo-interstitial load + ↓ interstitial hypoxia ↓ ↓ activity of the afferent renal nerves + ↓ activity of OVLT ↓ ↓ sympathetic impulse to the kidney from CNS	↓ sympathetic impulse to the heart ↓ ↓ volume loading + ↓ fibrosis	↓ sympathetic impulse to the vessels + correction of the fluid retention + ↓ hypoxia + ↓ RAAS + ↓ neprilyzin activity ↓ ↑ vascular reactivity ↑ natriuretic peptides

Adapted from Wan N et al. 2018 [56], Sano M. 2017 [83], and Sano M. 2018 [95]. OVLT: Organum vasculosum of the lamina terminalis; CNS: Central nervous system; RAAS: Renin-angiotensin-aldosterone system.

soconstriction of afferent arterioles and reduction of hyperfiltration by decreasing intraglomerular pressure [102]. Increased sodium delivery to macula densa also affects other neuro-hormonal factors such as the renin angiotensin aldosterone system [46, 103].

SGLT2 Inhibition Counteracts Sympathetic Nerve Hyperactivity – Cons

Reduction in arterial blood pressure has been observed in renal transplant patients on SGLT2 inhibitors. Since the transplanted kidney is denervated, this findings reject a direct neurogenic effect of SGLT2 inhibition [104]. The reduced plasma volume has been suggested to be the most likely underlying mechanism in this case. Plasma volume is tightly controlled, rapidly recovering when altered through multiple compensatory mechanisms. Just a 5 % decrease in plasma volume is necessary to activate the sympathetic nervous system and the renin angiotensin aldosterone system and to suppress natriuretic peptides, which results in activation of water and sodium reabsorption in the kidney and recovery of baseline plasma volume. The increase of plasma osmolality is also related to fluid release into the extracellular space. Plasma volume is retained reduced even after years of treatment with SGLT2 inhibitors, because the osmotic effect of glucose and the presence of more sodium outside the proximal renal tubules is perceived by the nephron as a sign of excessive filtration, such as this occurs with increased plasma volume or sodium retention. In fact, plasma volume and sodium are not increased [105], and even the total amount of sodium in the body is reduced after administration of an SGLT2 inhibitor [14]. Nevertheless, these signs result in homeostatic changes, including a new steady state of the body associated with reduced plasma volume [105].

Contrary to the above, data from some studies have implied not only the lack of effect on sympathetic nerve activity, but also stimulation of the sympathetic nerve tone as a result of SGLT2 inhibition. Some previous studies have shown that the increased hepatic glucose production, observed in subjects treated with dapagliflozin, cannot be explained only by insulin suppression and direct stimulation of glucagon by alpha cells [106]. It has been presumed that this process might be mediated by stimulation of the renal sympathetic nerves, which communicate directly with the liver through the portal bloodstream, or might be indirectly stimulated by the renal sympathetic nerves via impulses to the central nervous system and subsequently generation of efferent signals to the liver [107]. In line with this, two other studies have not demonstrated a beneficial effect of the combination of a DPP-4 inhibitor and an SGLT2 inhibitor on glucose levels, highlighting the role of other factors beyond elevated glucagon levels and decreased insulin levels, such as renal sympathetic nerve activation, which is likely to play a significant role in stimulating liver glucose production [108, 109]. However, if the effects on glucagon have been associated with generalized sympathetic nerve hyperactivity, the heart rate would have increased rather than decreased in the EMPAREG OUTCOME study [55].

A study in patients with type 1 diabetes without chronic complications treated with empagliflozin, applying clamp technique, has shown that heart rate variability and plasma adrenaline and norepinephrine concentrations remain unchanged in both clamps under euglycemic and hyperglycemic conditions [57]. There has also been no change in muscle sympathetic nerve activity and heart rate, despite increased urine volume, following short-term administration of emagliflozin in patients with type 2 diabetes [110]. Therefore, further prospective studies focusing on the relationship between SGLT2 inhibition and sympathetic nervous system function are needed. Data from EMBODY trial, a prospective, multicenter, randomized, double-blind, placebo-controlled study in patients with acute myocardial infarction and type 2 diabetes, will add further clarity on the effect of empagliflozin on sympathetic nerve activity [111].

Conclusion

In summary, there is accumulating evidence on the putative suppressive effect of SGLT2 inhibition on sympathetic nerve activity in subjects with type 2 diabetes, but still there are a lot of controversies and a need for further research in the field to address this issue and to answer the unresolved questions.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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