Role of SGLT2 in ketone body metabolism and NLRP3 inflammasomes

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Sodium–glucose transporter 2 inhibitors (SGLT2i) can increase serum ketone levels. Nevertheless, the mechanisms of which various ketogenic organs upregulate serum ketone levels in response to SGLT2i have not been fully elucidated. We investigated the SGLT2i-induced changes of ketogenic enzymes and transporters in mice models. In both normal and diabetic mice, SGLT2i increased tissue beta-hydroxybutyrate (BHB) contents in liver and kidney as well as in serum and urine. In these organs, SGLT2i upregulated the mRNA expressions of ketogenic enzymes, 3-hydroxy-3-methylglutaryl-coenzyme A synthase 2 (HMGCS2) and 3-hydroxy-3-methylglutaryl-coenzyme A lyase (HMGCL). Similar patterns were observed in kidney for the protein expression of sodium-dependent monocarboxylate transporters (SMCT), which mediate the cellular uptake of BHB and butyrate.

SGLT2 inhibitors significantly reduce cardiovascular events in humans with T2D; however, the underlying mechanism remains unclear. Activation of NLRP3 inflammasome and subsequent IL-1β release induces atherosclerosis and heart failure. Recently, it was revealed that ketone bodies, (i.e. BHB) suppresses activation of NLRP3 inflammasome in macrophages. As SGLT2 inhibitors cause increases in serum BHB by pharmacologic profile, we assessed the effect of SGLT2 inhibitor on NLRP3 inflammasome activity.

In a randomized, active-controlled study, a total of 61 patients with T2D and high cardiovascular risk (mean age and HbA_{1C} were 64.4 years and 7.32 %, respectively) received SGLT2 inhibitor or sulfonylurea for 30 days. NLRP3 inflammasome activation was analyzed in macrophages and the serum levels of glucose, BHB, and insulin from baseline to the end of treatment were tested.

While SGLT2 inhibitor's glucose-lowering capacity was similar to sulfonylurea, it significantly decreased IL-1β secretion compared to baseline (2,394 ± 236 to 1,748 ± 295 pg/mL, p <0.001), whereas sulfonylurea had no effect on IL-1β secretion (2,273 ± 279 to 2,755 ± 331 pg/mL, p = 0.05) (time × group interaction p <0.001). SGLT2 inhibitor caused a significant increase in fasting serum BHB and decrease in serum insulin, while sulfonylurea had no significant effects on these measurements. We performed ex vivo experiments using human macrophages to investigate whether BHB and insulin could affect NLRP3 inflammasome activity. BHB dose-dependently inhibited IL-1β secretion from macrophages. However, co-treatment with insulin attenuated the inhibitory effect of BHB on NLRP3 inflammasome activation.

In conclusion, SGLT2 inhibitors attenuate NLRP3 inflammasome activation, in part, via increased serum BHB and decreased serum insulin and glucose, which might help to explain the cardioprotective effects of SGLT2 inhibitor (clinicaltrials.gov NCT02964572).