Dapaglifl ozin downregulates G protein-coupled receptor Kinase-2 and upregulates regulator of g protein signaling-4 in adrenals to exert sympatholysis in heart failure

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Dapaglifl ozin is a sodium-glucose co-transporter (SGLT)-2 inhibitor with beneficial cardiovascular effects independent of its anti-diabetic actions. Among these is sympatholysis, i.e., norepinephrine (NE) lowering which is beneficial in chronic human heart failure (HF). Adrenal G protein-coupled receptor kinase (GRK)-2 upregulation is a major driver of circulating catecholamine (CA) elevation and sympathetic nervous system (SNS) hyperactivity in HF due to dysregulation of adrenal sympatho-inhibitory α2-adrenergic receptors (ARs) [1]. On the other hand, we recently reported that signaling by neuronal free fatty acid receptor (FFAR)-3, which stimulates NE release from sympathetic neurons, is blocked by Regulator of G protein Signaling (RGS)-4 [2,3]. We hypothesized herein that dapaglifl ozin may lower SNS hyperactivity in the adrenal gland by improving α2AR, and antagonizing FFAR3 signaling in adrenal chromaffin cells. We used the rat pheochromocytoma PC12 cell line expressing human α2A-AR, as well as freshly isolated adrenal glands from rats treated with dapaglifl ozin in vivo. Dapaglifl ozin treatment for 7 consecutive days (20 mg/kg/d in drinking water) led to a significant reduction in blood circulating NE levels (217+67 pg/ml, n=6), compared to control, vehicle-treated rats (363+77 pg/ml, n=6, p<.05), suggesting reduced SNS activity. This was accompanied by reduced GRK2 and tyrosine hydroxylase (TH) mRNA and protein levels in dapaglifl ozin-treated rat adrenals vs. vehicle-treated animal-derived glands. In contrast, RGS4 mRNA levels were increased in dapaglifl ozin-treated adrenals. Adrenal α2AR density was higher in dapaglifl ozin- vs. vehicle-treated rats (51.3+7.3 vs. 26.1+8.1 fmol/mg of protein, respectively; n=12 glands from 6 animals per group, p<.05). These results (i.e., GRK2 & TH downregulation with RGS4 upregulation) were completely recapitulated in PC12 cells in culture, treated with 5 microM dapaglifl ozin (or vehicle) for 24 hours. Importantly, α2AR-dependent G protein-mediated signaling towards inhibition of CA secretion was markedly enhanced, whereas FFAR3-dependent phospholipase C/calcium signaling was reduced, at 24 hrs post-dapaglifl ozin treatment of PC12 cells. GRK2 overexpression partially reversed dapaglifl ozin’s effect on cholinergic-induced CA secretion. In conclusion, dapaglifl ozin exerts a sympatholytic action in the adrenal medulla via a) downregulation of TH, which reduces CA biosynthesis, and GRK2, which reduces α2AR desensitization; and b) upregulation of RGS4 to block FFAR3-stimulated CA secretion (Figure).

Figure