

GPCR STIMULATED HYPOTHALAMIC PVN $G\alpha_{i2}$ PROTEIN-GATED PATHWAYS – THE KEY TO RENAL SYMPATHETIC NERVE MEDIATED SODIUM HOMEOSTASIS AND THE LONG-TERM CONTROL OF BLOOD PRESSURE

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Aim: We have demonstrated CNS $G\alpha_{i2}$ proteins, which are highly expressed in the hypothalamic PVN, mediate the renal sympathoinhibition and natriuresis evoked by α_2 -adrenoceptor activation and volume expansion *in-vivo*. Therefore, we examined the role(s) of PVN $G\alpha_{i2}$ proteins in fluid & electrolyte homeostasis and MAP regulation following elevated dietary salt-intake.

Methods: Intact or bilateral renal denervated (RDNX) Sprague-Dawley rats received a bilateral PVN or posterior hypothalamic (PH) infusion of a scrambled (SCR) or $G\alpha_{i2}$ oligodeoxynucleotide (ODN-300ng/side/day) and a normal 0.4% (NS) or high 8% NaCl (HS) diet for 7-days. On day-7 MAP, 24h metabolic balance, plasma norepinephrine, (NE) and PVN $G\alpha_{i2}$ protein levels were determined (N=5/group).

Results: HS-intake evoked a significant 3-fold site-specific increase in PVN $G\alpha_{i2}$ proteins. ODN-mediated PVN $G\alpha_{i2}$ down-regulation, but not PH miss-injection or PVN SCR ODN pre-treatment, caused renal nerve-dependent sodium retention (24h Na^+ balance [meq] PH $G\alpha_{i2}$ + HS 0.5 ± 0.2 , PVN $G\alpha_{i2}$ + HS $2.3\pm 0.4^*$, PVN $G\alpha_{i2}$ RDNX + HS $0.8\pm 0.3^{\tau}$), global sympathoexcitation (plasma norepinephrine [nmol/L] PH $G\alpha_{i2}$ + HS 17 ± 4 , PVN $G\alpha_{i2}$ + HS $75\pm 9^*$, PVN $G\alpha_{i2}$ RDNX + HS $24\pm 6^{\tau}$) and hypertension (MAP [mmHg] PH $G\alpha_{i2}$ + HS 128 ± 3 , PVN $G\alpha_{i2}$ + HS $140\pm 2^*$, PVN $G\alpha_{i2}$ RDNX + HS $131\pm 3^{\tau}$) * $p < 0.05$ vs. PH $G\alpha_{i2}$ + HS, $^{\tau}p < 0.05$ vs. PVN $G\alpha_{i2}$ + HS.

Conclusion: Renal nerve dependent dysregulation of sympathetically driven sodium retaining mechanisms occurred following PVN $G\alpha_{i2}$ -protein down-regulation evoking salt-sensitive hypertension. We conclude PVN $G\alpha_{i2}$ protein-gated pathways regulate renal nerve-dependent sodium excretion to facilitate sodium homeostasis and maintenance of a salt-resistant phenotype – R01HL107330.