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Dopamine β-hydroxylase inhibitor etamicastatprevents high blood pressure in mice lacking salt-inducible kinase 1

In human genetic studies a single nucleotide polymorphism within the salt-inducible kinase 1 (SIK1) gene was associated with hypertension (1).Moreover, it was recently shown that loss of SIK1 triggers an increase in blood pressure (BP) upon a chronic high-salt intake in mice (2). Here, we addressed possible acute mechanisms that may relate to the observed high BP in mice lacking SIK1. SIK1 knockout (*sik1*$^{-/-}$) and C57BL/6 wild-type (*sik1*$^{+/+}$) littermate mice were challenged for seven days with a normal- (0.3% NaCl) or high-salt (8% NaCl) diet. All comparisons were done using Unpaired t-test. Systolic BP (SBP) was significantly increased in *sik1*$^{-/-}$mice (137.0±17.2 mmHg, n=6) after seven days of high-salt intake, as compared to *sik1*$^{+/+}$mice counterparts (120.6±4.5 mmHg, n=6). The renin-angiotensin system (RAS) and the sympathetic nervous system (SNS) were assayed (ELISA and photometric enzymatic assay, respectively) in order to investigate the possible causes for the increase in SBP in *sik1*$^{-/-}$mice fed a high-salt diet. No differences in renin (normal-salt: 463.4±17.9, high-salt: 462.9±28.9 pg/ml) and angiotensin II (normal-salt: 45.8±10.0, high-salt: 39.0±8.5 pg/ml) serum levels were observed (n=6/group). The activity of dopamine β-hydroxylase (DβH), the enzyme that converts dopamine (DA) to noradrenaline (NA), was significantly increased in adrenal glands of *sik1*$^{-/-}$mice fed a high-salt diet (356.7±32.8 nmol/mg protein, n=5) as compared to *sik1*$^{-/-}$ mice on a normal-salt diet (184.4±14.4 nmol/mg protein, n=5). Similarly, urinary catecholamines (DA, NA andadrenaline) and L-DOPA were significantly increased (3- to 7-fold increase) in *sik1*$^{-/-}$mice fed a high-salt diet as compared to *sik1*$^{-/-}$mice on a normal-salt intake. Altogether, this data supports the view that *sik1*$^{-/-}$ mice fed a high-salt diet develop SNS overactivity. Next, we addressed the question if reducing SNS activity in *sik1*$^{-/-}$ mice fed a high-salt diet would ameliorate hypertension. For that purpose, the effect of the peripheral reversible DβH inhibitor etamicastat [also known as BIA 5-453] was evaluated on the development of high BP upon high-salt diet (3). Etamicastat treatment (50 mg/kg/day in drinking water), started prior to high-salt feeding, completely prevented SBP increase in *sik1*$^{-/-}$ mice fed a high-salt diet (116.8±4.7 mmHg, n=5). In summary, it is concluded that the SNS is involved in the development of salt-induced hypertension in *sik1*$^{-/-}$ mice and that the DβH inhibitor etamicastat is able to reduce SNS overactivity and high BP in this mouse model of hypertension.

(1) Popov *et al*. (2011).*J Hypertens* **29**: 2395-2403.

(2) Bertorello*et al*. (2015).*Circ Res* **116**: 642-652.

(3) Beliaev *et al*. (2006).*J Med Chem* **49**:1191-1197.