Dopamine β-hydroxylase inhibitor etamicastat prevents 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 (DBH), 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 and adrenaline) 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 DBH 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 DBH inhibitor etamicastat is able to reduce SNS overactivity and high BP in this mouse model of hypertension.