Paraoxonase1 deficiency in mice is associated with hypotension and increased levels of 5,6-epoxyeicosatrienoic acid

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Serum paraoxonase 1 (PON1) is an HDL-associated lipolactonase and its association with hypertension is controversial. We studied the possible role of PON1 in blood pressure (BP) regulation, by using PON1 knockout (PON1KO) mice. Both, systolic and diastolic BPs were lower in PON1KO compared to C57 mice. Hypotension detected in PON1KO is probably neither related to nitric oxide / guanylate cyclase-mediated vasodilation nor to angiotensin II or aldosterone-mediated vasoconstriction. Surprisingly, when challenged by high-salt diet, BP was further reduced in PON1KO mice. The later, pointed to a possible involvement of transient receptor potential vanilloid 4 (TRPV4), and indeed, administration of Ruthenium Red, a specific TRPV4 blocker, resulted in a sharp rise in BP. The protein levels of TRPV4 in kidneys of PON1KO were not higher than in C57. However, the renal level of 5,6 epoxyeicosatrienoic acid (5,6-EET), a TRPV4 specific agonist, was significantly higher in PON1KO compared with C57 mice. 5,6-EET levels were further elevated under high-salt diet or administration of arachidonic acid. Injection of recombinant human PON1 resulted in elevation of BP and a concomitant reduction in renal content of 5,6-EET. PON1, in-vitro, metabolized 5,6-EET to its corresponding diol. In conclusion, the present study shows causal, direct relationship between PON1 and blood pressure which is mediated, at least in part, by the regulation of TRPV4 agonist, 5,6-EET.