Involvement of nitric oxide and hydrogen sulfide in glucorticoid-induced hypertension in rat

R. d'Emmanuele di Villa Bianca, E. Mitidieri, E. Donnarumma, G. Cirino and R. Sorrentino

Dept. of Pharmacy, University of Naples Federico II, Italy

Excess of glucocorticoid, either endogenous, as in Cushing syndrome, or exogenous, via pharmacological administration of glucorticoids, induces hypertension. This form of hypertension is commonly related to activation of the mineralcortocoids receptor whereas it certainly has a role (Baid S et al., 2004). However, evidences indicate that glucocorticoid elevated blood pressure independently by mineralcorticoid receptor, in both humans and animal model (Kalimi M et al., 1989; Bertagna C et al., 1986). Furthermore, glucorticoid receptor is present in both vascular smooth muscle (Provencher PH et al., 1995) and endothelium (Wallerath T et al., 1999). To date, the mechanism(s) underlying glucocorticoid induced increase in blood pressure is still unclear. The gaseous transmitters nitric oxide (NO) and hydrogen sulphide (H_2S) together with endothelial-derived hyperpolarizing factor (EDHF) play a key role in the regulation of vascular homeostasis. In cardiovascular system, NO derived from endothelial NO synthase (eNOS) while H_2S is predominantly produced by cisthationine-β synthase (CBS) and/or cystathionine-γ lyase (CSE). Published data suggest that H_2S is EDHF (d'Emmanuele di Villa Bianca et al., 2011; Tang G et al., 2013). Therefore, we investigated the involvement of NO and H_2S/EDHF signalling in glucocorticoid-induced hypertension. Male Wistar rats were treated with dexamethasone (DEX, 1.5mg/kg subcutaneously) or vehicle (saline) for 8 days. During treatment, blood pressure was recorded by using a tail cuff apparatus, in conscious rats. Perfused arterial mesenteric plexus was used to evaluate the NO and the EDHF contribute. Thereafter, western blot study was performed to appreciate phoshorylated-eNOS/eNOS ratio or CBS and CSE expression in mesenteric tissue. The production of NO and H_2S was also measured. DEX treatment caused a significant increase in blood pressure. The contribute of NO mediated vasodilation was higher in the mesenteric bed of DEX-treated rats. Conversely, EDHF-mediated vasodilatation resulted significantly reduced in DEX group. In line with these findings, the p-eNOS/eNOS ratio as well as NO production were significantly increased in DEX group compared with vehicle. On the other hand, CBS and CSE expression was markedly reduced in DEX group and well correlated with H_2S production. Consistently with the fact that H_2S is EDHF, this latter result strongly support the reduction in EDHF-vasodilation occurring in DEX-group. In conclusion, our data indicate that exists a cross-talk between NO and H_2S in glucorticoid-induced hypertension. In this scenario H_2S pathway could represent a novel target opening new pharmacological strategies in the control of blood pressure.

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