Impairment of EDHF/H_2S pathway in early state of glucocorticoid-induced hypertension in rat

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Chronic administration of glucocorticoids (GCs), as well as an endogenous increase of GCs, such as in Cushing's syndrome, leads to hypertension (Pimenta E et al., 2012). Although the involvement of multiple factors has been suggested, the mechanism whereby GC increase blood pressure remains an enigma. Nevertheless, different data suggest the involvement of GCs in the regulation of blood pressure through a wide variety of extra-renal tissues, including the vascular smooth muscle and endothelium (Goodwin JE & Geller DS, 2012). It's well known that the GC receptor is present in both vascular smooth muscle (Provencher PH, et al., 1995; Kornel L, et al., 1993; Tsugita M, et al., 2008). and in the vascular endothelium (Kornel L, et al., 1993; Wallerath T, et al., 1999; Ray KP and Searle N, 1997). In response to hemodynamic shear stress, endothelium continuously releases nitric oxide (NO), endothelial-derived hyperpolarizing factor (EDHF) and prostacyclin to provide vasodilatation. Beside, it has been demonstrated that hydrogen sulfide (H_2S), endogenously produced by the enzymes cysthationine-γ-lyase (CSE) and cysthationine-β-synthase (CBS), has a pathophysiological role in several organs and apparatus. In this regard its involvement in vasculature has been clearly proved. More recently H_2S has been proposed as a candidate for EDHF. On this basis we investigated the role played by H_2S in mesenteric arterial bed and carotid artery from rats treated with vehicle or dexamethasone (DEX; 1.5 mg/kg/ day) for 8 days. The measurement of systolic blood pressure (SBP) in conscious rats revealed that daily DEX treatment significantly increased SBP compared with vehicle. A concentration-response curve of acetylcholine (Ach) was performed in presence of a combination of indomethacin (INDO) and L-NG-Nitroarginine methyl ester (L-NAME) to evaluate EDHF contribution in both mesenteric bed and carotid artery. Our results revealed that DEX treatment markedly reduced EDHF-mediated relaxation compared with control group in both vascular districts. EDHF-mediated relaxation was also completely abolished by pre-treatment with both apamin and charybdotoxin, inhibitors of small and big calcium-dependent potassium channels respectively. Interestingly propargylglycine, an inhibitor of CSE, significantly inhibited the EDHF relaxation induced by Ach. In addition, we observed a significant reduction of CBS and CSE expression in homogenates of mesenteric arterial bed and carotid harvested by rats daily treated with DEX. In line with this data, we demonstrated that H_2S production, measured in both vascular districts, as well as H_2S plasma levels, were markedly reduced in DEX compared to vehicle group. In conclusion, our results clearly show an impairment in EDHF/H_2S signaling in the earlier state of GC-induced hypertension. Based on these findings, the development of GC-H_2S-releasing compounds could represent a useful therapeutic tool to manage the GC-induced hypertension.

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