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INVESTIGATION OF EFFECT OF PROLYL 4-HYDROXYLASE INHIBITION ON DIABETIC NEPHROPATHY AND ASSOCIATED ENDOTHELIAL DYSFUNCTION IN UNINEPHRECTOMIZED DIABETIC RAT

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Hypoxia plays a critical role in diabetic nephropathy which is a progressive development of renal insufficiency in the setting of hyperglycemia and is the major single cause of chronic renal failure (CRF). Endothelial dysfunction also appears to be a consistent finding in diabetic nephropathy. We evaluated the efficacy of cobalt chloride, a prolyl 4-hydroxylase (PHD) inhibitor, in amelioration of renal injury and endothelial dysfunction, as well as its effect on hyperglycemia in uninephrectomized diabetic rat. The effect of cobalt chloride ($CoCl_2$,10 mg/kg, i.p. OD) treatment on various biochemical parameters like plasma urea, creatinine, uric acid, electrolytes sodium, potassium, chloride, as well as blood glucose levels were checked. Contractile responses to angiotensin II (10^{-10} to 10^{-6}M) in an aortic preparation of control rats and uninephrectomized diabetic rats along with measurement of the dry weight of contralateral kidney in different groups were recorded. Aortic endothelial nitric oxide synthase (eNOS), nitrate/nitrite (NOx), superoxide dismutase, catalase and reduced glutathione levels were checked in the different groups. Cobalt chloride treatment for seven continuous days, followed by intermittent dosing for 30 days resulted in significant fall in the plasma urea, creatinine and uric acid levels with restoration to partially normal values with a significant change in plasma electrolyte levels along with a reduction in the dry weight of kidney. A significant attenuation of the augmented responses to angiotensin II was observed with an increase in aortic eNOS and NOx levels as well as antioxidants levels. Chronic hypoxia augments angiotensin II responses in the thoracic aorta of uninephrectomized diabetic control rats. $CoCl_2$ attenuates these enhanced vascular responses with a significant decrease in blood glucose signifying stabilization of the hypoxia-inducible factor in the alleviation of endothelial dysfunction in diabetic nephropathy.

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