

ROLE OF BRAIN RENIN ANGIOTENSIN SYSTEM IN THE ACUTE HYPERTENSIVE RESPONSE TO INTRACEREBROVENTRICULAR CADMIUM

Varoni M.Vittoria, Palomba Domenico, Anania Vittorio, Demontis M.Piera

D.B.A - Division of Pharmacology, Faculty of Veterinary Medicine – University of Sassari

Essential hypertension is a common disease caused by a combination of genetic and environmental factors. Cadmium, an important pollutant, may contribute to the pathogenesis of hypertension in humans. In the rat, intracerebroventricular (icv) cadmium administration causes a sustained increase in arterial blood pressure which was prevented by a pre-treatment with calcium antagonists. Arterial hypertension is associated with decreased activity of the renal kallikrein-kinin system in humans and rats. Moreover, rats with low renal excretion of kallikrein (LKR) differ from normal kallikrein rats (NKR) in their pressure response to cadmium icv⁽¹⁾. Furthermore, the hypotensive effect of calcium antagonists in LKR treated with cadmium is significantly reduced compared to NKR suggesting that calcium is not the only mechanism involved⁽²⁾. It is possible that, among other mechanisms, the cerebral RAS is modified by the chronic reduction of kallikrein and, consequently, plays a part in the increase in arterial blood pressure levels due to loss of balance in the vasodilation systems. In order to elucidate the cadmium mechanism of action we evaluated the effects of an icv injection of cadmium in 4 LKR and in 4 NKR groups, which were icv pre-treated with (1) saline (control), (2) saralazine, a competitive angiotensin receptor antagonist, (3) enalapril and (4) captopril, both ACE inhibitors. The hypertensive cadmium peak was significantly attenuated by saralazine ($P < 0.0001$) in LKR only, and by enalapril ($P < 0.00001$ and $P < 0.05$ in LKR and in NKR respectively) and captopril in both strains ($P < 0.000001$ and $P < 0.005$ in LKR and in NKR respectively). This better pharmacological response of ACE-inhibitors and AI and AII competitive receptor antagonists, on blood pressure control in LKR, suggests that the chronic deficit of kallikrein could have modified the cerebral RAS activity. We hypothesize that, as postulated peripherally, the defective kallikrein kinin system activity could have enhanced the cerebral Angiotensin due to the lack of balance between the two systems. In conclusion, our results indicate that the pressor effect of icv cadmium can be reduced, in addition to calcium antagonists, by RAS inhibitors even though the importance of this remains to be established.

1. Varoni M.V., Palomba D., Satta M., Satta A. and Anania V. (2003) *Pharm. Res.* 47: 157-162.

2. Varoni M.V., Palomba D., Satta M. and Anania V. (2003) *Vet. Hum. Toxicol.* 45(4): 202-206.