Interruption of central neuronal pathway of imidazoline I1 receptor mediates the hypertensive effect of cyclosporine in rats.

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Abstract

Increased central sympathetic outflow secondary to afferent sympathetic excitation has been implicated in the hypertensive effect of the immunosuppressant drug cyclosporine (CSA). The present study investigated the roles of central alpha(2)-adrenoceptors and I(1)-imidazoline receptors in modulating the hypertensive action of CSA. The blood pressure (BP) response to CSA in conscious rats was assessed in the absence and presence of peripherally or centrally acting sympatholytic drugs. Also, the effect of selective pharmacologic blockade of alpha(2) or I(1) receptors by yohimbine and efaroxan, respectively, on the pressor response to CSA was evaluated. CSA (20 mg/kg i.v.) produced a rapid increase in BP that peaked (25 +/- 4 mm Hg) after approximately 4 min and continued for the 45 min study duration. Ganglionic (hexamethonium 20 mg/kg) or alpha(1)-adrenoceptor (prazosin 1 mg/kg) blockade reduced the pressor effect of CSA. Pressor responses to phenylephrine (alpha(1)-adrenoceptor agonist) were not affected by CSA, thereby eliminating a possible role for alterations of vascular alpha(1)-adrenoceptor responsiveness in CSA hypertension. CSA hypertension was attenuated in rats pretreated intravenously with drugs that reduce central sympathetic tone including clonidine (mixed alpha(2)/I(1)-receptor agonist, 30 microg/kg) or moxonidine (selective I(1)-receptor agonist, 100 microg/kg) in contrast to no effect for guanabenz (selective alpha(2)-receptor agonist, 30 microg/kg). Intracisternal (i.c.) administration of moxonidine also reduced CSA hypertension. Selective blockade of central I(1) (efaroxan, 0.15 microg/rat, i.c.) but not alpha(2) (yohimbine, 25 microg/5 microl/rat, i.c.) receptors abolished the hypertensive response to CSA. Together, these findings highlight that CSA elicits its hypertensive effect via disruption of central sympathoinhibitory pathways which include I(1)-imidazoline receptors.