

## Pharmacological characterization of $\alpha$ -adrenoceptors which mediate clonidine-induced sedation

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Clonidine induces sedation in animals and man, and this effect, like its antihypertensive action, is thought to be mediated via  $\alpha$ -adrenoceptors in the central nervous system (Delbarre & Schmitt, 1971; 1973). In the periphery there are two groups of  $\alpha$ -adrenoceptors; those located postsynaptically on smooth muscle and those located presynaptically on autonomic postganglionic nerve terminals. The pre- and postsynaptic  $\alpha$ -adrenoceptors differ in their sensitivity to  $\alpha$ -agonists and antagonists (Starke, 1977). In particular, the presynaptic  $\alpha$ -adrenoceptors are much less sensitive than the postsynaptic receptors to the agonist effects of phenylephrine and methoxamine, and to the antagonist effects of thymoxamine and labetalol (Drew, 1977). The experiments reported here were carried out to determine which type of  $\alpha$ -adrenoceptor, if either, mediates the sedative effect of clonidine.

Sedation was measured in male PVG strain hooded rats (40-60 g) in terms of a reduction in the length of time that the animals could remain on an accelerating rotarod (Jones & Roberts, 1968). After intracerebroventricular (i.c.v.) injection (Popick, 1976) clonidine (0.6-5  $\mu$ g/rat), oxymetazoline (5-40  $\mu$ g/rat), xylazine (5-40  $\mu$ g/rat), naphazoline (5-40  $\mu$ g/rat) and methoxamine (10-80  $\mu$ g/rat) caused sedation. The doses of the agonists required to reduce rotarod performance time by 50% ( $ED_{50}$ ) were 1.2, 12.0, 15.1, 15.4 and 70  $\mu$ g/rat i.c.v. respectively. Phenylephrine (20  $\mu$ g/rat i.c.v.) caused slight sedation and higher doses caused death. Clonidine also produced sedation after intraperitoneal injection; the  $ED_{50}$  was 60  $\mu$ g/kg. The sedative effect of these agonists is unlikely to be related to a fall in blood pressure because hypotensive

doses of hydralazine (0.5-2.0 mg/kg i.p.) did not affect rotarod performance.

The interaction between clonidine and  $\alpha$ -adrenoceptor antagonists was investigated by injecting the antagonists i.c.v. ten minutes prior to clonidine (100  $\mu$ g/kg i.p.). Twenty minutes after the administration of clonidine the animals were tested on the rotarod. The sedative effect of clonidine was antagonized by phentolamine, yohimbine, piperoxan and tolazoline; the minimum effective doses were 8, 20, 100 and 100  $\mu$ g/rat i.c.v. respectively. In contrast thymoxamine (up to 200  $\mu$ g/rat) and labetalol (up to 80  $\mu$ g/rat) did not antagonize clonidine and did not themselves produce sedation. Higher doses of these two antagonists caused death.

The orders of potency of the  $\alpha$ -agonists and antagonists suggest that the  $\alpha$ -adrenoceptors which mediate the clonidine-induced sedation more closely resemble the peripheral presynaptic  $\alpha$ -adrenoceptors than the postsynaptic  $\alpha$ -adrenoceptors.

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