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Letter to the Editor

(3,4-Dihydroxyphenylimino)-2-imidazoline (DPI): a stimulant of α-adrenoceptors and dopamine receptors

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In a recent series of studies van Oene et al (1982a, b; 1983) described several pharmacological effects of the drug (3,4-dihydroxyphenylimino)-2-imidazoline (DPI). We originally described the dopamine (DA) receptor stimulating properties of this drug in neurons of the snail *Helix aspersa* in 1975 (Struyker-Boudier et al 1975b). In their paper published in this Journal in 1983, van Oene et al conclude that 'the designation of DPI as a DA agonist should be abandoned'. This conclusion is not justified, since it is reached by ignoring several important facts. First, van Oene et al (1983) performed their studies on the pharmacology of DPI in slices of rat neostriatum. Our studies as well as those of others (Cools 1977; Cools & Oosterloo 1983; Pijnenburg et al 1976; Blackburn et al 1978; Costall et al 1979; Springer et al 1981) have shown that the nucleus accumbens, but not the neostriatum, contains DPI-sensitive sites. Van Oene et al (1983) from that point of view have simply reconfirmed the outcome of the above mentioned study.

Second, Van Oene et al (1983) claim that, 'in view of these potent stimulating properties at both α_1/α_2-adrenoceptors. DPI has to be designated as a mixed α_1/α_2-adrenoceptor agonist'. There is no doubt that DPI is a potent α-adrenoceptor agonist. In fact, we were the first (Struyker-Boudier et al 1975a) to report its potent α-adrenoceptor stimulating properties in the rabbit isolated intestine. Later a number of authors have confirmed DPI's agonist behaviour at α-adrenoceptors in different tissues, including rat aorta (Ruffolo et al 1980), rabbit ear artery (Hieble & Pendleton 1979), rat kidneys (Baggio & Ferrari 1981) and rat cortical neurons (Bevan et al 1979). However, in view of its chemical structure, an α-adrenoceptor stimulation of DPI is not surprising. Other agents containing a catechol group including DA itself, can stimulate both DA receptors and α-adrenoceptors. DA is capable of stimulating α-adrenoceptors with an affinity only slightly lower than that of noradrenaline (van Rossum 1965). Thus, again van Oene et al (1983) confirmed a pharmacological property of DPI that was established before.

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The point van Oene et al (1983) fail to recognize is that in certain preparations DPI behaves as a DA receptor stimulant. There are now at least four independent observations to support this conclusion: (1) The ganglia of the snail *Helix aspersa* contain dopamine as their major catecholaminergic neurotransmitter. Dopamine causes neural inhibition of some cells and excitation of other neurons. In both cases the effects are mediated by receptors different from classical α- or β-adrenoceptors (Struyker-Boudier et al 1974; Struyker-Boudier 1975; Woodruff 1979). The endogenous stimulants of all types of adrenoceptors, i.e. noradrenaline and adrenaline, are weaker agonists than dopamine at the receptors mediating dopamine-induced inhibition or excitation. Moreover, the pattern of activity of antagonistic drugs differs from that at adrenoceptors. Thus, ergot alkaloids, such as ergometrine, were found to be very potent antagonists of dopamine-induced neuronal inhibition, whereas certain neuroleptics, such as haloperidol, strongly antagonized dopamine-induced excitation. The classical adrenoceptor blockers phentolamine (α_1- and α_2-blocker) and propranolol (β_1- and β_2-blocker) were ineffective with respect to antagonism of dopamine-induced inhibition and excitation (Struyker-Boudier et al 1974; Struyker-Boudier 1975; Woodruff, 1979). Therefore, a classification of these receptors as dopamine receptors seems fair on the basis of molecular pharmacological criteria. DPI selectively stimulates DA receptors mediating neuronal inhibition (Struyker-Boudier et al 1975b). The inhibitory effects of DPI were blocked by ergometrine, thus supporting that its effects were mediated by dopamine receptors (Struyker-Boudier 1975b). (2) DPI activates DA receptors in particular areas of the brain, e.g. the feline caudate nucleus and septum (Cools et al 1976; Megens & Cools 1981) and the rat nucleus accumbens (Cools & Oosterloo 1983; Springer et al 1981). Also in this case, DPI only affects one type of DA receptor, viz. the apomorphine-insensitive DA receptor (for review: Cools & van Rossum 1980). Again, the effects of DPI in these brain areas were not mimicked by classical α- and β-adrenoceptor stimulants nor blocked by the adrenoceptor antagonists phentolamine and propranolol (Pijnenburg et al 1976; Cools et al 1976;

Cools & Oosterloo 1983; Megens & Cools 1981). (3) In the dog coronary vasculature, in contrast to the renal vascular bed, both DPI and DA produce an increase in blood flow (Woodman et al 1981). This effect could not be blocked by the α-adrenoceptor antagonists phentolamine or yohimbine, whereas it was effectively antagonized by the DA receptor antagonist ergometrine (Woodman et al 1981). DA receptor stimulation by DPI in snail ganglia, rat and cat brain and dog coronary vasculature was concluded in part on the basis of the selective antagonism by ergometrine. Data from receptor binding assay studies support the view that ergometrine has a strong affinity as an antagonist at particular types of DA receptors (Burt et al 1976; Drummond et al 1978; Sibley & Creese 1983). (4) The rabbit isolated ear artery contains prejunctional DA receptors, stimulation of which reduces noradrenaline release. Medgett (1983) recently showed that DPI strongly stimulates these prejunctional DA receptors and that this effect is antagonized by the DA receptor antagonist metoclopramide.

In conclusion, DPI, like dopamine, acts as an agonist at α-adrenoceptors as well as DA receptors. The outcome of its effect depends on the presence of either receptor type. Disregarding its DA receptor stimulating potential is similar to denying that DA is a DA receptor agonist.

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