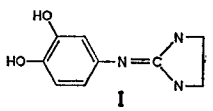
(3,4-Dihydroxy-phenylamino)-2-imidazoline (DPI), a new potent agonist at dopamine receptors mediating neuronal inhibition

Dopamine, like noradrenaline, is known to act on sympathetic α-receptors. There is, however, also evidence for the existence of separate dopamine receptors in peripheral mammalian tissues and in the nervous system of both vertebrates and invertebrates (van Rossum, 1966; Woodruff, 1971; Goldberg, 1975). We recently showed the existence of two types of dopamine receptors in the brain of the snail *Helix aspersa* on the basis of differential sensitivity of the respective receptors towards antagonistic drugs (Struyker Boudier & van Rossum, 1974; Struyker Boudier, Gielen & others, 1974). Ergot derivatives like ergometrine were shown to be antagonists at dopamine receptors mediating neuronal inhibition (DI receptors), whereas some neuroleptic drugs like haloperidol and droperidol were antagonists at dopamine receptors mediating neuronal excitation (DE receptors). With respect to agonistic drugs slight differences were found in the relative potencies of a number of dopamine analogues such as (−)- and (+)-noradrenaline, (−)-adrenaline and (−)-isoprenaline (Struyker Boudier & others, 1974). A more dramatic difference was found with apomorphine: this drug behaved as an agonist at DE receptors whereas it lacked agonistic activity at DI receptors but rather behaved as an antagonist at higher doses (Struyker Boudier & others, 1974).

In a series of experiments concerning the dopamine-like actions of imidazoline derivatives we came across a drug (I) [(3,4-dihydroxy-phenylamino)-2-imidazoline; DPI] with interesting properties which are reported here.



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Experiments were performed on the isolated suboesophageal ganglionic mass of the garden snail *Helix aspersa*. The ganglionic mass was dissected free and mounted in a bath of 17 ml volume. The ganglia were perfused at a rate of about 2 ml min^{-1} with a snail Ringer solution of following composition: (mM) NaCl 80, KCl 4, $CaCl_2$ 7, $MgCl_2$ 5 and tris HCl 5. The pH of this Ringer solution was 7·8–8·0. Intracellular recordings were made using glass microelectrodes, tip diameter less than 1 μm filled with M potassium acetate. The resistance of these electrodes ranged from 5 to 30 MΩ. The membrane potentials of the cells were amplified using a negative capacitance amplifier with output to a Tektronix 502 A oscilloscope. Drugs were solved freshly in snail Ringer and added to the bath in a volume of 0·1 ml. Doses are expressed as nmol of the salts added to the bath.

Dopamine (0·5–50 nmol) caused a dose-dependent inhibition of neuronal activity of a number of cells (n = 13). DPI mimicked this dopamine-induced inhibition in 11 of the 13 cells tested (Table 1). The duration of the inhibition depended upon the dose of DPI injected with dose–response characteristics similar to those of dopamine. On a molar basis DPI was about equipotent with dopamine in inducing neuronal inhibition. There were slight differences with dopamine in the sense that dopamine–induced inhibitions were usually accompanied by a hyperpolarization of the cellular membrane (2–18 mV) whereas the degree of hyperpolarization after DPI was usually smaller (0–7 mV). Moreover, after repeated (more than 5 times)

Table 1. *Effects of dopamine and DPI on different neurons of the snail* Helix aspersa (n = 22).

	DPI+	DPI−	DPI 0
Dopamine +	1	1	4
Dopamine −	1	11	1
Dopamine 0	1	0	2

administration of DPI a tachyphylaxis with respect to inhibitory activity occurred in a few cases. In five cells the effect of two doses of dopamine (1–10 nmol) and two doses of DPI (1–10 nmol) was compared before and after the administration of the DI receptor antagonist ergometrine (10 nmol). The inhibitory effect of both doses of dopamine and DPI was totally abolished after this dose of ergometrine. The effects of DPI (0·5–300 nmol) were also tested on cells that were excited by dopamine (0·5–50 nmol). In 4 out of 6 cases no appreciable effect could be obtained with DPI, in one case the neuron was inhibited and in one case it was excited. However, these effects only occurred at relatively high doses when compared with dopamine.

The imidazoline derivative clonidine (St 155; 2,6-dichloro-phenylamino-2-imidazoline) was ineffective both with respect to DI and DE receptor agonistic activity.

On the basis of these results we conclude that DPI is a specific, potent agonist at DI receptors. This specific action is interesting from the point of view of the topography of dopamine receptors (Woodruff, 1971). Moreover, this drug may be a valuable tool for testing the existence of more than one type of dopamine receptor in the mammalian brain as was suggested recently by Cools & van Rossum (1975) and Cools, Janssen & others (1975). Such existence may have important implications for the design of psychotropic agents potentially interferring with dopamine receptors.

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