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COMMUNICATIONS

Some benzhydryl derivatives as central dopamine receptor stimulating agents

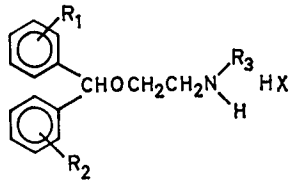
Since the introduction of L-dopa to treat parkinsonism, comparatively few novel compounds analogous in action, i.e. capable of stimulation of the central dopamine receptors, have been reported. Cotzias, Dûby & others (1970) have suggested 2-(3',4'-dihydroxybenzyl)piperidine in addition to apomorphine but report no clinical data on the former compound. Piribedil (Corrodi, Fuxe & Ungerstedt, 1971; Poignant, Laubie & others, 1972; Corrodi, Farnebo & others, 1972; Med. News Tribune, 1972) would appear to be pharmacologically dopamine-like and has been used with positive results clinically. The pharmacological profile of 2(*p*-nitrobenzylthio)imidazoline (3H) (Menon, Clark & Aures, 1972a,b) is also reminiscent of that of a dopamine-like drug.

During pharmacological work on a series of compounds that had shown cns stimulant activity, we discovered a group of benzhydryl derivatives that caused "bizarre social behaviour" (BSB) in the rat. This property is characteristic of compounds with (central) dopaminergic activity (Lammers & van Rossum, 1968).

Doses of 0·08 mmol of the test compounds were administered intraperitoneally as a suspension in 1% amylum gel to groups of 4–6 male TNO-rats of the Wistar strain, 200–250 g. For reference purposes, several known centrally acting dopamine-like drugs were also given by the same route, except apomorphine, which was administered intravenously since it is known to produce only relatively weak BSB intraperitoneally. BSB, stereotypy and tremor were scored at the time of maximal activity, using a scale that ranged from 0 (no effect) to 5 (very strong effect).

Table 1 lists the results of the five most potent test compounds together with those of some known, centrally acting dopamine-like drugs.

Table 1. *Dopamine-like activity of a series of benzhydryl derivatives and of some reference compounds on i.p. administration to the intact rat.*



Cpd	R_1	R_2	R_3	HX	Dose mg kg^{-1} i.p. (0·08 mmol)	Relative activity[1] BSB	Stereotypy	Tremor	Duration (h)	Anti-Ach act. pA_2*	Anti-hist. act. pA_2**
I	*p*-F	*p*-F	H	HCl	24	5	3	5	36–48	5·8	6·1
II	*p*-F	*p*-Cl	H	mal§	32	4–5	2	–	36–48	5·9	6·0
III	*o*-F	*p*-F	H	— §§	24	5	3	2	36–48	5·2	5·5
IV	*p*-F	*p*-F	Me	mal§	32	4	3	2–3	36–48	6·1	7·2
V	*o*-F	*p*-F	Me	HCl	25	4	2	1	36–48	6·1	6·9
L-Dopa	..	..	..	..	200	0–1	0–1	–	1		
L-Dopa + MK 486		..	..	..	200 + 25	4	3	–	2–3		
Apomorphine	..	..	..	..	1·25 (i.v.)	5	5	–	1		
Piribedil	..	..	..	..	100	4	3	–	24–28		

[1]Scored on a scale from 0 (no effect) to 5 (very strong effect).
mal§ = maleic acid, §§ = free base.
* Against furtrethonium acc. to Ariëns. Molecular Pharmacology.
** Against histamine acc. to Ariëns. Acad. Press, New York, 1964.

The effects of the novel compounds were very strong and lasted much longer than those of L-dopa or apomorphine. The BSB as seen 36–48 h after dosage of I–IV was definitely more pronounced than that 24 h after piribedil.

We conclude that I–IV possess central dopamine-like activity. Compound I was subjected to several experiments in rats, to substantiate the above conclusion. The experiments and the results obtained are summarized below.

(*a*) BSB produced by I (0·08 mmol kg^{-1}, i.p.) was inhibited completely by haloperidol (1 mg kg^{-1}, i.p.), spiramide (1 mg kg^{-1}, i.p.) or chlorpromazine (5 mg kg^{-1}, i.p.).

(*b*) Catecholamine depletion as caused by pretreatment with reserpine (15 mg kg^{-1}, i.p.) did not prevent the occurrence of BSB after I (0·08 mmol kg^{-1}, i.p.), given 18 h later. When dopamine synthesis was inhibited by α-methyl-*p*-tyrosine (αMT), BSB could nevertheless be elicited by I although to a lesser extent. These observations have led to the conclusion that I possesses a direct and probably a weak indirect dopamine-like activity.

(*c*) In rats with unilateral lesion of the substantia nigra (Cotzias & others, 1970; Ungerstedt, 1971) produced by either electric coagulation or administration of 6-hydroxydopamine, rotational behaviour can be induced by dopamine-like drugs such as L-dopa and apomorphine and by treatment with I (0·08 mmol kg^{-1}, i.p.).

(*d*) The dopamine level in the striatum is enhanced (Andén, 1972) by dopamine antagonists and lowered (Andén, Rubenson & others, 1967) by dopamine-mimicking drugs such as apomorphine; these antagonists and mimetics respectively stimulate and inhibit the synthesis of dopamine through a similar feedback mechanism. In a dose of 0·08 mmol, I appears to lower the dopamine level in the rat 5 h after administration.

Although I–IV stimulate the central dopaminergic system, we observed no signs of peripheral dopamine-like activity. Non-toxic doses caused no emesis in dogs and cats. In the anaesthetized dog, a dose of I (20 mg kg^{-1}, i.v.) given as a 10-min infusion, did not alter cardiac activity significantly, nor did it change the flow in the dog femoral artery (dopamine is known to increase this flow [Goldberg, Sonneville & McNay, 1968]).

Gist-Brocades NV, Research & Development,
Postbus 523, *Parklaan* 125,
Haarlem, Netherlands.

M. C. VAN BEEK
H. TIMMERMAN

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