Biochemical interaction between anorectic drugs and piribedil

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As anorectic drugs have various effects on brain monoamines (Garattini, Bizzi & others, 1975a) it would appear possible that these neurotransmitters may have some part in the mechanism of their action. Catecholamines may be involved in the effect of anorectic drugs with stimulating properties, such as amphetamine (Weissman, Koe & Tenen, 1966; Holtzman & Jawett, 1971; Garattini & others, 1975a), mazindol and diethylproprion (Samanin, Bernasconi & Garattini, 1975). In contrast, 5-hydroxytrytamine (5-HT) (Samanin & others, 1975) seems to play a role in the anorectic effect of the agents with no stimulant activities, such as fenfluramine, S992 and SKF1–39728 (Groppetti, Misher & others, 1972).

These compounds have a common biochemical effect on the dopamine metabolism, increasing the concentration of its metabolite homovanillic acid (HVA) in the rat striatum (Jori & Bernardi, 1969, 1972; Jori & Dolfini, 1974). However, amphetamine and fenfluramine have been found to produce a similar increase in HVA concentrations by means of opposite mechanisms. Amphetamine is an indirect dopamine agonist (Iversen, Horn & Miller, 1975) which accumulates HVA by releasing the dopamine from nerve endings (Glowinski, 1970); it has been suggested that fenfluramine blocks the dopamine receptors and increases HVA concentrations through a feedback mechanism (Jori, Cecchetti & others, 1974a; Garattini, Buczko & others, 1975b) similar to that elicited by neuroleptic agents (Andén, Butcher & others, 1970).

This work was undertaken to investigate whether other anorectic compounds such as *N*-methylamphetamine, mazindol, diethylpropion, S992 and SKF1–39728 act on the dopamine metabolism by an amphetamine- or a fenfluramine-like mechanism. The experimental approach used was the study of the interaction occurring between these anorectics and piribedil, a dopaminergic agonist (Corrodi, Fuxe & Ungerstedt, 1971).

Female Charles River rats, 180 ± 20 g, were housed six to each cage, at room temperature 20° and relative humidity 56%, with free access to food and water. Rats were injected intraperitoneally with the following anorectic drugs: (+)-amphetamine sulphate, (—)-fenfluramine HCl, methylamphetamine-HCl, S992 (trifluoro-methylphenyl (benzoyloxy) ethyl-amino-2-propane), SKF1–39728 (1-*N*-benzyl-methoxy-3-trifluoromethylphenethylamine), mazindol (5-(*p*-chlorophenyl)2-5-dihydro-3H-imidazo[2,1]isoindol-5-ol) and diethylpropion (2-diethylamino propiophenone), at the doses reported in the Tables. One hour before these drugs, piribedil was administered intraperitoneally at doses of 60 or 120 mg kg^{-1}. Rats were decapitated 1 h after injection of the anorectics, their brains were removed and dissected, and striata were frozen on dry ice and stored at –20° until assayed for HVA on pools of 3 striata by the method of Korf, Ottema & Van Der Veen (1971).

Table 1 reports the results obtained when drugs were given alone or after piribedil. All the drugs tested raise HVA concentrations from 50 and 180% compared with control animals. When piribedil was given before the drugs, the effect of fenfluramine, S992 and SKF1–39728 was strongly counteracted (significant interaction). Conversely, pretreatment with piribedil did not inhibit amphetamine (significant interaction), methylamphetamine or maxindol (for these two drugs the interaction was not significant because of data variability). The effect of diethylpropion was reduced but not blocked by piribedil. Similar results were obtained when double the doses of piribedil or diethylpropion were used (Table 2). HVA concentrations after these combined treatments were always lower than after diethylpropion alone, the quantitative difference being about the same as the decrease caused by piribedil alone.

Piribedil is known to stimulate dopamine receptors (Corrodi & others, 1971; Corrodi, Farnebo & others, 1972), reduce dopamine turnover (Corrodi & others, 1972) and lower the HVA concentration (Jori, Cecchetti & others, 1974b) by a feedback mechanism. Similarly to apomorphine it also counteracts the increase in striatum HVA concentration induced by dopamine receptor blocking agents such as phenothiazines and

Table 1. *Effect of piribedil on the increase in HVA concentrations induced by anorectic drugs.*

Treatment (mg kg^{-1}, i.p.)		Striatum HVA (ng g^{-1} ± s.e.) Saline	Piribedil	Statistical F	Interaction *P*
Saline		238 ± 5	153 ± 7*		
(±)-Amphetamine sulphate	15	486 ± 10	481 ± 12	F_{obs} (1·17) 5·9	<0·05
N-Methyl amphetamine	30	524 ± 44	437 ± 24	" (1·17) <1	n.s.
Mazindol	15	454 ± 64	490 ± 49	" (1·17) 1·3	n.s.
Diethylpropion	15	358 ± 18	208 ± 19*	" (1·18) 2·1	n.s.
(±)-Fenfluramine HCl	15	676 ± 19	262 ± 23*	" (1·17) 48·2	<0·001
S 992	15	411 ± 14	125 ± 5*	" (1·18) 34·9	<0·001
SKF1–39728	15	448 ± 27	244 ± 9*	" (1·16) 7·4	<0·05

Piribedil or saline were given 1 h before the test drugs and 2 h before decapitation. (2 × 2) Factorial experiment: unweighted means analysis and Tukey (b) Test. Seven experimental designs were followed, each including the saline and piribedil groups.
* $P < 0·01$.

* Correspondence.

Table 2. *Effect of piribedil on the increase in HVA concentrations induced by diethylpropion in various treatment schedules.*

Group	Pretreatment mg kg^{-1}	Treatment mg kg^{-1}, i.p.	Striatum HVA ng kg^{-1} ± s.e.
1	Saline	Saline	220 ± 8
2	Saline	Diethylpropion 15	321 ± 10
3	Piribedil 120	Saline	118 ± 12
4	Piribedil 120	Diethylpropion 15	233 ± 13
5	Saline	Diethylpropion 30	412 ± 12
6	Piribedil 60	Saline	125 ± 0·8
7	Piribedil 60	Diethylpropion 30	338 ± 7

Conditions are as reported in Table 1.
Analysis of variance (2 × 2) of groups 1, 2, 3, 4 or 1, 5, 6, 7 as reported in Table 1 indicate the effects of the single treatments were significant, but there were no significant interactions between piribedil and diethylpropion.

haloperidol (Lahti, McAllister & Wozniak, 1972; Jori & others 1974a, b). It has been found that piribedil prevents the effect of fenfluramine but not that of amphetamine (Jori & others, 1974b). On this basis a post-synaptic neuroleptic type of effect on the striatal dopamine metabolism was postulated for fenfluramine (Jori & others, 1974a).

The findings reported here suggest that S992 and SKF1-39728 increase HVA concentrations by a similar mechanism, namely consequent to increased dopamine turnover following a block of the dopaminergic receptors. Mazindol and methylamphetamine are not counteracted by piribedil, supporting the hypothesis that, like amphetamine, they may act presynaptically by releasing dopamine at the nerve endings.

The effect of piribedil on diethylpropion is not so clear. Diethylpropion might be a less powerful dopamine agonist or it might act through more than one mechanism. This agrees with other findings that 6-OH dopamine, which completely blocks amphetamine, only partially inhibits diethylpropion anorectic activity (Samanin & others, 1975). In conclusion, although all the anorectic drugs tested have the same biochemical effect on striatal HVA, the mechanism by which they affect the dopamine metabolism to achieve this effect is different; these drugs can therefore be divided into two groups, one comprising amphetamine, methylamphetamine, mazindol and—partly—diethylpropion, and the other fenfluramine, S992 and SKF1-39728.

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