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Effects of Prolintane on 3,4-Dihydroxyphenylacetic Acid Concentration in Rat Brain After Spiperone Treatment

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FULLER, R W AND H D SNODDY *Effects of prolintane on 3,4-dihydroxyphenylacetic acid concentration in rat brain after spiperone treatment* PHARMAC BIOCHEM BEHAV **10**(4) 561–563, 1979 —Prolintane (1-[α-propylphenethyl]-pyrrolidine) but not l-(α-methylphenethyl)-pyrrolidine markedly enhanced the increase in 3,4-dihydroxyphenylacetic acid concentration in the brains of rats treated with spiperone, a neuroleptic drug. This action and other properties of prolintane described in the literature place it in a group of stimulant drugs that includes methylphenidate, cocaine and amfonelic acid with properties that differ from those of amphetamine

Prolintane CNS stimulants Brain DOPAC Spiperone

ROSS [5] reported recently that prolintane (1-[α-propylphenethyl]-pyrrolidine) resembled methylphenidate and cocaine in that its inhibition of ^{3}H-dopamine accumulation by synaptosomes from rat brain was not enhanced by prior treatment of the rats with reserpine. In contrast, the concentrations of d- and l-amphetamine, ephedrine and phenmetrazine required to inhibit ^{3}H-dopamine accumulation into synaptosomes *in vitro* were reduced by a factor of 5–10 when reserpine was given to the rats 18 hr prior to the time they were killed for preparation of brain synaptosomes.

The methylphenidate-like drugs (including cocaine and amfonelic acid) are known to enhance brain dopamine turnover in rats treated with neuroleptic drugs, whereas the amphetamine class (d- and l-amphetamine and methamphetamine) do not have this effect [7] Since prolintane has structural similarity to amphetamine (Fig. 1), its similarity to methylphenidate rather than amphetamine in regard to dopamine uptake inhibition not being enhanced by reserpinization stimulated our interest in seeing if prolintane would also resemble methylphenidate in enhancing the turnover of dopamine after neuroleptic treatment.

We determined the effect of prolintane on the increase of 3,4-dihydroxyphenylacetic acid (DOPAC) in rat brain after treatment with spiperone, a potent neuroleptic drug This report shows that prolintane markedly enhanced the elevation of DOPAC, placing prolintane in the category of drugs that includes methylphenidate, cocaine, amfonelic acid, mazindol, and certain other indirectly-acting dopaminergic agonists

METHOD

Male Wistar rats weighing 130–150 g from Harlan Industries, Cumberland, Indiana were given food and water ad lib.

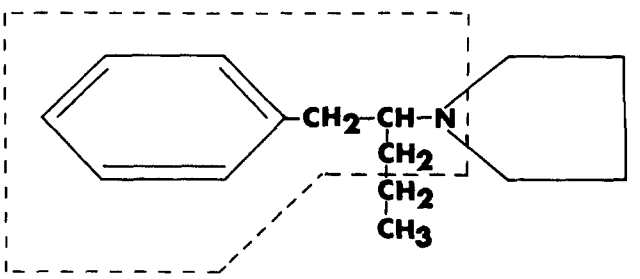

FIG 1 Chemical structure of prolintane with the amphetamine nucleus outlined

Spiperone was a gift from Janssen Pharmaceutica, Beerse, Belgium Prolintane hydrochloride was a gift from Boehringer Ingelheim Ltd., Ridgefield, CT, U.S A. 1-(α-Methylphenethyl)-pyrrolidine was synthesized in the Lilly Research Laboratories Drugs were injected IP, and rats were killed by decapitation Whole brains were quickly removed, frozen on dry ice, and stored at −15°C prior to analysis. DOPAC concentration was determined spectrofluorometrically by use of the methods of Murphy, Robinson and Sharman [4] and Spano and Neff [8]

RESULTS

The effects of prolintane on brain DOPAC concentration in control rats and in rats pretreated with spiperone are shown in Table 1. Prolintane did not change DOPAC concentration when given alone. Spiperone caused about a four-fold increase in DOPAC as is characteristic of dopamine

TABLE 1

ENHANCEMENT OF BRAIN DOPAC ELEVATION BY PROLINTANE BUT NOT 1-(−α−-METHYLPHENETHYL)-PYRROLIDINE IN SPIPERONE-PRETREATED RATS

Treatment	Brain DOPAC, ng/g	
	Control	Spiperone-pretreated
Saline	71 ± 1	290 ± 13
Prolintane	69 ± 4	655 ± 39*
1-(−α−Methylphenethyl)pyrrolidine	60 ± 9	275 ± 16

*Significantly different from corresponding saline-treated group, $p < 05$

The test drugs were injected i p at 15 mg/kg 1 hr after spiperone (0 5 mg/kg, i p) and 1 hr before the rats were killed Mean values ± standard errors for 5 rats per gorup are shown

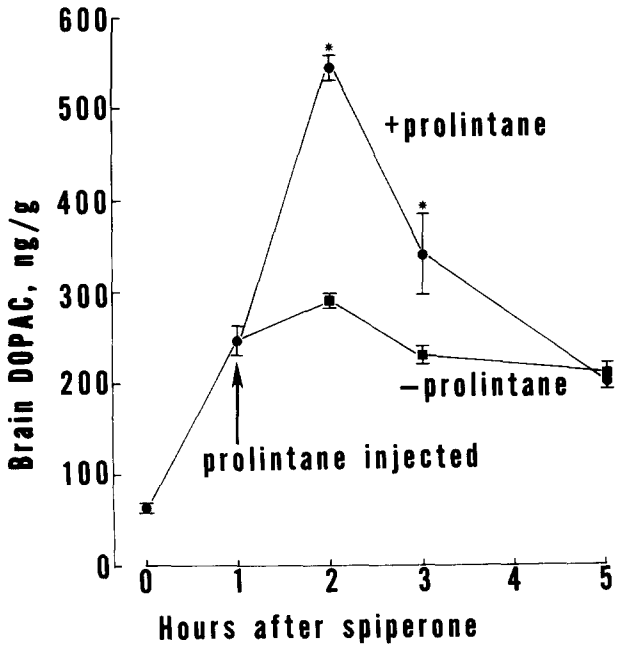

FIG 2 Duration of the effect of prolintane on brain DOPAC after spiperone pretreatment Spiperone (0 5 mg/kg, IP) was injected at zero time Prolintane (15 mg/kg, IP) was injected at 1 hr as indicated by the arrow Mean values ± standard errors for 5 rats per group are shown

antagonists The concentration of DOPAC in rats that received prolintane in addition to spiperone was more than twice that in rats treated with spiperone alone This enhancement of DOPAC elevation by spiperone did not occur with 1-(α-methylphenethyl)-pyrrolidine, which is simply amphetamine with the nitrogen incorporated into a pyrrolidine ring, i e is the analog of prolintane having an α-methyl rather than an α-propyl substituent on the alkyl side chain

The duration of the elevation of DOPAC by prolintane in spiperone-treated rats is shown in Fig 2 The concentration of DOPAC after spiperone alone was increased within 1 hr and remained elevated throughout the five-hour period of study When prolintane was injected at 1 hr, the concentration of DOPAC was markedly increased during the next hour and remained elevated at 2 hr after prolintane injection in comparison to rats treated with spiperone alone However, by 4 hr after prolintane injection, DOPAC concentration was not different from that in rats treated with spiperone alone

DISCUSSION

These effects of prolintane are similar to those observed earlier with amfonelic acid [2] and methylphenidate [3] CNS stimulant drugs in this group have other properties in common that distinguish them from amphetamine Table 2 summarizes some characteristics of the two classes of CNS stimulants The amphetamine group (including both

TABLE 2

COMPARISON OF BEHAVIORAL AND BIOCHEMICAL CHARACTERISITICS OF VARIOUS STIMULANT DRUGS

Drug	Stereotyped Hyperactivity blocked by	Dopamine uptake inhibition enhanced by reserpine	Enhances dopamine turnover increase after neuroleptic treatment
d-Amphetamine	$-\alpha-$MT [7]	Yes [1,8]	No [2,5]
l-Amphetamine	$-\alpha-$MT [7]	Yes [1]	No [2]
Methamphetamine	$-\alpha-$MT [7]	?	No [2]
Phenmetrazine	$-\alpha-$MT [7]	Yes [1]	?
Cocaine	Reserpine [9]	No [1,8]	Yes [2]
Amfonelic acid	Reserpine [7]	?	Yes [2,5]
Methylphenidate	Reserpine [7]	No [1]	Yes [2,6]
Prolintane	?	No [1]	Yes*

*This paper

stereoisomers of amphetamine itself, methamphetamine, and phenmetrazine) produce stereotyped hyperactivity that is blocked by α-methyltyrosine and not by reserpine [1]. These drugs inhibit dopamine accumulation by brain synaptosomes *in vitro*, and this inhibitory effect is enhanced when reserpine is injected into the rats prior to removal of the brain for the preparation of synaptosomes [5,6] These drugs do not enhance the increase in dopamine turnover resulting from treatment with dopamine receptor antagonists [2,7]. The amfonelic acid/methylphenidate/cocaine group of drugs, to which prolintane apparently belongs, differ in that (a) their stereotyped hyperactivity is blocked by reserpine and not α-methyltyrosine [1], (b) their inhibition of dopamine uptake by synaptosomes *in vitro* is not affected by prior reserpinization of the rats [5,6], and (c) they markedly enhance the increased dopamine turnover produced by dopamine receptor antagonists [2, 3, 7]. Some gaps in information with these drugs are indicated in the table, and other CNS stimulant drugs have to be studied further to determine if this categorization into two groups is valid for these and other drugs The precise differences in mechanism of action between the two groups of drugs that lead to the differing characteristics in these experimental situations also remain to be elucidated

REFERENCES

1 Braestrup, C and J Scheel-Kruger Methylphenidate-like effects of the new antidepressant drug nomifensine (HOE 984) *Eur J Pharmac* **38:** 305–312, 1976

2 Fuller, R W , K W Perry, F P Bymaster and D T Wong Comparative effects of pemoline, amfonelic acid, and amphetamine on dopamine uptake and release *in vitro* and on brain 3,4-dihydroxyphenylacetic acid concentration in spiperone-pretreated rats *J Pharm Pharmac* **30:** 197–198, 1978

3 Fuller, R W and H D Snoddy Synergistic elevation of brain 3,4-dihydroxyphenylacetic acid concentration by methylphenidate and spiperone in control but not reserpine-pretreated rats *J Pharm Pharmac* , submitted for publication

4 Murphy, G F , D Robinson and D F Sharman The effect of tropolone on the formation of 3,4-dihydroxyphenylacetic acid and 4-hydroxy-3-methoxyphenylacetic acid in the brain of the mouse *Br J Pharmac* **36:** 107–115, 1969

5 Ross, S B On the mode of action of central stimulatory agents *Acta pharmac toxicol* **41:** 392–396, 1977

6 Ross, S B Potentiation by reserpine of the inhibition by amphetamine of ^{3}H dopamine accumulation in the rat striatum *J Pharm Pharmac* **29:** 433–434, 1977

7 Shore, P A Actions of amfonelic acid and other non-amphetamine stimulants on the dopamine neuron *J Pharm Pharmac* **28:** 855–857, 1976

8 Spano, P F and N H Neff Procedure for the simultaneous determination of dopamine, 3-methoxy-4-hydroxyphenylacetic acid and 3,4-dihydroxyphenylacetic acid in brain *Analyt Biochem* **42:** 113–118, 1971

9 Van Rossum, J M and J A Th M Hurkmans Mechanism of action of psychomotor stimulant drugs Significance of dopamine in locomotor stimulant action *Int J Neuropharmac* **3:** 227–239, 1964