Effect of neuroleptics on brain amphetamine concentrations in the rat

Within certain dose ranges promazine, chlorprothixene (Halliwell, Quintin & William, 1964) and triflupromazine prolong amphetamine-induced stereotyped behaviour (ASB). Perphenazine has no potentiating effect. We now report the effect of these four neuroleptics on brain amphetamine concentration.

Male Sprague-Dawley rats, about 150 g, were housed in pairs in wire cages, and groups of six injected with either triflupromazine hydrochloride (Vesperin, Squibb), promazine hydrochloride (Sparine, Wyeth), chlorprothixene (Tarasan, Roche), each in a dose of 5 mg/kg, perphenazine (Trilafon, Schering), 1 mg/kg, or distilled water 2 h before (+)-amphetamine sulphate (Smith, Kline and French), 10 mg/kg containing 66 μCi/kg [^{3}H]amphetamine (New England Nuclear). Two animals in each group were killed at 30, 120 and 240 min and amphetamine concentrations measured in the brain. The procedure for extraction and measurement of [^{3}H]amphetamine was that of Lemberger, Witt & others (1970).

For behavioural effects, animals received similar treatment except that radioactive amphetamine was not added to the cold amphetamine. The duration of ASB was recorded by direct observation. Additional control rats received either distilled water or neuroleptic but no amphetamine. The pH of urine was found to range from 6·8–7·4.

All drugs were given in 1 ml aqueous solution intraperitoneally. Doses are expressed as the base.

The semilogarithmic plot in Fig. 1 shows the disappearance of amphetamine from brain under the different experimental conditions. The half-life for controls was

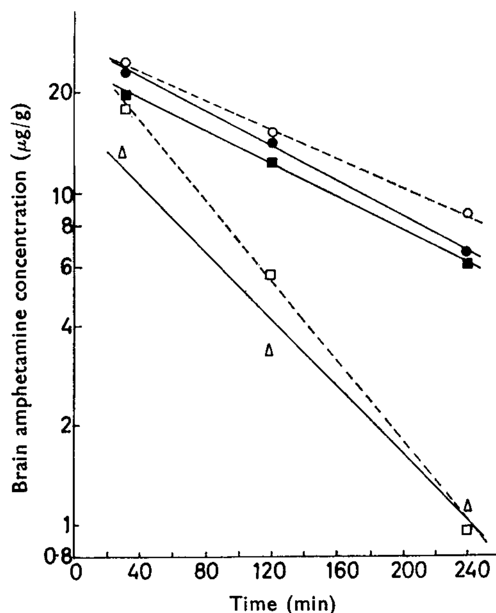

FIG. 1. Rats were treated with perphenazine (□) (1 mg/kg), triflupromazine (○), promazine (●), chlorprothixene (■) (5 mg/kg) or distilled water (△) i.p. 2 h before amphetamine (10 mg/kg, i.p. containing 66 μCi/kg [^{3}H]amphetamine/rat). Animals were killed at 30, 120 or 240 min and brains assayed for [^{3}H]amphetamine. Each point represents the mean of 2 animals. The parameters of the regression lines were estimated by the method of least squares. The slopes for perphenazine and control-treated rats are not significantly different from one another; the slopes for the other three drugs are significantly different from those for perphenazine and controls.

Table 1. *Effect of neuroleptics on amphetamine-induced sterotyped behaviour in the rat.* Rats were injected with tranquillizing agent 2 h before amphetamine (10 mg/kg). All drugs were given i.p. Onset refers to time interval between injection of amphetamine and initiation of stereotypy. Termination refers to time interval from injection of amphetamine to termination of stereotypy. *** = $P < 0.001$.

Pretreatment	Dose (mg/kg)	n	Onset (min)	Termination (min, $\bar{X} \pm$ s.e.)
Control	—	16	10	272 ± 9
Perphenazine	1	4	inhibition	—
Triflupromazine	5	4	30–480	878 ± 23***
Chlorprothixene	5	4	10–20	585 ± 9***
Promazine	5	4	10	570 ± 21***

59 min. This may be compared with the value of 52 min found by Lemberger & others (1970). When perphenazine was given before the amphetamine the initial brain concentration of amphetamine (estimated by extrapolation of the curves to time zero) was increased, but the half-life was only 50 min, indicating a more rapid disappearance of the labelled compound. The other drugs tested also increased the initial concentration of amphetamine to the same range of values, but the half-life for the radioactive amine was much extended (Fig. 1). The values for triflupromazine were 137, for promazine 112, and for chlorprothixene 125 min. Triflupromazine-treated rats at 30 or 120 min did not show ASB, even though brain concentrations of amphetamine were raised. Those at 240 min, however, had already initiated ASB about 30 min before.

In the second experiment, animals treated with amphetamine alone developed ASB within 10 min and this terminated about 4·5 h after injection of the amphetamine. Again, triflupromazine had a delaying, though somewhat variable, effect on the appearance of sterotyped behaviour, but ASB was markedly prolonged (Table 1). Promazine and chlorprothixene also prolonged ASB whereas perphenazine (1 mg/kg) completely inhibited it (Table 1).

The results show that prolongation of behavioural effects of amphetamine by neuroleptics is related to increased half-life of amphetamine in the brain. Chlorprothixene, like chlorpromazine and prochlorperazine, impairs hydroxylation of amphetamine (Lewander, 1969; Borella & Herr, 1971). Chlorpromazine, propericiazine and haloperidol increase brain amphetamine concentrations in the rat (Borella, Herr & Wojdan, 1969; Lemberger & others, 1970; Sulser & Dingell, 1968; Valzelli, Dolfini & others, 1968). This suggests that drug interaction at the level of hepatic drug-metabolizing enzymes is a general mechanism whereby tissue amphetamine concentrations are raised and hence behavioural effects of amphetamine are influenced by neuroleptics. The delayed onset of ASB with triflupromazine is presumably related to the competing central actions of amphetamine and tranquillizer on the striatal dopamine system in the brain which is believed to subserve ASB (Randrup & Munkvad, 1970). The failure of perphenazine to prolong the half-life of amphetamine may be related to the small dose used, relative to the other drugs. This dose may have been sufficient for blockade of dopamine receptor sites but insufficient to impair the biotransformation of amphetamine.

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Cross tolerance between methylamphetamine and morphine in the mouse

Recent work has attempted to explain the mechanism of narcotic agonist action in terms of interference with chemical transmission in the central nervous system. Evidence for the involvement of both cholinergic and monoaminergic systems has been reported (Harris, 1970).

Amongst the evidence in support of these hypotheses is the fact that both sympathomimetics (Colville & Chaplin, 1964) and cholinomimetics (Gross, Holland & others, 1948; Chen, 1958) possess antinociceptive activity.

The characteristics of morphine and sympathomimetic antinociception have been compared by Major & Pleuvry (1971). They showed that drugs known to cause changes in the content of putative transmitters in the central nervous system had a qualitatively similar effect upon the antinociceptive activity of morphine and methylamphetamine. Antinociception was increased when 5-hydroxytryptamine content was raised relative to noradrenaline, dopamine or both. Subsequent work in this laboratory has shown that whilst physostigmine antinociception has similar characteristics to that of morphine and methylamphetamine, oxotremorine antinociception has not.

Tolerance development is a characteristic of both morphine-like agonists and the sympathomimetics. In a further attempt to examine similarities between these various antinociceptive agents, the characteristics of tolerance to them has been compared.

Antinociception was estimated by the hot plate reaction time test (Bousfield & Rees, 1969). Drugs were administered twice daily for five days. The drugs were morphine sulphate (10 mg/kg, i.p.), methylamphetamine hydrochloride (10 mg/kg, i.p.), physostigmine salicylate (0·1 mg/kg, s.c.), oxotremorine (0·05 mg/kg s.c.) and saline (0·1 ml i.p. or s.c.). Single injections of the above doses of antinociceptive agents were approximately equipotent in the hot plate reaction time test. Reaction times in groups of 12 mice were measured at 5 min intervals for the first 30 min after the first injection each day and then at 10 min intervals until the reaction times were not significantly different from those of saline pretreated control mice.

In the afternoon of the fifth day, mice pretreated with methylamphetamine, physostigmine or oxotremorine were injected with 10 mg/kg morphine sulphate and the concurrently tested morphine-treated mice injected with either methylamphetamine, physostigmine or oxotremorine. Saline-pretreated mice were injected with either morphine, methylamphetamine, physostigmine or oxotremorine. The reaction