Short communications

Effect of some amphetamine analogues on α-methyl-*p*-tyrosine-induced catalepsy in rats

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A single dose of α-methyl-*p*-tyrosine induced catalepsy in rats, commencing 6 h after administration. This catalepsy was strongly enhanced by (+)-amphetamine and (−)-ephedrine, but was antagonized by other amphetamine-like drugs. The implication of these findings is briefly discussed.

The excitatory effects of amphetamine are prevented by pretreatment with α-methyl-*p*-tyrosine, αMPT (see for example Weissman & Koe (1965), Randrup & Munkvad (1966)). Recently, we observed that rats developed catalepsy after administration of H 44/68 (the methylester hydrochloric of αMPT) alone, or in combination with amphetamine. Although Bédard, Larochelle, Poirier & Sourkes (1970) reported recently that catatonia occurs in both intact and monkeys with brain lesions after repeated doses of αMPT, there has been no previous report of such a state occurring after a single dose of αMPT alone or in combination with amphetamine.

A short account is presented of our initial studies with combinations of H 44/68 and some amphetamine-like drugs.

Methods.—All experiments were performed using home bred female Wistar rats weighing 100–140 g. The animals were fed on a conventional 41B cube diet, and kept in the investigation room at 25°C for 24 h before use. During the experiments, the rats were grouped five per cage. H 44/68 (250 mg/kg) was administered intraperitoneally, and the second drug was given 4 h later subcutaneously.

Prior experiments were performed to determine the ED50 for stereotyped behaviour (characteristic continous sniffing and side to side head movements) for each stimulant drug, and these drugs were then administered at approximately twice that dose level. No attempt was made to score the stereotyped behaviour, which was judged simply as present or absent. Catalepsy, defined as the acceptance and retention of abnormal postures, was quantified by a modification of the method described by Courvoisier, Ducrot & Julou (1957). The front paws of the rat were placed on a 7 cm high column and the length of time the animal remained in this unnatural position, was recorded. Animals still on the column after 45 s were removed. Normal animals remained on the column, at the most, for only 1–2 seconds.

The following drugs were used: fencamfamin HCl (3·0 mg/kg), methylphenidate HCl (20.0 mg/kg), pyrovalerone HCl (6·0 mg/kg), aminoxaphen fumarate (5·0 mg/kg), phenmetrazine HCl (20·0 mg/kg), (−)-ephedrine (40·0 mg/kg), (−)-amphetamine sulphate (10·0 mg/kg), and (+)-amphetamine sulphate (5·0 mg/kg). Additional doses of (−)-amphetamine (20 mg/kg) and (+)-amphetamine (2·5, 10, and 20 mg/kg) were used. Ten to fifteen animals were used at each dose level with the exception of (+)-amphetamine (5 mg/kg) where the total number was 40. Statistical significance was determined by means of Student's *t* test.

Results.—H 44/68 blocked the stereotyped behaviour induced by (−)-ephedrine, (−)-amphetamine and (+)-amphetamine (2·5–10 mg/kg). At the 20 mg/kg dose level (+)-amphetamine induced weak stereotyped behaviour in 50% of the animals for about 1 hour. Phenmetrazine caused stereotyped behaviour in about 70% of the animals, but lasting only 20–30 minutes. In the case of the remaining stimulant drugs the duration of the stereotyped behaviour was shortened, but not appreciably altered in regard to intensity.

The single dose of H 44/48 followed by a saline injection induced a slight degree of catalepsy, commencing at 6 h and rising to just under 10±3 s at 9 h (Fig. 1). This was completely inhibited by fencamfamin, and attenuated and delayed by methylphenidate, pyrovalerone, aminoxaphen, and phenmetrazine. In contrast, (−)-amphetamine, (Fig. 1c), at both dose levels, slightly enhanced the catalepsy, peaks of 12±5 s (10 mg/kg) and 17±6 s (20 mg/kg) being

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reached at 8 hours. Similarly the lowest dose (2·5 mg/kg) of (+)-amphetamine induced a slight increase in catalepsy from 6 to 8 h (Fig. 1b). Higher doses of this latter compound significantly enhanced the catalepsy ($P<0·001$), although its onset was progressively delayed with increasing doses (Fig. 1a). Maximum values were obtained at 8–9 h, of the order of 31 ± 2 s (5 mg/kg), 38 ± 3 s (10 mg/kg) and 40 ± 3 s (20 mg/kg).

The catalepsy was also strongly and significantly ($P<0·001$) enhanced by (−)-ephedrine, a peak of 32 ± 5 s again

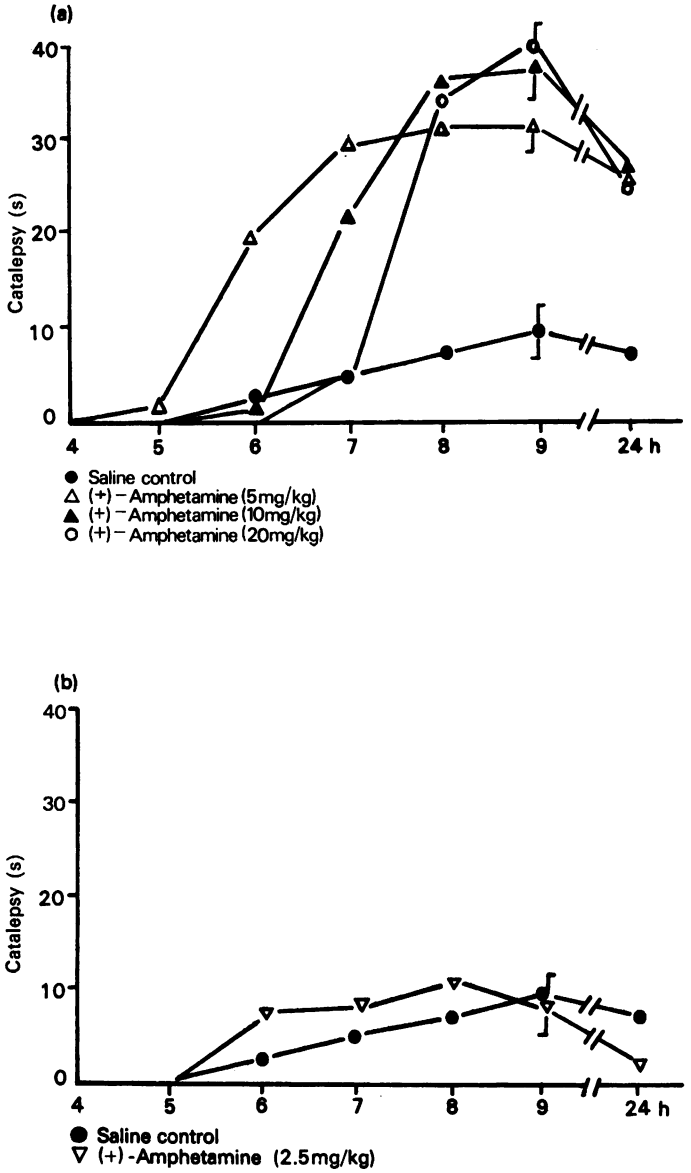

FIG. 1. Catalepsy in rats after administration of a combination of H 44/68 (250 mg/kg i.p.) with either (+)-amphetamine, (−)-amphetamine or (−)-ephedrine. The sympathomimetic drug was given subcutaneously 4 h after H 44/68. Each point represents the average of ten to fifteen animals, except in the case of (+)-amphetamine (5 mg/kg), where $n=40$, and the saline control where $n=25$. Vertical bars: S.E.M. Fig. 1 continued on the next page.

being reached at 8 h (Fig. 1d.). Although in these experiments only the degree of catalepsy was measured the animals additionally showed other signs of a catatonic state (as defined by De Jong, 1945), characterized by hypokinesia, hunched back, slightly splayed hindlimb, increased muscle tone and negativism.

Discussion. — Although H 44/68 is widely used in amine turn-over experiments to block amine synthesis, the catalepsy induced by this compound alone in rats has not been previously reported. Enhancement of this catalepsy by (+)-amphetamine was characterized by a dose-dependent delay of onset. This could be explained by a direct action on the receptors to an extent which antagonizes the catalepsy but which does not induce, or only weakly (20 mg/kg dose level), induces, stereotyped behaviour. The marked difference in degree of enhancement of catalepsy induced by (+)-amphetamine and (−)-amphetamine was surprising in view of the fact that equipotent doses of the two drugs, in respect of stereotyped behaviour, were used. It would appear that a stereospecific mechanism is involved.

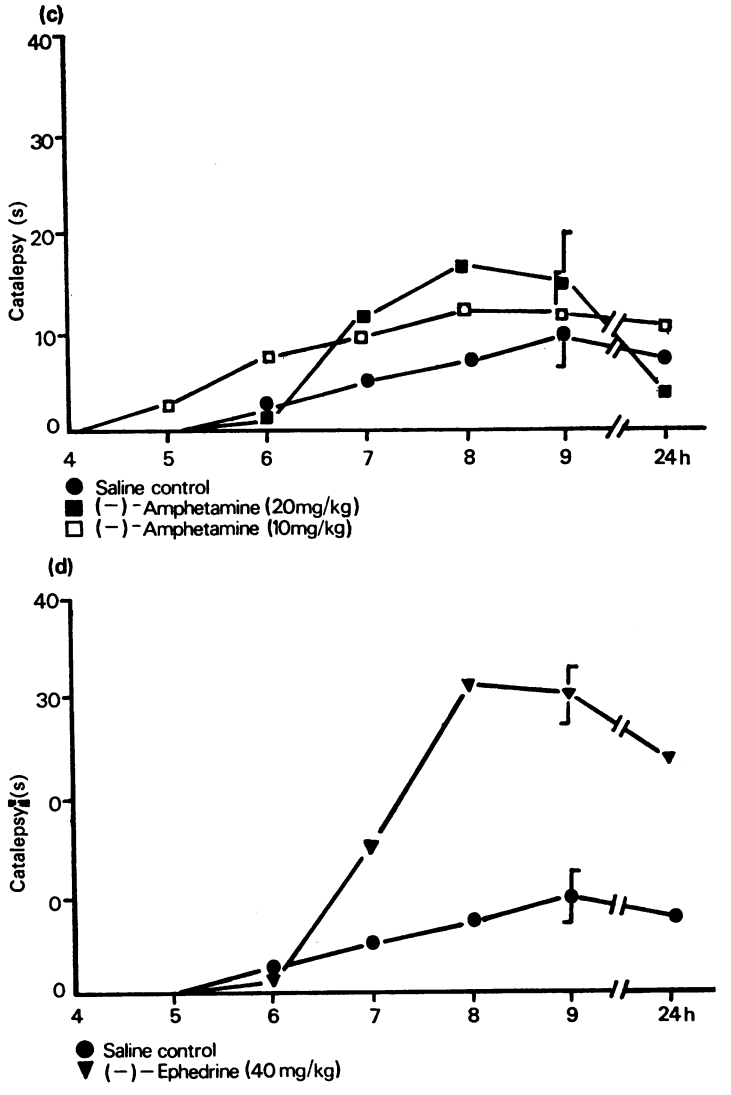

FIG. 1—*continued.* Legend as on previous page.

The failure of phenmetrazine to enhance the catalepsy is interesting in view of the fact that this drug, using other criteria, has been grouped with amphetamine and methamphetamine. Thus in common with these drugs, it still induced a picture of excitation, consisting of increased locomotor activity and stereotyped behaviour, following pretreatment with high doses of reserpine, but was strongly inhibited by α-MPT (Scheel-Krüger, 1971).

The cause of enhancement of the H 44/68 induced catalepsy is for the moment a matter of conjecture. It is unlikely that depletion of dopamine (DA) is responsible, since Corrodi, Fuxe & Hökfelt (1967), have shown that brain DA concentrations 6 h after H 44/68 are not significantly lowered by amphetamine in doses similar to those used in these experiments. The possibility must be considered that interaction between H 44/68 and (+)-amphetamine or (−)-ephedrine respectively produces a metabolite interfering with synaptic transmission.

The results of the combination of H 44/68 and the stimulant drugs on stereotyped behaviour are largely in agreement with the literature, with the exception of phenmetrazine. Although it has been reported that the excitatory effects of this drug were blocked by pretreatment with αMPT (Weissman, Koe & Tenen, 1966), in our current experiments we did observe weak, transitory stereotyped behaviour in about 70% of the animals. In all of the cases where stereotyped behaviour still occurred in the presence of H 44/68, the duration of such behaviour was considerably shortened.

This may indicate that these compounds (fencamfamin, methylphenidate, pyrovalerone, and aminoxaphen) may act to a certain extent by release of newly synthesized amines. Conversely the stereotyped behaviour induced by the highest dose of (+)-amphetamine (20 mg/kg) in the presence of H 44/ 68 could be due either to a release of amines from the storage granules, or to a direct action on the receptors. After pretreatment with reserpine (5 mg/kg, 18 h previously) and H 44/ 68 (250 mg/kg, 4 h previously), (+)-amphetamine was still capable of inducing stereotyped behaviour at the 20 mg/kg dose level (unpublished results), suggesting that it does in fact exert some direct action on the receptors.

Further work is in progress to elucidate the findings presented.

A Sayers is on study leave from Dr. A. Wander Ltd., Berne, Switzerland.

REFERENCES

BÉDARD, P., LAROCHELLE, L., POIRIER, L. J. & SOURKES, T. L. (1970). Reversible effect of L-DOPA on tremor and catatonia induced by α-methyl-p-tyrosine. *Can. J. Physiol. Pharmac.*, **48**, 82–84.

CORRODI, H., FUXE, K. & HÖKFELT, T. (1967). The effect of some psychoactive drugs on central monoamine neurons. *Europ. J. Pharmac.*, **1**, 363–368.

COURVOISIER, S., DUCROT, R. & JULOU, L. (1957). In: *Psychotropic Drugs*, ed. Garattini, S. & Ghetti, V. Amsterdam: Elsevier.

DE JONG, H. (1945). *Experimental Catatonia.* Baltimore: Williams & Wilkins.

RANDRUP, A. & MUNKVAD, T. (1966). On the role of catecholamines in the amphetamine excitatory response. *Nature, Lond.*, **211**, 540.

SCHEEL-KRÜGER, J. (1971). Comparative studies of various amphetamine analogues demonstrating different interactions with the metabolism of the catecholamines in the brain. *Europ. J. Pharmac.*, **14**, 47–59.

WEISSMAN, A. & KOE, B. K. (1965). Behavioural effects of 1-α-methyl-tyrosine, an inhibitor of tyrosine hydroxylase. *Life. Sci.*, **4**, 1037–1048.

WEISSMAN, A., KOE, B. K. & TENEN, S. S. (1966). Anti-amphetamine effects following inhibition of tyrosine hydroxylase. *J. Pharmac. exp. Ther.*, **151**, 339–352.

(*Received April* 19, 1971)