of propranolol in dogs with ablated vagi suggests that there is a common denominator, unrelated to β-blockade in the action of these drugs. The abolition of anti-arrhythmic efficacy of UM-272 and reduction of propranolol effect in bilaterally vagotomized dogs cannot be attributed to a general resistance of such arrhythmias to drug treatment since diphenylhydantoin successfully antagonized ouabain VT in animals with intact and ablated vagi (Table 1). The present results clearly indicate the involvement of vagus in the anti-arrhythmic effect of propranolol and UM-272. The fact that both propranolol and UM-272, but not timolol, inhibited cholinesterase enzyme (Alkondon et al 1983) and also exhibited anti-arrhythmic effect suggests a possible correlation between these two effects and supports the above contention. Though there is evidence that diphenylhydantoin may antagonize ouabain arrhythmias by an inhibitory action on cardiac sympathetic neurons (Gillis et al 1971), it can be stated from our experiments that the vagus nerve does not play a significant role in the anti-arrhythmic action of this drug.

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# The effects of phenylpropanolamine and other sympathomimetics on food consumption and motor activity in mice

M. J. CAIRNS, JANET E. FOLDYS, J. M. H. REES*, *Department of Pharmacology, Materia Medica and Therapeutics, Stopford Building, University of Manchester, Manchester, M13 9PT, UK*

The effects of phenylpropanolamine on motor activity and on food intake were compared with those of *S*-amphetamine, ephedrine, 2-aminoindane and fenfluramine in groups of mice. Motor activity was additionally measured in mice pretreated with levodopa and benserazide, and food intake in mice pretreated with α-methyl-*p*-tyrosine. Amphetamine (2·5 mg kg$^{-1}$) increased motor activity, phenylpropanolamine (10–40 mg kg$^{-1}$) and 2-aminoindane (2·5–10 mg kg$^{-1}$) decreased activity whilst ephedrine (2·5–40 mg kg$^{-1}$) had a biphasic effect. Fenfluramine (10–40 mg kg$^{-1}$) had negligible effect on activity. In mice pretreated with levodopa and benserazide both phenylpropanolamine and 2-aminoindane caused a massive increase in motor activity whilst fenfluramine's action was not affected in the same way. Whilst the anorectic action of fenfluramine was considerably potentiated in mice pretreated with α-methyl-*p*-tyrosine, that of amphetamine, ephedrine, 2-aminoindane and phenylpropanolamine was either unaffected or initially antagonized. It is concluded that the mechanisms of motor and anorectic actions of phenylpropanolamine are similar to those of amphetamine.

Phenylpropanolamine is a widely used sympathomimetic (Editorial 1981, 1982; Pharm. J. 1984). It has been used as an anorectic in the USA and an attempt was made to introduce the drug in the UK for that purpose by mail order (Pharm. J. 1981). Its ready availability contrasts with the severe restrictions imposed on its chemical relative, amphetamine. The mechanism of phenylpropanolamine's anorectic action is unclear (Hoebel 1977).

Drugs chemically related to amphetamine can suppress appetite by different mechanisms. Fenfluramine has been reported to act via tryptaminergic mechanisms whereas amphetamine releases catecholamines (Garattini 1980). We have previously found that these two type substances can be distinguished by pretreatment of mice with α-methyl-*p*-tyrosine (α-mpt). This pretreatment considerably potentiates the anorectic action of fenfluramine, though has little effect, or may even antagonize the anorectic action of amphetamine and similar drugs (Ginawi 1981).

Fenfluramine also differs from amphetamine in that it is sedative. In rodents many amphetamine-like sympathomimetics also decrease locomotor activity but these may be distinguished from fenfluramine by pretreatment with levodopa which unmasks a marked stimulant action.

Using these two pretreatment courses we have characterized the anorectic and motor activity actions of phenylpropanolamine.

* Correspondence.

*Method*

Groups of Manchester strain mice of either sex (30–50 g) were used. They were housed in normal lighting (light from 8–18 h).

For the anorectic studies mice were deprived of food for 18–20 h before testing. α-mpt (150 mg kg$^{-1}$) or 0·9% NaCl (saline) was injected i.p. 4 h before testing.

Groups of 5 fasted mice were then injected with the test drug or with saline and placed in a cage (350 cm$^2$) with access to a weighed amount of their normal food pellets (ca 20 g). The pellets were reweighed at 30 min intervals for 5 h and food consumption calculated. Doses of test drugs and saline controls were randomized each day with up to 15 groups of mice being tested at each time. Between 4 and 8 groups of each dose of each test drug were examined in saline and in α-mpt-pretreated mice. Results are expressed as percentage change from appropriate controls.

In the activity studies, groups of 5 unfasted mice were injected with saline or levodopa (150 mg kg$^{-1}$) and benserazide (30 mg kg$^{-1}$), and 15 min later with the test drug or saline. The mice were then placed in a transparent cage of floor area 600 cm$^2$ on an Animex meter set at 40 μA. Activity was recorded at 5 min intervals for at least 2 h. Results are expressed as differences from concurrent saline controls.

Pretreatment drugs were levodopa (Koch-Light), benserazide hydrochloride (Roche), α-methyl-*p*-tyrosine methyl ester (Sigma). The test drugs and the doses used (in mg kg$^{-1}$) were phenylpropanolamine hydrochloride (10,40): *S*-amphetamine sulphate (2·5), ephedrine hydrochloride (2·5, 10), fenfluramine hydrochloride (10, 40) and 2-aminoindane hydrochloride (10). We are grateful to Roche Products and to Servier Laboratories for kind donations of drugs.

*Results*

A control group of mice injected with saline ate about 2 g of food in the first 30 min, thereafter eating steadily at a rate of 0·5 g in each 30 min period. Mice pretreated with α-mpt ate less than those pretreated with saline. This was not significant during the first 30 min when the rate of feeding was greatest, though by the end of the 5 h period the total food consumed was about half that of controls.

All five anorectic agents caused a significant fall in food intake during the first hour following injection, and thereafter there was a variable increase in feeding. Fig. 1 contrasts the effects of α-mpt pretreatment on the time course of anorectic action of 2-aminoindane and of fenfluramine. The anorectic action of 2-aminoindane was initially antagonized whereas that of fenfluramine was enhanced throughout the observational period to such an extent that in the fifth hour the mice ate nothing. Table 1 compares the food intake of selected doses of phenylpropanolamine and three other anorectic agents in control mice and in those pretreated with α-mpt. The percentage intake of food following amphetamine, phenylpropanolamine and ephedrine during the first hour was similar whether the mice had been pretreated with saline or α-mpt. Following this there was some reduction in feeding in the α-mpt pretreated group, and the pattern of feeding following phenylpropanolamine was similar to that following amphetamine in these pretreated mice. In contrast α-mpt pretreatment caused a marked potentiation of fenfluramine's anorectic action.

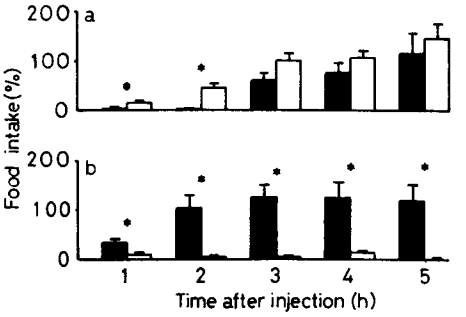


FIG. 1. The time course of effect of 2-aminoindane (10 mg kg$^{-1}$, a) and fenfluramine (10 mg kg$^{-1}$, b) on food intake in groups of saline pretreated mice (closed columns), and in mice pretreated with α-methyl-*p*-tyrosine (150 mg kg$^{-1}$, open columns). Results are expressed as % change from appropriate controls (± s.e.m.). n = 4, * denotes $P < 0·05$.

On the Animex meter phenylpropanolamine (10, 40 mg kg$^{-1}$) and 2-aminoindane (2·5 and 10 mg kg$^{-1}$) decreased activity; ephedrine 2·5, 10 and 40 mg kg$^{-1}$) decreased activity during the first 30 min following injection, this being followed by an increase in activity; whilst amphetamine caused a marked increase in the

Table 1. The food intake (expressed as % ± s.e.m.) during the 1st, 3rd and 5th hour following injection of four anorectic drugs into groups of control mice (C), and into mice pretreated with α-methyl-*p*-tyrosine (150 mg kg$^{-1}$, α-mpt). n = 4, * denotes $P < 0·05$.

| | Dose mg kg$^{-1}$ | Hours after injection 1 C | 1 α-mpt | 3 C | 3 α-mpt | 5 C | 5 α-mpt |
|---|---|---|---|---|---|---|---|
| Fenfluramine | 10 | 35 ± 7 | *14 ± 1 | 124 ± 23 | *3 ± 4 | 112 ± 33 | *0 ± 0 |
| Amphetamine | 2·5 | 24 ± 8 | 20 ± 7 | 217 ± 33 | *98 ± 21 | 106 ± 35 | 70 ± 12 |
| Phenylpropanolamine | 10 | 37 ± 10 | 58 ± 9 | 193 ± 31 | *81 ± 16 | 110 ± 29 | 144 ± 77 |
| Ephedrine | 2·5 | 54 ± 13 | 49 ± 6 | 120 ± 25 | 89 ± 21 | 95 ± 12 | 115 ± 43 |

activity count. Fenfluramine (10, 40 mg kg$^{-1}$) had no significant effect on activity.

Levodopa and benserazide treatment reduced motor activity significantly for the 1 h after injection. In combination with both phenylpropanolamine and with 2-aminoindane, activity was massively increased (Fig. 2). The characteristics of locomotion were the same as those of mice treated with amphetamine, namely characteristic stilted gait, stereotyped behaviour, piloerection and Straub tail. The movement of pretreated mice challenged with fenfluramine was quite different. The animals lay prone with their feet splayed out, and tail extended flat on the floor. The little recorded motor activity was due to shaking. All behavioural effects were readily reversible.

*Discussion*

The mechanism of anorectic action of amphetamine can easily be distinguished from that of fenfluramine since the former interferes with one or more of the catecholamine neurotransmitters, whilst fenfluramine interferes with tryptaminergic pathways. The methods most commonly used to identify these mechanisms have involved chemical and surgical lesioning and the use of neurotransmitter antagonists.

Whilst we have found that brain depletion by *p*-chlorophenylalanine has some differential action on the two type substances, the pattern was not clear cut, and we note that Sugrue et al (1975) failed to antagonize fenfluramine anorexia by *p*-chlorophenylalanine pretreatment.

We have found that the two type substances can most easily be distinguished by the peripheral administration of α-mpt (see Fig. 1). A reduction in amphetamine's action following α-mpt has been reported by Clineschmidt et al (1974), though they did not see an enhancement in fenfluramine's action. However, the experimental conditions differed from ours and their dose of α-mpt was smaller. 6-Hydroxydopamine pretreatment has also been reported to differentiate between the two mechanisms of action in a similar qualitative way that we have shown using α-mpt (Hoebel 1977).

Hoebel (1977) also summarized some experiments with phenylpropanolamine. Like amphetamine it caused anorexia when applied directly to the lateral hypothalamus, but unlike amphetamine or fenfluramine it was unaffected by 6-hydroxydopamine pretreatment. Hoebel concluded that the mechanism of action was 'a mystery'.

In our experiments using α-mpt, phenylpropanolamine's anorectic action was influenced in the same way as was that of amphetamine and related drugs.

Many amphetamine derivatives, in contrast to the parent compound, are sedative, and this is manifest as a decrease in motor activity in rodents. The characteristics of this differ from that of fenfluramine and can be distinguished by pretreatment with levodopa.

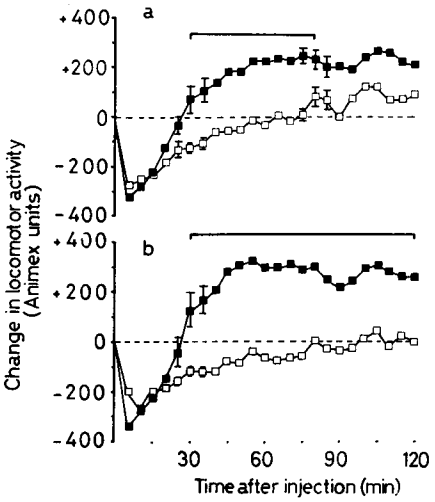


FIG. 2. The time course of change in motor activity count caused by 2-aminoindane (10 mg kg$^{-1}$, a) and phenylpropanolamine (40 mg kg$^{-1}$, b) in groups of saline pretreated mice (open symbols), and in those pretreated with levodopa (150 mg kg$^{-1}$) + benserazide (30 mg kg$^{-1}$) (closed symbols). Each point is the mean of at least 4 groups of 5 mice. Representative s.e.m. are included at the times when change becomes significant ($P < 0.05$). Horizontal bars indicate the durations of significant differences.

The potential excitatory action of phenylpropanolamine exposed by levodopa (Fig. 2) represents a degree of excitation rarely seen with amphetamine alone or in combination with levodopa. The behavioural characteristics of this excitation confirm a catecholaminergic component in phenylpropanolamine action. This mechanism is compatible with the recent publicized hazards of this widely used drug including hypertensive (Pentel et al 1982) and psychotomimetic actions (Dietz 1981), and abuse potential (Editorial 1981).

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