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# The effect of β-phenethylamine upon spontaneous motor activity in mice: A dual effect on locomotor activity

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The effect of intraperitoneal injections of β-phenethylamine on spontaneous motor activity in mice has been examined. Doses 75 mg/kg and higher produced a biphasic type of activity. A first phase of increased activity occurred about 5 min after injection, and a second about 30 min after injection. Pharmacological examination of these curves showed the first peak to be an indirect effect requiring newly synthesized noradrenaline, while the second peak appeared to be caused by a direct action. Thus it was not affected by reserpine, α-methyldopa, protriptyline, desipramine, disulfiram or α-methyl-*p*-tyrosine. These results suggest that phenethylamine differs from amphetamine in its effect on spontaneous motor activity.

β-Phenethylamine has been found in the tissues of animals (Nakajima, Kakimoto & Sano, 1964; Jackson & Temple, 1970), and of man (Asatoor & Dalgleish, 1959; Levine, Nirenberg, & others, 1964). Although phenethylamine is a normal constituent of human tissues, it is excreted at an abnormal rate in phenylketonuria (Oates, Nirenberg & others, 1963; Levine & others, 1964).

An amphetamine-like effect on spontaneous motor activity (SMA) is produced when phenethylamine is given to animals treated with monoamine oxidase (MAO) inhibitors (Mantegazza & Riva, 1963; Fischer, Ludmer & Sabelli, 1967; Saavedra & Fischer, 1970). Most authors have been unable to demonstrate its stimulant effect on motor activity without the use of MAO inhibitors, and have shown that higher doses of phenethylamine cause inhibition of SMA (Fischer & others, 1967). While some authors (Nakajima & others, 1964) have found that intraperitoneal injection of the amine increases SMA in mice for only 15 min after injection, others (Mantegazza & Riva, 1963; Fischer & others, 1967) have made their measurements 30 min or later after intraperitoneal or subcutaneous injection.

Phenethylamine antagonizes the depressant effects of 5-hydroxytryptamine (5-HT), tryptamine and reserpine on SMA, and Fischer, Saavedra & Heller (1968) and Saavedra & Fischer (1970) have postulated that phenethylamine may play a role in the cns as a neurotransmitter.

I have examined the effect of phenethylamine on SMA in mice and attempted to elucidate its mode of action.

## METHODS

QS strain male mice, 23–28 g, were kept at 20–23° in groups of at least five with noise and ambient light levels constant. Food and water were allowed freely until the experiment was begun. After premedication, or on the day of the experiment, the animals in groups of five were injected with phenethylamine, or distilled water as a

control, immediately placed in the actophotometer for at least 1 h, and readings taken every min for the first 20 min, and every 5 min thereafter.

The actophotometer was of 46 cm diameter and 55 cm height. The circular enclosure was divided by six light beams at 3 cm from the floor, each beam being connected to a counter. The total number of movements in a given period of time was estimated by summing the number of counts.

All drugs were dissolved in distilled water and administered in a dose volume of 1 ml/100 g (i.p.) except where stated otherwise. Reserpine was dissolved in 20% ascorbic acid, and diluted with distilled water. Disulfiram was suspended in water with Lissapol D (ICI) 0·1%.

Origin of drugs: α-methyl-*p*-tyrosine methyl ester HCl (Sigma); β-phenethylamine hydrochloride was prepared from the base (Sigma); reserpine base (Hamilton); iproniazid phosphate (Roche); desipramine (Geigy); α-methyldopa (Merck, Sharp & Dohme); methysergide and lysergic acid diethylamide (Sandoz); disulfiram (Antabuse. Winthrop).

## RESULTS

Phenethylamine was tested in doses of 2·5 to 150 mg/kg. No apparent increase in SMA above control values was noted with doses less than 25 mg/kg (Fig. 1). A dose

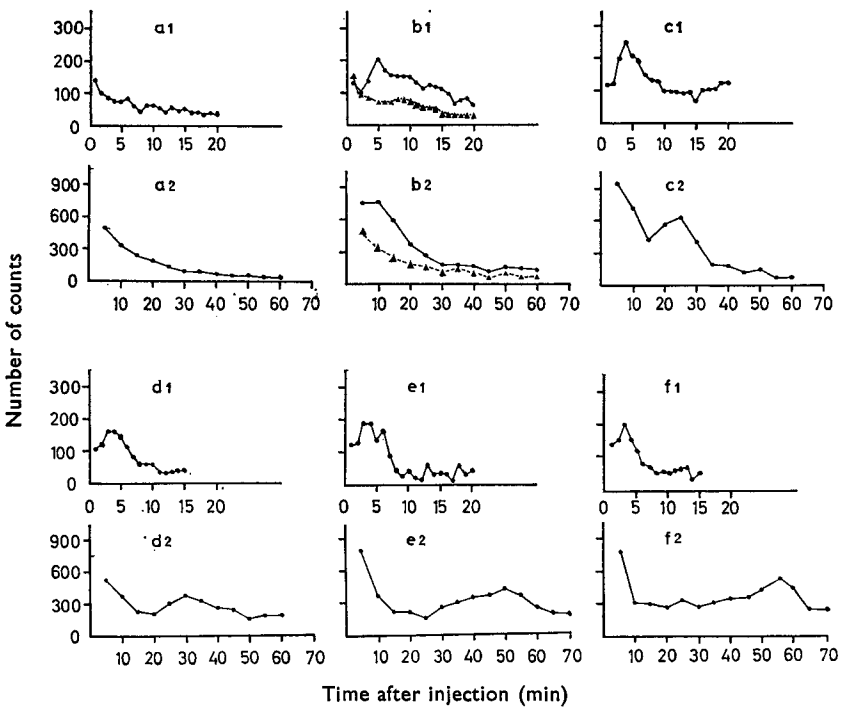


FIG. 1. The effect of phenethylamine upon SMA in mice. Mice were injected with a dose and immediately placed in the cage for at least 1 h and readings of activity made every min for 20 min, then every 5 min. Graphs a1, b1, c1 etc., represent the SMA between 0 and 20 min plotted at 1 min intervals, while a2, b2, c2, are the data from the same experiments but represent the SMA between 0 and 60 min plotted at 5 min intervals. The standard errors have been omitted for clarity. A distilled water control is included in b(1) and b(2) but has been omitted in the other graphs for clarity. Phenethylamine (all doses) ●, control ▲. a1, a2 = 25; b1, b2 = 50; c1, c2 = 75; d1, d2 = 100; e1, e2 = 125; f1, f2 = 150 mg/kg.

of 50 mg/kg produced an increase in SMA with a peak 5 min after injection. A 75 mg/kg dose produced a peak in SMA in 4 min, then a decline to 15 min, and a second peak at 25 min. Doses of 100 mg/kg and above produced two distinct phases of activity. The higher the dose the earlier the first and the later the second peak (Fig. 1). Total SMA has been calculated between 0 and 20 min and between 20 and 60 min after injection because of the two distinct phases of activity. These data indicate that a dose of 75 mg/kg has the most marked effect on SMA between 0 and 20 min and that higher doses caused reduction in SMA. SMA produced by doses of 100 mg/kg and higher was not significantly different from the control value (Table 1). Observation of the animals suggested that the reduction in SMA between 0 and 20 min with doses greater than 75 mg/kg was caused by toxic effects of the drug; tremors, twitching, licking and various stereotyped behaviour patterns were evident. Between 20 and 60 min after injection, however, there was a dose-dependent increase in SMA with doses of phenethylamine as high as 150 mg/kg (Table 1). With the higher doses, the initial toxic symptoms had worn off within 20 min.

The monoamine oxidase inhibitor iproniazid, 100 mg/kg, 24 h before phenethyl-

Table 1. *The effect of phenethylamine (PE) on locomotor activity in mice.* The animals, grouped in five, were injected with PE or with $H_2O$ and immediately placed in the actophotometer and readings made for 1 h. The standard error of the mean is given and the values in brackets represent the number of experiments. The probability (*P*) is the significance level of each value compared to the water control (doses from 2·5–25 mg do not differ significantly from the control value). The left side of the table is the data between 0 and 20 min and the right side of the table the data between 20 and 60 min.

| Dose of PE mg/kg(n) | Total counts between 0 and 20 min | % diff.* | *P* | Total counts between 20 and 60 min | % diff.* | *P* |
|---|---|---|---|---|---|---|
| 50·0 (8) | 2476 ± 278 | 195 | <0·001 | 1324 ± 193 | 160 | 0·05–0·1 |
| 75·0 (5) | 2714 ± 182 | 214 | <0·001 | 1925 ± 151 | 232 | <0·001 |
| 100·0 (8) | 1543 ± 130 | 122 | 0·05–0·1 | 2043 ± 167 | 246 | <0·001 |
| 125·0 (5) | 1621 ± 136 | 128 | 0·1 –0·2 | 2631 ± 195 | 317 | <0·001 |
| 150·0 (5) | 1718 ± 188 | 136 | 0·2 –0·5 | 3005 ± 185 | 362 | <0·001 |
| Water Control (10) | 1267 ± 67 | 100 | | 830 ± 165 | 100 | |

* From Control as 100%.

amine, 10 or 25 mg/kg, caused a rise in SMA both between 0 and 20 and between 20 and 60 min (Table 2). The duration of action of phenethylamine was prolonged. Iproniazid alone produced a significant rise in SMA when compared to untreated controls (see Tables 1 and 2).

Reserpine, 1 mg/kg 48 and 24 h before phenethylamine, markedly sedated the animals (Table 2) and caused an average weight loss of 25%. Although the SMA between 0 and 20 min produced by phenethylamine, 50 or 100 mg/kg, combined with reserpine was lower than that produced by either of the two doses alone, it was much higher than reserpine + water controls. Little effect was noted between 20 and 60 min.

To minimize the toxic effects caused by the total dose of 2 mg/kg reserpine, 750 μg/kg of reserpine was given separately to some mice. No obvious toxicity or weight loss occurred, although some reduction in SMA was observed (Table 2). Between 0

Table 2. *The effect of various drug pretreatments on the SMA produced by phenethylamine (PE).* The animals were pretreated at various time intervals before PE (see text) and immediately placed in the cage for 1 h. The standard error of the mean is given and the values in brackets represent the number of experiments. The probability (*P*) is the significance level of each drug treatment compared to the control.

| Injection 1st | Injection 2nd mg/kg | Total counts between 0 and 20 min | % diff.* | *P* | Total counts between 20 and 60 min | % diff.* | *P* |
|---|---|---|---|---|---|---|---|
| α-Methyl dopa | PE 25 (5) | 1368 ± 52 | 157 | 0·001–0·01 | 1294 ± 104 | 262 | <0·001 |
| 400 mg/kg | PE 50 (5) | 2691 ± 206 | 309 | <0·001 | 1727 ± 131 | 350 | <0·001 |
| | PE 100 (5) | 996 ± 108 | 114 | 0·4 –0·5 | 1944 ± 170 | 394 | <0·001 |
| | $H_2O$ (4) | 870 ± 112 | 100 | | 493 ± 33 | 100 | |
| Iproniazid | PE 10 (5) | 2495 ± 445 | 197 | 0·1 –0·2 | 1191 ± 219 | 143 | 0·2 –0·3 |
| 100 mg/kg | PE 25 (4) | 3881 ± 178 | 306 | <0·001 | 5512 ± 570 | 664 | <0·001 |
| | $H_2O$ (4) | 1635 ± 63 | 129 | | 1861 ± 129 | 224 | <0·001 |
| Reserpine | PE 50 (4) | 598 ± 48 | 757 | | 468 ± 119 | 77 | |
| 2 mg/kg total | PE 100 (5) | 1199 ± 130 | 1517 | | 1869 ± 204 | 308 | |
| | $H_2O$ (2) | 79 | 100 | | 606 | 100 | |
| Reserpine | PE 50 (5) | 1518 ± 116 | 168 | 0·01–0·001 | 667 ± 69 | 62 | 0·02–0·05 |
| 750 μg/kg total | PE 100 (5) | 1086 ± 59 | 120 | 0·05–0·1 | 1730 ± 144 | 161 | 0·01–0·02 |
| | PE 125 (4) | 1067 ± 72 | 118 | 0·1 –0·2 | 2339 ± 136 | 218 | <0·001 |
| | $H_2O$ (4) | 905 ± 65 | 100 | | 1075 ± 141 | 100 | |
| Protriptyline | PE 25 (5) | 1060 ± 49 | 103 | 0·7 –0·8 | 504 ± 69 | 88 | 0·6 –0·7 |
| 10 mg/kg | PE 50 (5) | 1427 ± 278 | 139 | 0·2 –0·3 | 675 ± 41 | 118 | 0·4 –0·5 |
| | PE 100 (5) | 1151 ± 102 | 112 | 0·3 –0·4 | 1625 ± 166 | 284 | 0·01–0·001 |
| | $H_2O$ (5) | 1029 ± 90 | 100 | | 572 ± 127 | 100 | |
| Desipramine | PE 25 (5) | 817 ± 113 | 83 | 0·2 –0·3 | 348 ± 126 | 77 | 0·6 –0·7 |
| 25 mg/kg | PE 50 (5) | 1728 ± 161 | 177 | 0·01–0·001 | 766 ± 40 | 169 | 0·05–0·10 |
| | PE 100 (6) | 750 ± 85 | 77 | 0·05–0·1 | 1262 ± 283 | 279 | 0·02–0·05 |
| | $H_2O$ (5) | 979 ± 90 | 100 | | 453 ± 149 | 100 | |
| Desipramine | PE 25 (5) | 413 ± 73 | 73 | 0·2 –0·3 | 249 ± 34 | 137 | 0·2 –0·3 |
| 50 mg/kg | PE 50 (6) | 1310 ± 206 | 231 | 0·01–0·001 | 290 ± 50 | 159 | 0·1 –0·2 |
| | PE 100 (5) | 1056 ± 78 | 187 | 0·01–0·001 | 1011 ± 50 | 555 | <0·001 |
| | $H_2O$ (5) | 566 ± 94 | 100 | | 182 ± 46 | 100 | |
| Methysergide | PE 50 (5) | 2135 ± 200 | 204 | 0·01–0·02 | 594 ± 89 | 93 | 0·7 –0·8 |
| 5 mg/kg | PE 100 (5) | 1572 ± 88 | 150 | 0·01–0·02 | 1424 ± 279 | 258 | 0·02–0·05 |
| | $H_2O$ (4) | 1049 ± 127 | 100 | | 551 ± 85 | 100 | |
| Disulfiram | PE 25 (6) | 1166 ± 140 | 94 | 0·6 –0·7 | 829 ± 140 | 91 | 0·7 –0·8 |
| 100 mg/kg | PE 50 (6) | 1394 ± 140 | 112 | 0·3 –0·4 | 911 ± 177 | 100 | >0·9 |
| | PE 100 (6) | 1167 ± 163 | 94 | 0·6 –0·7 | 1679 ± 148 | 184 | 0·01–0·02 |
| | $H_2O$ (6) | 1241 ± 54 | 100 | | 912 ± 216 | 100 | |

* From control as 100%.

Table 3. *Effect of α-methyl-*p*-tyrosine on locomotor activity induced by phenethylamine (PE).* α-Methyl-*p*-tyrosine (MT), 500 mg/kg was administered 0·5 to 6 h before a dose of PE or water, and the SMA then measured with groups of five mice for 1 h. The values in brackets represent the number of experiments. The standard error of the mean is given. The probability (*P*) is the significance level of each dose of methyltyrosine compared to the control.

| Time after MT (h) | Treatment before testing (mg/kg) | Total counts between 0 and 20 min | % diff.* | *P* (0 and 20 min) | Total counts between 20 and 60 min | % diff.* | *P* (20 and 60 min) |
|---|---|---|---|---|---|---|---|
| 0·5 | PE 50 (3) | 1967 ± 150 | 189 | 0·01–0·02 | 294 ± 43 | 49 | 0·3 –0·4 |
| | PE 100 (4) | 1387 ± 231 | 133 | 0·2 –0·3 | 2011 ± 246 | 332 | 0·01–0·02 |
| | Water (3) | 1041 ± 176 | 100 | | 604 ± 258 | 100 | |
| 1·0 | PE 50 (3) | 2399 ± 629 | 226 | 0·05–0·10 | 457 ± 81 | 167 | 0·1 –0·2 |
| | PE 100 (3) | 1339 ± 112 | 129 | 0·05–0·10 | 1675 ± 116 | 611 | <0·001 |
| | Water (3) | 1036 ± 47 | 100 | | 274 ± 40 | 100 | |
| 2·0 | PE 50 (4) | 1792 ± 164 | 171 | 0·01–0·02 | 408 ± 61 | 110 | 0·7 –0·8 |
| | PE 100 (4) | 1566 ± 124 | 149 | 0·02–0·05 | 1413 ± 157 | 385 | 0·01–0·001 |
| | Water (3) | 1048 ± 145 | 100 | | 372 ± 79 | 100 | |
| 4·0 | PE 50 (4) | 655 ± 80 | 123 | 0·4 –0·5 | 244 ± 40 | 249 | 0·02–0·05 |
| | PE 100 (4) | 1548 ± 205 | 287 | 0·001–0·01 | 1358 ± 298 | 1386 | 0·01–0·001 |
| | Water (3) | 540 ± 128 | 100 | | 98 ± 24 | 100 | |
| 6·0 | PE 50 (3) | 382 ± 117 | 113 | 0·7 –0·8 | 128 ± 40 | 152 | 0·4 –0·5 |
| | PE 100 (3) | 822 ± 56 | 242 | 0·01–0·001 | 532 ± 23 | 633 | <0·001 |
| | Water (3) | 339 ± 22 | 100 | | 84 ± 39 | 100 | |

* From control as 100%.

and 20 min the SMA produced by 50 mg/kg phenethylamine was significantly higher than the control value. Between 20 and 60 min, 100 and 125 mg/kg caused significantly higher SMA than the control values. Although reserpine did not significantly reduce the SMA produced by an injection of phenethylamine (Table 2), the shape of the curve of the first phase of activity was markedly changed, while 50 mg/kg produced a rounded curve with a marked peak at 5 min (Fig. 1), pretreatment with reserpine abolished this rounded peak.

*α-Methyldopa*, 400 mg/kg, was administered in a dose volume of 40 ml/kg 24 h before phenethylamine. α-Methyldopa depressed SMA compared to water (Tables 1 and 2). Between 0 and 20 min, the SMA produced by 25 mg/kg phenethylamine in mice premedicated with α-methyldopa was significantly higher than the control value although phenethylamine, 25 mg/kg, when given with no pretreatment was not significantly different from a water control (Table 1). α-Methyldopa also potentiated the action of a 50 mg/kg dose when compared to the action of that dose by itself. α-Methyldopa potentiated the effect of all doses of phenethylamine on the SMA of mice between 20 and 60 min when compared to the same dose without pretreatment.

*Protriptyline*, 10 mg/kg, administered 0·5 h before phenethylamine, completely inhibited the stimulant effects of 50 and 100 mg/kg between 0 and 20 min. Between 20 and 60 min, the SMA produced by 100 mg/kg was significantly higher than the control value (Table 2).

*Desipramine*, 25 and 50 mg/kg, 1 h before testing depressed SMA of mice. The high dose depressed (although not significantly) the effect of phenethylamine 25, 50 and 100 mg/kg on SMA between 0 and 20 min. Between 20 and 60 min, the SMA produced by phenethylamine, 100 mg/kg, was significantly higher than the control value (Table 2).

*Methysergide*, 5 mg/kg, 0·5 h before phenethylamine, has no effect on SMA produced by phenethylamine, 50 or 100 mg/kg (Table 2).

*Disulfiram*, 100 mg/kg, 6 h before phenethylamine, had little effect on the SMA of mice by itself. Between 0 and 20 min however, it completely prevented the SMA normally produced by phenethylamine, 50 and 100 mg/kg. Between 20 and 60 min, the SMA produced by phenethylamine, 100 mg/kg, was significantly higher than the control (Table 2).

*α-Methyl*-p-*tyrosine*, 500 mg/kg, given at various times before phenethylamine, produced a progressive time dependent decrease in SMA both between 0 and 20, and between 20 and 60 min (Table 3). Phenethylamine, 50 mg/kg, administered 4 and 6 h after methyltyrosine, had no significant effect on SMA between 0 and 20 min when compared to control values. Phenethylamine, 100 mg/kg, produced a significant increase in SMA above control values 2, 4 and 6 h after injection of methyltyrosine, but not 0·5 and 1 h after injection. The effect of 100 mg/kg on SMA between 20 and 60 min was significantly greater than control values in all cases.

## DISCUSSION

It is important in the study of the effects of sympathomimetic amines on animal behaviour to distinguish locomotor or voluntary activity from stereotyped behaviour (D'encarnacao, D'encarnacao & Tapp, 1969). Amphetamine, the most widely studied and the most understood of the sympathomimetic amines, produces an increased

turnover of dopamine accompanying an increase in stereotyped behaviour (Jonas & Scheel-Kruger, 1969). Diethyldithiocarbamate, which blocks the dopamine metabolizing enzyme dopamine β-hydroxylase, potentiates small stereotyped movement but inhibits directed hypermotility (D'encarnacao & others, 1969). Methyltyrosine, a tyrosine hydroxylase inhibitor, blocks both stereotyped behaviour and hypermotility (Jonas & Scheel-Kruger, 1969). This block can be achieved with doses that do not cause sedation or affect brain catecholamine concentrations (Dingell, Owens & others, 1967; Dominic & Moore, 1969). In addition, workers have shown that the locomotor activity produced by amphetamine is potentiated by reserpine (Smith, 1963; Stolk & Rech, 1967; Jonas & Scheel-Kruger, 1969). These published results suggest that amphetamine requires the synthetic pathway for noradrenaline and dopamine to be intact for its central actions (since methyltyrosine completely inhibits locomotor activity), and that both dopamine and noradrenaline are important. There is little evidence in the literature that amphetamine has a purely direct action on the cns.

In the present series of experiments phenethylamine has been shown to produce a marked stimulant action on locomotor activity of mice. This action was potentiated by iproniazid in agreement with the result of Mantegazza & Riva (1963). Most authors have been unable to demonstrate any action of locomotor activity (except inhibition in high doses) without the use of MAO inhibitors (Mantegazza & Riva, 1963; Fischer & others, 1967). It appears, however, that the number of animals used, and the strain and sex are of utmost importance in these studies (Jackson, 1970, unpublished observation) since marked SMA was noted in the present studies without the use of MAO inhibitors.

With suitable doses of phenethylamine a distinct difference in type of activity was distinguished in the 0 and 20 and the 20 and 60 min periods. The second period of activity became evident with higher doses of phenethylamine (75 mg/kg and above). The first peak occurring between 0 and 20 min (best exemplified with a dose of 50 mg/kg phenethylamine, when no toxicity was evident), appeared to fulfil some of the requirements for an indirectly acting sympathomimetic amine, i.e., blocked by protriptyline and completely inhibited by disulfiram and α-methyl-*p*-tyrosine. However, its action was not blocked by reserpine. The second area of activity occurred between 20 and 60 min, and the results suggested a direct mode of action. Thus it was insensitive to reserpine, protriptyline and desipramine, disulfiram or methyltyrosine. These results suggest that the first phase of activity produced by an injection of a suitable dose of phenethylamine (between 0 and 20 min) resembles the SMA produced by amphetamine. Thus both phenethylamine and amphetamine require the presence of newly synthesized catecholamines (especially noradrenaline). The second phase of activity however suggests that a large component of the action of phenethylamine on SMA in mice is due to a "direct" sympathomimetic effect. Although 100 mg/kg after methyltyrosine produced a significantly higher level of SMA than control values between 0 and 20 min, it is possible that the high dose of phenethylamine in this instance caused some direct action between 0 and 20 min, and this was sufficient to produce significant SMA. α-Methyldopa has been shown to potentiate the action of amphetamine on locomotor activity (Smith, 1963), and a similar effect on locomotor activity induced by phenethylamine was observed by the present author.

The SMA produced by phenethylamine 50 mg/kg, could not be completely inhibited with even high doses of desipramine, although protriptyline, a drug which has been thought to have a similar mode of action, caused complete inhibition. Recent evidence

suggests that desipramine and protriptyline may have different actions on the catecholamine storage sites (Chesher & Taylor, personal communication).

At present the chemical entity (or entities) causing the two distinct peaks is unknown. It is possible that both areas of SMA are due to unchanged phenethylamine. Alternatively, a metabolite rather than the original material could be responsible for the second period of SMA.

The sudden and short lived first period of activity could be caused by uptake of phenethylamine into catecholamine storage areas in the brain and the subsequent immediate release of catecholamines. The second peak could be due to a metabolite being released slowly since phenethylamine in the granule stores may be stabilized against the action of MAO.

Whatever the reason for the dual effect on SMA in mice the material under study here differs significantly in some respects from amphetamine in its action on the cns. Unlike amphetamine, phenethylamine has a dual mode of action. Although the doses used were high, it is a substrate for MAO (Blaschko, 1952) which accounts for its short duration of action, and its relative low potency.

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## REFERENCES

ASATOOR, A. M. & DALGLEISH, C. E. (1959). *Biochem. J.*, **73**, 26P.

BLASCHKO, H. (1952). *Pharmac. Rev.*, **4**, 415–458.

D'ENCARNACAO, P. S., D'ENCARNACAO, P. & TAPP, J. T. (1969). *Archs int. Pharmacodyn. Thér.*, **182**, 186–189.

DINGELL, I. V., OWENS, M. L., NORVICH, M. R. & SULSER, F. (1967). *Life Sci.*, **6**, 1155–1162.

DOMINIC, J. A. & MOORE, K. E. (1969). *Archs int. Pharmacodyn. Thér.*, **178**, 166–176.

FISCHER, E., LUDMER, R. I. & SABELLI, H. C. (1967). *Acta physiol. latinoam.*, **17**, 15–21.

FISCHER, E., SAAVEDRA, J. M. & HELLER, B. (1968). *Arzneimittel-Forsch.*, **18**, 780–786.

JACKSON, D. M. & TEMPLE, D. M. (1970). *Comp. gen. Pharmac.*, **1**, 155–159.

JONAS, W. & SCHEEL-KRUGER, J. (1969). *Archs int. Pharmacodyn. Thér.*, **177**, 379–389.

LEVINE, R. J., NIRENBERG, P. Z., UDENFRIEND, S. & SJOERDSMA, A. (1964). *Life Sci.*, **3**, 651–656.

MANTEGAZZA, P. & RIVA, M. (1963). *J. Pharm. Pharmac.*, **15**, 472–478.

NAKAJIMA, T., KAKIMOTO, Y. & SANO, I. (1964). *J. Pharmac. exp. Ther.*, **143**, 319–325.

OATES, J. A., NIRENBERG, P. Z., JEPSON, J. B., SJOERDSMA, A. & UDENFRIEND, S. (1963). *Proc. Soc. exp. Biol. Med.*, **112**, 1078–1081.

SAAVEDRA, J. M. & FISCHER, E. (1970). *Arzneimittel-Forsch.*, **20**, 952–956.

SMITH, C. B. (1963). *J. Pharmac. exp. Ther.*, **142**, 343–350.

STOLK, J. M. & RECH, R. H. (1967). *Ibid.*, **158**, 140–149.