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Some further observations of the effect of β-phenethylamine on locomotor activity in mice

β-Phenethylamine (PE), identified as a naturally occurring amine in man and other animals (Nakajima, Kakimoto & Sano, 1964; Oates, Nirenberg & others, 1963; Jackson & Temple, 1970), on injection into mice and rats produces increased locomotion, particularly after monoamine-oxidase inhibition (MAOI) (Mantegazza & Riva, 1963; Fischer, Ludmer & Sabelli, 1967; Fuxe, Grobecker & Jonsson, 1967; Jackson, 1972). Without MAOI, higher doses must be given to produce an effect and in these circumstances a biphasic stimulation has been reported to occur in mice (Jackson, 1972, 1975).

A first phase occurred almost immediately and appeared to be produced by release of newly synthesized endogeneous catecholamines, and a temporally later phase was postulated to be due to direct dopamine receptor stimulation by a PE metabolite (Jackson, 1972), which metabolite, however, did not appear to be β-hydroxy-β-phenethylamine (Jackson, 1975). Recently, Jackson, Andén & Dahlström (1975) applied PE bilaterally to the nucleus accumbens of rat brain and produced a marked rise in coordinated locomotor activity in MAOI pretreated rats. This activity was markedly reduced by prior reserpine pretreatment, and completely blocked by the tyrosine hydroxylase inhibitor, α-methyltyrosine (α-MT). No direct receptor stimulation was seen in this model.

Because of the suggestion by some authors (Saavedra & Fischer, 1970; Sabelli & Mosnaim, 1974) that PE may be a "modulator" in the central nervous system, and because of the reported direct receptor stimulant action in non-MAOI mice (Jackson, 1972) in contrast to the purely indirect actions reported after direct application to the nucleus accumbens (Jackson & others, 1975), I decided to reinvestigate the mode of action of systemically administered PE in producing locomotor stimulation. Mice were pretreated with nialamide, a MAOI, to prevent the production of potentially active deaminated metabolites.

Female N.M.R.I. mice (Anticimex, Stockholm) 20–24 g, kept at 25 ± 1° for at least 2 days before use, under normal lighting conditions, were pretreated with various

drugs (see Table 1), and in *all* cases, nialamide hydrochloride* 110 mg kg^{-1}, i.p. was administered 1 h before either 5 mg PE kg^{-1} or saline (as a control).

All drugs were dissolved in saline, except pimozide* and FLA-63* [bis(4-methyl-1-homopiperazinylthiocarbonyl)disulphide], which were initially dissolved in a minimum of glacial acetic acid, and water then added to volume. Reserpine* (Serpasil) ampoules were diluted to appropriate volume with water and all drugs were administered in a dose-volume of 1 ml/100 g body weight. Locomotor activity was measured in a set of four matched "Motron" activity cages (previously described by Strömberg & Waldeck, 1973). After PE or saline (both i.p.), animals were immediately placed in the cages, and the activity counts accumulated from 5 to 35 min after injection. PE, 5 mg kg^{-1} (Table 1) produced a significant rise in coordinated locomotor activity, devoid of any typical stereotypies such as gnawing and licking, although signs of peripheral sympathetic stimulation were observed. If blockade of the stimulant effect of PE occurs with a particular pretreatment, one would expect the activity of the PE-treated group, with no premedication, *i.e.* 1502 $\pm$ 142 counts (Table 1), to fall to a value not significantly different from the activity of animals receiving the same pretreatment, but no PE. Thus, by this criteria, reserpine (10 mg kg^{-1}, i.p. 6 h pretreatment), FLA-63 (a specific dopamine-β-hydroxylase inhibitor, 25 mg kg^{-1}, i.p. 2 h) and phenoxybenzamine (a centrally active α-adrenoceptor blocking agent, 10 mg kg^{-1}, i.p. 1 h) were ineffective in preventing the PE induced locomotor stimulation. In contrast, pimozide (a specific dopamine receptor blocking agent (1 mg kg^{-1} i.p. 3 h) and DL-α-methyl-*p*-tyrosine methylester hydrochloride (H 44/68*, α-MT, a tyrosine hydroxylase inhibitor, 250 mg kg^{-1}, i.p. 4 h) were able to block PE induced stimulation. However, when the activity of animals which were administered PE only is compared to the activity of animals treated with FLA-63 or phenoxybenzamine or reserpine, plus PE, some reduction in the PE induced stimulation was observed, i.e. 1502 $\pm$ 142 to 378 $\pm$ 119, 1502 $\pm$ 142 to 596 $\pm$ 155 and 1502 $\pm$ 142 to 651 $\pm$ 167, respectively (see Table 1). But in each of these cases the activity of the PE-treated groups is significantly greater than that of animals receiving the pretreatment (plus saline) alone. The apparent reduction in stimulation just described could be due to (1) a decrease in available functional noradrenaline which may be required for the locomotor stimulation produced by PE (since FLA-63, phenoxybenzamine and reserpine block, albeit through different mechanisms of actions, the central effects of noradrenaline), or to (2) the general non-specific depressant effects of these drugs. The depressant effects of the drug

Table 1. *The effect of various drug pretreatments on locomotor activity in mice after β-phenethylamine, 5 mg kg^{-1}, or saline.* All mice received nialamide HCl 110 mg kg^{-1}, 1 h before PE or saline, and the activity of groups of three mice was accumulated between 5 and 35 min after injection. Each experiment was repeated 4 times, and comparisons were made between the appropriate PE treated and control group by Student's *t*-test. The data are the total number of counts $\pm$ the standard error of the mean.

	Total activity		
Pretreatment	Saline treated	Phenethylamine treated	Significance *P* level
—	356$\pm$45	1502$\pm$142	<0·001
α-Methyltyrosine	111$\pm$42	93$\pm$15	>0·5
FLA-63	61$\pm$5	378$\pm$119	<0·05
Pimozide	64$\pm$16	14$\pm$6	<0·025
Phenoxybenzamine	70$\pm$8	596$\pm$155	<0·025
Reserpine	19$\pm$4	651$\pm$167	<0·01

pretreatments themselves on locomotor activity are expected, for apart from any non-specific depressant effects, all the drugs used in one way or another interfere with the function of both dopamine and noradrenaline, both of which amines are implicated in locomotor activity (Andén, Strömbom & Svensson, 1973). These data confirm previous biochemical, histochemical and functional findings that PE exerts its stimulant action indirectly, i.e. by releasing endogenous newly synthesized catecholamines, and in particular dopamine (Fuxe & others, 1967; Fuxe & Ungerstedt, 1970; Jackson, 1972, 1975; Jackson & others, 1975). The relative inability of FLA-63 to block the locomotor stimulation, produced by PE, confirms the earlier suggestion that β-OH-β-PE, a confirmed metabolite of PE (Inwang, Mosnaim & Sabelli, 1973; Saavedra & Axelrod, 1973) is not responsible for the PE induced stimulation (Jackson, 1975). The data also show that the direct receptor stimulatory effect previously reported when PE is administered to untreated mice in high doses (Jackson, 1975) is probably produced by deaminated metabolite of PE, since no direct effects were seen in this present study, nor when PE was applied directly to the brain substance (Jackson & others, 1975), which method bypasses any possible metabolism in the periphery. The deaminated metabolite(s) involved, either phenylacetaldehyde, phenylethanol, phenylacetic acid, or a substituted derivative of one of these, warrants further investigation because of its possible pharmacological activity.

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