tendency for the animals to become increasingly sensitive to ergometrine between days 13 and 23 after the operation; for this reason no attempt was made to relate the total number of turns to the dose of ergometrine injected. The intraperitoneal injection of 0·9% NaCl caused no turning behaviour.

The effect of ergometrine (10 mg kg^{-1}) was completely abolished by haloperidol (1·0 mg kg^{-1}), injected 30 min before the ergot alkaloid (Fig. 1). With higher doses of ergometrine this same dose of haloperidol caused attenuation of the response, but not complete block.

Recently, Corrodi, Fuxe & others (1973) have shown that ergocornine and 2-Br-α-ergocryptine cause a similar turning towards the innervated side in unilaterally lesioned rats. The effect of 2-Br-α-ergocryptine was 'markedly reduced' by a high dose of pimozide (1 mg kg^{-1}).

Our results lend support to the suggestion (Pijnenburg & others, 1973; Pijnenburg & van Rossum, 1973) that the central stimulant action of ergometrine is due to a direct action on dopamine receptors in the brain.

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Department of Physiology and Biochemistry,
University of Southampton,
Medical & Biological Sciences Building,
Bassett Crescent East,
Southampton SO9 3TU, U.K.

G. N. WOODRUFF
A. O. ELKHAWAD
A. R. CROSSMAN

January 18, 1974

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The effect of β-phenethylamine on noradrenaline and dopamine turnover in rat brain

β-Phenethylamine (PE) has recently been found in various animal tissues including brain (Nakajima, Kakimoto & Sano, 1964; Jackson & Temple, 1970; Inwang, Mosnaim & Sabelli, 1973). PE on injection into animals produced a depletion of brain noradrenaline in guinea-pigs (Jackson, 1971), both noradrenaline and dopamine in rats (Jonsson, Grobecker & Holtz, 1966; Fuxe, Grobecker & Jonsson, 1967; Jackson & Smythe, 1973) and noradrenaline, dopamine and 5-hydroxytryptamine in mice (Jackson & Smythe, unpublished observations). The central nervous stimulant effect of PE on locomotor activity in mice has been shown to be mediated via dopamine receptors (Jackson, 1972, 1974). In addition the distribution of (4T)- PE in rat brain after the administration of a behaviourally active dose (100 mg kg^{-1}, i.p.) paralleled the distribution of dopamine. We therefore decided to examine the effect of PE on noradrenaline and dopamine turnover in rat brain. Male Sprague-Dawley rats (150–300 g) were given two doses of PE (each 50 mg kg^{-1}, i.p.) 4 and 1 h before death.

Table 1. *Noradrenaline and dopamine concentrations in rat brain 4 h after a first dose of β-phenethylamine (50 mg kg^{-1}, i.p.), with a second dose (50 mg kg^{-1}, i.p.) given 3 h later, and 3 h after α-methyl-*p*-tyrosine (375 mg kg^{-1}).* The data are expressed as a percentage of normal values ± the standard error of the mean and are uncorrected for recovery [control values are noradrenaline 416 ± 23 ng g^{-1} wet weight (75 ± 5% recovery, n = 7), dopamine 844 ± 66 ng g^{-1} (72 ± 11% recovery, n = 8)].

Treatment	Dopamine %	Noradrenaline %
Control	100 ± 8 (8)	100 ± 6 (8)
α-MT	43 ± 3 (7)*	56 ± 2 (8)*
β-Phenethylamine	87 ± 4 (5)	87 ± 3 (6)
β-Phenethylamine	35 ± 3 (7)*	28 ± 1 (7)*
+ α-MT		

* $P < 0.05$ from control

Three h before death, animals received α-methyl-*p*-tyrosine methyl ester hydrochloride (α-MT) (375 mg kg^{-1}, i.p.) a tyrosine hydroxylase inhibitor (Spector, Sjoerdsma & Udenfriend, 1965). Brains were rapidly removed and noradrenaline and dopamine extracted according to Anton & Sayre (1962) and the former estimated according to Haggendal (1963) and the latter according to Anton & Sayre (1964). Drugs were dissolved in distilled water and administered in a dose volume of 1 ml per 100 g. The dose of PE is expressed as the hydrochloride salt.

Table 1 shows that the dose schedule of PE used did not by itself cause significant depletion of either noradrenaline or dopamine ($t = 2{\cdot}082$, n = 14 and $t = 1{\cdot}39$, n = 13 respectively). However α-MT produced a significant depletion of both. PE accelerated the noradrenaline loss after α-MT, but did not significantly enhance dopamine loss. This suggests a significant increase in noradrenaline turnover with no change in dopamine turnover. A similar effect of PE on noradrenaline turnover was observed by the present authors using FLA63 an inhibitor of dopamine-β-oxidase (Corrodi, Fuxe & others, 1970). These findings are difficult to relate to behavioural studies because the stimulant effect of PE on locomotor activity has been reported to involve dopamine, but not noradrenaline (Jackson, 1974). However, a parallel situation has been reported for the effect of amphetamine on brain amine turnover by Corrodi, Fuxe & Hökfelt (1967) who found, using a similar technique to study brain amine turnover, that amphetamine, while increasing noradrenaline turnover in rat brain, was without effect on dopamine turnover. As with PE many of the behavioural effects of amphetamine, e.g. stereotyped behaviour, have been explained by an interaction with dopamine neurons (Randrup & Munkvad, 1970). Clearly then, studies on amine turnover are not of themselves adequate to explain the stimulant effect of PE. However, a possible clue to the involvement of noradrenaline systems in PE-induced behavioural changes in mice comes from preliminary experiments in this laboratory which show that clonidine, a centrally acting noradrenaline receptor stimulant (Andén, Corrodi & others, 1970), is able to potentiate the increased locomotor activity produced by the injection of β-phenethylamine in mice pretreated with reserpine or α-MT, suggesting that central noradrenaline systems are in fact required for maximum PE effect.

Department of Pharmacology,
University of Sydney,
Sydney, N.S.W. 2006, Australia,

D. M. JACKSON
D. B. SMYTHE

October 26, 1973

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Effect of muscarinic agonists on the release of [^{3}H]noradrenaline from the guinea-pig perfused heart

The administration of low doses of acetylcholine or muscarinic agonists decreases the release of noradrenaline following sympathetic nerve stimulation to the various tissues (Löffelholz & Muscholl, 1969; Malik & Ling, 1969; Steinsland, Furchgott & Kirpekar, 1973; Vanhoutte, Lorenz & Tyce, 1973). This has given rise to the hypothesis that acetylcholine released from a cholinergic nerve inhibits the release of noradrenaline from an adjacent adrenergic nerve via an inhibitory action on muscarinic receptors. We now report that both acetylcholine and methacholine prevent the release of [^{3}H]noradrenaline (^{3}H-NA) by nicotine in the guinea-pig perfused heart and show that acetylcholine fails to release [^{3}H]noradrenaline from the guinea-pig perfused heart except when used in very high concentrations (10^{-3}M). However, if atropine (10^{-5}M) is added to the perfusion solution, acetylcholine at 10^{-6}M will readily release ^{3}H-NA.

Hearts from male guinea-pigs (200–400 g) were removed under sodium pentobarbitone anaesthesia and immediately connected to a coronary perfusion apparatus (Anderson-Craver; Metro Scientific Co.) via the aorta. The normal perfusion medium contained (mmol litre^{-1}): NaCl, 119·8; KCl, 5·63; $CaCl_2$, 2·16; $MgCl_2$, 2·10; dextrose, 100 and $NaHCO_3$, 25·0. The solution was bubbled with 5% CO_2 in oxygen; the temperature was maintained at 38 $\pm$ 1° and pH 7·32–7·45. Hearts were perfused at 6·0 $\pm$ 1·0 ml min^{-1} with a Harvard perfusion pump.

After an equilibration period, hearts were perfused with 1·0 ng ml^{-1} of (−)-[^{3}H]-noradrenaline (specific activity 5·8 Ci mmol^{-1}) for 20 min to label the endogenous store. The perfusate was changed to a noradrenaline-free medium and the efflux of ^{3}H-NA was collected and analysed.

Drugs used were: (−)-[7-^{3}H]noradrenaline (New England Nuclear); acetylcholine chloride, acetyl-β-methylcholine chloride (methacholine) (Sigma); nicotine hydrochloride (K & K Labs, Inc., Plainview, N.Y.) and atropine sulphate (Mallinckrodt).

Two types of experiments were carried out. First, the effect of the addition of acetylcholine or methacholine to the perfusion medium on the release of ^{3}H-NA by