Br. J. Pharmac. (1981), **74**, 119–122

DOPAMINE-LIKE PROPERTIES OF EPHEDRINE IN RAT BRAIN

M.R. ZARRINDAST

Department of Pharmacology, Faculty of Medicine, University of Tehran, Tehran, Iran

1 Ephedrine (3.1–50 mg/kg) was given intraperitoneally to rats and was found to cause a marked increase in spontaneous locomotor activity.

2 In rats with a unilateral lesion in the substantia nigra made by stereotaxic injection of 6-hydroxydopamine, ephedrine (12.5–150 mg/kg i.p.) caused a dose-dependent turning towards the lesioned side.

3 Turning behaviour and increase in locomotion produced by ephedrine were antagonized by pretreatment of the animals with pimozide, amino-oxyacetic acid or reserpine plus α-methyl-*p*-tyrosine, but not by pretreatment with phenoxybenzamine, propranolol or methergoline.

4 In *in vitro* studies with synaptosomes prepared from rat brain, ephedrine blocked the uptake and caused the release of [^{3}H]-dopamine.

5 Similar results with regard to locomotion and turning behaviour were obtained with (+)-amphetamine.

6 It is concluded that the increase in locomotion and turning behaviour produced by ephedrine is mediated through an indirect dopaminergic mechanism.

Introduction

Ephedrine is one of the ancient drugs and different observations (Chen & Schmidt, 1925; Angrist, Rotrosen, Kleinberg, Merriam & Gershon, 1977) suggest that this drug, like amphetamine, might act on adrenoceptors and dopamine receptors. Its central nervous system stimulant properties have made it the drug of choice in the treatment of narcolepsy. Psychosis from therapeutic doses of ephedrine and amphetamine have been observed in narcoleptic patients (Young & Scoville, 1938). In asthmatics treated with ephedrine, psychosis has also been reported (Herridge & a'Brook, 1968). Kane & Florenzano (1971) reported a case of psychosis with a bronchodilator containing ephedrine in a very low dose. It should be noted that the role of dopamine in the pathogenesis of psychotic symptomatology is of current interest (Snyder, Banerjee, Yamamura & Greenberg, 1974). There is experimental evidence showing that γ-aminobutyric acid (GABA) carrying neuronal pathways exert an inhibitory control over central dopaminergic neurones (Roth & Suhr, 1970; Andén, 1974; Stevens, Wilson & Foote, 1974; Carlsson, 1975; Fuxe, Hokfelt, Ljungdahl, Agnati, Johansson & Perez de la Mora, 1975). In the present study, the effects of ephedrine on the locomotor activity and turning behaviour of rats and its possible interaction with the GABAergic system were investigated.

Methods

Male albino rats weighing 200–250 g were used in these experiments.

Locomotor activity

Locomotor activity was measured with an activity meter, Animex, Type S (LKB Farrad). Groups of 4 animals were injected intraperitoneally with drugs and placed in a plastic cage for test trials lasting 3 h. Counts were made for 5 min at the times indicated in the Figures.

Turning activity

Groups of rats were anaesthetized with sodium pentobarbitone (40 mg/kg i.p.) and placed in a David Kopf stereotaxic frame. A unilateral injection of 6-hydroxydopamine (6-OHDA, 25 μg/rat) in 5 μl was made in the region of zona compacta of the substantia nigra at coordinates A 2.4, L 1.7, V 1.9–2.9 (Konig & Klippel, 1967). Turning responses to drugs were determined 14 days post-operatively. At least 4 days separated drug treatments. Turning activity was measured by direct observation of individual rats placed in round bottom plastic bowls of 40 cm diameter. The number of turns was recorded for 5 min at the times indicated in the Figures. Each point represents the result of at least 6 experiments.

0007-1188/81/090119-04$01.00

Uptake and release studies

Male rats (200–250 g) were killed by a blow on the head and exsanguinated. Brains were removed immediately and striatal synaptosomes were prepared. The ability of ephedrine to inhibit uptake and to release [^{3}H]-dopamine from synaptosomes was tested according to the method described previously (Kruk & Zarrindast, 1976).

Statistical analysis was carried out by Student's *t* test.

Drugs

The following drugs were used: (−)-ephedrine hydrochloride (Sigma), amino-oxyacetic acid (AOAA, Sigma), (+)-amphetamine sulphate (SK&F), pimozide (Janssen), 6-hydroxydopamine hydrobromide (Sigma), DL-α-methyl-*p*-tyrosine methylester (AMPT, Sigma), reserpine (Serpasil amp., Ciba-Geigy), [^{3}H]-dopamine hydrochloride (8.5 Ci/mmol) (The Radiochemical Centre, Amersham), phenoxybenzamine hydrochloride (SK&F), (−)-propranolol (ICI) and methergoline (Pharmatalia).

Results

Behavioural activity

Turning activity Dose-response curves of turning induced by ephedrine (12.5–150 mg/kg i.p.) are shown in Figure 1. Ephedrine caused a dose-dependent turning response to the lesioned side. The maximum turning response was achieved with 100 mg/kg of ephedrine. In parallel experiments with (+)-amphetamine, similar results were obtained, 2.5 mg/kg of (+)-amphetamine producing maximum response. Indirect receptor stimulant drugs such as (+)-amphetamine cause turning towards the lesioned side by releasing dopamine from the unlesioned side (Ungerstedt, 1971). Therefore, it can be concluded that ephedrine acts indirectly in a manner similar to (+)-amphetamine. Pretreatment with reserpine (5 mg/kg i.p., 16 h before the injection period) plus AMPT (250 mg/kg i.p., 1 h), the GABA-transaminase inhibitor, amino-oxyacetic acid (AOAA, 40 mg/kg i.p., 90 min) or pimozide (0.5 mg/kg i.p., 2 h) antagonized the turning effects of ephedrine (50 mg/kg, Figure 2) and (+)-amphetamine (2.5 mg/kg). Phenoxybenzamine (5 mg/kg i.p., 1 h), propranolol (10 mg/kg i.p., 1 h) or methergoline (0.5 mg/kg i.p., 2 h) did not alter the turning responses induced by ephedrine.

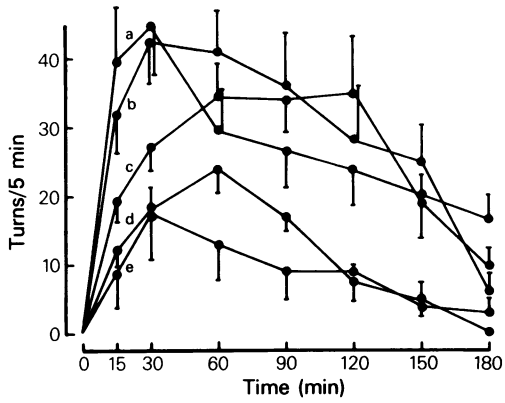

Figure 1 Turning behaviour caused by ephedrine in rats with a unilateral 6-hydroxydopamine lesion in the substantia nigra. Rats were injected intraperitoneally with ephedrine (a) 150, (b) 100, (c) 50, (d) 25 and (e) 12.5 mg/kg. Abscissa scale: time in min after injection of the drug; ordinate scale: turns/5 min (towards the side of the lesion). Each point is the mean of at least 6 observations. Vertical bars indicate the s.e.mean.

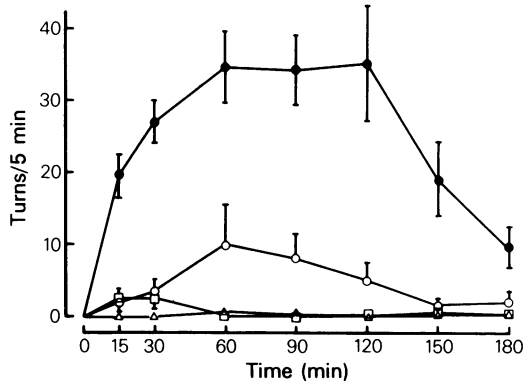

Figure 2 Turning behaviour caused by ephedrine (50 mg/kg, i.p.) in rats with a unilateral 6-hydroxydopamine lesion in the substantia nigra. Rats were injected with ephedrine alone (●) or in combination with (△) pimozide (0.5 mg/kg, i.p., 2 h); (○) amino-oxyacetic acid (40 mg/kg, i.p., 90 min) or (□) reserpine (2.5 mg/kg, i.p., 16 h) plus α-methyl-*p*-tyrosine (250 mg/kg, i.p., 1 h). Abscissa scale: time in min after injection of ephedrine; ordinate scale: turns/5 min (towards the side of the lesion). Each point is the mean of at least 6 observations. Vertical bars indicate s.e.mean.

Locomotor activity Dose-response curves of locomotor activity induced by ephedrine are shown in Figure 3. Rats receiving either ephedrine (3.1–50 mg/kg i.p.) or (+)-amphetamine (1.25–5 mg/kg i.p.) showed a significant increase in locomotor activity. Pretreatment with reserpine plus AMPT, AOAA or pimozide inhibited the locomotor activity induced by ephedrine (Figure 4) or (+)-amphetamine. Phenoxybenzamine, propranolol or methergoline did not alter the responses to ephedrine.

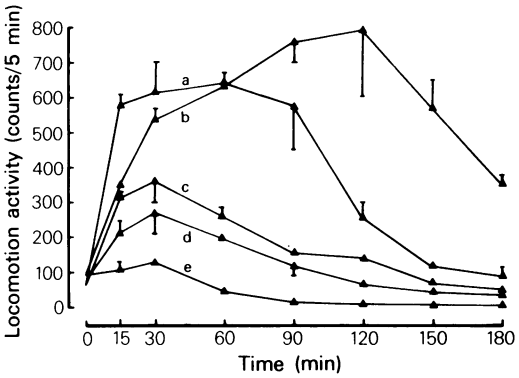

Figure 3 Ephedrine-induced locomotor activity. Rats were injected intraperitoneally with ephedrine: (a) 50, (b) 25, (c) 12.5, (d) 6.25 and (e) 3.1 mg/kg. Abscissa scale: time in min after injection of ephedrine; ordinate scale: locomotor activity, counts/5 min. Each point is the mean of at least 6 observations. Vertical bars indicate s.e.mean.

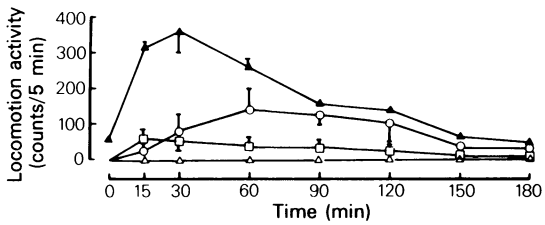

Figure 4 Ephedrine-induced locomotor activity. Rats were injected with ephedrine (12.5 mg/kg, i.p.) alone (▲) or in combination with (△) pimozide (0.5 mg/kg, i.p., 2 h), (○) amino-oxyacetic acid (40 mg/kg, i.p., 90 min) or (□) reserpine (2.5 mg/kg, i.p., 16 h) plus α-methyl-*p*-tyrosine (250 mg/kg, i.p., 1 h). Abscissa scale: time in min after injection of ephedrine; ordinate scale: locomotor activity, counts/5 min. Each point is the mean of at least 6 observations. Vertical bars indicate s.e.mean.

Biochemical assays

Effects of ephedrine on uptake and release of [^{3}H]-dopamine in striatal synaptosomes are shown in Table 1. Ephedrine blocked the uptake of [^{3}H]-dopamine into rat striatal synaptosomes (IC_{50} = 120 ± 11 nM). It also released [^{3}H]-dopamine but this latter effect was very weak (RC_{50} = 115 ± 5 μM) as compared with amphetamine (Kruk & Zarrindast, 1976).

Discussion

Intraperitoneal injection of either ephedrine or (+)-amphetamine to rats caused a marked increase in locomotion. These drugs, injected intraperitoneally in rats with unilateral lesion in the substania nigra, made them turn to the side of the lesion. Pretreatment with reserpine, a depletor of catecholamines, and AMPT, an inhibitor of the synthesis of catecholamines, antagonized these effects of both drugs. Amphetamine is thought to exert its influence on locomotor hyperactivity and stereotyped behaviour via endogenous catecholamines (Weissman, Koe & Tenen, 1966). From the present experiments one can conclude that locomotion and turning behaviour induced by ephedrine is similar to (+)-amphetamine and is mediated through the build up of the level of endogenous catecholamines. Turning and locomotion induced by ephedrine and (+)-amphetamine were abolished by pimozide, a dopamine receptor blocker, but not by phenoxybenzamine, propranolol or methergoline which are α-adrenoceptor, β-adrenoceptor and 5-hydroxytryptamine receptor blockers, respectively. Therefore, it seems likely that both effects were achieved through dopaminergic systems. Our results support the observation of Angrist *et al.* (1977) on stereotyped behaviour of rats induced by ephedrine. Ephedrine inhibits the uptake of [^{3}H]-dopamine into synaptosomes at a concentration three orders of magnitude lower than that needed to release [^{3}H]-dopamine from synaptosomes. The doses of ephedrine needed to induce turning and locomotor activity are in the range of dopamine-releasing concentration of the drug. Therefore, it is suggested that the drug acts indirectly possibly through both the inhibition of uptake and release of dopamine.

Pretreatment with the GABA-transaminase in-

Table 1 Effects of ephedrine and (+)-amphetamine on the uptake and release of [^{3}H]-dopamine by rat neostriatum synaptosomes

Drug	*IC_{50} uptake*	*RC_{50} release*
Ephedrine	120 ± 11 nM (6)	115 ± 5 μM (6)
(+)-Amphetamine*	66 ± 15 nM (6)	0.25 ± 0.22 μM (6)

*Data for (+)-amphetamine are from Kruk & Zarrindast (1976). Figures in parentheses indicate number of experiments.

hibitor AOAA (Wallach, 1961) reduced turning and locomotion induced by ephedrine and (+)-amphetamine. This finding suggests that the brain GABA system might exert an inhibitory influence on the behavioural parameters measured in the present study.

I wish to thank Professor M.A. Khoyi for his suggestions and criticism of the manuscript and Mr M. Bafekr Shirvan for his skilful technical assistance.

References

ANDÉN, N.E. (1974). Inhibition of the turnover of the brain dopamine after treatment with the gamma-aminobutyrate: 2-oxyglutarate transaminase inhibitor aminooxyacetic acid. *Naunyn-Schmiedebergs Arch. Pharmac.*, **283,** 419–424.

ANGRIST, B., ROTROSEN, J., KLEINBERG, D., MERRIAM, V. & GERSHON, S. (1977). Dopaminergic agonist properties of ephedrine – theoretical implications. *Psychopharmac.*, **55,** 115–120.

CARLSSON, A. (1975). Receptor mediated control of dopamine metabolism. In *Pre- and Postsynaptic Receptors.* ed. Usdin, E. & Bunney, W. pp. 49–63. New York: Marcel Dekker.

CHEN, K.K. & SCHMIDT, C.F. (1925). The action of ephedrine, the active principle of the Chinese drug Ma Huang. *J. Pharmac. exp. Ther.*, **24,** 339–357.

FUXE, K., HOKFELT, T., LJUNGDAHL, A., AGNATI, L., JOHANSSON, O. & PEREZ de la MORA, M. (1975). Evidence for an inhibitory gabergic control of the mesolimbic dopamine neurons: possibility of improving treatment of schizophrenia by combined treatment with neuroleptics and gabergic drugs. *Med. Biol.*, **53,** 177–183.

HERRIDGE, C.F. & a'BROOK, M.F. (1968). Ephedrine psychosis. *Br. med. J.*, **2,** 160.

KANE, F.J. & FLORENZANA, R. (1971). Psychoses accompanying use of a bronchodilator compound. *J. Am. med. Ass.*, **215,** 2116.

KRUK, Z.L. & ZARRINDAST, M.R. (1976). Mazindol anorexia is mediated by activation of dopaminergic mechanism. *Br. J. Pharmac.*, **58,** 367–372.

ROTH, R.H. & SUHR, Y. (1970). Mechanism of the γ-hydroxybutyrate-induced increase in brain dopamine and its relationship to 'sleep'. *Biochem. Pharmac.*, **19,** 3001–3019.

SNYDER, S.H., BANERJEE, S.P., YAMAMURA, H.I. & GREENBERG, D. (1974). Drugs, neurotransmitters and schizophrenia. *Science*, **184,** 1243–1253.

STEVENS, J., WILSON, K. & FOOTE, W. (1974). GABA blockade, dopamine and schizophrenia: experimental studies in the cat. *Psychopharmacologia* (Berl.), **39,** 105–119.

UNGERSTEDT, U. (1971). Postsynaptic supersensitivity after 6-hydroxydopamine-induced degeneration of the nigrostriatal dopamine system. *Acta physiol. scand.* (Suppl.), **367,** 69–93.

WALLACH, D.P. (1961). Studies on the GABA pathway. 1. The inhibition of γ-aminobutyric acid-α-ketoglutaric acid transaminase in vitro and in vivo by U-7524 (aminooxyacetic acid). *Biochem. Pharmac.*, 323–331.

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

YOUNG, D. & SCOVILLE, W.B. (1938). Paranoid psychosis in narcolepsy and the possible danger of benzedrine treatment. *Med. Clin. North. Am.*, **22,** 637–646.

(Received February 26, 1981.
Revised April 27, 1981.)