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INFLUENCES OF DIFFERENT ADRENOCEPTOR AGONISTS AND ANTAGONISTS ON AMPHETAMINE-INDUCED CLIMBING IN MICE

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ABSTRACT

Administration of apomorphine and amphetamine induces climbing behavior in mice due to stimulation of brain dopamine receptors. In the present study, the effects of adrenoceptor agonists and antagonists on amphetamine-induced climbing have been investigated. Intraperitoneal (i.p.) injection of different doses of amphetamine (2,4 and 8 mg/kg) induced climbing in mice ($p<0.0001$). The α_2-adrenoceptor agonist clonidine decreased the climbing induced by amphetamine ($p<0.01$). The adrenoceptor antagonists prazosin, yohimbine and propranolol did not alter amphetamine response.

It may be concluded that α_1- and α_2-adrenoceptor stimulation decreases amphetamine-induced climbing behavior indirectly through changing dopamine levels.

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INTRODUCTION

Pharmacological studies of dopaminergic-controlled behavior in the mouse may be demonstrated by climbing behavior.[1-3] The test allows easy behavioral scoring and is reliable in detecting the effects of pharmacological manipulation of brain dopaminergic systems. The importance of meso-limbic and nigro-striatal dopamine-containing pathways in the mediation of these behaviors is well documented.[4,5] Administration of dopamine agonists including apomorphine, amphetamine, bromocriptine, bupropion and other dopaminergic agents such as pergoline also induce climbing. In mice, apomorphine-induced stereotyped climbing probably occurs by a combined activation of D_1- or D_2-postsynaptic receptors.[6] Blockade of D_1 or D_2 dopamine receptors can antagonize stereotyped behaviors induced by apomorphine.[3,7-11]

There is evidence that dopamine-induced locomotor and stereotyped behavior are differentially influenced (in opposite direction) by both α_1 and α_2-adrenoceptor antagonists.[15] Thus it has been suggested that the noradrenergic system may modulate the expression and character of behavior by influencing dopamine function in certain brain areas.[2,12]

In the present work, the influences of α_1 and α_2 adrenoceptor agonists or antagonists on amphetamine-induced climbing have been studied.

MATERIALS AND METHODS

Animals

Male albino mice (25-30g) were used in these experiments (n= 200). They were kept 10 per cage, in a room on a 12h/12h light-dark cycle at 22±2°C. Food and water were freely available except during experiments. Each animal was used only once.

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Climbing measurement

A wire mesh wall (9 cm wide, 11 cm long, 1 cm mesh size) was placed in a glass cylinder (9 cm diameter, 11 cm high) in a vertical position, covered with a mesh roof and used for assessing the climbing behavior. An initial 30 minutes period was allowed for animals to acclimatize to the environment. Immediately after drug administration, the animals were put into the cylinders and the position of each animal was observed and scored as described by Marcais et al.[13] every 2 min as follows: four paws on the floor (0), forefeet holding the wall (1), and four paws holding the wall (2). At each time period, the mean ± SEM of climbing scores for six mice during the first hour after amphetamine or apomorphine administration are presented.

Drugs

The drugs used were amphetamine sulphate (SK & F), propranolol (ICI), phenylephrine HCl, prazosin HCl, clonidine HCl and yohimbine (Sigma). Amphetamine was given intraperitoneally (i.p.) in a volume of 10 mL/kg and other drugs were given intracerebroventricularly (i.c.v.) in a volume of 5 μL/mouse and prepared immediately before use. The control groups received saline.

Statistical analysis

One-way analysis of variance (ANOVA) followed by Newman Keuls test were used for statistical analysis. Differences between means were considered statistically significant if $p<0.05$.

RESULTS

Climbing behavior induced by amphetamine

Intraperitoneal (i.p.) administration of different doses of amphetamine (2,4,8 mg/kg) to mice induced climbing behavior ($p<0.0001$) (Fig. 1).

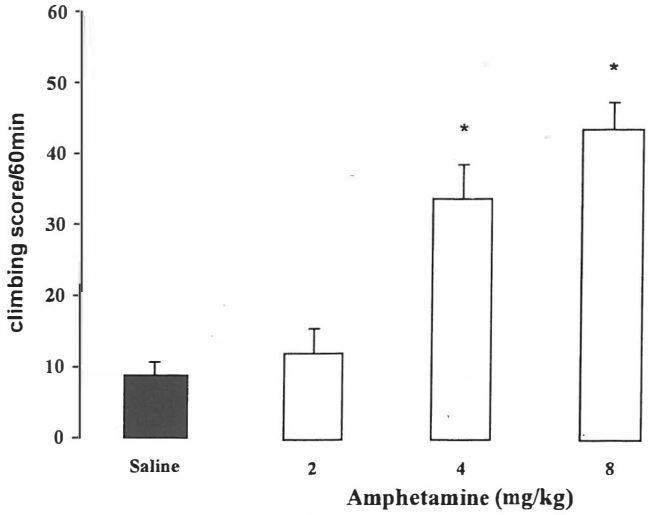


Fig. 1. Effect of different doses of amphetamine on spontaneous climbing behavior. Mice were administered saline (Sal, 10 mL/kg, ip) and different doses of amphetamine (Am, 2,4,8 mg/kg, ip). Each point is the mean±SEM of climbing score/60 min (n= 10). *$p<0.0001$, different from respective control groups.

Effects of adrenoceptor agonists on amphetamine-induced climbing

The α_2 adrenoceptor agonists clonidine (0.5,1,2, μg/mouse, i.c.v.) 30 min after amphetamine, reduced climbing induced by 4 mg/kg of the drug ($p<0.05$, $p< 0.01$) (Fig. 2). But the α_1 adrenoceptor agonist phenylephrine (0.5,1,4 μg/mouse) did not alter climbing behavior induced by 4 mg/kg of amphetamine (Fig. 2).

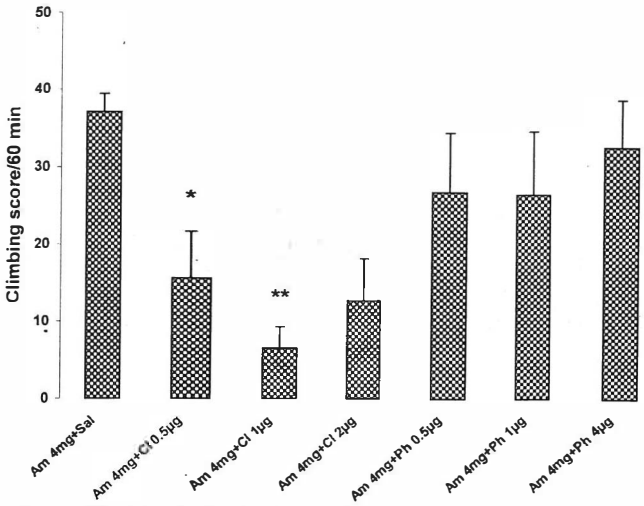


Fig. 2. Climbing behavior induced by amphetamine in the presence of α_1 and α_2 adrenoceptor agonists. Mice were administered amphetamine (Am, 4 mg/kg, ip) in combination with saline (Sal, 5 μL/mouse), phenylephrine (Ph, 0.5, 1 and 4 μg/mouse, icv), and clonidine (Cl, 0.5, 1 and 2 μg/mouse, icv). Each point is the mean±SEM of climbing score/60 min (n= 6). *$p<0.05$, **$p<0.01$, different from respective control groups.

Effects of adrenoceptor antagonists on amphetamine-induced climbing

Effects of adrenoceptor antagonists are shown in Fig. 3. Pretreatment of animals with the α-adrenoceptor antagonists prazosin (0.5, 1,4 μg/mouse, i.c.v.) and yohimbine (0.5, 1,4 μg/mouse, i.c.v.) did not alter climbing induced by 4 mg/kg amphetamine (Fig. 3).

The β-adrenoceptor antagonist propranolol pretreatment (0.5, 1,4 μg/mouse, i.c.v.) also did not alter the amphetamine effect (Fig. 3). Because of reports concerning the probable effects of clonidine on α_1 adrenoceptors[14] clonidine was used after blocking the α_2 adrenoceptors. Clonidine was injected (1, 2μg/mouse, i.c.v.) 15 minutes after injecting 4 mg/kg of amphetamine and 2,3 mg/kg of yohimbine. Table I shows the responses of clonidine in the presence of amphetamine and yohimbine. Comparing these results, it is shown statis-

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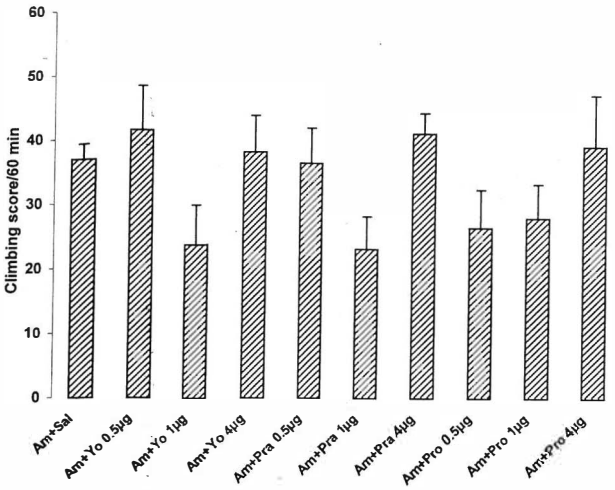


Fig. 3. Effect of α and β adrenoceptor antagonists on climbing induced by amphetamine in mice. Animals were injected with amphetamine (Am, 4 mg/kg, ip) in combination with saline (Sal, 5 µL/mouse, icv), prazosin (Pra), yohimbine (Yo), and propranolol (Pro) (0.5, 1, 4 µg/mouse, icv). Each point is the mean±SEM of climbing score/60 min (n= 6).

tically that yohimbine inhibited the reduced effect of clonidine on amphetamine induced-climbing behavior ($p<0.01$, $p<0.001$).

DISCUSSION

Assessment of climbing behavior in mice may be a precise test for measurement of dopaminergic agents.[8,13] The drugs with dopaminergic agonistic properties have been shown to increase spontaneous climbing (see *Introduction*). Interaction between dopaminergic and noradrenergic systems has been indicated.[12] Noradrenergic neurons in the locus coeruleus have been shown to elicit an influence on dopamine neurons mediating locomotion.[15] [^{3}H]-dopamine from nucleus accumbens slices is increased by β- and decreased by α_2 adrenoceptor agonists.[16]

In the present study, the influences of adrenoceptor agonists and antagonists on amphetamine-induced climbing have been investigated. The present results show that intraperitoneal (i.p.) injection of amphetamine induced a dose-dependent climbing. The response was greatest with 8 mg/kg of the drug. This response has been shown to be mediated through an indirect dopaminergic mechanism.[7] Amphetamine has also been suggested to elicit its effects on locomotion and stereotyped behavior via endogenous catecholamines. The mesolimbic dopaminergic system is considered to mediate the locomotor response to dopamine and dopamine agonists. Apomorphine, a dopamine agonist, induced cage climbing behavior in mice by directly stimulating postsynaptic mesolimbic D_2 dopamine receptors.[17] Neuroleptics like haloperidol antagonize apomorphine-induced cage climbing behavior by blocking postsynaptic mesolimbic D_2 dopamine receptors,[18] and apomorphine and amphetamine stereotypies.[19-22] Amphetamine might be inducing cage climbing behavior indirectly by releasing dopamine.[17]

The present data indicate that pretreatment with clonidine, an α_2-adrenoceptor agonist, effectively decreased

Table I. Clonidine responses in the presence of amphetamine and yohimbine.

Pretreatment mg/kg, ip	Treatment µg/mouse, icv	Climbing Score/60min (mean ±SEM)
———	Saline	8.8±1.9
Amphetamine 4	Saline	47.2±12.7*
Amphetamine 4	Clonidine 1	6.5±2.8*
Amphetamine 4	Clonidine 2	12.7±5.5*
Amphetamine 4 + Yohimbine 2	Clonidine 1	62±9.4**
Amphetamine 4 + Yohimbine 2	Clonidine 2	26.3±11.6
Amphetamine 4 + Yohimbine 3	Clonidine 1	53±9.6**
Amphetamine 4 + Yohimbine 3	Clonidine 2	88.5±11.08***

Animals were administered saline (5 µL/mouse, icv) alone or 15 minutes after amphetamine (4 mg/kg, ip), and clonidine (1, 2 mg/mouse, icv) 15 minutes after amphetamine (4mg/kg, ip) alone, or a combination of amphetamine and yohimbine (2, 3 mg/kg, ip). Climbing behavior was recorded 60 minutes after icv injection of drugs. Each value is the mean±SEM of six experiments.
*$p<0.05$, **$p<0.01$ and ***$p<0.001$, statistical differences from respective groups.

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amphetamine-induced cage climbing behavior. Therefore, it can be suggested that the α_2-adrenoceptor interacts with the present response. In previous investigations, the effects of clonidine on a number of parameters believed to be expressed through central dopaminergic mechanisms have been studied in rodents. Clonidine caused a dose-dependent sedation in dopamine-intact mice.[23] This drug dramatically reduced the locomotor response to amphetamine in a dose related fashion. In contrast, clonidine had no effect on stereotyped head movement or the duration of the behavioral response to amphetamine. The lower dose of clonidine reduced amphetamine-induced licking/biting while higher doses potentiated amphetamine-induced licking/biting. Thus the behavioral effects of clonidine vary depending upon the dose of amphetamine and the particular behavior selected for study.[24] Therefore, on the basis of our results, it can be suggested that the α_2-adrenergic receptor interacts with the present response. It is apparent that clonidine acts through a secondary neuron system which modifies the effects of dopamine receptor stimulation, although the exact site of this interaction is not clear.[23]

In the present study yohimbine, an α_2-adrenoceptor antagonist, was not effective in antagonising amphetamine-induced climbing behavior. Therefore yohimbine does not block postsynaptic striatal and mesolimbic dopamine receptors. In our study yohimbine, phenylephrine and prazosin (α_2-adrenoceptor agonist and antagonist) pretreatment neither significantly potentiated nor antagonised amphetamine-induced climbing behavior in mice. This suggests that these drugs do not have a facilitatory and inhibitory effect at or beyond the postsynaptic striatal and mesolimbic dopamine receptor. It has been reported that yohimbine increases dopamine synthesis and turnover in the rat brain.[25,26] This effect has been attributed to an indirect action of yohimbine on dopamine neurons exerted through changes in noradrenergic neurotransmission.[26]

On the basis of our results we conclude that since amphetamine is a releaser of monoamines and induced climbing behavior through an indirect dopaminergic mechanism, therefore α_2-adrenoceptor mechanism(s) may possibly influence amphetamine's effect by interacting with the release of dopamine.

REFERENCES

1. Protais P, Chagraoui A, Arbaoui J, Mocaer E: Dopamine receptor antagonist properties of S14506, 8-OH-DPAT, raclopride and clozapine in rodents. Eur J Pharmacol 271: 167-177, 1994.
2. Costall B, Eniojukan JF, Naylor RJ: Spontaneous climbing behavior of mice, its measurement and dopaminergic involvement. Eur J Pharmacol 85: 125-132, 1982.
3. Gianutsos G, Palmeri JL: Effects of three dopamine agonists on cage climbing behavior. Psychopharmacol 79: 329-331, 1983.
4. Costall B, Fortune HD, Hui SG, Naylor RG: Neuroleptic antagonism of the motor inhibitory effect of apomorphine within the nucleus accumbens: drug interaction at presynaptic receptors. Eur J Pharmacol 63: 347-358, 1980.
5. Makanjula ROA, Dow RC, Ashcroft GW: Behavioral responses to stereotactically controlled injections of monoamine neurotransmitters into the accumbens and caudate-putamen nuclei. Psychopharmacol 71: 227-235, 1980.
6. Moore NA, Axton MS: The role of multiple dopamine receptors in apomorphine and N-n-propylnorapomorphine-induced climbing and hypothermia. Eur J Pharmacol 178: 195-201, 1990.
7. Zarrindast MR, Khajenabi Y, Pourgholami MH: Bupropion-induced climbing through D_1 and D_2 dopamine receptor activation. Med JIR Iran 6: 285-289, 1993.
8. Zarrindast MR, Shahed-Dirin K: Bromocriptine induces climbing: possible D_1 or D_2 dopamine receptor involvement. Psychopharmacol 100: 275-280, 1990.
9. Vasse M, Chagraoui A, Protais P: Climbing and stereotyped behaviors in mice required stimulation of D_1 dopamine receptors. Eur J Pharmacol 148: 221-229, 1988.
10. Boyce S, Kelly E, Davis A, Fleminger S, Jenner P, Marsden CD: SCH23390 may alter dopamine-mediated motor behavior via striatal D_1 receptors. Biochem Pharmacol 34: 1655-1669, 1985.
11. Martres MP, Sokoloff P, Delandre M, Schwartz JC, Protais P, Costentin J: Selection of dopamine antagonists: discriminating values, behavioral responses and radioligand binding sites. Naunyn-Schmied Arch Pharmacol 325: 102-11, 1984.
12. Dickinson SL, Gadie B, Tulloch IF: α_1 and α_2 adrenoceptor antagonists differentially influence locomotor and stereotyped behavior induced by d-amphetamine and apomorphine in the rat. Psychopharmacol 96: 521-527, 1988.
13. Marcais H, Protais P, Costentin J, Schwarts JC: A gradual score to evaluate the climbing behavior elicited by apomorphine in mice. Psychopharmacol 56: 233-234, 1978.
14. Semnanian S, Hajisayah S, Zarrindast MR: Involvement of supraspinal alpha-adrenergic receptors in tonic pain. Med JIR Iran 10: 279-283, 1997.
15. Plaznik A, Kostowski W: The interrelationship between brain noradrenergic and dopaminergic neuronal systems in regulating animal behavior: possible clinical implications. Psychopharmacol Bull 19: 5-11, 1983.
16. Nurse B, Russell VA, Taljaard JJF: α_2 and β adrenoceptor agonists modulate [^{3}H]-dopamine release from rat nucleus accumbens slices: implications for research into depression. Neurochem Res 9: 1231-1238, 1984.
17. Bhosale KB, Balsara JJ, Gaonkar RK, Bhosale BB, Gupta SK: Dose-dependent response of central dopaminergic systems to metoclopramide in mice. Indian J Exp Bio 35: 618-622, 1997.
18. Bhosale BB, Balsara JJ: Effects of pentazocine on dopamine-dependent behaviors in mice. Indian J Exp Bio 35: 448-

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450, 1997.
19. Seeman P: Brain dopamine receptors. Pharmacol Rev 32: 229-313, 1980.
20. Randrup A, Munkvad I: Pharmacology and physiology of stereotyped behavior. J Psychiatr Rev 11: 1-10, 1974.
21. Wallach MB: Drug-induced stereotyped behavior, similarities and differences, In: Usdin E, (ed.), Neuropsychopharmacology of Monoamines and Their Regulatory Enzymes. New York: Raven Press, pp. 241-260, 1974.
22. Bende MM, Bapat TR, Balsara JJ, Chandorkar AG: Effects of yohimbine on dopamine dependent behaviors in rats and mice. Indian J Physiol Pharmacol 34(3): 195-200, 1990.
23. Starr MS, Starr BS: Potentiation of dopamine-dependent locomotion by clonidine in reserpine-treated mice is restricted to D_2 agonists. J Neural Transm Park Dis Dement Sect 7(2): 133-142, 1994.
24. Mueller K, Nyhan WL: Modulation of the behavioral effects of amphetamine in rats by clonidine. Eur J Pharmacol 83(3-4): 339-342, 1982.
25. Papeschi R, Thesis P: The effect of yohimbine on the turnover of brain catecholamines and serotonin. Eur J Pharmacol 33: 1-12, 1975.
26. Anden NE, Grabowska M: Pharmacological evidence for a stimulation of dopamine neurons by noradrenaline neurons in the brain. Eur J Pharmacol 39: 275-282, 1976.

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