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Beta Adrenoceptor Blockade Mimics Effects of Stress on Motor Activity in Mice

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Reduced central noradrenergic function has been implicated as a factor in reduced behavioral activity after stress. The present studies examined the role of reduced beta adrenergic neurotransmission in mediating this effect. This was done by testing the ability of beta receptor antagonists to mimic the behavioral actions of stress. Mice were subjected to stress or given various beta antagonists and tested for swimming behavior, locomotor activity, or grooming behavior. As previously reported, stress reduced swimming and locomotor activity and increased grooming. Both the nonselective antagonist, l-propranolol, and the beta-1 selective antagonist, betaxolol, produced the same effects as stress on all three measures. A beta-2 selective antagonist, ICI 118,551, was effective only on swimming, whereas a membrane stabilizing agent, d-propranolol, was effective only on grooming behavior. The peripherally active beta-1 antagonist, atenolol, was not effective on any measure. The nonspecific dopaminergic receptor blocker, fluphenazine, reduced locomotion but tended also to reduce grooming. The results indicate that blockade of beta-1 receptors in the CNS selectively mimics the action of stress on gross motor activity in mice and, along with previous data, suggest that stress leads to a relative deficiency in central beta-1 noradrenergic neurotransmission in these animals.
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KEY WORDS: *Stress; Beta adrenoceptors; Propranolol; Betaxolol; ICI 118,551; Atenolol; Motor activity; Swimming; Grooming*

Stress is known to produce a reduction in various types of gross motor activity in rodents. Behaviors affected include locomotor activity in an open field (Stone 1970; Kennett et al. 1985; Armario et al. 1991), exploratory behavior in a maze (Berridge and Dunn 1989), avoidance and escape behavior (Weiss et al. 1975; Anisman et al. 1980) and swimming activity (Simon et al. 1986). Because these changes resemble decreases in psychomotor activity frequently seen in clinical depression and can be reversed by antidepressant treatment, they have been hypothesized to represent a component of an animal model of depression (Stone 1979a; Anisman et al. 1980; Willner 1984; Kennett et al. 1987).

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The mechanism by which stress causes hypoactivity has been under investigation for a number of years. One of the factors that has been implicated is a reduced release of brain norepinephrine (NE). The noradrenergic system is known to be involved in the regulation of psychomotor function (Stafford and Jacobs 1990; Aston-Jones et al. 1991b) and is also known to undergo a decrease in its transmitter during most types of stress (reviewed in Stone 1975). Moreover, agents that enhance NE release prevent or reverse stress-induced behavioral inactivity (Stone 1970; Stone and Mendlinger 1974; Glazer et al. 1975; Anisman et al. 1980; Lehnert et al. 1984), whereas agents that inhibit NE release worsen the hypoactivity (Anisman et al. 1979; Gil et al. 1992).

Although NE release has been implicated, relatively little work has been done to elucidate which postsynaptic adrenergic receptor is involved in this phenomenon. As an initial step toward this end the present experiment was undertaken to explore the role of the beta adrenergic receptor. The latter receptor represents one of the major adrenergic receptors in the forebrain and is

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known to be affected by antidepressant agents (Sulser 1982). There have been isolated reports that blockade of brain beta receptors reduces motor activation (Hermansen 1969; Fabian and Izquierdo 1972; Barar and Madan 1973; Almgren et al. 1978), but the reliability of this effect and the subtypes of receptors involved are presently unclear. The aim of the present experiment was to determine whether blockade of brain beta receptors produces a decrease in motor behavior similar to that produced by stress and, if so, which receptor subtype is involved. For this purpose, mice were administered either stress or one of several beta receptor antagonists and were tested for motor activity. The latter tests included swimming behavior and locomotor activity so as to assess the generality of the findings with regard to different behaviors. A third behavior, grooming, was also recorded because stress has been found to elevate the latter (Gispen and Isaacson 1991), which could therefore serve as a control for nonspecific changes in overall activity.

METHODS

Animals

Male Swiss Webster mice (Taconic Farms) 6 to 8 weeks old were used as subjects. The animals were housed in groups of 6 under a 12-hour light/dark cycle (lights on at 0700 hours) with food and water given ad lib.

Stress Administration

The stress employed was immobilization (IMO) for 1 hour. Immobilization is a behaviorally and physiologically effective form of stress that does not involve the application of painful stimulation. The animal is immobilized on a platform using masking tape to tape the limbs to the platform. Masking tape does not adhere strongly to the skin or fur, so that it can be removed painlessly as determined by the experimenters in tests on themselves. None of the aspects of the stressor are painful as judged from the lack of vocalization of the mice who normally vocalize loudly when in pain (tail pinch or conspecific bite). The stress, however, evokes autonomic (defecation and urination), behavioral (struggling), and neuroendocrine (plasma corticosterone increase) signs of stress. The stress protocol had been approved by the IUCAC of New York University School of Medicine.

MEASUREMENT OF ACTIVITY

Activity Chamber

A 30 × 30 × 30 cm aluminum and Plexiglas box was used as the observation chamber. The floor was mopped with water before each animal. Twenty-four hours prior to the test, the animals were habituated for 15 minutes to the chamber. This habituation session was used to reduce the novelty of the chamber. It did not markedly reduce the amount of locomotor activity on subsequent exposure. On the day of the experiment, the animals were placed in the chamber and videotaped for 14 minutes. The tapes were rated by a trained observer who was ignorant of the treatment of the mice. The number of corners the animal visited, defined as 5-cm squares at the corners of the chamber in which the animal entered with all four limbs, was taken as a measure of locomotion. The amount of time the animal engaged in any kind of grooming was taken as the measure of grooming behavior.

Swim Activity

Swimming activity was measured in a cylinder 16 cm in diameter and 19 cm high filled to 12 cm with 25°C water. The animal was immersed in the water and observed for 5 minutes. The amount of time the animal emitted any swimming behavior (paddling movement with the fore or hind limbs) was taken as the measure of active swimming behavior.

Rotorod Test

Mice were placed on an elevated (30 cm) wooden cylinder, 11 mm in diameter, rotating at 6 RPM. The time to fall off was recorded. Maximum time was 3 minutes.

Experimental Procedure

The animals were either administered a drug or given IMO stress prior to the behavioral test. Drugs were administered 2 hours and stress started 1.5 hours prior to the test. The half-hour difference was imposed to allow for absorption of the drug, so that both the drug and the stress would be active for similar lengths of time prior to the test.

Drugs Used

l-Propranolol, d-propranolol, betaxolol, ICI-118,551, atenolol, fluphenazine, and midazolam were dissolved or diluted in saline. Drugs were administered SC in a volume of 10 ml/kg (20 ml/kg for atenolol).

RESULTS

The effects of IMO stress and the above drugs on swimming, locomotion, and grooming are shown in Table 1. Each of the groups in the table was run with a corresponding vehicle control group, and its scores were con-

Table 1. Effect of Stress and Drugs on Various Forms of Motor Activity in Mice

	Percent of Corresponding Control Group		
Treatment[a]	**Swimming**	**Locomotion**	**Grooming**
IMO stress	82.8 ± 4.0 (18)[b]	58.1 ± 6.7 (12)[b]	850.0 ± 107.6 (12)[b]
l-Propranolol			
2 mg/kg	ND	87.3 ± 6.7 (9)	100.0 ± 38.6 (9)
10 mg/kg	80.7 ± 3.1 (12)[c]	48.9 ± 10.7 (12)[d]	224.6 ± 40.4 (12)[c]
Betaxolol			
2 mg/kg	ND	80.3 ± 6.8 (9)	153.1 ± 37.1 (9)
10 mg/kg	77.2 ± 5.8 (12)[d]	55.8 ± 5.4 (15)[b]	264.4 ± 52.4 (15)[d]
ICI 118,551			
2 mg/kg	78.4 ± 4.7 (12)[b]	104.3 ± 12.2 (12)	99.2 ± 21.4 (12)
d-Propranolol			
10 mg/kg	102.1 ± 4.8 (6)	92.5 ± 9.9 (12)	199.6 ± 36.8 (12)[c]
Atenolol			
10 mg/kg	96.7 ± 4.0 (12)	102.7 ± 11.3 (12)	71.7 ± 23.4 (12)
Midazolam			
1 mg/kg	77.5 ± 4.1 (10)[b]	71.7 ± 7.5 (12)[d]	95.2 ± 27.3 (12)
Fluphenazine			
0.075 mg/kg	ND	40.1 ± 6.0 (6)[b]	70.7 ± 32.9 (6)

Values are mean ± SEM for number of mice in parentheses. Overall mean raw values ± SD non-treated controls, swimming, 3.94 ± 0.34 min (n = 72); locomotion, 56.9 ± 16.0 corners (n = 99); grooming, 2.16 ± 2.46 min (n = 99). ND = not determined.

[a] Doses in molar equivalents in text.

[b] $p < .001$.

[c] $p < .05$.

[d] $p < .01$.

verted into percentage of mean control. Except where indicated, statistical comparisons were of the planned type and were evaluated by independent t-tests between each group and its control.

Immobilization stress significantly decreased swimming and locomotor activity and significantly increased grooming. l-Propranolol at 10 mg/kg (38.6 mmol/kg) significantly reduced both swimming and locomotion and increased grooming. Betaxolol at 10 mg/kg (32.6 mmol/kg) also significantly reduced swimming and locomotion and significantly increased grooming. ICI 118,551 at 2 mg/kg (5.7 mmol/kg) significantly reduced swimming behavior but had no effect on locomotor activity or grooming. d-Propranolol at 10 mg/kg (38.6 mmol/kg) had no effect on swimming or locomotor activity but significantly increased grooming behavior. Atenolol at 10 mg/kg (37.6 mmol/kg) had no effect on swimming, locomotion, or grooming. Fluphenazine at 0.075 mg/kg (0.17 mmol/kg) significantly reduced locomotion but did not significantly alter grooming although it tended to decrease the latter (swimming not examined). Midazolam at 1 mg/kg (3.1 mmol/kg) significantly reduced swimming and locomotion but had no effect on grooming.

An additional group of animals was administered betaxolol (10 mg/kg) 0.5 hour rather than 2 hours prestress and tested as above. The results were not significantly different from those above (data not shown).

Rotorod performance was not affected by stress or betaxolol 10 mg/kg (32.6 mmol/kg) (means and SEMs, control 1.51 ± 0.20 min, IMO stress, 1.52 ± 0.18, betaxolol, 1.09 ± 0.19 (all ns = 12, one way analysis of variance not significant).

DISCUSSION

The present results show that blockade of central beta adrenoceptors can mimic the changes in gross motor activity produced by acute stress in mice. In agreement with past research (cited in the introduction), IMO stress was found to reduce two forms of motor activity, swimming and locomotion, and elevate a third, grooming. l-Propranolol, which is known to block both beta-1 and beta-2 receptors, resulted like stress in a reduction in swimming and locomotor activity and an increase in grooming. The effects of l-propranolol on swimming and locomotion were not a result of its membrane stabilizing property because d-propranolol, which has an identical membrane stabilizing effect but lacks beta receptor activity had no effects on these behaviors (see below for grooming). The selective beta-1 receptor blocker, betaxolol, also reproduced all three effects of stress and did so at a dose that has been reported to be selective for beta-1 receptors in the rat brain (Tondo et al. 1985). The effects of l-propranolol and betaxolol on locomotor activity and grooming appear to be a result of their beta-1 antagonist action because the selec-

tive beta-2 antagonist, ICI 118,551, had no effect on these behaviors. The latter drug did, however, produce a decrease in swimming indicating possible involvement of both beta-2 and beta-1 receptors in this behavior.

The extent to which membrane stabilizing effects of these drugs were involved in the increase in grooming behavior is not presently clear. Both d-propranolol, which has a membrane stabilizing effect, and betaxolol, which does not (Cavero et al. 1983), produced an equivalent increase in grooming behavior. It is possible therefore that both membrane stabilization and beta-1 receptor blockade can produce an increase in grooming behavior.

The syndrome of reduced locomotion and swimming coupled with an increase in grooming appears to be selective to blockade of noradrenergic receptors. Fluphenazine, which nonselectively blocks dopaminergic receptors, reduced locomotion but did not increase grooming. In fact, it tended to reduce the latter in agreement with the findings that dopamine receptor blockade produces a more general depressant effect on all forms of active behavior.

That the behavioral effects of the above drugs were a result of their actions on central rather than peripheral beta adrenoceptors was shown by the finding that the peripherally active beta-1 antagonist had no effect on any of the above behaviors.

The present results thus confirm and extend earlier findings that beta receptor blockers can induce a reduction in evoked gross motor activity in the mouse (cited in the introduction). Presumably, there is sufficient evoked activity in locus coeruleus neurons during these behavioral tests to cause significant activation of postsynaptic brain beta receptors by NE (Rasmussen et al. 1986). They also demonstrate the novel finding that these drugs increase the level of grooming behavior. The results indicate therefore that blockade of beta-1 receptors can mimic the effects of stress on a variety of active behaviors in mice. This finding suggests that a deficient noradrenergic neurotransmission at beta-1 receptors is a factor in producing changes in motor activity after stress.

The present findings would appear to disagree with those of Gorman and Dunn (1993), who have found that beta blockers tend to antagonize effects of stress on emergence and exploratory behavior. We did not use the same tests as Gorman and Dunn in the present experiment, although in a separate study we have found that propranolol lengthens the increase in latency caused by stress in an emergence test similar to the one these authors used (Stone et al. 1994). Also, Gorman and Dunn utilized singly housed VAF plus CD-1 mice, whereas we used group-housed Swiss Webster mice, which may have caused the difference.

What aspect of beta-1 noradrenergic transmission is reduced by stress is not known. It has been suggested on the basis of stress-induced depletion of brain NE and the effects of drugs that alter brain levels of NE that NE release is reduced post stress possibly in response to an excessive release during stress (Stone 1970; Weiss et al. 1975; Anisman et al. 1980; Lehnert et al. 1984). However, most dialysis studies of brain NE release have not found a poststress decrease (Abercrombie et al. 1988), and a number have reported persistent poststress increases (Yokoo et al. 1990; Tanaka et al. 1991). Also, measures of locus coeruleus unit activity (Simson and Weiss 1988) and of NE turnover in the brain (Stone 1973; Lehnert et al. 1984) after stress have supported a persistent poststress increase in NE release. Another possibility is that the need for NE at these receptors is increased by stress, (i.e., the system needs a greater input of NE to function normally after stress). In this regard, Lehnert et al. (1984) found that the NE precursor, tyrosine, was effective in restoring motor activity after stress and that it increased NE turnover beyond the already elevated poststress level. This suggests that neuronal systems postsynaptic to the noradrenergic require a greater NE input following stress and that failure to maintain this heightened input might lead to a relative noradrenergic deficiency. A third possibility is that the reduced neurotransmission at these receptors results from receptor desensitization. Prolonged agonist exposure is known to result in the desensitization and/or downregulation of neurotransmitter receptors. It has been found that stress produces a desensitization and/or downregulation of alpha-1 (Stone 1979b) and beta (Torda et al. 1981) receptors, which would reduce transmission accordingly. Further research will be required to determine how each of these factors is involved in the putative reduction of brain beta-1 neurotransmission after stress.

Precisely what the reduced swimming and locomotor activity and the increased grooming behavior after stress represent and how they are functionally related to beta adrenoceptors is not completely understood. There are several possibilities, however. One factor is impaired motor function. Weiss and Glazer (1975) proposed that hypoactivity following stress results from a motor activation deficit because they found that stressed rats had more difficulty learning effortful than effortless tasks. This is in agreement with findings that central noradrenergic neurons are involved in the control of motor functions (Stafford and Jacobs 1990). However, it does not agree with the findings that both stressed and beta-blocked animals showed increases in grooming, and that neither stressed nor betaxolol-treated mice showed impaired rotorod performance.

A second factor that may be involved is fear. Noradrenergic mechanisms and stress have been implicated in fear behavior (Berridge and Dunn 1989; Charney et al. 1992). It is unlikely, however, that fear

was an important factor in inducing hypoactivity because stressed animals were observed to spend less than 5% of their time freezing in the activity chamber. An alternative possibility is that fear motivated the active behavior of the animals in the chamber and swimming tests and that a reduction in fear caused by the beta blockers and stress resulted in reduced activity (Gorman and Dunn 1993; Kurose et al. 1993). This is supported by the finding that midazolam produced similar effects as beta-blockers and stress on swimming and locomotion. Although stress is not generally thought to produce a reduction in anxiety, it is possible that under some circumstances it can desensitize fear responses (Deakin and Graeff 1991).

A final possibility is that the hypoactivity after stress represents a diminished motivation to interact with the environment and that the increased grooming represents a turning inward of attentional processes. According to this view as a result of stress, active behavior directed at the environment is less reinforcing and consequently there is an increase of self-directed activities such as grooming. This is supported by the findings that stress reduces the rewarding effects of brain stimulation (Zacharko et al. 1983, 1984), sweet solutions (Willner et al. 1987) and amphetamine (Papp et al. 1991) and that beta adrenoceptors have been implicated in mechanisms of reinforcement (Watson and McElligott 1984; McElligott and Freedman 1988; Decker et al. 1990; Crowe et al. 1991) and attentional processes (Berridge and Foote 1991). Moreover, noradrenergic activity in the locus coeruleus is inversely correlated with self-directed activities such as grooming (Aston-Jones et al. 1991a), and under some conditions there is an inverse correlation between brain noradrenergic activity and the concentration of corticotropin releasing factor (Brady et al. 1991; Veith et al. 1993), a neuropeptide implicated in stress-induced grooming (reviewed in Dunn and Berridge 1990).

Based on the above considerations we propose that stress causes a disturbance or an excessive need for beta-1 adrenergic neurotransmission in the brain and that this change, which can be mimicked by beta-1 blockers, produces changes in the level of fear and/or other motivations such that the animal shows less externally and more self-directed motor activity.

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