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Stress-induced subsensitivity to modafinil and its prevention by corticosteroids

Eric A. Stone[a,*], Yan Lin[a], Raymond F. Suckow[b], David Quartermain[c]

[a]*Department of Psychiatry, TH HN510, School of Medicine, New York University Medical Center, 550 First Avenue, New York, NY 10016, USA*
[b]*Analytical Psychopharmacology Laboratory, New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032, USA*
[c]*Department of Neurology, New York University School of Medicine, 550 First Avenue, New York, NY 10016, USA*

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Abstract

Brain α_1-adrenoceptors are known to be necessary for motor activity in rodents and have been shown to be altered by stress and corticosteroids but only in biochemical experiments. To determine if the behaviorally coupled receptors are also affected by stress, the present study examined the effect of stress and corticosteroids treatment on the motor activity response to modafinil, a putative α_1-adrenoceptor agonist, which is unique in that it elicits extremely high levels of activity via these receptors. Mice were subjected to various schedules of restraint stress for 1–6 days and were subsequently tested for either modafinil-induced or dopaminergically induced behavioral activity in the home cage using videotape recording. In experiments on corticosteroid treatment, mice received exogenous corticosterone or dexamethasone in the drinking water before and during the stress and were tested for modafinil-induced activity as above. It was found that the stress significantly reduced the response to the drug by the third daily session. Motor responses to dopaminergic agents including apomorphine, amphetamine, dihydrexidine and quinpirole were either not altered or were increased at this time. Treatment of animals with corticosterone or dexamethasone prior to and during stress prevented the behavioral subsensitivity to modafinil. Corticosterone pretreatment markedly suppressed the plasma corticosterone response to the stress. The present results provide further support for the hypothesis that stress produces a selective desensitization or inhibition of motor-related brain α_1-adrenoceptors and that this effect can be prevented by corticosteroid treatment.

Keywords: Stress; Modafinil; Motor activity; α_1-Adrenoceptor agonist; Spontaneous activity; Corticosterone; Dexamethasone

1. Introduction

Behavioral inactivity is a symptom, or part of a group of symptoms, that occurs across a number of psychiatric conditions including depression, schizophrenia and anxiety disorders, and is believed to be caused by an inhibition or impairment of central dopaminergic neurotransmission (Cabib and Puglisi-Allegra, 1996; Weiss et al., 1998). The primary neurobiological alteration in these states, however, need not occur in the dopaminergic system itself but could involve other neuronal systems that modulate dopaminergic activity. One of these is the α_1-adrenergic system. α_1-Adrenoceptors, among their other behavioral functions, have long been known to be involved in motor activity (Anden and Grabowska, 1976; Anden et al., 1973; Anden and Strombom, 1974; Pichler and Kobinger, 1981; Blanc et al., 1994) and reinforcement mechanisms (Spealman, 1995; Woolverton, 1987), and are known to modulate dopaminergic neurotransmission at presynaptic as well as postsynaptic levels (Drouin et al., 2002; Tuinstra and Cools, 2000; Grenhoff et al., 1995; Blanc et al., 1994; Lategan et al., 1990; Antelman and Caggiula, 1977; Anden et al., 1973). We have recently shown that brain α_{1B}-adrenoceptors are, in fact, essential for all spontaneous activity and movement in mice (Stone et al., 1999, 2001a,b).

Central α_1-adrenoceptors are of particular relevance to behavioral inactivity because they have been found, in biochemical studies, to be desensitized both in depressed patients (Asnis et al., 1992; Checkley and Crammer, 1977) and in animals subjected to repeated stress (Izumi et al., 1996; Stone et al., 1986), a major precipitant of affective disorders. Furthermore, corticosteroids, hormones associated with both affective and psychotic disorders, have been

* Corresponding author. Tel.: +1-212-263-5740; fax: +1-212-263-0712.
E-mail address: eric.stone@nyu.edu (E.A. Stone).

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shown to have pronounced actions on the expression and desensitization of these receptors (Day et al., 1999; Sakaue and Hoffman, 1991; Stone et al., 1987), while certain antidepressant agents have been found by some (Maj et al., 2000; Blendy et al., 1991; Vetulani et al., 1984; Menkes et al., 1983), though not by all, investigators (Nowak and Przegalinski, 1988; Stockmeier et al., 1987; Heal, 1984) to enhance the density, affinity and/or functional responses of α_1-receptors, and to reverse the desensitizing effects of stress (Izumi et al., 1997).

Despite the above evidence, there has been only one study of the effect of stress on behavioral responsiveness to α_1-adrenoceptor stimulation in animals (Zebrowska-Lupina et al., 1988), and this study failed to find an effect using methoxamine as the agonist. However, one of the problems in this research is that most α_1-adrenoceptor agonists by themselves have relatively weak effects on motor activity (Wellman and Davies, 1992; Heal, 1984) and, in order to produce substantial increases in this behavior, need to be given either at high doses, which also elicit anxiety (Berridge and Dunn, 1989) and a halting intermittent movement (Stone EA, unpublished results), or in combination with dopamine receptor agonists after pretreatment with reserpine or 6-hydroxydopamine (Eshel et al., 1990; Zebrowska-Lupina et al., 1977; Anden et al., 1973). The stimulant modafinil, however, appears to be an exception to this rule and has been found to produce extremely high levels of coordinated activity by itself via these receptors without significant anxiety and even in the home cage environment (Simon et al., 1994, 1995; Duteil et al., 1990). While modafinil has effects on other neurotransmitter systems including dopamine (Wisor et al., 2001; Ferraro et al., 1996), γ-aminobutyric acid (GABA) (Tanganelli et al., 1992) and orexin (Scammell et al., 2000; Chemelli et al., 1999), its motor effect is nevertheless dependent on α_1-adrenoceptor activity (Simon et al., 1995; Lin et al., 1992; Duteil et al., 1990) and can be abolished by drugs that block α_{1B}-adrenoceptors (Stone et al., in press). Therefore, it was of interest to determine the actions of stress on the behavioral response to modafinil. To assess whether changes in dopaminergic neurotransmission were involved, responses to dopamine receptor agonists were also studied. As the results of the present study indicated that stress did, in fact, reduce responsiveness to modafinil, further experiments were undertaken to determine how treatment with corticosteroids influenced this effect because of the relevance of these hormones to stress, affective disorders and α_1-adrenoceptor regulation noted above.

2. Methods

2.1. Subjects

Male Swiss Webster mice 7–8 weeks old (30–40 g) at the start of the experiments were used. Mice were housed singly with nesting material for the duration of the study (10 days) because fighting among group-housed male mice can inhibit motor activity. All mice were on a 12:12-h light:dark cycle (lights on at 0500 h) with food and water available ad libitum with ambient temperature at 23.6 ± 0.5 °C.

2.2. Stress

Mice were subjected to restraint stress for 1 h/day for either 1, 3 or 6 days in an aerated plastic cylinder 3 × 9 cm. The stress was administered either between 0900 and 1000 h or between 1200 and 1300 h, depending on the experiment. To reduce habituation to the stress, the restrained animals were given two pinches to the tail at 15-min intervals with a 12.7 × 0.2-cm forceps. The amount of pressure used was the least necessary to elicit any behavioral reaction. All experiments were conducted in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 85-23, revised 1985) and were approved by the New York University School of Medicine IUCAC.

2.3. General procedure

At various post stress intervals (see below), the mice in their home cages were brought into the test room in groups of four and the cages placed 1 cm from each other in a quadrangle on a table beneath a videocamera. Behavioral activity was studied in the home cage rather than in a novel test chamber as it has been shown that stress is more effective in inhibiting active behavior in the home environment (Lacosta et al., 1999; Stone et al., 1997), and also to avoid neophobia. Indirect daylight (100–200 lx) was used. Visual contact between the animals was prevented with partitions. The animals were given 2–3 h of habituation prior to injection. All injections were administered intraperitoneally as subcutaneous injection was found to be more stressful and to interfere with the motor activity response to modafinil. The period of recording varied with the drug used as follows: modafinil, 0–2.5 h; apomorphine, 0–35 min; amphetamine, 0–2 h; dihydrexidine, 0–1 h; and quinpirole, 30–60 min postinjection. These intervals were chosen because they yielded the greatest differences in activity scores between drug and vehicle treatment.

In experiments involving corticosteroid pretreatment, corticosterone (0.25, 2.5, 25.0 μg/ml) or dexamethasone (1, 10 μg/ml) was administered in the drinking water (tap) in 0.2% ethanol for 2 days prior to and throughout the stress period. Vehicle controls received only the ethanolic tap water.

2.4. Behavioral measures

Videotapes were rated manually for the following four measures: number of gross movements (GM), number of cage quadrants entered (squares entered, SE), number of

vertical movements (VM) and time spent grooming (GR). Gross movements were defined as all acts involving at least displacement of the head and forelimbs, other than grooming, that were followed by a momentary pause. Sniffing without forward movement was excluded. The segmented nature of these acts (move, pause, move, etc.) was found to be much more apparent when the tape was played at a fast speed (5 × actual speed) and, consequently, all ratings were done at this speed. Cage quadrants were marked off on the TV screen and the number entered with all four paws was recorded to measure locomotion. Vertical movements were defined as all investigative movements that were made toward or at the top of the cage. These included head raises, rearing responses and number of different points paused at on the wall or top of the cage. All tape scorings were made by a trained observer who was unaware of the animal's treatment. A second trained observer who was also blind to treatments rated a randomly chosen 25% of the tapes as a control for reliability. The interrater agreement was found to be above 0.90 for all four measures.

2.5. Plasma corticosterone

Stressed and control mice treated with exogenous corticosterone or vehicle were sacrificed by decapitation for collection of trunk blood either immediately after the third stress or 24 h after the second stress. Corticosterone was determined in the plasma by commercial radioimmunoassay.

2.6. Drugs used

Modafinil (gift of Lafon Laboratories) was dissolved in a heated (50 °C) mixture of 0.4:0.6:4.0 polyethylene glycol:methanol:water by volume and used immediately while warm. Apomorphine, amphetamine, quinpirole and dihydrexidine were obtained from RBI and were dissolved in distilled water. All injection volumes were 10 ml/kg. Corticosterone and dexamethasone (Sigma, St. Louis, MO) in the drinking water were dissolved in a small volume of ethanol and diluted with tap water (final ethanol concentration, 0.2%).

2.7. Statistics

All data were analyzed by two- or three-way analyses of variance (ANOVAs) coupled with Bonferroni-corrected multiple planned comparisons.

3. Results

3.1. Time course of stress effect

Twenty independent groups of animals were subjected to either control conditions (picked up once—10 groups) or daily restraint plus tailpinch (10 groups) for either 1, 3 or 6 days and then were challenged with either vehicle or modafinil (40 mg/kg) at either 0, 4 or 24 h after stress for the 1-day groups or 4 h after stress for the 3- and 6-day groups. Tapes were rated for GM only. The results are shown in Fig. 1. As there were no significant differences among the five nonstressed groups given either vehicle [$F(4,23)=1.02$, NS] or 40 mg/kg modafinil [$F(4,42)=0.19$, NS], each of these sets of groups was pooled to form two nonstressed groups, which were then used with their respective five stressed groups in 6×2 (Stress × Modafinil) ANOVAs. Stress was found to produce a significant effect on the GM response [$F(5,140)=3.80$, $P<.003$] with a significant Modafinil × Linear Trend of Stress interaction [$F(1,140)=6.84$, $P<.01$], indicating that the reducing action of stress was greater in the modafinil- than vehicle-challenged animals. Multiple comparisons revealed that there were significant reductions in the responses of the 3- and 6-day stressed groups compared to the pooled nonstress group [3-day group, $F(1,140)=7.55$, $P<.01$; 6-day group, $F(1,140)=5.31$, $P<.03$].

3.2. Further behavioral characterization of the stress effect

As 3 days of stress produced the maximum decrease in modafinil-induced GM, this time point was chosen to evaluate the effects of the stress on the other two measures of motor activity (SE and VM) and on GR grooming time. The results are shown in Table 1. For this analysis, the tapes of the above animals were scored for these variables and two independent groups (nonstressed and 3-day-stressed groups) tested at 20 mg/kg modafinil were included to determine the dose dependency of effects.

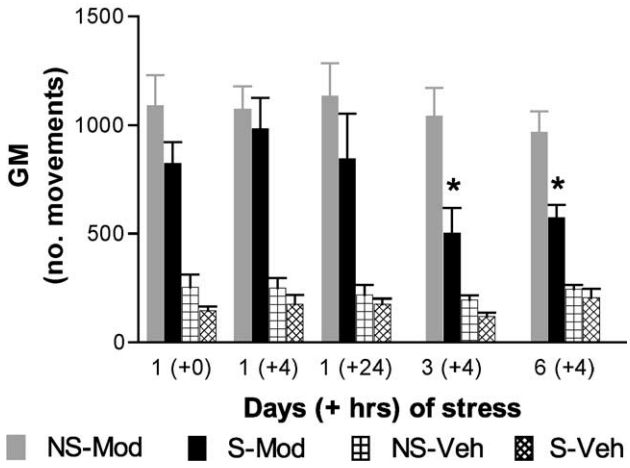

Fig. 1. Time course of effect of daily restraint stress with tailpinch (1 h) on gross movement (GM) response to modafinil (Mod). Top plot: 20 mg/kg; bottom plot: 40 mg/kg and vehicle (Veh). S, stressed; NS, nonstressed. Drug was given either immediately (+0), +4 or +24 h after last stress; behavior was measured for the following 2.5 h. Bars represent the means and S.E.M. of independent groups of 8–11 mice. * $P<.05$ versus pooled nonstressed control.

Table 1
Effect of 3 days of restraint stress on behavioral responses to modafinil (40 mg/kg)

Pretreatment	Drug (mg/kg)	Gross movements	Squares entered	Vertical movements	Grooming (min)
Nonstressed	Veh	230.1 ± 19.7	59.5 ± 5.5	46.7 ± 3.4	24.5 ± 2.7
	Mod 20	733.8 ± 173.3	380.7 ± 137.3	301.3 ± 83.3	21.5 ± 6.4
	Mod 40	1042.5 ± 129.0	679.7 ± 100.7	635.9 ± 90.8	37.6 ± 5.0
Stressed	Veh	119.5 ± 17.4	39.8 ± 13.0	23.6 ± 7.6	20.5 ± 3.1
	Mod 20	309.8 ± 82.0 *	171.2 ± 42.1 *	116.6 ± 45.0	22.2 ± 4.0
	Mod 40	501.3 ± 116.4* * *	312.4 ± 78 * *	248.6 ± 80.5 * *	53.2 ± 4.0

Values are means and S.E.M. for 7–10 mice given 20 or 40 mg/kg vehicle (Veh) or modafinil (Mod).
* $P < .05$.
** $P < .005$.
*** $P < .0001$.

The data were analyzed for each behavior by 2 × 3 (Stress × Modafinil) ANOVAs. For the GM response, the data for the 40 mg/kg dose and vehicle have already been presented above. Similar to that found for the 40-mg/kg dose, a decrease in the stressed group occurred at the 20-mg/kg dose [$F(1,48) = 4.17$, $P < .05$]. For the SE response, there was a significant overall reducing effect of stress [$F(1,50) = 6.97$, $P < .02$] with a significant Stress × Linear Trend of Modafinil interaction [$F(1,50) = 4.13$, $P < .05$]. A significant decrease was found at the 40-mg/kg dose [$F(1,50) = 13.18$, $P < .005$] but not at the 20-mg/kg dose or vehicle response. For the vertical movements response, there was also a significant overall reducing effect of stress [$F(1,50) = 8.62$, $P = .005$] with a significant Stress × Linear Trend of Modafinil interaction [$F(1,50) = 5.32$, $P = .05$]. The reduction at the 40-mg/kg dose was significant [$F(1,50) = 12.87$, $P < .003$] while that at the 20-mg/kg dose was of borderline significance [$F(1,50) = 4.51$, $P = .08$] with no effect in the vehicle-treated group. No significant main effect or interaction effect of stress was found for the GR response.

3.3. Motor impairment

To determine if the stress-induced reduction in activity was due to a direct impairment of motor systems, the 3-day-stressed and nonstressed control mice were exposed to a novel mouse cage for 5 min, which elicits very high levels of activity from both groups of animals. There was no difference between the nonstressed and stressed groups in the 5-min test (gross movements/5 min: nonstressed, 71.1 ± 2.2; stressed, 70.1 ± 2.8; $n = 8$).

Table 2
Effect of 3 days of restraint stress on gross movement responses to apomorphine

Dose (mg/kg)	Movements	
	Nonstressed	Stressed
0	226.7 ± 50.9	134.7 ± 12.4 *
1	102.0 ± 32.4	214.3 ± 40.4 *
2	382.8 ± 27.2	396.1 ± 24.5
4	531.4 ± 14.9	550.5 ± 11.6

Responses were recorded 0–35 min postinjection. Values are means and S.E.M. of six to eight mice.
* $P < .05$ versus respective nonstressed group.

3.4. Effect of stress on dopaminergic function

The effects of 3 days of restraint stress on gross movement responses to dopaminergic agents are shown in Tables 2 and 3. With respect to the response to apomorphine (Table 2), a 2 × 4 (Stress × Apomorphine) ANOVA showed no significant effect of stress [$F(1,51) = 0.46$] but a significant Stress × Drug interaction [$F(3,51) = 3.83$, $P < .02$], which was due both to a borderline significant reduction in the stress vehicle compared to the nonstress vehicle group [$F(1,51) = 4.84$, $P = .06$] and a significant increase in the stress–1 mg/kg versus the nonstress–1 mg/kg group [$F(1,51) = 6.57$, $P < .05$]. The activity response to either 2 mg/kg amphetamine, 6 mg/kg dihydrexidine or 4 mg/kg quinpirole (Table 3) was not significantly altered by the stress.

3.5. Effects of corticosteroids

Fig. 2 shows the effects of pretreatment with (supplemental) corticosterone on the GM response to modafinil in 3-day-stressed mice. The average daily intakes of the exogenous hormone for the 0.25-, 2.5- and 25-μg/ml doses

Table 3
Effects of 3 days of restraint stress on motor responses to dopaminergic agents

Drug	Dose (mg/kg)	Nonstressed	Stressed
Amphetamine	0	235.1 ± 46.3	129.3 ± 9.9
	2	936.0 ± 84.8	871.5 ± 73.3
Dihydrexidine	0	219.1 ± 43.4	147.2 ± 15.0
	6	378.8 ± 31.4	418.8 ± 41.0
Quinpirole	0	12.5 ± 11.7	3.8 ± 11.7
	4	76.8 ± 15.7	110.2 ± 9.0

Values are means and S.E.M. of groups of six to eight mice. Mice were tested from 0 to 2 h after amphetamine, from 0 to 1 h after dihydrexidine and from 30 to 60 min after quinpirole with corresponding vehicle groups. The vehicle scores for the quinpirole groups are much lower than for the other groups since the mice had quieted down by the start of the 30- to 60-min period.

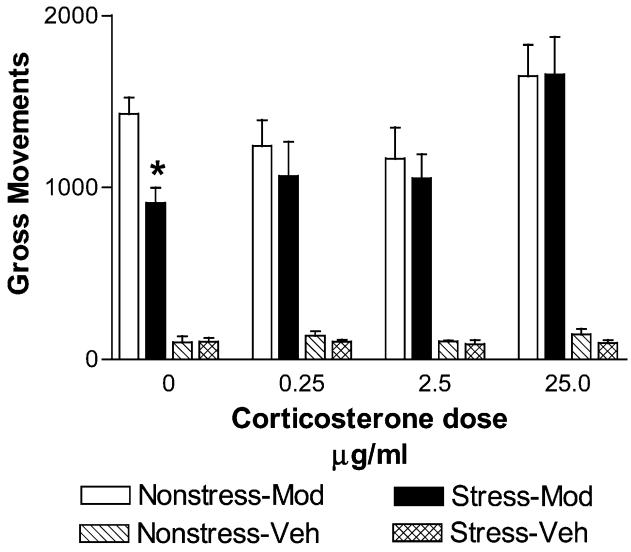

Fig. 2. Effect of corticosterone pretreatment in drinking water on GM response to modafinil (40 mg/kg) or vehicle in 3-day-stressed or nonstressed mice. Values are means and S.E.M. of five to seven mice. * $P < .001$ versus modafinil-injected nonstressed control.

were 0.08 ± 0.004, 0.87 ± 0.05 and 8.5 ± 0.4 mg/kg, respectively ($n = 10–14$). The data were analyzed with a 2 × 4 × 2 (Stress × Corticosterone × Modafinil) ANOVA. Corticosterone produced an overall increase in GM [$F(3,73) = 2.98$, $P < .05$]. There was a significant Stress × Linear Trend for Corticosterone interaction in the modafinil-treated mice [$F(1,73) = 7.92$, $P < .01$], with the stressed group showing a significant linear trend [$F(1,73) = 27.6$, $P < .0001$] and the nonstressed group showing no linear trend [$F(1,73) = 0.6$, NS]. Multiple comparisons indicated that stress significantly reduced the GM response in the vehicle-pretreated (0.2 % ethanol) mice [$F(1,73) = 20.07$, $P < .001$] but failed to affect the response in any of the corticosterone-pretreated groups.

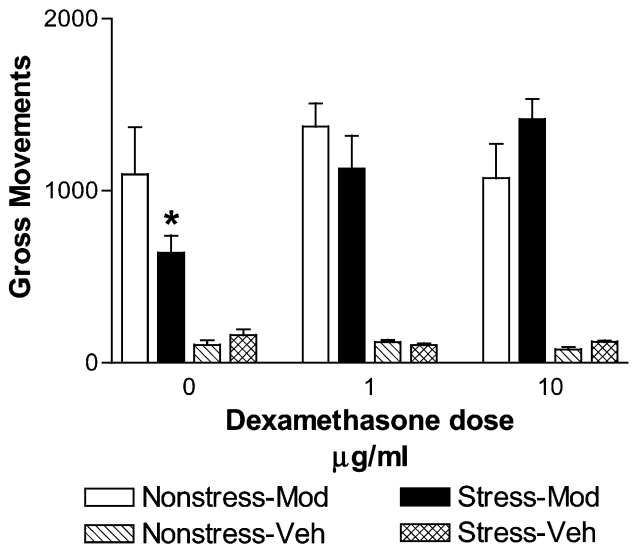

Fig. 3. Effect of dexamethasone pretreatment on GM response to modafinil in stressed and nonstressed mice (see legend to Fig. 2). Values are means and S.E.M. of five to seven mice. * $P = .07$ versus modafinil-injected nonstressed control.

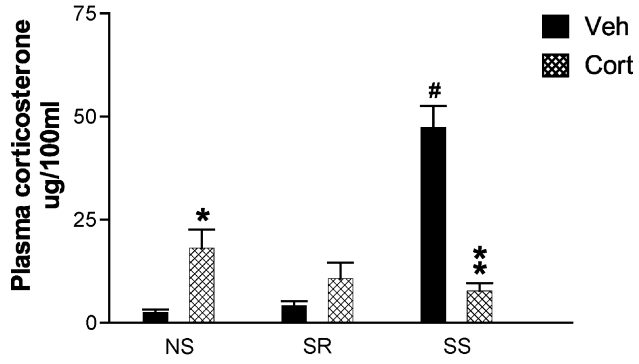

Fig. 4. Effect of corticosterone pretreatment on plasma corticosterone levels in nonstressed and stressed animals. NS, nonstressed; SR, killed 24 h post second stress; SS, killed immediately after third stress. Values are means and S.E.M. of eight mice. * $P < .01$, ** $P < .0001$ versus corresponding vehicle; # $P < .0001$ versus NS vehicle.

The effects of dexamethasone are shown in Fig. 3. Average daily intakes for the 1- and 10-μg/ml doses were 0.34 ± 0.02 and 3.12 ± 0.2 mg/kg ($n = 11–13$). A 2 × 3 × 2 (Stress × Dexamethasone × Modafinil) ANOVA revealed that dexamethasone did not have an overall effect on the GM response [$F(2,53) = 1.27$, NS] but that there was a significant Stress × Linear Trend for Dexamethasone interaction in the modafinil-injected mice [$F(1,53) = 8.53$, $P = .005$], with the stressed group showing a significant linear trend [$F(1,53) = 25.9$, $P < .0001$] and the nonstressed group showing no linear trend [$F(1,53) = 0.006$, NS]. Multiple comparisons indicated that stress had a borderline suppressive effect on the response to modafinil in the vehicle-pretreated mice [$F(1,53) = 5.26$, $P = .07$] but had no effect in either the 1- or 10-μg/ml dexamethasone-pretreated animals.

The effects of pretreatment with 25 μg/ml exogenous corticosterone on the resting and stress plasma corticosterone levels are shown in Fig. 4. Three groups were assayed: a nonstressed group (NS), a stressed group at rest (24 h after the second stress, SR) and a stressed group immediately after the third stress (SS). A 2 × 4 (Stress × Corticosterone) ANOVA revealed significant effects of both corticosterone pretreatment [$F(1,42) = 4.62$, $P < .05$] and stress [$F(1,42) = 21.1$, $P < .0001$] and a significant interaction of the two [$F(1,42) = 39.29$, $P < .0001$] on the level of hormone. Multiple comparisons indicated that corticosterone pretreatment increased resting levels in nonstressed mice [$F(1,42) = 10.76$, $P < .01$] but markedly suppressed the increase produced by stress [$F(1,42) = 70.5$, $P < .00001$].

4. Discussion

The present results show that repeated stress selectively inhibits the motor activity response to modafinil and that

pretreatment with corticosterone or dexamethasone prevents this effect of stress. Three daily sessions of restraint plus tailpinch, a stressor that produces high plasma corticosterone levels in these animals, were sufficient to induce marked and significant reductions in three measures of motor activity in response to a 40-mg/kg dose of the stimulant. Reductions of the 20-mg/kg responses were more variable but of similar magnitude. Responses to the vehicle were unaffected. Stress is known to produce an increase in grooming behavior (Dunn, 1988), which is incompatible with other forms of motor activity and may have produced the latter effect. While there was a tendency for grooming times to be increased in the stressed mice given 40 mg/kg modafinil, this was not statistically significant. Furthermore, no tendency toward an increase in grooming was apparent in the stressed mice given 20 mg/kg, which showed a similar proportional decrease of motor activity to the 40-mg/kg group.

The effects of stress were selective to the response to modafinil since no reductions in motor activity responses were found to a range of doses of apomorphine, or single doses of amphetamine, dihydrexidine or quinpirole. Furthermore, when placed briefly in a novel cage which, unlike the home cage, maximally stimulates motor activity, there was no reduction in activity of the stressed animals, suggesting that they can exhibit proficient motor behavior if suitably stimulated.

Modafinil is a putative α_{1B}-adrenoceptor agonist since it can stimulate an α_{1B}-dependent increase (to 70% that of a full agonist) in the phosphorylation of mitogen-activated protein kinase (MAPK) in cultured DDT1 MF-2 cells, which have only α_{1B}- and β-adrenoceptors and glucocorticoid receptors (Stone et al., 2001c). The present results, thus, are in agreement with the hypothesis that stress either desensitizes or otherwise inhibits these receptors as found in the previous biochemical studies cited above.

It should be emphasized, however, that modafinil was the only α_1-agonist used in this study and, therefore, the possibility cannot be excluded at present that stress acted through an effect on another neurotransmitter system affected by this drug (dopamine, orexin, GABA). Hence, the above conclusion remains tentative until confirmed with other selective α_1-agonists that activate α_{1B}-receptors. Studies are currently in progress to determine if other full agonists at α_{1B}-adrenoceptors can stimulate coordinated motor activity in these animals. Why modafinil differs from other α_1-agonists in its ability to stimulate motor activity is not presently understood but may be related to differences in efficacy at different α_1-receptor subtypes. For example, phenylephrine, the classical α_1-agonist, has very little efficacy compared to the full agonists, norepinephrine and epinephrine, at the α_1-receptor that potentiates cAMP responses in rat brain slices (Johnson and Minneman, 1986) and which is known to be desensitized by stress (Stone et al., 1984).

Pretreatment with either corticosterone or dexamethasone was found to dose-dependently prevent the actions of stress on the modafinil response. Exogenous corticosteroids have been found by a number of authors to reverse stress-induced behavioral inactivity in animals (Ainsah et al., 1999; Papolos et al., 1998; Pezeshki et al., 1996; Sandi et al., 1996) and humans (DeBattista et al., 2000; Schelling et al., 1999), although others have found an exacerbation of the effects of stress (Kennett et al., 1985). Exactly how exogenous corticosteroids protected against the stress effect in the present experiment is not known. However, two possible mechanisms can be suggested. The first assumes that these hormones have a direct enhancing action on α_1-adrenoceptor function, which is supported by some previous findings (Sakaue and Hoffman, 1991), and that some stressors deplete endogenous corticosteroids causing a poststress lowering of plasma levels (Yehuda, 2001; Schelling et al., 1999), which would then be reversed by administering the exogenous compound. No reduction in poststress plasma corticosterone was found in the present study, although we did not assay animals systematically at several time points after the third stressor. The second mechanism assumes that the impairment in α_1-receptor function results from actions of stress hormones and/or cytokines released during the stress, and that the exogenous steroids, by a feedback mechanism, suppress the release of these other stress factors indirectly restoring receptor function (DeKloet et al., 1998; Prasad et al., 1996; McEwen, 1987; Keller-Wood and Dallman, 1982). The latter suppression was clearly evident in the present study from the marked reduction in the corticosterone response to restraint stress in the hormone-treated mice. Further research will be required to evaluate these possible mechanisms.

The results of the present experiments may have relevance to the study and treatment of affective disorders in several ways. First, modafinil may prove to be a useful probe for directly assessing brain α_1-adrenoceptor function in depressive and bipolar patients to test further if a stress-like impairment is present in these disorders. Second, if it occurs in these disorders, the impairment of α_1-receptor function may represent a contributing factor to one of the core symptoms of depression—the loss of interest in previously enjoyable activities. Finally, the protective effect of corticosteroids on this impairment may help elucidate the latter's biochemical nature and lead to new therapeutic methods that prevent or reverse it.

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