BRAIN RESEARCH

Short communication

Single restraint stress sensitizes acute chewing movements induced by haloperidol, but not if the 5-HT_{1A} agonist 8-OH-DPAT is given prior to stress

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Accepted 18 February 1997

Abstract

The objective of this study was two-fold: (i) to analyze behavioral sensitization to haloperidol 2 weeks after single restraint stress, and (ii) to establish the effects of 8-OH-DPAT treatment prior to stress on sensitized behavioral responses. Overall behavior was analyzed and not only catalepsy, but also sedation (immobility), grooming, exploration and vacuous chewing movements were evaluated. Results indicated that single restraint stress induced a long-lasting sensitization of acute vacuous chewing movements induced by haloperidol (0.25, 0.5 mg/kg i.p.). Interestingly, this behavioral sensitization was prevented by 8-OH-DPAT (0.35 mg/kg s.c.) prior to stress. Finally, haloperidol-induced sedation was not disrupted by either restraint stress or 8-OH-DPAT treatment.

Keywords: Stress; Restraint; Sensitization; Haloperidol; 8-OH-DPAT; 5-HT_{1A}; Vacuous chewing movement; Catalepsy; Rat

Stress is known to induce a long-lasting behavioral sensitization to haloperidol, a D_2 dopamine receptor blocker. Thus, haloperidol treatment produces higher cataleptic effects in singly stressed rats than in non-stressed rats 2 weeks after stress [1,2]. Stress-induced sensitization is a common phenomenon with many drugs, and a significant number of studies have shown that the effects of a stressful event multiply with the passage of time, as manifested by a later challenge with a drug or other stressor [15,26,34,36,37]. However, a fully behavioral study of haloperidol sensitization after single stress in rats has not been performed so far. On the other hand, the ability of the 5-HT_{1A} serotonin receptor agonist 8-OH-DPAT (8-hydroxy-2-(di-*n*- propylamino)tetralin) to reverse haloperidol-induced catalepsy in rats is well documented [3,22,33], but the potentially protective role of 8-OH-DPAT on stress-induced sensitization to haloperidol still has not been clarified. In this context, preteatment with 5-HT_{1A} receptor compounds appears to modulate long-lasting neural changes induced by stress in rats. Van Dijken et al. reported that flesinoxan (5-HT_{1A} receptor agonist) reversed shock-induced locomotion deficits and immobility in rats 2 weeks after stress [37]. Furthermore, 8-OH-DPAT has been suggested to be efficient in protecting anxiety-promoting effects of certain forms of stress [6,21,31]. The objective of this study was two-fold: (i) to analyze behavioral sensitization to haloperidol 2 weeks after single restraint stress, and (ii) to establish the effects of 8-OH-DPAT treatment prior to stress on sensitized behavioral responses. Behavior was analyzed from an ethological point of view, and not only catalepsy, but also sedation (immobility), grooming, exploration and vacuous chewing movements (VCMs) were evaluated.

Subjects and drugs. Male Wistar rats (275–325 g) from the breeding colony of the Faculty of Medicine of Seville were housed in the vivarium, the laboratory temperature was kept at 22 ± 1°C, and a 12-h light–dark cycle (lights on at 08.00 h) was maintained throughout the experiment. Food (lab chow) and water were available ad lib. Animals were never handled or habituated to the experimental procedure before test sessions. Restraint stress and behavioral tests were carried out in the same room. Injections were performed in an independent room. 8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) was purchased from RBI (Natick, MA, USA), dissolved in saline (0.9% NaCl), and administered s.c. (back of the neck) at a dose of 0.35 mg/kg. Haloperidol was purchased from Syntex Latino (Madrid, Spain) in phials of 15 ml, each containing 30 mg haloperidol dissolved in solution of methylparaben (10.8 mg), propylparaben (1.2 mg) and lactic acid. This solution

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PII S0006-8993(97)00242-4

was further diluted to a concentration of 1 mg/ml haloperidol with doubled distilled water. All drugs were administered in a volume of 1 ml/kg body weight.

Experimental groups, apparatus and procedure. Rats were randomly assigned to four groups: (i) saline s.c. injection followed by single stress and later haloperidol challenge (Sal-Stress group, $n = 21$), (ii) saline, no stress and haloperidol challenge (Sal-No Stress group, $n = 18$), (iii) 8-OH-DPAT injection followed by single stress and later haloperidol challenge (8-OH-Stress group, $n = 18$), and (iv) 8-OH-DPAT treatment, no stress and haloperidol challenge (8-OH-No Stress group, $n = 18$). Each group was separated into three independent subgroups, and haloperidol was injected i.p. at a dose of 0 ($n = 7–6$), 0.25 ($n = 7–6$), and 0.5 mg/kg ($n = 7–6$). Haloperidol effects were studied 30 min after injection.

A rat restrainer box was used for inducing stress, consisting in a Plexiglas container ($9 \times 7 \times 20$ cm). Each animal was placed into the restrainer box for 20 min and then returned to its home cage. Rats were injected with either 8-OH-DPAT or saline 30 min before the restraint test. Two weeks after stress or single injections with either 8-OH-DPAT or saline, haloperidol-induced effects were evaluated. Sensitization effects on locomotor activity were studied on a neutral arena, made up from transparent Plexiglas ($50 \times 50 \times 34$ cm). Rats were placed on the neutral arena for 10 min (30–40 min post injection). The arena floor was cleaned up with a wet towel in between test sessions. Shortly after the neutral arena test, cataleptic effects were studied by using the bar test (42 min post injection), being animals placed with their front paws on a horizontal bar raised 10 cm above the floor level. The intensity of catalepsy was measured by the length of time the animals took to move both forepaws off the bar. A maximal duration of 120 s was scored if the animal failed to move the front paws off the bar within this period of time. The rat's behavior was videotaped under white light illumination. Video tapes were later played and behavior analyzed automatically after direct keyboard entry to a computer programmed to perform statistical and ethological analyses. Video tapes were scored ''blind'' by two highly trained observers (inter- and intra-rater reliability ≥ 0.9). Behavior was encoded ethologically by using the complete sampling method [32]. An ethogram comprising immobility, vacuous chewing movement (VCM), exploration and grooming was used. Exploration included sniffing (mobile or quiet olfactory exploration) and rearing (upright exploratory posture). Frequency of VCMs and duration of the remainder patterns were evaluated. VCMs are oral movements which occur in isolation and they are unrelated to grooming, gnawing or eating. They are mostly displayed while rats are eliciting immobility, being performed as a single movement or like bursts of individual oral movements, which are usually associated with jaw tremors [7]. Tape speed could be modified ($\times 2$, $\times 1$, $\times 1/5$) for better scoring behavioral responses, e.g., the ''bursts'' of VCMs where VCMs are elicited in rapid succession.

The effect of haloperidol on behavioral measures was evaluated by two-way ANOVA (group and dose, between factors). Post-hoc analyses were performed using one-way ANOVA for comparisons among the four groups at the same dose point, followed by Student's *t*-test (independent groups). One-way ANOVA was also employed for comparing dose effects within the same group, followed by Student's *t*-test (independent groups). Statistical significances were evaluated on logarithmically (log[x]) transformed data, since size population was small and variance was not homogeneous. Experiments were performed in accordance with the European Communities Council Directive for the employment of laboratory animals (24 November 1986; 86/609/EEC).

Results and discussion. Two-way ANOVA indicated a significant interaction effect for VCM ($F_{6,63} = 2.6$, $P < 0.05$). Post-hoc analyses revealed that VCM frequency, at 0.25 mg/kg haloperidol, was significantly lower in the Sal-No Stress ($t = 2.1$, $P < 0.05$), 8-OH-Stress ($t = 2.3$, $P < 0.05$) and 8-OH-No Stress groups ($t = 3.3$, $P < 0.02$), with respect to the Sal-Stress group. At 0.5 mg/kg haloperidol, statistical analyses also revealed significantly lower VCM values in the Sal-No Stress ($t = 2.2$, $P < 0.05$), 8-OH-Stress ($t = 2.7$, $P < 0.03$) and 8-OH-No Stress groups ($t = 4.2$, $P < 0.01$). Frequencies of VCM in every group are shown in Fig. 1 (left). One-way ANOVA revealed significant dose effects ($P < 0.0001$) for VCM within every group (Sal-Stress, $F_{2,18} = 145.6$; Sal-No Stress, $F_{2,15} = 209$; 8-OH-Stress, $F_{2,15} = 133.8$; 8-OH-No Stress, $F_{2,15} = 134.7$). Thus, haloperidol induced a significantly progressive increase in VCM in all the rats ($P < 0.001$) at 0.25 and 0.5 mg/kg vs. the corresponding control group. Finally, ANOVA did not reveal significant interaction effects for catalepsy duration, as shown in Fig. 1 (right), or other behavioral measures. Catalepsy was similarly enhanced in every group across the tests, as indicated by a significant dose effect ($F_{6,63} = 31.8$, $P < 0.0001$). Mean duration values of immobility, exploration and grooming are shown in Table 1. Immobility was progressively enhanced, and exploration and grooming were decreased after haloperidol, as revealed by significant dose effects (df 6, 63; $P < 0.0001$).

The present study demonstrates that single stress is able to induce sensitization of acute VCMs after haloperidol challenge 2 weeks after stress. This finding hence confirms that single stress induces a long-lasting behavioral sensitization to haloperidol [1,2]. Restraint stress and behavioral tests were performed in the same room, hence sensitization of VCMs is likely to have context-dependent components [16,34]. Stress-induced catalepsy sensitization was not found, because catalepsy duration was quite similar in every group. In this context, the time point for measuring catalepsy seems to be critical. Antelman et al. [2] reported that a single black-box situation induced sensitization of

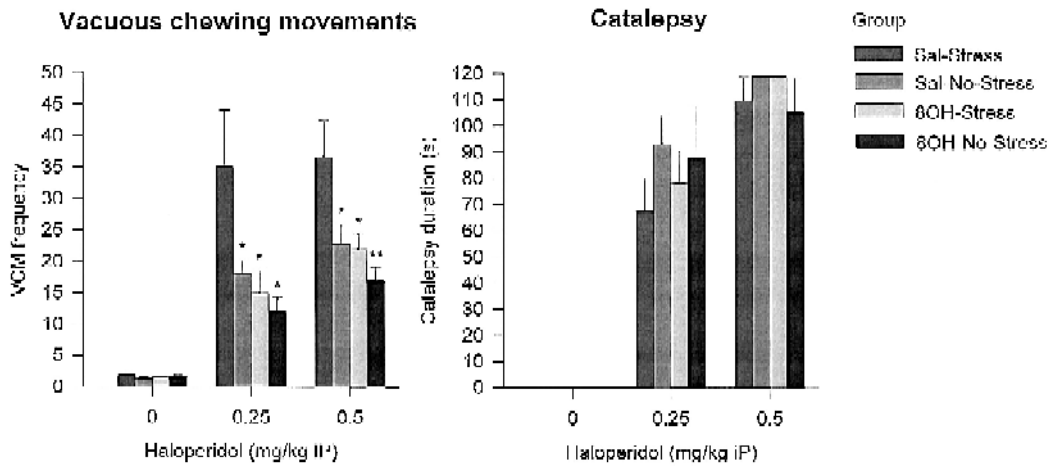

Fig. 1. Left: VCM frequency in every group after haloperidol treatment. Right: catalepsy in every group after haloperidol treatment (an immobility duration in the bar test of 120 s was considered as maximal catalepsy). VMCs were quantified from 30 to 40 min after injection, and catalepsy was measured 42 min after haloperidol administration. Mean ± S.E.M. * $P < 0.05$, ** $P < 0.01$ vs. the Sal-Stress group (Student's *t*-test). Groups: Sal-Stress (saline + restraint stress); Sal-No Stress (saline + no stress); 8-OH-Stress (8-OH-DPAT + Stress); 8-OH-No Stress (8-OH-DPAT + No Stress).

the cataleptic response after 0.2 mg/kg haloperidol, but this effect appeared when catalepsy was measured 28–42 min after injection, but not beyond this period of time, as in this study. To sum up, single restraint stress induced sensitization of acute VCMs, hyperkinetic responses, but catalepsy, and hypokinetic response was not sensitized when measured 42 min after haloperidol. It is noteworthy that acute VCMs emerged in every group, because a rapid onset of VCMs after haloperidol is not found in all the studies. In this context, the route of administration seems to be quite important, because acute VCMs are reported to be induced by oral [28] and i.p. administration [8,29], as in this study. On the other hand, depot haloperidol decaonate induces VCMs only after prolonged treatment [9]. Finally, immobility, an index of sedation, was progressively enhanced in every group after haloperidol. Hence, neither stress nor 8-OH-DPAT disrupted the sedative properties of neuroleptic treatment.

Acute VCMs, like catalepsy, are considered as extrapyramidal side effects induced by haloperidol treatment [38]. VCMs are mostly induced by selective stimulation of D_1 dopamine receptors [18,24,27] and haloperidol is known to bring about a rebound hyperactivity of D_1-modulated circuits [11]. Catalepsy is induced by selective blockade of striatal D_2 receptors [10,25,30]. Interestingly, VCMs were not sensitized after 8-OH-DPAT prior to stress. This effect was specifically related to the stress-induced haloperidol sensitization, because 8-OH-DPAT behaved quite similarly to saline in rats without stress.

Although the neurophysiological mechanisms of action concerning VCM sensitization and 8-OH-DPAT effect are obscure, several working hypotheses can be proposed. It is well known that restraint stress enhances dopamine (DA) release in nucleus accumbens and, to a lesser extent, striatum [12,15,23,39,40]. These phenomena would subserve the long-lasting sensitization to haloperidol, since

Table 1
Duration (s) of immobility, exploration and grooming in every group after haloperidol

Parameter	HAL dose (mg/kg)	Group			
		Sal-Stress	Sal-No Stress	8-OH-Stress	8-OH-No Stress
Immobility	0	0	0	0	0
	0.25	486.2 ± 15.5	507.4 ± 12.5	500.6 ± 15	479.2 ± 21.7
	0.5	566.7 ± 8.8	558.2 ± 10.2	548.5 ± 13.4	553.8 ± 10.4
Exploration	0	492.2 ± 18.8	518.6 ± 22.4	517.1 ± 22.5	505.5 ± 10.5
	0.25	81.2 ± 13.5	77.8 ± 10.2	79.2 ± 8.8	102.3 ± 20.1
	0.5	20.3 ± 7.7	34.1 ± 8.5	28.4 ± 13.2	37.0 ± 9.9
Grooming	0	107.8 ± 12.3	81.4 ± 17.5	82.9 ± 23.7	98.8 ± 20.1
	0.25	32.6 ± 17.4	14.8 ± 10.6	20.2 ± 2.9	18.5 ± 6.6
	0.5	13.0 ± 6.2	7.7 ± 6.7	23.1 ± 13.2	9.2 ± 2.3

Mean ± S.E.M. Groups: Sal-Stress, saline + restraint stress; Sal-No Stress, saline + no stress; 8-OH-Stress, 8-OH-DPAT + stress; 8-OH-No Stress, 8-OH-DPAT + no stress. HAL, haloperidol. Total duration of each test: 10 min.

enduring changes in the mesolimbic dopaminergic system underlie the behavioral sensitization to many drugs and stressors [15,16,34,35]. Furthermore, restraint stress also increases the release of glutamate in basal ganglia [23], and VCMs are known to be mediated by stimulation of striatal glutamate receptors [14]. Moderate doses of 8-OH-DPAT, as in this study, have been reported to reduce DA release in striatum by acting through 5-HT_{1A} autoreceptors [20]. The ventrolateral striatum is critically involved in oral motor control [5,13,17,19,39], hence reduced striatal DA release might be related to the protective role of 8-OH-DPAT on stress. On the other hand, 8-OH-DPAT, through corticofrontal and tegmental 5-HT_{1A} receptors, facilitates the firing of mesocortical DA neurons, which in turn inhibit corticostriatal glutamatergic inputs. In this context, it has been reported that restraint favors effects of 8-OH-DPAT on corticofrontal 5-HT_{1A} receptors [21]. Since VCMs are also mediated by striatal glutamate receptors [14], the protective effect of 8-OH-DPAT could be related to reduced striatal glutamatergic activity. Finally, 8-OH-DPAT also possesses affinity for α_2 and D_2 receptors [4], which could also contribute to the effects of this compound. Evidently, all these hypotheses need further investigation.

In summary, this study supports the assumptions that single restraint stress is able to induce a long-lasting alteration in the rat's behavior after haloperidol, e.g. sensitizing acute VCMs, and that there is a functional separation of dopaminergic pathways mediating hypokinetic and hyperkinetic signs. Moreover, stress-induced sensitization of VCMs is prevented by 8-OH-DPAT prior to stress. Findings might have clinical importance, because acute VCMs are related to acute motor side-effects of neuroleptics.

Acknowledgements

This study was supported by a grant to E.F.E. from Consejería de Educación y Ciencia, Andulusian Government, Spain (Research Group No. CVI 0127, P.A.I.).

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