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Dopamine-NO Interactions in the Nucleus Accumbens during Stress-Induced Inhibition of Exploratory Behavior

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Experiments on Sprague–Dawley rats using vital intracerebral microdialysis showed that stress accompanied by the acquisition of a conditioned reflex fear reaction leads, at one day, to inhibition of exploratory activity and reductions in exploratory activity-induced increases in extracellular citrulline level (citrulline is a coproduct of NO synthesis) in the nucleus accumbens). Administration of the D_2 dopamine receptor antagonist raclopride (10 μM) after acquisition of the conditioned reflex fear reaction led, one day after administration, to recovery of the parameters of exploratory behavior and reversal o the increase in the extracellular citrulline level in the nucleus accumbens accompanying this behavior. These data provide the first evidence that inhibition of exploratory behavior by previously experienced stress may be mediated by a stress-induced decrease the activity of the nitrergic system of the nucleus accumbens formed with the involvement of dopamine D_2 receptors in this structure.

Keywords: citrulline, exploratory behavior, nucleus accumbens, vital intracerebral microdialysis, dopamine-NOergic interactions.

Previously experienced pain and emotional stress and the resultant fear can subsequently have significant influences on behavior. Exploratory activity in a novel context constitutes one form of behavior adversely affected by the consequences of stress and which is used for evaluating the severity of these consequences in experimental animals [6, 22, 23]. Published data indicate that the regulation of exploratory activity involves the following system: hippocampal formation → nucleus accumbens, in which the hippocampal formation is "responsible" for detecting spatial novelty [16], and the nucleus accumbens, activated by hippocampal glutamatergic signals, initiates and maintains exploratory activity by means of connections between this nucleus and the lateral preoptic area, the lateral hypothalamus, and the mediodorsal nucleus of the thalamus [13]. Some hippocampal glutamatergic afferents terminate on NO-producing interneurons in the nucleus accumbens, in which the neuronal isoform of NO synthase is detected [10], this enzyme catalyzing the formation of NO from arginine, along with the synthesis coproduct citrulline [11]. These NO-producing interneurons in turn control the excitability of projection neurons and interneurons in this nucleus [9] and can thus influence the functions of this structure. Our recent studies provided the first demonstration that exploratory activity is accompanied by increases in extracellular citrulline (a coproduct of NO synthesis) levels in the nucleus accumbens, this being prevented by administration into this structure of a neuronal NO synthase inhibitor [4] and thus reflects local activation of this enzyme and, probably, increases in NO production. All this is evidence that the nitrergic system of the nucleus accumbens is involved in controlling exploratory behavior. However, it remains unknown whether the inhibition of exploratory activity by previously experienced stress described in the literature [6, 22, 23] occurs because of or with the involvement of the nitrergic system of the nucleus accumbens. We have previously demonstrated that the dopaminergic input of the nucleus accumbens controls the activity of the nitrergic system of this structure via dopamine D_1 and D_2 receptors [3, 5, 19]. However, there are no data indicating

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whether dopamine-NOergic interactions in the nucleus accumbens are involved in forming the consequences of stress reflected as inhibition of exploratory behavior in new contexts.

The first aim in the present investigation was to study the effects of stress experienced one day before testing, this stress being accompanied by the acquisition of a conditioned reflex fear reaction (CFR) (combination of a tone with an unavoidable electric shock), on changes in extracellular citrulline (a coproduct of NO synthesis) levels in the medial segment of the nucleus accumbens during exploratory behavior in a novel chamber and on measures of exploratory behavior. A further aim of the study was to investigate the effects of administration of the dopamine D_2 receptor antagonist raclopride into the medial segment of the nucleus accumbens after acquisition of the conditioned reflex fear reaction on changes in the extracellular citrulline level in the medial segment of the nucleus accumbens during exploratory activity and on exploratory behavior itself, tested one day after raclopride administration.

Methods

Experiments were performed using 28 male Sprague–Dawley rats weighing 270–350 kg. Under anesthesia (Rometar 1.4 μg/100 g body weight and Zoletil 5 mg/100 g body weight, i.m.), rats underwent implantation of dialysis cannulae into the medial segment of the nucleus accumbens, as described previously [18]. Experiments were performed on the second and third days after cannula implantation. At the beginning of the experimental day, each rat was placed in the daytime home cage and dialysis perfusion of the nucleus accumbens with artificial cerebrospinal fluid was started [18] at a rate of 2 μl/min. Animals were divided into four groups, two experimental groups and two control groups, each of seven animals. On experimental day 1, rats of the experimental CFR → New chamber experimental group and the CFR → Raclopride → New chamber experimental group acquired the conditioned reflex fear reaction as described previously [19]. Animals were placed in the conditioned reflex chamber with a grid floor, twice, with a 1-h interval, and were presented with the conditioned stimulus (a tone of 1000 Hz for 10 sec) combined with electrocutaneous stimulation of the paws (0.5 mA, 1 sec). Animals of two control groups Control → New chamber and Control → Raclopride → New chamber groups followed the same procedure but without electrocutaneous stimulation. Dialysis perfusion of the nucleus accumbens with artificial cerebrospinal fluid was started at 25 min in animals of all groups; at 30 min, the perfusion solution for the CFR → Raclopride → New chamber and Control → Raclopride → New chamber groups was supplemented with the dopamine D_2 receptor antagonist raclopride (10 μM); the composition of the perfusion solution for rats of the CFR → New chamber and Control → New chamber groups remained unaltered. Dialysis perfusion of the nucleus accumbens was continued for a further 2 h in all groups. During this time, animals of the CFR → New chamber and CFR → Raclopride → New chamber groups previously subjected to unavoidable pain stimulation underwent a procedure reminding them of stress on two occasions with a 1-h interval: rats were returned to the conditioned reflex chamber for 5 min and were presented with a tone (1000 Hz, 10 sec) once a minute, without pain stimulation. Animals of the Control → New chamber and Control → Raclopride → New chamber groups continued the same procedure. Dialysis perfusion was then terminated and each rat was rapidly placed in an open field apparatus (80 × 80 cm, height 40 cm) for 10 min, in which horizontal exploratory activity (crossing of sector boundaries in the apparatus) and the number of rearings were assessed. After completion of this test, animals of the CFR → Raclopride → New chamber and Control → Raclopride → New chamber groups continued additional dialysis perfusion of the nucleus accumbens with artificial cerebrospinal fluid for 30 min to eliminate raclopride residues from the cannula and surrounding brain tissues. On the following day, each rat was placed in its daytime home cage and dialysis perfusion of the nucleus accumbens with artificial cerebrospinal fluid was performed (2 h). After 30 min, six baseline portions of dialysate (5 min each) were collected. Each rat was then placed in a new round chamber (diameter 40 cm, height 40 cm) for 10 min, this inducing exploratory activity. Horizontal movement activity (crossing of sector boundaries), the number of rearings, and the total duration of exploratory movements were recorded. The animal was then returned to its daytime home cage and the experiment was completed 20 min later. Nucleus accumbens dialysate (5-min portions) was collected before, during, and after behavioral testing.

Citrulline levels were measured by high-performance liquid chromatography with electrochemical detection [1]. The chromatography system described previously [18] was used. Citrulline contents in nucleus accumbens dialysate were expressed as percentages of individual baseline values (the six baseline points) before placing the rat in the novel chamber. When experiments were complete, cannula positions were checked morphologically. Analyses included rats in which the cannula was located in the medial segment of the nucleus accumbens (medial nucleus accumbens shell and part of the adjacent most medial part of the nucleus accumbens core).

Statistical analysis was performed using the standard statistics suite Sigma Stat (3.0). Changes in the citrulline level relative to baseline values were compared by unifactorial analysis of variance for repeat measures (the F test), followed by comparison of changes at individual time points relative to baseline using Student's *t* test. Intergroup comparison were performed by two-factor analysis of variance (the F test) followed by comparison of groups at individual time points using Student's *t* test. Measures of exploratory behavior were compared using Student's *t* test.

TABLE 1. Measures of Exploratory Behavior in the Novel Chamber in Animals Subjected (CFR → Novel chamber) and Not Subjected (Control → Novel chamber) to Stress Associated with Acquisition of a Conditioned Reflex Fear Reaction (CFR) 24 h before the Test and after Administration of Raclopride into the Nucleus Accumbens in Rats Subjected (CFR → Raclopride → Novel chamber) and Not Subjected (Control → Raclopride → Novel chamber) to This Stress

Groups	CFR → Novel chamber	Control → Novel chamber	CFR → Raclopride → Novel chamber	Control → Raclopride → Novel chamber
Movement time, sec	127 ± 20	141 ± 41*	258 ± 39**	289 ± 47**
Horizontal activity, crossings	12.2 ± 1.4	21.0 ± 3.3*	22.2 ± 4.1*	19.3 ± 2.0*
Rearings	8.7 ± 2.5	10.9 ± 3.5	12.6 ± 4.0	13.4 ± 3.5
Number of animals	7	7	7	7

Note. Comparison with the CFR → Novel chamber group: *$p < 0.05$, **$p < 0.01$.

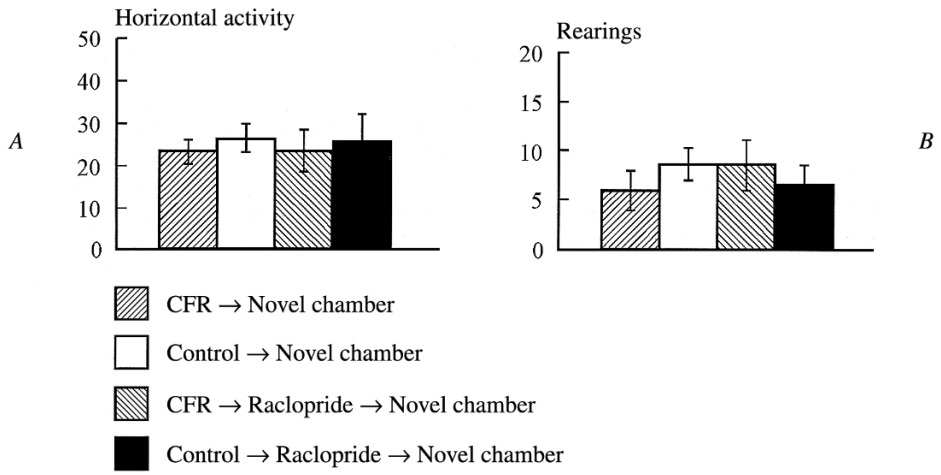

Fig. 1. *A*) Horizontal motor activity (crossings); *B*) number of rearings in the open field test in animals subjected (CFR → Novel chamber) and not subjected (Control → Novel chamber) to stress associated with acquisition of a conditioned reflex fear reaction (CFR) 3 h before the test, and in rats given raclopride into the nucleus accumbens after acquisition of the CFR (CFR → Raclopride → Novel chamber) or after the control procedure for acquisition of the CFR (Control → Raclopride → Novel chamber).

Results

The baseline citrulline level in nucleus accumbens dialysate in these experiments was 42 ± 4 nM (n = 28), which was close to our previous results [1, 3, 5, 18, 19].

Stress imposed on animals of the CFR → New chamber experimental group during acquisition of the conditioned reflex fear reaction had no effect on exploratory activity in the open field on testing 3 h after stress. This was evidenced by the absence of any significant differences in horizontal movement activity (Fig. 1, *A:* $t = 0.67$, $p = 0.52$) or the number of rearings (Fig. 1, *B*; $t = 1.0$, $p = 0.33$) between animals of the CFR → New chamber experimental group and the control → New chamber control group. Administration of raclopride into the nucleus accumbens also had no effect on the exploratory activity in the open field test of rats subjected and not subjected to stress 3 h before this test (Fig. 1, *A*, *B*). No significant changes were seen in horizontal activity or the number of rearings during this test between animals of the CFR → raclopride → New chamber group and the CFR → New chamber group (t = = 0.03, $p = 0.98$ and $t = 0.97$, $p = 0.35$, respectively) or between rats of the Control → Raclopride → New chamber group and the Control → New chamber group ($t = 0.12$, p = = 0.91 and $t = 0.81$, $p = 0.44$, respectively), or between the CFR → Raclopride → New chamber group and the Control → Raclopride → New chamber group ($t = 0.28$, $p = 0.78$; $t = 0.62$, $p = 0.55$).

In contrast to this, at one day after stress induced by acquisition of the conditioned reflex fear reaction, the exploratory activity in the novel chamber of animals of the CFR → Novel chamber was inhibited as compared with that in the Control → Novel chamber group with no prior experience of stress (see Table 1). Rats of the CFR → Novel chamber group demonstrated a lower level of horizontal

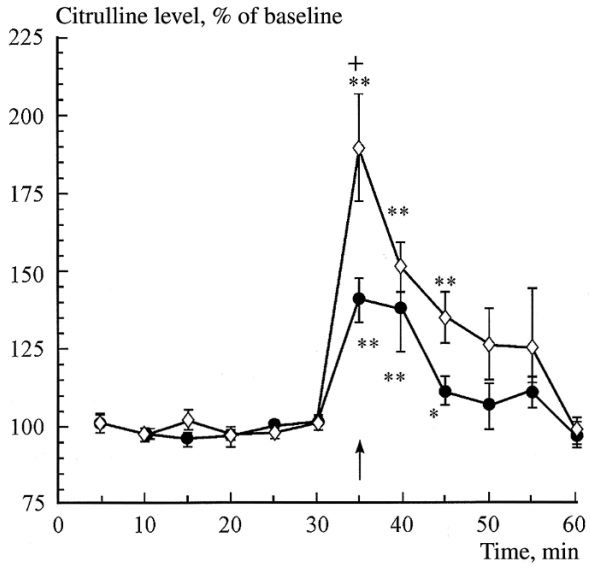

Fig. 2. Extracellular citrulline levels in the nucleus accumbens during exploratory behavior in the novel chamber in rats subjected (CFR → Novel chamber) and not subjected (Control → Novel chamber) to stress associated with acquisition of the conditioned reflex fear reaction (CFR) 24 h before testing). The *x* axis shows time, min; the *y* axis shows the citrulline level, % of baseline; spread bars on plots show errors of the mean; the arrow shows the moment at which the animal was placed in the novel chamber. Comparison with baseline: $^{*}p < 0.01$, $^{**}p < 0.001$; intergroup comparison: $^{+}p < 0.05$. ●) CFR → Novel chamber; ◇) Control → Novel chamber.

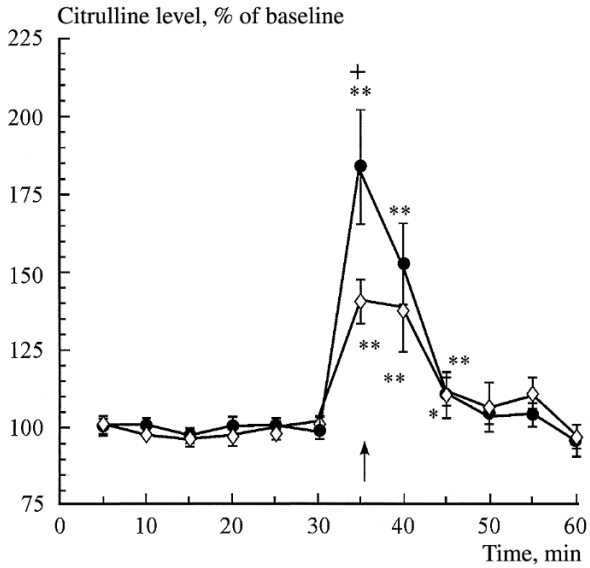

Fig. 3. Effects of administration of raclopride into the nucleus accumbens after stress evoked by acquisition of a conditioned reflex fear reaction on changes in extracellular citrulline levels in this structure during exploratory behavior in the novel chamber 24 h after stress. CFR → Raclopride → Novel chamber: animals given raclopride one day before testing. CFR → Novel chamber: rats not given raclopride. ●) CFR → Raclopride → Novel chamber; ◇) CFR → Novel chamber. For further details see caption to Fig. 2.

activity (t = 2.50, p = 0.03) and shorter-lived exploratory reactions (t = 2.48, p = 0.03) as compared with rats of the Control → Novel chamber group.

Exploratory behavior in the novel chamber in rats of the Control → Novel chamber control group was accompanied by an increase in the extracellular citrulline level in the nucleus accumbens from the individual baseline levels seen during and after testing, with a maximum (189 ± 17%) in the first 5 min in the novel chamber (Fig. 2, $F_{(11,77)}$ = 9.9, $p < 0.001$). Exploratory behavior in animals of the CFR → Novel chamber group subjected one day before testing to stress linked with acquisition of the conditioned reflex fear reaction was also accompanied by an increase in the extracellular citrulline level in the nucleus accumbens (Fig. 2; $F_{(11,66)}$ = 7.6, $p < 0.001$) with a maximum (141 ± 7%) seen in the first 5 min of testing. Two-factor analysis of variance showed that the magnitude of this increase was significantly smaller than that in rats of the Control → Novel chamber group not subjected to stress (Fig. 2, $F_{(11,144)} = 1.9$, $p = 0.041$).

Animals of the CFR → Raclopride → Novel chamber group given raclopride into the nucleus accumbens after acquisition of the conditioned reflex fear reaction, showed higher levels of horizontal activity (t = 2.3, p = 0.039) and longer-lasting exploratory reactions (t = 3.0, $p < 0.011$) in the novel chamber on the day after administration as compared with the CFR → Novel chamber group not given raclopride (see Table 1). The exploratory activity in the novel chamber of animals of the experimental CFR → Raclopride → Novel chamber group was not significantly different from that in the Control → Novel chamber group ($t = 0.23$, $p = 0.82$ for horizontal activity and $t = 0.31$, $p = 0.76$ for the number of rearings) and the Control → Raclopride → Novel chamber group (t = 0.65, p = 0.53 for horizontal activity and t = 0.51, p = 0.62 for the number of rearings) not exposed on the first day to stress associated with acquisition of the conditioned reflex fear reaction (see Table 1).

The exploratory behavior in the novel chamber of animals of the CFR → Raclopride → Novel chamber group, given raclopride one day before testing, was accompanied by an increase in the extracellular citrulline level in the nucleus accumbens from the individual baseline level (Fig. 3; $F_{(11,66)}$ = 13.7, $p < 0.001$). Two-factor analysis of variance showed that this increase was significantly greater than the increase in the citrulline level during exploratory behavior of rats of the CFR → Novel chamber group not given raclopride (Fig. 3; $F_{(11,144)} = 2.07$, $p = 0.026$) but was not significantly different from the increase in the citrulline level during this test in rats of the Control → Novel chamber group ($F_{(11,144)} = 0.79$, $p = 0.65$) not exposed to stress or given raclopride.

The exploratory behavior in the novel chamber of rats of the Control → Raclopride → Novel chamber, not subjected

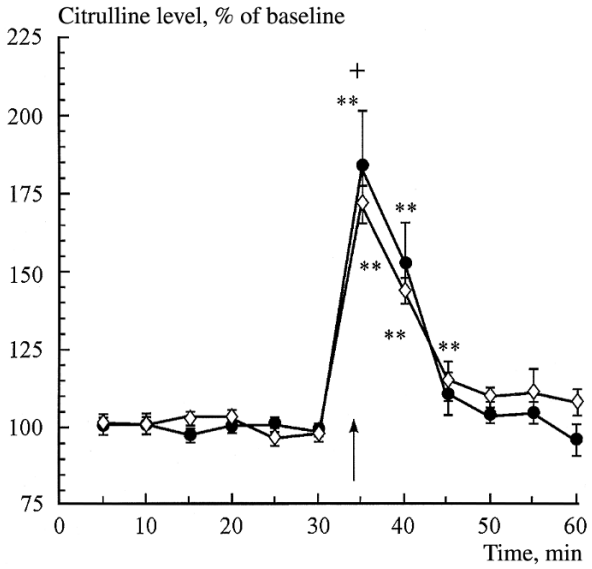

Fig. 4. Extracellular citrulline levels in the nucleus accumbens during exploratory behavior in the novel chamber in rats subjected (CFR → Raclopride → Novel chamber) and not subjected (Control → Raclopride → Novel chamber) to stress induced by acquisition of a conditioned reflex fear reaction 24 h before testing. Animals were given raclopride into the nucleus accumbens 24 after stress. ●) CFR → Raclopride → Novel chamber; ◇) Control → Raclopride → Novel chamber. For further details see caption to Fig. 2.

to stress on the first day of the experiment but given raclopride one day before testing, also led to an increase in the extracellular citrulline level in the nucleus accumbens relative to the individual baseline level (Fig. 4; $F_{(11,66)} = 32.9$, $p < 0.001$). Intergroup comparisons showed this increase was not significantly different from that occurring during exploratory activity in the CFR → Raclopride → Novel chamber group (Fig. 4; $F_{(11,144)} = 0.64$, $p = 0.79$) and the Control → Novel chamber group ($F_{(11,144)} = 1.1$, $p = 0.34$), but was greater than the increase in the extracellular citrulline level in the nucleus accumbens during exploratory behavior in rats of the CFR → Novel chamber group, previously subjected to stress associated with acquisition of the conditioned reflex fear reaction but not given raclopride ($F_{(11,144)} = 1.94$, $p = 0.039$).

Discussion

The response to novelty includes two opposing components: interest in the novel, which stimulates exploratory behavior, and suspiciousness and even fear of the novel (neophobia), which suppresses exploratory activity. Both processes are required for survival and their ratio is an important characteristic of individuals. Excessive appearance of the former is used as a diagnostic sign for the risk of forming a predilection to drugs and gambling [24]. Predominance of the phobic component of the reaction to novelty is a measure of increased anxiety [17] and even the risk of early death [8]. Experienced stress and the related fear can shift the balance between these processes towards the phobic component of the reaction to novelty, resulting in a decrease in exploratory activity [6, 22, 23]. In support of this, the present experiments showed that stress induced by acquisition of the conditioned reflex fear reaction leads, one day after acquisition, to decreases in exploratory activity in the novel chamber as compared with the level in animals of the control group not subjected to stress (see Table 1).

Published data provide evidence that the nucleus accumbens is one of the key structures involved in initiating and controlling the behavioral response to spatial novelty [13] and the dopaminergic inputs to this structure from the ventral tegmental area and the glutamatergic input from the hippocampal formation play an important role in this process [15, 16]. As both of these afferent inputs innervate NO-producing interneurons in this nucleus [10, 12] and control the activity of the nitrergic system of this structure [3, 5, 14, 19], the nitrergic system of the nucleus accumbens might be expected to be involved in this regulation. Our recent investigations provided the first support for this suggestion. This is evidenced by our previous finding [4] and the present report (Fig. 2) showing an increase in the extracellular citrulline level (this being a coproduct of NO synthesis) in the nucleus accumbens during exploratory activity in a novel spatial context, which could be blocked by local administration of an inhibitor of the neuronal isoform of NO synthase [4]. An important result of the present study is evidence that the nitrergic activation of the nucleus accumbens accompanying exploratory behavior in all probability "maintains" the exploratory but not the phobic components of the response to the novel spatial context. Evidence for this is the fact that inhibition of exploratory activity in rats subjected to stress 24 h before testing associated with acquisition of a conditioned reflex fear reaction (see Table 1) is accompanied by a decrease in the elevated extracellular citrulline level in the nucleus accumbens induced by exploratory behavior as compared with the level in animals not previously subjected to stress (Fig. 2). These data lead to a further conclusion. They provide evidence that inhibition of exploratory behavior by stress may be mediated by a decrease in nitrergic activation of the nucleus accumbens during this behavior.

This study demonstrated that the inhibitory action of stress on exploratory behavior is present 24 h after stress (see Table 1) but not 3 h after stress (Fig. 1, *A*, *B*), which is consistent with observations reported by other authors who have also used the stress of unavoidable electrocutaneous stimulation of moderate strength [22]. Our previous data indicate that the extent of nitrergic activation of the nucleus accumbens during exploratory behavior on testing 3 h after stress induced by acquisition of the conditioned reflex fear reaction was not different from that in animals of the control group not subjected to stress [2]. Thus, the stress-induced change in exploratory behavior and the extent of

nitrergic activation of the nucleus accumbens during this behavior are evidently related to each other, as they form in parallel under the influence of slow modifying processes triggered by stress.

An important result of the present study is the demonstration of the role of the dopaminergic system of the nucleus accumbens and dopamine D_2 receptors in these processes. We demonstrated that administration of the D_2 receptor antagonist raclopride into the nucleus accumbens after stress caused by acquisition of the conditioned reflex fear reaction led after one day to an increase in exploratory activity with a consequent increase in extracellular citrulline in the nucleus accumbens to the levels seen in control animals not previously subjected to stress. In other words, restoration of the level of nitrergic activation of the nucleus accumbens during exploratory activity seen in stressed rats after administration of raclopride restores stress-inhibited exploratory behavior, again providing evidence of the contribution of nitrergic activation of the nucleus accumbens to regulation of exploratory behavior.

It is important to note that the behavioral effects of raclopride demonstrated here are not associated with changes in the mobility of the animals induced by this agent, as raclopride at this dose did not influence exploratory activity in the open field during administration of the agent (Fig. 1) and had no effect on measures of exploratory behavior or the magnitude of the increase in the extracellular citrulline level during this behavior one day after administration in control animals not subjected to stress (see Table 1). Thus, an obligate condition for the activatory effect of raclopride on exploratory behavior and the extent of nitrergic activation of the nucleus accumbens during this behavior is the experience of stress one day before testing, which decreases both of these parameters.

Stress has been shown to have significant influences on the efficiency of synaptic transmission in the nucleus accumbens [7]. Furthermore, dopamine D_2 receptors in this structure have been shown to be involved in the stress-induced triggering of long-term plastic rearrangements regulating the individual's stress reactivity [20, 21]. However, the present report provides the first demonstration that at least part of the long-term effects of stress on exploratory activity may be related to dopamine-NOergic interactions in the nucleus accumbens. Further additional studies are needed to clarify the pathways and more detailed mechanisms of this interaction.

Overall, the data obtained here provide evidence that previous stress may inhibit exploratory behavior due to inhibition of the nitrergic activation of the nucleus accumbens accompanying this behavior, and these effects of stress are controlled by the dopaminergic system of the nucleus accumbens and dopamine D_2 receptors.

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