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GABA-Nitrergic Interactions in the Nucleus Accumbens during Inhibition of Exploratory Behavior by Danger Signals

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Vital intracerebral microdialysis experiments in Sprague–Dawley rats with high-performance liquid chromatography (HPLC) showed that presentation during exploratory behavior of a tone previously combined with pain stimulation decreased exploratory activity and inhibited the exploratory behavior-induced increase in the extracellular citrulline (a co-product of NO synthesis) level in the medial sector of the nucleus accumbens. Administration of the $GABA_A$ receptor antagonist bicuculline (20 μM) into the medial sector of the nucleus accumbens firstly produced partial recovery of the increase in the extracellular citrulline level in this structure induced by exploratory behavior and suppressed by a tone previously combined with pain stimulation and, secondly, prevented inhibition of exploratory behavior by this danger sound signal. The data obtained here provide the first evidence that inhibition of exploratory behavior by danger signals and the exploration-associated activation of the nitrergic system of the medial sector of the nucleus accumbens are mediated by $GABA_A$ receptor mechanisms.

Keywords: citrulline, nitric oxide, $GABA_A$ receptors, nucleus accumbens, microdialysis, fear, exploratory behavior.

The ability to rearrange behavior in response to the appearance of danger signals is a necessary condition for an individual's survival. However, the structural and neurochemical mechanisms underlying acute shifts in behavioral programs in response to the appearance of stimuli with high motivational significance have received insufficient study. The brain structures involved in these processes may include the medial sector of the nucleus accumbens (mNA), in the ventral striatal area, which plays an important role in motivation and reinforcement processes [9, 17, 20]. It has been suggested that the organization of the neural networks of all parts of the striatum, including the mNA, is based on mechanisms supporting the selection and switching of behavioral programs [10, 18, 21, 23], these being based largely on lateral inhibition via the axon collaterals of the GABAergic projection neurons of this structure (95% of the population) [23]. In the mNA, glutamatergic afferent inputs from the hippocampal formation, amygdala, and prefrontal cortex converge on these neurons in a variety of combinations, carrying information on the novelty, the motivational and emotional significance of incoming signals, and the spatial context, as well as possible variants of behavioral responses (see [14, 20]). These same neurons connect the mNA with brain areas involved in mediating the basal forms of feeding and the defensive exploratory behavior activated on receipt of reinforcement [14, 15]. It has been suggested that as a result of lateral inhibition, the strongest input signal, reflecting the dominant motivation, and its associated behavioral program are not only sent for execution, but also inhibit the conduction of weaker (i.e., less significant) signals transmitted via parallel channels [23]. This suggestion is supported by the previously demonstrated involvement of the mNA in the inhibition of feeding behavior by danger signals [4, 26, 30] and our recent studies have shown that competition between the defensive and exploratory behavioral strategies occurs with the involvement of the nitrergic system of the mNA [3]. In particular, we showed that presentation during exploratory behavior of danger signals decreasing exploration activity inhibited the exploratory behavior-induced increase in the extracellular citrulline (a coproduct of NO synthesis) level in the mNA [3].

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We report here studies seeking to test the suggestion that GABAergic transmission, which has an important role in selection mechanisms [23], may mediate these neurochemical and behavioral effects of danger signals. The aim of the present work was to study the effects of administration of the $GABA_A$ receptor antagonist bicuculline into the mNA on changes in extracellular citrulline levels in this structure in response to presentation during exploratory behavior of a tone previously associated with electrocutaneous stimulation and on the parameters of exploratory activity during this test. The literature contains no such data.

Methods

Experiments were performed using 34 male Sprague–Dawley rats weighing 270–350 g. Experiments were performed in compliance with international norms for the humane treatment of experimental animals (European Union Directives No. 86/609/EEC). Rats were anesthetized (Rometar 1.4 μg/100 g and Zoletil 5 mg/100 g i.m.) and concentric dialysis cannulae were implanted into the mNA as described previously [28]. Microdialysis experiments were performed on the second day after implantation. Each rat was tested for 10 min in an open field (80 × 80 cm, height 35 cm) immediately before microdialysis experiments to identify the baseline level of exploratory activity. Exploratory activity (crossing of sector boundaries in the apparatus) was recorded. The rat was then placed in its daytime cage and dialysis perfusion of the mNA with artificial cerebrospinal fluid (aCSF) [28] was started. After 15 min, animals were trained to a conditioned reflex fear reaction: the animal was placed in a conditioned reflex chamber with a mesh-covered floor for 5 min, where it was presented five times with the conditioned stimulus (a tone of 1000 Hz for 10 sec) with 50-sec intervals combined with electrocutaneous stimulation of the paw (0.5 mA, 1 sec) during the last second of sounding. The rat was then returned to its daytime cage. The training session was repeated 1 h later, after which the animal was again returned to its daytime home cage. After 25 min in the daytime home cage, collection of baseline portions of dialysate was started (six 5-min portions). The animals were then divided into four groups and test sessions were performed. Each rat in the "Novel chamber" group (n = 8; here and henceforth n is the number of animals) were placed in a novel round chamber (diameter 40 cm, height 40 cm) for 10 min during the test session, which induced exploratory behavior. Animals of the "Novel chamber + tone" group (n = 8) were also placed in the novel chamber for 10 min during the test session and, 5 sec after the rat initiated exploratory behavior, it was presented with the tone (1000 Hz, 10 sec, 10 times with 50-sec intervals) which had previously been combined with electrocutaneous stimulation. In rats of the "Bicuculline + novel chamber" group (n = 6) and the "Bicuculline + novel chamber + tone) group (n = 12), collection of baseline dialysate portions was followed by supplementation of the aCSF with the $GABA_A$ receptor antagonist bicuculline (Fluka, Switzerland, 20 μM)

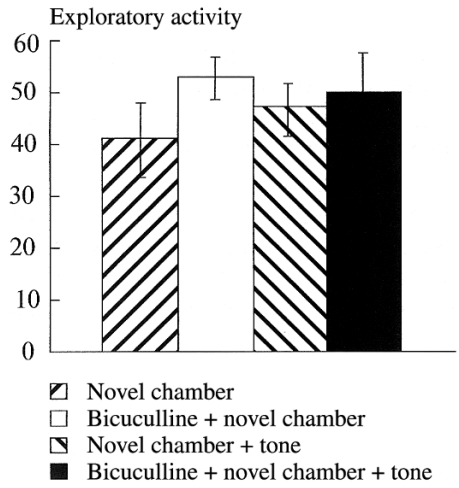

Fig. 1. Exploratory activity in the open field (number of sectors crossed) of rats of different experimental groups before microdialysis experiments.

and eight portions of dialysate (each of 5 min) were collected. The test session was then performed: animals of these groups were placed in the unfamiliar chamber for 10 min. Rats of the "Bicuculline + novel chamber + tone" group, 5 sec after they initiated exploratory behavior, were presented with the tone previously combined with electrocutaneous stimulation (1000 Hz, 10 sec, 10 times with 50-sec intervals), while animals of the "Bicuculline + novel chamber" group were not presented with the tone while in the novel chamber. After being in the unfamiliar chamber for 10 min, the animals were returned to their daytime home cages for 20 min, after which the experiment was terminated. While in the unfamiliar chamber, exploratory activity (in terms of crossing of sector boundaries in the chamber) was measured. If the tone was presented during this test, the durations of periods of freezing (no movements other than respiratory) during sounding were measured, this being a parameter characterizing the level of expectation of the pain stimulus [19]. Video recordings were made during behavioral tests using a personal computer and a Logitech (China) webcam. Dialysate (5-min portions) were collected throughout the experiment. Citrulline levels were estimated by high-performance liquid chromatography (HPLC) with electrochemical detection [1]. The chromatography system described previously [28] was used. Dialysate citrulline contents were expressed as percentages of the mean pre-test baseline level (six baseline points). Once experiments were complete, delivery points were verified morphologically. Processing included rats with cannulas located in the mNA.

Statistical analysis was performed using SigmaStat 3.0. Changes in citrulline levels relative to baseline were compared by one-way analysis of variance for repeat measures (F test) followed by comparison of changes at individual time points relative to baseline using Student's t test.

Intergroup comparisons were performed by two-way analysis of variance (*F* test) followed by comparison of groups at specific time points using Student's *t* test. Behavioral parameters were compared using the Mann–Whitney test.

Results

The baseline extracellular citrulline level in the mNA in these experiments was 35 ± 4 nM (n = 34), which was close to our previous results [1, 2, 6, 7, 28, 29].

There were no differences in levels of exploratory activity between the groups of animals before microdialysis experiments started (Fig. 1). Administration of the GABA receptor antagonist bicuculline (20 μM) in the "Bicuculline + novel chamber" (n = 6) group and the "Bicuculline + novel chamber + tone" group (n = 12) had no significant effect on the baseline extracellular citrulline level in this structure. A small and transient increase in this parameter was seen in the first 5 min after the beginning of administration (Fig. 2), after the citrulline level returned to the pre-bicuculline baseline level ($F_{11,55}$ = 0.40, p = 0.95 for the "Bicuculline + novel chamber" and $F_{11,121}$ = 0.52, p = 0.89 for the "Bicuculline + novel chamber + tone" group).

Exploratory behavior in the unfamiliar chamber in rats of the "Novel chamber" group (n = 8) led to an increase in the extracellular citrulline level in the mNA relative to baseline during and after the test (Fig. 3, *A;* $F_{11,77}$ = 23.9, p < < 0.001) with a peak in the first 5 min in the unfamiliar chamber. Presentation of the tone previously associated with electrocutaneous stimulation during exploratory behavior in the unfamiliar chamber to animals of the "Novel chamber + tone" group (n = 8) inhibited the exploratory behavior-induced increase in the extracellular citrulline level in this structure. No significant changes in the extracellular citrulline level in the mNA from the pre-test baseline level were seen during this test (Fig. 3, *A*; $F_{11,77}$ = 0.59, p = 0.83). Intergroup comparison showed that the extracellular citrulline level during the period in the unfamiliar chamber in animals of the "Novel chamber + tone" group presented during this test with the tone previously associated with pain stimulation was significantly lower than that in the "Novel chamber" group to which the tone was not presented ($F_{11,16}$ = 10.4, p < 0.001).

Administration of 20 μM bicuculline into the mNA of animals of the "Bicuculline + novel chamber + tone" group (n = 12), which did not affect the baseline extracellular citrulline level in this structure (Fig. 2), partially restored the increase in this parameter after suppression by presentation of a tone previously combined with electrocutaneous stimulation during exploratory behavior, and could even increase its late components seen after the test (Fig. 3, *A*). Presentation of rats of the "Bicuculline + novel chamber + tone) group with the tone during exploratory behavior increased the extracellular citrulline level in the nucleus accumbens relative to pre-test baseline (Fig. 3, *A*; $F_{11,121}$ = = 5.97, p < 0.001). This increase was seen 5 min after exploratory behavior began (the second 5 min of the test,

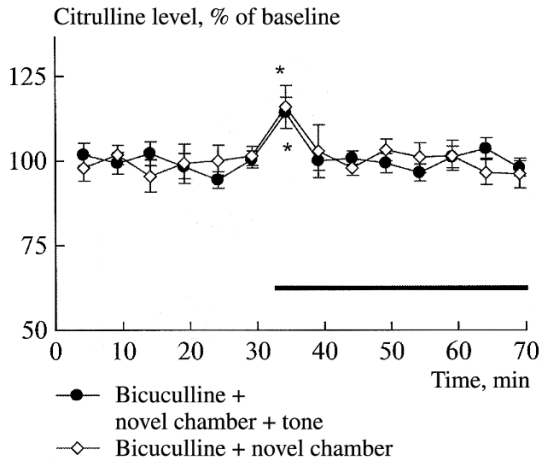

Fig. 2. Effects of administration of 20 μM bicuculline into the mNA on the baseline extracellular citrulline level in the mNA of rats of two experimental groups ("Bicuculline + novel chamber + tone" and "Bicuculline + novel chamber"). The abscissa shows time, min; the ordinate shows the citrulline level, % of baseline; spreads on plots show the error of the mean; the horizontal line shows the bicuculline administration period; *p < 0.001 compared with baseline (*t* test).

146 ± 16%, t = 6.8, p < 0.001), but also after it. Evaluation using two-way analysis of variance showed that the increase in the citrulline level during this test in animals of the "Bicuculline + novel chamber + tone" group was significantly greater ($F_{11,216}$ = 3.39, p < 0.001) than the citrulline level in rats not given bicuculline (the "Novel chamber + tone" group). Furthermore, the increase in the citrulline level in animals of the "Bicuculline + novel chamber + tone" group on presentation of the tone previously combined with pain stimulation during exploratory behavior was smaller in the first 5 min of the test (t = 5.3, p < 0.001) and larger during the 5 min after the test (t = 2.1, p = 0.049) than the increase in the citrulline level during exploratory behavior in the unfamiliar chamber in animals of the "Novel chamber" group (Fig. 3, *A*; $F_{11,216}$ = 3.99, p < 0.001).

Presentation of rats of the "novel chamber + tone" group, during exploratory behavior in the unfamiliar chamber, with the tone previously combined with pain stimulation inhibited exploratory activity as compared with the exploratory activity of animals in the "Novel chamber" group (Fig. 3, *B*; p = 0.003) and induced freezing during the sounding of the tone (Fig. 4). Administration of 20 μM bicuculline into the mNA of animals of the "Bicuculline + novel chamber + tone" group prevented inhibition of exploratory behavior in the unfamiliar chamber by the tone previously combined with pain stimulation (Fig. 3, *B*) and significantly decreased the duration of freezing induced by this danger sound signal (Fig. 4). The exploratory activity of rats in the "Bicuculline + novel chamber + tone" group was significantly greater than that in animals of the "novel chamber + tone" group (Fig. 3, *B*; p = 0.002) but was not

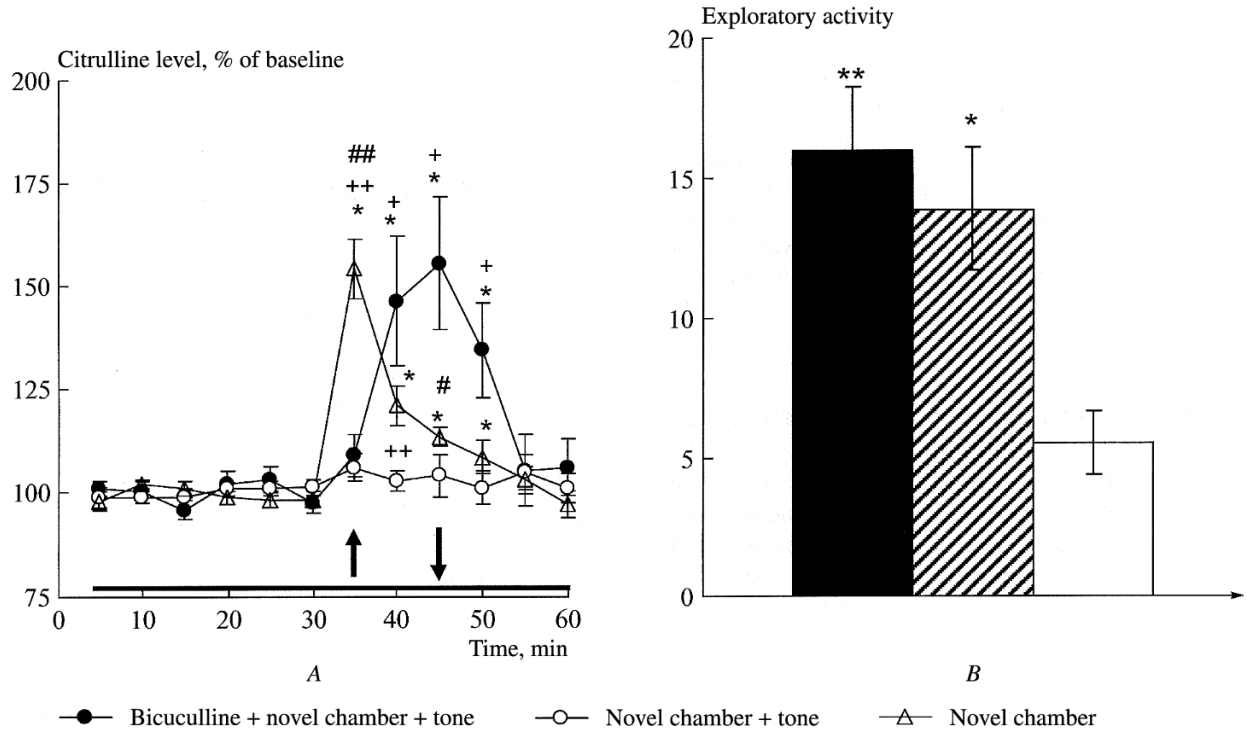

Fig. 3. Effects of administration of bicuculline (20 μM) into the mNA on changes in the extracellular citrulline level in this structure and on exploratory activity on presentation during exploratory behavior of a tone associated with pain stimulation. *A*) Citrulline level (% of baseline) on presentation during exploratory activity of the tone to animals given bicuculline into the mNA (the "Bicuculline + novel chamber + tone" tone) and rats not given bicuculline (the "Novel chamber + tone" group), as well as during exploratory behavior in rats not presented with the tone (the "Novel chamber" group). Arrows show the beginning and end of the test; $^{+}p < 0.05$, $^{++}p < 0.001$ compared with the "Novel chamber + tone" group (*t* test); $^{\#}p < 0.05$, $^{\#\#}p < 0.001$ compared with the "Bicuculline + novel chamber + tone" group (*t* test). For further details see caption to Fig. 2. *B*) Exploratory activity (number of crossings) in animals of the "Bicuculline + novel chamber + tone" (dark column), "Novel chamber" (shaded column), and "Novel chamber + tone" (white column) groups. $^{*}p < 0.05$, $^{**}p < 0.01$ on comparison with the "Novel chamber + tone" group (Mann–Whitney test).

different from the value in rats of the "Novel chamber" group (Fig. 3, *B*; $p = 0.59$). In addition, the level of freezing during sounding of the tone previously combined with pain stimulation in animals of the "Bicuculline + novel chamber + tone" group was significantly lower than that in rats of the "Novel chamber + tone" group (Fig. 4; $p = 0.002$).

The exploratory behavior in the unfamiliar chamber of rats given bicuculline into the mNA (the "Bicuculline + novel chamber" group, $n = 6$) was accompanied by an increase in the extracellular citrulline level in this structure, which was seen during and after the test (Fig. 5, *A*; $F_{11,55} = 4.13$; $p < 0.001$). Intergroup comparison showed that the magnitude of this increase in rats of the "Bicuculline + novel chamber" group during exploratory behavior in the unfamiliar chamber was not significantly different from the increase in this value in rats of the "novel chamber" group (Fig. 5, *A*; $t = 0.4$, $p = 0.7$ in the first 5 min in the unfamiliar chamber, and $t = 2.0$, $p = 0.06$ for the second 5 min in the unfamiliar chamber). However, once the test was completed, on return to the daytime home cage, animals of the "Bicuculline + novel chamber" group were characterized by higher and longer-lasting increases in citrulline levels in the mNA than rats of the "Novel chamber" group ($F_{11,137} = 2.3$, $p = 0.011$).

Rats given bicuculline into the mNA (the "Bicuculline + novel chamber" group) demonstrated the same level of exploratory activity in the unfamiliar chamber as animals of the "Novel chamber" group not given bicuculline (Fig. 5, *B*; $p = 0.95$).

Discussion

Nitric oxide (NO), produced in the nucleus accumbens by a group of GABAergic NO synthase-containing interneurons (1% of the neuron population) [12, 20], modulates the excitability of projection neurons in this nucleus [11] and is involved in regulating several of the functions of this structure: sensitization to psychostimulators [8, 13], acquisition and execution of conditioned-reflex place preference [27], the execution of conditioned-reflex fear [29] and exploratory behavior [3, 5], and the occurrence of phobic responses to novel foods [2]. In particular, our data indicate that the execution of types of behavior such as exploratory activity [3] and conditioned-reflex fear reactions [6, 7]

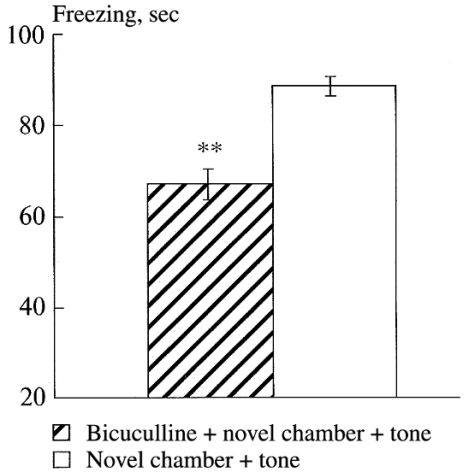

Fig. 4. Duration of freezing (sec) on presentation during exploratory behavior of a tone associated with pain stimulation in rats given ("Bicuculline + novel chamber + tone") and not given ("Novel chamber + tone") 20 μM bicuculline into the mNA. $^{**}p < 0.01$ compared with the "Novel chamber + tone" group (Mann–Whitney test).

(apparent as freezing of the animal on presentation of signals associated with pain stimulation [19]) are accompanied by activation of the nitrergic system of the mNA. This is evidenced by an increase in the extracellular citrulline (a coproduct of NO synthesis) level in the mNA, which is prevented by local administration of an inhibitor of the neuronal isoform of NO synthase, this reflecting activation of this enzyme and, very importantly, an increase in NO production in the mNA.

Working on the basis of data showing the existence of functionally diverse zones (or neuron ensembles) in the mNA [25], which have been suggested [14, 23] to compete for outputs to the executive centers of the brain, we have previously proposed that different groups of NO-producing interneurons responsible for different forms of behavior may also take part in this competitive struggle [3]. In support of this, we have recently shown that the inhibition of exploratory behavior by danger signals involves the nitrergic system of the mNA. Our data indicate that presentation, during exploratory activity of sound signals previously combined with pain stimulation firstly inhibits the exploratory behavior-induced increase in the extracellular citrulline level in the mNA and, secondly, decreases exploratory behavior itself [3, Fig. 3]. The main result of the present study is that it provides the first demonstration of the involvement of GABAergic transmission in the mNA in these processes. We have also established that administration of the $GABA_A$ receptor antagonist bicuculline (20 μM) into the mNA firstly prevented the inhibition of exploratory behavior by a tone previously combined with pain stimulation (Fig. 3, *A*) and, secondly, partially restored (during the test) and even increased (after the test) the exploratory behavior-induced increase in the extracellular citrulline level in the mNA which had been inhibited by the danger sound signal (Fig. 3, *B*).

It is important to note that the effects of bicuculline were not induced by additional motor activation of the animals by the agent or the resulting additional nitrergic activation of the mNA, as administration of bicuculline at this dose was not reflected in measures of exploratory activity on presentation of the novel chamber but without the tone (Fig. 5, *B*) or in the magnitude of the increase in the extracellular citrulline level in this structure during exploratory activity (Fig. 5, *A*). However, administration of bicuculline into the mNA still increased and prolonged the late components of the exploratory behavior-induced increase in the extracellular citrulline level seen after the test on return to the home cage (Fig. 5, *A*). This fact suggests that in normal conditions, GABAergic influences make nitrergic activation of the mNA more closely coincident with the period of behavioral testing, inhibiting the functionally unclear late components of activation.

A possible cause of the disinhibitory effects of bicuculline on presentation of danger signals during exploratory behavior may be the bicuculline-related decrease in the defensive motivation and the appearance of fear, with the consequence that it has a reduced influence on nitrergic activation of the mNA supporting exploratory behavior. This is supported by the evidence reported here that the decrease in freezing during sounding of the danger signal (a measure of fear characterizing expectation of pain stimulation [19]) in animals given bicuculline into the mNA (Fig. 4). This suggested is supported by published data indicating that administration of the $GABA_A$ receptor agonist muscimol into the mNA may initiate protective defensive reactions [24]. If our suggestion is correct, at least some GABAergic signals in the mNA may reflect the extents of aversive danger signals. An important conclusion of our study is that such GABAergic influences, which we believe transmit affective information, may adjust the activity of the nitrergic system of the mNA during exploratory behavior and the exploratory behavior itself.

A potential source of GABAergic signals controlling the activity of the nitrergic system of the mNA may consist of projection GABAergic neurons in the mNA, whose axon collaterals form synapses on NO-producing interneurons in this nucleus [20], as well as the NO-producing GABAergic interneurons themselves, which create large numbers of synapses on each other [12]. It may be that in conditions of competition between exploratory and defensive forms of behavior, functionally diverse groups of NO-producing interneurons in the mNA (directly or via the projection GABAergic neurons they control) tend to suppress each other's activity by means of such intrastructural inhibitory GABAergic connections. Another source of GABAergic influences transmitting affective signals may consist of parvalbumin-containing GABAergic interneurons in the mNA

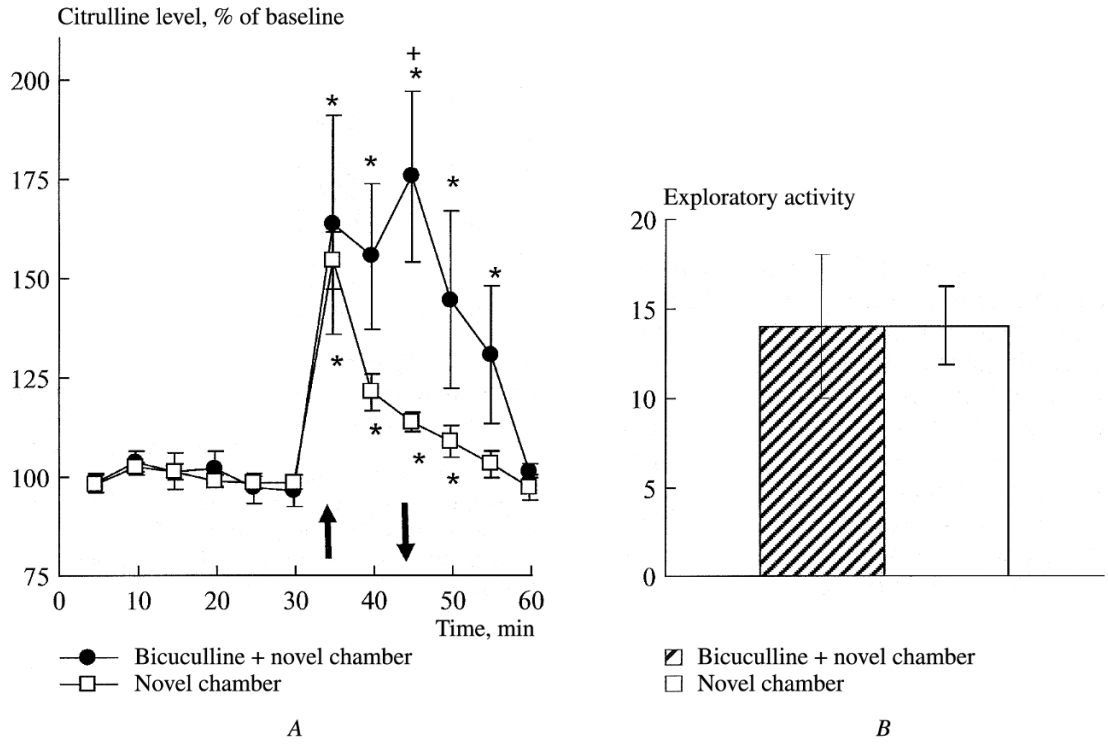

Fig. 5. Effects of administration of 20 μM bicuculline into the mNA on chagnes in the extracellular citrulline level in this structure during exploratory behavior and on measures of exploratory activity. *A*) Citrulline level (% of baseline) during exploratory behavior in rats given ("Bicuculline + novel chamber") and not given ("Novel chamber") bicuculline. $^{+}p < 0.05$ for intergroup comparison (*t* test). For further details see captions to Fig. 2 and Fig. 3. *A*. *B*) Exploratory activity (number of crossings) in animals given "Bicuculline + novel chamber" and not given "Novel chamber" bicuculline.

receiving glutamatergic inputs from the basolateral nucleus of the amygdala [20] and higher centers of the fear system (see [22]). It is known that in the striatum (which includes the mNA), such interneurons, which constitute the most powerful source of neuron inhibition in this part of the brain [16], form synapses on NO-producing interneurons [20]. Clarification of this question requires further studies.

Conclusions

1. Administration of the $GABA_A$ receptor antagonist bicuculline (20 μM) into the medial sector of the nucleus accumbens, while not altering the animals' exploratory activity, prevented inhibition by a tone previously combined with pain stimulation of exploratory behavior in a novel environment and partially restored the increase in the extracellular citrulline (a coproduct of NO synthesis) levels in this part of the brain after its suppression by the danger sound signal.

2. These data provide the first evidence that the GABAergic system of the medial sector of the nucleus accumbens may be a mediator in the transmission of the inhibitory influences of danger signals on exploratory activity. In addition, our results show that the involvement of GABAergic mechanisms in this process is mediated by inhibition of the nitrergic system of the medial sector of the nucleus accumbens, involving $GABA_A$ receptors.

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