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Interactions Between Dopamine and GABA in the Control of Ambulatory Activity and Neophobia in the Mouse

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ÅGMO, A. AND C. BELZUNG. *Interactions between dopamine and GABA in the control of ambulatory activity and neophobia in the mouse.* PHARMACOL BIOCHEM BEHAV **59**(1) 239–247, 1998.—Ambulatory activity in a familiar and novel environment as well as the time spent in a novel environment were evaluated using the free exploratory paradigm. Male mice treated with D-amphetamine, 2 mg/kg, displayed enhanced ambulatory activity in the familiar environment. The time spent in the novel environment was reduced by amphetamine, 1 and 2 mg/kg. The GABA transaminase inhibitor γ-acetylen GABA (GAG) reduced ambulatory activity and rearing as well as the time spent in the novel environment. The mixed $GABA_A$/$GABA_B$ agonist progabide, 200 mg/kg, reduced rearing both in the familiar and novel environments without affecting the time spent in the novel environment. Amphetamine, 1 mg/kg, was then combined with ineffective doses of GAG and progabide (50 and 100 mg/kg, respectively). The GABAergics did not reliably modify the effects of amphetamine on the time spent in the novel environment. Ambulatory activity and rearing were reduced both in comparison to amphetamine + saline and to control. These data show that GABAergic drugs are potentiated by enhanced dopaminergic neurotransmission with regard to their actions on ambulatory activity and rearing. The effects of progabide + amphetamine were then evaluated after treatment with the $GABA_A$ antagonist bicuculline or the $GABA_B$ antagonist CGP 35348. Neither bicuculline, 1 mg/kg, nor CGP 35348, 100 mg/kg, blocked the actions of progabide. The combined treatment with both antagonists was also unable to reduce the effects of progabide. These data suggest that the interaction between amphetamine and progabide with regard to motor effects depends on a non-$GABA_A$, non-$GABA_B$ receptor. © 1998 Elsevier Science Inc.

Dopamine GABA Ambulatory activity Neophobia Mouse

SEVERAL studies have shown that many behavioral consequences of stimulation of dopaminergic neurotransmission may be blocked by systemic administration of GABA agonists. For example, enhanced locomotor activity and stereotyped behavior produced by apomorphine are blocked by GABA agonists at doses where these latter are ineffective by themselves (14,29,48). Intravenous self-administration of cocaine is also reduced by the $GABA_B$ agonist baclofen (45). Furthermore, the disruptive effect of dopamine agonists on discrimination learning is inhibited by subeffective doses of GABAergic drugs (6). Microinjection of baclofen into the ventral tegmental area increases the current threshold for intracranial self-stimulation (59), a response widely believed to be dopamine dependent (60). On the other hand, muscimol reduces (64) or has no effect on current thresholds (59). Other studies have shown that systemic or intrastriatal administration of GABA agonists enhance stereotyped behaviors produced by large doses of amphetamine or apomorphine (13,54). It has also been reported that the $GABA_A$ antagonist bicuculline blocks amphetamine-induced stereotypies (25). On the other hand, GABA agonists are unable to reduce locomotor activation produced by large doses of amphetamine (3,6). Furthermore, neither conditioned place preference nor reduced water intake observed after treatment with amphetamine are blocked by the mixed $GABA_A$/$GABA_B$ agonist progabide or the GABA-transaminase inhibitor sodium valproate, respectively (15,55). It seems, therefore, that several behavioral effects of dopaminergic stimulation are not affected by GABAergic agents.

There is much neurochemical evidence showing that GABAergic systems can modify the activity of dopamine neurons.

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The $GABA_A$ agonist muscimol, baclofen, the GABA transaminase inhibitor γ-acetylen GABA or progabide reduce dopamine turnover both in the nigrostriatal and mesolimbic systems (29,53,58) after systemic administration. Baclofen reduces dopamine release in the frontal cortex (51,52) as well as in the striatum, while muscimol has only minor effects (24) when the drugs are infused locally. Moreover, infusion of baclofen into the ventral tegmental area reduces dopamine release in the nucleus accumbens, whereas muscimol stimulates it (26,63). These observations suggest that stimulation of the $GABA_B$ receptor reliably reduces dopamine release, whereas the $GABA_A$ receptor may have either the opposite or no effect.

One consequence of facilitated dopaminergic neurotransmission is anxiogenesis. Amphetamine has repeatedly been shown to have anxiogenic-like actions in several behavioral paradigms (17,20,56). It is not known whether GABAergic agents are able to reduce this effect. One purpose of the present studies was to determine if this is the case. In addition, the role of GABA receptor subtypes was evaluated. Possible effects of the combination amphetamine + GABAergic drugs on ambulatory activity and rearing were also analyzed. The free exploratory paradigm in mice (22) was used as behavioral test. In this procedure, ambulatory activity in a familiar and in an unknown environment as well as the preference for novelty can be quantified simultaneously. Reduced preference for novelty is taken as an indicator of neophobia or enhanced anxiety while increased novelty preference, as observed after treatment with several kinds of anxiolytic drugs, is considered an indicator of reduced neophobia or anxiety (22). Unlike most other animal models of anxiety, this procedure does not seem to be stressful to the animals because the test does not increase plasma corticosteroid concentrations (32,33,35,41). Because stress alters activity of both GABAergic and dopaminergic systems reviewed in (28,39), it could also alter their reactivity to drugs. A procedure where stress is minimal was therefore considered as most adequate.

In the free exploratory paradigm as well as in other tests for exploration and neophobia dopamine agonists have opposing effects on different parameters. While they enhance ambulatory activity in a familiar environment they reduce novelty preference, a consequence of enhanced neophobia (18,27,36,44). This latter effect is a result of amphetamine's anxiogenic actions.

GABA availability was enhanced by the GABA transaminase inhibitor γ-acetylen GABA (GAG). GAG was used because it has been shown to reliably and dose dependently reduce ambulatory activity in rats and mice (3,4,19), and because it enhances brain GABA concentrations with less effects on other transmitters than other transaminase inhibitors (31).

GABA receptors were stimulated with the receptor agonist progabide. This drug is itself a weak agonist at $GABA_A$ receptors, whereas one of its major metabolites, SL 75102 ([a(4-chlorophenyl) 5-fluoro 2-hydroxy benzilidene-amino]-4-butanoate), has almost equal affinity for $GABA_A$ and $GABA_B$ receptors (12). SL 75102 is rapidly formed after administration of progabide with peak levels in the brain about 1 h after injection (62). Both progabide and SL 75102 are highly specific for GABA receptors (30). In an effort to determine the role of $GABA_A$ vs. $GABA_B$ receptors, progabide was combined with either the $GABA_A$ antagonist bicuculline, the $GABA_B$ antagonist CGP 35348, or both. CGP 35348 is a specific antagonist at $GABA_B$ receptors, with no significant affinity for other transmitter receptors like dopamine or noradrenaline (37). This drug has been shown to antagonize electrophysiological, neurochemical, and behavioral effects of baclofen (34,37,40).

METHOD

Subjects

Male Swiss albino mice (30–40 g, Janvier, Le Genest Saint Isle, France) were housed under a reversed 12 L:12 D cycle (lights off 0800 h) with continuous access to commercial rodent pellets and tap water.

The experiments reported herein were performed in agreement with the Guide for the Care and Use of Laboratory animals as established and promulgated by the National Institutes of Health of the United States of America and with the European Community Council Directive 86/609/EEC.

Apparatus

Exploration and ambulatory activity were quantified in polyvinylchloride boxes (30 × 30 × 20 cm high) covered with Plexiglas and subdivided into six equal square exploratory units, which were all connected by small (4 × 4 cm) openings. The apparatus could be divided in halves lengthwise by closing a temporary partition. It was kept on a stand in the animal's living quarters, and the tests were made in dim red light. The observer stood next to the box being observed.

Procedure

The mice were familiarized with one side of the test box during 24 h immediately preceding the test. The temporary partition was in place. The floor on the familiar side was covered with sawdust. Food and water were freely available. At the test, the temporary partition was removed, exposing the subject to the novel environment. The novel side of the box had a clean polyvinylchloride floor. The mouse was observed for 10 min. The following behaviors were registered on a hand-held computer: the number of familiar exploratory units entered; the number of novel exploratory units entered; the time spent in the novel area; the number of rears (vertical position with only the hind legs and the tail touching the floor in the familiar area; the number of rears in the novel area. As defined here, rearing includes leaning against the walls with one or both forepaws. For the purpose of the present studies, it was not considered worthwhile to distinguish rearing without support from this latter kind of rearing. A detailed description of the procedure has been published elsewhere (22).

All tests were performed between the 5th and the 8th h of the dark phase.

Drugs

D-amphetamine sulfate (Research Biochemicals, Natick, MA) and CGP 35348 (Ciba-Geigy, Basel, Switzerland), were dissolved in physiological saline and injected 30 min before behavioral test. GAG (γ-acetylen GABA) (Merrell International, Strasbourg, France) was dissolved in distilled water and injected 3 h before the test. Progabide (Synthélabo, Bagneux, France) was suspended in physiological saline containing about 0.05% (v/v) of Tween 80. Injection was made 60 min before test. (+)-bicuculline (Sigma, St. Louis, MO) was dissolved in hot physiological saline to which acetic acid was added to a final concentration of about 0.01 M. This was made because bicuculline is unstable at physiological pH (38). The cooled solution was injected 10 min before test. Control injections of the appropriate vehicle were made at the same time before test as the corresponding drug. In the GABA agonist–amphetamine interaction experiment, the vehicle injection corresponding to the GABAergic drugs were made 90 min (the harmonic mean of the intervals for GAG and progabide) before test.

All doses mentioned in the text refer to the form of the compound indicated above and all drugs were injected intraperitoneally in a volume of 1 ml/100 g body weight.

Design

A parallel groups design was used. At each experimental session all doses of a given drug or combination of drugs were tested in an equal number of animals. Because it was not practically possible to run all animals in a given experiment simultaneously, a small number (three or four) of mice received each treatment. This was then repeated until a total of 9 or 10 animals had received all treatments in a given experiment.

Statistical Analysis

Data were analyzed with the Kruskal–Wallis ANOVA because the Bartlett test for homogeneity of error variances showed nonhomogeneity in several cases. A posteriori comparisons were made with the Mann–Whitney U-test. All probabilities given in tables and figures are two tailed.

RESULTS

Amphetamine increased ambulatory activity in the familiar environment, $\chi^2(3) = 9.598$, $p < 0.05$. When all groups were compared to control it was found that only the dose of 2 mg/kg had a significant effect. The time spent in the novel environment was reduced by amphetamine, $\chi^2(3) = 21.429$, $p < 0.001$. Doses of 1 and 2 mg/kg were effective (Fig. 1). The number of rears was not affected by amphetamine, $\chi^2(3) = 1.105$, NS, for the familiar environment and $\chi^2(3) = 0.071$, NS, for the novel environment.

GAG had a significant effect on ambulatory activity in the familiar, $\chi^2(5) = 14.375$, $p < 0.05$, as well as in the novel environment, $\chi^2(5) = 13.479$, $p < 0.05$. The dose of 25 mg/kg increased activity in the familiar environment, but somewhat higher doses, 50 and 100 mg/kg were ineffective. A very large dose, 200 mg/kg, reduced ambulatory activity in the novel environment while having no effect in the familiar. There was no effect of GAG on the time spent in the novel environment, $\chi^2(5) = 7.495$, NS. The GABA transaminase inhibitor had an effect on the number of rears in the familiar, $\chi^2(5) = 11.761$, $p < 0.05$, as well as in the novel environment, $\chi^2(5) = 20.464$, $p = 0.001$. It appeared to increase the number of rears in the novel environment after the three lower doses. However, this effect failed to reach statistical significance ($ps > 0.08$). On the contrary, a dose of 200 mg/kg reduced the number of rears in the novel environment. When each dose was compared to control with regard to the number of rears in the familiar environment, no significance was obtained despite the fact that the overall test was significant. This latter turned out to be due to the difference between the 25 and and 200 mg/kg doses. Data are illustrated in Fig. 2.

Progabide had an inhibitory effect on ambulatory activity in the novel environment, $\chi^2(3) = 7.855$, $p < 0.05$. However, only the dose of 50 mg/kg differed from control. Larger doses did not affect ambulatory activity, suggesting that the effect of the 50 mg/kg dose is spurious.

No effect was found on ambulatory activity in the familiar environment, $\chi^2(3) = 2.525$, NS, or on the time spent in the novel environment, $\chi^2(3) = 5.162$, NS. Progabide reduced the number of rears in both the novel, $\chi^2(3) = 10.297$, $p < 0.05$, and familiar, $\chi^2(3) = 8.221$, $p < 0.05$, environments. Doses of 50 and 100 mg/kg were ineffective, while 200 mg/kg had a significant effect. Data are shown in Fig. 3.

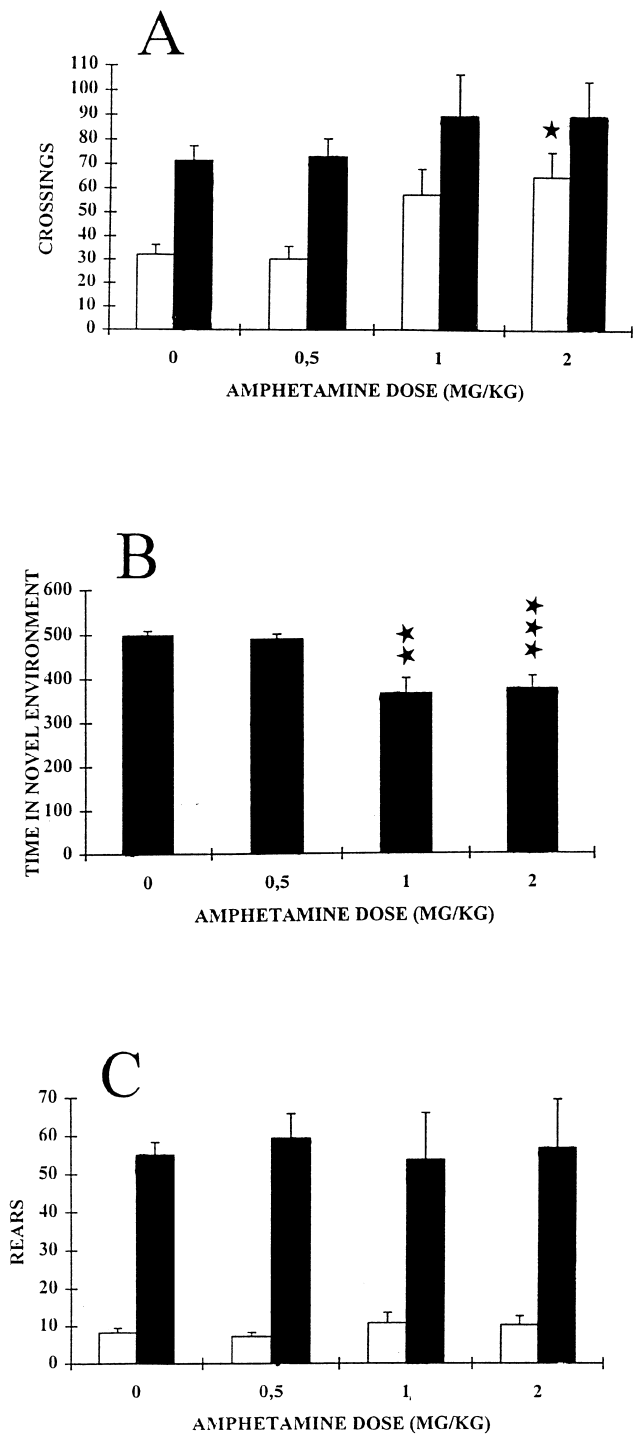

FIG. 1. Ambulatory activity (A) expressed as crossings between compartments, in the familiar and in the novel environment, the time spent in the novel environment (B) and the number of rears (C) during a 10-min test in mice treated with several doses of amphetamine. There were 9 or 10 mice per group. Data are mean ± SEM. White bars, familiar environment; dark bars, novel environment. *Different from saline, $p < 0.05$; *$p < 0.01$; **$p < 0.001$.

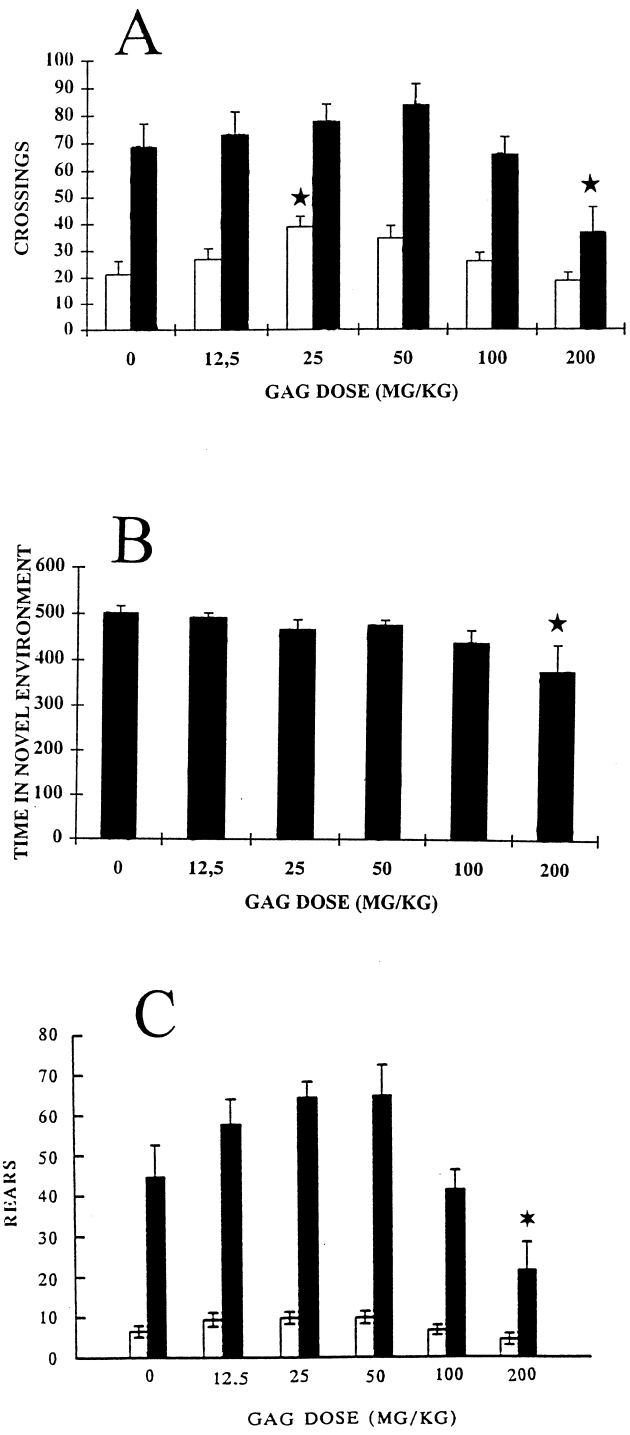

FIG. 2. Ambulatory activity (A) in the familiar and novel environment, time spent in the novel environment (B) and number of rears (C) in male mice treated with several doses of the GABA transaminase inhibitor GAG. There were 9 or 10 mice per group. Data are mean ± SEM. White bars, familiar environment; dark bars, novel environment. *Different from saline, $p < 0.05$.

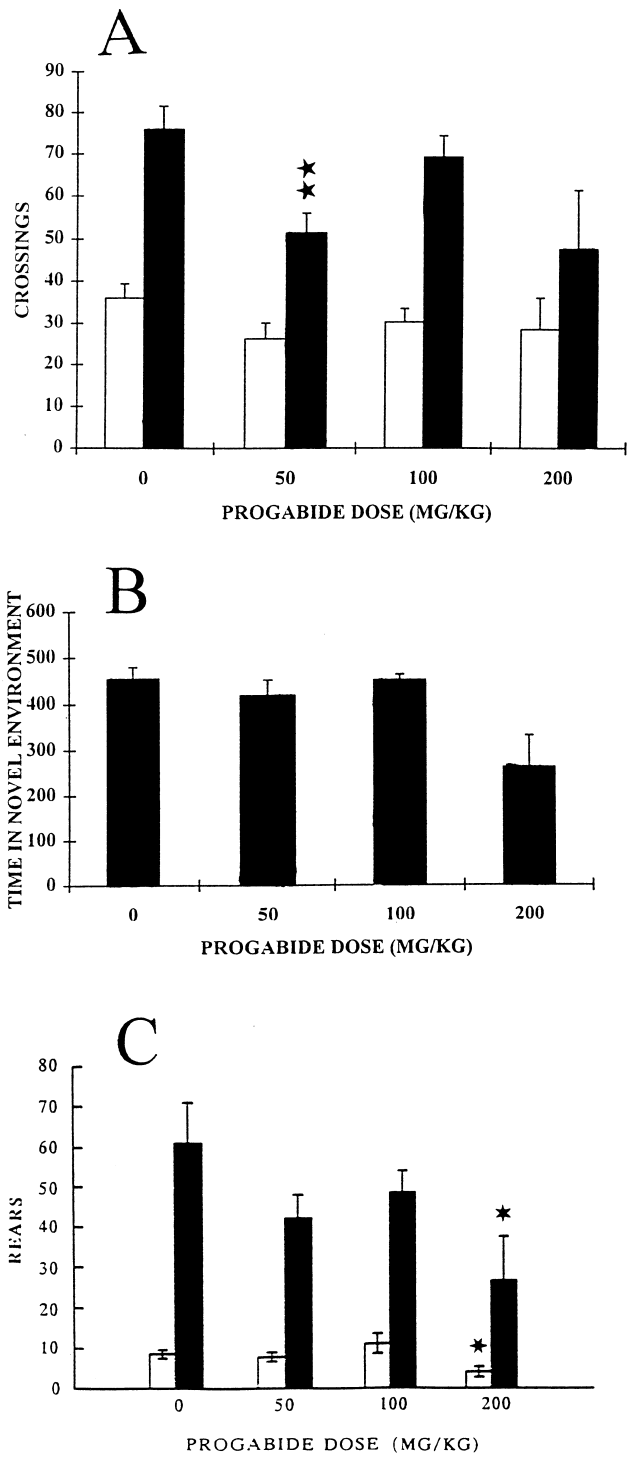

FIG. 3. Ambulatory activity (A) in the familiar and novel environment, time spent in the novel environment (B) and number of rears (C) in male mice treated with several doses of the mixed $GABA_A/GABA_B$ agonist progabide. There were 9 or 10 mice per group. Data are mean ± SEM. White bars, familiar environment; dark bars, novel environment. *Different from saline, $p < 0.01$.

Amphetamine, 1 mg/kg, was then combined with GAG, 50 mg/kg, and progabide, 100 mg/kg. The Kruskal–Wallis test showed significant effects on ambulatory activity in the familiar, $\chi^2(3) = 19.836$, $p < 0.001$, and in the novel, $\chi^2(3) = 20.437$, $p < 0.001$, environment. The time spent in the novel environment was also modified by the drug treatments, $\chi^2(3) = 14.346$, $p < 0.01$. When the number of rears was analyzed, significant effects were found both in the familiar, $\chi^2(3) = 21.638$, $p < 0.001$, and novel, $\chi^2(3) = 24.674$, $p < 0.001$, environments.

Amphetamine + saline reduced the time spent in the novel environment without affecting other parameters. The combination GAG + amphetamine had a strong inhibitory effect on ambulatory activity both in the familiar and novel environments. It is important to note that none of these effects were obtained when GAG and amphetamine, in the doses employed, were administered separately. The time spent in the novel environment differed neither from amphetamine + saline nor from control. The number of rears both in the familiar and novel environments was dramatically reduced by the combined treatment with GAG and amphetamine. It differed both from control and amphetamine + saline. When progabide was combined with amphetamine, ambulatory activity in the novel environment was much reduced. It differed both from control and from amphetamine + saline. No effect was found on activity in the familiar environment. The time spent in the novel environment was reduced in relation to control but was not different from that observed after treatment with amphetamine + saline. When the number of rears was analyzed, it was found that the combination amphetamine + progabide produced a strong reduction both in the novel and familiar environments. In fact, the number of rears was lower than after control treatment or after amphetamine + saline. Data are summarized in Fig. 4.

We then tried to block the effects of amphetamine, 1 mg/kg, + progabide, 100 mg/kg, with bicuculline, 1 mg/kg, or CGP 35348, 100 mg/kg. The effects of the antagonists administered together with saline were also evaluated. There was a significant inhibitory effect of treatment on ambulatory activity in the familiar, $\chi^2(6) = 44.476$, $p < 0.001$, and the novel, $\chi^2(6) = 44.476$, $p < 0.001$, environment as well as on time spent in the novel environment, $\chi^2(6) = 30.965$, $p < 0.001$. The number of rears in the familiar, $\chi^2(6) = 47.581$, $p < 0.001$, and in the novel, $\chi^2(6) = 46.181$, $p < 0.001$, environments was also reduced. When each treatment was compared to control it was found that the mice treated with amphetamine + progabide had a lower activity in the novel environment than controls. No effect was obtained on ambulatory activity in the familiar environment. The time spent in the novel environment as well as the number of rears in both the familiar and novel environments were also reduced by the combination amphetamine–progabide. These results replicate those obtained in the previous experiment. Neither bicuculline nor CGP 35348 reduced the effects of amphetamine + progabide. If anything, these appeared to be reinforced by the antagonists. Ambulatory activity and rearing in both the familiar and novel environments were lower after the combination amphetamine + progabide + bicuculline than after amphetamine + progabide + saline. CGP 35348 also reduced ambulatory activity in the familiar environment when given together with amphetamine + progabide.When both GABA antagonists were administered concurrently the time spent in the novel environment was lower than after amphetamine + progabide + saline, an effect not obtained when bicuculline or CGP 35348 were added separately to amphetamine + progabide. Ambulatory activity and rearing also appeared to be more reduced after concurrent treatment with both antago-

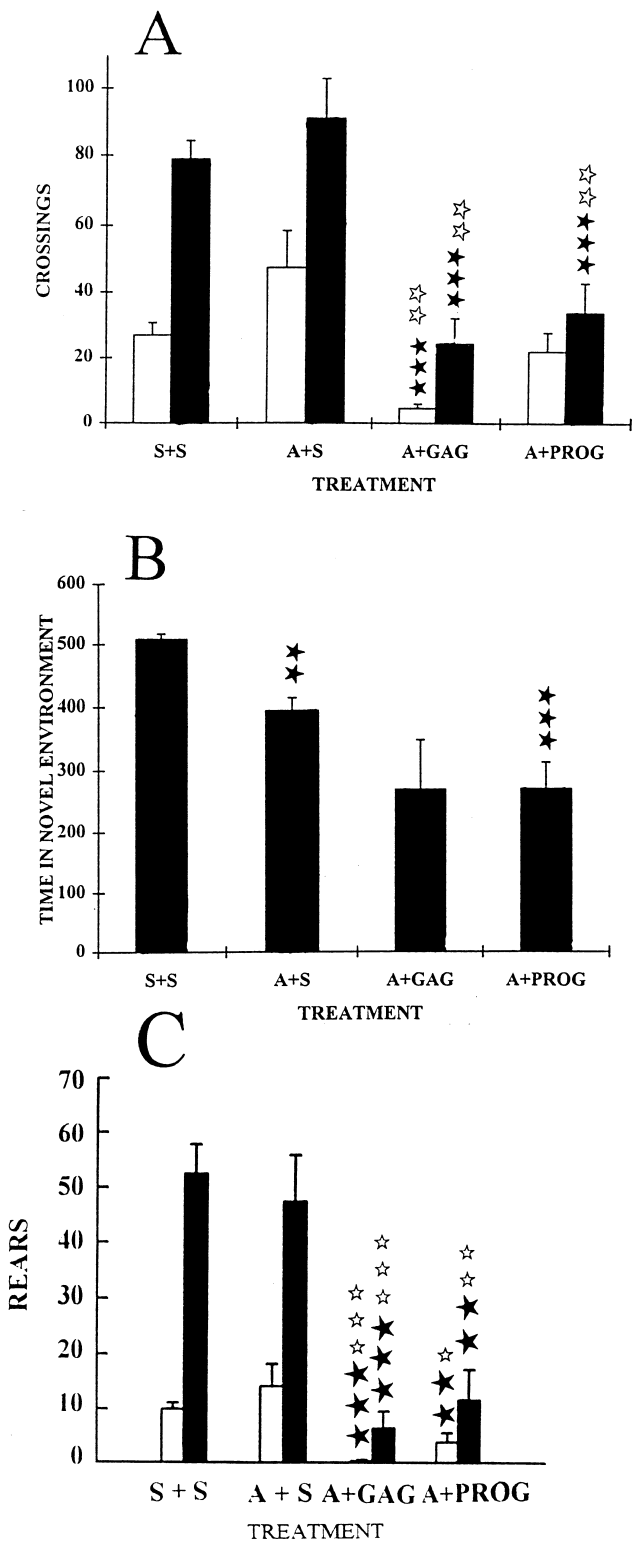

FIG. 4. Ambulatory activity (A) in the familiar and novel environment, time spent in the novel environment (B) and the number of rears (C) in male mice treated with amphetamine, 1 mg/kg, combined with GAG, 50 mg/kg, or progabide, 100 mg/kg. S, saline; A, amphetamine; PROG, progabide. There were 9 or 10 mice per group. Data are mean ± SEM. White bars, familiar environment; dark bars, novel environment. *Different from saline, $p < 0.01$; **$p < 0.001$. ☆Different from amphetamine, 1 mg/kg, + saline, $p < 0.01$.

nists then when they were given separately, but the differences did not reach statistical significance. Finally, bicuculline alone reduced all behaviors whereas CGP 35348 had no effect. In fact, the effects of bicuculline alone were not different from those of amphetamine + progabide + bicuculline with regard to ambulatory activity and time spent in the novel environment. However, the number of rears in the familiar environment was less reduced by bicuculline alone than by amphetamine + progabide + bicuculline.

Although the difference was statistically significant, it was small and its importance is unclear. Data are summarized in Fig. 5.

DISCUSSION

As expected, ambulatory activity in the familiar environment was enhanced by amphetamine while the time spent in the novel environment was reduced. It is most likely that these effects of amphetamine are due to stimulation of dopaminergic neurotransmission. Some noradrenergic antagonists have been reported to reduce amphetamine-induced hyperactivity in mice, but the dopamine-β-hydroxylase inhibitor FLA 63 had only marginal effects while the tyrosinhydroxylase inhibitor α-methyl-*p*-tyrosine abolished the effects of amphetamine (46). This observation suggests that dopaminergic stimulation is far more important than stimulation of noradrenaline. Thus, any possible effects of amphetamine on noradrenergic neurotransmission has not been considered in the present experiments.

The inhibitory effect of amphetamine on the time spent in the novel environment was not reliably modified by the GABAergic drugs. This could suggest an absence of functionally relevant interactions between dopamine and GABA with regard to neophobia or anxiogenic-like effects. However, other explanations are equally possible. The apparent inability of the GABAergic drugs to block amphetamine's effect on neophobia is a consequence of a sedative action of the combined treatments. Their strong effects on ambulatory activity and rearing suggest in fact that the combination of drugs was most sedative, and this could mask any effect on neophobia. Only further studies with additional doses of the GABAergic compounds could eliminate this possibility. It might also be the case that amphetamine-induced release of dopamine is different from physiological release, and this could mean that our conclusions are valid only for the effects of amphetamine. Dopamine itself or other dopaminergic agents could, in principle, interact with GABAergic compounds in a different way.

When a subeffective dose of GAG was administered together with amphetamine, ambulatory activity and the number of rears in the familiar as well as in the novel environment were dramatically reduced. It must be concluded, then, that GAG was strongly potentiated by amphetamine. Whereas an ineffective dose of progabide also reduced activity in the novel environment when combined with amphetamine, this drug did not significantly reduce activity in the familiar environment.

However, the number of rears was much reduced both in the familiar and novel environments. It appears, then, that progabide was potentiated in a way similar to that of GAG. It seems safe to conclude that enhanced dopaminergic activity potentiates the inhibitory actions of GABAergic drugs on ambulatory activity and rearing in the mouse. A similar potentiation in this same species was observed by Cott and Engel (14) with aminooxyacetic acid, valproate and baclofen. The minor differences between GAG and progabide are probably a consequence of the different mode of action of these drugs. While GAG has an indirect action through enhancement of cerebral GABA concentrations, progabide is a direct receptor agonist. Moreover, GAG also increases extraneuronal GABA (7), and extrasynaptic actions of the transmitter are not impossible.

Bicuculline had strong intrinsic effects both on the time spent in the novel environment and on ambulatory activity and rearing. The first action could be a result of an anxiogenic effect, because bicuculline has been reported to have anxiogenic-like actions in some procedures (21,42). The motor effects are more difficult to explain. In fact, bicuculline reduces motor activity in a way similar to that of GABA agonists

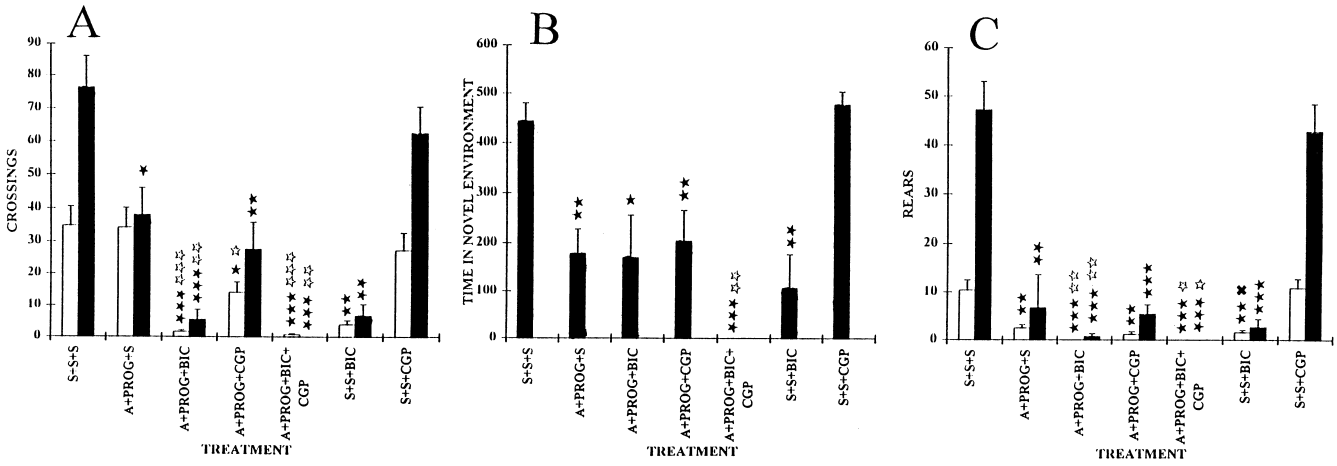

FIG. 5. Ambulatory activity (A) in the familiar and novel environment, time spent in the novel environment (B), and the number of rears (C) in male mice treated with amphetamine, 1 mg/kg, combined with progabide, 100 mg/kg, and bicuculline, 1 mg/kg or CGP 35348, 100 mg/kg. The effects of bicuculline and CGP 35348 when administered alone are also shown. S, saline; A, amphetamine; PROG, progabide; BIC, bicuculline; CGP, CGP 35348. There were 9 or 10 mice per group. Data are mean ± SEM. White bars, familiar environment; dark bars, novel environment. *Different from saline, $p < 0.05$; *$p < 0.01$; **$p < 0.001$. ☆Different from amphetamine, 1 mg/kg, + progabide, 100 mg/kg, + saline, $p < 0.05$; ☆☆$p < 0.01$; ☆☆☆$p < 0.001$. ×Different from amphetamine + progabide + bicuculline, $p < 0.05$.

[(1,2); present data]. In this context it may be noted that benzodiazepine inverse agonists also reduce ambulatory activity in mice (9–11). There is no immediate explanation for the fact that drugs enhancing or reducing GABAergic activity have similar effects on ambulatory activity.

It may be interesting to note that benzodiazepines enhance the locomotor-stimulatory effects of amphetamine and other stimulants (16,47,49,50). Because it is generally believed that benzodiazepines facilitate GABAergic neurotransmission through an action at the $GABA_A$ supramolecular complex, and because muscimol has similar effects (8), it appears that stimulation of the $GABA_A$ receptor enhances the locomotor activation produced by facilitated dopaminergic neurotransmission. This coincides with most neurochemical and behavioral data (see the introductory paragraphs). The inhibitory effects of GAG and progabide on ambulatory activity and rearing when administered together with amphetamine cannot, therefore, be mediated by the $GABA_A$ receptor. This notion is supported by the fact that the effects of progabide were not altered by simultaneous administration of bicuculline. It may be noted that the dose of bicuculline used here blocked the effects of a large dose of progabide on male sexual behavior (5). It may also be observed that the intrinsic effects of bicuculline do not invalidate the observation that it failed to antagonize the effects of progabide. To the contrary, they show that the bicuculline dose employed indeed had a functional effect at the $GABA_A$ receptor.

The effects of GAG and progabide do not seem to be mediated by the $GABA_B$ receptor, because CGP 35348 did not reduce their actions. The dose of the antagonist used here has previously been shown to block the effects of several doses of baclofen on sex behavior and motor coordination (40), making it unlikely that the ineffectiveness of CGP 35348 was due to an inadequate dose. The effects of progabide are not dependent on the simultaneous activation of $GABA_A$ and $GABA_B$ receptors either, because when both antagonists were administered together the effects of progabide were not reduced. In agreement with this, we have previously reported that the actions of progabide on ambulatory activity in the rat are unaffected by bicuculline and CGP 35348 (5). A possible explanation for this is that progabide acts at a receptor different from $GABA_A$ or $GABA_B$. The existence of a GABAC receptor with cis-4-aminocrotonic acid as selective ligand has been proposed (23), and its presence in the central nervous system has been confirmed (43,57). However, it is not known whether progabide binds to this receptor. In case that it did, enhanced GABA release produced by antagonist-induced blockade of autoreceptors could reinforce the effects of progabide on the GABAC receptor, and that could account for the larger effects of this drug when combined with the antagonists. It might be noted that neither bicuculline nor CGP35348 bind to this putative GABAC receptor (61).

Systemically administered drugs act at appropriate receptors throughout the nervous system and in the periphery. Data from the present studies do not allow for any conclusions as to the specific site of action. Moreover, there is not much known about which brain structures are important for neophobia or behaviors like rearing. Therefore, it would be premature to speculate about the neuronal systems involved in the effects observed here.

To summarize, present data show that the neophobic effects of amphetamine are not reliably modified by the simultaneous administration of GABAergic agents. The locomotor-reducing effects of GABAergic agonists are much potentiated by concurrent treatment with amphetamine. The potentiation could not be blocked by $GABA_A$ or $GABA_B$ receptor antagonists. It is possible, therefore, that another GABA receptor is involved.

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