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GABAergic Drugs Inhibit Amphetamine-Induced Distractibility in the Rat

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ÅGMO, A., A. MEDRANO, N. GARRIDO AND P. ALONSO. *GABAergic drugs inhibit amphetamine-induced distractibility in the rat.* PHARMACOL BIOCHEM BEHAV **58**(1) 119–126, 1997.—Drugs facilitating GABAergic neurotransmission have been reported to block some behavioral actions of dopaminergic stimulation but not others. The present experiments were performed with the purpose to extend the range of behaviors in which the interaction between GABA and dopamine have been studied. The ability of the $GABA_B$ agonist baclofen and the GABA transaminase inhibitor sodium valproate to block the enhanced distractibility produced by amphetamine was evaluated in a procedure especially designed for analyzing drugs' effects on distractibility. Briefly, rats were trained to traverse a straight runway with a sucrose solution as reinforcement. Once the response had been acquired, an additional runway ending in an empty box was connected. The time spent investigating this additional runway is the measure of distractibility. Male rats treated with amphetamine, 1 mg/kg, displayed an increase of the time spent in the additional runway. Baclofen, 2.5 and 5 mg/kg, and sodium valproate, 100 and 200 mg/kg, had no effect on distraction behavior when administered alone. However, when these drugs were administered together with amphetamine, 1 mg/kg, they completely inhibited the effects of the stimulant on distractibility. These data show that distractibility is similar to discrimination learning with regard to the capacity of GABAergic drugs to block the effects of dopaminergic stimulation. It is different from locomotor activity, however, where GABAergic drugs are ineffective in this respect. © 1997 Elsevier Science Inc.

Distractibility Amphetamine GABA agonists

MUCH data show that GABA or GABAergic drugs modify the activity of dopaminergic neurons. Systemic administration of several kinds of GABA agonists reduces dopamine turnover in the nigrostriatal and mesolimbic systems (20,30,32,33). Retrodialysis of the $GABA_B$ agonist baclofen in the frontal cortex reduces local dopamine release (28,29), and microinjection of this drug into the ventral tegmental area inhibits dopamine release in the nucleus accumbens (16,39). However, electrophysiological studies have shown that systemically administered GABA agonists may increase the firing rate of dopaminergic neurons both in the substantia nigra and the ventral tegmental area (13,23,34,35).

In behavioral studies it has been found that GABA agonists block some effects of dopaminergic stimulants. The deleterious effect of amphetamine on discrimination learning in rats is blocked by baclofen (7). However, this drug does not reduce the effects of amphetamine on locomotor activity in this same species (3,7). On the other hand, locomotor stimulation in mice produced by apomorphine or amphetamine are blocked by doses of GABA agonists that have no effect when administered alone (1,8). Apomorphine-induced stereotyped behaviors of rats are blocked either by the $GABA_A$ agonist THIP or the $GABA_B$ agonist baclofen (27). Furthermore, infusion of baclofen into the ventral tegmental area has inhibitory effects on intracranial self-stimulation reward whereas the $GABA_A$ agonist muscimol is ineffective (37). In contrast to these observations, amphetamine-induced place preference is not blocked by concurrent administration of the mixed $GABA_A$/$GABA_B$ agonist progabide (10). Furthermore, reduced water intake observed after treatment with amphetamine is not an-

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tagonized by the GABA transaminase inhibitor sodium valproate (31). Finally, a recent study showed that whereas amphetamine-induced hyperactivity in the mouse is readily antagonized by progabide or the GABA transaminase inhibitor γ-acetylen GABA, reduced exploratory behavior following treatment with amphetamine is not (1). It appears, then, that GABA agonists inhibit some behavioral consequences of dopaminergic stimulation but not others, and that there is species differences, at least between rats and mice. At present, there is no hypothesis available that can explain why some behavioral effects of dopaminergic stimulation are blocked by GABAergic drugs whereas others are not. One reason for this may be the limited range of behaviors in which the interactions between GABA and dopamine have been analyzed.

We have recently described a procedure that presumably quantifies distractibility in the rat (4). Dopaminergic stimulants such as amphetamine or amfonelic acid enhance distractibility. This effect is blocked by a dopamine antagonist. It was thought of interest to determine whether GABA agonists could inhibit the actions of amphetamine in this procedure. The $GABA_B$ agonist baclofen and the GABA transaminase inhibitor sodium valproate were used, basically because these drugs have been used in several of the studies cited above. Furthermore, both of them are used clinically, for the treatment of spasticiy and epilepsy, respectively (12). They have also different mechanisms of action. While baclofen is a specific, diret acting receptor agonist, sodium valproate increases brain GABA concentration (21). This means that the drugs do not necessarily have the same behavioral effect.

METHODS

Subjects

Male Wistar rats (300–400 g) from the animal facilities of the Faculty of Medicine, National Autonomous University of Mexico were housed singly in Macrolon© cages under a reversed light/dark cycle (12/12 h, lights off 0900) and given free access to commercial rat pellets and tap water. A temperature of 22 ± 1°C was maintained in the animal quarters. The studies reported in this manuscript have been carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the NIH and with applicable local laws.

Apparatus

A detailed description of the apparatus has been published elsewhere (4). Briefly, a start box was connected to a straight runway ending in a goal box. In the middle of the goal box, a drinking dish was fixed to the floor. At the middle of the runway, another runway could be perpendicularly connected. This additional runway ended in an empty box with dimensions different from the goal box (Fig. 1). The apparatus were located in a sound attenuating room, dimly lit by four 15 W white bulbs. A 60 dB white noise masked environmental sounds. Two apparatuses were located adjacent to each other in the same room, and two animals were run simultaneously. There was no indication that the behavior of one influenced the other.

Drugs

d-Amphetamine sulfate (Sigma, St. Louis, MO, USA), baclofen (Ciba-Geigy, Basel, Switzerland) and sodium valproate (Ciba-Geigy Mexicana, Mexico City) were dissolved in physiological saline and injected intraperitoneally (IP) in a volume of 1 ml/kg b.wt. The intervals between drug injection and test were the following: Sodium valproate, 15 min; baclofen, 20 min; amphetamine, 40 min.

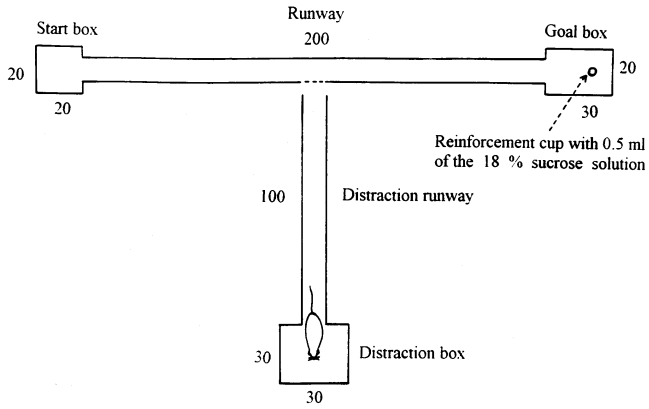


FIG. 1. Schematic representation of the distractometer apparatus. Dimensions in cm. The distraction runway was connected only at the test.

Procedure

Before beginning experiments, the subjects were allowed to drink an 18% (w/w) sucrose solution in water in their home cage for 48 h. This solution was later used as reinforcement in the distraction procedure. In addition to the ordinary water bottle, another bottle with 200 ml of the sucrose solution was freely available. After the home cage exposure to the sucrose solution, the rats were habituated to the apparatus during two sessions of 1 h each separated by 24 to 72 h. During habituation, 5 ml of the sucrose solution was available in the goal box. The variable interval between habituation sessions did not influence the animals' future performance, but made it possible to run the first habituation session on a Friday.

About one week after the last habituation session, runway training was initiated. One trial per day was performed for three consecutive days. At each trial, the subject was placed in the start box with the door closed. After 1 min the door was opened, and the subject was allowed a maximum of 5 min to enter the runway. Once inside the runway, the subject was allowed a maximum of 5 min to reach the goalbox, where it was allowed to stay for 1 min. At every trial, 0.5 ml of sucrose solution was available in the goal box. The following parameters were registered on a hand-held computer (Psion Organiser): *Exit latency* (time from the opening of the start box door until all four paws were inside the runway); *running time* (time from entering the runway until the animal was inside the goal box with 4 paws); *lick latency* (time from entry into the goal box until the beginning of licking the sucrose solution). Any subject that exceeded the time limits for entering the runway or the goal box or that did not drink at any of the trials was eliminated from the experiment. The proportion of subjects eliminated in this way ranged from 0 to 50%. This procedure assured that only subjects with reliable runway behavior were included in the test.

At the test, the additional arm was connected to the runway. In addition to the abovementioned parameters, the *distraction time* was recorded. This is the time that the subject spent in the additional runway (4 paws inside it). The running

TABLE 1
SUMMARY OF THE DRUG TREATMENTS

Drug	Dose (mg/kg)	N
Amphetamine	0	10
	1	10
Baclofen	0	10
	2.5	10
	5	10
Sodium valproate	0	10
	100	10
	200	10
Amphetamine + baclofen	0 + 0	8
	1 + 0	8
	1 + 2.5	8
	1 + 5	8
Amphetamine + valproate	0 + 0	9
	1 + 0	9
	1 + 100	9
	1 + 200	9

time registered at the test does not include the distraction time (i.e., the distraction time was subtracted from the total running time). Drug treatments were administered only at the test.

Design

A parallel groups design was used in such a way that all doses of a given drug or combination of drugs were run simultaneously together with saline control. Since it was not practically possible to run all subjects in an experiment at the same session, a small number of animals, 3 or 4 per treatment, were run at each session and this was then repeated until a total of 8 to 10 rats had received each treatment. A summary of the drug treatments at the test is shown in Table 1.

Statistical Analysis

Data were analyzed by two factor ANOVAs for repeated measures on one factor. The between groups factor was dose (treatment) and the within groups factor was trial (3 acquisitions and test). In case of significant interaction, tests for simple effects of dose within each trial were performed. The distraction time, that was only recorded at the test, was analyzed by one-factor ANOVA or the *t*-test where appropriate. *A posteriori* comparisons were made with Tukey's HSD procedure. Before using the results of any ANOVA, Hartley's F_{max} test for homogeneity of error variances was performed on the between groups factor and Box's M test for homogeneity of dispersion matrices was applied to the within groups factor. These tests were not significant in any case.

RESULTS

After treatment with amphetamine, 1 mg/kg, a significant main effect of treatment on running time, $F(1, 18) = 4.49$, $p < 0.05$, was obtained. The trials also differed, $F(3, 54) = 3.16$, $p < 0.05$, and the interaction treatment × trial was significant, $F(3, 54) = 4.28$, $p < 0.01$. Tests of simple effects showed that the running time was longer at the test in the group given amphetamine. No difference was found between groups at acquisition. Data from the test are shown in Fig. 2A. The distraction time was also increased by amphetamine, $t(18) = 2.82$, $p < 0.05$ (Fig. 2B). No effect was found on other parameters.

The $GABA_B$ agonist baclofen, 2.5 and 5 mg/kg, did not affect any parameter (all *p*s > 0.3) (Fig. 3). Sodium valproate, 100 and 200 mg/kg, was also ineffective on all parameters (*p*s > 0.4) (Fig. 4).

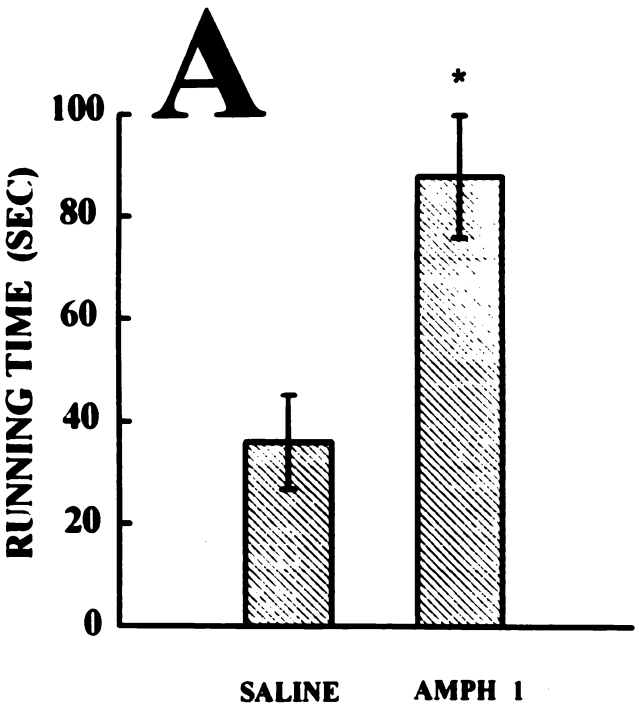
When amphetamine was combined with baclofen, 2.5 and 5 mg/kg, the main effect of treatment did not reach statistical significance with regard to running time, $F(3, 28) = 1.46$, NS. There was, however, a significant treatment effect on trials, $F(3, 81) = 4.69$, $p < 0.01$, and the interaction treatment × trial was significant as well, $F(9, 84) = 6.28$, $p < 0.001$. Tests for simple effects within each trial showed that the groups differed only at the test. Moreover, *a posteriori* comparisons established that only the amphetamine + saline group was different from control. There was a significant difference between amphetamine + saline and amphetamine + baclofen, 2.5 or 5 mg/kg. Thus, the effect of amphetamine on running time was completely blocked by baclofen. (Fig. 5A). When the distraction time was analyzed, a difference between treatments was obtained, $F(3, 21) = 4.87$, $p < 0.01$. *A posteriori* tests showed that the distraction time was longer after amphetamine + saline than after any other treatment. There was also a significant difference between amphetamine + saline and amphetamine + both doses of baclofen (Fig. 5B). Again, these data show that the effect of amphetamine on distraction time was totally blocked by baclofen. No significant effects were found on other parameters.

Sodium valproate, in doses of 100 and 200 mg/kg, were then combined with amphetamine, 1 mg/kg. ANOVA showed that there was no main effect of treatment on running time, $F(3, 32) = 1.96$, NS. On the other hand, there was a significant effect of trial, $F(3, 96) = 6.84$, $p < 0.001$, and the interaction treatment × trial was also significant, $F(9, 96) = 3.43$, $p < 0.01$. Tests for simple effects of treatment within each trial showed that there was a difference only at the test. Amphetamine + saline differed from all other treatments. Thus, both doses of valproate blocked the effect of amphetamine on running time. With regard to the distraction time, ANOVA established a significant treatment effect, $F(3, 24) = 5.31$, $p < 0.01$. *A posteriori* comparisons showed that amphetamine + saline differed from all other treatments. It is clear, therefore, that the actions of amphetamine are efficiently blocked by sodium valproate in doses of 100 or 200 mg/kg. Data are summarized in Fig. 6A and B.

To summarize, amphetamine, 1 mg/kg, increased distraction and running times without affecting other parameters. The GABAergic drugs baclofen, 2.5 and 5 mg/kg, and sodium valproate, 100 and 200 mg/kg, were ineffective when administered alone, but both baclofen and sodium valproate completely blocked the effects of amphetamine on running as well as on distraction time.

DISCUSSION

In agreement with a previous study (4), amphetamine increased the time spent in the additional runway as well as the running time. This effect of amphetamine may be a consequence of the incapacity to ignore irrelevant stimuli observed after treatment with dopaminergic stimulants (9,36). It is not likely that the enhanced distractibility observed here reflects increased exploratory behavior. First, it is known that amphetamine reduces exploration of unknown environments (11,14, 17,18,24,26). Second, when non-reinforced rats are treated



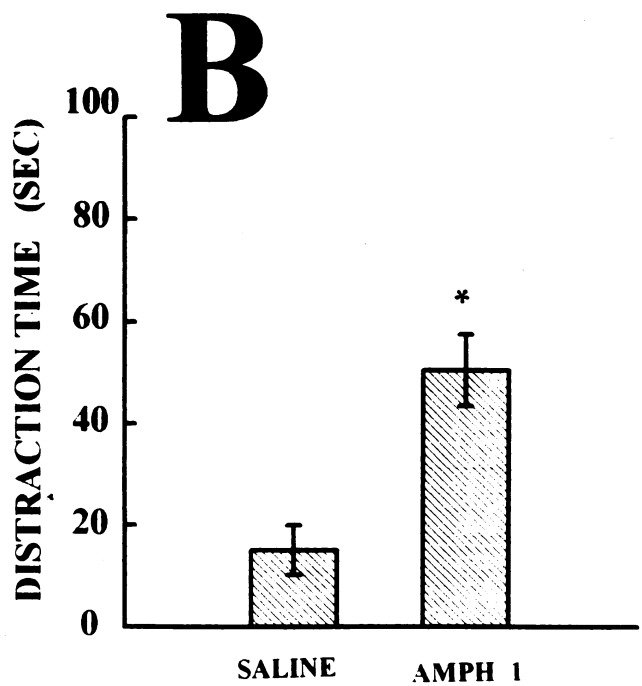
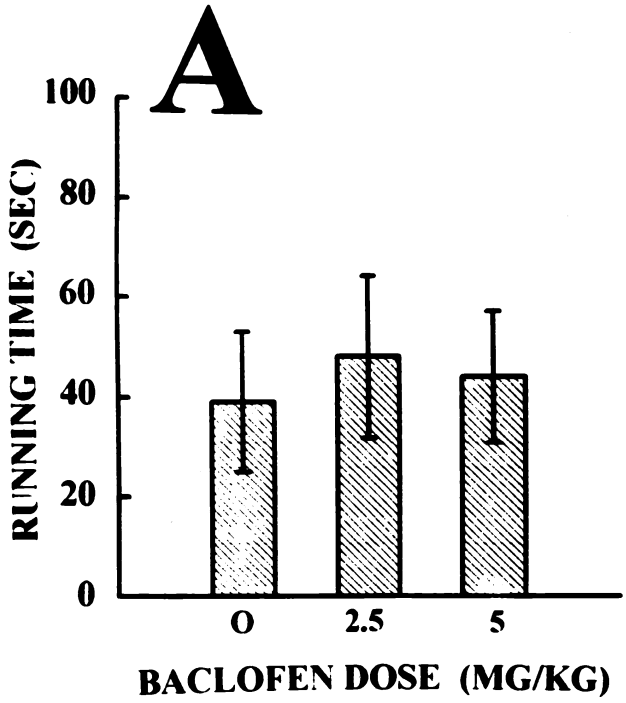


FIG. 2. Running (A) and distraction (B) times in rats treated with amphetamine, 1 mg/kg. Data are means ± SE. AMPH 1, amphetamine, 1 mg/kg. *Different from saline, $p < 0.05$.



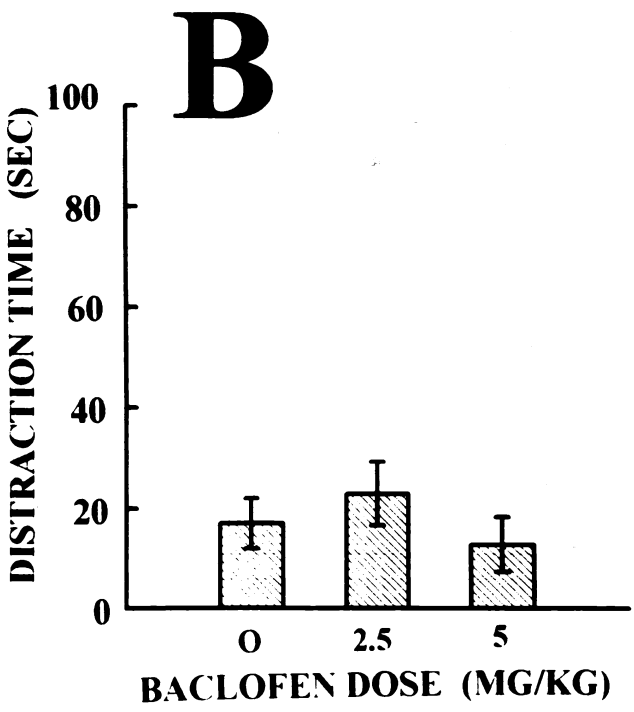
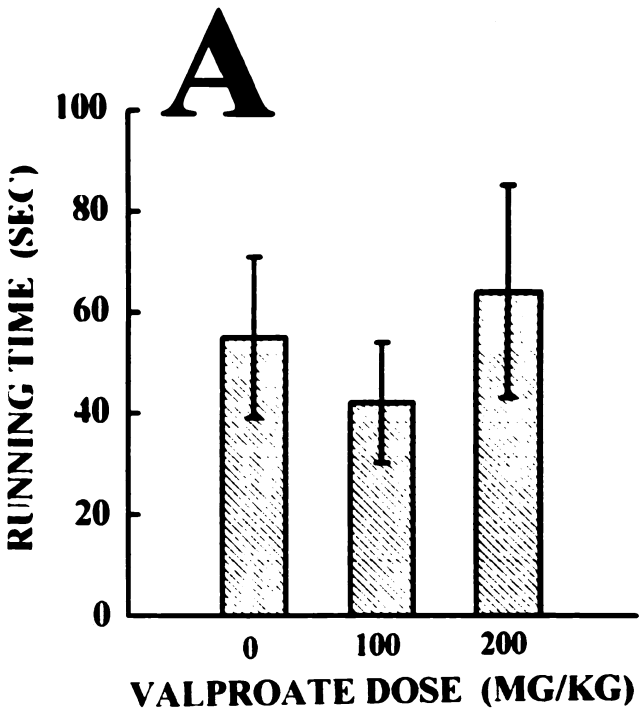


FIG. 3. Running (A) and distraction (B) times in rats treated with two doses of the $GABA_B$ agonist baclofen. Data are means ± SE.



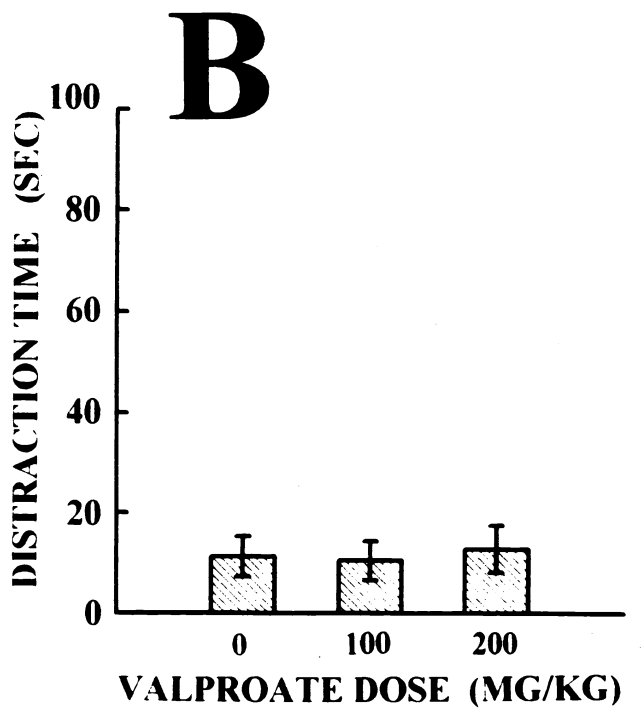
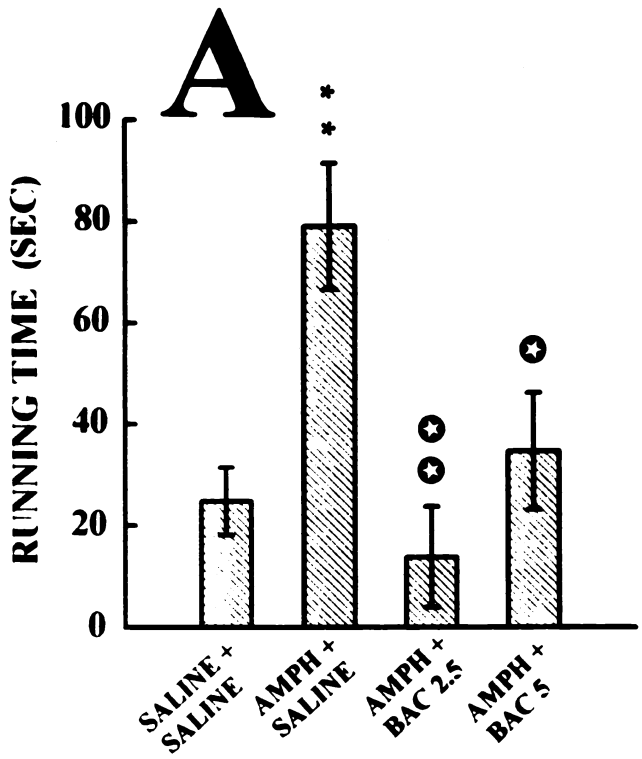


FIG. 4. Running (A) and distraction (B) times in rats treated with two doses of the GABA transaminase inhibitor sodium valproate. Data are means ± SE.



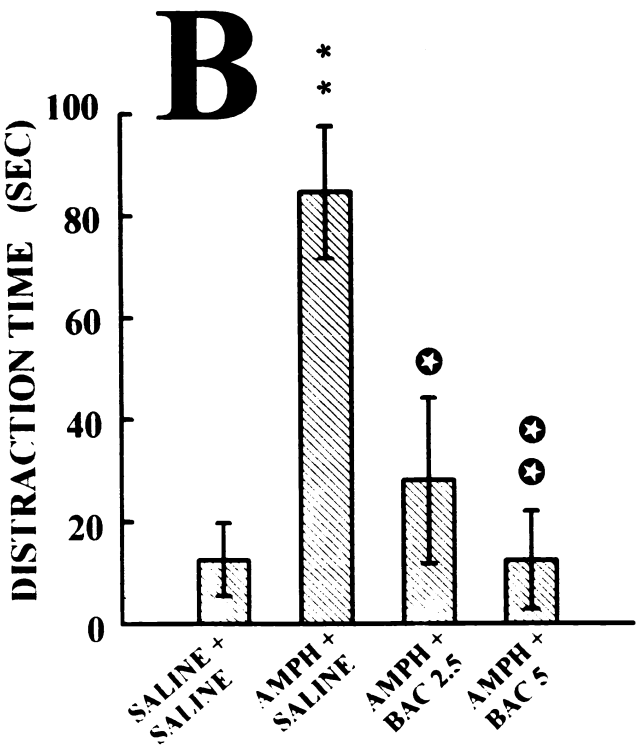


FIG. 5. Running (A) and distraction times (B) in rats treated with two doses of baclofen in combination with amphetamine, 1 mg/kg. Data are means ± SE. AMPH, amphetamine 1 mg/kg; BAC, baclofen, 2.5 mg/kg; BAC 5, baclofen 5 mg/kg. **Different from saline + saline, $p < 0.01$; white star in black circle Different from amphetamine + saline, $p < 0.05$; $\_p < 0.01$.

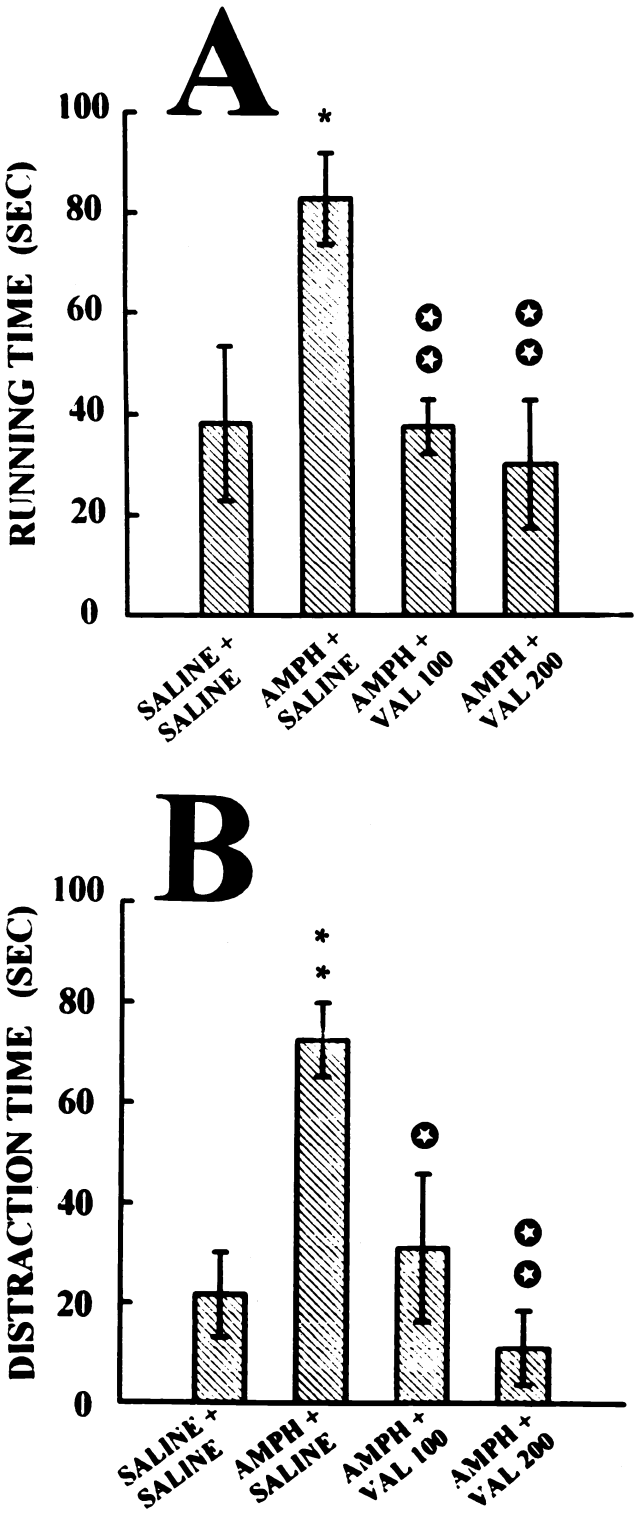


FIG. 6. Running (A) and distraction times (B) in rats treated with two doses of sodium valproate in combination with amphetamine, 1 mg/kg. Data are means ± SE. AMPH, amphetamine, 1 mg/kg; VAL 100, sodium valproate, 100 mg/kg; VAL 200, sodium valproate, 200 mg/kg. *Different from saline, $p < 0.05$; **$p < 0.01$. White star in black circle Different from amphetamine + saline, $p < 0.05$; $p < 0.01$.

with amphetamine in the present procedure, distraction time is reduced (4). In such animals, visits to the additional arm cannot be considered distraction, because no purposeful behavior is possible in the absence of programmed reinforcement. Distraction is conceptually relevant only in a context where purposeful behavior is possible. Thus, in non-reinforced animals, visits to the additional arm may rather be considered as exploration, and it is, then, logical that this behavior is reduced by amphetamine. The increase in running time observed in the present study is mainly a consequence of the fact that the rats spend much time investigating the additional arm's entry, and that may also reflect an incapacity to ignore irrelevant stimuli. For the purpose of the present studies, however, the exact nature of the behavior displayed by the amphetamine-treated animals is not crucial. Nevertheless, for convenience we use the term distractibility.

One possible explanation for the increased distraction and running times in amphetamine-treated animals is a reduced motivation to consume sucrose. However, this seems unlikely for two reasons. First, the dose of amphetamine used here does not modify sucrose consumption in a free drinking procedure (4). Second, the reduced motivation to drink water produced by a large dose of amphetamine is not blocked by sodium valproate (31), suggesting that at least this GABAergic drug does not affect the motivational consequences of amphetamine. To the contrary, in the present study sodium valproate did block the effects of amphetamine. This argues against a motivational interpretation of the drug's effect.

Baclofen and sodium valproate had no effect on distractibility by themselves. This coincides with a study showing that the GABA transaminase inhibitor vigabatrin was inactive in a task supposed to assess selective attention in rats (22). It might be noted that some doses used in that study were very large, and even doses having evident motor effects did not affect performance. The lack of effect in the present studies cannot be a consequence of inadequate doses. The lowest baclofen dose employed, 2.5 mg/kg, reduces locomotor activity but has no effect on motor coordination as evaluated by a rotarod test or on male rat sexual behavior (2,25). The larger dose, however, inhibits all these behaviors. In the case of sodium valproate, none of the doses affect locomotor activity, but 200 mg/kg has a deleterious effect on motor coordination and produces inhibition of sexual behavior (5,6). These data show that present doses have significant behavioral consequences in several other procedures. The absence of effect on distractibility is not surprising, however, because benzodiazepines, a kind of drugs generally believed to act through a facilitation of GABAergic neurotransmission, are also inactive (4).

The effects of amphetamine were blocked by baclofen and sodium valproate. This cannot be a consequence of actions on locomotor activity, because the GABAergic drugs do not reduce the stimulatory action of amphetamine in the doses used here (3). It is noteworthy that the lowest dose of sodium valproate, 100 mg/kg, while completely blocking the effects of amphetamine on distractibility, has no effect on any behavior studied when the drug is administered alone (5,6). It seems, therefore, that it can be safely concluded that the GABAergic drugs did not inhibit the effects of amphetamine because of an addition of opposite effects.

According to the present studies, GABAergic drugs block amphetamine-induced distractibility just as they block the disruptive effects of amphetamine on discrimination learning (7). Interestingly, in the latter report it was suggested that amphetamine produced a deficient interpretation of environmental stimuli, and that this was the cause of impaired learning. En-

hanced distractibility is most likely also a consequence of incorrect interpretation of environmental cues. It is possible, then, that facilitated GABAergic neurotransmission blocks attentional effects of dopaminergic hyperactivity. To the contrary and as mentioned in the Introduction, increased locomotion or conditioned place preference observed after dopaminergic stimulation is not blocked by GABA agonists in the rat (3,7,10). One explanation of this difference is that different brain structures are involved in attention on one hand and in locomotion and place preference on the other. These latter phenomena are dependent on dopaminergic activity within the nucleus accumbens (19,38). It is not known which brain sites that are important for attentional mechanisms, but it has been reported that microinjection of amphetamine into the nucleus accumbens does not disrupt latent inhibition (15), a procedure presumed to assay selective attention. This observation supports the notion that different brain structures are involved in attention and locomotion/reward.

To sum up, present data show that baclofen and sodium valproate block the effect of amphetamine on distractibility. This effect is also blocked by the dopamine antagonist cis(Z)-flupenthixol at a dose that by itself was unable to mofify distraction or running times (4). This fact together with neurochemical data showing that GABAergic agents reduce dopamine release and turnover makes it likely that activation of GABAergic systems inhibits dopaminergic activity. However, such an inhibition seems to be of slight importance under basal conditions, because neither baclofen nor sodium valproate were effective in the absence of dopaminergic activation. This coincides with a study where it was found that the reduction of dopamine turnover after treatment with GABAergic drugs was marginal under basal conditions but most significant after dopaminergic stimulation (20).

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