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Differential Effects of GABA Transaminase Inhibitors on Sexual Behavior, Locomotor Activity, and Motor Execution in the Male Rat

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AGMO, A., R. PAREDES AND H. FERNÁNDEZ. *Differential effects of GABA transaminase inhibitors on sexual behavior, locomotor activity, and motor execution in the male rat.* PHARMACOL BIOCHEM BEHAV **28**(1) 47–52, 1987.—The GABA transaminase inhibitors γ-acetylen GABA (GAG) and sodium valproate were administered intraperitoneally and their effects on locomotor activity, motor execution and sexual behavior were analyzed. It was found that sodium valproate, administered 15 min before observation, reduced locomotor activity only at a dose of 200 mg/kg. Doses of 100 and 400 mg/kg had no effect. Motor execution was impaired in a dose-dependent way, the lowest effective dose being 200 mg/kg. Sexual behavior was also dose-dependently reduced. Sodium valproate, administered 60 min before observation, inhibited all behaviors. The lowest effective dose was 200 mg/kg for locomotor activity and 400 mg/kg for motor execution and sexual behavior. GAG also inhibited all behaviors, in doses ranging from 25 mg/kg (locomotor activity) to 100 mg/kg (motor execution and sexual behavior). The data showed that there is no relation between effects on locomotor activity and the effects on sexual behavior, whereas sexual behavior is inhibited whenever motor execution is impaired. Moreover, there is no correlation between effects on locomotor activity and motor execution. It is suggested that GABA transaminase inhibitors affect sexual behavior only indirectly, via an impairment of motor execution. Therefore it is doubtful whether GABAergic mechanisms play any role in the normal regulation of sexual behavior.

Sexual behavior Locomotor activity Motor execution GABA transaminase inhibitors
γ-Acetylen GABA Sodium valproate

IN a recent study concerning GABAergic drugs and sexual behavior in the male rat it was found that the GABA receptor agonist baclofen strongly inhibited sexual behavior at a dose which had only slight effects on locomotor activity [1]. On the other hand, the GABA transaminase (GABA-T) inhibitors aminooxyacetic acid and γ-acetylen GABA (GAG) produced a strong inhibition of locomotor activity, but had only slight effects on sexual behavior. It was therefore concluded that the inhibitory effects of the GABA agonist baclofen on sexual behavior were not secondary to an inhibition of locomotor activity. However, the question of whether other kinds of motor disturbances were responsible for the effects remains open.

The purpose of the present studies was to further elucidate the relationship between inhibitory actions of GABA-T inhibitors on motor functions and their possible effects on sexual behavior. In the study mentioned above, the subjects were castrated animals treated with a low dose of testosterone propionate, displaying a subnormal level of sexual activity. Thus very few animals showed the complete copulatory pattern. It was therefore considered to be of interest to observe the effects of GABA-T inhibitors on sexual behavior in animals with a normal sexual activity. This would allow us to obtain a more precise idea about the physiological functions of GABAergic systems in the control of sexual behavior.

Two GABA-T inhibitors active after systemic administration were used. One, γ-acetylen GABA, is an irreversible inhibitor of the enzyme, thus producing a long-lasting elevation of brain GABA levels. This drug appears to be quite specific, and does not interfere with the metabolism of other amino acid transmitters such as glutamate and aspartate [8]. The other, sodium valproate, has a rapid onset of action, with significant increases in GABA levels within a few minutes of administration [10]. However, this drug has only a weak action on GABA-T. Rather it seems to increase the activity of the GABA synthesizing enzyme glutamic decarboxylase [9,12], and this might participate in the action of sodium valproate on GABA levels. Moreover, the drug is a potent inhibitor of succinic semialdehyde dehydrogenase,

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thus blocking the GABA forward reaction and indirectly GABA-T [9]. Thus, the two drugs used have different mechanisms of action, but produce the same end result. In that way, any similar effects of the drugs would be due to that common end result, an increase in brain GABA levels.

METHOD

Subjects

Male Wistar rats (300–400 g) from a local colony, maintained under a 12 hr light/dark cycle and fed commercial rat pellets and water ad lib were used in all experiments.

Animals to be used in studies of sexual behavior were given three mating tests of 30 min duration. Those animals that achieved at least one ejaculation in at least one of the tests were included in the experiments. They were castrated under ether anesthesia and subcutaneously implanted with a 20 mm long, testosterone filled silastic capsule (0.062 in. i.d.; 0.125 in. o.d.; Dow Corning Corp.). Such an implant has been shown to maintain a level of sexual behavior equal to that of intact rats [3]. Two weekly mating tests of 15 min duration, starting one week after castration, were performed before the beginning of drug treatments.

Females (Wistar, 200–300 g) used in the mating tests were ovariectomized under ether anesthesia at least two weeks before the experiments. They were injected with 25 μg/rat of estradiol benzoate (SIGMA) 53 hr before tests, and with 1 mg/rat of progesterone (Aldrich) 5 hr before. The steroids were dissolved in olive oil and administered SC in a volume of 0.2 ml/rat.

Males used in studies of locomotor activity and motor execution were left intact. Extensive pilot studies have shown that these behaviors are identical in intact and in castrated, testosterone-implanted rats.

Drugs

Sodium valproate (CIBA-GEIGY Mexicana, Mexico City) and γ-acetylen GABA (Merrell International, Strasbourg, France) were dissolved in distilled water and injected intraperitoneally in a volume of 5 ml/kg. Pilot studies on locomotor activity showed that sodium valproate had the most consistent effects 60 min after administration. However, the GABA levels in several brain areas have been reported to be maximal 5 to 15 min after injection [10]. It was therefore decided to observe the effects of sodium valproate 15 as well as 60 min after injection. Separate groups were used for the different intervals between injection and observation. GAG was administered 3 hr before behavioral observation.

Behavioral Observations

Sexual behavior. Mating tests were performed between the 5th and the 8th hr of the dark period under dim white light. The male was introduced in the observation cage (40×60×30 cm) where a receptive female had already been placed. The following parameters of sexual behavior were recorded:

Mount latency. Time from introduction of the male until the first mount with pelvic thrusting.

Intromission latency. Time from introduction of the male until the first mount with vaginal penetration.

Ejaculation latency. Time from the first vaginal penetration until ejaculation.

Postejaculatory interval. Time from ejaculation until the next intromission.

TABLE 1

MOTOR EXECUTION IN MALE RATS TREATED WITH THE GABA TRANSAMINASE INHIBITORS SODIUM VALPROATE OR GAG

Drug Treatment	Number of falls/3 min (mean ± SE)
Sodium valproate 15 min before observation	
Vehicle	4.9 ± 2.19
100 mg/kg	4.8 ± 2.75
Vehicle	6.4 ± 2.35
200 mg/kg	12.0 ± 3.07†
Vehicle	2.8 ± 1.04
400 mg/kg	14.0 ± 4.13†
Sodium valproate 60 min before observation	
Vehicle	4.5 ± 2.22
100 mg/kg	5.8 ± 2.50
Vehicle	4.6 ± 1.75
200 mg/kg	7.5 ± 3.52
Vehicle	2.5 ± 1.14
400 mg/kg	15.2 ± 4.23†
GAG	
Vehicle	2.7 ± 2.01
12.5 mg/kg	3.0 ± 2.37
Vehicle	5.6 ± 2.28
25 mg/kg	6.0 ± 2.22
Vehicle	4.8 ± 1.85
50 mg/kg	6.0 ± 2.22
Vehicle	4.3 ± 1.32
100 mg/kg	9.7 ± 1.61*

*Different from vehicle ($p<0.05$); †Different from vehicle ($p<0.01$).

Ten animals were used at each dose level.

Number of mounts. With pelvic thrusting.

Number of intromissions. (Including the intromission associated with ejaculation.)

In addition, two derived measures of the intensity of sexual behavior were calculated:

Intromission frequency. Number of intromissions divided by the time from the first intromission until ejaculation, or if no ejaculation occurred, until the end of the test.

This measure has previously been called "the neuromotor activity coefficient" [15], and is supposed to represent the motor aspects of sexual behavior.

Finally, an overall measure of the intensity of sexual behavior was calculated in the following way: The inverse of the mount, intromission and ejaculation latencies were multiplied by 15 and then transformed into natural logarithms (the shorter the latency the larger the value thus obtained); the number of mounts and intromissions were transformed into square roots; the presence of ejaculation was assigned a value of 4 and the absence of ejaculation a value of 0. The sum of the transformed numbers constitutes the Sexual Activity Index (SAI).

The mating tests were terminated at the first intromission after ejaculation, or if no ejaculation occurred, 15 min after the introduction of the male in the observation cage.

Locomotor Activity

The animal was placed in a circular arena (diameter 60 cm) surrounded by a 37.5 cm high wall. Six photocells covered by infrared filters were located around the wall, 2.5 cm above the grid floor. Locomotor activity was quantified as the number of beam interruptions during 10 min. To activate the counters, a beam interruption of at least 200 msec was required. This means that rapid movements such as grooming or tail flicks were not registered. The activity count thus mainly reflected ambulatory activity.

Before drug treatments, the animals were habituated to the activity cages during three 10 min sessions separated by 48 hr. All tests were performed between the 5th and the 8th hr of the dark period.

Motor Execution

A kind of treadmill or "rotarod" apparatus was used. In the experiments, the animals were placed on a cylinder (diameter 16 cm) rotating with a speed of 11 rpm. Whenever the animal fell down, it was replaced on the cylinder approximately 5 sec after that it had lost contact with the cylinder surface. The number of falls during 3 min was counted, and provided the measure of motor execution.

Before the experiments, the animals were trained to walk on the cylinder during a 15 min session. During the first 5 min, the cylinder rotated at 5 rpm, the next five minutes at 8 rpm, and during the last five minutes at 11 rpm, which is the speed used in experiments. If an animal fell down, it was immediately replaced on the cylinder. Further training did not improve performance.

Experimental Design

In all experiments, each animal served as its own control. For a given dose of a given drug, half the animals were injected with vehicle and the other half with drug on the first test, and 7 days later the treatment was reversed. Separate groups were used for the different doses and drugs, i.e., no animal received more than one drug treatment.

Statistical Analysis

Data from the experiments on sexual behavior were evaluated with the following tests: McNemar's test for the significance of changes or the binomial test where appropriate, for mount, intromission and ejaculation percentage; the Wilcoxon matched-pairs signed-ranks test for the number of mounts and intromissions; the Mann-Whitney U-test for the latencies and the intromission frequency (these parameters were usually registered from different number of animals in control and experimental treatments); the *t*-test for correlated samples for the SAI.

Activity data were evaluated with the *t*-test for correlated samples, and data from experiments on motor execution with the Wilcoxon matched-pairs signed-ranks test. All probabilities given are two-tailed.

RESULTS

Motor Execution

Data are summarized in Table 1. Sodium valproate, administered 15 min before test, produced an impairment of motor execution in doses of 200 and 400 mg/kg. When administered 60 min before test, this drug impaired performance only at the highest dose, 400 mg/kg. GAG, up to a dose of 50 mg/kg had no effect, whereas a dose of 100 mg/kg produced moderate motor deficiencies.

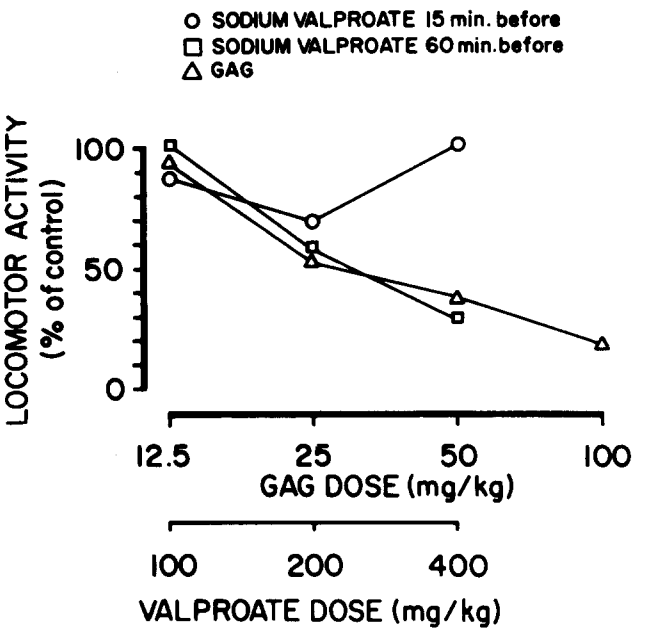

FIG. 1. Locomotor activity in animals treated with varying doses of GAG or sodium valproate. Control activity counts varied between 146.1 and 109.3 for experiments with GAG, between 164.6 and 121.3 for sodium valproate administered 15 min before observation, and between 162.6 and 138.7 for sodium valproate administered 60 min before observation. 10 rats per dose for animals treated with GAG or sodium valproate 60 min before observation, and 30 rats per dose for animals treated with sodium valproate 15 min before observation.

Locomotor Activity

As shown in Fig. 1, sodium valproate administered 15 min before observation, produced a peculiar dose-effect relation, with a clear reduction in locomotor activity at a dose of 200 mg/kg, and no effect at 100 or 400 mg/kg. This experiment was repeated twice, with similar results. The data shown represent the pooled data from all replications. When this drug was administered 60 min before observation, a dose-dependent reduction in locomotor activity was obtained, with the minimal effective dose being 200 mg/kg.

GAG also produced a dose dependent inhibition of locomotion, the lowest dose with a significant effect being 25 mg/kg.

Sexual Behavior

Sodium valproate, administered 15 min before observation, reduced the number of intromissions at all three dose levels (100, 200 and 400 mg/kg). At 200 mg/kg, the ejaculation percentage as well as the intromission frequency were also reduced. The reduction in intromission frequency may have been due to motor disturbances and not to a reduction in the intensity of sexual behavior. The mount/intromission ratio was 0.83 ± 0.33 (mean $\pm$ SE) for vehicle treated animals against 2.65 ± 0.54 for animals treated with sodium valproate,

TABLE 2

SEXUAL BEHAVIOR IN MALE RATS TREATED WITH SODIUM VALPROATE 15 MIN BEFORE OBSERVATION

Behavior Parameter	Vehicle	100 mg/kg	Vehicle	200 mg/kg	Vehicle	400 mg/kg
Mount percentage	94	88	94	71	69	8*
No. of mounts[a]	5.5 ± 0.84	8.2 ± 1.45	4.4 ± 0.91	8.2 ± 2.06	7.7 ± 1.95	0.6 ± 0.60*
Mount latency[a,b]	1.1 ± 0.39	1.4 ± 0.51	1.2 ± 0.35	1.8 ± 0.79	1.5 ± 0.40	1.11
Intromission percentage	94	81	88	59	62	8*
No. of intromissions[a]	8.9 ± 0.97	6.4 ± 0.90*	7.1 ± 0.98	3.4 ± 0.89*	4.5 ± 1.16	0.1 ± 0.08*
Intromission frequency[a,b]	1.6 ± 0.22	1.1 ± 0.13	1.0 ± 0.08	0.7 ± 0.15*	0.9 ± 0.07	0.07
Intromission latency[a,b]	1.4 ± 0.46	1.7 ± 0.46	1.6 ± 0.64	2.6 ± 0.78	2.9 ± 0.51	1.1
Ejaculation percentage	75	63	77	24*	54	0*
Ejaculation latency[a,b]	6.0 ± 0.67	6.7 ± 0.56	7.7 ± 0.65	6.9 ± 1.16	7.9 ± 0.73	—
Postejaculatory interval[a,b]	5.5 ± 0.25	5.8 ± 0.20	6.2 ± 0.25	6.7 ± 0.42	6.6 ± 0.51	—
Sexual activity index[a]	16.8 ± 1.77	14.1 ± 1.94	15.4 ± 1.59	8.8 ± 2.00*	10.6 ± 2.31	0.7 ± 0.69*

*Different from vehicle ($p<0.05$).
[a]Mean ± SE, latencies in min.
[b]For rats displaying mounts, intromissions and ejaculation respectively.
N=14 to 17 at each dose.

TABLE 3

SEXUAL BEHAVIOR IN MALE RATS TREATED WITH SODIUM VALPROATE 60 MIN BEFORE OBSERVATION

Behavior Parameter	Vehicle	100 mg/kg	Vehicle	200 mg/kg	Vehicle	400 mg/kg
Mount percentage	100	100	93	86	94	13*
No. of mounts	5.3 ± 0.89	6.5 ± 1.43	9.3 ± 1.52	8.9 ± 2.34	5.3 ± 0.96	0.4 ± 0.33*
Mount latency[a,b]	0.8 ± 0.38	0.6 ± 0.15	0.7 ± 0.20	1.4 ± 0.53	1.9 ± 0.59	3.5 ± 3.23
Intromission percentage	100	100	71	71	75	0*
No. of intromissions[a]	10.8 ± 0.48	10.5 ± 0.83	5.3 ± 1.15	6.6 ± 1.24	6.4 ± 1.21	0*
Intromission frequency[a,b]	1.5 ± 0.18	1.5 ± 0.18	1.2 ± 0.24	1.2 ± 0.15	1.4 ± 0.23	—
Intromission latency[a,b]	0.9 ± 0.41	0.9 ± 0.26	2.4 ± 0.99	1.9 ± 0.77	2.6 ± 1.00	—
Ejaculation percentage	94	69	43	50	50	0*
Ejaculation latency[a,b]	7.5 ± 0.76	6.6 ± 0.84	6.5 ± 1.39	8.6 ± 1.17	5.4 ± 0.84	—
Postejaculatory interval[a,b]	6.1 ± 0.24	5.9 ± 0.42	5.8 ± 0.41	6.2 ± 0.71	5.1 ± 0.26	—
Sexual activity index[a]	19.6 ± 0.83	17.9 ± 1.31	13.3 ± 1.80	12.3 ± 2.11	12.8 ± 1.79	0.5 ± 0.38*

*Different from vehicle ($p<0.05$).
[a]Mean ± SE, latencies in min.
[b]For rats displaying mounts, intromission and ejaculation respectively.
N=14 to 16 at each dose.

200 mg/kg ($p<0.01$, the Wilcoxon test). This shows that the probability of achieving intromission upon mounting was much reduced. Moreover, the intromission frequency, as defined in the present studies, has been used as a measure of motor capacities [15].

The highest dose of sodium valproate, 400 mg/kg, produced an almost complete inhibition of sexual behavior. Gross observation of the animals suggested that this was due to the serious motor deficits provoked by the drug. The results are summarized in Table 2.

When sodium valproate was administered 60 min before observation, the doses of 100 and 200 mg/kg had no effects, whereas a dose of 400 mg/kg almost abolished sexual behavior. Again, this dose produced marked motor disturbances, similar to those described above. Data are summarized in Table 3.

GAG had no effects on sexual behavior in the doses of 12.5, 25 and 50 mg/kg. At the highest dose, 100 mg/kg, the inhibitory effects were far less pronounced than those observed after treatment with sodium valproate, 400 mg/kg. Mounting behavior was not significantly affected by the drug. Intromission percentage and intromission frequency were reduced, and also the ejaculation percentage. The inhibition of behaviors related to intromission may have been a consequence of motor disturbances, since the animals mounted normally, but only occasionally achieved intromission. The mount/intromission ratio was actually 0.61±0.17 for vehicle treated animals, and 2.88±0.49 for animals treated with GAG 100 mg/kg ($p<0.01$, the Wilcoxon test). The reduction in intromission frequency was probably the reason for the increase in the ejaculation latency, since the number of intromissions necessary to achieve ejaculation was similar in control and experimental treatments (8.1±0.83 after vehicle; 8.5±1.19 after GAG 100 mg/kg).

The postejaculatory interval was also increased by GAG 100 mg/kg. This increase was apparently due to the difficulty

TABLE 4

SEXUAL BEHAVIOR IN MALE RATS TREATED WITH GAG

BAehavior Parameter	Vehicle	12.5 mg/kg	Vehicle	25 mg/kg	Vehicle	50 mg/kg	Vehicle	100 mg/kg
Mount percentage	93	93	94	81	100	94	92	69
No. of mounts[a]	5.1±1.33	5.7±1.36	3.9±1.02	3.8±0.85	7.1±1.48	6.5±1.84	3.6±0.90	4.7±1.51
Mount latency[a,b]	0.9±0.26	0.5±0.16	1.3±0.62	1.1±0.26	1.5±0.61	1.6±0.87	0.8±0.18	2.0±0.75
Intromission percentage	93	93	88	81	100	81	92	69*
No. of intromissions[a]	8.2±1.26	8.0±0.89	8.5±1.39	7.6±1.27	8.2±0.70	5.9±1.13	7.5±0.98	4.0±1.18*
Intromission frequency[a,b]	1.4±0.18	1.3±0.18	1.4±0.19	1.4±0.21	1.2±0.12	1.0±0.19	1.7±0.13	0.6±0.12*
Intromission latency[a,b]	1.6±0.82	1.1±0.47	1.6±0.64	1.7±0.55	2.0±0.68	2.1±1.02	1.3±0.31	3.3±0.92
Ejaculation percentage	86	79	63	63	69	50	92	31*
Ejaculation latency[a,b]	7.7±1.07	5.8±0.31	6.9±1.22	6.5±1.11	6.9±0.89	5.6±0.28	5.1±0.52	9.2±1.29*
Postejaculatory interval[a,b]	7.1±0.85	5.5±0.13	5.8±0.31	6.1±0.36	6.9±1.12	6.6±0.50	5.0±0.29	9.1±1.02*
Sexual activity index[a]	16.7±1.78	17.4±1.90	15.0±1.78	14.0±1.95	16.6±1.46	13.4±1.88	17.8±1.58	8.4±2.02*

*Different from vehicle ($p<0.05$).
[a]Mean ± SE, latencies in min.
[b]For rats displaying mounts, intromissions and ejaculation respectively.
N=12 to 16 at each dose.

in intromission behavior displayed by the drug treated animals. It might be remembered that the postejaculatory interval was defined as the time between ejaculation and the next intromission. However, if the time between ejaculation and the next mount is calculated, GAG 100 mg/kg had no effect (4.81±0.27 min after vehicle; 5.13±0.41 min after drug). The data obtained with GAG are shown in Table 4.

Relationship Between Impairment of Motor Execution, Reduction in Locomotor Activity, and Inhibition of Sexual Behavior

The Pearson correlation was calculated between the mean impairment of motor execution produced by the different drugs and doses and the mean reduction in locomotor activity produced by these same drugs and doses. It turned out to be low and nonsignificant ($r=0.34, p=0.17$). The inhibition of sexual behavior, expressed as reductions in the SAI between control and experimental treatments was correlated with the reduction in locomotor activity. The correlation between the two variables does not reach statistical significance ($r=0.50$, $p=0.069$). On the contrary, when the inhibition of sexual behavior is correlated with the impairment of motor execution, a high and significant correlation is obtained ($r=0.92$, $p<0.001$).

DISCUSSION

The results obtained in the present experiments show that there is no clear relation between the effects of GABA-T inhibitors on locomotor activity and on sexual behavior, e.g., GAG 50 mg/kg and sodium valproate 400 mg/kg, administered 60 min before observation, had about the same effects on locomotor activity. However, GAG had no effects on sexual behavior at this dose, whereas sodium valproate provoked an almost total inhibition of sexual behavior. Moreover, the lack of a significant correlation between reduction of locomotor activity and inhibition of sexual behavior suggests that these two functions are affected independently of each other by the GABA-T inhibitors. Similar conclusions were presented in an earlier study, where several GABA agonists were employed [1].

On the other hand, it seems that the effects on sexual behavior are related to those on motor execution. A high correlation was obtained between impairment of motor execution and inhibition of sexual behavior. This close relation can be explained in two ways. First, the neural mechanisms controlling sexual behavior are similar to those controlling motor execution, at least with regard to their sensibility to increased GABA levels. Second, a normal sexual behavior requires the capability of normal motor execution. Whenever motor execution is impaired, sexual behavior will thus also be impaired. The first possibility could be ruled out only by further pharmacological and behavioral studies. To date, however, it has not been possible to find a single drug, among GABA agonists and antagonists, benzodiazepines, barbiturates and dopamine antagonists, that affects motor execution without affecting sexual behavior (Agmo and Fernández, unpublished observations). It therefore seems more reasonable to suppose that the second possibility is correct. Since the GABA-T inhibitors affected sexual behavior only in doses where motor execution was much impaired, it might be concluded that these drugs do not have any direct effects on sexual behavior.

If the above arguments are correct, there is no reason to supose that GABAergic mechanisms exert a tonic inhibition of sexual behavior, nor that such mechanisms are activated during the course of sexual activity. If they were, some aspects of sexual behavior should have been modified by the GABA-T inhibitors independently from their effects on motor execution, since these drugs would become effective whenever the appropriate neurons begin to release GABA. However, GABA receptor agonists do inhibit sexual behavior at doses that do not affect motor execution, at least in animals with low sexual activity [1]. This inhibition was found to be precopulatory, that is the GABA agonists reduced the probability that sexual behavior would be initiated, but had no effects on that behavior in those animals which did copulate. It is possible that GABAergic neurons are activated only when the copulatory behavior has to be temporally inhibited by factors independent of that behavior itself.

Although our data support the above hypothesis, there

are observations suggesting that GABAergic mechanisms indeed are activated during sexual activity. Infusions of bicuculline or picrotoxin into the medial preoptic area shorten drastically the postejaculatory interval as well as the inter-intromission interval [4,6]. In another study, it was found that GABA agonists, including the GABA-T inhibitor ethanolamine-O-sulphate produced a strong inhibition of most aspects of sexual behavior [5]. If GABA is involved in inhibitory processes activated during copulatory behavior, as the authors suggest, these inhibitory processes should have been reinforced, but other aspects of the sexual behavior should not have been affected, as actually occurred.

Another interesting observation in the present studies is that locomotor activity and motor execution show at least a partial independence. Several doses of GAG and sodium valproate (administered 60 min before observation) reduced locomotor activity without having any effects on motor execution, whereas the opposite was true for sodium valproate 400 mg/kg, administered 15 min before observation. Actually, no significant correlation was found between effects on locomotor activity and motor execution. This could indicate that locomotor activity and motor execution are controlled by different neuronal systems. Indeed, there is much evidence supporting this possibility. The locomotor-stimulating effects of dopaminergic drugs are thought to be localized to the nucleus accumbens, while the stereotypies produced by such drugs depend on actions in the striatum [2,7]. It has also been shown that GABAergic drugs interact in a complex way with the dopaminergic system [13] and that GABA agonists, injected directly into the brain, may stimulate or reduce locomotor activity depending on the site of injection [14]. Thus, the effects of systemic administration of GABAergic drugs will be the result of multiple actions at multiple sites. These complexities could also explain the different effects of sodium valproate depending on the time between injection and observation. In several brain regions this drug produced a maximum elevation of GABA within 5 to 15 min after injection [10]. The return to control levels is variable between regions. The overall effect of sodium valproate must thus depend on the relative effects in different regions at different times.

The present experiments have made it possible to formulate a reasonable hypothesis as to the role of GABA (or lack of a role) in the control of sexual behavior. This hypothesis is presently being investigated.

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REFERENCES

1. Agmo, A. and R. Paredes. GABAergic drugs and sexual behavior in the male rat. *Eur J Pharmacol* **112:** 371–378, 1985.
2. Carey, R. J. Differential effects of limbic versus striatal dopamine loss on motoric function. *Behav Brain Res* **7:** 283–296, 1983.
3. Damassa, D. A., E. R. Smith, B. Tennent and J. M. Davidson. The relationship between circulating testosterone levels and male sexual behavior in rats. *Horm Behav* **8:** 275–286, 1977.
4. Fernández-Guasti, A., K. Larsson and C. Beyer. Comparison of the effects of different isomers of bicuculline infused in the preoptic area on male rat sexual behavior. *Experientia* **41:** 1414–1416, 1985.
5. Fernández-Guasti, A., K. Larsson and C. Beyer. GABAergic control of masculine sexual behavior. *Pharmacol Biochem Behav* **24:** 1065–1070, 1986.
6. Fernández-Guasti, A., K. Larsson and J. Vega-Sanabria. Depression of postejaculatory ultrasonic vocalization by (+)-bicuculline. *Behav Brain Res* **19:** 35–39, 1986.
7. Johnels, B. Locomotor hypokinesia in the reserpine-treated rat: Drug effects from the corpus striatum and nucleus accumbens. *Pharmacol Biochem Behav* **17:** 283–289, 1982.
8. Jung, M. J., B. Lippert, B. W. Metcalf, P. J. Schechter, P. Böhler and A. Sjoerdsma. The effect of 4-amino hex-5-ynoic acid (γ-acetylenic GABA, γ-ethynyl GABA) a catalytic inhibitor of GABA transaminase, on brain GABA metabolism in vivo. *J Neurochem* **28:** 717–723, 1977.
9. Löscher, W. Valproate induced changes in GABA metabolism at the subcellular level. *Biochem Pharmacol* **30:** 1364–1366, 1981.
10. Löscher, W. and M. Vetter. Relationship between drug-induced increases of GABA levels in discrete brain areas and different pharmacological effects in rats. *Biochem Pharmacol* **33:** 1907–1914, 1984.
11. Löscher, W. and M. Vetter. Drug-induced changes in GABA content of nerve endings in 11 rat brain regions. Correlations to pharmacological effects. *Neurosci Lett* **47:** 325–331, 1984.
12. Phillips, N. J. and L. J. Fowler. The effects of sodium valproate on gamma-aminobutyrate metabolism and behavior in naive and ethanolamine-O-sulphate pretreated rats and mice. *Biochem Pharmacol* **31:** 2257–2261, 1982.
13. Scheel-Krüger, J., J. Arnt, G. Magelund, M. Olianas, B. Przewlocka and A. V. Christensen. Behavioral functions of GABA in basal ganglia and limbic system. *Brain Res Bull* **5:** Suppl 2, 261–267, 1980.
14. Scheel-Krüger, J., G. Magelund and M. C. Olianas. Role of GABA in the striatal output system: Globus pallidus, nucleus entopeduncularis, substantia nigra and nucleus subthalamicus. *Adv Biochem Psychopharmacol* **30:** 165–186, 1981.
15. Soulairac, M. L. Etude éxperimentale des régulations hormono-nerveuses du comportement sexuel du rat mâle. Paris: Masson, 1963.