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ORIGINAL INVESTIGATION

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GABAergic drugs and sexual motivation, receptivity and exploratory behaviors in the female rat

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Abstract Female rats were allowed to pace sexual interactions in a bilevel chamber, where a sexually vigorous male was tethered to the bottom level. Exploratory behaviors (sniffing, rearing), locomotor activity (expressed as number of level changes and periods of inactivity) as well as items of sexual motivation (latency to descend to the male's level, approaches towards the male and genital exploration) were recorded. In addition, sexual receptivity was evaluated in a non-paced situation. A test for motor impairment was also performed. The GABA transaminase inhibitor γ-acetylene GABA reduced exploratory behaviors at doses much lower than those needed to reduce receptivity. The GABA reuptake inhibitor SKF 100330A did not affect any behavior category at doses of 15 and 30 mg/kg, but had a sedative action at 60 mg/kg. This was shown as impaired motor coordination and an almost total absence of activity in the bilevel chamber. Receptivity was not impaired, however. The mixed $GABA_A$/$GABA_B$ agonist progabide reduced exploratory behaviors and receptivity without producing motor impairment at a dose of 400 mg/kg. The $GABA_A$ agonist THIP impaired motor coordination and reduced receptivity and exploratory behaviors at a dose of 10 mg/kg. A larger dose, 20 mg/kg, had a strong sedative action. Only a small proportion of the animals descended to the males level. The $GABA_B$ agonist baclofen reduced receptivity at a dose that had no effect on motor coordination or exploratory behaviors. None of the drugs had a specific effect on sexual motivation. Whenever behaviors reflecting motivation were reduced, there were also other behavioral effects indicative of sedation. These data show that GABA receptor agonists, particularly the $GABA_B$ agonist baclofen, reduce sexual receptivity at doses that have only slight effect on motor functions or exploratory behaviors. In contrast, non-specific enhancement of GABAergic activity by a transaminase or reuptake inhibitor have effects on motor functions and exploratory behaviors at doses much lower than those needed to reduce receptivity.

Key words GABA · Lordosis · Receptivity · Sexual motivation · Antiepileptic drugs

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Introduction

Sexual dysfunction is common in women with epilepsy (Geschwind 1983). Estimations of the frequency of this problem in epileptic patients vary between studies and countries from 14% to more than 70% (Gastaut and Colomb 1954; Blumer and Walker 1967; Demerdash et al. 1991). A study of vaginal blood flow in response to erotic stimuli showed a significantly lower increase in epileptic women than in healthy controls. However, sexual arousal, as evaluated by a questionnaire, was not different in healthy and epileptic subjects (Morrell et al. 1994). The authors concluded that there was no reduction in libido. Endocrine abnormalities do not appear to be the cause of reduced physiological responsiveness to erotic stimuli in epileptic women, since sexual hormone concentrations are within the normal range (Bäckstrom and Jorpes 1979). The role of antiepileptic drugs as an iatrogenic factor for sexual dysfunction is not known (Morrell 1991; Bergen et al. 1992). However, several drugs used for the treatment of epilepsy, e.g. vigabatrin, sodium valproate, progabide and benzodiazepines, have actions on the GABAergic system, and such an action could contribute to sexual dysfunction. In fact, animal studies have shown that several GABAergic agents have inhibitory actions on

female sexual behavior (reviewed in Paredes and Ågmo 1992).

Female, as well as male, sexual behavior can be separated into arousal (libido, motivation) and performance (potency, execution of sexual reflexes) categories (Davidson 1980; Clark 1993). These categories apply to at least most mammalian species. In the human female, genital arousal (potency) is separable from psychological arousal (libido, motivation) (Rogers et al. 1985; Laan et al. 1995). A similar separation exists also in female rats (Pfeifle and Edwards 1983; Clark 1993). In that species, sexual activities are divided in proceptivity (behaviors designed to establish sexual contact with a male) and receptivity (reflexive activity during copulation) (Beach 1976). This division can be considered equivalent to the libido-potency distinction in humans. Animal studies of drug effects on proceptivity-motivation versus receptivity-potency may then give useful information as to possible effects of similar drugs in women.

GABAergic agents have been shown to modify receptivity in a complex way in rats and hamsters. The $GABA_A$ receptor antagonist bicuculline inhibits and the agonist muscimol facilitates receptivity after infusion into the ventromedial hypothalamus, midbrain central gray or the ventral tegmental area (McCarthy et al. 1990, 1991; Frye and de Bold 1992; Frye et al. 1993). In the preoptic area, GABA has inhibitory effects on receptivity (McCarthy et al. 1990). However, administration of an antisense oligonucleotide to the GABA synthesizing enzyme GAD into the preoptic area was ineffective (McCarthy et al. 1994). Systemic or intracerebroventricular administration of GABAergic drugs consistently inhibits receptivity. The $GABA_B$ agonist baclofen, the GABA transaminase inhibitors γ-vinyl GABA and γ-acetylene GABA (GAG), as well as $GABA_A$ receptor agonists, reduce receptivity in a dose-dependent way (Qureshi et al. 1988; Ågmo et al. 1989; Luine et al. 1991). Because most GABAergic agents have sedative or muscle relaxant actions (e.g. Ågmo and Paredes 1985; Ågmo et al. 1987, 1991), such effects may be totally or partially responsible for impaired receptivity. It must be noted that the inhibitory effects have been obtained with large doses, a fact that supports the notion that behaviorally non-specific effects are important. Moreover, there has been no systematic study of the effects of GABAergic agents on other aspects of sexual behavior, notably motivation.

In the following experiments, effects of GABAergic drugs on sexual motivation were distinguished from effects on the execution of sexual reflexes (receptivity). Indicators of sexual motivation as well as of exploratory behaviors were registered in a bilevel chamber where the male was tethered to one level. Then, receptivity was determined. Lastly, a test of motor coordination was performed. The drugs used were the $GABA_A$ agonist THIP, the $GABA_B$ agonist baclofen, the mixed $GABA_A$/$GABA_B$ agonist progabide, the GABA transaminase inhibitor γ-acetylene GABA (GAG) and the reuptake blocker SKF 100330A. In that way, GABAergic neurotransmission was stimulated by drugs having an indirect facilitatory action as well as by receptor agonists. If the doses needed to affect sexual motivation and receptivity were smaller than those needed to reduce exploratory behaviors and motor coordination, then it could be concluded that drug actions on sexual behavior are not a consequence of a general sedative effect. Furthermore, if doses effective on sex behavior were larger than those reported to be necessary for anticonvulsive activity, then it could be proposed that actions on GABAergic systems might be of slight importance for sexual dysfunction associated with the pharmacological treatment of epilepsy. No effort to determine anticonvulsive doses of the GABAergic drugs was made in the following study. This has been the subject of a large number of experiments (reviewed in Rastogi and Ticku 1986; Zorn et al. 1986; Krogsggard-Larsen et al. 1987) and the doses reported as effective are similar over different studies.

Materials and methods

Subjects

Female Wistar rats (250–300 g) were obtained from the animal facilities at the Faculty of Medicine, National Autonomous University of Mexico. They were housed in pairs in Makrolon cages and had free access to water and commercial rat pellets. The animal quarters were maintained under a reversed light/dark cycle (12/12 h, lights off 0900 hours) at constant room temperature (approximately 22°C) and humidity was not controlled. Ovariectomy was performed under methohexital (Brietal, Lilly, Indianapolis, Ind., USA) anesthesia (40 mg/kg) 2 weeks before the beginning of experiments.

Males (Wistar, 300–400 g) used as copulation partners were drawn from a stock of sexually experienced rats maintained in the same room as the females. Immediately before employing any male as stud, it was exposed to a non-experimental receptive female. Only males that vigorously mounted were selected for experimental use. Two or three intromissions were allowed in this screening test.

The work reported herein was performed according with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health of the United States of America, and in agreement with applicable local laws.

Drugs

R,*S*,-Baclofen HC1 [β-(*p*-chlorophenyl)-GABA, Ciba-Geigy, Basel, Switzerland], THIP HC1 [4,5,6,7-tetrahydroisoxazolo (5,4-c) pyridine-3-ol; Research Biochemicals, Natick, Mass. USA], GAG (γ-acetylene GABA; Merrell International, Strasbourg, France) and SKF 100330A {(*n*-[4,4-diphenyl3-butenyl])-guvacine HCl; Nova, Baltimore, Md., USA} were dissolved in physiological saline and injected intraperitoneally (IP) in a volume of 1 ml/kg body weight. Progabide (4-{[4-chlorophenyl) (5-fluoro-2-hydroxyphenyl)-methylene]amino} butanamide; Synthélabo, Bagneux, France) was suspended in distilled water together with two drops of Tween 80 and sonicated for several minutes. Solutions were vigorously shaken

before the IP injection (5 ml/kg). The intervals between injection and behavioral observation were the following: baclofen and THIP, 30 min; progabide and SKF 100330A, 1 h; GAG, 3 h.

Design

Estradiol benzoate (Sigma, St Louis, Mo., USA), 10 μg/kg, was administered about 52 h before every experimental session, and progesterone (Aldrich, Milwaukee, Wisc., USA), 2 mg/rat, about 4 h before. Both steroids were dissolved in corn oil and injected SC on the flank of the female in a volume of 1 ml/kg or 0.2 ml/rat. Drugs were administered according to a Latin square design so that all subjects received all doses of a given drug. There were 2 weeks between each experimental session, which should have been sufficient to assure that no effect of the previous drug treatment was being carried over. Furthermore, this interval maintained the response to the steroid hormones at a stable level.

Procedure

Behaviors reflecting sexual motivation as well as exploratory behaviors were observed in a bilevel chamber similar to the one described by Mendelson and Gorzalka (1987). The female could freely move between levels while the male was tethered to the bottom level. It has been reported that the female avoids contact with the male for a period after every sexual interaction, and the duration of that period depends on the degree of sexual contact (Peirce and Nuttall 1961). Ejaculation produces the longest avoidance period. Since drug treatments modified receptivity, hence the probability that the male achieved intromission and ejaculation, behaviors indicative of motivation could be affected indirectly via drug effects on receptivity. To avoid this, sexual interaction was kept constant by closing the females vagina with masking tape. In this way, only mounts without intromission were possible.

At the beginning of the test, the female was placed on the upper level. The latency to descend to the lower level was recorded. If the female did not descend within 5 min, the test was ended. Otherwise, the test lasted 5 min from the time that the female arrived at the male's level. The duration and frequency of the following behaviors were recorded on a keyboard connected to an electronic device: sniffing (movement of the head or whiskers while the animal explores); rearing (standing on the hindlegs); resting (standing still or lying without any overt activity); selfgrooming (licking or biting any area of the fur, limbs or hindlegs); genital exploration (licking or sniffing the male's genitals). The time spent on the upper level as well as the number of level changes (locomotor activity) and approach and aggressive behaviors towards the male were also recorded. In addition, the presence or absence of lordosis was registered upon every mount with pelvic thrusting.

Immediately after the test for sexual motivation and exploratory behaviors, the female, now with an open vagina, was transferred to a rectangular observation cage ($40 \times 60 \times 40$ cm) where a different sexually vigorous male already had been placed. The male was allowed to make five mounts with pelvic thrusting, after which the test was ended. The presence or absence of lordosis was again registered. After the receptivity test, a test of motor coordination (rotarod) was made. The female was placed on top of a rotating cylinder (diameter 16 cm, speed 11 rpm) and whenever she fell down she was immediately replaced on the cylinder. The number of falls during a 3-min test was the measure of motor coordination. This procedure has been described in detail elsewhere (Ågmo et al. 1987).

Starting 1 week after ovariectomy the females were familiarized with the bilevel chamber at two sessions of 1 h each separated by 48 h. No male was present in the chamber. In addition, they were trained to walk on the rotating cylinder for 15 min. During the first 5 min the cylinder rotated at 5 rpm, during the next 5 min at 8 rpm, and during the last 5 min at 11 rpm. Any animal that fell down more than 5 times during the last 5 min was eliminated from the experiment.

All tests were performed between the 7th and 10th hours of the dark phase under dim white light.

Statistical analyses

Items of sexual motivation and exploratory behaviors were analyzed with one-factor MANOVAs for independent groups. Duration and frequencies of the behaviors were analyzed separately. Only data from those females that descended to the male's level were used. Not all subjects descended after all treatments making the use of a repeated measures analysis impossible. After significant MANOVA, univariate ANOVA was performed for each behavioral item. Significance levels were adjusted with the Bonferroni correction.

For the analysis of receptivity data, the lordosis quotient [(number of lordosis/5) $\times$ 100] was calculated. Treatments were compared with a one factor ANOVA. In case of significance, Tukey's HSD test was used for a posteriori comparisons. Motor impairment was evaluated with Friedman's two-way ANOVA followed by the Wilcoxon test in case of significance. Parametric tests could not be used, because the distribution of data was not normal and error variances non-homogeneous according to Hartley's F_{max} test. This was the case because most animals had a value of 0 after saline treatment.

Results

MANOVA statistics for all drug treatments are summarized in Table 1 and are not mentioned in the text. Receptivity in the test for sexual motivation and exploration was always similar to that observed in the formal receptivity test. However, the number of mounts

Table 1 Summary of MANOVA statistics for sociosexual and exploratory behavior data

Treatment effect	Pillai's *V*	*df*	*F*	*P*
GAG[a]				
Duration	0.805	12,40	2.247	0.028
Frequency	0.967	16,36	2.108	0.031
SKF 100330A[a]				
Duration	0.817	12,16	1.036	0.460
Frequency	1.010	16,14	0.893	0.591
Progabide				
Duration	1.528	12,30	2.594	0.017
Frequency	1.223	16,30	2.073	0.048
THIP[a,b]				
Duration	2.892	12,30	3.615	0.002
Frequency	3.890	16,26	3.161	0.004
Baclofen				
Duration	0.697	12,40	1.784	0.085
Frequency	0.913	16,36	1.891	0.056

[a]The largest dose was excluded from the analysis because it produced a singular within cells error matrix or because only one or two animals descended to the male's level. In the former case, univariate analyses comparing this dose with saline were performed whenever possible, using appropriate non-parametric tests

[b]Hotellings T^2 statistic was calculated instead of Pillai's *V* because only two doses were analyzed. Univariate tests were performed with the *t*-test (with the Bonferroni correction for protection of significance levels)

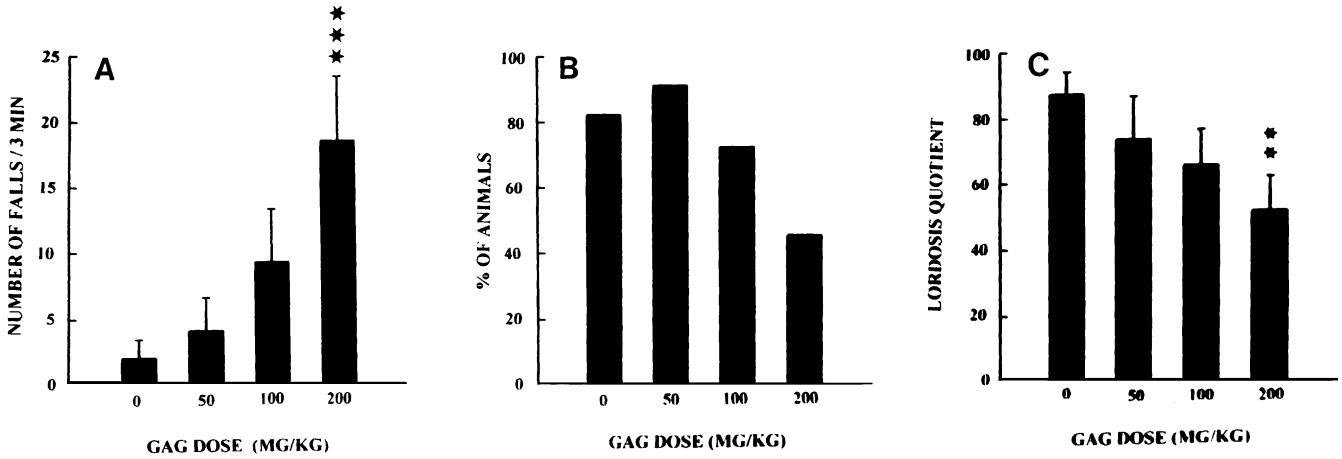

Fig. 1A–C Motor impairment (**A**), the proportion of subjects that descended to the male's level in the observation cage (**B**) and receptivity (**C**) in female rats treated with several doses of the GABA transaminase inhibitor GAG $n = 11$. Data are percentage or mean ± SEM. Different from saline, $^{**}P < 0.01$; $^{***}P < 0.001$

received by each female was variable. Therefore, lordosis quotients were not calculated, and receptivity data mentioned refer to the specific receptivity test. Female's exploration of the male's genitals had low frequency and duration in controls. This made it impossible to observe significant reductions of this behavior, although it seemed to be reduced by some drugs. In the animals treated with progabide, genital exploration was totally absent even in the controls. Interestingly, these animals received a particularly large number of mounts, perhaps making it unnecessary for the female to approach the male and explore his genitals. This behavior is not further discussed. The frequency of aggressive behaviors was low and is not reported.

The GABA transaminase inhibitor GAG had no effect on receptivity or on motor coordination in doses of 50 and 100 mg/kg (Fig. 1A, C). However both these doses much reduced exploratory behaviors and locomotor activity. In addition, approaches towards the male were reduced (Fig. 2). A dose of 200 mg/kg produced motor impairment and inhibited receptivity. Exploratory behaviors were almost eliminated, as was selfgrooming. The large increase in resting suggests that this dose had a strong sedative action.

Administration of the GABA reuptake inhibitor SKF 100330A had no significant behavioral effect at doses of 15 and 30 mg/kg (Figs 3 and 4). A dose of 60 mg/kg inhibited motor coordination in the rotarod test to a most significant degree (Fig. 3A). In the test for sexual motivation and exploratory behavior, only one female descended to the male's compartment (Fig. 3B). Therefore, data on the animals' behavior could not be statistically evaluated at this dose. Despite the pronounced motor effects, receptivity was not modified by the drug (Fig. 3C).

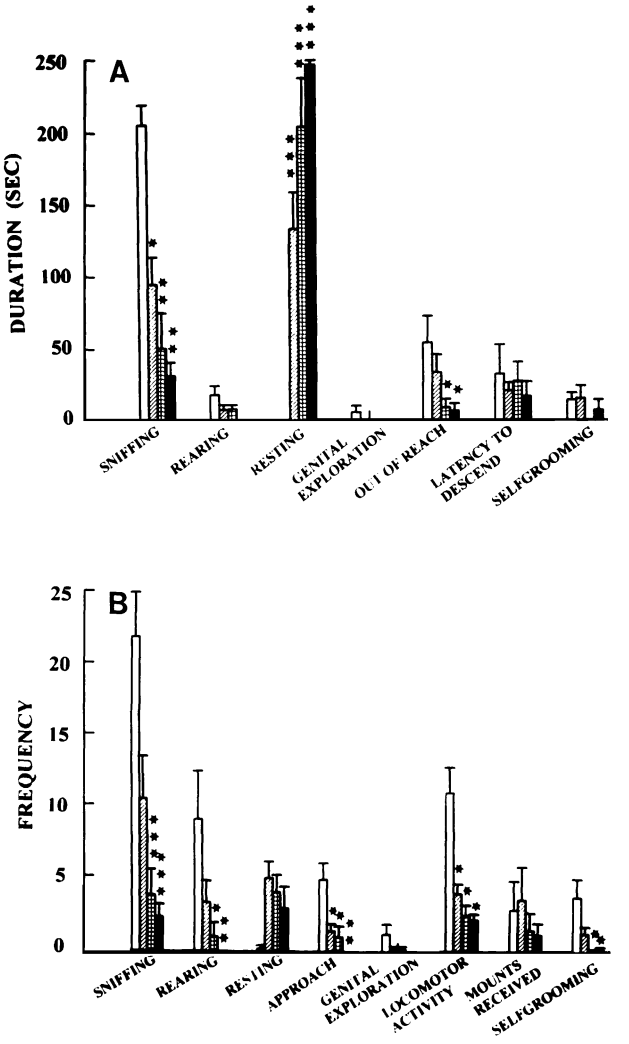

Fig. 2A, B Duration (**A**) and frequency (**B**) of items of sexual motivation and exploratory behaviors in female rats treated with several doses of GAG $n = 11$. *Open bars*, saline; *striped bars*, GAG, 50 mg/kg; *hatched bars*, GAG, 100 mg/kg; *black bars*, GAG, 200 mg/kg. Data are mean ± SEM. Different from saline, $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

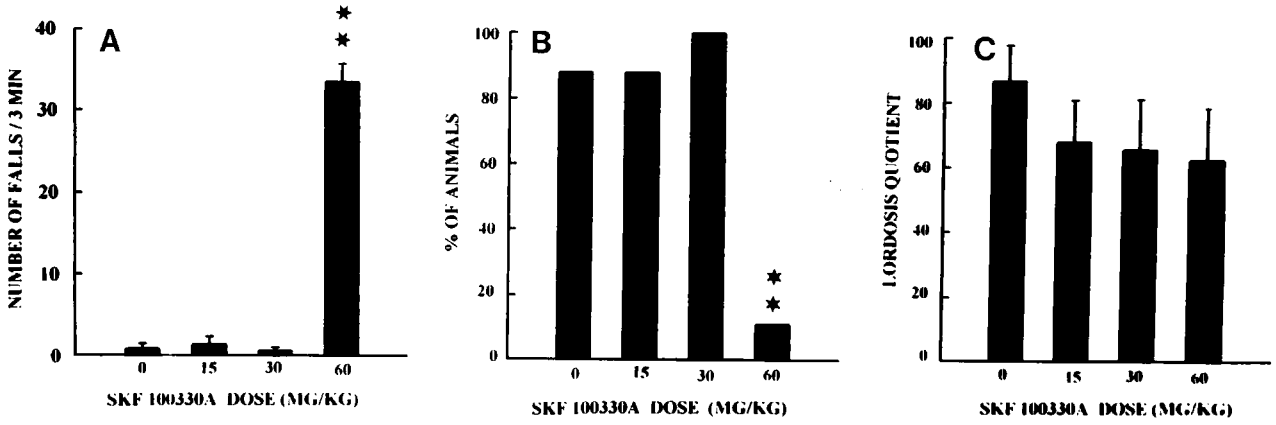

Fig. 3A–C Motor impairment (**A**), the proportion of subjects that descended to the male's level in the observation cage (**B**) and receptivity (**C**) in female rats treated with several doses of the GABA reuptake inhibitor SKF 100330A $n = 9$. Data are percentage or mean ± SEM. Different from saline, $^{**}P < 0.01$

The GABA receptor agonist progabide had no effect on motor coordination at any dose. The 400 mg/kg dose, however, appeared to impair performance (Fig. 5B), but the effect failed to reach statistical significance ($P = 0.16$). There was no effect on the proportion of subjects that descended to the male's level, but a dose of 400 mg/kg reduced receptivity (Fig. 5C). This dose had also a slight effect on exploratory behaviors, reducing the frequency of sniffing and locomotor activity. The frequency as well as the duration of resting were increased by this dose. Data are shown in Fig. 6.

The $GABA_A$ agonist THIP impaired motor coordination at doses of 10 and 20 mg/kg. The latter dose also reduced the proportion of animals that descended to the male's level (Fig. 7A, B). Only two animals did descend, making analysis of items of sexual motivation and exploratory behavior data for this dose impossible. Receptivity was reduced by 10 mg/kg, and it was almost eliminated after 20 mg/kg. The dose of 10 mg/kg increased the duration of resting (Fig. 8A) and reduced the number of mounts received (Fig. 8B). It may also be noted that the largest dose, 20 mg/kg, had a strong sedative action. The two animals that descended to the male's compartment spend most of the time immobile and were mounted only occasionally by the male. The subjects that did not descend were even more sedated.

The $GABA_B$ agonist baclofen impaired motor coordination at a dose of 5 mg/kg (Fig. 9A). The proportion of animals that descended into the male's compartment was not affected by the drug (Fig. 9B). A dose of 2.5 mg/kg reduced receptivity while 5 mg/kg almost completely suppressed it (Fig. 9C). As can be seen in Fig. 10, baclofen appeared to affect exploratory behaviors. However, the MANOVAs failed to reach significance (duration, $P = 0.085$; frequency,

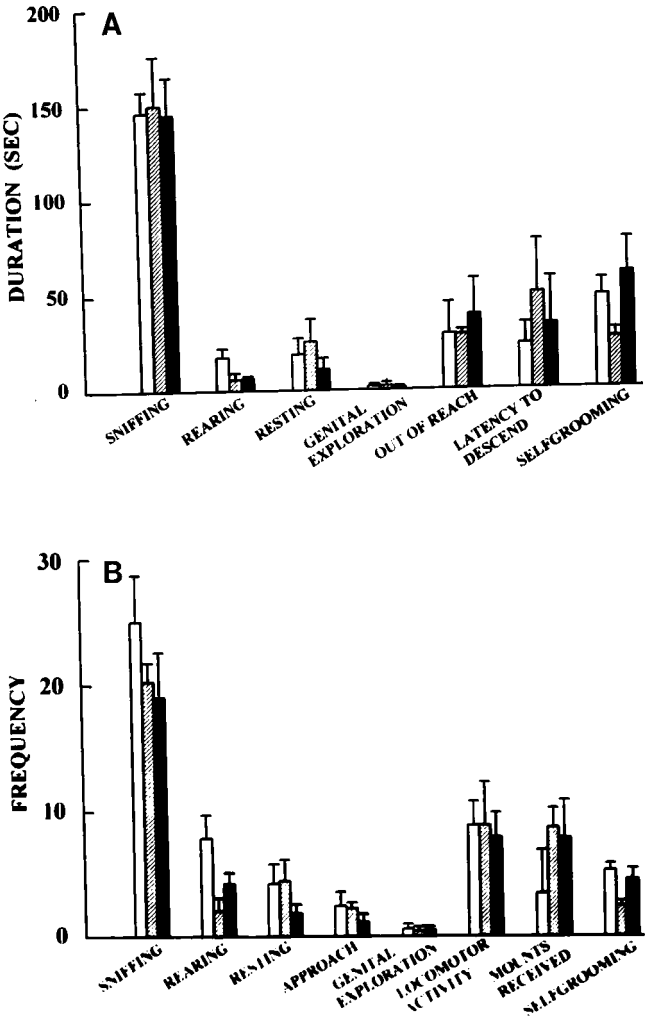

Fig. 4A, B Duration (**A**) and frequency (**B**) of items of sexual motivation and exploratory behaviors in female rats treated with several doses of SKF 100330A $n = 9$. *Open bars*, saline; *striped bars*, SKF 100330A, 15 mg/kg; *black bars*, SKF 100330A, 30 mg/kg. Data are mean ± SEM

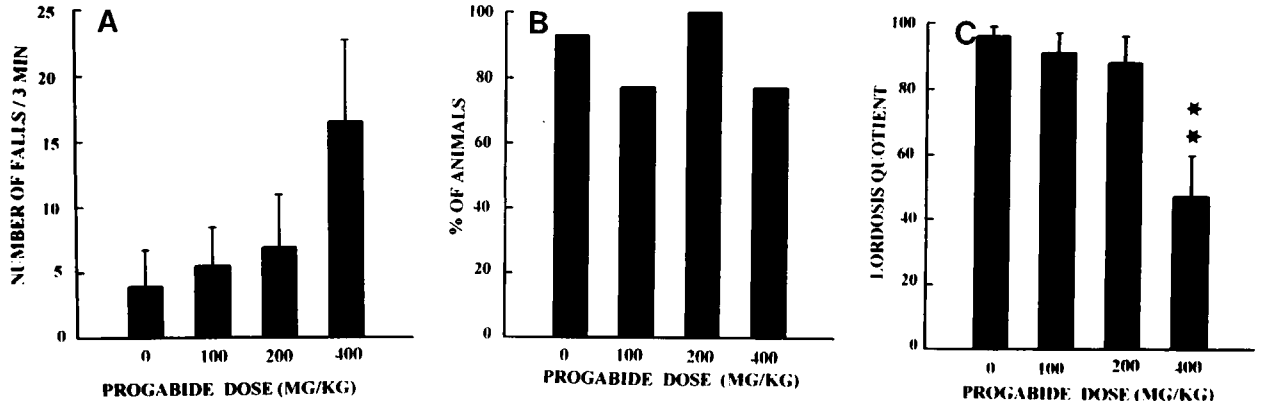

Fig. 5A–C Motor impairment (**A**), the proportion of subjects that descended to the male's level in the observation cage (**B**) and receptivity (**C**) in female rats treated with the mixed $GABA_A/GABA_B$ agonist progabide in doses of 100, 200 and 400 mg/kg $n = 15$. Data are percentage or mean ± SEM. Different from saline, $^{**}P < 0.01$

$P = 0.056$). Because of the borderline results, univariate ANOVAs were performed for heuristic reasons. The frequency of sniffing, approach, and selfgrooming was reduced after 5 mg/kg, and that of sniffing also after 2.5 mg/kg. The larger dose also reduced the duration of selfgrooming. However, since the MANOVAs were non-significant, these results indicate tendencies, at the best. Nevertheless, they might suggest that baclofen has some action on exploratory behavior in addition to its clear effects on motor coordination and receptivity.

Discussion

The bilevel observation chamber, with the male tethered to the lower level, allows the female to pace sexual interactions (Mendelson and Gorzalka 1987). This is not the case in the receptivity test, where the female has little possibility to control the male's approaches (Clark 1993). By using both these procedures, we distinguished drug effects on female sexual motivation, defined as the urgency to seek sexual contact with the male, from performance of sexual reflexes such as lordosis. The latency to descend to the male's level, the number of approaches to the male as well as the time spent on the upper level, out of reach of the male, may be considered as indicators of sexual motivation. It appears that none of the drugs affected sexual motivation, as defined here, in a systematic way. The largest doses of SKF 100330A and THIP almost eliminated any behavior, most likely because of their muscle relaxant or sedative actions, and cannot be considered to have any particular effect on sexual motivation. GAG reduced the time spent on the upper level, indicative of increased urge to be close to the male, but at the same time the number of approaches to the male was reduced. The absence of an effect on the latency to

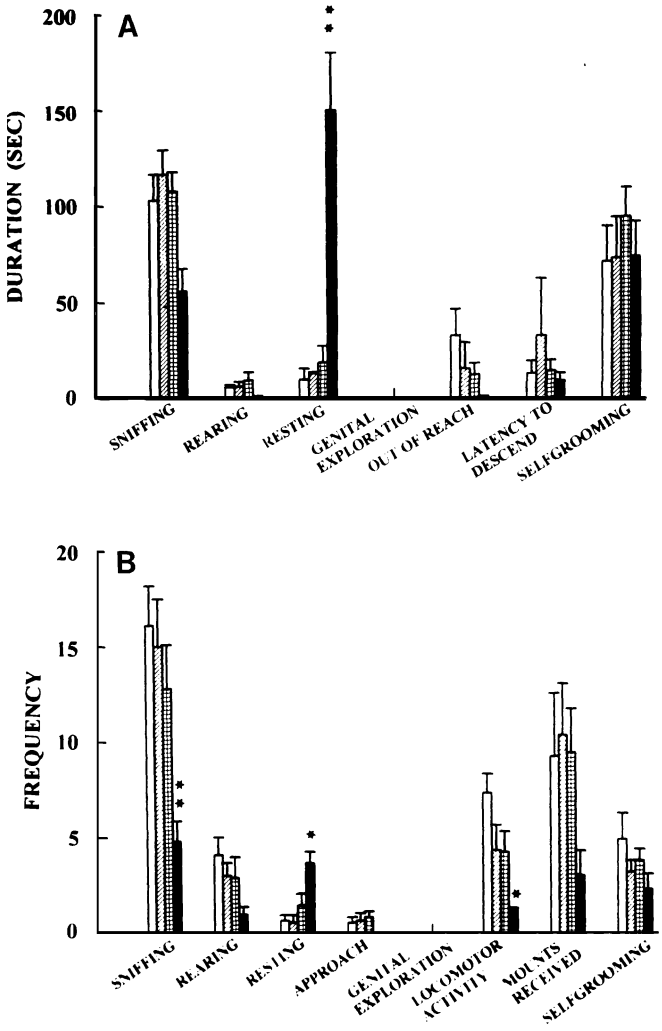

Fig. 6A, B Duration (**A**) and frequency (**B**) of items of sexual motivation and exploratory behaviors in female rats treated with several doses of progabide $n = 15$. *Open bars*, saline; *striped bars*, progabide, 100 mg/kg; *hatched bars*, progabide, 200 mg/kg; *black bars*, progabide, 400 mg/kg. Data are mean ± SEM. Different from saline, $^{*}P < 0.05$; $^{**}P < 0.01$

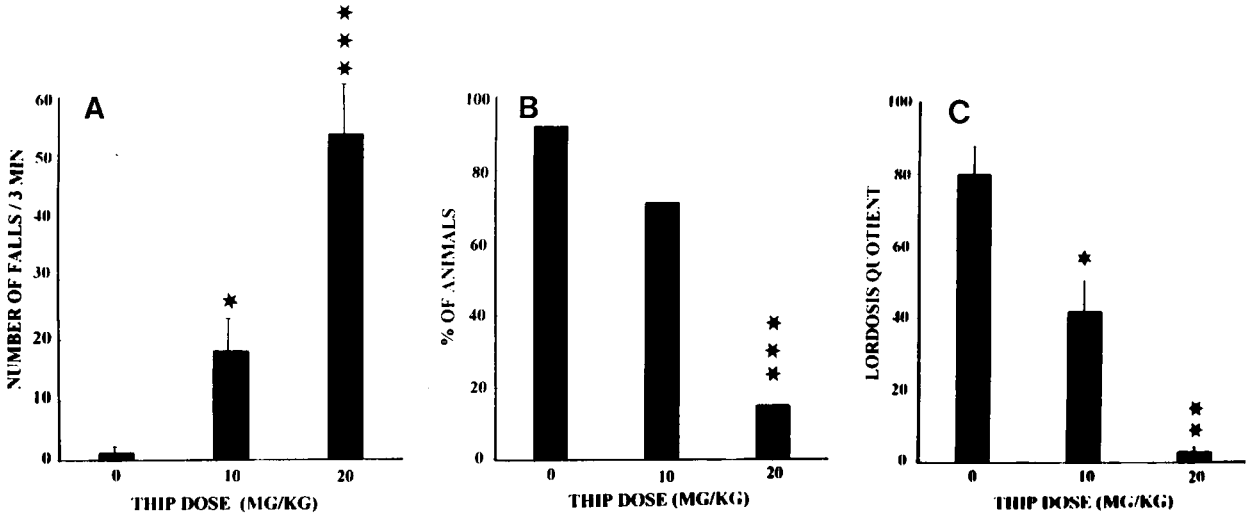

Fig. 7A–C Motor impairment (**A**), the proportion of subjects that descended to the male's level in the observation cage (**B**) and receptivity (**C**) in female rats treated with the $GABA_A$ agonist THIP, 10 or 20 mg/kg $n = 13$. Data are percentage or mean ± SEM. Different from saline, $*P < 0.05$; $**P < 0.01$; $P < 0.001$

descend to the male's level speaks against a motivational effect. It seems, then, that GABAergic drugs were unable to modify female sexual motivation at doses that did not have muscle relaxant or sedative actions.

Female behavior has many influences on the sexual behavior of the male. For example, females with reduced locomotor activity receive less mounts than active females do (Larsson 1973). In the present studies, several drugs altered locomotor activity. However, only THIP reduced the number of mounts performed by the male. This may be due to the fact that only males with extensive sexual experience were used as studs. In any case, it seems unlikely that the drug effects observed on female behavior is a consequence of modifications of male sex behavior, since mounting activity was not significantly altered by the majority of the drugs employed.

The dose of estradiol benzoate used in these studies is too low to produce much of proceptive behaviors like ear-wiggling, hopping or darting (Madlafousek and Hlinak 1978; Clark 1993). Therefore, drug effects on these behaviors could not be evaluated. However, these behaviors are activated by doses of estradiol larger than those needed to produce maximal effects on sexual motivation (Meyerson and Lindström 1973). It was considered important to use a submaximal dose of estradiol, although not all proceptive behaviors were obtained, because such doses are optimal for detecting drug effects on motivation and receptivity (Meyerson 1964).

GAG affected exploratory behaviors and locomotor activity at doses that did not reduce receptivity. A large dose, much reducing exploratory behaviors and producing motor impairment, reduced receptivity as well.

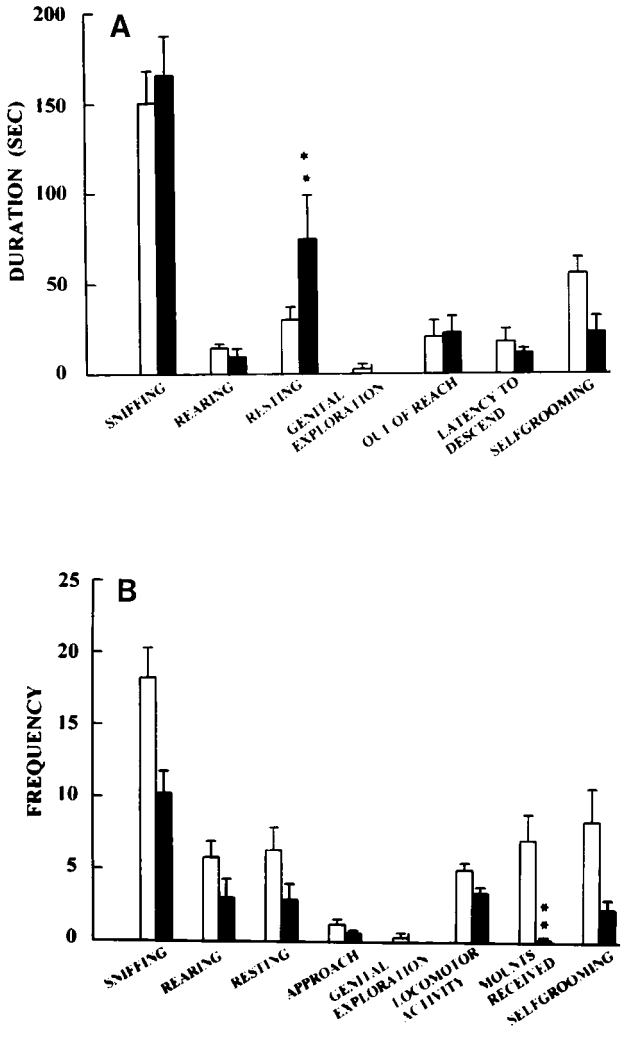

Fig. 8A, B Duration (**A**) and frequency (**B**) of items of sexual motivation and exploratory behaviors in female rats treated with saline or THIP $n = 13$. *Open bars*, saline; *black bars*, THIP, 10 mg/kg. Data are mean ± SEM. Different from saline, $**P < 0.01$

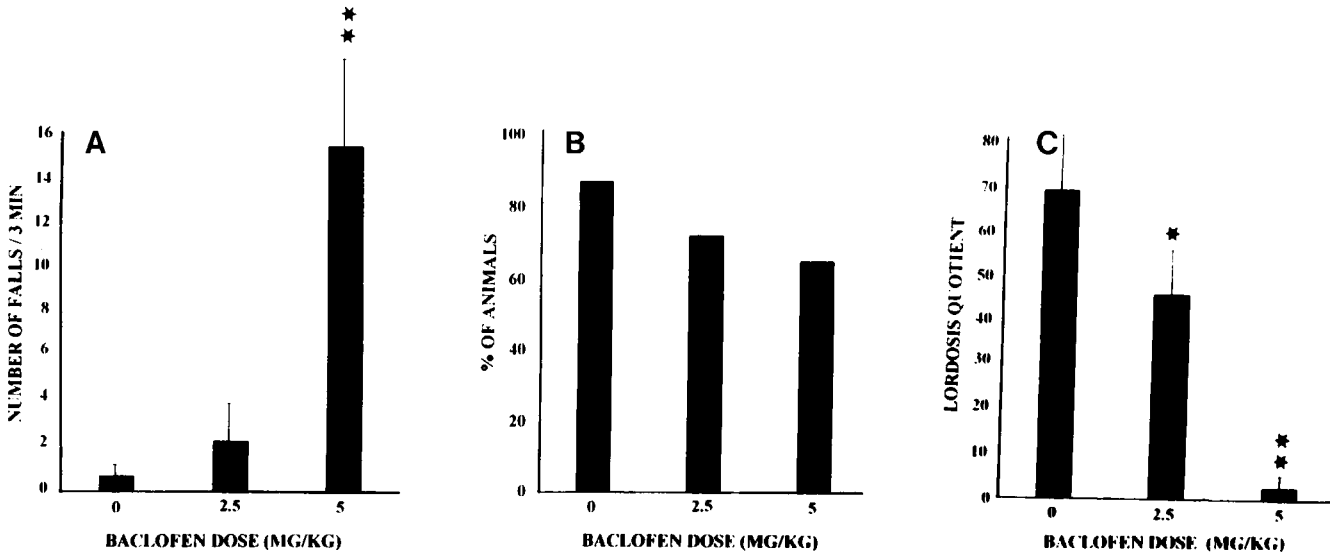

Fig. 9A–C Motor impairment (**A**), the proportion of subjects that descended to the male's level in the observation cage (**B**) and receptivity (**C**) in female rats treated with the $GABA_B$ agonist baclofen in doses of 2.5 and 5 mg/kg $n = 14$. Data are percentage or mean ± SEM. Different from saline, $^*P < 0.05$; $^{**}P < 0.01$

On the other hand, while the largest dose of SKF 100330A had strong sedative and muscle relaxant actions it did not affect receptivity. The differences in mechanism of action of these drugs could perhaps explain the inconsistencies in their effects on this behavior. The transaminase inhibitor GAG has been reported to enhance GABA concentrations in several brain areas but also that of other amino acid transmitters such as glutamate, glycine or aspartate (Löscher and Hörstermann 1994). GABA transaminase is an intracellular enzyme present in glial cells as well as in nerve terminals. Because of this and since synaptically released GABA is mainly inactivated by high affinity reuptake mechanisms (Fonnum 1987), it is uncertain whether GAG significantly facilitates transmission in GABAergic synapses or inhibits neuronal activity via overflow of GABA from the glia. In fact, GAG has been reported to have larger effects on GABA present outside than inside GABA nerve terminals (Andén et al. 1987). The reuptake inhibitor SKF 100330A may have a more specific effect. This drug has been shown to have pharmacological effects suggesting strong activation of GABAergic systems (Löscher 1985; Zorn et al. 1985) while having no or slight effect on other neurotransmitters (Yunger et al. 1984; Ali et al. 1985).

The mixed receptor agonist progabide and the $GABA_B$ receptor agonist baclofen were the only drugs that affected receptivity at doses that had no effect on motor coordination. Baclofen had no significant effect on exploratory behaviors although the drug showed a tendency to increase resting and decrease sniffing at the lowest dose that reduced receptivity. These effects were statistically significant after treatment with progabide.

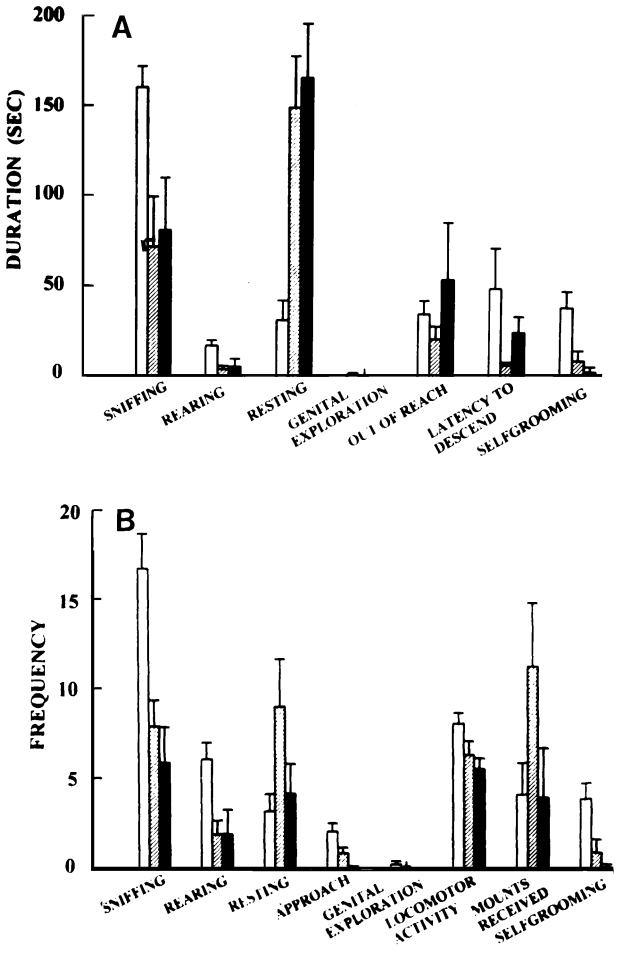

Fig. 10A,B Duration (**A**) and frequency (**B**) of items of sexual motivation and exploratory behaviors in female rats treated with two doses of baclofen. *Open bars*, saline; *hatched bars*, baclofen, 2.5 mg/kg; *black bars*, baclofen, 5 mg/kg $n = 14$. Data are mean ± SEM

However, it is unlikely that these minor effects on exploratory behaviors are the cause of reduced receptivity. The similarity between the actions of progabide and baclofen suggests that stimulation of the $GABA_B$ receptor is important for their inhibitory effects on sexual behavior. The results obtained with the $GABA_A$ agonist THIP supports this notion. First, THIP reduced receptivity only at a dose that affected motor coordination. Second, when the effects of THIP, 20 mg/kg, and baclofen, 5 mg/kg, are compared, it is found that both drugs have similar effects on receptivity. However, the sedative effects of THIP were most significant at this dose, while baclofen, although affecting motor coordination, neither reduced the proportion of females that descended to the male's level nor affected exploratory behaviors. This indicates that the sedative and/or muscle relaxant effects of THIP interfered with receptivity, whereas this was not the case for baclofen. Finally, a previous study with various $GABA_A$ agonists showed that systemic administration of this kind of drugs does not reliably affect receptivity and that the effect of THIP is not blocked by bicuculline (Ågmo et al. 1989). Taken together, these observations suggest that the $GABA_A$ receptor is of slight importance for the effects of systemically administered drugs on receptivity. In this context, it may be observed that other widely used drugs, the benzodiazepines, supposed to facilitate GABAergic transmission through an action at the $GABA_A$ receptor complex, appear to have a low incidence of sexual side effects (Woods et al. 1992). To our knowledge, the effects of benzodiazepines on female rat sexual behavior have not been systematically evaluated, but according to the present arguments their effect should be weak.

SKF 100330A show anticonvulsive activity in the rat at doses much lower than those needed to produce sedation. For example, the ED_{50} for protection against bicuculline-induced seizures is 6.4 mg/kg, for pentylentetrazol-induced seizures 1.8 mg/kg and for maximal electroshock seizures it is 11.4 mg/kg (Yunger et al. 1984). Similar doses are required for seizure protection in the epileptic gerbil (Löscher 1985). These data suggest that SKF 100330A offers seizure protection without any concomitant effect on sexual behavior, particularly since this drug failed to affect receptivity at any dose. Progabide has an ED_{50} for seizure protection that varies between 20 and 105 mg/kg depending on the procedure used (Worms et al. 1982). This is far below the dose, 400 mg/kg, that inhibited receptivity. GAG also offers seizure protection at doses somewhat below the one that inhibited receptivity in the present study (Palfreyman et al. 1981). THIP and baclofen are mostly void of anticonvulsive potency (reviewed in Paredes and Ågmo 1992). Baclofen may even have proconvulsive actions (Cottrell and Robertson 1987). However, these drugs were included in the present study in order to differentiate actions on $GABA_A$ and $GABA_B$ receptors. To conclude, it seems that GABAergic drugs are unlikely to have effects on sexual behavior when administered at anticonvulsive doses to rats. Whether this is the case for other antiepileptic drugs remains to be studied. These data suggest that at least the drugs studied have low potential for producing side effects on sexual behavior when used in the human clinic. This applies particularly to sexual motivation or arousal where no effect was found at non-sedative doses. Interestingly, epileptic women have, as mentioned in the Introduction, a reduced genital response to erotic stimuli (potency) while their arousability is not affected (Morrell et al. 1994). This coincides with present data, but it must be remembered that it is not known whether the cause of this reduced arousability is the antiepileptic drug treatment or the disease itself. Furthermore, whereas antiepileptic drugs are almost always taken chronically, acute effects were analyzed in this study. Until rat studies with chronic administration has been performed, present conclusions need to be regarded as tentative.

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