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Sexual Differentiation and the Effects of Alcohol on Aggressive Behavior in Mice

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LISCIOTTO, C. A., J. F. DEBOLD AND K. A. MICZEK. *Sexual differentiation and the effects of alcohol on aggressive behavior in mice*. PHARMACOL BIOCHEM BEHAV **35**(2) 357–362, 1990.—Male and female mice are differentially sensitive to the effects of alcohol on aggressive behavior. We investigated the role of testosterone during sexual differentiation in determining sex differences in alcohol effects on aggression. On the day of birth male mice were castrated or sham-operated. Neonatal female mice were injected with 250 μg of testosterone propionate (TP) or the oil vehicle. At approximately 75 days of age the mice which had not been gonadectomized at birth were gonadectomized. Control males and androgenized female mice then received 7.5 mm Silastic capsules containing testosterone, SC. Aggressive behavior toward an intruder was assessed following administration of ethanol (0.1–3.0 g/kg) or water, PO. Neonatally sham-gonadectomized male mice had a significant increase in aggressive behavior following administration of 1.0 g/kg alcohol, with no significant suppression of aggression at 3.0 g/kg. Neonatally androgenized female mice showed neither the male-typical response to adult testosterone and alcohol, nor did they show the female-typical response. Neonatally gonadectomized males showed an alcohol dose response curve that was similar to that of androgenized females. Postnatal testosterone did not appear to completely determine the male- and female-typical responses to alcohol on aggression. The critical period for this sexually dimorphic response to alcohol and testosterone may be primarily prenatal.

Alcohol Aggressive behavior Sexual differentiation Testosterone Mice

ALCOHOL has a similar pattern of effects on aggressive behavior in both castrated and gonadally intact male mice, suggesting that alterations in testosterone levels are not critical for the effects of alcohol on aggression (6). However, exogenous high levels of testosterone can alter the sensitivity to the effects of alcohol on aggressive behavior (6). Male mice maintained on high levels of testosterone produced by SC Silastic capsules show enhanced aggressive behavior in response to moderate doses (1.0–1.7 g/kg) of alcohol, and require a very high dose (5.6 g/kg) to suppress aggression (6).

The aggressive behavior of female mice is also altered by alcohol administration. However, females respond differently to alcohol than males (5). Ovariectomized female mice show a clear suppression of aggressive behavior when given 3.0 g/kg of alcohol, and do not show any enhancement in response to moderate doses. Even when maintained on high levels of testosterone, adult females do not show the male-typical enhanced aggressive behavior at moderate alcohol doses nor the reduced suppression at high doses. Likewise, males do not show a female-typical response to alcohol even in the absence of testosterone treatment (6).

Testosterone is important not only for mediating aggression in the adult animal, but also for determining the development of the potential for male-typical aggression during a critical period of sexual differentiation (9, 11, 17). The process of sexual differentiation begins during the fetal period and controls the development of anatomical and physiological sex differences. It also determines sex differences in sexual behavior and a wide range of nonreproductive behaviors in animals (2). Testosterone, secreted by the testes during sexual differentiation, induces the potential for male-typical responses in adulthood, a process referred to as masculinization. The absence of testosterone during this period results in adult female-typical behavior. This process occurs perinatally in mice. The sex differences in alcohol effects on aggression and testosterone's influence on alcohol's effects may be a function of sexual differentiation and the presence of testosterone during development. Females are not sensitive to the influence testosterone has on alcohol's effects on aggression. This may be because they are much less sensitive in general to androgens for the induction of male-typical aggressive behavior (16). Likewise males may not show female-typical changes in aggression in response to alcohol even in the absence of testosterone because their own androgens masculinized them during development. In order to evaluate the importance of sexual differentiation in the development of sexual dimorphisms in the effect of alcohol on aggression, the present study manipulated the hormonal milieu of neonatal male and female mice both in adulthood and as neonates.

METHOD

Subjects

Adult Swiss-Webster CFW mice (Charles River Breeding

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TABLE 1

SEQUENCE OF TREATMENTS

	Day of Birth	25 Days	75 Days	82 Days	96 Days	
Male pups	→ GDX →		→	→ pair with male	→	→ female intruder
			→ +7.5 mm T	→ pair with female	→	→ male intruder
	→ Sham GDX →	Wean + house by treatment	→ GDX + 7.5 mm T	→ pair with female	→ begin base-line tests	→ male intruder
			→ OVX + 7.5 mm T	→ pair with female	→	→ male intruder
Female pups	→ 250 μg TP →		→ OVX	→ pair with male	→	→ female intruder
	→ oil →		→ OVX	→ pair with male	→	→ female intruder

Gonadectomy (GDX), ovariectomy (OVX), testosterone (T), testosterone propionate (TP).

Laboratories, Wilmington, MA) were housed in polycarbonate cages (24 × 45 × 20 mm) with floors covered with pine shavings. The animals had continuous access to rodent chow and water. The animal colony temperature was maintained at 22 ± 1°C and humidity at 30–40%. The room lights were controlled by an automatic timer with lights on at 8 a.m. and off at 8 p.m.

Male and female mice were mated and their offspring were used as experimental subjects. On the day of birth the male offspring were either bilaterally gonadectomized or sham-operated under cryogenic anesthesia. The female offspring were injected (SC) with either 250 μg testosterone propionate (TP) or 0.025 ml of the sesame oil vehicle. For all treatment groups the time away from the dam was kept constant. All pups were toe clipped for later treatment identification. Only one sex was treated in each litter and only one of the treatments was performed on a given litter. The litters were not culled of untreated pups until weaning. Each group consisted of a number of litters. The pups were weaned at 25 days of age and housed according to their treatment in groups of 3–5.

At approximately 75 days of age all of the animals that had not been gonadectomized neonatally were gonadectomized as adults under sodium pentobarbital anesthesia (50 mg/kg). All of the neonatally sham-operated males, half of the neonatally castrated males and half of the neonatally TP-treated females were implanted (SC) with Silastic capsules containing testosterone (capsule construction: 7.5 mm in length, 1.575 mm inner diameter × 3.175 mm outer diameter; Dow Corning, Midland, MI). This treatment was meant to mimic the hormonal condition of the neonatally untreated males in our previous experiment, and has been shown to be sufficient to induce proliferation of the seminal vesicles (6). The remaining half of the neonatally castrated males, the other half of the TP-treated females and the oil-control females did not receive testosterone capsules. These animals were meant to simulate the hormonal condition of the neonatally untreated, adult ovariectomized females in our earlier experiment. After surgery and implantation all mice were singly housed in 48 × 27 × 20 cm cages and allowed one week to recover. Then the mice which had been implanted with testosterone capsules were pair housed with approximately equally aged females, and the nonimplanted mice were pair housed with males. Baseline levels of aggression were determined two weeks later.

The composition of these groups and the sequences of experimental manipulations are summarized in Table 1.

Behavioral Testing Procedure

The resident-intruder paradigm as described by Miczek and O'Donnell (13) was used to generate aggression. Intruder mice were housed in isosexual groups of ten. Female intruders were used to confront resident animals which had not been given testosterone capsules and had been pair housed with males. The mice which had received testosterone capsules and were pair housed with females confronted male intruders. All behavioral testing occurred during the light phase of the light-dark cycle. Just prior to the test for aggressive behavior the test animal's cagemate was removed, then the intruder was placed into the resident's cage. At the end of each test the intruder was removed and the cagemate was returned to the resident cage.

Behavioral measurements began with the first attack bite and continued for five minutes. If no attack bites occurred within five minutes after introducing the intruder, the test was ended. All tests were videorecorded and two observers whose reliability had been previously established viewed the videotapes and measured the salient acts, postures and movements. Behavioral measurements

were entered through an electronic interface into a PDP 11/23 minicomputer. This system encoded the start and end of each behavioral event, and allowed the summary of the frequency, latency, and duration of a range of aggressive behaviors shown by the resident mice, including attack bites, sideways threats, nips, tail rattles, and pursuits. Nonaggressive motor behaviors shown by the residents, including walking, rearing, and autogrooming, were measured as well. These behaviors have all been previously described and operationally defined for this species [e.g., (14)]. The frequency and duration of these behaviors were analyzed using a repeated measures analysis of variance which determined if alcohol treatment had a statistically significant effect on individual behaviors. When the F value from the ANOVA was significant, a Duncan New Multiple Range post hoc test was used to make comparisons between alcohol doses and baseline trials. Proportional data were analyzed post hoc with chi-square tests.

To establish a baseline rate of behavior three nondrug tests, separated by 3–4 days, were conducted before drug administration began. If no attacks occurred during the baseline trials, the animal was eliminated from further testing. If the resident did show attacks in the baseline tests, then the effects of a range of alcohol doses were assessed. The residents received alcohol doses of 0.1, 0.3, 1.0, 1.7, and 3.0 g/kg (PO); 15 minutes later they were confronted with an untreated intruder in their home cage. Each resident eventually received the full range of alcohol doses, which were administered once a week and in a randomized order. Alternating with alcohol tests, vehicle tests were conducted following distilled water administration. These tests were scheduled to assess possible intervening effects of dose sequence and repeated testing.

Alcohol Preparation and Administration

Alcohol solutions were prepared in concentrations ranging from 0 to 17% weight per volume using 100% ethanol and distilled water. Alcohol doses of 0.1, 0.3, 1.0, and 1.7 g/kg were administered in a volume of 1 ml/100 g body weight; the 3.0 g/kg dose was administered in a volume of 2 ml/100 g body weight. All doses were administered orally via a stainless steel gavage tube 15 minutes prior to the start of the behavioral test.

RESULTS

Effects of Neonatal and Adult Exposure to Testosterone on Aggressive Behavior

Mice were different in their aggressive behavior as a result of neonatal and adult hormone manipulations. Although at least some males and females from each group were aggressive, testosterone was not equally effective at influencing aggression in all groups. The behavioral response to adult testosterone depended at least partially on the presence of testosterone during postnatal development. Control males (i.e., neonatally sham-treated) given testosterone as adults were more likely to show aggressive behavior than control females (i.e., neonatally oil-treated). The proportion of animals in each hormonal condition showing attack behavior is shown in Fig. 1. Manipulating neonatal androgen exposure affected the number of animals that attacked an opponent. Neonatally androgenized females which received testosterone as adults were like males in their baseline levels of aggression. Both the percent of animals attacking and the attack frequency in this group were not different from the percent of attacking animals and the frequency of attacks in the group of control males (Fig. 1). Fewer androgenized females which did not receive testosterone as adults showed attack behavior than control males, although not as few as the control, oil-treated females. Neonatal gonadectomy reduced

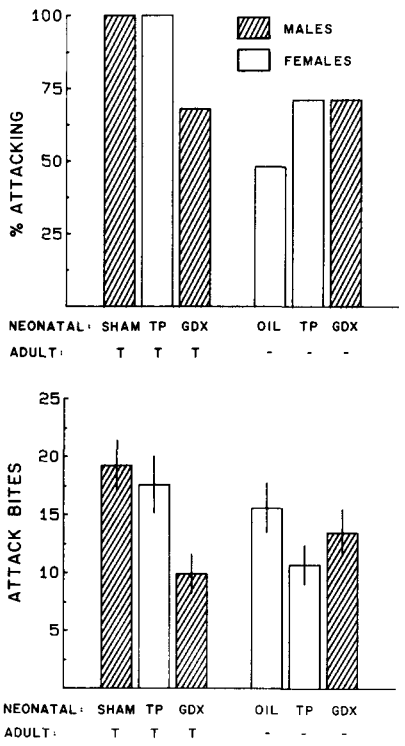

FIG. 1. The top panel shows the percent of animals attacking intruders in their home cage during baseline testing before the administration of any alcohol. The bottom panel shows the mean (±SEM) frequency of attack bites by those animals which did attack intruders during the baseline trials.

the attack frequency and the percent attacking relative to sham-operated males, independent of whether or not adult testosterone was present. Neonatal hormone manipulation did not affect adult body weight. There was no difference in body weight between gonadectomized males and sham-castrated males, nor was there a difference between TP- and oil-treated females.

Effects of Alcohol on Aggressive Behavior as a Function of Testosterone Exposure

The overall pattern of alcohol dose-response curves for aggressive behavior depended on both neonatal and adult hormone treatment. Control males and females responded differently to alcohol. The oil-treated control females did not show a reliable enhancement of aggression at any dose of alcohol, but they showed suppression of aggression at the 3.0 g/kg dose as assessed by frequency of attack bites, sideways threats, tail rattling, and pursuits. Sham-operated males displayed a statistically significant enhancement of attack bites at the 1.0 g/kg dose. At the 3.0 g/kg alcohol dose these mice exhibited no significant suppression of aggressive behavior. Although one measure of aggressive behavior, tail rattles, was suppressed at this dose, the number of attack bites, sideways threats, and pursuits were not different from the baseline values in the sham male group. This sex difference in the frequency of attack bites as a function of alcohol dose is shown in Fig. 2. The effects of alcohol on the other aggressive behaviors are summarized in Table 2.

The presence of testes during development appears to be necessary for the adult testosterone-dependent attenuation of the aggression-suppressing effect of 3.0 g/kg alcohol. Neonatally

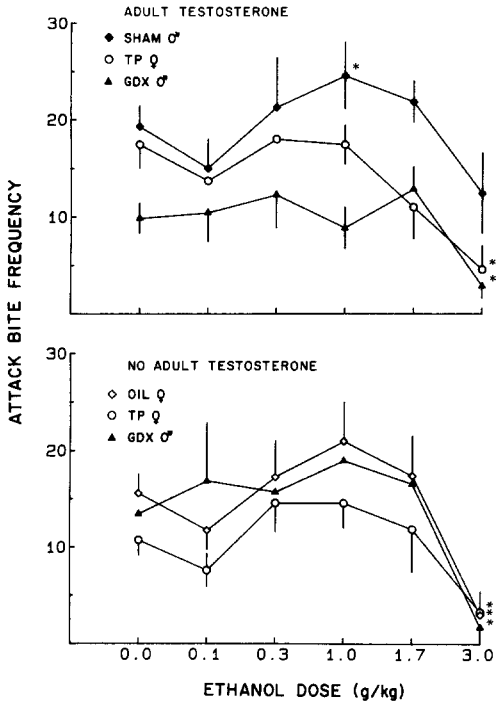

FIG. 2. The top panel shows the mean (±SEM) frequency of attack bites by mice receiving 7.5 mm testosterone capsules as adults and tested with male intruders. Closed diamonds represent the behavior of male mice sham-castrated at birth, open circles represent female mice treated with 250 μg TP at birth, and closed triangles represent male mice castrated at birth. The bottom panel shows the frequency of attack bites by mice not treated with testosterone as adults and tested with female intruders. Open diamonds represent the behavior of females injected with the sesame oil vehicle at birth, open circles represent female mice injected with 250 μg TP at birth, and closed triangles represent males gonadectomized at birth. Statistically significant differences ($p<0.05$) from the control tests (0 g/kg alcohol) are indicated by asterisks.

gonadectomized males which did not receive adult testosterone had an alcohol dose-response curve which resembled that of the control females. Aggression was not enhanced at any dose and was suppressed at the 3.0 g/kg dose. This suppression was evident in the measurements of sideways threats, tail rattles, pursuits, as well as attack bites. When the neonatally gonadectomized males received testosterone in adulthood they still displayed a suppression of aggressive behaviors at the high dose. The 3.0 g/kg dose of alcohol significantly suppressed attack bites, sideways threats, tail rattles, and pursuits (see Fig. 2 and Table 2).

Masculinization of alcohol response was not induced in the neonatally androgenized females. The dose-response curve of TP-treated females in the absence of adult testosterone was similar to that of control females. Enhancement of aggression did not occur at any dose, and suppression was seen at the 3.0 g/kg dose. At this dose there was a significant suppression of attack bites, sideways threats, tail rattles, and pursuits. Administration of adult testosterone to the androgenized females did not alter the alcohol dose-response curve for attack behavior. These females showed suppression of attack bites, sideways threats, tail rattles, and pursuits when given 3.0 g/kg alcohol, and again enhancement of aggressive behavior was not induced by any dose (see Fig. 2 and Table 2).

Effects of Alcohol and Testosterone on Nonaggressive Behaviors

Although there were some differences across groups in the baseline levels of nonaggressive behaviors, there were no clear interactive effects of testosterone and alcohol on these behaviors. Control males had significantly lower baseline durations and frequencies of rearing and grooming than females. Neonatally androgenized females which received testosterone in adulthood showed amounts of rearing and grooming which were more typical of males. The duration of grooming and rearing for this group was not significantly different from control males and was significantly lower than the control females. Androgenized females which did not receive testosterone as adults showed female-typical levels of rearing and grooming. Gonadectomized males which received testosterone as adults were more male-like in their grooming duration. The level of grooming appears to depend on adult testosterone, not on neonatal testosterone.

Alcohol had no systematic effects on grooming and walking duration in any of the treatment groups. However, there were a few differences in rearing. Control females, neonatally androgenized females and gonadectomized males all reared less after 3.0 g/kg alcohol. Control males, on the other hand, did not display this suppression. However, the control males reared infrequently before alcohol administration so it was not possible for them to show a significant reduction in this behavior. The pattern of effects on rearing is different from the more specific interactive effects of testosterone and alcohol on aggressive behaviors. The changes in alcohol dose-response curves for aggression cannot be attributed merely to differences in nondrug baseline. The baseline rates of aggression in all treatment groups were sufficient such that neither ceiling nor basement effects occurred.

TABLE 2

EFFECT OF ALCOHOL ON AGGRESSIVE BEHAVIOR OF MALE AND FEMALE MICE WITH DIFFERENT HORMONE TREATMENTS

	Alcohol Dose (g/kg)				
Treatment	0.1	0.3	1.0	1.7	3.0
			Sideways Threat		
Sham male + T	78.8%	102.6%	122.0%	118.9%	67.0%
TP female + T	82.7%	99.5%	101.5%	65.5%	29.5%*
GDX male + T	117.7%	134.6%	96.1%	142.5%	25.2%*
OIL female	88.6%	125.2%	134.0%	114.9%	26.8%*
TP female	73.5%	128.5%	149.0%	89.0%	32.6%*
GDX male	105.6%	116.2%	143.6%	103.0%	17.8%*
			Tail Rattle		
Sham male + T	77.1%	94.3%	111.0%	92.7%	46.2%*
TP female + T	86.1%	84.5%	84.1%	43.0%	17.5%*
GDX male + T	93.6%	90.7%	80.9%	103.9%	36.3%*
OIL female	94.5%	113.5%	113.5%	91.0%	18.3%*
TP female	89.5%	151.1%	105.5%	58.4%	26.9%*
GDX male	97.3%	78.5%	67.0%	59.8%	7.1%*
			Pursuit		
Sham male + T	124.6%	144.6%	129.2%	101.5%	36.9%
TP female + T	72.2%	105.5%	100.0%	77.7%	16.7%*
GDX male + T	40.0%	160.0%	95.0%	135.0%	25.0%*
OIL female	62.5%	90.0%	100.0%	52.7%	10.0%*
TP female	85.7%	78.6%	135.7%	171.4%	21.4%*
GDX male	152.0%	112.0%	120.0%	64.0%	28.0%*

Expressed as percent of baseline (water trials).
*Different from baseline $p<0.05$.

DISCUSSION

The present experiment demonstrates a sex difference in

TABLE 3

EFFECT OF ALCOHOL ON NONAGGRESSIVE BEHAVIOR OF MALE AND FEMALE MICE WITH DIFFERENT HORMONE TREATMENTS

Treatment	Alcohol Doses (g/kg) 0.1	0.3	1.0	1.7	3.0
			Grooming Duration		
Sham male + T	98.9%	134.4%	74.0%	65.6%	132.3%
TP female + T	148.9%	130.5%	172.1%	178.7%	112.8%
GDX male + T	175.3%	88.8%	104.5%	100.0%	47.2%
OIL female	54.7%	91.0%	110.2%	143.3%	74.7%
TP female	149.4%	91.9%	134.4%	108.5%	78.4%
GDX male	86.8%	88.9%	69.8%	103.7%	91.5%
			Rearing Duration		
Sham male + T	59.1%	45.4%	45.4%	27.3%	13.6%*
TP female + T	274.4%	88.4%	218.6%	86.0%	34.9%*
GDX male + T	48.9%	76.1%	56.8%	43.2%	17.0%*
OIL female	80.5%	113.8%	57.9%	24.5%	16.3%*
TP female	65.9%	46.8%*	74.5%	78.7%	35.5%*
GDX male	65.0%	31.7%	35.8%*	57.5%*	10.8%*
			Walking Duration		
Sham male + T	65.3%*	94.4%	118.3%	113.4%	131.7%
TP female + T	108.3%	84.8%	121.4%	109.0%	92.4%
GDX male + T	112.3%	84.5%	64.6%*	105.0%	77.6%*
OIL female	109.2%	89.5%	97.2%	98.1%	88.6%
TP female	104.1%	69.4%*	135.1%	85.1%	108.2%
GDX male	109.0%	110.3%	100.3%	97.9%	105.0%

Expressed as percent of baseline (water trial).
*Different from baseline $p<0.05$.

alcohol's effect on aggression that was most evident at 3.0 g/kg alcohol. At this dose, females showed suppression of aggressive behavior while the level of aggression in control males was not different from their baseline levels. The ability of testosterone to attenuate the aggression-suppressing effects of alcohol in males and not females has been previously demonstrated (5,6). The aggression-enhancing effects of 1.0 g/kg alcohol seen previously in adult testosterone-treated males (5,6) was also replicated in the sham-castrated males. The control females did not show significant enhancement of aggression in response to any dose of alcohol. This differs from the previous demonstration that 0.1 g/kg alcohol enhances aggression in females (5). The incomplete nature of our replication of the aggression-enhancing effect of alcohol may be related to treatment and handling of all animals at birth in the present experiment. The stress of the neonatal injections in the control females may have altered their response to alcohol as adults. Early handling, isolation from the dam, and other forms of stress have been shown to have effects on adult behavior and physiology (12).

Sexual differentiation appears to play a role in the behavioral interaction between testosterone and alcohol on aggressive behavior. The present study demonstrates that the presence of testes during postnatal development is necessary for the induction of an adult male-typical response to alcohol as measured by aggressive behavior. Neonatally castrated males showed the female-typical suppression of aggression at 3.0 g/kg. This suppression was evident even when they were maintained on a high level of testosterone as adults. If the sensitive period for the sexual differentiation of alcohol response occurs entirely postnatally, then administration of testosterone to newborn females should have masculinized their response. This did not occur. The androgenized females showed the female-typical suppression of aggressive behavior with the high dose of alcohol. Adult testosterone did not attenuate the aggression-suppressing effects of alcohol in these females.

The fact that neonatal gonadectomy blocks masculinization but that testosterone administration to females does not induce masculinization is on the surface somewhat contradictory. However, there are two explanations of this that need to be explored further. The simplest explanation is that the dose of testosterone used neonatally was insufficient to masculinize the response to testosterone and alcohol. This seems unlikely since this dose of TP given postnatally was sufficient to masculinize both sexual behavior and aggressive behavior in earlier studies (7,8). A more likely explanation for the failure to induce masculinization may be that the sensitive period for the differentiation of alcohol's effects on aggression may occur, at least in part, prenatally. It has been demonstrated that females, exposed to high titers of testosterone in utero by virtue of their intrauterine position between two males, are more aggressive when administered testosterone as adults than females positioned between two females in utero (18). Prenatal as well as early postnatal testosterone exposure has a critical role in determining the effects of adult testosterone an aggressive behavior. Combining prenatal and postnatal androgen treatment can have a greater effect on masculinization of female mice than either treatment alone (17). It is likely that exposure to testosterone during both pre- and postnatal periods is necessary for the interactive effects of testosterone and alcohol an aggressive behavior.

As has been shown previously, the interaction between testosterone and alcohol is specific to aggressive behavior (6). In the present study alcohol did not systematically affect grooming or walking in any of the treatment groups. Rearing was reduced by 3.0 g/kg alcohol in all but the control males, but the lack of a reduction in rearing in that group appears to be due to their low baseline level for this behavior, i.e., a basement effect. The more specific effect of testosterone on reducing the suppressant effect of 3.0 g/kg alcohol on aggressive behaviors in the control males cannot be explained by their nondrug baseline values for these behaviors. Some of the other treatment groups had baseline levels of aggression similar to that of the control males but did not show the same lack of suppression of fighting in response to 3.0 g/kg alcohol when testosterone was present.

Since the interaction between testosterone and alcohol appears to be specific to aggressive behaviors and not nonaggressive motor behaviors, the interaction does not appear to be due to alcohol metabolism. In addition, all animals were tested 15 min after administration of alcohol and we have not seen any sex difference in blood alcohol levels at this time point (5), although acute administration of alcohol has been shown to alter serum testosterone levels (1, 3, 10). Testosterone has also been reported to affect the metabolism of alcohol by reducing liver alcohol dehydrogenase activity (4,15). However, as has been suggested before (6) and is suggested presently by the behavioral specificity of the effects, the interaction between alcohol and testosterone on aggressive behavior probably occurs in the CNS.

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