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Testosterone-dependent antidepressant-like effect of noradrenergic but not of serotonergic drugs

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Abstract

The main objective of this study was to analyze the effect of testosterone on the actions of antidepressant drugs in the forced swimming test (FST), an animal model that predicts antidepressant effects. In addition, the effect of testosterone propionate (TP) supplementation was evaluated in the same animal model using orchidectomized male rats. Initially, different doses (2.5, 5.0, and 10.0 mg/kg sc, three injections before the test) of desipramine (DMI), fluoxetine (FLX), and clomipramine (CMI) were administered to intact male rats to detect the effective dose in the FST. All drugs (at 10 mg/kg) produced an antidepressant effect, reflected as a reduction of immobility behavior. Neither orchidectomy per se nor TP supplementation (0.5 and 1.0 mg/rat sc, for 10 days) modified the behaviors evaluated in the FST. Orchidectomy blocked the antidepressant effect of DMI, FLX, and CMI (10 mg/kg), while TP supplementation (0.5 mg/rat, for 10 days) restored the antidepressant action of DMI, but not that of CMI or FLX. These findings indicate that testosterone participates in the antidepressant actions of DMI, a noradrenaline reuptake inhibitor, while other gonadal hormones might be involved in the antidepressant effects of the serotonin reuptake inhibitors (SSRIs) like FLX and CMI.

Keywords: Testosterone propionate; Antidepressant effect; Forced swimming test; Desipramine; Serotonin reuptake inhibitors; Fluoxetine; Orchidectomy; Clomipramine

1. Introduction

It has been reported that the decline in the circulating levels of testosterone may be associated with changes in somatic and psychological features in men, such as loss of energy, diminished libido, low mood, irritability, and sexual dysfunction (Seidman and Walsh, 1999; Margolese, 2000; McNicholas et al., 2003; Seidman, 2003). Indeed, some authors have found a negative correlation between the hormone levels of hypogonadal patients and the intensity of the depressive disorder (Yesavage et al., 1985; Schweiger et al., 1999). An interesting observation on the role of androgens in affective disorders is that therapy with anabolic–androgenic hormones produces an alleviation of depression in hypogonadal patients. This effect was produced in a percentage of patients comparable to that induced by conventional antidepressants (O'Connor et al., 2002; Wagner et al., 1996; Vogel et al., 1985). Moreover, it has been suggested that testosterone facilitates the antidepressant effects of serotonin reuptake inhibitors (SSRIs), although this idea is sustained in scarce clinical studies showing controversial results (Seidman and Rabkin, 1998; Margolese, 2000).

Some studies showing an interaction between steroid hormones and antidepressants have been conducted in animal models sensitive to antidepressant drugs, like the forced swimming test (FST; Porsolt et al., 1977). In this test, rats are subjected to a stressful condition, which induces an increase of a passive behavior, immobility, considered a behavioral despair state (Porsolt et al., 1977). The duration of the immobility behavior is reduced by pharmacological and nonpharmacological antidepressant treatments, i.e., tricyclic antidepressants, SSRIs, or electroconvulsive shocks (Porsolt et al., 1977). A new scoring method, reported by

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Detke et al. (1995), also analyzes the active behaviors in the FST: swimming and climbing. This analysis permits to propose the participation of specific neurotransmitter systems in the antidepressant actions. Thus, in addition to a reduction of immobility behavior, noradrenergic antidepressants [i.e., desipramine (DMI)] consistently increase climbing while serotonergic drugs [i.e., fluoxetine (FLX)] produce an increase in swimming (Detke et al., 1995; López-Rubalcava and Lucki, 1998).

Sex differences in the immobility behavior have been reported in the FST. Thus, intact male rats show higher levels of immobility (Alonso et al., 1991; Barros and Ferigolo, 1998) and a reduced sensitivity to antidepressants (Contreras et al., 1995; Barros and Ferigolo, 1998) when compared to females. Interestingly, this animal model is also sensitive to actions of steroid hormones. Thus, progesterone and different estrogenic compounds produce antidepressant-like effects in ovariectomized rats (Martínez-Mota et al., 1999; Estrada-Camarena et al., 2002, 2003; Rachmann et al., 1998). Moreover, it has been reported that 17β-estradiol facilitate the antidepressant effect of DMI and FLX, through a reduction of immobility and an increase of climbing or swimming behaviors, respectively (Estrada-Camarena et al., 2004). Regarding androgens, it has been shown that testosterone treatment in males produces similar antidepressant actions to DMI (Bernardi et al., 1989). However, systematic studies to evaluate the possible interaction between androgens and antidepressants have not been conducted.

Based on the previous evidence, the main objective of the present study was to analyze the possible interaction between testosterone and several antidepressants in the FST. The antidepressants used in the present study, DMI, FLX, and clomipramine (CMI), were selected on the bases of their clear effects in females (Fernández-Guasti et al., 1999; Martinez-Mota et al., 2000; Estrada-Camarena et al., 2004) and on their neuropharmacological mechanism of action: DMI as a noradrenaline reuptake inhibitor, and FLX and CMI as SSRIs. In addition, because testosterone modulates several nonreproductive behaviors like aggression, anxiety, or immobility (Bernardi et al., 1989; Bitar et al., 1991; Fernández-Guasti and Martínez-Mota, 2003), the other aim of this study was to determine possible changes in the FST associated to orchidectomy or testosterone propionate (TP) supplementation.

2. Materials and methods

2.1. Animals

Male Wistar rats (200–250 g) were housed in polycarbonate cages, 8 per cage (60 × 40 × 20 cm), and maintained in a room under inverted 12-h light–dark schedule (lights on at 2200 h). All animals had ad libitum access to food and water. Animal management was according to the general principles of laboratory animal care (NIH publication 85-23, 1985). The local ethical committee for animal use approved the protocol for these experiments.

2.2. Surgery

Male rats were orchidectomized under anesthesia with sodium pentobarbital (40 mg/kg ip). Briefly, a single midline incision was made in the scrotum and the testes exposed and removed. Animals were sutured and returned to their home cages following surgery and left to recover, for at least 3 weeks, before the experiments.

2.3. Treatments

DMI–HCl, CMI–HCl (Sigma-Aldrich, MO), and FLX–HCl (Eli–Lilly, Mexico City) were dissolved in saline solution (0.9%). Solutions of all antidepressants were freshly prepared before each experiment. TP (Sigma-Aldrich, MO) was dissolved in corn oil with two drops of dichloromethane.

2.4. Forced swimming test

Swimming sessions (Porsolt et al., 1977) were conducted by placing the rats in individual glass cylinders (46 cm height × 20 cm diameter) containing 30 cm of water at 23 (± 2) °C. During the first session (pretest), rats were forced to swim for 15 min. Twenty-four hours later, animals were subjected to a 5-min session (test). At the end of two sessions, animals were removed from the jars, dried with tissue paper and placed in a warm cage (23 ± 2 °C) during 15 min. The test session was videotaped and later scored by two observers who were blind to the treatments applied. To control for putative observer differences, some video scores were selected at random and compared.

A time-sampling technique was employed to score, every 5 s, one of the following behaviors: (a) immobility, when rats float without struggling and make only those movements necessary to keep their head above the water; (b) swimming, characterized by active motions, i.e., moving around the jar and diving; (c) climbing, defined as strong movements executed with forepaws in and out of the water, usually against the walls (Detke et al., 1995, 1997). According to the interpretation of Detke et al. (1995, 1997), this scoring method allows the identification of the neurotransmitter system affected by the antidepressant drug. Thus, the noradrenaline reuptake inhibitors (i.e., DMI or maprotiline) produce a reduction of immobility with a concomitant increase of climbing behavior, while the SSRIs (i.e., FLX or paroxetine) decrease immobility with a concurrent increase of swimming behavior.

2.5. Experimental series

A first experimental series was designed to determine the effective dose of the antidepressant drugs—DMI, FLX, or CMI—in intact male rats. Independent groups of animals

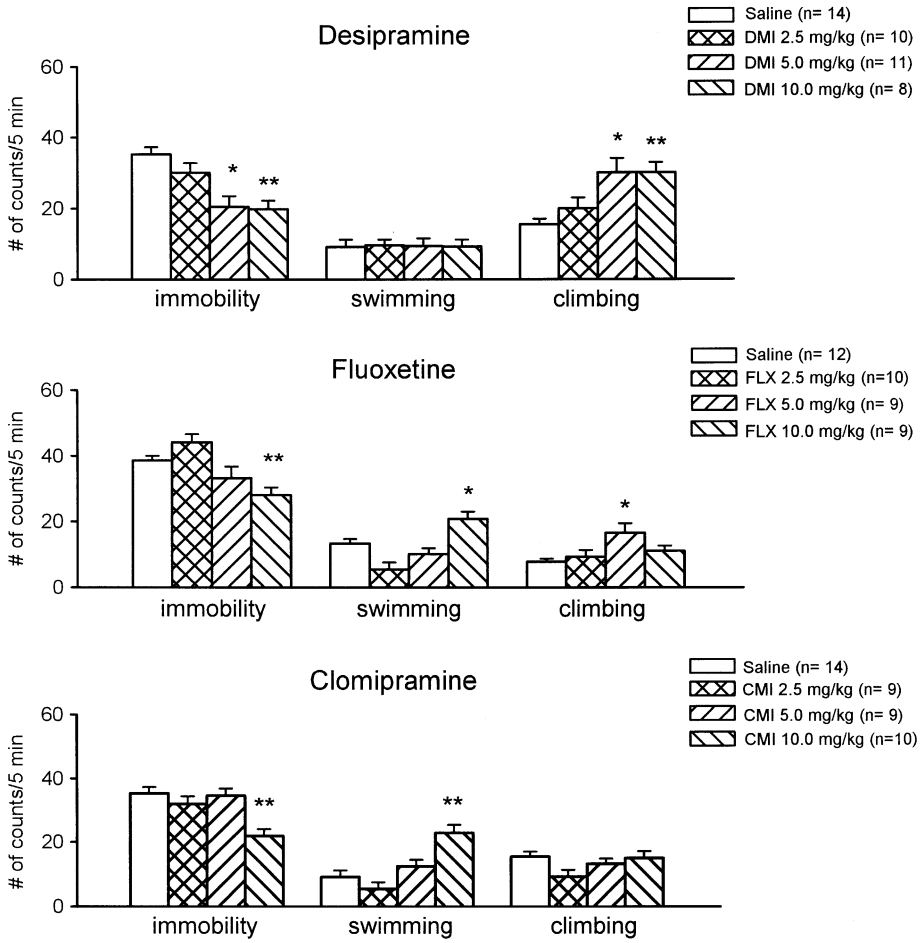

Fig. 1. Effect of different doses (mg/kg) of DMI (upper panel), FLX (middle panel), or CMI (lower panel) in intact male rats subjected to the FST. Results of one-way ANOVA in text. Dunnett's test: $*P<.05$; $**P<.001$.

(8–14 per group) received different doses of DMI, FXL, or CMI (2.5, 5.0, and 10.0 mg/kg for each drug) and were evaluated in the FST. A control group received saline solution (0.9%, 2 ml/kg) as vehicle. Treatments were administered in a standard subacute drug-testing procedure consisting of three injections subcutaneously applied 23.5, 5, and 1 h before to the test. All FST sessions for each experiment were conducted between 1300 and 1500 h. The doses and the administration schedules were selected taking into consideration previous studies (Detke et al., 1995; Estrada-Camarena et al., 2004).

The second series was conducted to evaluate the repercussion of orchidectomy on the performance of animals in the FST, as well as its possible influence on the effect of antidepressant drugs. For the first objective, intact and orchidectomized rats were treated with three injections of saline solution (0.9%) before the FST. Besides, independent groups of orchidectomized male rats (8–14 per group) were administered with one of the following treatments: (a) vehicle (saline solution 0.9%); (b) DMI, FLX, or CMI at 10 mg/kg; or (c) DMI, FLX, or CMI at 20 mg/kg. Antidepressants and vehicle were administered in a subacute schedule, as it was mentioned in the first experiment. Both doses of antidepressants were chosen taking into account their effectiveness in intact animals in the FST.

In a third experimental series, the effect of TP supplementation was explored in the FST. Independent groups of orchidectomized rats (10–13 rats per group) received different doses of TP (0.5 or 1.0 mg/rat sc). This chronic treatment consisted of one injection per day, for 10 days. The last injection of TP or vehicle was applied 4 h before the pretest session and 28 h before the test. Data were compared with a group of castrated males chronically treated with vehicle (corn oil, 0.2 ml sc, for 10 days). TP doses and schedule were selected due to their effectiveness

Table 1
Effect of orchidectomy on the performance of rats in the FST

Groups	Immobility	Swimming	Climbing	*n*
Intact rats	35.63 ± 1.20	10.55 ± 1.15	14.02 ± 1.37	36
OrX rats	36.73 ± 1.79	8.66 ± 1.56	14.16 ± 1.56	30
t Test	*P*=.60	*P*=.25	*P*=.14	

OrX: orchidectomized. The data were obtained by pooling results of different control groups. All animals received three injections of saline solution before the FST. The table shows the mean ± S.E.M.

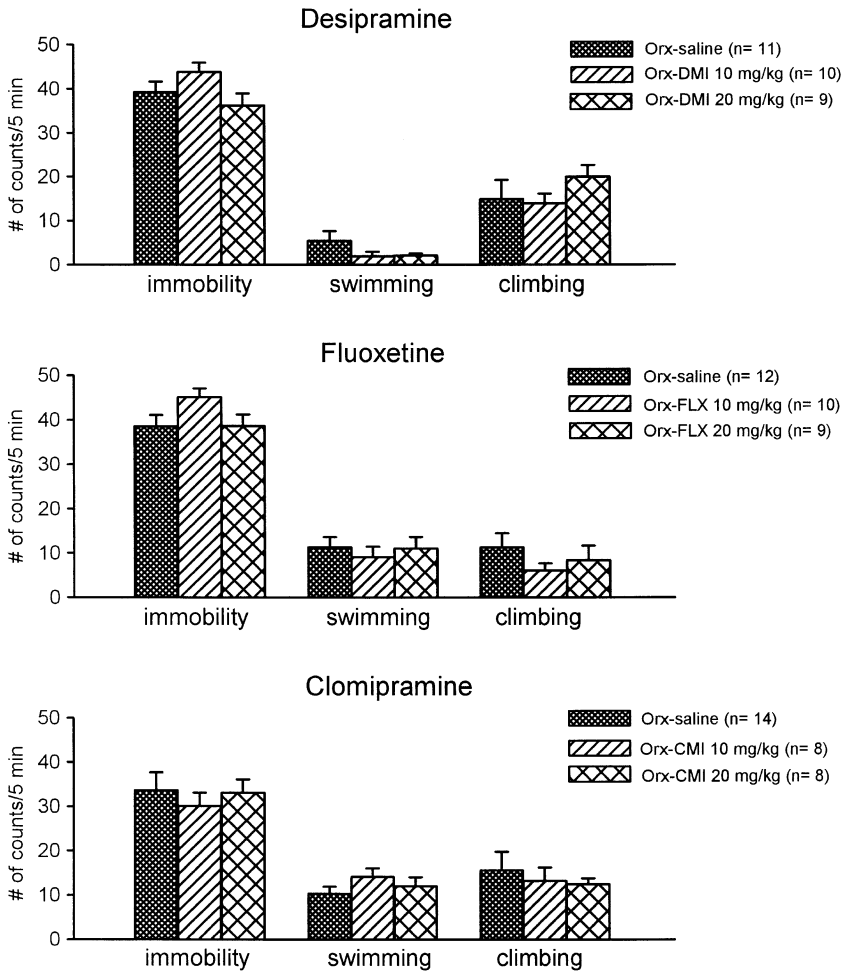

Fig. 2. Effect of the DMI (upper panel), FLX (middle panel), or CMI (lower panel) in orchidectomized (OrX) male rats. Results of one-way ANOVA in text.

in recovering the sexual activity of castrated rats (Putman et al., 2001).

Later, it was analyzed if the TP supplementation was able to restore the antidepressant effect of the drugs in orchidectomized rats. For this proposal, independent groups of orchidectomized rats (9–14 rats per group) were administered with one of following combinations: (a) corn oil plus saline solution; (b) corn oil plus antidepressant drugs (DMI, FXL, or CMI at 10 mg/kg); (c) TP 0.5 mg/rat plus saline solution; or (d) TP 0.5 mg/rat plus antidepressant drugs (DMI, FXL, or CMI at 10 mg/kg). TP and corn oil were chronically injected (0.2 ml/rat sc, for 10 days) and the last injection was applied 4 h before the pretest session. All antidepressants and saline solution were administered in the subacute schedule as it was described in the first experiment.

Because TP at 0.5 mg/rat did not restore the antidepressant action of the serotonergic drugs, an additional dose of TP was tested together with these serotonergic antidepressants. Groups of orchidectomized rats were assigned to one of the following treatments: (a) corn oil plus saline solution (0.9%), (b) TP at 1.0 mg/rat plus FLX (10 mg/kg), or (c) TP at 1.0 mg/rat plus CMI (10 mg/kg). TP and corn oil was chronically applied (subcutaneously, 0.2 ml/rat for 10 days) while FLX and CMI were administered in a subacute schedule.

Table 2
Effect of chronic treatment with TP in orchidectomized rats in the FST

Groups	Immobility	Swimming	Climbing	*n*
Oil	39.27 ± 2.40	5.45 ± 2.18	14.81 ± 1.33	11
TP 0.5 mg/rat	40.70 ± 1.75	7.90 ± 1.43	11.40 ± 1.73	10
TP 1.0 mg/rat	43.38 ± 1.75	7.38 ± 1.34	9.23 ± 1.80	13
One-way ANOVA	$F(2,33)=1.02$	$F(2,33)=0.56$	$F(2,33)=2.97$	
	$P=.37$ (NS)	$P=.57$ (NS)	$P=.06$ (NS)	

TP: testosterone propionate; NS: nonsignificant. TP was subcutaneously administered for 10 days. The table shows the mean ± S.E.M.

2.6. Statistical analysis

The effects of orchidectomy were analyzed with a Student's *t* test. The effect of different doses of antidepressants in intact or castrated males as well as the effect of TP supplementation was analyzed with a one-way ANOVA followed by Dunnett's test. The effect of antidepressant drugs in orchidectomized rats with or without TP supplementation was analyzed with a two-way ANOVA, followed by Tukey's test. For all tests, the significance level was

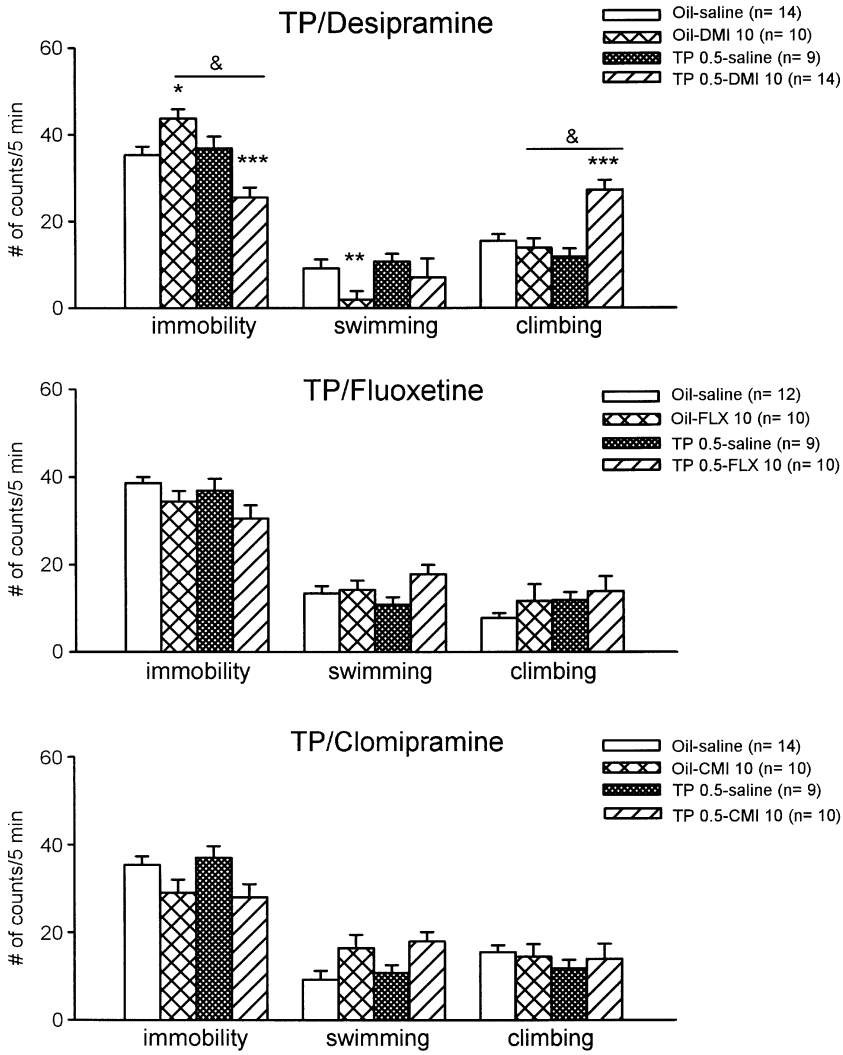

Fig. 3. Effect of the DMI (upper panel), FLX (middle panel), or CMI (lower panel) in orchidectomized rats with TP supplementation (0.5 mg/rat). Antidepressants were administered in milligrams per kilogram. Results of two-way ANOVA in text. Tukey's test: $^{*}P<.05$; $^{**}P<.01$; $^{***}P<.001$ versus oil–saline group. Brackets: comparison between DMI's groups with or without TP supplementation, Tukey's test: $^{\&}P<.001$.

established at $P<.05$. All results were expressed as mean ± S.E.M.

3. Results

Fig. 1 shows the effect on the FST of DMI (upper panel), FLX (middle panel), and CMI (lower panel) in intact male rats. As expected, DMI (upper panel) produced a statistically significant reduction of immobility [$F(3,39)=9.22$, $P<.001$] with an increase of climbing behavior [$F(3,39)=6.86$, $P<.001$] and no changes in swimming behavior [$F(3,39)=0.01$, $P=.99$]. FLX at 10 mg/kg (Fig. 1, middle panel) produced a reduction of immobility [$F(3,36)=8.22$, $P<.001$] accompanied by an increase of swimming behavior [$F(3,36)=11.78$, $P<.001$]. This antidepressant also increased climbing behavior [$F(3,36)=3.95$, $P<.01$], but at this dose (5 mg/kg) did not modify immobility. CMI (lower panel) produced a reduction of immobility [$F(3,38)=7.72$, $P<.001$], an increase of swimming behavior [$F(3,38)=4.32$, $P<.001$], and no changes in climbing behavior [$F(3,38)=1.57$, $P=.40$].

Orchidectomy per se did not produce statistically significant changes in the FST, as is shown in Table 1 (results of one-way ANOVA are described in the table). Additionally, in Fig. 2, it is illustrated that orchidectomy blocked the effect of all antidepressant drugs in the FST. Indeed, a dose as high as

Table 3
Effect of FLX or CMI (three injections of 10 mg/kg) in orchidectomized (OrX) rats treated with TP (1.0 mg/rat, for 10 days)

	Immobility	Swimming	Climbing	*n*
Oil–saline	33.60 ± 1.20	12.55 ± 1.12	14.02 ± 1.37	8
TP 1.0 + FLX	32.00 ± 2.08	15.60 ± 1.50	12.70 ± 3.30	10
TP 1.0 + CMI	29.20 ± 3.52	16.10 ± 1.99	13.70 ± 3.65	10
One-way ANOVA	$F(2,25)=1.05$	$F(2,25)=1.29$	$F(2,25)=0.96$	
	$P=.32$ (NS)	$P=.28$ (NS)	$P=.60$ (NS)	

Dunnett's test versus oil–saline OrX group; NS: nonsignificant. The table shows the mean ± S.E.M.

20 mg/kg of antidepressants also was ineffective to reduce the immobility behavior in castrated male rats. In correspondence, the one-way ANOVA showed no statistically significant differences for DMI [immobility $F(2,27)=1.98$, $P=.16$; swimming $F(2,27)=1.91$, $P=.16$; climbing $F(2,27)=2.42$, $P=.10$, upper panel], FLX [$F(2,28)=2.69$, $P=.06$; swimming $F(2,28)=1.44$, $P=.25$; climbing $F(2,28)=0.33$, $P=.72$, middle panel], or CMI [immobility $F(2,27)=1.60$, $P=.21$; swimming $F(2,27)=2.07$, $P=.14$; climbing $F(2,27)=0.34$, $P=.71$, lower panel].

In Table 2, it is illustrated that TP supplementation produced no changes on the behaviors of orchidectomized rats in the FST. Interestingly, in Fig. 3, it is observed that TP treatment, at 0.5 mg/rat, restored the sensitivity of castrated rats to DMI. In correspondence, the two-way ANOVA showed statistically significant differences for immobility [hormonal condition $F(1,43)=13.13$, $P<.001$; treatment $F(1,43)=0.42$, $P=.51$; interaction $F(1,43)=18.85$, $P<.001$] and climbing [hormonal condition $F(1,43)=5.58$, $P=.23$, treatment $F(1,43)=11.55$, $P=.001$; interaction $F(1,43)=12.15$, $P<.001$] but not for swimming behavior [hormonal condition $F(1,43)=4.43$, $P=.04$; treatment $F(1,43)=11.61$, $P=.001$; $F(1,43)=1.26$, $P=.26$].

Fig. 3 also shows that this dose of TP did not restore the antidepressant action of FLX or CMI. Thus, the two-way ANOVA did not attain statistical significance [FLX: immobility: hormonal condition $F(1,37)=1.15$, $P=.29$; treatment $F(1,37)=4.39$, $P=.04$; interaction $F(1,37)=0.17$, $P=.67$. Swimming $F(1,37)=0.06$, $P=.79$; treatment $F(1,37)=4.41$, $P=.04$; interaction $F(1,37)=2.88$, $P=.10$. Climbing: hormonal condition $F(1,37)=0.59$, $P=.44$, treatment $F(1,37)=0.29$, $P=.58$; interaction $F(1,37)=0.32$, $P=.57$. CMI immobility: hormonal condition $F(1,39)=0.02$, $P=.87$; treatment $F(1,39)=9.04$, $P=.005$; interaction $F(1,39)=0.22$, $P=.63$. Swimming: hormonal condition $F(1,39)=0.44$, $P=.51$, treatment $F(1,39)=9.64$, $P=.004$; interaction $F(1,39)=0.01$, $P=.98$. Climbing: hormonal condition $F(1,39)=0.71$, $P=.43$, treatment $F(1,39)=0.04$, $P=.83$; interaction $F(1,39)=0.41$, $P=.52$].

In Table 3, it is shown that a higher dose of TP (1.0 mg/rat) also was ineffective in restoring the sensitivity of orchidectomized rats to the serotonergic antidepressants, FLX and CMI.

4. Discussion

This study shows that neither orchidectomy nor TP supplementation modified the behaviors evaluated in the FST. Additionally, orchidectomy blocked the antidepressant-like effect of DMI, FLX, and CMI. The antidepressant actions of DMI, but not those produced by the SSRIs, were restored in castrated animals by TP supplementation.

In our study, the lack of behavioral changes in the FST by orchidectomy or TP treatment contrasts with the results obtained by Bernardi et al. (1989), who reported an increase of immobility behavior in castrated mice. In addition, they found that hormonal treatment with testosterone reversed the behavioral despair to the levels observed before orchidectomy. Such discrepancy can be explained considering some differences in procedure and animal species used in each study. Thus, while we tested male rats after 3 weeks of castration, they evaluated behavioral despair of mice 4.5 weeks postsurgery. Additionally, in the present study, testosterone treatment was administered for 10 days, while Bernardi et al. (1989) reported a testosterone treatment for 4 days. These results suggest that, at least in male rats, a reduction in gonadal hormones (provoked by orchidectomy) does not exert any influence on immobility behaviors in the FST.

Our study confirms a huge body of evidence on the effects of antidepressant drugs in the FST: reduction of immobility with a concomitant increase of active behaviors. In this test, antidepressants acting via the noradrenergic system—such as DMI and maprotiline—produce an increase in climbing, while compounds modifying the serotonergic system—i.e., SSRIs—increase swimming (Detke et al., 1995; López-Rubalcava and Lucki, 1998). In the present study, orchidectomy completely blocked the antidepressant effect of doses of DMI, CMI, or FLX that produce such action in intact male rats. This finding is interesting taking into account that traditionally testicular secretions are not considered to influence the effect of psychotropic medications, including antidepressant drugs. However, recent data suggest that androgens might modulate the actions of antidepressants (Margolese, 2000). In fact, a clinical study indicates that some hypogonadal depressive patients—with resistance to SSRIs—reported a reduction of depression after chronic treatment with testosterone (Seidman and Rabkin, 1998). The present study constitutes the first evidence showing that the effects of antidepressants may depend on testosterone or other gonadal hormones.

A possible pharmacokinetic mechanism may underlie the lack of effect of antidepressants in castrated rats. This idea is based on the fact that both testosterone and trycyclic antidepressants are metabolized by the same cytochrome (Wilson and Biscardi, 1992). In addition, it has been reported that orchidectomy decreases the demethylation rate of imipramine in the liver leading to higher levels of DMI (Skett et al., 1980). Present data indicate that a dose as high as 20 mg/kg of the three antidepressants was ineffective in reducing immobility behavior in orchidectomized rats. All these findings, taken together, argue against a lack of action based on a pharmacokinetic interpretation. Pharmacodynamic changes produced after androgen withdrawal is another possible explanation for the blockade of the effects of DMI in castrated animals. Recently, it was reported that orchidectomy reduces [^{3}H]-nisoxetine binding to norepinephrine uptake sites in olfactory bulb and prefrontal cortex (Shang et al., 1999). Therefore, a reduction in the density of norepinephrine transporters, produced by castration, might partially underlie the blockade of the antidepressant-like

actions of DMI (Shang et al., 1999). Long-term castration also produces a decrease of dopamine levels, measured in the medial preoptic area (MPOA), in concurrence with a loss of copulatory activity (Putman et al., 2001). TP treatment, in a similar schedule to that used in our study, restored dopamine levels in the MPOA and sexual behavior (Putman et al., 2001). It has been reported that the integrity of dopamine levels is needed for the antidepressant-like actions of DMI in the FST (Cervo and Samanin, 1987). Therefore, it is possible that changes in dopamine levels after castration and their restoration after TP treatment underlie the blockade and recovery of the antidepressant-like effect of DMI in the FST.

In the present study, castration cancelled the antidepressant-like actions of FLX and CMI. TP supplementation was unable to reestablish the response to these serotonergic compounds. An interaction between testosterone and the serotonergic system has been reported by Sandrini et al. (1989), who found that testosterone treatment (15 mg/kg, three injections) reversed the reduced density of [^{3}H]imipramine binding sites in cortex and hypothalamus produced by orchidectomy. In addition, Bitar et al. (1991) reported that orchidectomy reduced serotonin (5-HT) levels in hypothalamus and hippocampus and increased 5-hydroxy-indolacetic acid (5-HIAA), the main metabolite of 5-HT, in hypothalamus, hippocampus, and striatum. Chronic administration of testosterone normalized 5-HIAA levels in striatum; however, the levels of 5-HT and 5-HIAA in hypothalamus and hippocampus were restored to precastration levels only following estradiol benzoate treatment (Bitar et al., 1991). Moreover, Kendall et al. (1982) showed that orchidectomy blocked the decline in 5-HT$_2$ receptor binding produced by imipramine, while long-term treatment with estradiol, but not with testosterone or dihydrotestosterone, restored the action of imipramine on the density of these receptors. This information suggests that other hormones, like estradiol, may participate in the antidepressant actions of serotonergic compounds.

The results of the present study, together with those of others (Estrada-Camarena et al., 2004) permit an interesting sex comparison in the response to antidepressant treatments. Thus, while ovariectomy increases the antidepressant-like action of FLX and DMI (Estrada-Camarena et al., 2004), orchidectomy, by contrast, impairs such actions (present results). Moreover, estradiol in females, but not testosterone in males, synergizes with DMI and FLX promoting a maximized antidepressant-like response in the FST (Estrada-Camarena et al., 2004; present results). On this basis, it can be concluded that ovarian hormones modulate the effects of antidepressant drugs, whereas androgens and their derivatives are needed for the expression of the behavioral actions of these antidepressants. Such changes may be sex or hormonal specific.

To summarize, orchidectomy and testosterone produce no changes in normal behavior expressed by rodents in the FST. Interestingly, the antidepressant actions of DMI, CMI, and FLX were completely blocked by orchidectomy and TP supplementation fully restored the action of DMI without reestablishing that of CMI and FLX.

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