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Antipsychotic-Like Properties of 5-α-Reductase Inhibitors

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Recent evidence indicates that neuroactive steroids may participate in the pathogenesis of schizophrenia spectrum disorders, yet the mechanisms of this involvement are elusive. As 5-α-reductase (5AR) is the rate-limiting enzyme of one of the two major metabolic pathways in brain steroidogenesis, we investigated the effects of its blockade in several rat models of psychotic-like behavior. The 5AR inhibitor finasteride (FIN, 60 or 100 mg/kg, intraperitoneal, i.p.) dose- and time-dependently antagonized prepulse inhibition (PPI) deficits induced by apomorphine (APO, 0.25 mg/kg, subcutaneous, s.c.) and *d*-amphetamine (AMPH, 5 mg/kg, s.c.), in a manner analogous to haloperidol (HAL, 0.1 mg/kg, i.p.) and clozapine (CLO, 5 mg/kg, i.p.). Similar results were observed with the other 5AR inhibitors dutasteride (DUT, 40 or 80 mg/kg, i.p.) and SKF 105111 (30 mg/kg, i.p.). FIN (60 or 100 mg/kg, i.p.) also reduced hyperlocomotion induced by AMPH (1 or 3 mg/kg, s.c.) and attenuated stereotyped behaviors induced by APO (0.25 mg/kg, s.c.). Nevertheless, FIN (100 mg/kg, i.p.) did not reverse the PPI disruption induced by the *N*-methyl-*d*-aspartate receptor antagonist dizocilpine (0.1 mg/kg, s.c.). FIN (60–300 mg/kg, i.p.) induced no catalepsy in either the bar test or the paw test. Our results suggest that 5AR inhibitors elicit antipsychotic-like effects in animals and may be proposed as a putative novel target in the management of psychotic disorders.
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INTRODUCTION

The role of neuroactive steroids (NSs) in psychotic disorders has been extensively documented by converging lines of clinical and experimental evidence. Although schizophrenia-spectrum disorders are equally prevalent in the two sexes, their course is typically more severe in men, with earlier onset, higher incidence of negative symptoms and worse premorbid functioning, and clinical outcome (Castle *et al*, 1998; Leung and Chue, 2000). Although estrogens play a protective role in schizophrenia (Grigoriadis and Seeman, 2002; Riecher-Rossler, 2002), androgens have also been reported to modulate the expression of psychotic phenomena. For instance, synthetic androgens might also induce and precipitate psychotic-like abnormalities (Trenton and Currier, 2005). Conversely, testosterone and dehydroepiandrosterone may have antipsychotic potential (Strous, 2005; Strous *et al*, 2003; Van den Buuse and Eikelis, 2001) and their levels are typically low in schizophrenia patients (Goyal *et al*, 2004; Huber *et al*, 2005; Taherianfard and Shariaty, 2004).

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The implication of NSs in schizophrenia is not limited to sex hormones. NS levels have been correlated to the severity of symptoms in schizophrenic patients (Akhondzadeh *et al*, 2006; Goyal *et al*, 2004; Shirayama *et al*, 2002). This possibility is supported by the notion that environmental stress, a major factor in the etiology of psychosis (Howes *et al*, 2004), has been shown to affect the metabolism of several NSs (Barbaccia *et al*, 2001). Moreover, NSs influence the function of all the major key substrates involved in the pathophysiology of psychotic disorders, such as the dopaminergic mesolimbic system (Barrot *et al*, 1999; Jaworska-Feil *et al*, 1998; Rouge-Pont *et al*, 2002), as well as the *N*-methyl-*d*-aspartate (NMDA) glutamate receptor (Monnet *et al*, 1995).

This background prompted us to investigate the role of 5-α-reductase (5AR), the rate-limiting enzyme of one of the two major metabolic pathways in brain steroidogenesis, in the pathophysiology of psychotic phenomena. 5AR converts ketosteroid precursors (such as progestagens, androgens, and glucocorticoids) into their active 5-α-reduced metabolites (Martini *et al*, 1993, 1996). Two isoforms of 5AR have been identified, differing from each other in chemical characteristics and tissue distribution. In the rat brain, 5AR type 1 is constantly present throughout all developmental stages, whereas the expression of 5AR type 2 in the adult is mainly driven by androgen signaling (Poletti *et al*, 1998; Torres and Ortega, 2003).

5-α-Reductase plays a key role in the stress-mediated conversion of progesterone into the NS allopregnanolone (AP), an endogenous anxiolytic compound acting on the γ-aminobutyric acid $(GABA)_A$ receptor. Notably, both progesterone and AP may play a role in the modulation of psychotic-like behaviors in rodents (Khisti *et al*, 2002; Rupprecht *et al*, 1999). This enzyme, however, is also responsible for the metabolism of several other steroid precursors into their 5-α-reduced metabolites. For example, 5AR converts testosterone into 5-α-dehydrotestosterone (DHT), the most potent androgen that stimulates the acquisition of most secondary sexual traits in men (Breedlove, 1992). The 5AR-mediated synthesis of DHT is one of the most remarkable endocrine changes occurring in adolescence and late puberty, the developmental stage with the highest incidence of schizophrenia in men. Taken together, these premises highlight a potential involvement of 5AR in the pathogenesis of psychotic disorders.

The present study focuses on the antipsychotic-like effects of finasteride (FIN) and other 5AR inhibitors on rat models of psychotic-like behaviors. Although in humans FIN acts as a selective inhibitor of the peripheral 5AR type-2, in rats it is known to block efficiently both 5AR isozymes, and is in fact generally used to inhibit neurosteroid synthesis in rats (Concas *et al*, 1998; Finn *et al*, 2006). We focused on the ability of FIN and other 5AR inhibitors to reverse psychotic-like behaviors in rats induced by the dopaminergic agonists apomorphine (APO) and *d*-amphetamine (AMPH), as well as the NMDA receptor antagonist dizocilpine (DIZ). Specifically, we tested the ability of FIN to prevent a number of behavioral effects induced by these psychotomimetic agents, including the reduction in prepulse inhibition (PPI) of the acoustic startle, locomotor hyperactivity, and stereotyped behaviors. These behavioral alterations are considered isotypic with preattentional, motor, and cognitive abnormalities in schizophrenia (Randrup and Munkvad, 1974; Evenden and Robbins, 1983; Costall and Naylor, 1995; Giuliani and Ferrari, 1997; Geyer *et al*, 2001) and are countered by antipsychotic drugs (Bakshi *et al*, 1994; Geyer *et al*, 2001; Hoffman *et al*, 1993).

MATERIALS AND METHODS

Animals

A total of 748 male Sprague–Dawley albino rats (Charles River, Como, Italy) weighing 225–300 g were kept on a 12/12-h dark/light cycle with food and water available *ad libitum*. All experimental protocols were accepted by the Ethical Committee at the University of Cagliari and performed in strict accordance with the Italian Ministry of Health regulation for the care and use of laboratory animals (DL 11692).

Drugs

Finasteride (Polichimica, Bologna, Italy), dutasteride (DUT) (Andachem, Taiyuan, China), and SKF 105111 (synthesized in our facilities as described in Holt *et al* (1990)) were suspended in Tween 80 and diluted with distilled water (1% Tween 80/distilled water; 1 : 9 vol : vol). APO (Sigma Aldrich, Italy) was dissolved in a solution containing 0.9% saline with 0.1 mg/ml ascorbic acid.

Haloperidol (HAL) and clozapine (CLO) (Sigma Aldrich) were dissolved in a single drop of 1 N hydrogen chloride (HCl) and diluted with saline. DIZ and AMPH (Sigma Aldrich) were dissolved in 0.9% saline.

The doses of APO, AMPH, DIZ, HAL, and CLO used in the study were selected based on previous experiments, in which they elicited fully significant effects in the behavioral parameters tested, under our experimental conditions.

The maximal doses of FIN and DUT used in this study (80 and 100 mg/kg, intraperitonially, i.p., respectively) were selected based on preliminary investigations from our group and on evidence showing their ability to produce a full inhibition of 5AR in rodents after acute treatment (Kokate *et al*, 1999; Reddy *et al*, 2001; Reddy and Rogawski, 2002).

All drugs were administered in an injection volume of 1 (subcutaneously, s.c.) or 2 ml/kg body weight (i.p.).

Experimental Design and Procedures

Acoustic startle and PPI. Acoustic startle reflex and PPI were studied as described (Bortolato *et al*, 2005). Briefly, rats were placed in a startle reflex apparatus (Med Associates, St Albans, VT, USA) for a 5-min acclimatization period with a 70 dB background noise, which continued for the remainder of the session. Each session consisted of three consecutive sequences of trials. During the first and the third sequence, the rats were presented with five pulse-alone trials of 115 dB. The second sequence consisted of 50 trials in pseudorandom order, including 12 pulse-alone trials, 30 trials of pulse preceded by 73, 76, or 82 dB prepulses (10 for each level of prepulse loudness), and eight no-stimulus trials, where only the background noise was delivered. The duration of pulses and prepulses was 80 and 40 ms, respectively. Prepulse–pulse delay amounted to 100 ms. Intertrial intervals were selected randomly between 10 and 15 s. Percent PPI was calculated with the following formula: 100−((mean startle amplitude for prepulse–pulse trials/mean startle amplitude for pulse-alone trials) × 100).

In the first experiment, we tested the effects of FIN on the PPI disruption mediated by APO, in comparison to the antipsychotics HAL and CLO. Thus, we injected rats ($n = 8$–12 per group) with either FIN (60 or 100 mg/kg, i.p.), HAL (0.1 mg/kg, i.p.), CLO (5 mg/kg, i.p.), or their respective vehicles. Sixty minutes later, rats were treated with either APO (0.25 mg/kg, s.c.) or saline, and immediately subjected to behavioral testing.

The goal of the second experiment was to identify the duration of FIN effects on startle amplitude and PPI in rats. Thus, separate groups of animals received FIN (100 mg/kg, i.p.) at several time intervals (0, 15, 30, 60, and 120 min) before APO treatment (0.25 mg/kg, s.c.) ($n = 11$ per group), and were tested immediately after APO injection.

The third and the fourth experiments mirrored the first one in studying the ability of DUT (40 or 80 mg/kg, i.p.) and SKF 105111 (30 mg/kg, i.p.) to prevent the PPI impairment mediated by APO (0.25 mg/kg, s.c.) ($n = 8$ animals per group). Both compounds were injected 60 min before APO.

In the fifth experiment, we injected either FIN (60 or 100 mg/kg, i.p.) or its vehicle 50 min before either AMPH (5 mg/kg, s.c.) or saline. We also tested the effects of HAL (0.1 mg/kg, i.p., 45 min before AMPH) and CLO (5 mg/kg,

i.p., 30 min before AMPH) in the same paradigm, in comparison with their vehicle (saline with one drop of 1 N HCl). Ten minutes after AMPH treatment, rats were placed in the startle chamber and tested ($n = 8$–11 per group).

In the sixth experiment, we used the same treatment schedule to study the impact of FIN (100 mg/kg, i.p.), HAL (0.1 mg/kg, i.p.), and CLO (5 mg/kg, i.p.) against DIZ (0.1 mg/kg, s.c.)-mediated PPI disruption ($n = 8$ per group).

Locomotor activity. We then investigated the antipsychotic-like effects of FIN on the hyperlocomotion induced by AMPH (1 or 3 mg/kg, s.c.). Motor activity was measured by placing the animals individually in novel motility cages (Omnitech Digiscan Animal Activity Monitor, Columbus, OH, USA), in a dimly lit experimental room. Each cage had two sets of 16 photocells located at right angles to each other, projecting horizontal infrared beams 2.5 cm apart and 2 cm above the cage floor. Motor activity was defined as the horizontal activity counts and collected every 10 min via custom software.

In the first experiment, animals were placed in the locomotor activity cage 40 min after injection with FIN (60 or 100 mg/kg, i.p.), its vehicle, or HAL (0.1 mg/kg, i.p.) ($n = 12$ per group). This time interval was selected based on the observation that the maximal effect of FIN was observed between 30 and 60 min.

In the second series of experiments, animals received FIN (100 mg/kg, i.p.), its vehicle, or HAL (0.1 mg/kg, i.p.). Forty minutes later, they were placed in the activity cages. After 10 min in the cages, they received AMPH (1 or 3 mg/kg, s.c.). Locomotor activity was monitored for 80 min ($n = 12$ per group).

Stereotyped behaviors. Stereotyped behavior was measured while the rats were located in perspex cages with a wire grid floor. After two habituation sessions (60 min), animals received FIN (100 mg/kg, i.p.) or its vehicle, HAL (0.1 mg/kg, i.p.) or CLO (5 mg/kg, i.p.) 30 or 60 min before APO (0.25 mg/kg, s.c.) ($n = 8$ per group). Following APO injection, their behavior was recorded by an independent observer unaware of the drug treatment. Stereotyped behavior was quantified for 30 min according to the Iversen and Creese scale (Iversen and Creese, 1975). Each animal was finally assigned a final stereotypy score, defined as the average value of all the scores of the session.

Bar and paw tests. To assess the liability of 5AR inhibitors to induce extrapyramidal symptoms, we tested FIN-induced catalepsy. This behavior, consisting of the inability to modify a body posture imposed by the experimenter, is generally interpreted as isomorphic to extrapyramidal symptoms in humans (Burki, 1979), such as acute dystonia, akathisia, and parkinsonism. Catalepsy was assessed via the bar test, as described in Sanberg *et al* (1988). Sixty minutes following treatment with FIN (60–300 mg/kg, i.p.), its vehicle ($n = 8$ per group), HAL (1 mg/kg, i.p.), or CLO (5 mg/kg, i.p.), the forepaws of the rats were placed on a 9-cm high bar and the length of time during which the animal retained this position was recorded 60 min after treatment by an observer unaware of the treatment. The longest time of three consecutive trials was recorded. Rats were removed from the bar if their catalepsy duration on the test exceeded 300 s.

To further characterize the potential degree of motor impairment produced by 5AR blockade, we studied the effect of FIN, HAL, and CLO on the spontaneous paw retraction of the forelimbs and the hindlimbs of the rat in the paw test, a well-validated model of antipsychotic screening. Paw test was performed as described in Ellenbroek *et al* (1987). Immediately following the bar test, rats were placed on a perspex box (30 cm × 30 cm; 20 cm height), with two holes (diameter: 4 cm) for the forepaws, two holes (diameter: 5 cm) for the hindpaws, and a slit for the tail. Two dependent variables were scored: (i) forelimb retraction time (FRT) and (ii) hindlimb retraction time (HRT).

Experimental Design and Statistical Analyses

All experiments had a between-subjects design. Results are expressed as the mean ± SEM of n experiments. All analyses were conducted using Statistica (Statsoft, Tulsa, USA). The significance of differences between groups was determined by one-, two-, or three-way analysis of variance (ANOVA) followed by Tukey's test for multiple comparisons, as appropriate.

RESULTS

Effects of 5AR Inhibitors on Startle and PPI of Startle

The first experiment was aimed at testing the impact of FIN (60 or 100 mg/kg, i.p.), HAL (0.1 mg/kg, i.p.), and CLO (5 mg/kg, i.p.) on the disruption of PPI mediated by APO (0.25 mg/kg, s.c.). The effect of FIN on startle amplitude (as compared to its vehicle) was studied with a two-way ANOVA (with pretreatment and treatment as independent factors).

Finasteride significantly reduced baseline startle magnitude (main effect of pretreatment: $F(2, 66) = 31.34$, $p < 0.001$). Tukey's test revealed that this effect was due to the dose of 100 mg/kg ($p < 0.001$ in comparison with VEH) (Table 1). Furthermore, APO significantly increased startle amplitude ($F(1, 66) = 9.56$, $p < 0.01$). No significant interactions between pretreatment and treatment were found. As shown in Table 1, a parallel analysis performed on the effects of HAL and CLO in comparison to their vehicle (SAL) revealed that both HAL (main effect of pretreatment: $F(1, 36) = 39.89$, $p < 0.001$) and CLO (main effect of pretreatment: $F(1, 30) = 42.01$, $p < 0.001$) significantly decreased startle reflex. However, no significant pretreatment × treatment interaction was found for either treatment (HAL: $F(1, 36) = 1.74$, NS; CLO: $F(1, 30) = 1.08$, NS).

Subsequently, a three-way ANOVA (with pretreatment and treatment as independent factors and prepulse levels as repeated measures) assessed that FIN did not affect baseline PPI at any loudness level, but prevented APO-mediated PPI reduction (main effect of pretreatment: $F(2, 66) = 8.81$, $p < 0.01$; main effect of treatment: $F(1, 66) = 4.39$, $p < 0.05$; main effect of prepulse level: $F(2, 132) = 7.09$, $p < 0.01$; interaction treatment × pretreatment $F(2, 66) = 9.01$, $p < 0.001$; ANOVA) in a fashion similar to HAL (main effect

of pretreatment: $F(1,36)=15.13$, $p<0.001$; main effect of treatment: $F(1,36)=11.75$, $p<0.001$; interaction treatment × pretreatment: $F(1,36)=28.25$, $p<0.001$; ANOVA) and CLO (main effect of pretreatment: $F(1,30)=19.12$, $p<0.001$; main effect of treatment: $F(1,30)=15.14$, $p<0.001$; interaction treatment × pretreatment: $F(1,30)=6.26$, $p<0.01$; ANOVA) (Figure 1a). *Post-hoc* comparisons revealed that both 60 and 100 mg/kg FIN, as well as HAL and CLO, significantly reversed the PPI deficit induced by the dopaminergic agonist ($p<0.01$ for comparisons VEH + APO *vs* FIN 60 + APO; $p<0.001$ for comparisons VEH + APO *vs* FIN 100 + APO, SAL + APO *vs* HAL + APO, and SAL + APO *vs* CLO + APO; Tukey's).

Table 1 Effects of Finasteride (FIN), Haloperidol (HAL), and Clozapine (CLO) on the Alterations of Startle Reflex Induced by Apomorphine (APO)

		Mean startle amplitude ± SEM	
VEH	SAL	763.5 ± 21.3	
VEH	APO 0.25	894.4 ± 28.8	
FIN 60	SAL	761.3 ± 24.5	
FIN 60	APO 0.25	791.9 ± 28.2	
FIN 100	SAL	587.1 ± 32.2	###
FIN 100	APO 0.25	640.3 ± 33.3	###
SAL	SAL	728.7 ± 16.8	
SAL	APO 0.25	871.4 ± 36.8	
HAL 0.1	SAL	478.4 ± 24.5	***
HAL 0.1	APO 0.25	465.6 ± 28.7	***
CLO 5	SAL	403.4 ± 30.3	***
CLO 5	APO 0.25	422 ± 38.7	***

Values represent mean startle amplitude ± SEM following each treatment. For all groups, $n=8$–12. Doses are given in mg/kg. VEH, vehicle (of FIN); SAL, saline. ###$p<0.001$ in comparison to VEH (pretreatment); ***$p<0.001$ in comparison to SAL (pretreatment).

In the second experiment, startle analysis was run by one-way ANOVA (with time as independent factor). Although startle amplitudes gradually decreased across time, no significant effect was detected ($F(4,50)=0.55$, NS) (data not shown). PPI was analyzed by a two-way ANOVA, with time as the independent factor and prepulse levels as the repeated measures. FIN (100 mg/kg, i.p.) antagonized APO-mediated PPI disruption in a time-dependent fashion (main effect of time: $F(4,50)=33.40$, $p<0.001$), reaching its maximal efficacy 30–60 min following administration ($p<0.01$ for comparisons 0–30 min and 0–60 min; Tukey's test) (Figure 1b). Furthermore, a significant effect was found for prepulse levels ($F(2,100)=19.74$, $p<0.001$), although no time × prepulse level interaction was detected ($F(8,100)=1.01$, NS).

We then characterized the effects of the 5AR inhibitor DUT (40 or 80 mg/kg, i.p.) on PPI disruption mediated by APO (0.25 mg/kg, s.c.) (Figure 2a). Startle magnitudes were analyzed by a two-way ANOVA (with pretreatment and treatment as factors) (Table 2). The main effect was found for pretreatment ($F(2,42)=3.40$, $p<0.05$). Tukey's test detected that the dose of 80 mg/kg DUT induced a significant reduction of startle magnitude in comparison to VEH ($p<0.05$). No significant effects were found for treatment or pretreatment × treatment interaction. PPI was analyzed by a three-way ANOVA, with pretreatment and treatment as independent factors and prepulse levels as repeated measures. ANOVA revealed main effects of

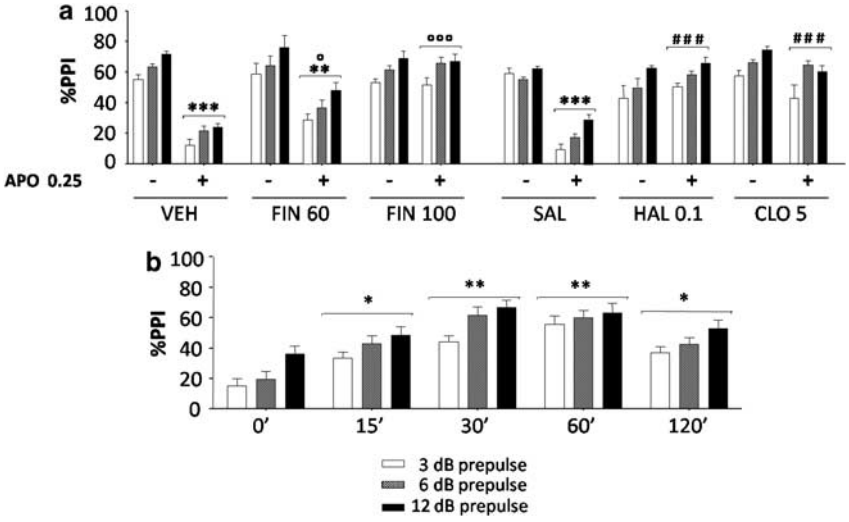

Figure 1 (a) Effects of finasteride (FIN), haloperidol (HAL), and clozapine (CLO) on apomorphine (APO)-induced PPI deficits. (b) Time course of FIN (100 mg/kg, i.p.)-mediated reversal of PPI deficits induced by APO. Values represent mean ± SEM for each treatment. VEH, finasteride vehicle; SAL, haloperidol and clozapine vehicle (saline + 1 drop NaOH). For all groups, $n=9$–12. Doses are given in mg/kg. Time is given in minutes. Prepulses are indicated by the intensity corresponding to decibels above background noise. *$p<0.05$, **$p<0.01$, ***$p<0.001$ in comparison to controls (a) and 0 min (b); °$p<0.05$, °°°$p<0.001$ in comparison to VEH + APO 0.25.

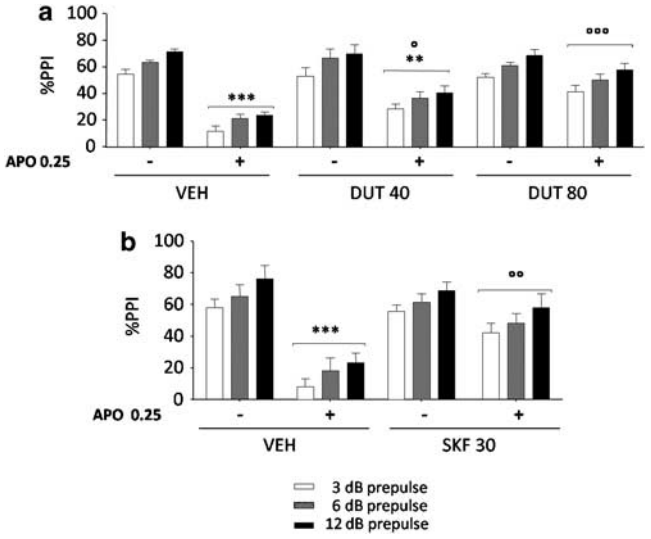

Figure 2 Effects of (a) dutasteride (DUT) and (b) SKF 105111 (SKF) on apomorphine (APO)-induced PPI deficits. Values represent mean ± SEM for each treatment. VEH, finasteride vehicle. For all groups, $n = 11$. Doses are given in mg/kg. Prepulses are indicated by the intensity corresponding to decibels above background noise. $^{**}p < 0.01$, $^{***}p < 0.001$ in comparison to controls; $^{\circ}p < 0.05$, $^{\circ\circ}p < 0.01$, $^{\circ\circ\circ}p < 0.001$ in comparison to VEH + APO 0.25.

Table 2 Effects of Dutasteride (DUT) on the Alterations of Startle Reflex Induced by Apomorphine (APO)

		Mean startle amplitude ± SEM
VEH	SAL	735.6 ± 27.9
VEH	APO 0.25	906.28 ± 34.4
DUT 40	SAL	826.1 ± 16.6
DUT 40	APO 0.25	763.1 ± 34.1
DUT 80	SAL	608 ± 19.9 } #
DUT 80	APO 0.25	676.1 ± 17.6 } #

Values represent mean startle amplitude ± SEM following each treatment. For all groups, $n = 8$. Doses are given in mg/kg. VEH, vehicle. $^{\#}p < 0.05$ in comparison to VEH (pretreatment).

pretreatment ($F(2, 42) = 6.51$, $p < 0.01$) and treatment ($F(1, 42) = 28.66$, $p < 0.001$), as well as a statistical trend for prepulse levels ($F(2, 42) = 4.96$, $p < 0.10$). A significant treatment × pretreatment interaction was also found ($F(2, 42) = 4.96$, $p < 0.05$). *Post-hoc* analysis revealed that both doses of DUT countered APO-induced PPI disruption (Figure 2a).

The fourth experiment (analyzed with the same statistical design as the previous one) revealed that SKF 105111 (30 mg/kg, i.p.) significantly reduced startle amplitude (main effect of pretreatment: $F(1, 28) = 6.70$, $p < 0.05$; ANOVA) (Table 3). The analysis of PPI disclosed significant main effects of pretreatment ($F(1, 28) = 29.61$, $p < 0.001$), treatment ($F(1, 28) = 16.74$, $p < 0.001$), and prepulse level ($F(2, 56) = 4.00$, $p < 0.05$), as well as a significant pretreatment × treatment interaction ($F(1, 28) = 4.12$, $p < 0.05$). This effect was due to the ability of SKF 10511 to antagonize the PPI deficit mediated by APO ($p < 0.01$ for comparison SKF-APO *vs* VEH APO; Tukey's test) (Figure 2b).

Table 3 Effects of SKF 105111 (SKF) on the Alterations of Startle Reflex Induced by Apomorphine (APO)

		Mean startle amplitude ± SEM
VEH	SAL	750.1 ± 37.8
VEH	APO 0.25	833.4 ± 31.1
SKF 30	SAL	574.8 ± 27.1 } #
SKF 30	APO 0.25	571.5 ± 20.8 } #

Values represent mean startle amplitude ± SEM following each treatment. For all groups, $n = 8$. Doses are given in mg/kg. VEH, vehicle. $^{\#}p < 0.05$ in comparison to VEH (pretreatment).

Subsequently, we tested the ability of FIN to reverse the PPI disruption mediated by AMPH (5 mg/kg, s.c.), in comparison with HAL and CLO (Figure 3a). Startle analysis for FIN (60 or 100 mg/kg, i.p.) and its VEH did not reveal any significant effect (Table 4). In contrast, both antipsychotic treatments significantly reduced startle amplitude in comparison to their vehicle (main effect of pretreatment: $F(2, 42) = 12.21$, $p < 0.001$). FIN reversed the PPI impairment produced by AMPH (main effect of pretreatment: $F(2, 60) = 17.45$, $p < 0.001$; main effect of treatment: $F(1, 60) = 82.83$, $p < 0.001$; pretreatment × treatment interaction: $F(2, 60) = 27.76$, $p < 0.001$; ANOVA), in a fashion similar to both antipsychotic agents. In parallel, HAL and CLO significantly reversed AMPH-mediated PPI deficit (main effect of treatment: $F(1, 42) = 34.69$, $p < 0.001$; interaction treatment × pretreatment: $F(2, 42) = 19.24$, $p < 0.001$; ANOVA) (Figure 3a).

In the sixth experiment, no significant effect of FIN (100 mg/kg, i.p.) or DIZ (0.1 mg/kg, s.c.) was detected on startle amplitude, whereas both HAL and CLO significantly reduced this parameter in comparison to their vehicle (main effect of pretreatment: $F(2, 42) = 11.42$, $p < 0.001$) (Table 5). Neither the 5AR inhibitor nor the HAL affected the PPI disruption mediated by DIZ (main effect of treatment: $F(1, 56) = 401.96$, $p < 0.001$). Conversely, CLO attenuated this effect (interaction pretreatment × treatment: $F(1, 28) = 16.22$, $p < 0.001$) (Figure 3b).

Effects of FIN on Spontaneous Locomotor Activity and AMPH-Mediated Hyperlocomotion

We next tested the ability of FIN and HAL to affect locomotor activity and to reduce hyperlocomotion produced by AMPH and DIZ, two validated animal models of psychotic-like behaviors. As indicated in Figure 4, both FIN (60 or 100 mg/kg, i.p.) and HAL (0.1 mg/kg, i.p.) significantly reduced spontaneous locomotor activity ($F(3, 44) = 53.62$, $p < 0.001$), in a time-dependent fashion (main effect of time: $F(7, 308) = 98.86$, $p < 0.001$; interaction time × treatment: $F(21, 308) = 8.37$, $p < 0.001$). *Post-hoc* comparisons revealed that the reduction in locomotor

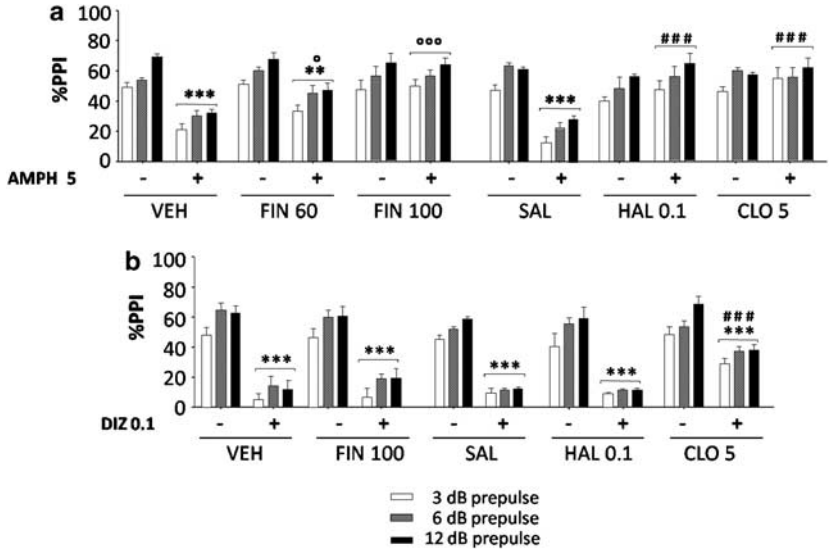

Figure 3 Effects of finasteride (FIN, 60 or 100 mg/kg, i.p.), haloperidol (HAL, 0.1 mg/kg, i.p.), and clozapine (CLO, 5 mg/kg, i.p.) on (a) *d*-amphetamine (AMPH)- and (b) dizocilpine (DIZ)-induced PPI deficits. Values represent mean ± SEM for each treatment. VEH, finasteride vehicle; SAL, haloperidol and clozapine vehicle (saline + 1 drop NaOH). For all groups, $n = 7$–11. Doses are given in mg/kg. Prepulses are indicated by the intensity corresponding to decibels above background noise. $^{**}p < 0.01$, $^{***}p < 0.001$ in comparison to controls; $^{\circ}p < 0.05$, $^{\circ\circ\circ}p < 0.001$ in comparison to VEH-AMPH; $^{\#\#\#}p < 0.001$ in comparison to SAL-DIZ.

Table 4 Effects of Finasteride (FIN), Haloperidol (HAL), and Clozapine (CLO) on the Alterations of Startle Reflex Induced by *d*-Amphetamine (AMPH)

		Mean startle amplitude ± SEM	
VEH	SAL	758 ± 22.5	
VEH	AMPH 5	816.9 ± 30.7	
FIN 60	SAL	676.4 ± 28.3	
FIN 60	AMPH 5	718.1 ± 37.3	
FIN 100	SAL	626.4 ± 18.8	
FIN 100	AMPH 5	642.4 ± 22.2	
SAL	SAL	747.7 ± 27.3	
SAL	AMPH 5	759.7 ± 14.3	
HAL 0.1	SAL	462.4 ± 19.6	***
HAL 0.1	AMPH 5	561.7 ± 19.3	
CLO 5	SAL	459.7 ± 27.3	***
CLO 5	AMPH 5	578.4 ± 20.8	

Values represent mean startle amplitude ± SEM following each treatment. For all groups, $n = 8$–11. Doses are given in mg/kg. VEH, vehicle (of FIN); SAL, saline. $^{***}p < 0.001$ in comparison to SAL (pretreatment).

Table 5 Effects of Finasteride (FIN), Haloperidol (HAL), and Clozapine (CLO) on the Alterations of Startle Reflex Induced by Dizocilpine (DIZ)

		Mean startle amplitude ± SEM	
VEH	SAL	767.9 ± 94.5	
VEH	DIZ 0.1	870.8 ± 79.4	
FIN 100	SAL	683.2 ± 30.2	
FIN 100	DIZ 0.1	729.9 ± 54.5	
SAL	SAL	768.6 ± 41.9	
SAL	DIZ 0.1	861.4 ± 42	
HAL 0.1	SAL	488.4 ± 18	***
HAL 0.1	DIZ 0.1	657.7 ± 15.3	
CLO 5	SAL	363.8 ± 11.8	***
CLO 5	DIZ 0.1	545.3 ± 14.4	

Values represent mean startle amplitude ± SEM following each treatment. For all groups, $n = 8$. Doses are given in mg/kg. VEH, vehicle (of FIN); SAL, saline. $^{***}p < 0.001$ in comparison to SAL (pretreatment).

activity produced by 60 mg/kg FIN was significant only 60 min after injection ($p < 0.05$; Tukey's test), whereas 100 mg/kg FIN and HAL significantly decreased spontaneous activity until 70 and 80 min after administration, respectively (Figure 4).

In the second experiment (Figure 5a), FIN (100 mg/kg, i.p.) and HAL (0.1 mg/kg, i.p.) significantly attenuated the hyperlocomotion mediated by AMPH (3 mg/kg, s.c., injected 50 min after either VEH, FIN, or HAL) (main effect of pretreatment: $F(2, 33) = 247.13$, $p < 0.001$; two-way ANOVA).

Furthermore, ANOVA revealed a significant time-related reduction in locomotor activity ($F(7, 231) = 98.19$, $p < 0.001$) and a significant time × pretreatment interaction

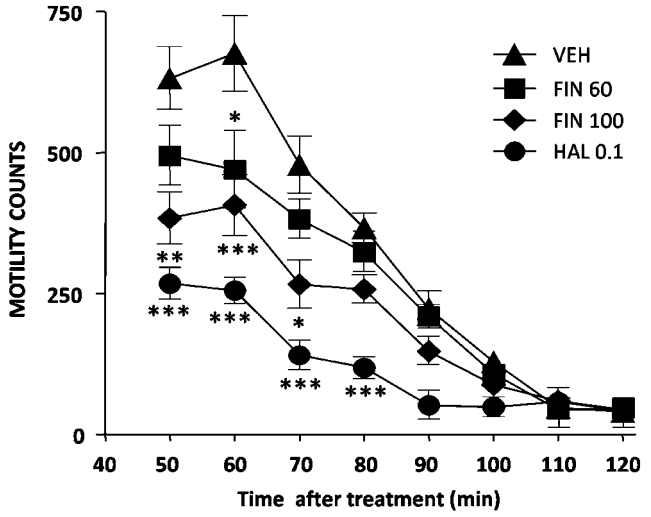

Figure 4 Effects of finasteride (FIN) and haloperidol (HAL) on spontaneous motor activity. All values represent mean ± SEM. Animals were placed in the motility cages 40 min after vehicle (VEH), FIN, or HAL. Doses are given in mg/kg. For all groups, $n = 8$–12. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ in comparison to vehicle (VEH)-treated animals. For further details, see text.

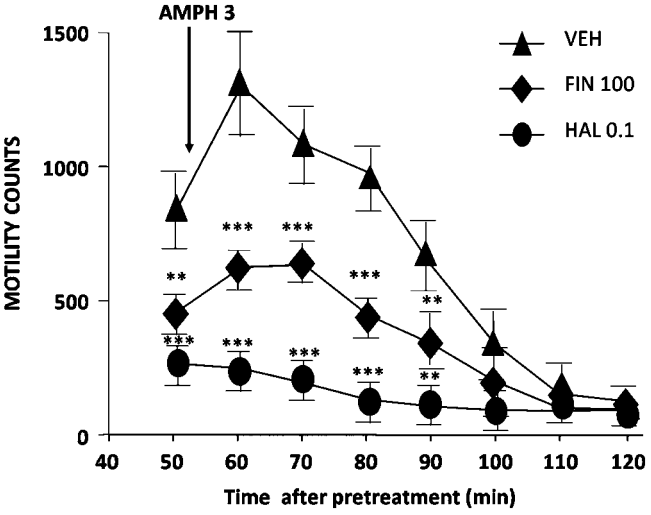

Figure 5 Effects of finasteride (FIN) and haloperidol (HAL) on hyperlocomotion mediated by *d*-amphetamine (AMPH). Animals were placed in the motility cages 40 min after vehicle (VEH), FIN, or HAL (pretreatments), and were injected with AMPH after 10 min (arrows). All values represent mean ± SEM. Doses are given in mg/kg. For all groups, $n = 8$–12. **$p < 0.01$; ***$p < 0.001$ in comparison to VEH-treated animals. For further details, see text.

($F(14, 231) = 29.19$, $p < 0.001$). *Post-hoc* analyses revealed that both FIN- and HAL-mediated effects lasted for 40 and 50 min following AMPH injection, respectively (FIN: $p < 0.05$ and HAL: $p < 0.01$ for both comparisons; Tukey's test). In separate experiments, FIN (100 mg/kg, i.p.) also reversed the hyperlocomotion induced by lower doses of AMPH (1 mg/kg, s.c.) (data not shown).

Effects of FIN on APO-Mediated Stereotyped Behaviors

The antipsychotic-like properties of FIN (100 mg/kg, i.p.) were further evaluated on the stereotyped behavior induced by APO (0.25 mg/kg, s.c.), in comparison with HAL (0.1 mg/kg, i.p.) and CLO (5 mg/kg, i.p.). As shown in Figure 6a, both FIN and the two antipsychotic agents elicited a significant reduction in time spent in chewing, gnawing, and licking, with a general reduction in Creese and Iverson score. Such decrease was observed both 30 min ($F(3, 28) = 42.28$, $p < 0.001$; ANOVA) and 60 min ($F(3, 28) = 15.77$, $p < 0.001$; ANOVA) after FIN, antipsychotic or vehicle injection. Tukey's test revealed that FIN, HAL, and CLO produced at both times a highly significant reduction of stereotyped behaviors ($p < 0.001$ for FIN-VEH, HAL-VEH, and CLO-VEH comparisons at both times).

Notably, *post-hoc* analyses also revealed that the effects of HAL and CLO were significantly higher than those elicited by FIN ($p < 0.01$ for all comparisons; Tukey's test).

Effects of FIN on Catalepsy and Paw Test

In the bar test, HAL induced a significant cataleptic effect in comparison to the other groups ($F(4, 35) = 211.21$; $p < 0.001$, $p < 0.001$; Tukey's test) (Figure 6b). Conversely, FIN did not produce catalepsy at any dose (60–300 mg/kg, i.p.). The dose of 1000 mg/kg (i.p.) FIN was tested only in two rats, as it induced tonic-clonic seizure-like events and malaise.

The results from the impact of FIN in the paw test mirrored the responses observed in the previous test, showing no effect on either forepaw or hindpaw retraction times. Conversely, HAL and CLO produced a significant HRT increase ($F(5, 42) = 30.78$; $p < 0.001$, $p < 0.001$ for HAL-VEH and CLO-VEH comparisons). Furthermore, HAL, but not CLO, also augmented FRT ($F(4, 35) = 35.09$, $p < 0.001$ for comparison HAL-VEH) (Figure 6c).

DISCUSSION

The results of the present study show that, in rats, 5AR blockade counters several psychotic-like behavioral effects induced by APO, a potent dopamine receptor agonist, and AMPH, an enhancer of dopamine release.

Specifically, we showed that FIN and other 5AR inhibitors exert an array of behavioral actions similar to those induced by the potent D_2 dopamine receptor antagonist HAL in well-validated rat models of schizophrenia, such as the reduction of AMPH-mediated hyperlocomotion, the antagonism of PPI deficits induced by APO and AMPH, and the attenuation of the stereotyped behavior triggered by APO. Notably, such effects are typically dose- and time-dependent, peaking after 30–60 min following i.p. administration.

To the best of our knowledge, this is the first report to highlight the involvement of 5AR in the modulation of psychotic-like behavioral reactions in rodents.

A parsimonious interpretation of our findings is that 5AR inhibitors may temper a large spectrum of responses mediated by the activation of dopamine receptors. This concept is in agreement with previous studies, showing the ability of FIN to counter other behavioral functions regulated by this neurotransmitter, such as cocaine-induced conditioned place preference (Romieu *et al*, 2003).

As binding analyses attest that FIN binds to neither D_1 nor D_2 dopamine receptors (S Ruiu, personal communication), the ability of this agent and other 5AR inhibitors to

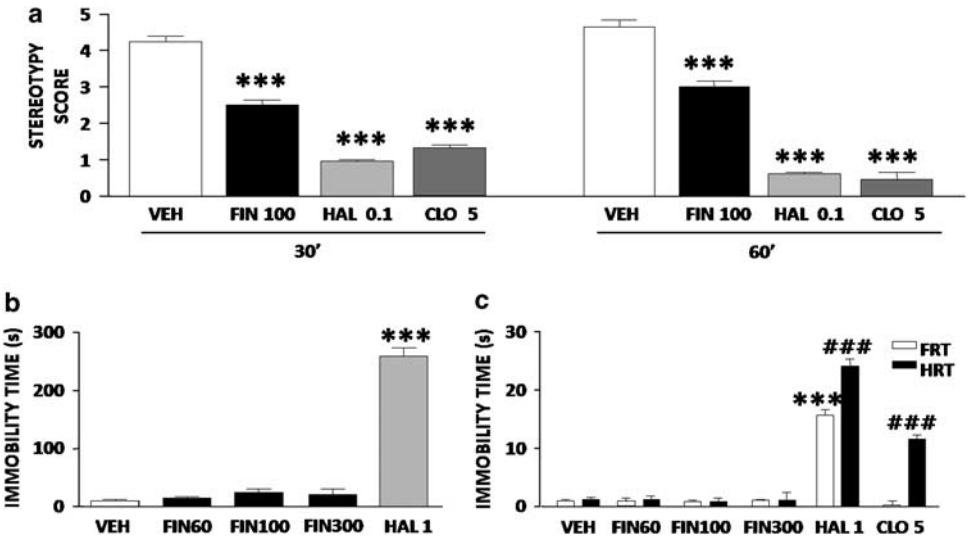

Figure 6 (a) Effects of finasteride (FIN, 100 mg/kg, i.p.) and its vehicle (VEH) on apomorphine (0.25 mg/kg, s.c.)-mediated stereotyped behaviors, in comparison to haloperidol (HAL, 0.1 mg/kg, i.p.) and clozapine (CLO, 5 mg/kg, i.p.). Times (in minutes) indicate the period between injection and beginning of behavioral testing. $^{**}p<0.01$; $^{***}p<0.001$ in comparison to VEH-treated animals; (b) effects of FIN and HAL on catalepsy in the bar test. Doses are given in mg/kg. $^{***}p<0.001$ in comparison to VEH-treated animals. (c) Effects of FIN, HAL, and CLO on forepaw retraction time (FRT) and hindpaw retraction time (HRT) in the paw test. Doses are given in mg/kg. All values represent mean ± SEM for each group. For all groups, $n=8$. Doses are given in mg/kg. $^{***}p<0.001$ in comparison to FRT in VEH-treated animals; $^{###}p<0.001$ in comparison to FRT in VEH-treated animals. For more details, see text.

antagonize the behavioral actions of APO and AMPH strongly suggests that this enzyme may be involved in the modulation of brain dopaminergic signaling beyond the synapse, via direct or indirect mechanisms. 5AR isoforms are expressed in most brain areas and catalyze the conversion of androgens, progestagens, and corticosteroids into their 5-α-reduced metabolites. Thus, the low specificity of FIN and other 5AR inhibitors for 5AR isozymes in rats (Thigpen and Russell, 1992) and our lack of data on the brain regional levels of NSs following 5AR blockade currently limit the identification of the molecular bases of the antipsychotic-like properties of these compounds. Nevertheless, our findings support previous functional and anatomical evidence on the modulatory role of NSs on striatal and cortical dopaminergic functions (Beatty *et al*, 1982; Bitar *et al*, 1991; Dluzen *et al*, 1986; Engel *et al*, 1979; Fabre-Nys, 1998; Hernandez *et al*, 1994; Menniti and Baum, 1981; Savageau and Beatty, 1981). NSs have been shown to affect the extracellular levels of dopamine in prefrontal cortex and striatum (Cabrera *et al*, 2002; Petitclerc *et al*, 1995). Nevertheless, the effects of FIN and other 5AR inhibitors on dopamine release are still unclear, and may vary according to the specific involvement of the NSs metabolized by this enzyme. For example, FIN enhances stress-mediated release of dopamine (Dazzi *et al*, 2002), but prevents ethanol-induced increase in extracellular dopamine concentration (Dazzi *et al*, 2007).

Previous evidence suggests that the ability of these compounds to affect the relative ratios of testosterone, progesterone, and their 5-α-reduced metabolites may be critical for their behavioral properties. Progesterone, but not AP, has been shown to reverse both PPI disruption (Rupprecht *et al*, 1999) and stereotyped behaviors (Palermo-Neto and Dorce, 1990) mediated by APO in rats. Furthermore, some reports have suggested antipsychotic-like properties of progesterone in animals and humans (Bower and Altschule, 1956; Palermo-Neto and Dorce, 1990). Similarly, testosterone, but not DHT, increases PPI in rats (Van den Buuse and Eikelis, 2001). Testosterone levels are also inversely correlated to the incidence of negative symptoms in schizophrenia and to the poverty of clinical outcome (Akhondzadeh *et al*, 2006; Goyal *et al*, 2004). The participation of other NSs, such as glucocorticoids, in the effects of 5AR inhibitors cannot be completely ruled out, in view of their major role in stress and psychosis (Wada *et al*, 2001). This possibility, however, is partially challenged by preliminary clinical observations, reporting that FIN does not significantly alter circulating cortisol levels (Rittmaster *et al*, 1994; Uygur *et al*, 1998).

Throughout this study, the behavioral effects mediated by FIN and other 5AR inhibitors were observed within a short time after administration, suggesting that the NSs responsible for the behavioral effects may act through nongenomic interactions. Indeed, many NSs are known to influence behavioral and cognitive functions through fast-acting interactions with numerous neurotransmitter systems (Heinlein and Chang, 2002).

It is worth noting that some of the PPI responses in these studies were remarkably 'atypical' in comparison to the available evidence in the literature. For example, Sprague–Dawley rats in our facility presented very high levels of spontaneous PPI and were sensitive only to high subcutaneous doses of amphetamine. Although these specific differences may depend on substrain differences, in view of concurrent findings by our group (unpublished results) and others (Swerdlow *et al*, 2000), the potential impact of these variations on the effects of 5-α-reductase inhibitors in PPI has been ruled out in parallel studies with different rat strains (Bortolato *et al*, unpublished results).

Finasteride was unable to reverse the gating disruption induced by the NMDA receptor antagonist DIZ, in a fashion similar to the typical antipsychotic HAL, but differently

from the atypical antipsychotic CLO. The failure of FIN to affect PPI disruption mediated by NMDA receptor blockade is consistent with the possibility that 5AR inhibition specifically affects dopamine-dependent molecular mechanisms of psychosis. Indeed, NMDA antagonists produce psychotic-like alterations that do not generally respond to dopamine receptor blockade and are surmised to simulate clusters of psychotic symptoms less responsive to selective D_2 receptor antagonists.

FIN-induced reduction in locomotor activity may reflect several concurrent mechanisms, mediated by different 5AR substrates. For example, progesterone has been shown to block several receptors that may modulate psychotic-like actions, such as sigma or 5-HT_3 receptors (Monnet and Maurice, 2006; Wetzel *et al*, 1998). Indeed, the blockade of these receptors has previously been shown to reduce spontaneous activity in rodents and to antagonize AMPH-mediated hyperactivity (Costall *et al*, 1987; Wang *et al*, 1992). Regardless of the mechanisms, it should be pointed out that FIN-induced attenuation of AMPH-mediated hyperactivity may partially reflect a spurious effect, due to the overall reduction of spontaneous activity.

Despite its antipsychotic-like profile, high doses of FIN did not produce cataleptic reactions in either the bar or the paw test. However, these findings are not conclusive, as we could not assess the effects induced by 1000 mg/kg (i.p.) FIN (equivalently high as the cataleptogenic HAL dose of 1 mg/kg), because of the malaise and seizure-like phenomena induced by this dose.

With this limitation in mind, these findings suggest that FIN and other 5AR inhibitors may be a promising strategy for psychotic disorders with limited side effects. Accordingly, preliminary clinical observations show that FIN may also exert therapeutic effects in schizophrenia. FIN (5 mg/day) induced some improvements in general and negative symptoms (without detectable side effects), in a patient affected by chronic schizophrenia and poorly responsive to various antipsychotic drugs (including HAL, CLO, and quetiapine) (Koethe *et al*, in press). Although 5AR inhibitors have been generally shown to have few untoward effects and to be well tolerated by patient, they have been shown to sporadically induce erectile dysfunction and gynecomastia (Wilton *et al*, 1996), which may in turn limit the medication compliance. Nevertheless, it is important to emphasize that these side effects are reportedly rare (Wilton *et al*, 1996; Wessells *et al*, 2003) and are also triggered by antipsychotic agents (Segraves, 1989; Macdonald *et al*, 2003).

Although the main goal of the study was to analyze the behavioral effects of FIN and other 5AR inhibitors in schizophrenia-like behaviors, the present results may also be extended to a number of other neuropsychiatric disorders underpinned by excessive dopaminergic neurotransmission, such as manic disturbances and Tourette's syndrome (TS). Interestingly, both disorders display alterations in gating and psychomotor functions (Braff and Geyer, 1990) and are predominantly present in male subjects. For example, androgens have been shown to induce manic symptoms (Pope *et al*, 2000; Weiss *et al*, 1999), and the frequency of manic episodes is higher in bipolar male patients than in their female counterparts (Hendrick *et al*, 2000; Kawa *et al*, 2005). Similarly, TS incidence in men is four times higher than that in women (Pauls *et al*, 1990), and anabolic androgens exacerbate TS symptoms (Leckman and Scahill, 1990).

Notably, we recently documented that chronic treatment with FIN induced marked improvements in tics and obsessive–compulsive symptoms in a case of TS unresponsive to traditional treatment (Bortolato *et al*, 2007).

In conclusion, our results highlight the role of 5AR and NSs in the modulation of dopaminergic responses in animal models of psychosis and related disorders. Although further investigations are warranted to explore the molecular mechanisms underlying the effects of 5AR inhibitors reported in this study, our findings may contribute to the opening of new therapeutic avenues for the treatment of neuropsychiatric disorders underpinned by alterations of dopaminergic signaling.

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DISCLOSURE/CONFLICT OF INTEREST

The authors declare that except for income received from their primary employer, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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