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Inhibition of 5 α -reductase attenuates behavioral effects of D₁-, but not D₂-like receptor agonists in C57BL/6 mice

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Summary

Converging lines of evidence point to the involvement of neurosteroids in the regulation of dopamine (DA) neurotransmission and signaling, yet the neurobiological bases of this link remain poorly understood. We previously showed that inhibition of steroid 5 α -reductase (5 α R), the key rate-limiting enzyme in neurosteroidogenesis, attenuates the behavioral effects of non-selective DA receptor agonists in rats, including stereotyped responses and sensorimotor gating deficits, as measured by the prepulse inhibition (PPI) of the acoustic startle reflex. Since previous findings suggested that the role of DA D₁- and D₂-like receptor families in behavioral regulation may exhibit broad interspecies and interstrain variations, we assessed the impact of 5 α R blockade on the behavioral effects of DAergic agonists in C57BL/6 mice. The prototypical 5 α R inhibitor finasteride (FIN; 25–50 mg/kg, intraperitoneally, IP) dose-dependently countered the PPI deficits and the enhancement of rearing responses induced by the full D₁-like receptor agonist SKF-82958 (0.3 mg/kg, IP); however, FIN did not significantly affect the hyperlocomotive and startle-attenuating effects of SKF-82958. Whereas the D₂-like receptor agonist quinpirole (QUIN; 0.5 mg/kg, IP) did not induce significant changes in PPI, the combination of this agent and FIN surprisingly produced marked gating and startle deficits. In contrast with previous data on rats, FIN did not affect the reductions of startle reflex and PPI produced by the non-selective DAergic agonist apomorphine (APO; 0.5 mg/kg, IP). These findings collectively indicate that, in C57BL/6 mice, 5 α R differentially modulates the effects of D₁- and D₂-like receptor agonists in behavioral regulation.

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Conflicts of interest

The Authors certify that there is no actual or potential conflict of interest in relation to this article.

Contributors: RF designed the experiments, monitored data collection, analysed behavioral data and performed statistical analyses, drafted and revised the manuscript. GP, VB and ST designed and performed behavioral tests and statistics. PD discussed and revised the paper. MB supervised the experimental design and execution, monitored data collection, performed statistical analyses, wrote and revised the manuscript.

Keywords

Finasteride; 5 α -reductase; dopamine; D₁-like receptors; D₂-like receptors; prepulse inhibition of the startle

1. Introduction

Cogent evidence indicates that most physiological functions of neuroactive steroids in the brain, including the regulation of gender-specific processes and stress responsiveness (Kelly et al, 1999; Zinder and Dar, 1999), are mediated by a complex array of interactions with all the major neurotransmitter systems (Rupprecht and Holsboer, 2001; Do Rego *et al*, 2012). In particular, neurosteroids (NSs) – i.e., steroids that are synthesized directly in neural tissues (Baulieu, 1998) – have been shown to exert a pleiomorphic influence on dopamine (DA) signaling (Di Paolo, 1994; Sánchez *et al*, 2010). For example, progesterone, testosterone and 17- β -estradiol have all been shown to induce different effects on DA release and turnover across various brain regions in male and female rodents (Sánchez *et al*, 2010). The elucidation of the interplay between NSs and DA may be a critical step to understand the neurochemical underpinnings of the gender differences and adverse effects of stress typically observed in schizophrenia (Myin-Germeys *et al*, 2002; Häfner, 2003; Jansen *et al*, 2003;), Tourette syndrome (Chappell *et al*, 1994; Santangelo *et al*, 1994; Corbett *et al*, 2008) and other neuropsychiatric disorders related to DAergic perturbations.

Our group has recently shown that the pharmacological inhibition of 5 α -reductase (5 α R), the key rate-limiting enzyme in NS and androgen metabolism (Martini *et al*, 1993; Martini *et al*, 1996; Paba *et al*, 2011), counters several behavioral effects of non-selective DAergic receptor agonists in Sprague-Dawley rats, including hyperlocomotion, stereotypies and sensorimotor gating deficits (Bortolato *et al*, 2008; Devoto *et al*, 2012). In addition, we have documented that the antiDAergic actions of the prototypical 5 α R inhibitor finasteride (FIN), albeit strikingly akin to those induced by classical antipsychotic agents, are not accompanied by catalepsy (Bortolato *et al*, 2008). These results have been supported by preliminary clinical observations documenting the efficacy and high tolerability of FIN in adult male, treatment-refractory patients affected by Tourette syndrome (Bortolato *et al*, 2007; Muroi *et al*, 2011) and chronic schizophrenia (Koethe *et al*, 2008). These promising translational findings highlight the possibility that 5 α R may be a valuable therapeutic target for several mental conditions (Paba *et al*, 2011). The biological bases of the neuropsychiatric effects of 5 α R inhibitors, however, remain elusive. In particular, a crucial yet unresolved issue concerns the specific involvement of the two main DA receptor families, D₁- and D₂-like, in the antipsychotic-like profile of 5 α R inhibitors. To address this problem in the present study, we analyzed the impact of FIN on the behavioral responses to DA receptor agonists in C57BL/6 mice, including the disruption of the prepulse inhibition (PPI) of the acoustic startle reflex. This index is a highly reliable operational parameter for the measurement of sensorimotor gating and informational processing, and is typically impaired in schizophrenia and TS (Braff and Geyer, 1990; Braff *et al*, 2001; Castellanos *et al*, 1996), as well as in rodents treated with DA receptor agonists (Geyer *et al*, 2001).

Previous studies have documented that the activation of D₁-like, but not D₂-like receptors induces hyperlocomotion and PPI deficits in C57BL/6 mice (Geter-Douglass *et al*, 1997; Halberda *et al*, 1997; Ralph-Williams *et al*, 2003a; Ralph and Caine, 2005), the most common inbred murine strain used in research and the only one whose genome has been entirely sequenced to date (Waterston *et al*, 2002). This background prompted us to test the differential effect of FIN on PPI and other behavioral responses of C57BL/6 male mice to D₁- and D₂-like, as well as non-selective agonists. The rationale for these experiments was

further informed by our need to broaden the translational value of our previous findings with an additional preclinical platform that may allow for future investigations on transgenic mice.

2. Materials and Methods

2.1. Animals

We used 253 male adult C57BL/6 mice (25–35 g), purchased from Charles River (Como, Italy, for the startle and catalepsy testing; Wilmington, MA, USA, for the open field studies). Animals were group-housed in cages (n=4) with *ad libitum* access to food and water. The room was maintained at 22±0.2°C on a 12/12-h dark/light cycle (with lights off at 07:00 PM). All experimental procedures were executed in compliance with the National Institute of Health guidelines and approved by the Animal Use Committees at the University of Cagliari and University of Southern California.

2.2. Drugs

For systemic injections, FIN (Sigma Aldrich, St Louis, MO, USA) was suspended in a vehicle (VEH) of 1% Tween 80 in 0.9% saline (SAL). Apomorphine (APO; Sigma Aldrich) was dissolved in SAL with 0.1 mg/ml ascorbic acid to prevent oxidization. The full D₁-like agonist SKF-82958 and D₂-like agonist quinpirole (QUIN) (Sigma-Aldrich) were dissolved in SAL. Systemic administration volume was 10 ml/kg body weight (intraperitoneal, IP). The antipsychotic agent haloperidol (HAL; Sigma-Aldrich) was dissolved in a single drop of 1 N hydrogen chloride (HCl) and diluted with saline.

2.3. Startle reflex and PPI

Startle and PPI testing were performed as previously described (Bortolato *et al*, 2007), between 10 AM and 3 PM. Animals were injected with either FIN (25–50 mg/kg, IP) or VEH, followed, 30 min later, by a DAergic agonist [SKF-82958 (0.3 mg/kg, IP), QUIN (0.5 mg/kg, IP), APO (0.5 mg/kg, IP)] or SAL. Behavioral testing began 10 min after the last injection; each session lasted 28–30 min and was performed with a 70-dB white-noise background. Following a 5-min acclimatization period, mice were exposed to five consecutive 115-dB pulse-alone bursts; subsequently, the speakers delivered a pseudo-random sequence of trials, including: 1) pulse-alone 115-dB trials (n=17); 2) pre-pulse + pulse trials, in which the same pulse was preceded by 74, 78 or 82 dB pre-pulses (n=60; 20 for each pre-pulse level); 3) no-stimulus trials, in which only background noise was delivered (n=8). Sound levels were assessed using an A Scale setting. Percent PPI was

calculated with the following formula:
$$\%PPI = \left[100 \times \left(1 - \frac{\overline{S_{pp}}}{\overline{S_{pa}}} \right) \right]$$
 with $\overline{S_{pp}}$ and $\overline{S_{pa}}$ representing the mean startle amplitudes for all pre-pulse+pulse trials and pulse alone trials, respectively. The first 5 pulse-alone bursts were excluded from the calculation. Whenever significant changes in startle amplitude were found, statistical analyses were also performed on ΔPPI values, defined as the absolute differences between startle magnitudes on pulse-alone and prepulse+pulse trials ($\Delta PPI = \overline{S_{pa}} - \overline{S_{pp}}$) (Devoto *et al*, 2012).

2.4. Open-field locomotor behavior

Locomotor activity was measured in a novel open field. The apparatus was a Plexiglas square grey arena (40 × 40 cm) surrounded by 4 black walls (40 cm high). On the floor, two concentric zones of equivalent areas were defined: a central square quadrant and a peripheral frame directly adjacent to the walls. Background light and noise were maintained at 10 lux and 70 dB, respectively. Each experimental session lasted 120 min. Mice were initially

placed in the center of the arena; after 30 min, they were briefly removed and treated with either FIN (50 mg/kg, IP) or VEH, and quickly repositioned in the center of the open field. Thirty min later, mice were treated with SKF-82958 (0.3 mg/kg, IP), QUIN (0.5 mg/kg, IP) or SAL, and monitored for the remainder of the session (60 min). Analyses of locomotor activity were performed using Ethovision pathway tracking software (Noldus Instruments, Wageningen, The Netherlands). Behavioral measures included the distance travelled, time spent in the central zone, number of rearing episodes and meandering (defined as the ratio between turn-angle degrees and total distance) (Kalueff et al, 2007).

2.5. Stereotyped behavior

Mice were injected with either FIN (50 mg/kg, IP) or its vehicle; 30 min later, they received either APO (3 mg/kg, IP) or saline. Stereotyped behaviors were then evaluated throughout the following 30-min period, by two separate trained observers blinded to the treatments. Behaviors were monitored for 30 s, at intervals of 2 min, for a total of 15 observations. At the end of each period, behaviors were assigned numerical scores based on a modified version of the rating scale used by Benus et al. (1991) for the evaluation of APO-induced stereotyped behaviors (for a detailed description of the scale, please see the legend of Fig. 6). Stereotypy scores were calculated as mean values of the scores of the two observers. Inter-observer consistency was evaluated by Cronbach's alpha coefficient, which was consistently higher than 0.85.

2.6. Catalepsy

Catalepsy was assessed via the bar test as previously described (Bardin *et al.*, 2005). Thirty minutes following treatment with vehicle, FIN (25–200 mg/kg, IP) or HAL (1 mg/kg, IP), the forepaws of the mice were placed on a cylindric metal bar positioned 3.5 cm above a table; the duration of time during which the mouse retained this position was recorded by an observer unaware of the treatment (with a cut-off time of 60 s). The test was repeated three times (with 1-min interval in between trials) and the highest duration recorded was used for statistical analyses.

2.7. Data analysis

Normality and homoscedasticity of data distribution were verified by using the Kolmogorov-Smirnov and Bartlett's tests. Analyses were performed by multiple-way ANOVAs (with repeated measures for the analyses of the time-related effects on locomotor behaviors in the open field and stereotypies), as appropriate, followed by Tukey's test (with Spjøtvoll-Stoline correction for unequal N whenever required) for post-hoc comparisons of the means. For %PPI analyses, data relative to different prepulse levels were collapsed, since no interactions were found between prepulse levels and other factors throughout the study. For the analyses of open-field and stereotyped behaviors, drug-induced effects were calculated in comparison to the baseline values, corresponding to the last counts before injection (30 min for FIN and 60 min for DAergic agonists considered as baseline values). Significance threshold was set at 0.05.

3. Results

3.1 Effects of FIN and DAergic agonists on startle magnitude and PPI

The first experiment (n=63; 9–14/group) was aimed at the evaluation of the effects of FIN (25–50 mg/kg, IP) or VEH on the PPI disruption induced by the D₁-receptor agonist SKF-82958 (0.3mg/kg, IP) (Fig. 1). The effects of FIN on startle amplitude were studied with a two-way ANOVA, with pretreatment (FIN vs VEH) and treatment (SKF-82958 vs SAL) as independent factors (Fig. 1A). ANOVA revealed that SKF-82958 significantly

decreased baseline startle magnitude [Main effect: $F(1,57)=4.54$, $P<0.05$]. Conversely, FIN did not reduce startle amplitude [Main effect: $F(2,57)=1.50$, NS]; furthermore, no significant pretreatment $\times$ treatment interactions were detected [$F(2,57)=0.05$, NS]. The same design was used to run %PPI analyses (Fig. 1B). Significant main effects were found for both pretreatment [$F(2,57)=8.30$, $P<0.001$] and treatment [$F(1,57)=28.53$, $P<0.001$]. Furthermore, pre-treatment $\times$ treatment interactions were also statistically significant [$F(2,57)=5.16$, $P<0.01$]. *Post-hoc* comparisons revealed that SKF-82958 produced a PPI impairment ($P<0.001$ for VEH+SAL vs VEH+SKF-82958 comparisons) which was completely reversed by the highest FIN dose ($P<0.001$ for VEH + SKF-82958 vs FIN 50 + SKF-82958; Tukey's test).

In the second experiment ($n=57$; 8–10/group), we studied the combined impact of FIN (25–50 mg/kg, IP) and QUIN (0.5 mg/kg, IP) on the startle magnitude and PPI (Fig. 2). Analyses of startle amplitude (Fig. 2A) revealed significant effects for the pre-treatment (FIN vs VEH) [Main effect: $F(2,51)=4.10$, $P<0.05$], treatment (QUIN vs SAL) [Main effect: $F(1,51)=46.91$, $P<0.001$], and their interaction [$F(2,51)=7.19$, $P<0.01$]. This latter effect was found to reflect a significant reduction induced by the combination of the highest FIN dose with QUIN as compared with their counterparts treated with FIN and SAL ($P<0.001$ for comparison FIN 50 + QUIN vs FIN 50 + SAL). The analysis of %PPI revealed significant main effects for pre-treatment [$F(2,51)=4.76$, $P<0.05$], treatment [$F(1,51)=37.62$, $P<0.001$] and their interaction [$F(2,51)=3.80$, $P<0.05$]. *Post-hoc* analyses revealed that, while neither FIN nor QUIN significantly affected PPI, this parameter was markedly reduced by their combination ($P<0.001$ for FIN 50 + QUIN vs FIN 50 + SAL; Tukey's test) (Fig. 2B). These results were confirmed by Δ PPI analyses {main effect for pre-treatment: [$F(2,51)=3.78$, $P<0.05$]; main effect for treatment: [$F(1,51)=42.91$, $P<0.001$]; pre-treatment $\times$ treatment interaction: [$F(2,51)=4.42$, $P<0.05$]; *post-hoc* comparisons: $P<0.001$ for FIN 50 + QUIN vs FIN 50 + SAL} (data not shown).

The third experiment ($n=32$; 8/group) (Fig. 3) was aimed at the assessment of the combined effects of FIN and APO (0.5 mg/kg, IP). With respect to startle, ANOVA detected a main effect only for the treatment [$F(1,30)=28.61$, $P<0.001$], but not for either pre-treatment [$F(1,30)=2.44$, NS] or pre-treatment $\times$ treatment interactions [$F(1,30)=3.38$, NS] (Fig. 3A). Similarly, %PPI analyses highlighted a main effect for treatment [$F(1,30)=46.21$, $P<0.001$], but not for either pre-treatment [$F(1,30)=0.07$, NS] or pre-treatment $\times$ treatment interactions [$F(1,30)=0.01$, NS] (Fig. 3B). The evaluation of Δ PPI also revealed a significant effect for treatment [$F(1,30)=38.59$, $P<0.001$], but not pre-treatment [$F(1,30)=1.67$, NS] or their interactions [$F(1,30)=1.64$, NS] (data not shown).

3.2 Effects of FIN and DAergic agonists on open-field behaviors

We then studied the combined impact of FIN and DAergic agonists (SKF-82958 and QUIN) on locomotor activity and other open-field behaviors. After 30 min in the arena, FIN (50 mg/kg, IP) produced a significant reduction in locomotor activity [Main effect for treatment: $F(1,43)=60.67$, $P<0.001$] at 15–20 min after administration [time $\times$ treatment interaction: $F(6,258)=17.05$, $P<0.001$; $P<0.05$ for comparisons with baseline values, Tukey's]. Subsequently, mice were injected with either SAL or DAergic agonists, and their behavior was studied for further 60 min. The analysis of the effects of FIN and SKF-82958 on locomotor parameters was run with 3-way ANOVA designs, factors being pre-treatment (FIN vs VEH), treatment (SKF-82958 vs SAL) and time (repeated measures, using the last measure before SKF-82958/SAL injection as baseline). FIN significantly reduced the locomotor activity {main pre-treatment effect: [$F(1,26)=24.85$, $P<0.001$]}, while SKF-82958 increased it {main treatment effect: [$F(1,26)=29.33$, $P<0.001$]}. A significant interaction between these two drugs was also found [$F(1,26)=9.89$, $P<0.01$], which was shown to reflect the ability of SKF-82958 to enhance locomotor activity in both VEH- and

FIN-pretreated animals, as compared to SAL-treated counterparts ($P < 0.001$ for both comparisons, Tukey's). A significant effect for time [$F(12,312) = 6.22$, $P < 0.01$] was found. Dunnett's test revealed that the hyperlocomotive effect of SKF-82958 was significant after 15' from its injection (Fig. 4A).

Meandering was significantly increased by FIN {main pre-treatment effect: [$F(1,24) = 18.35$, $P < 0.001$]}. Notably, ANOVA detected a significant pre-treatment $\times$ treatment $\times$ time interaction [$F(12, 288) = 3.23$, $P < 0.001$]. Post-hoc comparisons revealed that SKF-82958 significantly reduced meandering in VEH-, but not FIN-pretreated mice for the whole duration of the experiment, with the greatest effects measured at 25–30 min after treatment (Fig. 4B). Rearing behavior was significantly reduced by FIN [$F(1,24) = 8.70$, $P < 0.01$] and increased by SKF-82958 [$F(1,24) = 11.80$, $P < 0.01$]. Significant pre-treatment $\times$ treatment [$F(1,24) = 5.05$, $P < 0.05$] and pre-treatment $\times$ treatment $\times$ time [$F(6,144) = 2.25$, $P < 0.05$] interactions were found. Post-hoc scrutiny of this effect indicated that SKF-82958 increased rearing in VEH-pretreated mice, at 20–40 min after treatment. Of note, this effect was significantly antagonized by FIN pretreatment (Fig. 4C).

No statistically significant differences were detected with respect to the effect of SKF-82958 on the duration of the time spent in the central compartment (Fig. 4D).

The analysis of the effects of QUIN and FIN co-treatment on locomotor activity was conducted with the same design as described for the experiment with SKF-82958. ANOVA revealed main effects for pre-treatment [$F(1,26) = 39.69$, $P < 0.001$], treatment [$F(1,26) = 4.51$, $P < 0.05$] and time [$F(12,312) = 4.41$, $P < 0.001$], but not for their interactions (Fig. 5A). No significant differences were observed on meandering, rearing or time spent in center (Figs. 5B–D).

3.3. Effect of FIN on APO-induced stereotypies and on catalepsy

As shown in Fig. 6A, APO caused a significant increase in stereotyped behavior in a time-related fashion [$F(6,84) = 96.36$, $P < 0.001$], which was not affected by FIN (50 mg/kg, IP) at any time [pre-treatment $\times$ time interaction: $F(6,84) = 1.31$, NS]. In line with our previous results in rats (Bortolato et al, 2008), FIN did not induce catalepsy at any tested dose [$F(4,20) = 0.76$, NS]; conversely, the antipsychotic agent haloperidol (HAL) induced a robust cataleptic effect [$F(1,8) = 114.06$, $P < 0.001$] (Fig. 6B).

4. Discussion

The results of the present study showed that, in C57BL/6 mice, the prototypical 5 α R inhibitor FIN reduced locomotor activity, but did not modify startle reflex, impair PPI, or induce catalepsy. Furthermore, this agent exerted divergent modulatory actions on the effects of D₁- and D₂-like receptor activation, insofar as it reduced the PPI deficits and rearing responses induced by the full D₁ receptor agonist SKF-82958, but surprisingly *synergized* with the D₂-like activator QUIN to produce marked gating impairments. Taken together, these findings complement previous evidence on the anti-DAergic properties of 5 α R blockers (Bortolato *et al*, 2008; Devoto *et al*, 2012) and suggest that, in C57BL/6 mice, the role of 5 α R in behavioral organization may vary in relation to the differential engagement of distinct DAergic receptor classes.

In agreement with previous results, the full D₁ receptor agonist SKF-82958 significantly reduced startle amplitude and PPI, increased locomotor activity and enhanced rearing responses (Wang and McGinty, 1997; Ralph-Williams *et al*, 2002; Ralph-Williams *et al*, 2003). Notably, FIN potently prevented the gating and rearing alterations, but not the startle deficits, induced by SKF-82958. Furthermore, although FIN countered the overall motor

activation evoked by D₁ receptor stimulation, this phenomenon did not reflect a specific effect, but rather FIN's intrinsic hypolocomotive properties, as revealed by the lack of significant statistical interactions between the two treatments. Of note, rearing activity is often postulated to be more representative of exploratory behaviors than horizontal locomotion. Thus, our results may signify that 5 α R modulates the role of D₁ in select behavioral domains, such as sensorimotor gating and exploratory behavior, but not on general motor organization. This selectivity may reflect a brain-regional specificity of action; in fact, we recently found that the nucleus accumbens, but not the dorsal striatum contribute to the anti-DAergic effects of systemic FIN administration on sensorimotor gating (Devoto *et al*, 2012). Accordingly, whereas the nucleus accumbens plays a key role in the organization of gating and motivational behaviors in response to limbic activation (Wilson, 1982; Swerdlow *et al*, 2001; Groenewegen and Trimble, 2002), the dorsal striatum exerts a pivotal function in motor activity (Voorn *et al*, 2004).

Irrespective of these issues, the ability of SKF-82958 to significantly increase locomotion in FIN-treated animals, together with previous binding data (see Bortolato *et al*, 2008) clearly indicates that FIN is not a D₁-like receptor antagonist; nonetheless, it is likely that this compound may still affect open-field behaviors through the negative modulation of D₁ downstream signaling cascade. In further support of this possibility, multiple studies have shown that the negative modulation of D₁ receptors does not produce intrinsic changes in PPI (Doherty *et al*, 2008; Ralph *et al*, 2001; Ralph-Williams *et al*, 2003), but markedly reduces locomotor activation (Centonze *et al*, 2003; Kelly *et al*, 2001).

In conformity with other reports, the D₂ receptor agonist QUIN did not elicit any significant change in PPI in C57BL/6 mice (Ralph-Williams *et al*, 2003). Nevertheless, its combination with FIN dose-dependently reduced PPI. Furthermore, in striking contrast with our previous findings in Sprague-Dawley rats (Bortolato *et al*, 2008), FIN failed to affect the PPI deficits and stereotyped behaviors induced by the mixed D₁-D₂ agonist APO. The divergent effects mediated by FIN on the behavioral outcomes of the two families of DA receptors may suggest that the signaling of these targets may be distinctively modulated by different balances in NSs, at least with respect to their roles on the regulation of PPI and other specific behavioral responses.

Ample evidence has documented that, while both D₁- and D₂-like receptors participate in the regulation of sensorimotor gating and information processing, the relative contribution of these two subfamilies vary in relation to the species and the genetic background of rodents (Kinney *et al*, 1999; Ralph and Caine, 2005; Ralph and Caine, 2007; Swerdlow *et al*, 2000). While most D₁-like agonists have been shown to have no intrinsic PPI-disrupting effects in rats, they robustly impair this index in C57BL/6 and other commonly used inbred and outbred strains of mice (Holmes *et al*, 2001; Ralph and Caine, 2005); in contrast, activation of D₂-like receptors appears to be a fundamental prerequisite for the PPI deficits induced by DAergic compounds in rats (Geyer *et al*, 2001), but not in C57BL/6 mice (Ralph-Williams *et al*, 2003; Ralph and Caine, 2005). These differences notwithstanding, the DAergic regulation of PPI, locomotor and exploratory activity has been shown to be the result of a complex set of synergistic and antagonistic interactions between D₁- and D₂-like receptors (Eagle *et al*, 2011; Ralph and Caine, 2005; Swerdlow *et al*, 2005; Wan *et al*, 1996). The finding that the same doses of FIN that attenuated the PPI-disrupting effects of SKF-82958 precipitated the gating impairments induced by QUIN suggests that different conditions of baseline NS concentrations may partially contribute to the interstrain and interspecies differences in DAergic regulation. In this respect, it is interesting to note that previous studies documented very low levels of progesterone, one of the key brain substrates for 5 α R, in C57BL/6 mice (Phan *et al*, 2002).

The signaling of D₁-like receptors is largely mediated by G α_s and G α_{olf} proteins, which stimulate adenylyl cyclase and trigger the activation of cyclic-AMP-dependent protein kinase (PKA) and its downstream targets, including several ion channels, CREB and DARPP-32 (Romanelli *et al*, 2010). Conversely, D₂-like receptors exert opposite intracellular effects through the inhibition of adenylyl cyclase mediated by G_i and G_o proteins. Given that the action of FIN on PPI regulation are likely to be postsynaptic (Devoto *et al*, 2012), our results may signify that the neurochemical changes induced by 5 α R inhibition may interfere with the common signaling pathways of D₁ and D₂ receptor signaling.

The lack of data on the effect of FIN on regional NS concentrations in the present report limits our ability to elucidate the specific molecular mechanisms underlying the antiDAergic properties of FIN. Nevertheless, given that 5 α Rs catalyze the rate-limiting step of neurosteroidogenesis (Paba *et al*, 2011), it is likely that their inhibition results in profound imbalances in NS concentrations, due to the decreased synthesis of allopregnanolone and DHT and accumulation (or metabolic shift towards alternative pathways) of ketosteroid precursors, such as progesterone and testosterone. Previous studies have documented that progesterone and other NSs interact with the signaling and functions of D₁ receptors (Apostolakis *et al*, 1996; Dong *et al*, 2007; Petralia and Frye, 2006). Moreover, the protein DARPP-32 has been shown to mediate some of the actions of progesterone on D₁-like receptors (Mani *et al*, 2000; Frye and Walf, 2010). Another interesting possibility to partially account for the observed effects may reflect the action of progesterone and other NSs on σ_1 receptors; indeed, recent studies show that these targets amplify DA D₁ receptor signaling (Fu *et al*, 2010) and form heteromers with D₁ receptors in the brain (Navarro *et al*, 2010).

The hypolocomotive effects of FIN in the open field were paralleled by a marked increase in meandering and a decrease in rearing responses and time of permanence in the center, indicating a shift of locomotor patterns from broad exploratory movements across the arena to a predominantly local activity in the periphery. This variation was not induced by intrinsic alterations in motor competence, as indicated by the absence of catalepsy in the present study and/or impairments in the rotorod test (unpublished results). The decrement in the time spent in the center quadrant of the open field may signify an increase in anxiety-like behavior; this interpretation is consistent with the notion that 5 α R inhibition results in the block of the synthesis of allopregnanolone, which exerts an anxiolytic action by positive modulation of GABA_A receptors (Dubrosky *et al*, 2006; Eser *et al*, 2008). Nevertheless, this possibility is challenged by several ideas: first, we previously showed that the same doses of FIN used in the present study reduced, instead of increasing, marble burying in mice (Bini *et al*, 2009); second, in our experimental setting FIN was injected after 30 min of acclimation to the open field; evaluation of thigmotaxis are generally considered meaningful of anxiety during the first 5–10 min of introduction of a rodent in an open arena; third, alterations in locomotor activity greatly limit the interpretation of variations in locomotor trajectory as dependent on anxiety-like responses. This caveat is particularly relevant in the interpretation of our data, in consideration of the highly significant correlation between locomotor activity and time spent in center in FIN-treated animals.

In contrast with our previous data in Sprague-Dawley rats, FIN did not prevent the PPI deficits or the stereotyped responses mediated by the mixed D₁/D₂ agonist APO (Bortolato *et al*, 2008). Although most of the behavioral effects of APO have been shown to depend on the synergism of D₁ and D₂ receptors (Bordi and Meller, 1989; Braun and Chase, 1986; LaHoste and Marshall, 1996; Plaznik *et al*, 1989), previous research documented that, in C57BL/6 mice, the PPI deficits induced by this drug depend on the activation of D₁, rather than D₂ receptors (Ralph-Williams *et al*, 2003a; 2003b). In this perspective, it is somewhat

surprising that the same dose that fully antagonized the PPI deficits induced by SKF-82958 did not attenuate the behavioral outcomes of APO on gating; nevertheless, the PPI-disrupting potential of FIN in the presence of D₂ receptor activation may have offset and counterbalanced its PPI-ameliorating properties related to the outcomes of D₁ receptor. More in general, the divergent effects of FIN on APO-mediated effects in Sprague-Dawley rats and C57BL/6 mice are likely to depend on interspecies and interstrain differences in the role of DA receptors on the regulation of sensorimotor gating. For example, unlike C57BL/6 mice, Sprague-Dawley rats do not generally exhibit PPI deficits following activation of D₁ receptors (Bortolato *et al*, 2005; Wan *et al*, 1996; Wan and Swerdlow 1994), although these targets afford a major contribution to the PPI-disrupting properties of APO (Hoffman and Donovan, 1994; Wan *et al*, 1996). On the other hand, QUIN produces a significant reduction of PPI in rats, but not in C57BL/6 mice (Ralph and Caine, 2005). These divergences parallel other differential outcomes of QUIN on locomotor activity: while this drug yields biphasic effects on locomotor activity in rats, it lowers locomotor activity in C57BL/6 mice irrespective of the dose (Halberda *et al*, 1997), possibly reflecting different patterns of D₂ and D₃ receptor activation across different species and strains. Further studies on the effects of FIN on the PPI-disrupting effects of DAergic agonists in Sprague-Dawley rats are needed to better qualify potential interspecies differences in the role of NSs in gating regulation.

Throughout our experiments, startle amplitude was significantly reduced by all DA receptor agonists, in line with previous results (Byrnes *et al*, 2007; Iverson and Else, 2000; Zhang *et al*, 2000). These results suggest that activation of both D₁- and D₂-like receptors may exert a startle-attenuating effect in mice. Indeed, previous studies showed that the reduction in startle amplitude induced by APO remains unaffected in D₁ or D₂ knockout mice (Ralph-Williams *et al*, 2002), potentially suggesting a contribution of both DA receptor subfamilies in this phenomenon. In contrast with our results in rats, FIN did not inherently affect startle amplitude in C57BL/6 mice, potentially suggesting a different role of NSs in the modulation of startle responses. While future studies are warranted to explore the neurobiological bases of these differences, the fact that the marked reduction in locomotor activity induced by FIN was not paralleled by changes in startle amplitude confirms the dissociation between these two phenomena, in line with previous results (Davis *et al*, 1986).

Several limitations of the present study should be acknowledged, including the lack of experiments that may better differentiate the relative contribution of subtypes within D₁-like and D₂-like receptors. Furthermore, the high affinity of FIN for both 5αR1 and 5αR2 isozymes in rodents (Thigpen and Russell, 1992) does not allow us to elucidate the specific contribution of each isoenzyme to the antipsychotic-like effects of 5αR inhibition. Whereas further research is needed to address these limits, our findings highlight the critical role of 5αR in the pathophysiology of gating deficits and psychosis, and point to an important functional link between NSs and the signaling cascade of D₁ receptors, which may be involved in the pathophysiology of a number of neuropsychiatric disorders, including Tourette syndrome and schizophrenia.

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Figure 1.

Effects of systemic finasteride (FIN, 25–50 mg/kg, IP) and SKF-82958 (SKF, 0.3 mg/kg, IP) on startle reflex (A) and %PPI (B) in C57BL/6 mice. FIN doses are indicated in mg/kg.

VEH, vehicle of FIN; SAL, saline. Values are expressed as mean $\pm$ S.E.M. N = 9–14/group.

* $P < 0.05$, *** $P < 0.001$ vs rats treated with SAL (pre-treatment $\times$ treatment interaction); °°

° $P < 0.001$ vs rats treated with VEH and SKF (pre-treatment $\times$ treatment interaction).

Figure 2.

Effects of systemic finasteride (FIN, 25–50 mg/kg, IP) and quinpirole (QUIN, 0.5 mg/kg, IP) on startle reflex (A) and %PPI (B) in C57BL/6 mice. FIN doses are indicated in mg/kg. VEH, vehicle of FIN; SAL, saline. Values are expressed as mean $\pm$ S.E.M. N = 8–10/group. **P < 0.01, ***P < 0.001 vs rats treated with SAL (pre-treatment $\times$ treatment interaction); °P < 0.01 vs rats treated with VEH and QUIN (pre-treatment $\times$ treatment interaction).

Figure 3. Effects of systemic finasteride (FIN, 50 mg/kg, IP) and apomorphine (APO, 0.5 mg/kg, IP) on startle reflex (A) and %PPI (B) in C57BL/6 mice. VEH, vehicle of FIN; SAL, saline. Values are expressed as mean $\pm$ S.E.M. N = 8/group.

Figure 4.

Effects of systemic finasteride (FIN, 50 mg/kg, IP) and SKF-82958 (SKF, 0.3 mg/kg, IP) on locomotor and exploratory behavior in an open field. (A) Distance traveled, (B) Meandering (C) Rearing behaviors (D) Time spent in the central compartment. VEH, vehicle of FIN; SAL, saline. Arrows correspond to the times of injection. Values are expressed as mean $\pm$ S.E.M. $N = 8-12$ /group. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ for comparisons with baseline values at 60 min; ° $P < 0.05$, °° $P < 0.01$ for comparisons between VEH+SKF and FIN+SKF (pre-treatment $\times$ treatment $\times$ time interaction).

Figure 5.

Effects of systemic finasteride (FIN, 50 mg/kg, IP) and quinpirole (QUIN, 0.5 mg/kg, IP) on locomotor and exploratory behavior in an open field. (A) Distance traveled, (B) Meandering (C) Rearing behaviors (D) Time spent in the central compartment. VEH, vehicle of FIN; SAL, saline. Arrows correspond to the times of injection. Values are expressed as mean $\pm$ S.E.M. N = 8–12/group.

Figure 6.

(A) Effects of systemic finasteride (FIN, 50 mg/kg, IP) on the stereotyped responses induced by apomorphine (APO, 3 mg/kg, IP). The average stereotypy score was based on a modification of the rating scale of Benus and colleagues (1991), as follows:

- **0** : Non-stereotyped behaviors (locomotion, grooming, rearing, sniffing, digging, sitting)
- **1** : Hypolocomotion and behavioral freezing
- **2** : Hypolocomotion with bouts of stereotyped sniffing and gnawing the sawdust
- **3** : Stereotyped behavior in a particular pattern
- **4** : Compulsive sniffing and gnawing the sawdust; front paws occasionally on cage wall
- **5** : Slow climbing or stretched-out, near-vertical position
- **6** : Continuous gnawing and/or licking the walls and bars of the cage

(B) Effects of FIN and haloperidol (HAL) on catalepsy. FIN and HAL doses are indicated in mg/kg. VEH, vehicle of FIN. Values are expressed as mean $\pm$ S.E.M. N=8/group. ***P<0.001 for comparisons with baseline values at 30 min.