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Targeting neurosteroid synthesis as a therapy for schizophrenia-related alterations induced by early psychosocial stress

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ABSTRACT

Background: Cogent evidence has shown that schizophrenia vulnerability is enhanced by psychosocial stress in adolescence, yet the underpinnings of this phenomenon remain elusive. One of the animal models that best capture the relationship between juvenile stress and schizophrenia is isolation rearing (IR). This manipulation, which consists in subjecting rats to social isolation from weaning through adulthood, results in neurobehavioral alterations akin to those observed in schizophrenia patients. In particular, IR-subjected rats display a marked reduction of the prepulse inhibition (PPI) of the startle reflex, which are posited to reflect imbalances in dopamine neurotransmission in the nucleus accumbens (NAcc). We recently documented that the key neurosteroidogenic enzyme 5α-reductase (5αR) plays an important role in the dopaminergic regulation of PPI; given that IR leads to a marked down-regulation of this enzyme in the NAcc, the present study was designed to further elucidate the functional role of 5αR in the regulation of PPI of IR-subjected rats.
Methods: We studied the impact of the prototypical 5αR inhibitor finasteride (FIN) on the PPI deficits and NAcc steroid profile of IR-subjected male rats, in comparison with socially reared (SR) controls.
Results: FIN (25–100 mg/kg, i.p.) dose-dependently countered IR-induced PPI reduction, without affecting gating integrity in SR rats. The NAcc and striatum of IR-subjected rats displayed several changes in neuroactive steroid profile, including a reduction in pregnenolone in both SR and IR-subjected groups, as well as a decrease in allopregnanolone content in the latter group; both effects were significantly opposed by FIN.
Conclusions: These results show that 5αR inhibition counters the PPI deficits induced by IR, possibly through limbic changes in pregnenolone and/or allopregnanolone concentrations.

1. Introduction

Ample empirical evidence has shown greater schizophrenia vulnerability in individuals chronically exposed to psychosocial stressors throughout early developmental stages (Nuechterlein et al., 1992; Norman and Malla, 1993; Walker et al., 2008). Although several studies have focused on the pathophysiological link between juvenile stress and psychosis onset (Corcoran et al., 2003), the neurobiological underpinnings of this phenomenon remain elusive.

One of the best tools to explore the molecular bases of the stress-diathesis model of schizophrenia is afforded by isolation rearing (IR), an experimental manipulation consisting in subjecting rodents to prolonged social deprivation from weaning through adulthood. This manipulation results in an array of neurobehavioral aberrations reminiscent of core phenotypes observed in psychotic patients (Fone and Porkess, 2008), such as the disruption of sensorimotor gating, measured via the prepulse inhibition (PPI) of the acoustic startle reflex (Geyer et al., 1993). In comparison with other behavioral alterations induced by IR, PPI deficits feature several operational advantages, including their correspondence with similar impairments in schizophrenia patients (Braff et al., 1992) and their sensitivity to antipsychotic agents (Bakshi and Geyer, 1999; Binder et al., 2001). Recent findings have shown that the PPI deficits and other behavioral changes in IR-subjected rats are underpinned by alterations in dopamine (DA) (Jones et al., 1992; Hall et al., 1998; Roncada et al., 2009), one of the key neurotransmitters implicated in the pathophysiology of psychotic disorders. In particular, IR has been shown to lead to PPI disruption

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through DAergic imbalances in the nucleus accumbens (NAcc) (Powell et al., 2003), the terminal of the mesolimbic DA system. Indeed, ample evidence has shown that stimulation of DAergic receptors in the NAcc disrupts PPI in rodents (for a review, see Geyer et al., 2001).

Several lines of evidence suggest that neuroactive steroids may contribute to the pathogenic role of psychosocial stress in schizophrenia (Walker et al., 2008). First, psychosocial stress leads to alterations in the levels of circulating steroids synthesized in the adrenal glands and gonads, which trigger multiple functional changes in the brain (Johnson et al., 1992; Huether, 1996; Kajantie and Phillips, 2006). Secondly, stress causes changes in the synthesis and metabolism of neurosteroids (i.e., steroids synthesized de novo in the brain; see Baulieu, 1998), which in turn play an important role in the orchestration of the behavioral response to stress (Fig. 1) (Purdy et al., 1991; Barbaccia et al., 1996, 2001; Dong et al., 2001; Agis-Balboa et al., 2007; Sanchez et al., 2008, 2009). Thirdly, neurosteroids and circulating neuroactive steroids have been shown to play a key role in the regulation of DA neurotransmission and signaling (Di Paolo, 1994; Sanchez et al., 2009). Finally, schizophrenia patients have been shown to feature abnormalities of neuroactive steroid profiles (Shirayama et al., 2002; Ritsner and Strous, 2010; Bicikova et al., 2013); in particular, Marx et al. (2006) have documented high concentrations of pregnenolone and dehydroepiandrosterone (DHEA) in the posterior cingulate and parietal cortex of schizophrenia patients. These neurosteroids may be effective adjunctive therapies for the management of cognitive and negative symptoms (Strous et al., 2003; Marx et al., 2009, 2011).

Building on these premises, our group has recently studied the implication of neuroactive steroids in the modulation of behavioral responses induced by DAergic agonists relevant to schizophrenia-associated phenotypes. In particular, we focused on 5α-reductase (5αR), the enzyme catalyzing the rate-limiting step of neurosteroidogenesis as well as the conversion of testosterone into its major androgenic metabolite 5α-dihydrotestosterone (DHT) (Paba et al., 2011). Notably, we found that 5αR inhibitors oppose the PPI deficits induced by DAergic agonists in rodents, likely through the involvement of postsynaptic DA receptors in the NAcc (Bortolato et al., 2008; Paba et al., 2011; Devoto et al., 2012; Frau et al., 2013). Furthermore, the prototypical 5αR inhibitor finasteride (FIN), which is already approved for clinical use as a therapy for benign prostatic hyperplasia and androgenic alopecia, was found to have antipsychotic effects in a treatment-refractory case of chronic schizophrenia (Koethe et al., 2008). The specific molecular mechanisms by which FIN and other 5αR inhibitors exert anti-DAergic properties, however, remain elusive to date.

Conversely to these premises, we recently showed that IR results in a profound reduction in 5αR expression in the NAcc (Bortolato et al., 2011). This finding, however, did not qualify whether this down-regulation is etiologically relevant with respect to the PPI deficits observed in IR-subjected rats, or rather represent a compensatory adaptive response aimed at balancing other molecular changes associated with those impairments. To address this question, in the present study we examined the functional role of 5αR in IR-induced PPI deficits by testing the impact of FIN on the PPI deficits and steroid profile in the NAcc of IR-subjected rats, as compared with socially reared (SR) counterparts. Specifically, we predicted that, if the IR-induced PPI deficits are caused by the reduction in 5αR expression, they should be exacerbated by FIN administration; vice versa, if FIN elicited antipsychotic-like effects in IR-subjected rats, this scenario would likely signify that the down-regulation of 5αR in these animals does not lead to sensorimotor gating impairments.

2. Materials and methods

2.1. Animals and isolation procedure

Sprague–Dawley dams (Harlan Italy, S. Pietro al Natisone, Italy) were mated with sires and single-housed for the whole duration of their pregnancy. Following delivery, litters were culled to 6 pups. At postnatal day 22, rats were weaned and males were randomly assigned to either IR or SR groups. To avoid litter effects, no more than two SR littermates were placed together in the same cage. IR-subjected rats were reared individually in plastic cages, while SR rats were housed four per cage. The sizes of the cages for IR and SR rats were 41 × 26 × 20 cm and 52 × 32 × 20 cm,

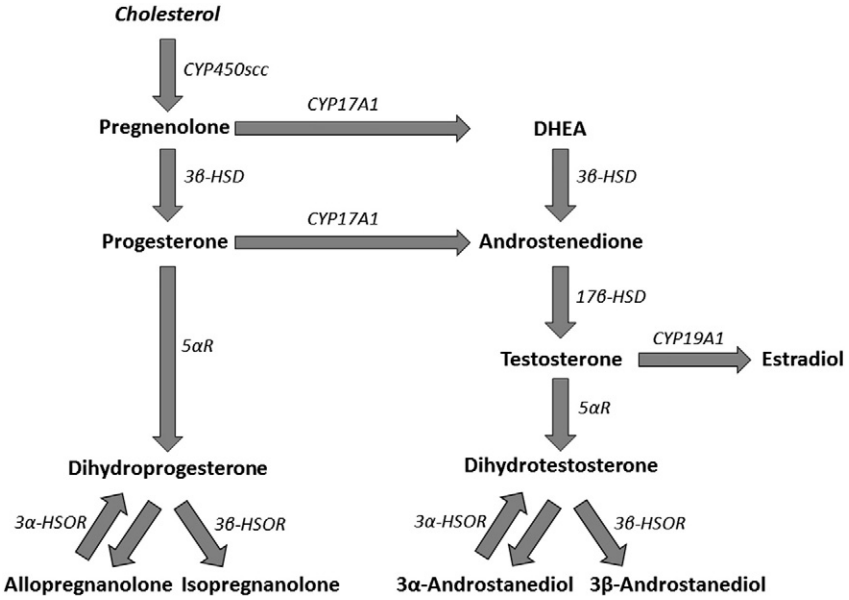

Fig. 1. Schematization of the major biosynthetic pathways of neurosteroids. Cholesterol is converted to pregnenolone by cytochrome P450 side-chain cleavage (scc). Pregnenolone is then processed either to progesterone by 3β-hydroxysteroid dehydrogenase (3β-HSD) or to dehydroepiandrosterone (DHEA) by 17-hydroxylase/17,20 lyase (CYP17A1). The conversion of progesterone to dihydroprogesterone is catalyzed by 5α-reductase (5αR). Dihydroprogesterone can be metabolized by the reversible enzyme 3α-hydroxysteroid oxidoreductase (3α-HSOR) and 3β-hydroxysteroid oxidoreductase (3β-HSOR) for the synthesis of allopregnanolone and isopregnanolone, respectively. DHEA is metabolized to androstenedione, which is then converted to testosterone by 17β-hydroxysteroid dehydrogenase (17β-HSD). Testosterone is the converted into estradiol by aromatase (CYP19A1); alternatively, the combined metabolic reactions of 5αR, 3α- and 3β-HSOR metabolize testosterone into its androgenic derivatives dihydrotestosterone (DHT), 3α- and 3β-androstanediol, respectively.