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Research report

Finasteride administration potentiates the disruption of prepulse inhibition induced by forced swim stress

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HIGHLIGHTS

- Acute swim stress decreases prepulse inhibition.
- Finasteride potentiates the stress-induced sensory gating alteration.
- Plasma allopregnanolone/pregnenolone in response to stress modulates sensory gating.

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ABSTRACT

Acute stress has been demonstrated to alter sensory gating processes, measured by the prepulse inhibition of the startle response (PPI). It is well known that brain and plasma levels of the neurosteroid allopregnanolone (ALLO) increase after acute environmental stress, fact that has been considered a homeostatic mechanism in restoring normal function following stress. Thus, it is of great interest to study the contribution of stress-altered plasma ALLO levels on PPI function. For this purpose, animals were injected with finasteride, an ALLO synthesis inhibitor, and submitted to swim stress before PPI testing. In order to obtain ALLO plasma levels, a separate set of animals that followed the same experimental procedure was used. We hypothesize that the blockade of ALLO production in response to stress can increase the stress-induced PPI disruption. In accordance with other authors, our results indicate that acute swim stress disrupted the normal PPI evolution (increase) related to the increase in prepulse intensities, and also decreased PPI at the highest prepulse intensity level (15 db above background). Finasteride potentiated the PPI decrease induced by swim stress in the intermediate prepulse intensity (10 db above background). As expected, plasma ALLO levels were increased in stressed animals and this increase was neutralized by prior finasteride administration. These results indicate that the neutralization of the physiological plasma ALLO levels increase after acute stress potentiates stress-induced PPI disruption. This data suggests that alterations in homeostatic ALLO synthesis mechanism may be linked to some neuropsychiatric disorders related to stress, such as anxiety/depression disorders.

1. Introduction

Prepulse inhibition (PPI) consists on the inhibition of the startle response to a high intensity stimulus when it is preceded by a weak stimulus (prepulse). PPI represents an index of sensorimotor gating, which seems governed by central inhibitory mechanisms [1,2], and its deterioration is present in several neuropsychiatric disorders, including schizophrenia [3,4] or obsessive compulsive disorder [5]. This fact explain why PPI has been validated and used as an animal model of deficient sensorimotor gating to study the pathophysiology and new treatments of schizophrenia [6,7]. Previous studies have shown that distinct acute or chronic stress paradigms can decrease PPI responses. This effect of stress on PPI has been described in social isolated mice [8] and Wistar [9] or female Long-Evans hooded rats [10], after acute restraint stress in C57BL/6 mice [11] or repeated restraint stress in Brown Norway rats [12], and

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after rapid eye movement sleep deprivation [13] or predator exposure [14] in male Sprague-Dawley rats. In this way, the injection of stress hormones such as corticosterone [15], corticotrophin-releasing factor [14] or cortisol in humans [16] also deteriorates PPI responses. Moreover, neonatal stress induced by early maternal separation has also been documented to decrease PPI in adult age [17]. Interestingly, PPI disturbances have been observed in patients with anxiety disorder [18] and a trend of lower PPI values has also been reported in major depressive disorder patients [19].

On the other hand, it is well known that the levels of the neurosteroid allopregnanolone (ALLO) increase in the brain after acute stress [20], fact that can serve as homeostatic mechanism in restoring normal GABAergic and hypothalamic–pituitary–adrenal (HPA) function following environmental stress [21]. However, chronic stress induces important reductions in cerebrocortical and plasma concentrations of ALLO [22], which seem related to several disturbances in emotional and motivational responses, and in reward functions [23]. In any case, whether acute or chronic stress, it seems that the maintenance of adequate levels of plasma and/or brain ALLO levels can be protective against the deleterious effects of environmental stress. In this way, the administration of exogenous ALLO either during or following a period of chronic stress can prevent or normalize HPA dysfunction, precluding the establishment of depressive/anxiety-like behaviors [24].

Finasteride is a synthetic 5-α reductase inhibitor used for the treatment of human benign prostatic hyperplasia and androgenic alopecia, which has been associated with sexual dysfunction and anxiety/depression, side effects that have been attributed to impairments in the levels of neuroactive steroids such as ALLO [25,26]. In vitro studies have shown that finasteride is an inhibitor of the type-1 and type-2 5-α reductase enzyme [27] and it has been documented that a 10 mg/kg dose of finasteride can almost completely deplete ALLO in the rat brain [28]. Although it has been described that 5-α reductase inhibitors such as finasteride can antagonize rat PPI deficits induced by apomorphine or D-amphetamine administrations in a manner analogous to the antipsychotic drugs haloperidol or clozapine [29], data about the effects of finasteride administration *per se* on PPI response are missing. In contrast to this previous result and given that: (1) finasteride decreases brain and plasma ALLO levels; (2) ALLO levels are necessary to restore the normal GABAergic and HPA axis activity after acute stress; and (3) acute stress can decrease PPI response (see above for references); it is expected a further sustained reduction in PPI after the combination of finasteride administration and acute environmental stress.

The aim of the present work is to investigate whether a previous finasteride administration, and the expected subsequent reduction in plasma ALLO levels, can modify the putative disruption of PPI response induced by acute forced swim stress, which has been effective in increasing plasma and brain ALLO concentrations in previous experiments [30]. Given that finasteride significantly decreases ALLO synthesis in adult rats [28], we hypothesize that this reduction in ALLO levels can increase the deleterious effects of environmental stress on PPI response. In order to test this hypothesis, we have analyzed the effects of forced swim stress on PPI response when is applied 1 h after vehicle or finasteride administration. We have also measured the plasmatic levels of ALLO and other neurosteroids (3β-hydroxy-5α-pregnan-ol-20-one (epiallopregnanolone, EPIALLO); 3α,21-dihydroxy-5α-pregnan-20-one (tetrahydrodeoxycorticosterone, THDOC); 3β-hydroxy-pregn-5-en-20-one (pregnenolone, PREG) after the combination of swim stress and finasteride injections. In our knowledge, this is the first time that the effects of finasteride administration and the combination of finasteride administration with acute stress on PPI response are studied; focusing the hypothesis that finasteride could increase the negative effects of stress on sensory gating processes.

2. Methods

2.1. Subjects

The subjects were 55 male Wistar rats allowed food and water *ad libitum*. The rats were housed in a temperature-controlled animal room (22–24 °C) on a 12 h light/dark cycle (lights on at 8:00 h). They were housed in groups of 2–4 subjects and aged 80 days at the beginning of the experiments. Experimental sessions were always carried out in the morning, between 10:00 h and 14:00 h. Thirty-four rats were used in behavioural experiment and 21 subjects for biochemical determinations. All animals were obtained, housed, and killed in accordance with protocols approved by the Animal Care and Use Committee in the Autonomous University of Barcelona and the Department of the Environment of the Generalitat de Catalunya (Regional Government), and with guidelines approved by the European Community Council Directive (2010/63/EU).

2.2. Drug administration

Finasteride (50 mg/kg) was dissolved in 10% cyclodextrin ((2-hydroxypropyl)-β-cyclodextrin) in 0.9% NaCl and was i.p. injected in a volume of 1 ml/kg body weight. A vehicle solution (10%-cyclodextrin dissolved in 0.9% NaCl) was used as control injections. All drugs were obtained from Sigma (Deisenhofen, Germany). Dose and timing of injection prior behavioral manipulations was based on previous experiments [28,29,31].

2.3. Forced swim procedure

One hour after injections, animals ($n = 16$) were placed in a transparent Plexiglas cylindrical tank (height: 40 cm, internal diameter: 19 cm), containing water (36 °C) to a depth of 24 cm during 5 min. The apparatus was located in a chamber with lights off. After swim, each animal was gently dried with a cotton towel and was left in an individual cage in the dark room for 15 min until the PPI test was evaluated. The rest of the rats ($n = 18$) were not submitted to swim stress before PPI, but they were also placed in the dark room for 20 min in individual cages, 1 h after injection. The final composition of the experimental groups was: Vehicle + Swimming ($n = 8$); Finasteride + Swimming ($n = 8$); Vehicle + No Swimming ($n = 7$); Finasteride + No Swimming ($n = 11$).

2.4. Prepulse inhibition of the acoustic startle response

PPI was tested in a StartFear system (Letica, Panlab, Barcelona, Spain) that records and analyzes the signal generated by the animal movement through a high sensitivity weight transducer, as previously described [32,33]. The PPI session was started with a 5 min habituation period, followed by 10 blocks of five trials to measure PPI. Each block consisted of one startle trial (120 dB, 20 ms broad band burst, to measure basal startle responsiveness), one no-stimulus condition, and three different prepulse–startle pairings administered pseudo-randomly. In these pairings the prepulse was 5, 10, or 15 dB above background. Prepulses were 20 ms broadband bursts and given 100 ms before the startle pulse. The interval between two trials was 10–20 s. The startle amplitude was calculated as the mean of 10 delivered startle trials. PPI (percentage) was calculated according: 100 − (Mean of all startle amplitudes on prepulse trials/Basal startle amplitude) × 100.

2.5. Neurochemical determination

Plasma neurosteroids levels were measured in a parallel experiment. Twenty-one subjects were submitted to the same