Psychoneuroendocrinology (2006) 31, 924–934

PNEC

www.elsevier.com/locate/psyneuen

Ovarian steroids counteract serotonergic drugs actions in an animal model of obsessive-compulsive disorder

Alonso Fernández-Guasti[a], Daniella Agrati[b], Rebeca Reyes[a], Annabel Ferreira[c,*]

[a]*Departamento de Farmacobiología. CINVESTAV, Calzada de los Tenorios 235, México D.F., México*
[b]*Laboratorio de Neurosciencias, Facultad de Ciencias, Iguá 4225, Montevideo, Uruguay*
[c]*Sección Fisiologíay Nutrición, Facultad de Ciencias, Iguá 4225, Montevideo, Uruguay*

Received 14 June 2005; received in revised form 22 February 2006; accepted 2 May 2006

KEYWORDS
Obsessive-compulsive disorder;
Ovarian steroids;
Estrous cycle;
Serotonin;
Fluoxetine;
8-OH-DPAT

Summary Recently, we reported the existence of differences according to the reproductive stage of female rats in a pharmacologically induced animal model of obsessive-compulsive disorder. Therefore, the aim of the present study was to examine the role of endogenous and exogenous ovarian steroids in the induction of perseverative responses in a T-maze by the 5-HT_{1A} agonist 8-OH-DPAT (1.0 and 2.0 mg/kg, SC) and in the preventive action of the selective serotonin reuptake inhibitor, fluoxetine (10.0 mg/kg, three times, SC). The results showed that the perseverant action of 8-OH-DPAT as well as the prevention of such perseverance by fluoxetine were reduced during the estrous–metestrous phases of the female reproductive cycle, and by the exogenous ovarian steroids administration to ovariectomized animals. Data are discussed from the standpoint of the action of ovarian steroids on the serotonergic system and on the putative influence of these hormones on the physiopathology and treatment of this disorder in women.

1. Introduction

Fluctuations in ovarian steroid levels during various reproductive stages of women are associated with changes in several mood disorders such as anxiety and depression (Robinson and Stewart, 1986; Abramowitz et al., 2003). Additionally, increasing clinical evidence indicates the existence of sex-related differences in the etiology and in the expression of obsessive-compulsive disorder (OCD), probably caused by changes in steroid hormones (Charney et al., 1988; Mundo et al., 1999; Zohar et al., 1999). However, to our knowledge, there is no systematic clinical study analyzing

*Corresponding author. Tel.: +5982 525 86 18 x7151; fax: +5982 525 86 17.
E-mail address: anna@fcien.edu.uy (A. Ferreira).

0306-4530/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.psyneuen.2006.05.003

the putative differences in the expression or etiology of OCD across the reproductive cycle of women or after the exogenous administration of steroid hormones.

Regarding the physiopathology of OCD, a dysfunction of the serotonergic system has been postulated as a major contributing factor, due in part, to the effectiveness of serotonin reuptake inhibitors (SRIs) in its treatment (Zohar et al., 1988; Barr et al., 1992). The clinical efficacy of these compounds has been attributed to their ability to increase the availability of extracellular serotonin (5-HT) (Zohar et al., 1988; Barr et al., 1992). Interestingly, ovarian steroids also importantly modify the serotonergic neurotransmission (Rubinow et al., 1998; Bethea et al., 2002a), an action that may influence the onset, development and treatment of psychiatric alterations. In the case of OCD, Mundo et al. (1999) observed that women have a better antiobsessional response to clomipramine treatment than men and proposed that sexual hormones might be responsible for this difference.

A pharmacological paradigm extensively used for studying OCD consists of the disruption of spontaneous alternation by the administration of the 5-HT_{1A} agonist, 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) in rats (Yadin et al., 1991; Fernández-Guasti et al., 2003a; Ulloa et al., 2004; Agrati et al., 2005). Spontaneous alternation behavior (SAB) is defined as the natural tendency exhibited by rodents to enter first one and then the other alley of a T-maze in two successive, equally rewarded trials (Ellen and Deloache, 1968). The perseverative choice of the same alley of the maze is considered analogous to compulsive-like behavior. The validity of this model is sustained by pharmacological evidence revealing that clomipramine and fluoxetine, effective drugs in the treatment of OCD, prevent the perseveration induced by 8-OH-DPAT, while drugs ineffective in clinics, like desimipramine, lack an effect in this paradigm (Yadin et al., 1991; Fernández-Guasti et al., 2003a).

Recently, we reported differences in the perseverant behavior induced by 8-OH-DPAT according to the reproductive stage of females, including the estrous cycle, gestation and lactation (Agrati et al., 2005). Thus, perseveration was induced by the administration of this 5-HT_{1A} agonist, in metestrus, diestrus, proestrus and on mid-pregnancy. Conversely, during estrus, late gestation and lactation a blunted perseverant response to 8-OH-DPAT was observed. These data could be interpreted in the light of the modulatory role of the endocrine milieu that characterizes each stage of the reproductive cycle on the serotonergic system. Hence, estrogens and progestins are known to affect serotonergic transmission at different levels (Rubinow et al., 1998; Bethea et al., 2002a, b), including the 5-HT_{1A} receptor and the 5-HT transporter (5-HTT), which have been proposed to mediate the antidepressant actions of selective serotonin reuptake inhibitors (SSRIs) (De Vry et al., 2004; Estrada-Camarena et al., 2006). Thus, based on the observation that 8-OH-DPAT's perseverant effect was significantly reduced during estrus at a dose of 1.0 mg/kg (Agrati et al., 2005), we firstly aimed at analyzing whether the blunted response to this serotonergic agonist remains at a higher dose and whether the preventive action of fluoxetine on such perseverance is modified depending upon the ovarian steroids variations during the estrous cycle. Secondly, we determined the effect of estrogen and progesterone, exogenously administrated to ovariectomized females, both on the perseveration induced by 8-OH-DPAT and on the prevention of such perseverance by fluoxetine.

2. Materials and methods

2.1. Animals

Nulliparous female Wistar rats of around 3 months of age (weighting 220–250 g) were used in this study. All females were kept in groups of four in cages measuring 45 × 28 × 26 cm, housed in a room under an inverted 12-h light–dark cycle (lights off at 1000 h) with ad libitum access to water and rat chow throughout the experiment, except for the 24-h food-deprivation period required before testing.

Ovariectomy was performed through a ventral incision under pentobarbital anesthesia (40.0 mg/kg, IP) and animals were left to recovery for a period of at least 15 days before testing.

The Local Committee of Ethical Animal Experimentation approved all the experimental procedures, which followed the regulations established in the Mexican official norm for the use and care of laboratory animals "NOM-062-ZOO-1999".

2.2. Apparatus

The testing apparatus for alternation consisted of a wooden T-maze with goal arms characterized by distinctive visual cues (Yadin et al., 1991). All arms (including the main arm and the two goal boxes) measured 50 × 10 × 10 cm. Guillotine doors separated the main and goal arms from the main body of