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ÍNDICE

Artículos

INDEX

Articles

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ESTROUS CYCLE AND SEX AS REGULATING FACTORS OF BASELINE BRAIN OXIDATIVE METABOLISM AND BEHAVIOR

Natalia Arias, Camino Álvarez, Nélida Conejo, Héctor González-Pardo, and Jorge L. Arias

Laboratory of Neurosciences, Faculty of Psychology, University of Oviedo.

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Abstract

The existence of sex differences in brain function is still today a controversial issue, and contradictory results are reported in the scientific literature. Part of this controversy would be solved by taken into consideration the rhythmic changes in the levels of circulating gonadal steroids during the menstrual or estrous cycle in females as compared to males. The aim of this study was to evaluate the changes in oxidative metabolism of limbic brain regions in male and female rats at two different stages of estral cycle (estrous and diestrous). Cytochrome oxidase activity was used as a reliable marker of neuronal oxidative metabolism. We found the highest levels of oxidative metabolism during the diestrous phase in several brain regions, when estrogen levels are high. Males displayed similar cytochrome oxidase activity as compared to females in estrous phase. Our results support behavioral and neurobiological studies reporting sex differences in rodents and humans.

Keywords: Limbic system, cytochrome oxidase, sex difference, estrous cycle, rat

Resumen

La existencia de diferencias sexuales en la función cerebral es actualmente un tema controvertido y existen resultados contradictorios en la literatura científica. Parte de esta controversia sería resuelta teniendo en consideración los cambios rítmicos en los niveles de esteroides gonadales circulantes durante el ciclo menstrual o estral en hembras en comparación con machos. El objetivo de este estudio fue evaluar los cambios en el metabolismo oxidativo de regiones límbicas cerebrales en ratas macho y hembra en dos etapas diferentes del ciclo estral (estro y diestro). La actividad citocromo oxidasa fue usada como un marcador fiable del metabolismo oxidativo neuronal. Encontramos los mayores niveles de metabolismo oxidativo durante la fase de diestro en algunas regiones cerebrales, cuando los niveles de estrógenos son elevados. Los machos mostraron una actividad citocromo oxidasa similar en comparación con las hembras en estro. Nuestros resultados apoyan los trabajos conductuales y neurobiológicos que muestran diferencias sexuales en roedores y seres humanos.

Palabras clave: Sistema límbico, citocromo oxidasa, diferencias sexuales, ciclo estral, rata

Correspondence: Laboratorio de Neurociencias, Facultad de Psicología, Plaza Feijoo, s/n, E-33003 Oviedo, Spain, Telephone: (+34)985103212, Fax: (+34)985104144, E-mail: UO172871@uniovi.es

Introduction

Gonadal steroids have a wide range of actions on different tissues through organizational effects during development and activational effects on adulthood. The organizational effects of gonadal steroids on the nervous system have received much attention during their long-lasting or permanent consequences on brain structure and function. However, less is known about how cycling levels of circulating gonadal steroids transiently affect brain function, for example across phases of the estrous cycle in mammals. It is known that gonadal steroids modulate neural plasticity by altering synaptic transmission and synaptogenesis, and are thus able to modify brain function.

Recently, it has been shown that estrogens and progesterone could also regulate metabolic functions related to the energetic demands of neuronal activation by directly affecting cellular respiration (Irwin et al., 2008). Pioneer studies by Moguilevsky and Malinow (1964) and Schiaffini, Marín, & Gallego (1969) showed that oxygen utilization in vitro increased in several limbic regions of rat brain during the estrous phase. In addition, local brain glucose utilization measured by 2-[14C]-deoxyglucose autoradiography showed sex differences as well as significant fluctuations of this parameter during different stages of the estrous cycle in rats, especially in the hypothalamus and other limbic structures (Nehlig, Porrino, Crane, & Sokoloff, 1985). In particular, estrogens can modulate the activity of key mitochondrial enzymes involved in cellular respiration and oxidative metabolism of several tissues, including the nervous tissue (Luine, Khylchevskaya, & McEwen, 1974).

One of the respiratory enzymes most significantly affected by estradiol seems to be cytochrome c oxidase, whose mRNA levels quickly and specifically increase after estradiol treatment in rat hippocampus and hypothalamus (Bettini & Maggi, 1982). Moreover, it has been reported that cytochrome c oxidase activity increases after estrogen and progesterone treatment in rat brain mithocondria (Irwin et al., 2008). Cytochrome c oxidase (CO, EC 1.9.1.3) is a mitochondrial enzyme responsible for oxygen consumption in animal cells, and it catalyzes the transfer of electrons to molecular oxygen, a metabolic process coupled to energy formation by oxidative phosphorylation. In the nervous system, neurons require large amounts of

energy to maintain and restore the resting electrical potential after synaptic signal transmission. It is estimated that 60-80% of ATP (the molecule responsible for energy storage) is used to maintain ionic gradients involved in establishing the resting potential required for neuronal excitability (Nicholls & Budd, 2000). Therefore, CO activity can be considered as an index of neuronal oxidative metabolic capacity indirectly related to neuronal activity (Wong-Riley, 1989). Changes in CO activity in particular brain regions have been related with spatial memory and other behaviors that show sexual dimorphism in rodents and other animal species (Conejo, González-Pardo, Vallejo, & Arias, 2007; Sakata, Crews, & Gonzalez-Lima, 2005).

In the current study, we investigated the possible differences in baseline CO activity of particular limbic regions included in the Papez circuit. These regions are involved in spatial memory of male and female rats at different stages of estral cycle (diestrous and estrous) showing high and low levels of circulating estrogens respectively.

Method

Subjects

90-day-old Wistar rats (250-300g) from the vivarium of Oviedo University were used in this study. The animals were divided into three groups: males (n=10) and females in estrous (n=10) or diestrous phase (n=10). The animals were housed in groups of five in transparent polycarbonate cages. All the animals had ad libitum access to food and tap water and were maintained at constant room temperature (23±2ºC), with a relative humidity of 65±5% and artificial light-dark cycle of 12 h (lights on from 8:00 to 20:00). The procedures and manipulation of the animals used in this study were carried out according to the Directive 86/609/EEC of the European Communities Committee and Royal Decree 1201/2005 relative to the protection of the animals used for experimentation and other scientific purposes, and the study was approved by the local committee of animal studies (University of Oviedo).

Neurological Tests

The basic functionality of the nervous system was evaluated by neurological tests like flexion leg reflex, startle reactions, pupillary reflex, head shaking, righting and equilibrium reflex, placing reactions, grasping, and some additional equilibrium tests. No significant alterations were detected in the different experimental groups. After neurological examination, all the animals were handled daily for five days (5 min/day).

Cytochrome oxidase histochemistry

Females were decapitated when they were at the optimal phase of the estrous cycle (estrous or diestrous). Males were paired with females for decapitation. Brains were removed, frozen rapidly in isopentane (Sigma-Aldrich, Madrid, Spain) and stored at -40ºC until processing with quantitative CO histochemistry, described by Gonzalez-Lima and Cada (1994). In order to quantify enzymatic activity, and control for staining variability across different baths, sets of tissue homogenate standards from Wistar rat brain were cut at different thicknesses (10, 30, 40 and 60 µm) and included with each bath of slides. The sections and standards were incubated for 5 min in 0.1 M phosphate buffer with 10% (w/v) sucrose and 0.5 % (v/v) glutaraldehyde at pH 7.6. After this, baths of 0.1 M phosphate buffer with 10% (w/v) sucrose were given for 5 min each. Subsequently, sections were immersed in a solution containing 0.05 M Tris buffer, 275 mg/l cobalt chloride, 10% w/v sucrose, and 0.5 % (v/v) dimethylsulfoxide at pH 7.6 for 10 min. Then, sections and standards were incubated in a solution of 0.06 g cytochrome c, 0.016 g catalase, 40 g sucrose, 2 ml dimethylsulfoxide, and 0.4 g diaminobenzidine tetrahydrochloride (Sigma-Aldrich, Madrid, Spain) in 800 ml of 0.1 M phosphate buffer at 37 ºC for 1 h. The reaction was stopped by fixing the tissue in buffered formalin for 30 min at room temperature with 10% (w/v) sucrose and 4% (v/v) formalin. Finally, the slides were dehydrated, cleared with xylene, and coverslipped with Entellan (Merck, Germany).

Densitometric Analysis

Quantification of CO histochemical staining intensity was done by densitometry using a computer-assisted digital image analysis workstation (MCID Core, InterFocus Imaging Ltd., Linton, England) composed of a high precision illuminator, a digital

camera and a computer with specific image analysis software. The mean optical density (OD) of each region was bilaterally measured on selected brain regions using three consecutive sections in each subject. On each section, four non-overlapping readings were taken using a square-shaped sampling window that was adjusted for the region size. A total of twelve measurements were taken per region by an investigator blind to the experimental groups. These measurements were averaged to obtain one mean per region for each animal. OD values were then converted to CO activity units, determined by the enzymatic activity of the standards measured spectrophotometrically (Gonzalez-Lima & Cada, 1994).

The regions of interest were anatomically defined according to Paxinos & Watson´s atlas (2005). The antero-posterior level in mm of the selected brain regions from bregma point were: +3.20 for the infralimbic cortex (ILc), prelimbic cortex (PLc), the cingulate cortex (CG) and the motor cortex (MC); -1.20 for CA1, CA3, and dentate gyrus (DG) subfields of the dorsal hippocampus; -4.80 for CA1, CA3, and dentate gyrus (DG) subfields of the ventral hippocampus; -1.40 for the anterodorsal thalamus (ADT), the anteroventral thalamus (AVT) and the mediodorsal thalamus (MD); +4.52 for the supramammillary nucleus (SuM), the medial mammilary nucleus (MM) and the lateral mammillary nucleus (LM).

Data analysis

Group differences in CO activity were evaluated for each brain region using one-way ANOVA followed by Tukey's post-hoc tests. When the normality test failed, a Kruskal-Wallis one way analysis of variance on ranks was used, followed by Dunn's post-hoc tests. The total number of subjects in each experimental group used for the analysis of CO activity was different in most brain regions. This discrepancy was due to the fact that some subjects were discarded for the analysis of CO activity when the quality of the tissue was not good enough or it was lost during processing. Values are expressed as mean ± s.e.m. and $p<0.05$ was considered significant in this study.

Results

The results of the CO activity measures obtained from the different brain regions studied are illustrated in Table 1. CO values measured in the cingulate and

motor cortex showed significant differences between groups of males and diestrous females, $H(2,29)=8.631$; $p<0.05$) and, $F(2,38)=7.241$; $p<0.01$, respectively. Post hoc tests revealed that in cingulate cortex the male group had lower CO activity as compared to diestrous females ($p<0.05$). Comparisons between groups in the motor cortex revealed that diestrous group showed higher CO activity than estrous ($p<0.05$) and male groups ($p<0.01$). In addition, significant differences were found between groups in the anteroventral thalamus, $H(2,51)=8.440$; $p<0.05$. Post hoc tests revealed higher CO activity in the diestrous group as compared to the estrous group ($p<0.05$). In the mediodorsal thalamus, CO activity showed differences between groups, $F(2,42)=4.789$; $p<0.05$, with significantly higher CO values in diestrous group as compared to males ($p<0.05$) and estrous ($p<0.05$) groups.

Regarding the dorsal dentate gyrus, $F(2,37)=7.419$; $p<0.01$, CO activity was different between males and diestrous females ($p<0.01$) and between diestrous and estrous females ($p<0.05$), being the CO activity higher in the diestrous group in both cases.

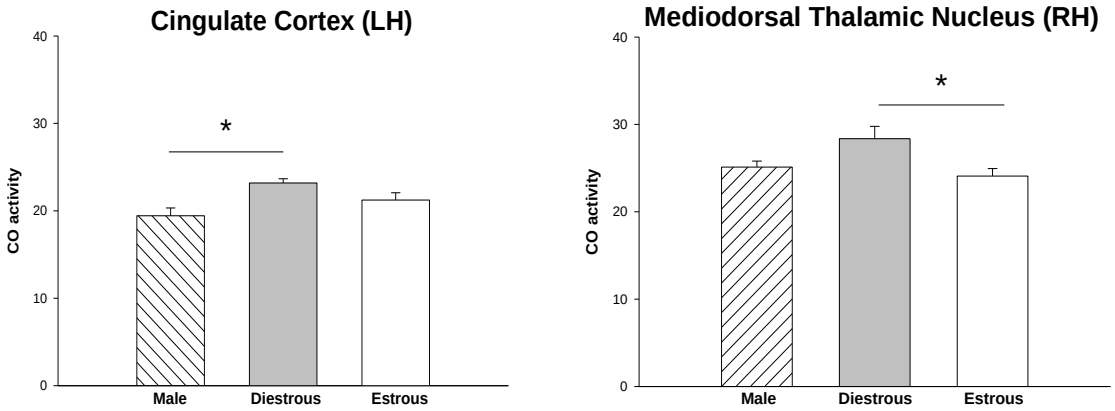
The results of the CO activity measures obtained from both brain hemispheres studied are illustrated in Figure 1. With respect to the right hemisphere, differences were found in the cingulate cortex between the groups, $F(2,14)=5.479$; $p<0.05$. The CO activity of the cingulate cortex revealed significant differences between groups of diestrous females and males ($p<0.05$). Finally, ANOVA performed in the mediodorsal thalamus revealed differences between groups, $F(2,21)=4.727$; $p<0.05$. An increased in CO activity was found in the diestrous group as compared to estrous group ($p<0.05$).

Table 1. Cytochrome oxidase activity units (µmol/min/g tissue wet weight) measured in the selected brain regions.

Location	Males	Diestrous female	Estrous female
Prefrontal Cortex			
Cingulate Area	19.8±0.9*	23.1±0.5	21.2±0.6
Motor Area	23.1±0.8*	26.9±0.9	23.2±0.5*
Prelimbic Area	19.5±0.3	21.3±0.5	20.9±0.7
Infralimbic Area	19.3±0.4	20.8±0.5	20.5±0.4
Diencephalo			
Anterodorsal thalamus	39.8±0.7	46.3±1.9	40.1±1.1
Mediodorsal thalamus	24.5±0.8*	27.6±1.0	24.5±0.6 *
Anteroventral thalamus	31.0±0.5	34.0±1.3	29.5±0.6 *
Supramammilary nucleus	21.9±1.3	21.7±5.3	20.9±1.7
Medial mammilary nucleus	29.9±1.3	25.9±3.7	28.7±2.3
Medial lateral mammilary nucleus	23.3±0.7	22.9±3.1	23.2±1.6
Lateral mammilary nucleus	31.2±0.8	27.2±1.5	28.9±1.3
Hippocampus			
Dorsal CA1 subfield	20.6±0.6	22.1±0.4	20.2±0.5
CA3 subfield	20.3±0.8	20.0±0.8	19.6±0.6
Dentate gyrus	27.9±0.6*	32.1±1.2	28.4±0.6*
Ventral CA1 subfield	26.2±0.7	27.9±2.1	25.7±0.5
CA3 subfield	26.3±0.8	27.7±1.9	26.8±0.8
Dentate gyrus	27.3±2.0	29.9±2.3	27.6±3.7

Note: Data represent mean±S.E.M. Abbreviations: prelimbic (PRL) and infralimbic (IL) cortex, cingulate cortex (CG), motor cortex (MC), dorsal hippocampal dentage gyrus (DG) and subfields (CA1 and CA3), anterior thalamic anterodorsal (ADT) and anteroventral (ATV) nuclei, mediodorsal thalamic nuclei (MD) mammillary bodies medial (MM) and lateral (ML) nuclei, and amygdala medial (MeA) and basolateral (BLA) nuclei and the supramammillary nucleus (SuM). *p<0.05 as compared to the diestrous group.

Figure 1. CO activity in cingulate cortex and mediodorsal thalamic nucleus in the three experimental groups.



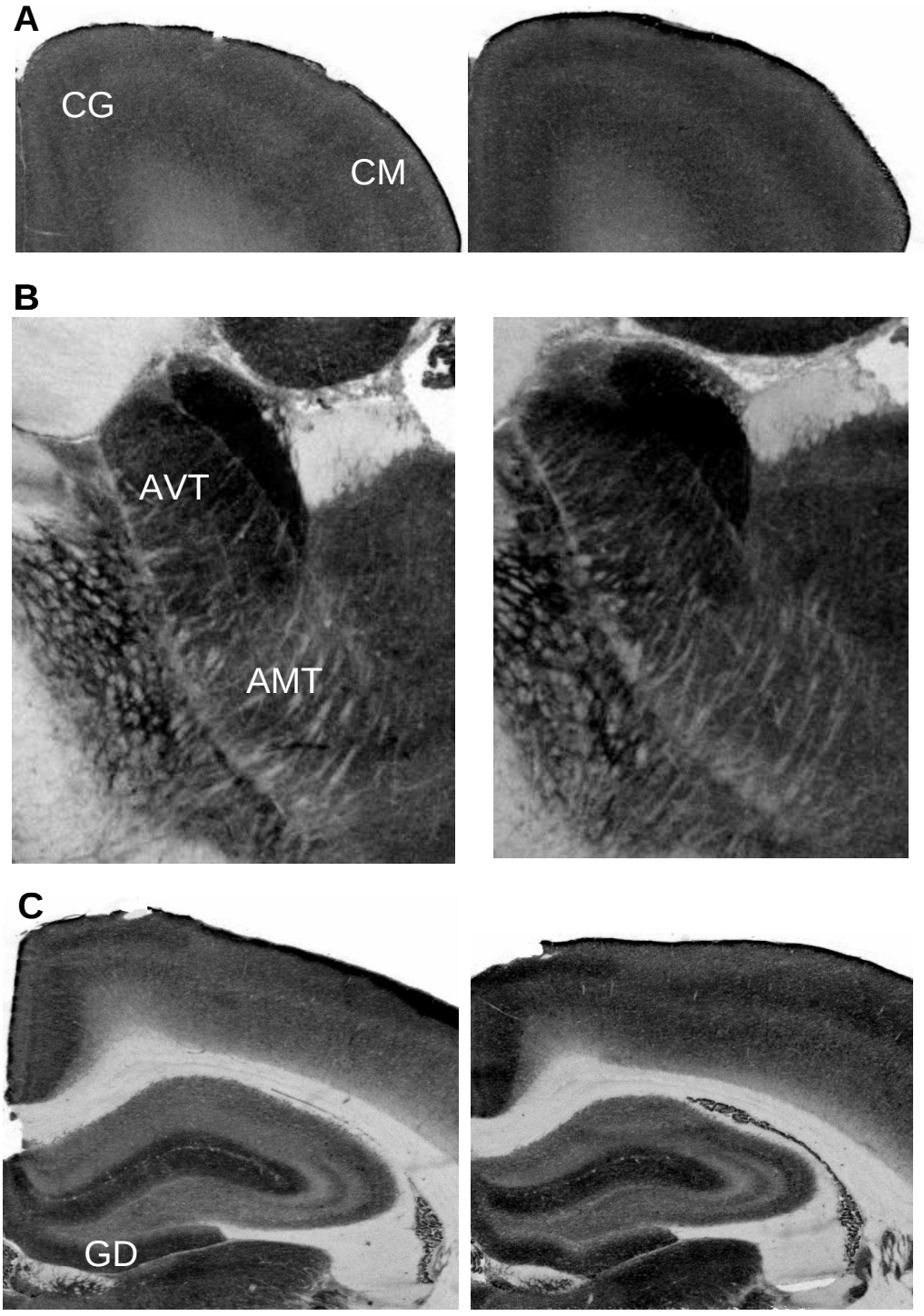
Note: *p<0.05, significant difference between groups. Data are represented as means±S.E.M. RH = right hemisphere; LH = left hemisphere.

Discussion

This study demonstrated that gonadal steroids can modify the oxidative metabolism of particular brain regions in male and female rats at different stages of the estral cycle. Fluctuations in circulating blood levels of estrogens and progesterone during the estrous cycle in female rats influenced CO activity in a few brain regions (motor cortex, thalamic nuclei, and dentate gyrus of the hippocampus). Moreover, sex differences in CO activity were observed between males and diestrous females in the cingulate cortex, mediodorsal thalamus, and the dentate gyrus. Our results are agree with previous studies reporting that estrogens increase CO activity in the brain (Irwin et al., 2008; Bettini & Maggi, 1992). Accordingly, the highest CO activity values were observed in diestrous females as compared to estrous females and males. Indeed, the levels of circulating estrogens (estradiol in particular) are higher in diestrous than in estrous phase. High estrogen levels in diestrous phase have been related to increased oxidative metabolism and glucose incorporation in brain tissue (Namba & Sokoloff, 1984, Puerta, Rocha, González-Covaleda, McBennett, & Andrews, 1998).

However, the enhancement of neuronal metabolic capacity caused by estrogens was region-specific. Strikingly, the brain regions showing CO changes did not necessarily match the distribution of estrogen receptors in rat brain, since regions like

Figure 2. Photographs of CO stained coronal sections from a male (left) and a female rat (right) at the level of the prefrontal cortex (A), anterior thalamic nuclei (B) and dorsal hippocampus (C).



Note: CG= cingulate cortex; CM= motor cortex; AVT = anteroventral thalamic nuclei; AMT = anteromedial thalamic nuclei; DG = dentate gyrus. Scale bar: 500 µm.

the dentate gyrus and thalamus display low density of estrogen receptors, whereas the cingulate cortex and motor cortex have a high density of estrogen receptors (Pérez, Chen, & Mufson, 2003; Shugrue, Lane, & Merchenthaler, 1997). Although the general pattern of higher CO activity in diestrous phase as compared to both estrous females and males suggests the involvement of estrogens in regulating CO activity, other factors should be taken into consideration to explain the region-specific effects of estrogens.

In this regard, indirect effects of estrogens on brain networks could explain the neuronal activation of particular brain regions in baseline conditions. Alternatively, action of gonadal steroids on the endocrine system could be related to the reported results. In particular, plasma corticosterone levels are higher in diestrous as compared to estrous (Atkinson & Waddell, 1997), a finding linked to higher anxiety scores of rats in diestrous phase (Marcondes, Miguel, Melo, & Spadari-Bratfisch, 2001).

Alternatively, region-specific effects of gonadal steroids on CO activity could be overlapped with the organizational effects of these hormones on brain anatomy. Therefore, particular brain regions could be more sensitive to the action of estrogens on neuronal activity. For example, some authors found that oxygen consumption by the hippocampus was high during diestrous, whereas basolateral amygdala has the lowest oxidative metabolism during estrous (Schiaffini, Marín, & Gallego, 1969). In our study, the dentate gyrus of the hippocampus had the highest CO activity during diestrous in agreement with previous studies. Remarkably, some authors report that estradiol modulates neurogenesis in the dentate gyrus of adult female rats, a result related to spatial memory processes (Galea et al., 2008). Moreover, there is wide evidence in studies with rodents that estradiol has profound effects on spatial navigation strategy use mainly within the hippocampus, and it enhances place learning when administered locally in the hippocampus (Zurkovsky, Brown, Boyd, Fell, & Korol, 2007). As regards to the differences found in CO activity of the mediodorsal thalamus and the motor cortex, neuroimaging studies using PET at different stages of human menstrual cycle reported similar results, with the highest glucose metabolism in similar regions during the late follicular phase, when estradiol levels are high like the diestrous phase in rats (Reiman, Armstrong, Matt, & Mattox, 1996).

On the other hand, the observed changes in neuronal oxidative metabolism at different stages of estrous cycle and the sexual dimorphism found in particular brain regions should be related to behavioral studies. In fact, sexual dimorphism has been

consistently reported for spatial abilities in rodents and humans (for an extensive review, see Andreano & Cahill, 2009; Jonasson, 2005). In general, males outperform females in spatial learning or spatial orientation tasks, and this finding is also related to the levels of circulating gonadal steroids. Performance level in these tasks is directly related to the amount of circulating androgens and inversely related to estrogen levels (Galea et al., 2008). Neuroimaging studies reported sexual dimorphism in the patterns of brain activation, including also differences across different stages of the menstrual cycle in humans (Schöning et al., 2007, Reiman et al., 1996). Moreover, we found a functional lateralization of CO activity for sex and estrous cycle stage in the cingulate cortex and mediodorsal thalamus. As far as we know, this is the first study reporting functional cerebral asymmetries in rats. Gonadal steroids are powerful modulators of the dynamics of functional organization of the central nervous system in females, and functional asymmetries have also been reported in humans using neuroimaging techniques (Fernández et al., 2003). Functional lateralization seems to depend on the action of estrogens by inhibition of the hemisphere dominance on particular tasks in women (Weis & Hausman, 2009).

Although the existence of sex differences in brain function is a controversial issue, there are many confounding factors because in most studies the stage of ovarian cycle is not taken into account to assess sex differences. We hope that our study will help to provide further evidence about the relevance of considering the levels of gonadal steroids in order to explain sexual dimorphism in behavior and brain function.

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