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Early postnatal treatment with clomipramine induces female sexual behavior and estrous cycle impairment

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ABSTRACT

Administration of clomipramine (CMI), a tricyclic antidepressant, in early stages of development in rats, is considered an animal model for the study of depression. This pharmacological manipulation has induced behavioral and physiological alterations, *i.e.*, less pleasure-seeking behaviors, despair, hyperactivity, cognitive dysfunction, alterations in neurotransmitter systems and in HPA axis. These abnormalities in adult male rats are similar to the symptoms observed in major depressive disorders. One of the main pleasure-seeking behaviors affected in male rats treated with CMI is sexual behavior. However, to date, no effects of early postnatal CMI treatment have been reported on female reproductive cyclicity and sexual behavior. Therefore, we explored CMI administration in early life (8–21 PN) on the estrous cycle and sexual behavior of adult female rats. Compared to the rats in the early postnatal saline treatment (CTRL group), the CMI rats had fewer estrous cycles, fewer days in the estrous stage, and longer cycles during a 20-day period of vaginal cytology analysis. On the behavioral test, the CMI rats displayed fewer proceptive behaviors (hopping, darting) and had lower lordosis quotients. Also, they usually failed to display lordosis and only rarely manifested marginal or normal lordosis. In contrast, the CTRL rats tended to display normal lordosis. These results suggest that early postnatal CMI treatment caused long-term disruptions of the estrous cycle and female sexual behavior, perhaps by alteration in the hypothalamic-pituitary-gonadal (HPG) axes and in neuronal circuits involved in the regulation of the performance and motivational of sexual behavior as the noradrenergic and serotonergic systems.

1. Introduction

Depression is the most common psychiatric disorder, as it affects approximately 17% of the population (Duman, 2014). It is characterized by a profound loss of interest (anhedonia), dysregulation of affect and mood, decreased libido, cognitive dysfunction, fatigue, and sleep and appetite disorders (American Psychiatric Association, 2013). Significantly, women run a lifetime risk of suffering depression twice as high as that of men (Kessler et al., 2003; Kessler and Bromet, 2013; Marcus et al., 2005). Their predisposition to depression involves social, psychosocial and biological factors like hormonal fluctuations such as estrogen and progesterone that it has been linked to the reproductive cycle and premenstrual syndrome, with associated mood disturbances, regularly recurs during the luteal phase of each menstrual (ovarian) cycle (Noble, 2005; Sassarini, 2016). It is well known that estrogen interacts with neurotransmitter systems. For instance, estrogens increased the syntheses of serotonin and decreased the activity of the monoamine-oxidase, the enzyme that is involved in the catabolism of monoamines (Gundlah et al., 2002; Hiroi et al., 2006; Lu et al., 2003). Moreover, noradrenergic system participates in the ovarian-steroid feedback of secretory luteinizing hormone (Miller and Zhu, 1995; Szawka et al., 2013, 2007). These data suggest an interaction between steroid hormones and neurotransmitter systems, which have a participation in the neurobiology of depression.

Animal models are useful tools for studying the neurobiology of depression and screening new molecules with antidepressant activity (Valvassori et al., 2013; Yan et al., 2010). Most of such models employ different types of stressors to induce depressive-like behaviors, though some involve long-term manipulations that promote a predisposition to developing depression, such as early postnatal administration of clomipramine (CMI) (Willner and Mitchell, 2002).

Administering CMI, a tricyclic antidepressant, in early life is

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considered a neurodevelopmental model for the study of depression that has high face validity (Willner and Mitchell, 2002). Depression is induced by administering CMI, a tricyclic antidepressant that inhibits serotonin and noradrenaline reuptake during the early postnatal stage (8–21 PN). This pharmacological manipulation induces several behavioral and physiological alterations that are analogous to the symptomatology observed in major depression disorder (Feng and Ma, 2003; Justel et al., 2011; Vijayakumar and Meti, 1999; Vogel et al., 1990a; Yannielli et al., 1998). Male rats treated in early postnatal stage with CMI show hyperactivity (Hartley et al., 1990; Hilakivi et al., 1984; Mirmiran et al., 1983; Yannielli et al., 1999), abnormalities in sleep characterized by a shorter latency to REM and increased REM fragmentation, to mention only a few effects (Savelyev et al., 2012; Vogel et al., 1990b). Male rats also exhibit less aggressive behavior (Vogel et al., 1988), decreased pleasure- and reward-seeking behaviors (e.g. intracranial self-stimulation) (Vogel et al., 1990c), and cognitive alterations that may affect learning and memory (Bhagya et al., 2008). On the forced swimming test, CMI rats display greater immobility accompanied by reduced active swimming behavior, and a possible alteration in the serotonergic system (Bhagya et al., 2008; Bonilla-Jaime et al., 1998; Vázquez-Palacios et al., 2005; Velazquez-Moctezuma and Diaz Ruiz, 1992). In fact, observations show that CMI rats exhibit alterations in neurotransmission, especially in the serotonergic, dopaminergic and noradrenergic systems (Andersen et al., 2002; Bhagya et al., 2011; Hansen and Mikkelsen, 1998; Yavari et al., 1993).

Early postnatal CMI administration also induces abnormalities in male sexual behavior. Although CMI rats display more mounts, the number of intromissions and ejaculations tends to diminish. Additional findings include increased latencies to mounting, intromitting and ejaculating, and a lower post-ejaculation latency, all of which are indicators of motivation (Bonilla-Jaime et al., 1998; Feng et al., 2001; Neill et al., 1990; Vogel et al., 1996). Moreover, CMI rats have been seen to spend less time in proximity to a female incentive, a finding that corroborates the lack of sexual motivation (Limón-Morales et al., 2014). These negative effects on male sexual behavior and performance and on the motivational component are reflected in a reduced libido and the failure to reach orgasm and ejaculation (Hendrick et al., 2000). It is important to mention that most studies that have used the early postnatal CMI administration model have involved only male rats. Female rats treated with CMI in early life have exhibited anxiety-like behaviors and reduced levels of monoamines in the limbic region (Andersen et al., 2002), but there are no reports on the effects of early postnatal CMI administration on pleasure-seeking behaviors in females like sexual behavior.

Female sexual behavior involves a series of behavioral, interactional and postural adjustments that are classified as proceptive and receptive (Beach, 1976; Erskine, 1989; Sakuma, 1995). Proceptive behaviors are defined as a complex series of appetitive activities that estrous females display to encourage the male to mate. They include hopping and darting (Beach, 1976; Erskine, 1989), and indicate the intensity of sexual motivation (Uphouse, 2014). Receptive behaviors, meanwhile, involve the postural changes that are necessary and sufficient to allow copulation with a potent male. This is also known as lordosis behavior (Beach, 1976; Fabre-Nys et al., 2003).

Sexual behavior and ovulation is regulated by the HPG axis and serotoninergic system. In fact, lordosis reflex depends on estrogens priming while progesterone is required for procreativity and to facilitate the response of lordosis (Blaustein, 2008; Erskine, 1989; Ogawa et al., 1994), while the serotonergic system exert a dual action on sexual behavior (facilitation or inhibition) through different signaling pathways (serotonergic receptors family and serotonin transporter (SERT) (Angoa-Pérez and Kuhn, 2015; Uphouse, 2014, 2000), where some drugs which increased serotonin levels inhibits proceptive and receptive responses (Uphouse, 2014, 2000). Additionally, hormonal facilitation of lordosis behavior involves the expression of adrenergic receptors in preoptic area and hypothalamus (Etgen, 2003).

It is important to mention that serotonergic system is critical in early neurodevelopment due to its involvement in neuronal proliferation, migration, differentiation and synaptogenesis (Deneris and Gaspar, 2017). Early in life, at the 12-postnatal day (PN), SERT is also expressed in non-serotonergic neurons from thalamus, somatosensory cortex and corticolimbic structures

An increased in SERT expression occurs in hippocampus to regulate process such as neurogenesis neutrophil formation, axon myelination and synaptogenesis (Glover and Clinton, 2016; Millard et al., 2017). Moreover, serotonergic system and adrenergic are involved in sexual differentiation and in HPG axis development and the hypothalamus is radiated by the axons from the cell bodies of the raphe nuclei (Döhler, 1991; Jarzab and Döhler, 1984). In addition, noradrenergic neurons of the brainstem finished the differentiation during embryonic period but the formation of their neuronal terminals finished until the third week of postnatal period (Murrin et al., 2007). Then, manipulation of neurotransmitter system during early life, especially serotonergic system, could lead to several alterations in adulthood.

Studies with humans, show that the exposition to antidepressants during gestation and or postnatal period increased risk of low birth weight, neonatal abstinence syndrome, cardiac defects and fine and gross motor alterations (Belik, 2008; Oberlander et al., 2010). Some longitudinal and retrospective studies show motor alterations, presence of anxiety, low social and emotional behaviors, higher risk of autism spectrum disorder and attention deficit hyperactivity disorder in children (Boukhris et al., 2016; Figueroa, 2010; Hanley et al., 2015); while in early adolescence increased the risk of autism spectrum disorder and depression (Harrington et al., 2014; Malm et al., 2016). Nevertheless, clinical data about the effect of early exposition to antidepressant on reproductive parameters is unknown.

Some animal studies reported that perinatal exposure to fluoxetine (SSRI, a selective serotonin reuptake inhibitor) seems to foster proceptive and receptive behaviors in young females (Rayen et al., 2014), although exposure during gestation and lactation seems to produce a delay in reaching puberty (Dos Santos et al., 2016). Hence, it is possible that female rats treated with CMI in the early postnatal stages develop alterations in these physiological and behavioral reproductive parameters, given that males treated with CMI in early stages show a diminished capacity for pleasure-seeking behaviors such as sexual activity (Bonilla-Jaime et al., 1998; Feng et al., 2001; Neill et al., 1990; Limón-Morales et al., 2014). Thus, the aim of this study was to evaluate the effect of the early postnatal CMI administration on the estrous cycle and female sexual behavior.

2. Materials and methods

2.1. Animals and early postnatal clomipramine treatment

Six pregnant Wistar rats were obtained from the vivarium at the Universidad Autónoma Metropolitana. Three days after delivery, which is not a late period of adoption (Barbazanges et al., 1996; Darnaudéry et al., 2004), the female pups were separated from their biological mothers and lodged with foster mothers, with the aim the litter size was same (n = 6) (Bonilla-Jaime et al., 1998, 2003; Neill et al., 1990; Vázquez-Palacios et al., 2005; Vogel et al., 1990a, 1990b). Since maternal care differs by sex of the pub, male pups were set aside for a different experiment and cross-fostered with different mothers to those used for the females (Moore and Chadwick-Dias, 1986; Richmond and Sachs, 1984). From postnatal (PN) day 8–21, the female pups in the experimental group (CMI) were treated with clomipramine (15 mg/kg; 0.1 ml, sc, twice per day). This dose was chosen due to its effectiveness in producing the behavioral and physiological abnormalities required for the study protocol (Andersen et al., 2002; Bonilla-Jaime et al., 1998; Hartley et al., 1990; Vázquez-Palacios et al., 2005; Velazquez-Moctezuma et al., 1993; Vogel et al., 1990a, 1990b). The female pups in the control group received subcutaneous injections of saline in the same