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Research Report

Prolactin and its receptors in the chronic mild stress rat model of depression

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ABSTRACT

Prolactin (PRL) exhibits many physiological functions with wide effects on the central nervous system including stress responses. Our study aimed to investigate the effect of chronic unpredictable mild stress (CMS) – which is a good animal model of depression – on PRL receptor (PRLR) expression in the rat brain. Rats were exposed to CMS for two weeks and subsequently to CMS in combination with imipramine (IMI) treatment for five consecutive weeks. Behavioral deficit measured in anhedonic animals is a reduced intake of sucrose solution. Two weeks of CMS procedure allowed the selection of animals reactive to stress and displaying anhedonia, and the group which is considered as stress-non-reactive as far as behavioral measures are concerned. In this group the elevated level of PRL in plasma was observed, decrease in dopamine release in the hypothalamus, increase in [^{125}I]PRL binding to PRLR in the choroid plexus, increase of mRNA encoding the long form of PRLR in the arcuate nucleus and the decrease of mRNA encoding its short form, and decrease in the mRNA encoding dopamine D2 receptor. All these alterations indicate these parameters as involved in the phenomenon of stress-resilience. The prolongation of the CMS procedure for additional five weeks shows the form of habituation to the stressful conditions. The most interesting result, however, was the up-regulation of PRLR in the choroid plexus of rats subjected to full CMS procedure combined with treatment with IMI, which may speak in favor of the role of this receptor in the mechanisms of antidepressant action.

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Abbreviations: PRL, prolactin; PRLR, prolactin receptor; $PRLR_{Long}$, long form of prolactin receptor; $PRLR_{Short}$, short form of prolactin receptor; CMS, chronic mild stress; DRD2, dopamine D2 receptor; IMI, imipramine; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; 3-MT, 3-methoxytyramine; HVA, homovanillic acid; HPLC, high performance liquid chromatography; CNS, central nervous system; ACTH, adrenocorticitropic hormone

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1. Introduction

Prolactin (PRL) has a wide range of effects on the central nervous system (CNS), including actions of maternal behavior (Bridges et al., 1997), sexual behavior (Drago, 1984; Galdiero et al., 2012), feeding behavior (Moore et al., 1986), sleep–wake cycle (Roky et al., 1993), metabolism of neurotransmitters and neuropeptides (Tong and Pelletier, 1992) and stress responses (Babenko et al., 2012; Fujikawa et al., 2004). All these functions of PRL are mediated by PRL receptors (PRLR) (Bole-Feysot et al., 1998). PRLR expression has been detected in various brain regions, with the highest level in choroid plexus (Tabata et al., 2012; Pi and Grattan, 1998; Bakowska and Morrell, 1997; Roky et al., 1996; Chiu and Wise, 1994; Mangurian et al., 1992). The peripheral and central administration of PRL has been shown to increase prolactin receptors expression in choroid plexus (Muccioli and Di Carlo, 1994; Fujikawa et al., 2004), the role of which is to transport PRL molecules from the blood to CSF during exposure to stress (Walsh et al., 1987). Chronic restraint stress enhances the expression of gene encoding the long form of prolactin receptor ($PRLR_{Long}$) in the choroid plexus (Fujikawa et al., 1995). Prolactin is released into the blood from pituitary lactotroph cells in response to exposure to different stressors (Seggie and Brown, 1975). Recently, it has been shown that PRL protects neurogenesis in the dentate gyrus of hippocampus in chronic restraint stress (Torner et al., 2009). All of these reports suggest the involvement of PRL in stress response mechanism.

Although changes in the PRL level after acute or chronic (2 weeks) predictable stress (restraint or foot shock models) are well described in the literature, there is no information about changes in the level of prolactin following the chronic unpredictable mild stress (CMS), which is a good animal model of depression (Willner, 1997). In this model rats are exposed to CMS procedure (such as: periods of food and water deprivation, small temperature reductions, changes of cage mates, and other similar individually mild manipulations) for 2 weeks and subsequently to CMS in combination with imipramine (IMI) treatment for 5 consecutive weeks. Behavioral results obtained in CMS experiments showed that after 2 weeks of mild stress, anhedonia in rats is manifested by reduced consumption of sucrose solution. Next 5 weeks of stressful stimuli maintained this effect, and the administration of an antidepressant drug reversed anhedonia. This indicates that the CMS model is a very good animal model to monitor the action of antidepressant drugs, and it has been proposed to model some of the environmental factors that contribute to the induction of depressive disorders in humans (Willner, 1997, 2005; Jayatissa et al., 2006; Żurawek et al., 2013). Additionally the CMS paradigm allows the study of the correlation between behavioral response to stress, antidepressant treatment and PRL levels. Although it has been demonstrated that depressive disorders are more frequently found in women than in men (Kendler et al., 1995; Kessler, 2003), we decided to use male rats, which are more biologically stable than female rats. The dopamine reward circuit in female rats is strongly affected by hormonal changes during the estrus cycle (Becker, 1999). Estrogen and progesterone modulate dopamine activity and receptor levels in the striatum and nucleus accumbens in female rats. In contrast, estrogen does not affect striatal dopamine release in male rats. Furthermore, male hormones such as testosterone do not affect the brain dopamine reward circuit (Becker, 1999, 2009). It has been demonstrated that female rats are more vulnerable to CMS model with disruption in corticosterone levels, alteration in estrous cycle and decreased serotonergic activity in hippocampus and hypothalamus. On the contrary, in males the CMS protocol elicited only behavioral changes, such as disruption in sucrose intake and decreased open field (Dalla et al., 2005).

Moreover, using other rat models, e.g., chronic sustained stress, no difference between male and female in plasma PRL level or anterior pituitary PRL mRNA levels has been observed not only in non stressed groups but also after 1, 3 and 14 days of stress exposure (Dave et al., 2000).

The pituitary–adrenal hormonal response to stress has been described well (Martí and Armario, 1998). Depression is characterized by an over activity of the hypothalamic–pituitary–adrenal (HPA) axis that resembles the neuroendocrine response to stress (Swaab et al., 2005). It has been shown in rats that after a short term of acute stress, pro-opiomelanocortin (POMC)-derived hormones (e.g., ACTH) and PRL appear to reflect the intensity of stress (Meyerhoff et al., 1988). PRL acting through brain PRLR exerts an inhibitory tone on HPA axis activity in rats (Torner et al., 2001). PRL regulates its own release by affecting the dopaminergic neurons via a short loop negative feedback; it reaches the arcuate nuclei by retrograde blood flow from the pituitary (Oliver et al., 1977) or from the cerebrospinal fluid via receptor-mediated uptake at the choroid plexus (Mangurian et al., 1992). The PRLR colocalize with neurons expressing tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis (Grattan, 2001).

Because PRL stimulates dopamine (DA) release from tuberoinfundibular neurons in the arcuate nucleus of the hypothalamus, which in turn suppresses the production of PRL (Ben-Jonathan et al., 2008), we also investigated how the CMS influenced the PRLR and dopamine D2 receptor (DRD2) level in hypothalamus and rat pituitary. In addition, the level of DA release in the hypothalamus of the tested animals was investigated. Especially interesting was to compare the response of animals subjected to shorter (2 weeks) CMS paradigm to the longer one (5 weeks) and to compare the measured biochemical parameters in rats responsive to stress procedure to the non-responsive ones as well as in animals responsive to antidepressant treatment with the non-responsive group.

2. Results

2.1. *Behavioral experiments*

Independent analyses using repeated measures ANOVA test did not show any significant difference of sucrose consumption among animals during the training procedure in 2 and 7 weeks of chronic mild stress experiment ($F(2, 26)=0.831$; $p=0.433$, and $F(2, 29)=3.485$; $p=0.052$, respectively). In the final baseline test after 2 weeks of stress, sucrose intake was

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