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Maternal separation induces hippocampal changes in cadherin-1 (*CDH-1*) mRNA and recognition memory impairment in adolescent mice

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ABSTRACT

In rodents, disruption of mother-infant attachment induced by maternal separation (MS) is associated with recognition memory impairment and long-term neurobiological consequences. Particularly stress-induced modifications have been associated to disruption of cadherin *(CDH)* adhesion function, which plays an important role in remodeling of neuronal connection and synaptic plasticity. This study investigated the sex-dependent effect of MS on recognition memory and mRNA levels of classical type I and type II *CDH* and the related β -catenin (β *-Cat*) in the hippocampus and prefrontal cortex of late adolescent mice. We provided evidence that the BALB/c mice exposed to MS present deficit in recognition memory, especially females. Postnatal MS induced higher hippocampal *CDH-2* and *CDH-8* mRNA levels, as well as an upregulation of *CDH-1* in the prefrontal cortex in both males and females. MS-reared female mice presented lower *CDH-1* mRNA levels in the hippocampus. In addition, hippocampal *CDH-1* mRNA levels were positively correlated with recognition memory performance in females. MS-reared male mice exhibited higher β *-Cat* mRNA levels in the hippocampus. Considering sex-specific effects on *CDH* mRNA levels, it has been demonstrated mRNA changes in *CDH-1,* β *-Cat,* and *CDH-6* in the hippocampus, as well as *CDH-1*, *CDH-8* and *CDH-11* in the prefrontal cortex. Overall, these findings suggest a complex interplay among MS, *CDH* mRNA expression, and sex differences in the PFC and hippocampus of adolescent mice.
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1. Introduction

Neural plasticity comprises dynamic alterations throughout life produced by adaptive responses to environmental challenges, which include neurochemical rearrangement that allows the rewiring of neural connections and stabilization of synapses (McEwen & Gianaros, 2011; Pittenger & Duman, 2008). Early-life stress (ELS) has been considered an exposure to an environmental stressor that potentially leads to long-lasting effects on the developmental trajectory (McEwen et al., 2015a; Teicher et al., 2003). In addition, ELS is able to promote alterations in neuronal architecture and function (McEwen & Gianaros, 2011; Teicher et al., 2003), leading to biological embedding of early stressful events throughout the lifespan.

The hippocampus and interconnected prefrontal regions are both targets that appear to be susceptive to early stress-induced changes (McEwen, 1999; McEwen, Nasca, & Gray, 2015b), since they mediate neuroendocrine stress responses by neuronal connections with the hypothalamic-pituitaryadrenal (HPA) axis. The repeated activation of the HPA axis in response to environmental challenges during immature periods of brain development is involved in long-term consequences of ELS, contributing to changes in brain remodeling, volumetric modifications, and dendritic branching that underlie adaptive responses to stress (McEwen, 1999, 2007; McEwen et al., 2015b; Woon, Sood, & Hedges, 2010).

Disruption of mother-infant attachment has been extensively investigated to explain the long-term effects of early stressors across different species of rodents (Marco et al., 2015; Nishi, Horii-Hayashi, & Sasagawa, 2014; Tractenberg et al., 2016).

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Specifically, previous studies have suggested that the BALB/c is one of the most vulnerable mice strain to the MS effects later in life (Mehta & Schmauss, 2011; Millstein & Holmes, 2007; Tractenberg et al., 2016). In this context, daily-prolonged periods of maternal separation (MS) were associated with long-term neurobiological and behavioral consequences (Millstein & Holmes, 2007; Tractenberg et al., 2016; Viola et al., 2016; Wearick-Silva et al., 2016). Notably, previous studies demonstrated that daily-prolonged periods of MS produce long-lasting effects on object recognition memory in male rodents (de Lima et al., 2011; Garcia et al., 2013; Martisova, Aisa, Guereñu, & Ramírez, 2013; Pinheiro et al., 2015). Although a considerable debate has concentrated on whether the hippocampus participates in non-spatial versions of object recognition at short-term intervals between training and retrieval, a previous report demonstrated that temporary inactivation of the hippocampus with muscimol has blocked short-term retention of object recognition memory (de Lima, Luft, Roesler, & Schröder, 2006). In addition, a recent review has posed that temporary or permanent ablation of the hippocampus consistently disrupts object recognition memory when a delay of 10 min or greater is imposed between the training and test sessions (Cohen & Stackman, 2015).

There is increasing evidence for a sex-related differential response to prolonged MS in rodents (Kundakovic, Lim, Gudsnuk, & Champagne, 2013; Tractenberg et al., 2016). Considering findings derived from 84 studies involving direct MS effects on behavioral phenotypes in mice (Tractenberg et al., 2016), sex-dependent responsiveness to MS has been demonstrated by increased depressive-like behavior and anxiety-like behavior in males, as well as memory performance deficits in BALB/c males. In addition, considering data derived from studies that investigated the effects of MS on biological markers, it was demonstrated that differential patterns of neurobiological modifications in response to MS, such as high peripheral corticosterone levels, and reduced mRNA expression of glucocorticoid receptor and neurotrophins in brain areas related to learning and memory (Tractenberg et al., 2016). In addition, there are studies indicating that early-life experiences across the lifespan have long-term consequences on hippocampal structure and function (Lajud, Roque, Cajero, Gutiérrez-Ospina, & Torner, 2012; Lajud & Torner, 2015; Naninck et al., 2015), and other reports demonstrate that males are more susceptible to ELS than females (Loi, Koricka, Lucassen, & Joëls, 2014; Mak, Antle, Dyck, & Weiss, 2013). Although the exact sex-dependent mechanism that underlies ELS-induced effects on structural and functional plasticity of the hippocampus is not completely understood, the dynamic fluctuation of adult neurogenesis in hippocampal development in response to stress could promote spatiotemporal changes in synaptic interconnected networks, remaining functionally different throughout life (Mirescu, Peters, & Gould, 2004).

The cell adhesion molecules are involved in several stages of the neural development, in which include formation and segmental organization of the central nervous system (McCarthy, Na, Neyt, Langston, & Fishell, 2001; Park, Falls, Finger, Longo-Guess, & Ackerman, 2002), neuroblast migration (Schnädelbach et al., 2000), axon fasciculation (Treubert-Zimmermann, Heyers, & Redies, 2002), and synapse formation (Arikkath & Reichardt, 2008). In addition, cell adhesion molecules have been associated with neural plasticity, such as occurs in long-term potentiation (LTP) of hippocampal synaptic strength (Huntley, Gil, & Bozdagi, 2002; Huntley et al., 2012; Tang, Hung, & Schuman, 1998). These observations indicate that cell adhesion molecules could be important in a remodeling of neuronal connections and synaptic plasticity in response to ELS. Classical cadherin (*CDH*) is a family of transmembrane proteins characterized by an extracellular domain containing five *CDH* repeat sequences mediating specific calcium-dependent interactions (Brasch, Harrison, Honig, & Shapiro, 2012). In addition, *CDH* adhesion molecules are grouped into type I and type II subfamily, playing an substantial role in the regulation of synaptic plasticity and specificity (Basu, Taylor, & Williams, 2015; Gärtner, Fornasiero, & Dotti, 2015; Seong, Yuan, & Arikkath, 2015; Takeichi, 2007). *β -Catenin (β-Cat)* is a cell adhesion molecule associated with the cytoplasmic domain of *CDH* and directly linked to the acting-binding proteins in synaptic junctions (McCrea, Maher, & Gottardi, 2015), regulating the synaptic connectivity and activity (Salinas & Price, 2005; Seong et al., 2015). In addition to the role of *β -Cat* in *CDH*-mediated cell adhesion, it also plays a critical role in the canonical *Wnt* signal transduction pathway, and the *Wnt*/*β -Cat* complex is involved in modulating synaptic plasticity that is underlying long-term memory (Chen, Park, & Tang, 2006; Maguschak & Ressler, 2008, 2011). The remodeling and cell signaling capabilities of the *CDH* family molecules in the synaptic connections suggest that the *CDH* are important not only during synaptic assembly (Basu et al., 2015), but also in fine-tuning the synaptic response (Arikkath & Reichardt, 2008; Seong et al., 2015).

Despite the regulatory mechanisms driving typical development of cell adhesion molecules in the central nervous system are not well understood, it is known that the *CDH* expression during the neural development is modulated by transcription factors and signal transduction pathways (Paulson, Prasad, Thuringer, & Manzerra, 2014). Given the possibility that dynamic modifications in expression of cell adhesion molecules are implicated both in memory (Basu et al., 2015; Maguschak & Ressler, 2008) and brain development (Paulson et al., 2014), a possible effect of *CDH* function on synaptic plasticity could be related to the stress responses later in life. Considering the stress-induced molecular changes on cell adhesion molecules, there are no studies that examined the sex-specific effects of MS on *CDH* mRNA expression in late adolescent BALB/c mice. In this concern, adolescence is a transitional period before full sexual maturity in which occur various neurodevelopmental modifications (De Bellis et al., 2001; Schneider, 2013), such as myelination of fiber tracts and an overproduction of axons and synapses followed by rapid pruning. In this period, there is evidence demonstrating changes in behavioral patterns (i.e., high levels of exploration, play-like behavior and risk-taking) (Laviola, Macrì, Morley-Fletcher, & Adriani, 2003; Schneider, 2013; Spear, 2000) in adolescence. Given that adolescence is a crucial period in which occur behavioral and neurobiological alterations, the choice of late adolescent stage was due to the distinct timing of maturation of the neuroendocrine system for reproductive function, which is completed at postnatal day (PND) 32 in females (Safranski, Lamberson, & Keisler, 1993) and PND 40 in males (Divall et al., 2010). Considering that the BALB/c strain provides stress-susceptible profile to MS effects (Tractenberg et al., 2016), we attempted to investigate the effect of postnatal MS on mRNA levels of *β -Cat* and classical type I *CDH (CDH-1* and *CDH-2)* and type II *CDH* (*CDH-6, -8, -10*, and *-11)* in the hippocampus and prefrontal cortex of late adolescent mice. Since some neurobiological effects of MS could be modulated by biological sex differences, our study also addressed the sex-specific effects in terms of *CDH* and *β -Cat* mRNA levels in response to prolonged MS early in life.

2. Material and methods

2.1. Animals

Male and female BALB/c mice (total $n = 42$ animals) were obtained from the animal facility at Pontifical Catholic University of Rio Grande do Sul (PUCRS), Brazil. Mice were housed in standard

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