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Research paper

Correlations between changes in the hypothalamic-pituitary-adrenal axis and neurochemistry of the anterior cingulate gyrus in postpartum depression

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ABSTRACT

Background: This study aimed to investigate associations between indicators of hypothalamic-pituitary-adrenal axis (HPA) functioning and metabolite levels in the anterior cingulate gyrus (ACG) of women with postpartum depression (PPD).

Methods: The sample (mean age = 28.5 ± 4.6 years) consisted of 20 women with PPD and 19 postpartum euthymic (PPE) women. Brain metabolites were quantified by proton magnetic resonance spectroscopy (^{1}H-MRS). Salivary cortisol samples were collected upon awakening and 30 min and 12 h later, at 20.6 ± 6.6 (PPD) and 23.0 ± 7.4 (PPE) weeks after childbirth.

Results: There were no significant differences between groups in respect to metabolite levels in the ACG. Compared with PPE, PPD women had less diurnal variation (DVr%). In the PPD group, positive correlations were found between DVr% and myo-inositol (mI/Cr) levels, and between cortisol awakening response (CARi%) and glutamate + glutamine (Glx/Cr) levels. The correlation between CARi% and Glx/Cr remained significant even after controlling for the interval, in weeks, from birth and MR spectroscopy and to hormonal data collection, and the use of contraceptives.

Limitations: The limitations of the study include the small sample size and the use of oral contraceptives by around half of the sample.

Conclusions: In the remote postpartum period (mean 21.8 ± 6.9 weeks) and in the presence of depressive episodes, the decreased responsiveness of the HPA axis after awakening and a smaller decrease in cortisol levels over the day were associated with lower levels of metabolites in the ACG. These results may contribute to the development of biological models to explain the etiology of PPD.

1. Introduction

Major depressive episodes are prevalent in the postpartum period (Gaynes et al., 2005) and affect not only patients, but also their bonding with the newborn baby, who, in turn, may have cognitive and behavioral impairments in the future (Grace et al., 2003; Herrera et al., 2004; Murray et al., 1996). Therefore, the comprehension of the physiopathology of postpartum depression (PPD) can have significant impacts on the prevention and alleviation of harms to the mother-child dyad.

The etiology of PPD is multifactorial, but studies have suggested a possible influence of hormonal alterations in the physiopathology of PPD (Bloch, 2000; Kammerer et al., 2006), especially alterations in the function of the hypothalamic-pituitary-adrenal (HPA) axis (Harris et al., 1996; Jolley et al., 2007; O'Keane et al., 2011; Saleh el et al., 2013). Recently, our group described a reduction in HPA responsiveness in

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women in the postpartum compared to healthy controls, which were more pronounced in women with PPD compared to euthymic postpartum women (de Rezende et al., 2016).

Neuroimaging studies suggest the involvement of different brain regions in depressive disorders (Dougherty and Rauch, 1997; Mayberg, 1997), including the hypothalamus, amygdala, hippocampus, medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), and anterior cingulate gyrus (ACG), which are rich in glucocorticoid receptors (McEwen et al., 1986) and mediate the function of the HPA axis (Smith and Vale, 2006; Whitnall, 1993).

The ACG plays an important role in the mediation of HPA axis function through its projections to the hypothalamus (Boehringer et al., 2015; Herman et al., 2005). In healthy individuals, serum levels of adrenocorticotropic hormone (ACTH) were found to be positively correlated with blood flow in the left ACG and right insula (Ottowitz et al., 2004), as assessed with single-photon emission computed tomography (SPECT). Also in healthy subjects, during a stress paradigm, researchers found a relationship between increases in cortisol levels and decreased activity in the ACG (Pruessner et al., 2008). Furthermore, healthy elderly subjects who presented no suppression of cortisol levels in the dexamethasone suppression test (DST) had decreased ACG volume in the left hemisphere compared to subjects who presented the suppression response (MacLullich et al., 2006). Structural alterations in the ACG have also been described in association with other medical conditions that involve alterations in HPA axis function, such as Cushing's disease (Andela et al., 2013).

Besides functional and structural alterations, neuroimaging also allows the biochemical assessment of regions of interest (ROI) with the technique of proton magnetic resonance spectroscopy (^{1}H-MRS). ^{1}H-MRS is able to detect the signs of different metabolites in brain tissue (Rudkin and Arnold, 1999), thus providing parameters on energetic metabolism, neuronal integrity, and neurotransmitter availability (Bustillo, 2013; Grimm et al., 2012). The metabolites most consistently investigated with ^{1}H-MRS are glutamate (Glu), glutamate + glutamine (Glx), myo-inositol (mI), glycerophosphocholine + phosphocholine + choline (Cho), N-acetylaspartate + N-acetylaspartylglutamate (NAA), and creatine + phosphocreatine (Cr). Cr concentrations are relatively constant and resistant to changes and are therefore used as a reference for metabolic quotients (/Cr) (Malhi et al., 2002).

Metabolic alterations in the ACG of depressed patients relative to healthy controls have been described in ^{1}H-MRS studies and include reductions in the levels of metabolites of the glutamatergic complex (Glu and Glx) (Auer et al., 2000; Hasler et al., 2007; Merkl et al., 2011; Pfleiderer et al., 2003) and of mI/Cr (Coupland et al., 2005). Particularly, reduced concentrations of Glu and/or Glx in the ACG of depressed patients support the hypothesis of a glutamatergic dysfunction in the neurobiology of mood disorders (Auer et al., 2000; Hasler et al., 2007; Merkl et al., 2011). In addition to neuronal cells, glial cells responsible for replenishing the glutamate pool also seem to be implicated in the pathophysiological mechanisms of depressive states (Pfleiderer et al., 2003). A meta-analysis has shown that patients with major depressive episodes, when compared with controls, presented reduced levels of Glu and Glx when considering all brain regions and that this difference was more pronounced when only the ACG was considered (Luykx et al., 2012). In support of these findings, a recent study described significantly lower levels of glutamate in the ACG of medication-free unipolar patients compared to healthy controls (Wise et al., 2018).

It is important to emphasize that glutamatergic dysfunction is one of the possible complex mechanisms underlying depression, which include, beyond the "monoaminergic hypothesis" and the involvement of the HPA axis, the influence of environmental stressors, epigenetic changes, neuroplasticity abnormalities, neuroinflammation, and mitochondrial neuronal dysfunction, leading to changes in brain structures such as the ACG (Ferrari and Villa, 2017; Kim and Won, 2017; Nemoda and Szyf, 2017).

To date, few studies investigated metabolite alterations using ^{1}H-MRS in PPD, but there is evidence showing reduced levels of gamma-aminobutyric acid (GABA) in the occipital region of women who had given birth six months earlier compared to women out of the postpartum period, regardless of depression diagnosis (Epperson et al., 2006), and of increased Glu levels in the mPFC of women with PPD between three and nine weeks after childbirth compared to euthymic women in the postpartum (McEwen et al., 2012). In an earlier study (Rosa et al., 2017), our group found decreased levels of NAA and of metabolites of the glutamatergic complex in the left dorsolateral prefrontal cortex of women with PPD compared to euthymic postpartum women, but no differences were found between the two groups concerning metabolite levels in the ACG. However, women using progestogen contraceptives presented higher Glu and Glx levels in the ACG, independently of the diagnosis of a depressive episode, which suggests that changes in the hormonal environment could modulate the neurochemistry of the ACG.

Considering the evidence of abnormalities in the levels of ACG metabolites in depressed patients, HPA axis dysfunction in PPD, and the role of the ACG in the mediation of HPA axis function, we speculated whether women with PPD would have abnormalities in the relationship between endogenous cortisol levels and the functional neurochemistry of the ACG. To our knowledge, no studies to date investigated these relationships. Therefore, the objective of our study was to investigate the existence of associations between indicators of HPA axis functioning and ACG metabolites measured by ^{1}H-MRS. To do this, we analyzed the data of a subsample of depressed postpartum women compared to euthymic postpartum women who underwent magnetic resonance scans (Rosa et al., 2017) and assessment of HPA axis function (de Rezende et al., 2016).

In order to assess the function of the HPA axis, we used two auxiliary measures: HPA axis responsiveness, assessed through the cortisol awakening response (CAR), and diurnal variation (DV) in cortisol levels. The HPA axis is subject to variations linked to the circadian rhythm, with the cortisol secretion presenting peaks along the day (Young et al., 2001). The CAR is the most significant of such peaks and occurs approximately 30 min after awakening (Wilhelm et al., 2007). In healthy individuals, an increment of over 50% is expected in cortisol levels during the CAR (Pruessner et al., 1997), followed by a decrease of the cortisol levels along the day (Spiga et al., 2014). Although diverging evidence exists (Cheng and Pickler, 2009; Scheyer and Urizar, 2016), probably due to biases and heterogeneity of methodologies used in the different studies (Garcia-Leal et al., 2017), PPD women have been reported to present an attenuated CAR between 6 and 8 weeks (Taylor et al., 2009) and in about 6 months (de Rezende et al., 2016) after delivery.

Based on previous evidence that depressed patients have structural and functional alterations in the ACG and abnormal HPA axis function, our hypothesis was that correlations would exist between the levels of metabolites in the ACG, and measures of HPA functioning in depressed postpartum women compared to euthymic postpartum women.

2. Methods

2.1. Participants

The participants for this cross-sectional study were recruited from a larger study termed *BRISA* (Brazilian, Ribeirão Preto, and São Luís Birth Cohort Studies) (da Silva et al., 2014), which involved a sample of women in the postpartum who underwent diagnostic assessments for the screening of postpartum depression (Figueiredo et al., 2015) and ^{1}H-MRS scans, besides providing salivary cortisol samples. The women in this study were not recruited from mental health services, but from a convenience cohort of pregnant women (22–25 weeks of pregnancy) aimed to assess perinatal risks of prematurity and child health. These women were reassessed in the postpartum period (mean 21.8 ± 6.9 weeks) initially by telephone interviews and, once a possible