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Research report

Subchronic glucocorticoids, glutathione depletion and a postpartum model elevate monoamine oxidase a activity in the prefrontal cortex of rats

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ABSTRACT

Recent human brain imaging studies implicate dysregulation of monoamine oxidase-A (MAO-A), in particular in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC), in the development of major depressive disorder (MDD). This study investigates the influence of four alterations underlying important pathologies of MDD, namely, chronic elevation of glucocorticoid levels, glutathione depletion, changes in female gonadal sex hormones and serotonin concentration fluctuation, on MAO-A and MAO-B activities in rats. Young adult rats exposed chronically to the synthetic glucocorticoid dexamethasone at 0, 0.05, 0.5, and 2.0 mg/kg/day (osmotic minipumps) for eight days showed significant dose-dependent increases in activities of MAO-A in PFC (+17%, $p < 0.001$) and ACC (+9%, $p < 0.01$) and MAO-B in PFC (+14%, $p < 0.001$) and increased serotonin turnover in the PFC (+31%, $p < 0.01$), not accounted for by dexamethasone-induced changes in serotonin levels, since neither serotonin depletion nor supplementation affected MAO-A activity. Sub-acute depletion of the major antioxidant glutathione by diethyl maleate (5 mmol/kg, i.p.) for three days, which resulted in a 36% loss of glutathione in PFC ($p = 0.0005$), modestly, but significantly, elevated activities of MAO-A in PFC and MAO-B in PFC, ACC and hippocampus (+6–9%, $p < 0.05$). Changes in estrogen and progesterone representing pseudopregnancy were associated with significantly elevated MAO-A activity in the ACC day 4–7 postpartum (10–18%, $p < 0.05$ to $p < 0.0001$) but not the PFC or hippocampus. Hence, our study provides data in support of strategies targeting glucocorticoid and glutathione systems, as well as changes in female sex hormones for normalization of MAO-A activities and thus treatment of mood disorders.

1. Introduction

Monoamine oxidase A (MAO-A) is a high density enzyme that participates in the metabolism of major monoamines, creates oxidative stress and participates in apoptosis (Youdim and Bakhle, 2006). Greater MAO-A activity and/or levels, particularly in the prefrontal (PFC) and anterior cingulate cortex (ACC), are associated with major depressive episodes (MDE), dysphoric states, and high risk states for MDE, such as alcohol dependence, withdrawal from cigarette smoking, early postpartum and in perimenopause and borderline personality disorder (Bacher et al., 2011; Chiuccariello et al., 2014; Johnson et al., 2011; Kolla et al., 2016; Matthews et al., 2014; Meyer et al., 2006, 2009; Rekkas et al., 2014; Sacher et al., 2010, 2014). Given that major depressive disorder (MDD) is a leading cause of death and disability in moderate to high income nations, affecting 4% of the general population

Abbreviations: ACC, anterior cingulate cortex; DEM, diethyl maleate; DEX, dexamethasone; GR, glucocorticoid receptor; MAO-A, monoamine oxidase A; MAO-B, monoamine oxidase B; MDD, major depressive disorder; MDE, major depressive episode; PFC, prefrontal cortex.

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(World Health Organization, 2008), dysregulation of MAO-A activity is highly relevant for a strongly impactful psychiatric illness. Despite the importance of MAO-A dysregulation in relation to societal psychiatric burden, there are still gaps in our knowledge as to whether certain fundamental processes affect brain MAO-A activity during early adulthood when MDD frequently emerges.

Stressful events are implicated in the development of MDEs (Kendler and Gardner, 2016). While a substantial amount of information has accumulated with regard to the relationship between glucocorticoid agonism and MAO-A in cell lines, there is a lack of knowledge regarding this relationship during young adult age in brain regions implicated in affect, such as the PFC and ACC. Administration of the glucocorticoid receptor (GR) agonist dexamethasone (DEX) to neuroblastoma and glioblastoma cell lines for 2–4 days increases MAO-A and B activities and gene expression through direct binding to the promotor and influencing additional transcription factors, R1 and TIEG2 (Chen et al., 2011; Grunewald et al., 2012; Ou et al., 2006; Tazik et al., 2009). Consistent with this, Slotkin et al. found that chronic DEX treatment at brain-penetrant doses increased MAO-A activity in the PFC of aged rats, concluding that this relationship had important implications for geriatric depression (Slotkin et al., 1998). Subsequent groups also found that chronic DEX treatment increased MAO-A and B levels in the substantia nigra and MAO-A mRNA in the dorsal raphe nucleus of young rats (Arguelles et al., 2010; Jahng et al., 2008). Interestingly, chronic unpredictable mild stress is associated with elevated MAO-A activity in whole rat brain, but the more specific phenomenon of elevated glucocorticoid agonism was not investigated (Grunewald et al., 2012; Harris et al., 2015; Lin et al., 2005). Hence, while there is a substantial body of work evaluating the relationship between glucocorticoid agonism and MAO-A activity, it has not been selectively investigated in the PFC and ACC of young to moderate-aged adult mammalian brain.

It has been demonstrated that glutathione (GSH) levels in postmortem PFC are deficient in several psychiatric illnesses including MDD and bipolar disorder (Gawryluk et al., 2011). GSH is a key antioxidant in the mitochondria, where it neutralizes reactive oxygen species including hydrogen peroxide produced by MAO-A (Mari et al., 2009; Youdim and Bakhle, 2006). GSH levels have also been shown to be decreased *in vivo* in the occipital cortex in MDD, as measured with magnetic resonance spectroscopy (Godlewska et al., 2014; Shungu et al., 2012). Some oxidative stressors, such as the toxin rotenone, increase MAO-A mRNA, protein and activity levels in human neuroblastoma cells and MAO-A mRNA in cultured mouse dopamine neurons (Fitzgerald et al., 2014; Tao et al., 2012), but it is unknown whether the oxidative stress of GSH depletion influences MAO-A activity in the brain.

MDD rates are higher in women than men (Kuehner, 2003), and one highly impactful sex-specific factor is pregnancy. Postpartum depression (PPD) is the most common complication of child bearing, affecting 13% of mothers (O'Hara and Swain, 1996). Postpartum blues, a syndrome of sadness, is a healthy range prodromal state, affecting 70% of new mothers, that, when severe, is associated with PPD (Adewuya, 2006; O'Hara et al., 1991). Elevated MAO-A density is the strongest postpartum brain marker with the highest magnitude of change in early postpartum, being increased, on average, by 43% throughout cortical and subcortical brain regions (Sacher et al., 2010). MAO-A density is also increased in the PFC and ACC of women with first-onset PPD (Sacher et al., 2014). Changes in gonadal steroids may have a causal role in contributing to elevations in MAO-A. Estrogen levels drop by 100–1000 fold in women in the first 3–4 days postpartum (Nott et al., 1976; O'Hara et al., 1991). Furthermore, an inverse relationship between estrogen levels and MAO-A activity has been reported in cell lines and the rat brain. Estrogen administration to the human neuroblastoma cell line was shown to decrease MAO-A activity (Ma et al., 1993, 1995). Consistently, estrogen administration decreased brain MAO-A activity in ovariectomized and intact rats (Holschneider et al., 1998; Leung et al., 1980; Luine and McEwen, 1977). Conversely, MAO-A activity was increased following discontinuation of estrogen treatment in the brain of ovariectomized rats (Jones and Naftolin, 1990). However, brain MAO-A activity has never been investigated in any animal postpartum model. In the present study, we investigated MAO-A activity in the simulated pseudopregnancy rat model of PPD (Galea et al., 2001), applying a modified version of the model that administers estrogen and progesterone for 21 days at levels simulating human pregnancy (Suda et al., 2008).

In the present study, we wished to address the gaps of knowledge in the literature regarding the effects of specific influences, namely glucocorticoid agonism, oxidative stress induced by GSH depletion and changes in gonadal hormones early postpartum on MAO-A activity in the PFC, ACC and hippocampus. For the DEX and GSH experiments, the PFC was the primary region of interest given the previously observed effects of DEX treatment on PFC MAO-A activity/level in another model (Slotkin et al., 1998) and the finding of decreased GSH levels in the PFC in MDD (Gawryluk et al., 2011). The ACC and hippocampus were investigated as secondary regions as they are also important affect-modulating regions with altered MAO-A levels in MDD (Meyer et al., 2006, 2009). We hypothesized that DEX treatment and GSH depletion would increase MAO-A and B activities in the PFC of young rats. For the early postpartum experiment, the PFC and ACC were the primary regions of interest as MAO-A density is elevated in these regions in women with PPD (Sacher et al., 2010). We hypothesized that estrogen and progesterone withdrawal would increase MAO-A activity.

2. Results

2.1. DEX treatment

2.1.1. Dose-response DEX treatment

To examine the effect of GR agonism on MAO-A and B activities, rats were treated with a range of doses of DEX subchronically. One-way ANOVAs revealed that DEX treatment induced a significant increase in MAO-A activity in the PFC [$F(3,31) = 13.43$, $p < 0.0001$] and the ACC [$F(3,31) = 4.28$, $p = 0.01$], and showed a trend in the hippocampus [$F(3,31) = 2.72$, $p = 0.06$] (Fig. 1A). In the PFC, MAO-A activity was increased by 17% in the DEX 2.0 mg/kg/d and 7% in the DEX 0.5 mg/kg/d groups relative to controls. In the ACC, MAO-A activity was increased by 9%. Linear regression analyses also demonstrated that DEX plasma concentrations significantly predicted MAO-A activity in the PFC [$R^2 = 0.54$, $p < 0.0001$], the ACC [$R^2 = 0.32$, $p = 0.0004$], and the hippocampus [$R^2 = 0.19$, $p = 0.009$] (Fig. 1B).

One-way ANOVAs revealed that DEX treatment induced a significant increase in MAO-B activity in the PFC [$F(3,31) = 6.23$, $p = 0.002$], but not in the ACC [$F(3,31) = 0.45$, $p = 0.72$], nor the hippocampus [$F(3,31) = 1.84$, $p = 0.16$] (Fig. 2A). MAO-B activity was increased by 14% in the DEX 2.0 mg/kg/d group in the PFC. Linear regression analyses demonstrated that DEX plasma concentrations significantly predicted MAO-B activity in the PFC [$R^2 = 0.35$, $p = 0.0002$], but not in the ACC [$R^2 = 0.04$, $p = 0.24$], and with a trend in the hippocampus [$R^2 = 0.12$, $p = 0.054$] (Fig. 2B).

One-way ANOVAs revealed that, in the PFC, DEX treatment significantly increased 5-HIAA levels [$F(3,30) = 3.42$, $p = 0.03$] and serotonin turnover [$F(3,30) = 4.21$, $p = 0.01$], decreased L-tryptophan [$F(3,30) = 5.81$, $p = 0.003$] and tyrosine [$F(3,30) = 45.13$, $p < 0.001$], but did not alter 5-HT [$F(3,30) = 1.18$, $p = 0.34$] and NE [$F(3,30) = 1.74$, $p = 0.18$] levels (Supplementary Table 1).