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Research Report

Glutamate, GABA, and glutamine are synchronously upregulated in the mouse lateral septum during the postpartum period

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ABSTRACT

Dramatic structural and functional remodeling occurs in the postpartum brain for the establishment of maternal care, which is essential for the growth and development of young offspring. Glutamate and GABA signaling are critically important in modulating multiple behavioral performances. Large scale signaling changes occur in the postpartum brain, but it is still not clear to what extent the neurotransmitters glutamate and GABA change and whether the ratio of glutamate/GABA remains balanced. In this study, we examined the glutamate/GABA-glutamine cycle in the lateral septum (LS) of postpartum female mice. In postpartum females (relative to virgins), tissue levels of glutamate and GABA were elevated in LS and increased mRNA was found for the respective enzymes producing glutamate and GABA, glutaminase (Gls) and glutamate decarboxylase 1 and 2 (Gad1 and Gad2). The common precursor, glutamine, was elevated as was the enzyme that produces it, glutamate-ammonia ligase (Glul). Additionally, glutamate, GABA, and glutamine were positively correlated and the glutamate/GABA ratio was almost identical in the postpartum and virgin females. Collectively, these findings indicate that glutamate and GABA signaling are increased and that the ratio of glutamate/GABA is well balanced in the maternal LS. The postpartum brain may provide a useful model system for understanding how glutamate and GABA are linked despite large signaling changes. Given that some mental health disorders, including depression and schizophrenia display dysregulated glutamate/GABA ratio, and there is increased vulnerability to mental disorders in mothers, it is possible that these postpartum disorders emerge when glutamate and GABA changes are not properly coordinated.

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Abbreviations: GAD, glutamate decarboxylase; Gad1 (GAD67), glutamate decarboxylase 1; Gad2 (GAD65), glutamate decarboxylase 2; Gls, glutaminase; Glul, glutamate-ammonia ligase; GS, glutamine synthetase; LS, lateral septum; Pag, phosphate-activated glutaminase; Slc1a2 (GLT-1, Eaat2), solute carrier family 1 (glial high affinity glutamate transporter), member 2

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1. Introduction

The postpartum brain undergoes structural and functional reorganization to support multiple neuroendocrine and behavioral alterations required for parenting (Brunton and Russell, 2008; Kinsley and Amory-Meyer, 2011). The mechanisms underlying such a critical remodeling of the brain are complex and include changes in gene expression, synaptic plasticity, neurogenesis, morphology, structure, metabolism, and neurochemistry (Kinsley, 2008; Moltz et al., 1975; Salmaso et al., 2011; Shingo et al., 2003; Zhao et al., 2012a). Glutamate and GABA are critical excitatory and inhibitory CNS neurotransmitters and are involved in a broad variety of physiological events, including synaptic plasticity, neuroendocrine function, learning and memory, cell proliferation, and differentiation (Carver and Reddy, 2013; Ciceroni et al., 2010; Durand et al., 2008; Ogden et al., 2014; Zuure et al., 2013). Furthermore, the importance of glutamate and GABA signaling (i.e. excitation/inhibition balance) and its relationship with behavioral performance has been well established (Jocham et al., 2012; Yizhar et al., 2011).

In the CNS, the metabolic shuttle referred to as the glutamate/GABA-glutamine cycle between neurons and astrocytes supports the homeostasis of glutamate and GABA (Hertz, 2013; Schousboe et al., 2013), as neurons are not capable of synthesizing de novo glutamate and GABA from glucose (Hertz et al., 1999; Schousboe et al., 1997). In astrocytes, the cycle is initiated from the conversion of glutamate to glutamine by the astrocyte-specific enzyme glutamate-ammonia ligase (Glul, also known as glutamine synthetase – GS) (Martinez-Hernandez et al., 1977; Norenberg and Martinez-Hernandez, 1979). Astrocytic glutamine is subsequently transported into extracellular space and then imported to neurons via system transporters (Chaudhry et al., 2002; Jenstad et al., 2009; Solbu et al., 2010). In neurons, glutamine is metabolized to glutamate by the mitochondrial enzyme, glutaminase (Gls, also known as phosphate-activated glutaminase – Pag) (Kvamme et al., 2001). Neuronal glutamate is further converted to GABA by the rate-limiting enzymes glutamate decarboxylase 1 or 2 (Gad1 or Gad2) (also known as glutamic acid decarboxylase 1 and 2) (Martin and Tobin, 2000; Soghomonian and Martin, 1998). Alternatively, neuronal glutamate is released to extracellular space and taken up by astrocytes through the solute carrier family 1 (glial high affinity glutamate transporter), member 2 (Slc1a2, GLT-1, Eaat2) and member 3 (Slc1a3, GLAST, Eaat1) (Arriza et al., 1994; Pines et al., 1992). Finally, astrocytic glutamate is converted to glutamine by Glul, which completes the glutamate/GABA-glutamine cycle.

While GABA activity has been evaluated in the maternal brain, less research has focused on glutamate, and limited research has explored the concomitant dynamics of glutamate and GABA signaling in the postpartum brain. We recently found that Gad1 (also known as GAD67) and Gad2 (also known as GAD65), expression is increased in the postpartum lateral septum (LS) in an inbred strain of mice (Zhao et al., 2012a). In addition, our microarray study of whole septum (including LS) in the same strain identified Glul mRNA as upregulated in postpartum females (Zhao et al., 2012b). Interestingly, levels of glutamate, glutamine, and Glul were observed to be elevated in the cingulate cortex of postpartum rats compared with virgin females (Salmaso et al., 2011).

In this study, in order to determine to what extent glutamate and GABA signaling are altered and whether the ratio of glutamate to GABA changes, we systematically investigated the activity of glutamate/GABA-glutamine cycle in postpartum LS in outbred mice. We examined LS because GABA is remarkably abundant in this brain region (Castaneda et al., 2005; Onteniente et al., 1986; Panula et al., 1984) and we recently found that greater than 90% of the neurons in LS are GABA-positive (Zhao et al., 2013). Also, LS is critical in regulating maternal and non-maternal behaviors (Lee and Gammie, 2009; Sheehan et al., 2004; Singewald et al., 2011). As indicated above, there is an intimate crosstalk between GABA and glutamate signaling in other brain regions (Liang et al., 2006; Mora et al., 2008; Segovia et al., 1999), so an understanding of glutamate/GABA signaling in LS would provide missing information on the relationship of the glutamatergic excitation and GABAergic inhibition in this brain area. Based on the published data in literature, we hypothesized that the postpartum LS would display an elevated glutamate/GABA-glutamine cycle.

2. Results

2.1. *Neuronal glutamate synthesis was enhanced in LS during the postpartum period*

mRNA expression of Gls, the neuronal enzyme that catalyzes the conversion of glutamine to glutamate, was upregulated in LS of postpartum relative to virgin female mice ($p=0.031$, Fig. 1A). In parallel with the enhanced expression of the enzyme responsible for the biosynthesis of glutamate in neurons, ELISA immunoassay showed that the tissue level of glutamate, the Gls-catalyzed reaction product, was elevated in LS of postpartum females compared to the virgin mice ($p=0.027$, Fig. 1B).

2.2. *Neuronal GABA synthesis was elevated in LS during the postpartum period*

Consistent with our prior findings (Zhao et al., 2012a), expression of both Gad1 and Gad2 mRNAs was upregulated in LS of postpartum relative to virgin female mice ($p<0.001$ for Gad1, $p=0.031$ for Gad2, Fig. 2A). In parallel with the enhanced expression of enzymes (e.g., Gad1 and Gad2) that synthesize GABA in neurons, ELISA immunoassay showed that the tissue level of GABA was elevated in LS of postpartum females compared to the virgin mice ($p=0.023$, Fig. 2B).

2.3. *Astrocytic glutamine synthesis was heightened in LS during the postpartum period*

mRNA expression of Glul, the astrocytic enzyme that catalyzes the conversion of glutamate to glutamine, was upregulated in LS of postpartum relative to virgin female mice ($p=0.031$, Fig. 3A). In parallel with the enhanced expression of enzyme that synthesizes glutamine in astrocytes, ELISA

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