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Research Report

Effects of prenatal stress and monoaminergic perturbations on the expression of serotonin 5-HT$_4$ and adrenergic β_2 receptors in the embryonic mouse telencephalon

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ABSTRACT

The serotonin 5-HT$_4$ receptor (5-HT$_4$R) is coded by a complex gene that produces four mRNA splice variants in mice (5-HT$_{4(a)}$R, 5-HT$_{4(b)}$R, 5-HT$_{4(e)}$R, 5-HT$_{4(f)}$R). This receptor has highly dynamic expression in brain development and its splice variants differ in their developmental trajectories. Since 5-HT$_4$Rs are important in forebrain function (including forebrain control of serotonergic activity in the brainstem), we investigated the susceptibility of 5-HT$_4$R expression in the mouse embryonic telencephalon to prenatal maternal stress and altered serotonin (5-hydroxytryptamine, 5-HT) levels. Because the gene coding the adrenergic β_2 receptor (β_2AR) is embedded in the 5-HT$_4$R gene, we also investigated whether 5-HT$_4$R mRNA levels were modulated by selective β_2AR agents. Timed-pregnant C57BL/6 mice were treated beginning at embryonic day (E) 14 and quantitative reverse-transcription polymerase chain reaction (qRT-PCR) was used to assess the mRNA levels of all 5-HT$_4$R splice variants and β_2AR in the embryonic telencephalon at E17. Maternal prenatal stress and 5-HT depletion with *p*CPA, a tryptophan hydroxylase inhibitor, reduced the levels of the 5-HT$_{4(b)}$R splice variant. Terbutaline (a selective β_2AR agonist) and ICI 118,551 (a selective β_2AR antagonist) had no effect on β_2AR and 5-HT$_4$R mRNA levels. These results show that prenatal stress and reduced 5-HT levels can alter 5-HT$_4$R expression in the developing forebrain and that some 5-HT$_4$R splice variants may be more susceptible than others.

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1. Introduction

The serotonin (5-hydroxytryptamine, 5-HT) 5-HT$_4$ receptor (5-HT$_4$R) is coded by a complex gene that generates at least ten mRNA splice variants in humans and pigs and four splice variants in mice (5-HT$_{4(a)}$R, 5-HT$_{4(b)}$R, 5-HT$_{4(e)}$R, 5-HT$_{4(f)}$R) (Bockaert et al., 2004, 2006; Claeysen et al., 1999; Ray et al., 2009). The expression of this receptor in mouse and human brain development is highly dynamic (Lambe et al., 2011; Manzke et al., 2008; Slaten et al., 2010; Waeber et al., 1994, 1996) and, at least in the mouse brain, the 5-HT$_4$R splice variants have different developmental trajectories (Hernandez and Janušonis, 2010). This variant-specificity may carry important temporal and spatial information because 5-HT$_4$R splice variants differ in their constitutive activity (Claeysen et al., 1999, 2001), internalization properties (Mnie-Filali et al., 2010),

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and association with intracellular proteins (Joubert et al., 2004).

Altered 5-HT_4R function has been associated with autism spectrum disorders (ASDs) (Vincent et al., 2009), major depressive disorder (Lucas et al., 2007; Rosel et al., 2004), bipolar disorder (Hayden and Nurnberger, 2006), and attention deficit/hyperactivity disorder (Li et al., 2006). A recent study has suggested that 5-HT_4R is a molecular network hub that controls multiple neural processes (Hu et al., 2011), including those important for the neurobiology of several brain disorders. Different levels of 5-HT_4R expression have been reported in the amygdala of males and females, which may contribute to sex differences in the prevalence of affective disorders (Madsen et al., 2011).

Evidence suggests that 5-HT_4R may be a key component in the forebrain control of the brain serotonergic system. Some of this control is mediated by a projection that originates in the medial prefrontal cortex (mPFC) and terminates in the dorsal raphe nucleus (Gabbott et al., 2005; Goncalves et al., 2009; Hajos et al., 1998; Vertes, 2004). In the adult brain, cortical 5-HT_4Rs modulate the activity of this projection (Bockaert et al., 2011; Lucas et al., 2005) and can alter brain serotonin (5-hydroxytryptamine, 5-HT) levels by affecting raphe serotonergic neurons directly or through GABAergic interneurons (Celada et al., 2001; Jankowski and Sesack, 2004). It has implications for a number of brain disorders, including the biological action of antidepressants (Lucas et al., 2010; Vidal et al., 2009). Since in the embryonic mouse brain young mPFC neurons express 5-HT_4Rs before they establish synapses with raphe neurons (Slaten et al., 2010), a transient change in 5-HT_4R expression in the fetal mPFC can potentially result in permanent dysregulation of 5-HT levels in many brain regions.

In the present study, we investigated how maternal prenatal stress and 5-HT depletion affect the mRNA levels of all 5-HT_4R splice variants in the embryonic mouse telencephalon. Previous studies have shown that maternal stress and serotonergic perturbations can cause various alterations in the developing brain (Altamura et al., 2007; Miyagawa et al., 2011; Peters, 1990; Vitalis et al., 2007). We also investigated whether maternal stress and other environmental signals can affect the 5-HT_4R expression in the embryonic telencephalon through adrenergic β_2 receptors (β_2ARs). Evidence suggests that 5-HT_4Rs may be functionally associated with β_2ARs, since the β_2AR gene is nested within the 5-HT_4R gene (Bockaert et al., 2004) and 5-HT_4Rs can form heterodimers with β_2ARs (Berthouze et al., 2005, 2007). Also, concerns have been raised regarding a possible association between terbutaline (a selective β_2AR agonist used to treat preterm labor) and ASDs (Witter et al., 2009), in which serotonergic abnormalities have long been noted (Anderson, 2002).

2. Results

2.1. *Effects of prenatal stress, β_2AR agents, and 5-HT depletion on β_2AR mRNA levels*

Since the transcription of the 5-HT_4R gene can potentially be affected by the transcription of the β_2AR gene due to the nested arrangement of the genes (Bockaert et al., 2004; Gibson et al., 2005), we first investigated whether the β_2AR mRNA amount in the embryonic telencephalon was altered by any of the treatments used in the study (maternal prenatal stress, selective β_2AR agents (terbutaline and ICI 118,551), and 5-HT depletion with *p*CPA) (Fig. 1). The initial statistical model included these conditions as the fixed effect (Treatment). Adding a random litter effect to the intercept significantly improved the model ($L=16.8$, $p<0.0001$). Allowing each condition to have a different variance did not further improve the model ($L=4.60$, $df=4$, $p>0.3$). The final validated model revealed no significant Treatment effect ($F_{4,17}=0.65$, $p=0.63$). In summary, the analysis indicated the presence of inter-litter variability in the baseline β_2AR mRNA levels (with an estimated standard deviation of 17% of the baseline), but these levels were not significantly altered by any of the used experimental perturbations.

2.2. *Effects of prenatal stress and β_2AR agents on 5-HT_4R splice variants*

We next examined whether maternal restraint stress and a selective β_2AR agonist (terbutaline) affected the mRNA levels of the 5-HT_4R splice variants in the embryonic telencephalon. We also investigated whether a selective β_2AR antagonist (ICI 118,551), administered prior to restraint stress, attenuated the stress effect on the 5-HT_4R mRNA levels (Fig. 2). The selective β_2AR agents were included because stress-related signals can act on β_2ARs (Qu et al., 2008), β_2ARs have been shown to form heterodimers with 5-HT_4Rs (Berthouze et al., 2005, 2007), and the activity of one receptor in a heterodimer can affect the internalization and trafficing of the other receptor, with potential changes in its transcription (Renner et al., in press; Rozenfeld and Devi, 2011).

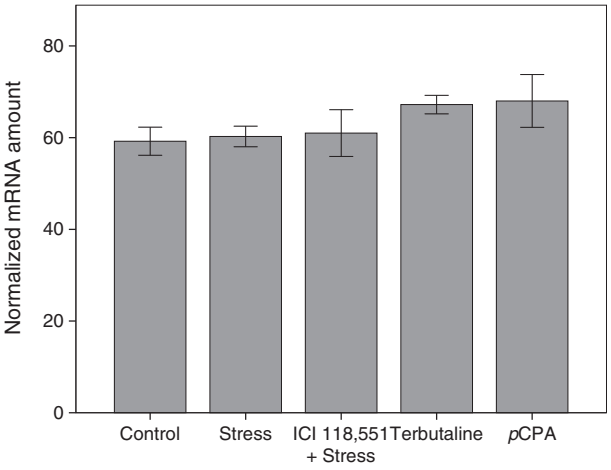

Fig. 1 – The normalized β_2AR mRNA amounts in the telencephalon of embryos (E17) from control dams injected with saline (Control) and from dams *(i)* injected with saline and exposed to maternal prenatal stress (Stress), *(ii)* injected with a β_2AR antagonist and exposed to maternal prenatal stress (ICI 118,551 + Stress), *(iii)* injected with a β_2AR agonist (Terbutaline), and *(iv)* injected with a tryptophan hydroxylase inhibitor (*p*CPA). The error bars are the standard errors of the means.

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