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Research Paper

Memantine rescues prenatal citalopram exposure-induced striatal and social abnormalities in mice

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ABSTRACT

Prenatal exposure to citalopram (CTM), an antidepressant drug, has been associated with altered behavior, including autism-like symptoms in both human and rodent offspring. However, the neurological basis underlying these abnormal behaviors is not well understood. Here, we examined behavioral, morphological, and biochemical alterations in the male and female offspring of C57BL/6 mouse mothers that had been exposed to CTM during the last trimester of gestation. We observed abnormal behavior such as anxiety, altered locomotion and disordered social interactions in 2–5 months old offspring with prenatal CTM exposure. Using Golgi-Cox staining, we found that CTM caused significantly reduced dendritic length and number of dendritic branches in striatal neurons, as well as altered subunit levels of *N*-methyl-D-aspartate receptors (NMDARs) and calcium/calmodulin-dependent protein kinase II (CaMKII). Memantine, a selective NMDAR antagonist, improved prenatal CTM-induced abnormal protein levels and social interaction deficits. These results highlight potential mechanisms underlying the abnormal behavior observed in children who are prenatally exposed to CTM.

1. Introduction

Antidepressants, belonging to a group of medicines known as selective serotonin reuptake inhibitors (SSRIs), are widely used during gestation for the treatment of depression (Glover, 2011). These medicines are thought to work by increasing the activity of a chemical, 5-hydroxytryptamine (5-HT), in the brain (Glover, 2011; Schaefer et al., 2013). It is estimated that 5.9% of women received pharmacological treatment with the SSRI, including citalopram, (CTM) during pregnancy (Munk-Olsen et al., 2012). Though there are studies showed weak association between antidepressant-use during pregnancy and persistent pulmonary hypertension (PPHN) (Andrade et al., 2009; Wichman et al., 2009), recent studies suggest that children whose mothers took SSRIs before and/or during pregnancy show an increased prevalence of autism spectrum disorders (ASDs) (Boukhris et al., 2016; Croen et al., 2011; Gentile, 2015; Gidaya et al., 2014; Harrington et al., 2014; Rai et al., 2013; Weisskopf et al., 2015) and psychomotor developmental deficits (Salisbury et al., 2011). SSRIs exposure also increased risk of PPHN and hyperactivity disorder (ADHD) in offspring in humans (CD et al., 2012; Kieler et al., 2012; Liu et al., 2017). Additionally, whether maternal antidepressant use results in advantageous outcomes in children remained controversial (Boukhris et al., 2015; Brown et al., 2016; Clements et al., 2015; Viktorin et al., 2016; Viktorin et al., 2017). Maternal antidepressant use causes long-term changes in the behavior of offspring, manifesting mainly as increased anxiety-related behavior, and as an extension of the time required for adaptation to new social situations (Gidaya et al., 2014). Given that antidepressants are likely to remain widely used during pregnancy (Nulman et al., 2012), a better understanding of the long-term neurodevelopmental effects of antidepressants on children should be a public health priority.

The effects of SSRI use in pregnant mothers on their children bear all the hallmarks of gestational stress, which is associated with an increase in the prevalence of autism-like behaviors in rats (Bayer et al., 1993; Belzung et al., 2005; Schneider and Przew, 2005), cognitive and concentration deficits, childhood emotional problems, early adulthood anxiety, and depressive disorders (Charil et al., 2010; Weinstock, 2008). Considerable efforts are now focused on understanding the neuropsychology and neuromorphological bases of ASDs using rodent model of ASDs to evaluate autism-like behaviors (Belzung et al., 2005; Schneider and Przew, 2005) by applying various methodologies for selection of rational targets and effective treatments (Berle et al., 2004). In rodents, prenatal stress results in changes in cortico-limbic organization, including the striatum, dendritic morphology, and spine density (Murmu et al., 2006; Mychasiuk et al., 2012), reflecting the amount of

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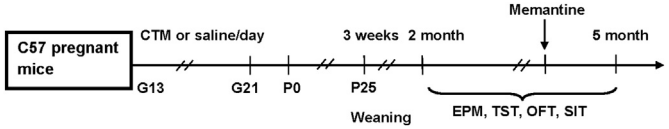

Fig. 1. Experimental design: Pregnant C57BL/6 females were divided into two groups, one group exposed prenatally to 20 mg/kg/day CTM and the other receiving saline from gestation day (GD) 13 to 21. Day of birth was designated P0. On P1, litters were culled using a random number table to 8 pups (4 males and 4 females). Weaning was done at three weeks, and the offspring were housed 4–6 per cage. At the age of 2–5 months, mice were subjected to the EPM test, the TST, the OFT, and the SI test. During this period, memantine at a dose of 10 mg/kg was administered prior to the SI test to measure its effect on behavior deficits induced by CTM.

connectivity between neurons regulating excitatory neurotransmission in the brain (Yoshihara et al., 2009). Dendritic structures are sensitive to stress and undergo transformations in an activity and experience-dependent manner (Carlisle and Kennedy, 2005). Thus, changes in dendritic density/morphology are crucial elements for synaptic function (Leuner and Shors, 2013).

The striatum coordinates multiple aspects of cognition, including motor and action planning, decision making, reinforcement, and reward perception (Gaume et al., 2016; Taylor et al., 2013). Defects in the striatum contribute to anxiety (Everitt and Robbins, 2013), depression (Lago et al., 2017), and social communication impairment (Santini et al., 2013). Neuroimaging studies have reported reduced striatal (caudate and putamen) volumes in major depressive disorder (Bora et al., 2012), and abnormal connectivity in striatal circuits in ASDs (Nair et al., 2013). Whether maternal CTM use is associated with alterations in striatal dysfunction in offspring remains unclear.

The aim of the present study was to examine the effects of prenatal CTM exposure during days 13–21 of gestation in mice, a period when the offspring develop socioemotional behavior and neuronal morphology (Bayer et al., 1993; Wallace and Lauder, 1983), which might be induced by the blockade of neurotrophin following SSRIs prenatal treatment (Ko et al., 2014; Zimmerberg and Germeyan, 2015). We hypothesized that CTM exposure would induce enduring effects on offspring behavior as a young adult. We employed Golgi-Cox staining, western blotting, electrophysiology, and behavioral assessment to determine any striatal and behavioral abnormalities and to explore potential underlying mechanisms.

2. Materials and methods

2.1. Animals

Female C57BL/6 mice were provided by Guangdong Medical Laboratory Animal Center. Mice were placed in a room at 22 ± 1 °C on a 12 h light-dark cycle from the initial day of pregnancy (identified by the appearance of a vaginal plug). Food and water were supplied *ad libitum* and cages were cleaned twice weekly. Mice in the experimental group were given 20 mg/kg CTM (2 mg/ml) diluted with saline *via* intraperitoneal (i.p.) injection once per day during the last trimester

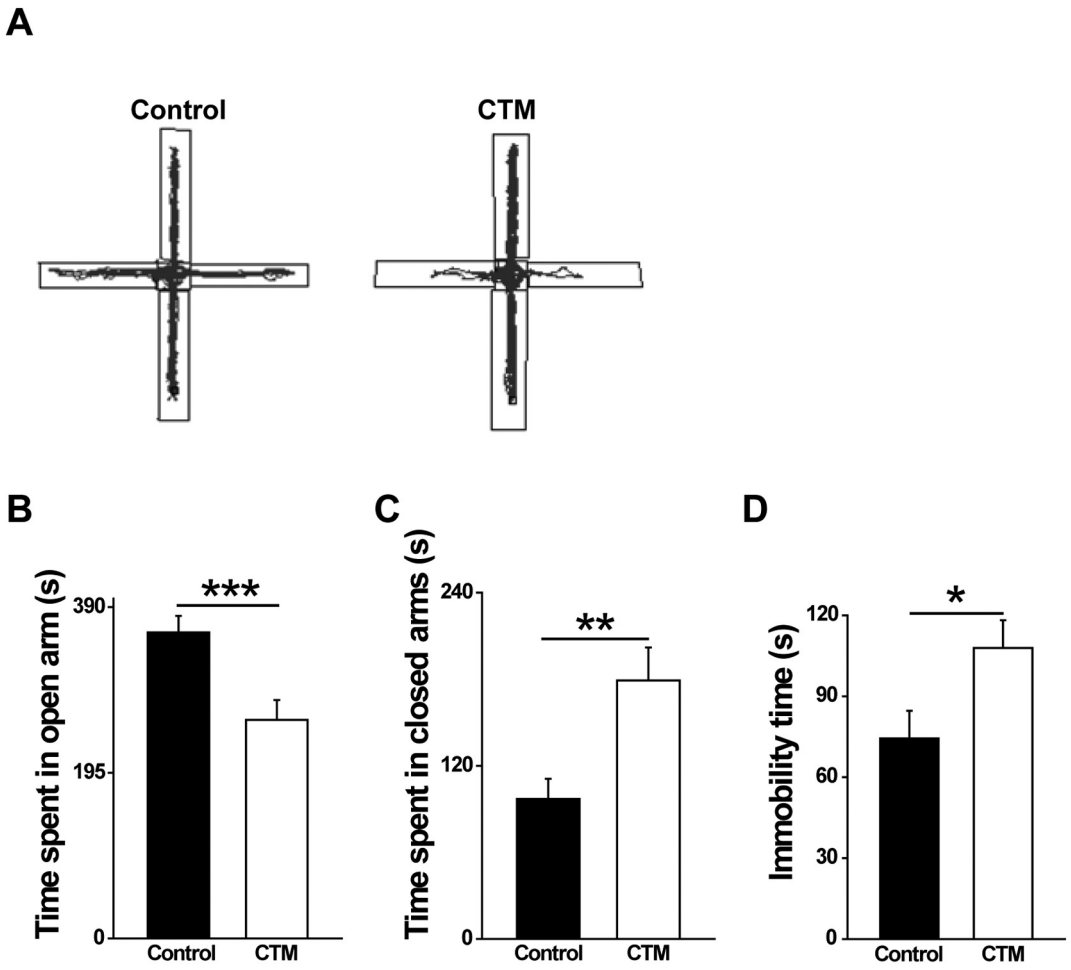

Fig. 2. EPM testing of mice prenatally exposed to CTM and control mice. (A) Track paths of control and CTM mice. (B) Time spent by mice in the open arms of the maze (n = 35, per group). (C) Time spent by mice in the closed arms (n = 34, per group). (D) Effect of CTM on immobility in maternally treated (n = 27) and control (n = 27) mice in the TST. Values represent mean ± SEM. *P < .05; **P < .01; ***P < .001; one-way ANOVA.