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Research report

Developmental minocycline treatment reverses the effects of neonatal immune activation on anxiety- and depression-like behaviors, hippocampal inflammation, and HPA axis activity in adult mice

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ABSTRACT

Neonatal infection is associated with increased lifetime risk for neuropsychiatric disorders including anxiety and depression, with evidence showing that dysregulation of the hypothalamic–pituitary–adrenal-(HPA)-axis system may be partly responsible. Preclinical and clinical studies demonstrate that minocycline exhibits antidepressant effects through inhibition of microglial activation and anti-inflammatory actions, and of interest is that recent studies suggest that minocycline alleviates the behavioral abnormalities induced by early-life insults. The current study was designed to determine if developmental minocycline treatment attenuates the neonatal immune activation-induced anxiety- and depression-like symptoms and HPA-axis-dysregulation later in life. To this end, neonatal mice were treated to either lipopolysaccharide or saline on postnatal days (PND) 3–5, then dams during lactation (PND 6–20) and male offspring during adolescence (PND 21–40) received oral administration of minocycline or water via regular drinking bottles. Anxiety- and depression-like behaviors, HPA-axis-reactivity (corticosterone), and hippocampal inflammation (TNF-α and IL-1β) after exposure to stress were evaluated. The results indicated that neonatal immune activation resulted in increased anxiety and depression-like symptoms, HPA-axis-hyperactivity, and elevated the levels of TNF-α and IL-1β in the hippocampus in response to stress in adulthood. Interestingly, developmental minocycline treatment significantly reduced the abnormalities induced by neonatal inflammation in adult mice. In addition, minocycline, regardless of postnatal inflammation, did not have any detrimental effects on the above measured parameters. Considering that minocycline is currently under exploration as an alternative or adjunctive therapy for reducing the symptoms of neurological disorders, our findings suggest that minocycline during development can decrease the behavioral abnormalities induced by early life inflammation in adulthood.

1. Introduction

Extensive research indicates that major depression and anxiety are among the most common psychiatric disorders which frequently cause significant functional impairment in humans (Fried and Nesse, 2015; Löwe et al., 2008; Ravindran and Stein, 2010; Toneatto and Nguyen, 2007). There is significant overlap between these two psychological problems which negatively affect daily activities and quality of life influencing other types of psychiatric disorders (Huppert et al., 2001; Mendlowicz and Stein, 2000). Accumulating evidence suggest that neurological diseases such as autism, schizophrenia, and affective disorders can be programmed by events such as stress and infection in early life (Boksa, 2010; Cottrell and Seckl, 2009; Depino, 2015; Dong et al., 2015; Enayati et al., 2012; Kinney et al., 2008). Although, the etiology of anxiety and depression remains unclear, recent studies by our group have provided evidence that infection/inflammation during the early stages of brain development including prenatal and early postnatal periods may be significantly involved in programming of these disorders in later life (Babri et al., 2014a,b; Doosti et al., 2013; Enayati et al., 2012; Majidi-Zolbanin et al., 2013, 2014, 2015). For

Abbreviations: LPS, lipopolysaccharide; PND, postnatal day; HPA, hypothalamic–pituitary–adrenal axis; IL, interleukin; TNF-α, tumor necrosis factor-alpha; CORT, corticosterone; ANOVA, analysis of variance; SEM, standard error of the mean.

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instance, we and others have developed an animal model of neonatal inflammation through lipopolysaccharide (LPS) administration in postnatal days (PND) 3 and 5 in mice (Doosti et al., 2013; Majidi-Zolbanin et al., 2013) and rats (Sominsky et al., 2012; Walker et al., 2004, 2012) leading to anxiety- and depressive-like behaviors, and persistent abnormalities in hypothalamic–pituitary–adrenal axis (HPA) axis function later in life. Dysregulation of HPA axis has a crucial role in the etiology of depression and anxiety-related disorders, both hypo and hyperactivity of the HPA-axis have indeed been found to be associated with higher risk of depression (Stetler and Miller, 2011; Tsigos and Chrousos, 2002).

Neonatal LPS administration has been shown to activate microglia cells and increase pro-inflammatory cytokines in the brain (Fan et al., 2005a,b). With regard to the relationship between neonatal immune activation and microglial activation, Sominsky et al. (2012) demonstrated that LPS administration in PNDs 3 and 5 results in increased anxiety-like behavior and microglial activation in the hippocampus of adult rats. In support of these findings, Walker et al. (2004, 2012) reported that immune activation with LPS on PND 3 and 5 increases anxiety-like symptoms and levels of tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1β in the hippocampus of adult rats in response to stress (Walker et al., 2010). Microglial activation and brain inflammatory cytokines have been implicated in mediating the effects of stress and both of them are known as major triggers for depression (Kreisel et al., 2014; Miller et al., 2009; Raison et al., 2006). In addition, previous studies have shown a relationship between elevated TNF-α and IL-1β and pathophysiology of anxiety and major depression (Bayramgürler et al., 2013; Dowlati et al., 2010; Goshen et al., 2008; Kaster et al., 2012; Krügel et al., 2013; Miller et al., 2009; Raison et al., 2006; Rossi et al., 2012; Simen et al., 2006). Given that hippocampus plays an important role in mediating anxiety- and depression-related behaviors in humans and rodents, this evidence suggests that the neuropathology of anxiety and depression induced by neonatal immune activation might be closely associated with hippocampal inflammation in adulthood.

Emerging evidence from preclinical and clinical studies also shows that the development of the therapeutic strategies against neuropsychiatric disorders with neurodevelopmental origin is an interesting topic for researchers. For example we reported that adolescent fluoxetine treatment can reduce the effects of early postnatal inflammation induced by LPS on anxiety and depression-like behaviors in offspring during adulthood (Doosti et al., 2013; Majidi-Zolbanin et al., 2013). While the majority of studies in this area of research originally tend to address how antidepressant and antipsychotic drugs at different windows of brain development such as prenatal, neonatal and adolescent periods can reduce psychiatric symptoms by regulating different neurotransmitter systems in the brain (Dickerson et al., 2012; Doosti et al., 2013; Ishiwata et al., 2005; Majidi-Zolbanin et al., 2013; Nagano et al., 2012; Rayen et al., 2011; Richtand et al., 2012), a few studies have recently considered the possibilities and ideas about early pharmacological intervention by minocycline, a second-generation tetracycline, for reducing brain inflammatory processes (Fan et al., 2005a,b Zhu et al., 2014a,b). In this context, a series of experiments indicate that minocycline can be a potential therapeutic drug for various neurological disorders, including major depression, anxiety, schizophrenia, Huntington's disease, Parkinson's disease, ischemia (Garrido-Mesa et al., 2013; Soczynska et al., 2012). Findings from animal and human studies support the hypothesis that minocycline can be a potential multi-target agent for the treatment of major depression and anxiety-related disorders through anti-inflammatory and microglial activities, and neuroprotective actions including neurogenesis and anti-glutamate excitotoxicity (Garrido-Mesa et al., 2013; Soczynska et al., 2012). It has been shown that minocycline decreases immobility and enhances the anti-immobility effect of desipramine in the forced swim test in animals showing an antidepressant effect (Molina-Hernández et al., 2008). Moreover, minocycline reduces the expression of pro-inflammatory cytokines and depression-like behavior induced by LPS in mice (O'connor et al., 2009). Minocycline has been used to prevent or ameliorate white matter damage after inflammation and hypoxic-ischemic injury in both adult and neonatal rats (Cai et al., 2006; Fan et al., 2005a). Fan et al. (2005a,b) demonstrated that minocycline treatment attenuates lipopolysaccharide-induced white matter injury in the neonatal rat brain on PND 5, probably through inhibition of microglial activation. In other studies, minocycline treatment during lactation in Fmr1 KO mice, a mouse model of Fragile X Syndrome, alleviated anxiety-like behavior in young mice (Bilousova et al., 2009; Dansie et al., 2013). Overall, the neuroprotective effects of minocycline are assumed to be exerted through antioxidant free-radical scavenging, inhibition of caspase expression and mitogen-activated protein kinases, and the suppression of microglial and astroglial activation and proliferation leading to reduced neuroinflammation and inhibition of apoptotic neuronal loss (Cheng et al., 2015; Soczynska et al., 2012). Minocycline is clinically well tolerated and almost completely absorbed when taken orally and which is also able to pass from the mother to the offspring through the breast milk (Lee et al., 2006; Lin et al., 2005; Luzi et al., 2009; Miyaoka et al., 2012). Since inflammation is thought to be one of the important player in the development of psychiatric diseases, and developmental drug treatment is currently receiving attention as a potential strategy for the treatment of neuropsychiatric disorders, we thought that minocycline could be considered a pharmacological candidate for the prevention of affective-like behaviors induced by neonatal immune activation.

2. Materials and methods

2.1. Subjects and ethics

Adult male and female NMRI mice (10–11 weeks old) were obtained from the animal house of Razi Institute. Animals were maintained under standard laboratory conditions on a 12:12 h light/dark cycle (lights on at 08:00 AM) and controlled temperature (23 ± 1 °C). Food and water were also available ad libitum. All procedures were approved by the Research and Ethics Committee of Tabriz University of Medical Sciences, and conducted in accordance with guidelines from the National Institutes of Health.

2.2. Newborn mice

Following a 2-week period of acclimatization to the new animal housing room, to facilitate the mating, male and female mice were kept together one-by-one in a cage. Female mice were visually monitored daily for confirmation of pregnancy, when it was confirmed the female mice were removed from the breeding cages and housed individually in standard cages. All pregnant animals were allowed to have normal delivery and the first day of birth was considered as PND 0. One day after the birth, all litters were culled to 4 male pups per mother. On the day 21, litters were weaned by removal of the mother and then were housed based on the treatment condition. In order to prevent the possible confounding factors of isolation housing, the offspring were kept in groups of 2 animals in the cages. Only one mouse per litter was used for each of the experiments to avoid the litter-effect.

2.3. Neonatal immune activation

A timeline diagram of the experiments is shown in Fig. 1. The dams were removed from their pups for approximately 5 min and