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Prenatal maternal factors in the development of cognitive impairments in the offspring

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ABSTRACT

Different environmental factors acting during sensitive prenatal periods can have a negative impact on neurodevelopment and predispose the individual to the development of various psychiatric conditions that often share cognitive impairments as a common component. As cognitive symptoms remain one of the most challenging and resistant aspects of mental illness to be treated pharmacologically, it is important to investigate the mechanisms underlying such cognitive deficits, with particular focus on the impact of early life adverse events that predispose the individual to mental disorders. Multiple clinical studies have, in fact, repeatedly confirmed that prenatal maternal factors, such as infection, stress or malnutrition, are pivotal in shaping behavioral and cognitive functions of the offspring, and in the past decade many preclinical studies have investigated this hypothesis. The purpose of this review is to describe recent preclinical studies aimed at dissecting the relative impact of various prenatal maternal factors on the development of cognitive impairments in offspring, focusing on animal models of prenatal stress and prenatal infection. These recent studies point to the pivotal role of prenatal stressful experiences in shaping memory and learning functions associated with specific brain structures, such as the hippocampus and the prefrontal cortex. More importantly, such experimental evidence suggests that different insults converge on similar downstream functional targets, such as cognition, which may therefore represent an endophenotype for several pathological conditions. Future studies should thus focus on investigating the mechanisms contributing to the convergent action of different prenatal insults in order to identify targets for novel therapeutic intervention.

1. Introduction

In the present article we aim to gain insight into the role of prenatal maternal factors in shaping cognitive functions in offspring. Based on the seminal work of David Barker conducted in the context of cardiovascular disease (Dover, 2009), the concept of "early-life programming of adult disease" refers to the phenomenon whereby specific environmental factors acting during sensitive prenatal or early postnatal developmental periods can induce persistent changes in physiological, emotional, and behavioral functions throughout life (Bale et al., 2010). Fetal brain development is a complex and delicate process that takes place in a protected environment inside the mother's body, and a variety of exogenous maternal factors can alter the course of fetal brain maturation, predisposing the individual to the development of multiple diseases later in life. Against this background, it is clear that prenatal maternal factors could be pivotal in shaping many behavioral and cognitive functions of the offspring, and this hypothesis has been repeatedly confirmed by several clinical and preclinical studies

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(Brown, 2011; Meyer, 2013). The impact of maternal exposure to adverse events during pregnancy, such as infection, stress, malnutrition or toxic substances has been extensively investigated in relation to the development of psychiatric conditions in offspring, and it is clearly holds relevance for the insurgence of cognitive impairments. Impaired cognitive functioning is, in fact, both an important characteristic of major psychiatric disorders, such as schizophrenia, bipolar disorder, and major depressive disorders (Iosifescu, 2012), and also a predictive factor for the functional outcome and treatment response in many of these diseases (Addington and Barbato, 2012; Andreou and Bozikas, 2013). Moreover, in the case of schizophrenia, cognitive symptoms appear to be present before the onset of the illness (Bellack et al., 2007; Reichenberg et al., 2010), as individuals show deficits in cognitive and academic performance, even before the first psychotic episode. Interestingly, mild cognitive impairments are also found in first-degree relatives of schizophrenic patients (Greenwood et al., 2007), highlighting how cognitive deficits could be regarded as an endophenotype of the disorder. Lastly, cognitive impairments are often present during the remission phase of many mental illnesses and can persist even after significant improvement of psychotic and depressive symptoms. These considerations, along with the observation that the improvement of cognitive symptoms remains a challenge for pharmacological treatment (Wallace et al., 2011), underline the importance of investigating the etiological mechanisms of cognitive deficits with particular focus on the role of early life adverse events. In the following sections, we will thus describe recent preclinical studies aimed at dissecting the relative impact of two prenatal factors, maternal stress and infection, which have been extensively investigated for their influence on cognitive impairments in offspring. However, it must be borne in mind that other prenatal factors may determine persistent changes in cognitive function (Raikkonen et al., 2012).

1.1. Maternal stress

Various studies conducted in humans suggest that exposure of the developing brain to severe and/or prolonged maternal stress might result in altered cognition and mood-related disorders (King and Laplante, 2005; Wadhwa, 2005; Weinstock, 2008). In particular, stressful events may elevate maternal concentrations of stress hormones, such as cortisol and placental CRH, which in turn could alter fetal brain development and growth, and also reprogram the fetal hypothalamus–pituitary–adrenal axis (Weinstock, 2008; Charil et al., 2010). In the past decade, many studies conducted in animals have thus investigated the consequences of prenatal exposure to stress in order to study the neurobiological basis of the association between maternal stress and impaired cognition. Given the evidence that prenatal stress (PNS) clearly affects the development of the hippocampus (reviewed in Charil et al., 2010), and that hippocampal synaptic plasticity in the form of long-term potentiation (LTP) and long-term depression (LTD) seems to be the predominant mechanism underlying certain types of learning and memory (Bliss and Collingridge, 1993), many preclinical studies initially focused on interrogating hippocampal-dependent memory functions.

Different paradigms of PNS have been employed in rats and mice, although the majority of these studies have focused on the exposure to variable stressors during the last week of gestation (Weinstock, 2008). Moreover, prenatal stress models mainly rely on a variable, unpredictable stress regimen (consisting of restraint stress, forced swim stress, overcrowding, exposure to bright light, and food deprivation), or on one single stressor, for example, severe restraint stress or inescapable foot shocks, applied for one or two weeks before delivery. Independently of the type of stressor applied, the studies have consistently shown that prolonged prenatal manipulations impair spatial learning and memory in mice and rats, both in adolescence and in adulthood (Lemaire et al., 2000; Son et al., 2006; Yang et al., 2006). These cognitive deficits were also associated with reduced hippocampal neurogenesis, decreased LTP, decreased NR2B and NR1 subunits of the *N*-methyl-D-aspartate (NMDA) receptor and decreased GluR1 of the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor (Lemaire et al., 2000; Son et al., 2006; Yang et al., 2006; Yaka et al., 2007). Moreover, recent studies have shown that PNS increases NMDA receptor density in the early phases of life after birth (Tavassoli et al., 2013); reduces hippocampal KIF17 (kinesin superfamily motor protein 17), which specifically transports and regulates the NR2B subunit of the NMDA receptor (Zhao et al., 2013); affects network properties of hippocampal neurons (Grigoryan and Segal, 2013); and decreases dendritic spine density in the dorsal hippocampus of juvenile rats (Paris and Frye, 2011). These results imply that prenatal maternal stress may impair spatial learning and memory by inducing long-lasting hippocampal changes, some of which are particularly related to specific components of the glutamatergic system. Markham and colleagues have recently extended the implications of PNS exposure for cognition beyond the hippocampus (Markham et al., 2010), showing that maternal stress disrupts the offspring's development of conditioned fear memory, a task that relies mainly on the amygdala. It also impairs, particularly in male offspring, extinction of discrete cue-associated conditioned fear memory, which is largely dependent on the ventromedial prefrontal cortex. The same group then goes on to show that PNS disrupts the peri-adolescent maturation of the prefrontal cortex in male rats (Markham et al., 2013). This finding, together with the notion that PNS reduces brain-derived neurotrophic factor (BDNF), an important determinant of synaptic plasticity, in the prefrontal cortex of adult rats (Fumagalli et al., 2004), highlights how this prenatal insult could increase vulnerability to the development of certain cortical-dependent cognitive impairments and psychiatric conditions. Further studies aimed at investigating the impact of PNS on higher order brain regions and the underlying molecular mechanisms that link maternal stress to alterations in cortical-dependent cognitive functions are definitely needed.

Valid PNS models that exhibit cognitive deficits relevant to psychiatric disorders could also prove useful for testing the efficacy of existing and novel therapeutic approaches.