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Review

The maternal deprivation animal model revisited

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ABSTRACT

Early life stress, in the form of MD (24 h at pnd 9), interferes with brain developmental trajectories modifying both behavioral and neurobiochemical parameters. MD has been reported to enhance neuroendocrine responses to stress, to affect emotional behavior and to impair cognitive function. More recently, changes in body weight gain, metabolic parameters and immunological responding have also been described. Present data give support to the fact that neuronal degeneration and/or astrocyte proliferation are present in specific brain regions, mainly hippocampus, prefrontal cortex and hypothalamus, which are particularly vulnerable to the effects of neonatal stress. The MD animal model arises as a valuable tool for the investigation of the brain processes occurring at the narrow time window comprised between pnd 9 and 10 that are critical for the establishment of brain circuitries critical for the regulation of behavior, metabolism and energy homeostasis. In the present review we will discuss three possible mechanisms that might be crucial for the effects of MD, namely, the rapid increase in glucocorticoids, the lack of the neonatal leptin surge, and the enhanced endocannabinoid signaling during the specific critical period of MD. A better understanding of the mechanisms underlying the detrimental consequences of MD is a concern for public health and may provide new insights into mental health prevention strategies and into novel therapeutic approaches in neuropsychiatry.

Contents

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1. Early life stress

In spite of the importance of genetic factors as determinants of adult behavior, the critical relevance of environmental factors in brain development is gaining ascendancy (Caspi and Moffitt, 2006; Knafo and Jaffee, 2013). From the prenatal period through the first years of postnatal life the brain undergoes rapid development, and is highly sensitive to the influence of external experiences, both positive and negative. There is now compelling evidence that exposure to stressful environments during prenatal or early neonatal life may alter development and predispose the individual to lifelong health problems, including susceptibility to mental illness (Bale et al., 2010). Clinical studies indicate that there is an association between early adverse experiences and an increased risk for the development of mental disorders (Kendler et al., 2002; Morgan and Fisher, 2007); however, these studies are based on associations or correlations and do not provide evidence of a cause-effect relationship. In this regard, animal models have provided an extensive literature supporting a causal relationship between early-life stress and psychopathology (Heim and Nemeroff, 2001; Teicher et al., 2006).

Brain development occurs during gestation and continues after birth through early postnatal stages, adolescence and until adult brain maturation is reached. However, brain development is not a uniform process, but a discontinuous one characterized by regional asynchrony (Giedd et al., 2009). The timing of brain development differs from one region to the other, and also between the different neural substrates, i.e. neurotransmitter systems, central endocrine circuitries, etcetera. These discontinuities in brain development are part of the so-called critical periods of brain development, periods of increased vulnerability to insults which are specific for each brain region or neurotransmitter systems. Among critical periods, the early postnatal period emerges as a highly sensitive period to environmental stimuli. Exposure to stressful events during the postnatal period may disrupt the programmed brain development, thus altering brain maturational endpoints, and consequently, increasing the risk for aberrant behavioral outcomes that may lead into adult psychopathology (Andersen et al., 2008; Marco et al., 2011; Meyer and Feldon, 2010).

In this regard, animal models are essential to understand the neurobehavioural outcomes of certain developmental manipulations. Actually, animal studies complement human observational and longitudinal studies, and offer a valid strategy to reveal the complex neurobiological mechanisms underlying anomalies in brain development caused by exposure to environmental insults that may result in aberrant behavioral outcomes typical of certain neuropsychiatric disorders (Branchi and Cirulli, 2014; Cirulli et al., 2009; Nestler and Hyman, 2010; Teicher et al., 2006). Despite the wide variety of animal models of early life stress, an important amount of them have been developed upon the disruption of the 'natural' patterning of dam-offspring interaction in mice and rats (see for example: Cirulli et al., 2009; Levine, 2005; Marco et al., 2009; Nishi et al., 2014). In rodents, the separation of pups from the dam during early postnatal life, typically from postnatal day (pnd) 2–14, has provided with an important contribution to understand the consequences of early life stress. A review on the different experimental protocols currently available for the application of maternal separation (specific age for separation, litter *versus* pup separation, duration of the separation episode, etc) is far beyond the scope of the present review. Herein, we will review the current literature on the consequences of a prolonged single episode (24 h) of maternal deprivation on pnd 9, the so-called early maternal deprivation animal model (MD), with a special emphasis in revealing some of the developmental signals – i.e. glucocorticoids, leptin and endocannabinoid (eCB) system – critically affected by the MD episode that may critically compromise adult metabolism and behavior.

2. The maternal deprivation (MD) animal model

Since the 90s decade, an extensive body of literature has investigated the short and long-term consequences of MD. Investigation first focused on the disruptive role of MD in the normal development of the HPA axis (Rots et al., 1996; van Oers et al., 1997), but it was Ellenbroek et al. (1998) who first proposed MD as "an interesting animal model for studying (aspects) of schizophrenia". At present, our concept of MD is more than that of an animal model of early-life stress highly suitable for the investigation of certain psychiatric disorders with a developmental origin, such as schizophrenia and depression. During the last decades, we (and others) have extended our knowledge on the behavioral consequences of this stressful procedure, we have analyzed its outcomes from different perspectives, and we have investigated such consequences at different time points, i.e. infancy, adolescence and adulthood (see Ellenbroek et al., 2005; Ellenbroek and Riva, 2003; Marco et al., 2009, 2011 for reviews). The MD animal model has emerged as a valuable tool for the investigation of the brain processes occurring at a narrow time window – comprised between pnd 9 and 10 – that exert a critical control over the normative development of the brain circuitries that will regulate adult behavior, metabolism and energy homeostasis, as well as immunological and nociceptive responses.

However, the MD protocol should not be considered exclusively as a separation stress, but a combination of stressors of different nature. First, the lack of maternal care during the 24 h seems to play a pivotal role, although nursing behaviors and/or tactile stimulation seem to augment immediately after dam-litter reunion, i.e. increase in licking-grooming frequency (Llorente-Berzal et al., 2011), thus suggesting that the dam may buffer or compensate the negative consequences of maternal deprivation, as suggested for periodic maternal separation (Macri et al., 2008). The lack of nutrients during the whole deprivation period may also play a critical influence. Indeed, a dramatic decrease in leptin levels, which main source at this age is the maternal milk, was described together with an important hypoglycemia during the MD episode (Viveros et al., 2010a). Moreover, MD may not only affect maternal behavior, but also milk production (Ellenbroek and Cools, 2002), providing an additional nutritional factor that may account for some of the effects of MD. Last, but not least, the decrease in body temperature – hypothermia – due to the lack of a mature thermal regulatory system in