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Review

Molecular mechanisms of early life stress—Lessons from mouse models

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ABSTRACT

Early life stress is one of the most explicit and undisputed environmental risk factors for disease later in life, including metabolic and psychiatric diseases. The developmental timing and context of stressful stimuli is thereby essential and determines the adaptive or maladaptive consequences. This review, which honors the invaluable accomplishments of one of the pioneers in the field, the late Seymour "Gig" Levine, focuses on the contribution of mouse models to the understanding of the molecular mechanisms that govern the acute and persistent effects of early life stress. The importance of the postnatal period and the complex role of maternal care in regulating the offspring's stress system activity are specifically addressed. Further, I discuss the possible molecular mechanisms that may be responsible for the persistent effects of early life stress, including the important issue of resilience and susceptibility to adverse life events.

Contents

1. Introduction

For the last several decades the role of the hypothalamic–pituitary–adrenal (HPA) axis in development has been of great interest. Numerous laboratories around the world have tried to unravel the unique regulation of the stress system in the prenatal, neonate and adolescent animal, often correlating their results with the adaptive or maladaptive long-term consequences of a disrupted HPA axis development. Historically most of this research was carried out with monkeys and rats, but the recent introduction of mouse models to developmental stress research has given the field new impulse. This review summarizes results of ours and others that illustrate how the data obtained in mouse models complement the results obtained in other species, while offering new insights into the molecular mechanisms of early life stress. Further, I discuss possible directions that early life stress research might take in the future and which questions should be addressed.

2. Development of the stress system

As the eminent stress researcher Seymour "Gig" Levine pointed out throughout his lifetime: "**Nothing is written in stone!**" He was referring to the development of animals that have constantly changing physiological states and highly adaptive flexibility. Over the course of ontogeny there are time windows of increased and decreased stress system (re)activity, which often correlate with an increased vulnerability to disruption of the stress system. The

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three main developmental phases in higher mammals, including rodents and humans, are the prenatal, the postnatal and the adolescent periods. Although the developmental timing and patterns differ between humans and rodents; there are also substantial similarities that support using rodents as a developmental model for humans (Rice and Barone, 2000). Each of the three main developmental periods is associated with specific environmental demands and is characterized by different phases of HPA axis development.

2.1. The prenatal period

During the prenatal period, which lasts from fertilisation to birth, the central components of the HPA axis emerge and start functioning (Challis et al., 2001). In the rat, the fetal HPA axis is responsive as early as gestational day 18 (Ohkawa et al., 1991), when the fetus is able to respond to maternal stress with increased adrenocorticotropic hormone (ACTH) production. Robust hypothalamic expression of corticotropin-releasing hormone (CRH) and vasopressin (AVP), both powerful activators of the HPA axis, can also be detected during the last week of gestation (Emanuel et al., 1989). However, the neuronal connections of the hypothalamus to the median eminence are not fully developed prenatally (Choy and Watkins, 1979). Therefore, while Ohkawa and colleagues observed a depletion of fetal hypothalamic CRH after maternal stress, it seems unlikely that adrenocortical glucocorticoid production was based solely on direct activiation by fetal AVP/CRH secretion.

The prenatal period is especially interesting and complex, as during this time the stress system of the neonate is closely linked to and influenced by the stress system of the mother. It has been shown that the fetal HPA axis can be activated by maternal CRH originating from the placenta (Weinstock, 2005). In addition, a substantial amount of fetal glucocorticoids are of maternal origin. The placenta plays a crucial role in regulating maternal influence on fetal glucocorticoid exposure, protecting the fetus from excess maternal glucocorticoids with high activity of the enzyme 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2), which converts corticosterone to inactive 11-keto forms. However, prolonged or excessive maternal stress, synthetic glucocorticoids or 11β-HSD2-deficiency may result in increased and potentially detrimental glucocorticoid exposure to the fetus (Darnaudery and Maccari, 2008; Kapoor et al., 2006; Seckl and Holmes, 2007). In humans, prenatal stress has been linked – among other things – to decreased birth weight, which is a risk factor for the development of a variety of diseases, including diabetes and heart disease (Barker, 1995; Van den Bergh et al., 2005).

In rats and mice, which deliver rather immature offspring in comparison to humans, the prenatal period corresponds to the early prenatal period in humans, while the postnatal period corresponds to late gestation in humans. Therefore, when modelling late gestational disruptions in humans, many researchers examine the postnatal period of rodents.

2.2. The postnatal period

The postnatal or neonatal period, which generally refers to the first 2 weeks after birth, is probably the most intensively studied developmental period in rodents (Levine et al., 2000). One of the earliest studies of the postnatal ontogeny of the HPA axis in rats came from Schapiro et al. (1962). This study was the first to describe the phenomenon of stress non-responsiveness in young rats during the first 2 weeks after birth. This period, which is characterized by very low blood levels of corticosterone and an inability of mild stressors to induce an enhancement of corticosterone secretion, was named the stress non-responsive period (SNRP). Additional experiments showed that in rats the SNRP lasts from about postnatal day (P)4 to P14 (Levine et al., 1967; Levine, 1970). However, these early data were based solely on corticosterone concentration in the blood and used relatively mild stressors. Therefore researchers doubted that the SNRP was absolute. In 1980, Schoenfeld and colleagues demonstrated that the HPA axis of the developing rat is capable of responding under specific circumstances, such as stimulation by ether fumes (Schoenfeld et al., 1980). It was then suggested that the SNRP be renamed the stress hyporesponsive period (SHRP). Additional studies by Walker and others supported Schoenfeld's findings, demonstrating that the HPA axis of the developing rat responds in a time and stressor dependent manner (Witek-Janusek, 1988; Walker et al., 1990, 1991; Walker and Dallman, 1993). The picture emerged that the developing HPA axis in the rat is capable of responding to a number of systemic stressors (e.g. ether or LPS), but not to stressors acting via limbic pathways (e.g. saline or novelty). An excellent historical overview of the SHRP was published in 2001 by Gig Levine (Levine, 2001).

2.3. The adolescent period

Adolescence, the final developmental period before adulthood, is a time of transition, sexual maturation and enhanced brain architecture plasticity. It is a difficult period to define in absolute margins, as no single event signals its onset or termination. However, a rather conservative and generally accepted estimate for the rodent is P28–P45 (Spear, 2000). While the importance of this developmental period in terms of increased vulnerability to, for example, psychiatric disorders is undisputed in humans (Paus et al., 2008); this period has only recently attracted more attention in preclinical research. Nonetheless it is clear that the function of the HPA axis during adolescence differs markedly from that of the adult. Corticosterone secretion to an acute stressor was demonstrated to be delayed, but more prolonged compared to adult secretion (Goldman et al., 1973; Vazquez and Akil, 1993). It was hypothesized that the prolonged release of glucocorticoids might be due to incomplete negative feedback control, although receptor levels of the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR) are at adult levels (Pryce, 2008). Interestingly, the effect of prolonged HPA axis activation during adolescence was not directly related to changing levels in sex hormones (Romeo et al., 2004).

The prolonged response to acute stress also seems to affect an adolescent animal's responsivity to repeated or chronic stress. Some reports suggest that during adolescence animals fail to adapt to repeated stressors and may mount a more pronounced response to chronic stress situations (McCormick and Mathews, 2007). These findings also support the hypothesis that there is a greater risk from chronic stress during adolescence. Furthermore, disruptions of HPA axis development during adolescence have been shown to influence disease susceptibility or resilience later in life (Hall, 1998; Barr et al., 2004; Mathews et al., 2008; Sterlemann et al., 2008).

3. The mouse in developmental stress research—new answers?

To cite another of Gig Levine's famous quotes: "A mouse is not a small rat." Even though these species are closely related, they differ markedly in terms of development and ecology. Although the mouse is being used more and more in stress research because of the benefit of transgenic modifications, stress system development in this species is far less understood compared to the rat. Most available developmental data in mice are from the postnatal period.