Neurobiology of Stress 1 (2015) 109–115

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: http://www.journals.elsevier.com/neurobiology-of-stress/

Synaptic rewiring of stress-sensitive neurons by early-life experience: A mechanism for resilience?

Akanksha Singh-Taylor [a], Aniko Korosi [b], Jenny Molet [c], Benjamin G. Gunn [a], Tallie Z. Baram [a, c, d, *]

[a] Department of Pediatrics, University of California-Irvine, Irvine, CA 92697-4475, USA
[b] Swammerdam Institute for Life Sciences, University of Amsterdam, Science Park 904, 1098 XH Amsterdam, The Netherlands
[c] Department of Anatomy/Neurobiology, University of California-Irvine, Irvine, CA 92697-4475, USA
[d] Department of Neurology, University of California-Irvine, Irvine, CA 92697-4475, USA

ARTICLE INFO

Article history:
Received 16 August 2014
Received in revised form
24 October 2014
Accepted 29 October 2014
Available online 6 November 2014

Keywords:
Synaptic plasticity
Resilience
Stress
Corticotropin releasing hormone (CRH)
Maternal care
Epigenetics

ABSTRACT

Genes and environment interact to influence cognitive and emotional functions throughout life. Early-life experiences in particular contribute to vulnerability or resilience to a number of emotional and cognitive illnesses in humans. In rodents, early-life experiences directly lead to resilience or vulnerability to stress later in life, and influence the development of cognitive and emotional deficits. The mechanisms for the enduring effects of early-life experiences on cognitive and emotional outcomes are not completely understood. Here, we present emerging information supporting experience-dependent modulation of the number and efficacy of synaptic inputs onto stress-sensitive neurons. This synaptic 'rewiring', in turn, may influence the expression of crucial neuronal genes. The persistent changes in gene expression in resilient versus vulnerable rodent models are likely maintained via epigenetic mechanisms. Thus, early-life experience may generate resilience by altering synaptic input to neurons, which informs them to modulate their epigenetic machinery.

1. Introduction

Resilience is defined as an active and adaptive biological, psychological, and social response to an event that may otherwise impair one's normal function (McEwen, 2007; Dudley et al., 2011; Russo et al., 2012). Resilience typically implies the presence of insult-related pathologies that are overcome by molecular, cellular, synaptic, and finally behavioral changes that enable coping and normal function.

Much has been written about the origins of resilience (Barker, 1989; Yehuda et al., 2006; Gluckman et al., 2007; Feder et al., 2009; Russo et al., 2012). There is clear evidence that resilience and vulnerability are influenced by genetic factors (Caspi et al., 2003; Binder et al., 2008) and gene-environment interactions (Caspi et al., 2003; Bale et al., 2010; Dincheva et al., 2014). In addition, a large body of work has supported strong correlations of early-life experience/environment and resilience to cognitive and emotional illnesses later in life (Schmidt et al., 2011; Baram et al., 2012; Lucassen et al., 2013; Huang, 2014; Insel, 2014; Santarelli et al., 2014). Several theories have been put forth that strongly suggest a causal and adaptive relationship between early-life experience and lifetime vulnerability or resilience to disease (Barker, 1989; McEwen, 2000; Gluckman et al., 2007; Baram et al., 2012; Sandman et al., 2012).

Whereas human studies produce associations which can strongly suggest a causal relationship between early-life experience and vulnerability or resilience to disease, direct manipulations of early-life experience in animal models have been shown to lead to persistent changes in aspects of brain function, including resilience to subsequent insults such as stress. Indeed, a large number of primate and rodent models have been created to directly manipulate early-life experience, in order to generate resilience or vulnerability (see Maras and Baram, 2012; Huang, 2014 for recent reviews). Broadly categorized, these paradigms aim to model early-life adversity such as chronic stress (Schmidt et al., 2011; Molet et al., 2014), or to create a nurturing early-life environment, typically based on optimized maternal care or novelty (see Akers et al., 2008; Champagne et al., 2008; Korosi and Baram, 2009; Baram et al., 2012; Tang et al., 2014). Indeed, rodents raised in these

* Corresponding author. Department of Pediatrics, University of California-Irvine, Med. Sci. I, ZOT 4475, Irvine, CA 92697-4475, USA. Tel.: +1 949 824 1131; fax: +1 949 824 1106.
E-mail address: tallie@uci.edu (T.Z. Baram).

http://dx.doi.org/10.1016/j.ynstr.2014.10.007

distinct environments generally develop vulnerability (Huot et al., 2002; Romeo et al., 2004; Brunson et al., 2005; Champagne et al., 2008; van Hasselt et al., 2012) or resilience (Liu et al., 1997; Fenoglio et al., 2005; van Hasselt et al., 2012) to future stress and to cognitive and/or emotional deficits.

Although the influence of early-life experience on life-time resilience and vulnerability are well established, the underlying mechanisms are not fully understood. It is now generally agreed that enduring changes in the expression of important genes might be involved, and that these changes might persist via epigenetic mechanisms including histone and DNA modifications (Meaney and Szyf, 2005; Borrelli et al., 2008; Roth et al., 2009; McClelland et al., 2011; Sun et al., 2013; Morrison et al., 2014). However, fundamental and crucial questions remain unanswered. For examples, what is the essence of the experience or environmental-signal that is perceived by the developing brain? How does the signal reach important neurons that change in response to the early-life experience? What are these neurons that are re-programmed to enable the structural and functional plasticity that underlies resilience? How do these neurons know to modulate their epigenetic machinery?

We attempt to address these questions here.

2. Early-life experience, maternal signals, and brain programming

As mentioned above, direct manipulation of maternal care patterns has yielded long-lasting resilience or vulnerability to cognitive and emotional deficits. We briefly describe the frameworks for bi-directional manipulation of maternal signals to young rodents that have been employed by our group, because the robust outcomes enable examination of the underlying mechanisms.

2.1. Controlled manipulation to augment maternal care

The handling paradigm (Levine, 1957; Plotsky and Meaney, 1993; Avishai-Eliner et al., 2001a), which involves brief (15 min) daily separation of rat pups from the mother during the first weeks of life, was used as a model of enhanced maternal care. These brief separations promoted increased maternal-derived sensory input upon reunion with their mothers (Fig. 1) (Liu et al., 1997; Fenoglio et al., 2006). This paradigm led to increased resilience to depressive-like behavior (Meaney et al., 1991) and improved learning and memory (Liu et al., 2000; Fenoglio et al., 2005).

2.2. Controlled manipulation to disrupt maternal care

Commonly, early-life stress is generated by maternal separation (MS), a manipulation believed to be stressful. Extended absence of the mother provokes hypothermia and starvation, so many models use intermittent maternal deprivation and hence intermittent stress. In the human condition, when infants and children grow up in famine, war, or in the presence of drug-abusing mothers, the stress is typically chronic rather than intermittent, and the mother is typically present. Maternal care behaviors during these conditions might be the source of stress in the infant (Whipple and Webster-Stratton, 1991; Koenen et al., 2003; Kendall-Tackett, 2007; Baram et al., 2012), as is particularly well documented in neglect/abuse situations, where maternal care is unpredictable and fragmented (Whipple and Webster-Stratton, 1991; Gaudin et al., 1996).

Aiming to recapitulate the human condition, we generated a model of chronic early-life stress (CES) where the mother is continuously present. The paradigm involves limiting the bedding and nesting material in the cage (for a detailed review, see Molet et al., 2014). This impoverished cage environment resulted in abnormal maternal care, i.e., fragmented maternal-derived sensory input to the pups. The latter, as reported in humans, provoked chronic uncontrollable early-life “emotional stress” (Gilles et al., 1996; Avishai-Eliner et al., 2001b; Ivy et al., 2008; Baram et al., 2012). There was minimal change in the overall duration of maternal care or of specific aspects of care (licking and grooming, nursing, etc) (Ivy et al., 2008). However, in both mice and rats, maternal care was fragmented and unpredictable: each bout of behavior is shorter and the sequence of nurturing behaviors is unpredictable (Rice et al., 2008; Baram et al., 2012). In some cases, especially when cage environment was altered later in the development of the pups (postnatal days 3–8 and 8–12 rather than 2–9), rough handling of the pups by the mother was noted (Moriceau et al., 2009; Raineki et al., 2010, 2012). The CES model of aberrant maternal care and early-life experience led to emotional and cognitive vulnerabilities, and eventually overt pathology, including early cognitive aging (for a detailed review, see Molet et al., 2014). For example, Raineki et al., found depressive-like symptoms measured as increased immobility time in the forced swim test (FST) in adolescent rats that experienced CES. When tested during adolescence and young adulthood using paradigms such as novelty induced hypophagia, open-field, and elevated plus maze, rodents stressed early in life showed anxiety-like behaviors (Wang et al., 2012; Dalle Molle et al., 2012; Malter Cohen et al.,

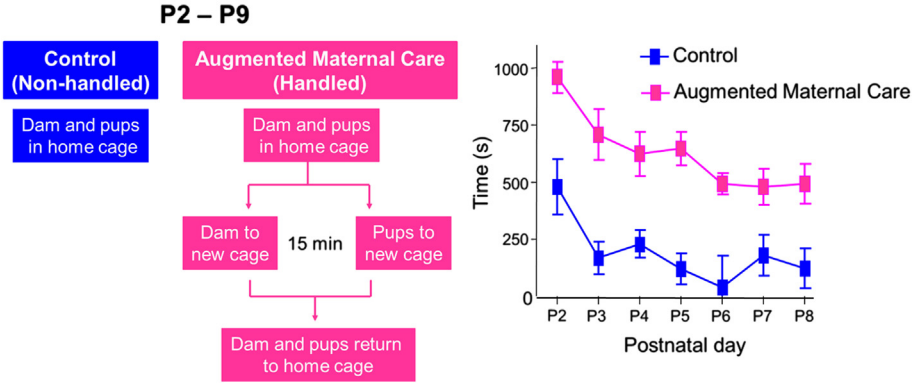

Fig. 1. Brief daily separations of rat pups from their mother lead to increased sensory input from the mother to the pups upon their reunion. A. A schematic of the handling paradigm: during postnatal day 2–9, the mother and the pups were separated for 15 min in different cages, and then reunited in the home cage. Control mother and pups remained in the home cage. B. Maternal sensory stimulation of the pups, specifically licking and grooming, was observed and quantified daily during the 30 min after the mothers and the pups were returned to home cages ($n = 6$ mothers per group). Adapted from Fenoglio et al. (2006) with permission.