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Emerging roles of epigenetic mechanisms in the enduring effects of early-life stress and experience on learning and memory

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ABSTRACT

Epigenetic mechanisms are involved in programming gene expression throughout development. In addition, they are key contributors to the processes by which early-life experience fine-tunes the expression levels of key neuronal genes, governing learning and memory throughout life. Here we describe the long-lasting, bi-directional effects of early-life experience on learning and memory. We discuss how enriched postnatal experience enduringly augments spatial learning, and how chronic early-life stress results in persistent and progressive deficits in the structure and function of hippocampal neurons. The existing and emerging roles of epigenetic mechanisms in these fundamental neuroplasticity phenomena are illustrated.

1. The clinical problem: association of early-life experience with learning and memory

Numerous clinical reports demonstrate a strong association between early-life experience and subsequent cognitive functions. Chronic childhood stress (such as extreme poverty, loss of parent, social deprivation or abuse) correlates with learning and memory impairments later in life (Kaplan et al., 2001; Nelson et al., 2007; Wilson et al., 2007). As examples, lower socioeconomic level early in life correlates with cognitive function in adulthood, and post-institutionalized orphans have abnormal neuronal function in limbic areas including the hippocampus, as shown by functional MRI studies (Chugani et al., 2001), and by worse cognitive performance when compared to never-institutionalized children (Nelson et al., 2007). Improving the experience of these institutionalized infants by placing them in families significantly improves learning and memory long-term. Remarkably, the timing of the placement into foster care is crucial, and placement before the age of two years is associated with improved outcome (Bos, Zeanah, Smyke, Fox, & Nelson, 2010). These data suggest that critical developmental periods exist for the processes by which early-life experience shapes cognitive function throughout life.

The impact of early-life experience, and especially of chronic stress, on the integrity of the hippocampus, a region subserving certain learning and memory processes (Andersen, Moser, Moser, & Trommald, 1996; Eichenbaum, Yonelinas, & Ranganath, 2007; Morris et al., 2003; Squire, Wixted, & Clark, 2007), is supported also by clinical studies suggesting that hippocampal volumes in adults that have experienced early-life abuse are smaller (Bremner et al., 1997). Whereas this view is not universally endorsed (Lenze, Xiong, & Sheline, 2008; Lyons, Yang, Sawyer-Glover, Moseley, & Schatzberg, 2001), this association and similar findings in other human studies (Buss et al., 2007) suggest that chronic early-life stress is associated with impairments in hippocampal structure and function in adulthood. In addition these correlational studies demonstrate the complexity of human research: elucidating the potential causal relationship between early-life stress and later-life cognitive outcomes is difficult, because of uncontrollable variables such as genetics and subtle environmental influences that may not be measurable. Such studies lead to the realization that use of animal models benefits our understanding of the causal relationship between early-experiences and life-long learning and memory. These enable prospective longitudinal studies as well as control of genetic background (Nestler & Hyman, 2010). In addition, parameters of interest can be manipulated and subsequent experiences can be controlled throughout the entire period of investigation.

Notably, uncovering the biological mechanisms involved in the long-term consequences of enhanced early-life experience is of

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paramount importance, because these mechanisms may be employed for therapeutic interventions and improved outcome. This has happened, for example, when infant position was found to govern sudden infant death, and care of infants was changed (Ponsonby, Dwyer, Gibbons, Cochrane, & Wang, 1993). In addition, discovering if chronic early-life stress directly impacts cognitive function is extremely important because over 50% of the world's children are exposed to chronic stress (UNICEF, 2005), and such stress cannot currently be prevented. Therefore, establishing causality and defining the molecular and cellular mechanisms for potential long-lasting effects of early-life experience and stress on learning and memory are prerequisites to preventive and therapeutic approaches in the future.

2. Animal models enable determination of causality and elucidation of the mechanisms by which early-life experience, including chronic stress, might govern learning and memory throughout life

For the past six decades, scientists have employed models in primates and rodents to manipulate environmental and genetic variables for the study of early-life experience on later-life cognitive functions (for review, see Korosi & Baram, 2009; Levine, 2000). In these animal models, early-life experience was modulated in a bi-directional manner (Fig. 1). Acute-intermittent stress, such as daily maternal separation, or chronic stress imposed via alteration of maternal behavior, were designed to mimic human conditions of poverty, illness or neglect/abuse (Avishai-Eliner, Brunson, Sandman, & Baram, 2002; Brunson, Chen, Avishai-Eliner, & Baram, 2003; Fenoglio, Brunson, & Baram, 2006; Heim, Plotsky, & Nemeroff, 2004; Levine, 2000). In contrast, enhanced early-life experience was generated via a naturalistic selection of high-caring dams (Hofer, 1994), or via procedures, such as brief daily handling of the pups, that augment maternal care and thus maternal-derived sensory input (Brunson, Avishai-Eliner, Hatalski, & Baram, 2001; Fenoglio, Chen, & Baram, 2006; Korosi & Baram, 2009; Korosi et al., 2010; Meaney, Aitken, van Berkel, Bhatnagar, & Sapolsky, 1988).

A majority of studies employing these structured alterations of early-life experience have focused on 'emotional' outcomes- the vulnerability or resilience of the adult 'graduates' of these early-life manipulations to depressive-like or anxiety-like behaviors. However, existing and emerging evidence indicates that early-life experience and stress also contribute significantly to learning and memory throughout life, as suspected from the clinical correlational studies of infants and children. In this paper, we review data that support a causal relationship of enhanced early-life experience (derived from augmented quality of maternal care) and learning and memory function during adulthood. We also discuss the causal relationship of chronic stress during the neonatal/infancy period and cognitive decline commencing in middle-age. In both cases we describe the molecular and cellular processes that are involved, and discuss the role of epigenetics in the persistently altered expression of key genes that contribute to these phenotypes.

3. Cellular and molecular changes resulting from enhanced early-life experience and from chronic early-life stress: a common theme

A key determinant of early-postnatal existence involves the interaction of the immature individual with his/her parent(s). Both clinical and experimental studies have confirmed the fundamental role of the presence and sensory input from a mother on the essence of the neonatal and infancy experience. Considered along a continuum, frequent and consistent nurturing care suppresses stress in the immature rat, monkey and human (Dent, Smith, & Levine, 1999; Gunnar, Larson, Hertsgaard, Harris, & Brodersen, 1992; Harlow & Suomi, 1971), whereas absence of the mother or abnormal quality or quantity of maternal care is a major provoker of the newborn/infant "stress system" (Fig. 1). Based on this body of information, many manipulations of early-life experience have utilized modulation of mother-infant interactions. In addition, the principal 'read-outs' of the effects of these modulations on the infant brain have included acute and persistent alterations in the expression and function of genes that are involved in regulation of the stress response (Avishai-Eliner, Eghbal-Ahmadi, Tabachnik, Brunson, & Baram, 2001; Fenoglio et al., 2005; Korosi et al., 2010; Plotsky & Meaney, 1993; Weaver et al., 2004).

As shown in Fig. 2, the response to stress is governed by a number of neurotransmitters, neuromodulators and steroids (Joels & Baram, 2009; McEwen, 1999; Ulrich-Lai & Herman, 2009). In essence, external (or internal) signals that are interpreted as indicat-

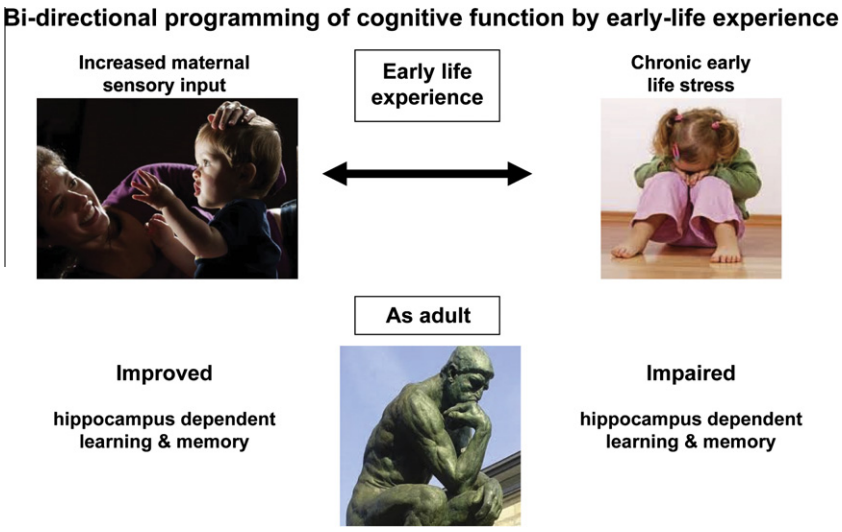

Fig. 1. Bidirectional effects of early-life experience on cognitive function throughout life. Chronic stress in the early postnatal period is associated with impaired cognition during middle-age in people. Animal models demonstrate that this type of stress causes loss of spines and eventual dendritic dying-back (atrophy), attenuated long-term potentiation and progressive deficits in spatial memory. In contrast, enriched early-life experience, and especially augmented sensory input from the mother, results in improved spatial learning compared to controls. In both cases, the mechanisms for the bidirectional plasticity involved persistently altered expression of genes involved in regulation of the 'stress-system'.