



Review

Opposing effects of positive and negative stress on hippocampal plasticity over the lifespan

Marlena Wosiski-Kuhn, Alexis M. Stranahan*

Physiology Department, Georgia Health Sciences University, Augusta, GA, USA

ARTICLE INFO

Article history:

Received 23 August 2011

Received in revised form 31 October 2011

Accepted 3 November 2011

Available online 10 November 2011

Keywords:

Exercise

Stress

Hippocampus

Neurogenesis

Epigenetics

ABSTRACT

Early developmental experience shapes neuronal circuits and influences the trajectory of cognitive aging. Just as adversity early in life can accelerate age-related synaptic impairments, enhancement of neuronal metabolism and function in the developing brain could potentially protect neurons against the synaptic consequences of aging. In this regard, metabolic enhancements following exercise directly oppose the deleterious consequences of adverse stress. In this review, we examine the relationship between exercise and other forms of stress over the lifespan. Exercise is a specialized form of stress in that it is predictable and voluntary, while other forms of psychological and physiological stress are unpredictable and uncontrollable, with distinct consequences for behavior and synaptic plasticity. Themes emerging from the literature surrounding the opposing effects of adversity and exercise include epigenetic mechanisms that converge on the regulation of neurotrophic factor expression and neurogenesis. These data suggest that exercise-induced neuroprotection and neuronal endangerment following adversity may both be transferable across generations, in a manner that has the potential to impact neuroplasticity over the lifespan.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

The central nervous system exhibits adaptive and maladaptive forms of plasticity. The capacity for changes in neuronal connectivity is greatest during prenatal and early postnatal development, but the adult brain retains a great deal of flexibility into old age and beyond. The nature and extent of neuronal changes can be viewed through a variety of mechanisms, under a vast array of environmental conditions. Every change in neuronal function can be viewed as an individual summation of the competing influences that arise following changes to the external and internal environment. Metabolic efficiency is a driving factor in determining whether neurons retain their plastic properties across the lifespan, or whether they succumb to the cumulative effects of negative stressors. Regular physical activity is one means to influence cellular metabolism, both in the central nervous system, and in a variety of endocrine organs that produce hormonal signals that instruct the rate and trajectory of brain aging.

Exercise is a form of chronic mild stress, distinguished from adverse stress by its predictable, volitional nature. Long-term exposure to exercise confers neuroprotection against a variety of insults.

On the other hand, unpredictable, uncontrollable stressors increase neuronal vulnerability to a variety of conditions, many of them neurodegenerative or neuropsychiatric in nature. Both humans and other animals live in a continual state of stress, and the outcome of competing stressors determines immediate neuronal responses as well as long-term alterations in neuronal circuitry. This review examines the opposite effects of exercise and adversity, with adversity defined as a negatively valenced experience that occurs repetitively over time. The literature in humans and in rodent models supports a dynamic interplay between these two stressors, which differ in their etiology and in terms of their consequences for neuroplasticity. While a wide variety of neurochemical, morphological, and functional alterations exhibit bidirectional regulation following exercise and adverse experience, we focus on emerging literature suggesting that epigenetic factors contribute to this relationship by modulating neurotrophic factor expression and neurogenesis.

2. Prenatal effects of positive and negative stress

2.1. Early life programming of the HPA axis following negative stress

Exposure to adverse stress in utero affects brain development and these deleterious impacts are long-lasting. Adverse events during prenatal development cause structural and functional changes

* Corresponding author at: Georgia Health Sciences University, Physiology Department, 1120 15th St, room CA3145, Augusta, GA 30912, USA.
Tel.: +1 706 721 7885; fax: +1 706 721 7299.

E-mail address: astranahan@georgiahealth.edu (A.M. Stranahan).

in the brain that persist over the lifespan (Seckl and Meaney, 2004). Exposure to negative stress early in life programs the hypothalamic–pituitary–adrenal (HPA) axis response to stress during adulthood and old age. Specifically, exposure of a pregnant female to stress or glucocorticoids intensifies fetal HPA activity, permanently modifying brain development and altering the trajectory of neuronal growth (Seckl, 2008). Receptors for glucocorticoids are highly expressed in the developing brain but, in normal, unstressed mothers, are protected during the first half of gestation by enzyme 11 β hydroxysteroid dehydrogenase 2, which catalyzes the conversion of active glucocorticoids to inert forms (Fuxe et al., 1985).

Neuronal development is governed both by genetic background and by alterations in the availability of existing genes for transcription. Changes in chromatin structure that govern accessibility of specific sequences include the addition of methyl groups to DNA, and changes in histone phosphorylation and acetylation. These epigenetic mechanisms permit or preclude transcription of a variety of genes involved in cellular stress responses, including transcripts associated with the response to elevated glucocorticoids. Prenatal stress suppresses gluco- and mineralocorticoid receptor expression via epigenetic mechanisms (Weaver et al., 2004). Loss of glucocorticoid receptors and mineralocorticoid receptors decreases negative feedback from the hippocampus on the HPA axis, resulting in prolonged responses to acute stress. Neuronal adaptations to early life stress are not limited to the hippocampus and HPA axis. In rats, prenatal exposure to stress also increases corticotrophin-releasing hormone levels in the central nucleus of the amygdala into adulthood (Cratty et al., 1995). In this regard, exposure to adverse stress during pregnancy has the potential to alter the brain circuitry of the developing fetus.

2.2. Positive stress in utero enhances hippocampal structure postnatally

Not all experiences that elicit activation of the HPA axis will produce hippocampal impairment. In fact, exercise during pregnancy enhances neuronal plasticity in the fetal hippocampus, despite acute elevations in glucocorticoid levels. While no studies to date have determined whether prenatal exposure to positive stress alters the expression of gluco- or mineralocorticoid receptors in offspring, there is some indication that the prenatal hippocampus responds to exercise with enhanced plasticity. In utero exposure to exercise increases postnatal neurogenesis in the hippocampus of rat pups (Bick-Sander et al., 2006). Prenatal exposure to aerobic exercise has the potential to correct the reprogramming of HPA axis function observed with early life stressors, although this possibility remains to be addressed in full. Moreover, the mechanisms that differentiate the neurogenic consequences of exercise-induced elevations in glucocorticoids and adverse stress-induced elevations in glucocorticoids remain to be elucidated.

3. Opposing effects of adversity and exercise during early postnatal development

3.1. Suppression of hippocampal plasticity with negative stress during adolescence

Negative stress during early postnatal development modulates the functional maturation of neural circuits (Plotsky and Meaney, 1993). Exposure to adverse stress early in life increases stress reactivity during adulthood, with associated cognitive deficits (Lupien et al., 2009). In addition to modulating cognition, dentate gyrus BDNF expression contributes to behavioral resilience in young rats. Natural variability in behavioral responses to chronic mild

stress partitions rats into resilient and non-resilient groups based on susceptibility to anhedonia (Taliaz et al., 2011). Resilient rats retain a preference for sucrose over water following chronic mild stress, while non-resilient rats exhibit reduced preference in this paradigm. Interestingly, hippocampal BDNF levels are significantly higher in the resilient group. Stress-induced downregulation of hippocampal BDNF expression also distinguished between resilient and non-resilient animals, with the resilient animals showing reduced susceptibility to suppression of BDNF levels following stress. This report identifies adolescence as a critical period during which negative stress has the potential to regulate BDNF, and thereby influence hippocampal synaptic function.

3.2. Positive stress promotes plasticity in the adolescent hippocampus

Exercise enhances hippocampal synaptic function during early postnatal development by recruiting multiple molecular pathways. BDNF promotes growth and survival of neurons across multiple brain regions and is required for activity-dependent survival of cortical neurons in vitro (Ghosh et al., 1994). BDNF expression, although widespread, is selectively enriched in the hippocampus (Hofer et al., 1990) where it contributes to learning, memory, and HPA axis stress responses. Among all the neurotrophic factors, BDNF is particularly responsive to upregulation following exercise.

Exercise-induced upregulation of BDNF modulates the function of intracellular signaling pathways. Physical activity in young rats increases the production and release of both insulin-like growth factor 1 (IGF-1) and VEGF (Ding et al., 2004), both of which regulate synaptic plasticity among the larger cohort of new and developmentally generated hippocampal neurons. These factors also enhance adult neurogenesis in the hippocampal dentate gyrus. NMDA receptors are crucial to the increase in BDNF, as blocking the NMDA receptor abolishes exercise-induced increases in BDNF and tyrosine kinase receptor B (TrkB) in the adult male rat (Vaynman et al., 2003). Exercise also inhibits histone deacetylation, which increases BDNF mRNA levels in embryonic rat hippocampal neurons (Tian et al., 2010). Therefore, physical activity may recruit epigenetic mechanisms to promote neuroplasticity by elevating BDNF.

3.3. Adverse stress programs hippocampal negative feedback on the HPA axis during early postnatal development

The hippocampus expresses both glucocorticoid receptors and mineralocorticoid receptors, and hippocampal activity facilitates termination of the hypothalamic–pituitary–adrenal axis response to stress. Prolonged maternal separation during the early postnatal period is stressful enough to activate the HPA axis during the stress hyporesponsive period (Huot et al., 2002) which, in unstressed neonates, is characterized by a blunted glucocorticoid response. Chronic, variable stress during the juvenile period delays shutdown of the HPA axis response to acute stress (Isgor et al., 2004). Extrahippocampal brain regions are also influenced by chronic elevations in HPA axis activity. Although it does not change basal measures of the HPA response in adulthood, early prolonged maternal separation in rats increases the density of CRH binding sites in the prefrontal cortex, amygdala, hypothalamus and hippocampus (Anisman et al., 1998). The differences in HPA axis regulation appear once the adult rat is exposed to stress, with animals that underwent prolonged maternal separation having lengthened increases in CRH, ACTH, and corticosterone levels (Plotsky and Meaney, 1993; Liu et al., 2000). Maternal separation also increases anxiety-like behaviors later in life (Huot et al., 2001). Thus, maternal separation deleteriously reprograms the HPA axis creating a markedly different response to stress in these animals that persists into adulthood.

Download English Version:

<https://daneshyari.com/en/article/1902318>

Download Persian Version:

<https://daneshyari.com/article/1902318>

[Daneshyari.com](https://daneshyari.com)