Neurobiology of Learning and Memory xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Review

Stress and glucocorticoid receptor-dependent mechanisms in long-term memory: From adaptive responses to psychopathologies

Charles Finsterwald, Cristina M. Alberini *

Center for Neural Science, New York University, NY, USA

ARTICLE INFO

Article history:
Received 5 August 2013
Revised 20 September 2013
Accepted 25 September 2013
Available online xxxx

Keywords:
Glucocorticoid
Glucocorticoid receptor
Memory
BDNF
PTSD
Stress
Trauma
Survival pathway

ABSTRACT

A proper response against stressors is critical for survival. In mammals, the stress response is primarily mediated by secretion of glucocorticoids via the hypothalamic–pituitary–adrenocortical (HPA) axis and release of catecholamines through adrenergic neurotransmission. Activation of these pathways results in a quick physical response to the stress and, in adaptive conditions, mediates long-term changes in the brain that lead to the formation of long-term memories of the experience. These long-term memories are an essential adaptive mechanism that allows an animal to effectively face similar demands again. Indeed, a moderate stress level has a strong positive effect on memory and cognition, as a single arousing or moderately stressful event can be remembered for up to a lifetime. Conversely, exposure to extreme, traumatic, or chronic stress can have the opposite effect and cause memory loss, cognitive impairments, and stress-related psychopathologies such as anxiety disorders, depression and post-traumatic stress disorder (PTSD). While more effort has been devoted to the understanding of the negative effects of chronic stress, much less has been done thus far on the identification of the mechanisms engaged in the brain when stress promotes long-term memory formation. Understanding these mechanisms will provide critical information for use in ameliorating memory processes in both normal and pathological conditions. Here, we will review the role of glucocorticoids and glucocorticoid receptors (GRs) in memory formation and modulation. Furthermore, we will discuss recent findings on the molecular cascade of events underlying the effect of GR activation in adaptive levels of stress that leads to strong, long-lasting memories. Our recent data indicate that the positive effects of GR activation on memory consolidation critically engage the brain-derived neurotrophic factor (BDNF) pathway. We propose and will discuss the hypothesis that stress promotes the formation of strong long-term memories because the activation of hippocampal GRs after learning is coupled to the recruitment of the growth and pro-survival BDNF/cAMP response element-binding protein (CREB) pathway, which is well-know to be a general mechanism required for long-term memory formation. We will then speculate about how these results may explain the negative effects of traumatic or chronic stress on memory and cognitive functions.

1. Introduction

Stress triggers physiological responses that are necessary for organisms to adapt to a changing environment and respond to immediate perturbation, threat, or danger. Animals' survival not only depends on their immediate response to a stressor, but also relies on their ability to memorize and integrate the information learned about the stressor in order to effectively respond to similar demands in the future.

In addition to the rapid physiological responses that include increases in blood pressure, heart rate, and pulmonary ventilation and a hypervigilance state, stress produces long-lasting changes in the central nervous system (CNS) that are responsible for memorization of the event. These reactions are governed by acute adrenergic neurotransmission in the sympathetic nervous system and, following activation of the hypothalamic–pituitary–adrenal (HPA) axis, the release of glucocorticoids from the adrenal glands. As a result, adrenergic neurotransmission and glucocorticoid secretion activate specific brain regions that include the hippocampus, amygdala, and prefrontal cortex. These regions are enriched in adrenergic and glucocorticoid receptors (GRs), which, in rodents as in humans are known to play critical roles in encoding, processing, and retaining the information of emotional events (de Kloet, Joels, & Holsboer, 2005; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007; McIntyre, McGaugh, & Williams, 2012; Roozendaal, Okuda, de Quervain, & McGaugh, 2006).

* Corresponding author. Address: Center for Neural Science, New York University, 4 Washington Place, New York, NY 10003, USA. Fax: +1 212 995 4011.
E-mail address: ca60@nyu.edu (C.M. Alberini).

1074-7427/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nlm.2013.09.017

The various parameters that characterize emotional experiences, such as arousal or stress intensity, duration, chronicity, predictability, and controllability are known to critically affect memory and cognition (Lupien et al., 2007). Whereas optimal levels of stress or arousal stimulate cognitive performance and the formation of a strong long-term memory by mediating and modulating consolidation, the process whereby an experience becomes a strong and long-lasting memory, exposure to severe or chronic stress can lead to cognitive impairments and the development of psychopathologies such as anxiety disorders, depression, and post-traumatic stress disorders (PTSD) (de Kloet et al., 2005; McEwen, 2000b). In this review, we will discuss the mechanisms by which one of the major pathways activated by stress, the release of glucocorticoids and activation of GRs, promotes long-term memory formation when stress and/or arousal are adaptive. Based on our recent data, we will propose the hypothesis that the activation of GRs promotes memory consolidation and strengthening because it critically and directly engages the activation of the brain-derived neurotrophic factor (BDNF)/cAMP response element-binding protein (CREB)-dependent pro-survival/growth pathway as a response to stress. We propose that this survival response to stress has been selected by evolution in brain cells as a fundamental mechanism that mediates memory storage. We will then summarize the knowledge of how high levels of stress and/or glucocorticoids may lead to memory impairments. We will conclude with speculations about how the knowledge of the molecular mechanisms activated by GRs in adaptive conditions may also explain the negative effects of stress on cognition, which lead to cognitive impairments and psychopathologies.

2. Stress, glucocorticoids and activation of GRs

2.1. Glucocorticoids and their receptors

Glucocorticoids are steroid hormones synthesized from cholesterol in the adrenal cortex. The predominant glucocorticoid in humans is cortisol and, in rodents, corticosterone. Their release fluctuates with circadian and ultradian rhythms made up of pulses at approximately hourly intervals. Cortisol and corticosterone are also the primary hormones responsible for the stress response because their release is regulated by the HPA axis activated in response to stress. In particular, glucocorticoids play a key role in restoring homeostasis following exposure to stress, and also modulate important physiological responses such as ion transport, glycogenolysis, immune response, and memory.

Because of their lipophilic properties, glucocorticoids can cross plasma membranes and activate two different intracellular receptors: mineralocorticoid receptors (MRs) and GRs, also known, respectively, as Type I and Type II receptors. MRs and GRs are homologous in their structural domains, which consist of the N-terminal transactivation domain (TAD), the DNA binding domain (DBD), and the C-terminal ligand binding domain (LBD) (Lu et al., 2006). In the absence of ligand, cytoplasmic MRs and GRs are bound to chaperone protein complexes, including heat shock protein 70 (hsp70), heat shock protein 90 (hsp90), and FK506 binding protein 5 (FKBP5) (Grad & Picard, 2007). On ligand binding, the receptors undergo conformational changes that lead to their dissociation from the chaperone complexes, their homodimerization and nuclear translocation, or their binding to other cytoplasmic proteins. In the nucleus, both MRs and GRs can bind to specific sequences of 15 nucleotides in the promoter of target genes, known as the glucocorticoid response elements (GREs) and directly activate transcription of target genes (Zalachoras, Houtman, & Meijer, 2013). Nuclear MRs and GRs can also interact with other transcription factors to control gene expression (Sandi, 2004). In addition, MRs and GRs can control rapid cellular responses by mechanisms that are independent of nuclear translocation and gene expression regulation, but instead occur through genomic-independent actions (Groeneweg, Karst, de Kloet, & Joels, 2011; Prager & Johnson, 2009). We will further discuss the genomic and non-genomic mechanisms of GR below.

2.2. Stress-mediated secretion of glucocorticoids and activation of GRs in the brain

A stressful experience triggers the acute release of catecholamines (adrenaline and noradrenaline) from the sympathetic nervous system, as well as activation of the HPA axis by first engaging secretion of corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus, then adrenocorticotropic hormone (ACTH) from the anterior lobe of the pituitary gland, and finally glucocorticoids from the adrenal cortex into the blood circulation. Once the stress ends, hormonal levels return to homeostasis by the negative feedback action of glucocorticoids on the HPA axis. In addition to the immediate reaction to the stressor by catecholamines and glucocorticoids, which evoke rapid physical responses (e.g., "fight or flight" response in the case of a threat), the release of glucocorticoids activate MRs and GRs in the brain. MRs and GRs are ubiquitously expressed throughout the brain in both glial cells and neurons, with highest levels in the hippocampus and amygdala, two areas that play critical roles in memories of fear, threat, and stressful experiences (de Kloet et al., 2005; Lupien et al., 2007). Importantly, MRs have a tenfold higher affinity for glucocorticoids than GRs and are largely occupied by the ligand in basal conditions, whereas GRs occupation highly depends on increases in glucocorticoid levels following stress response (de Kloet et al., 2005; Lupien et al., 2007). In this review, we will mainly discuss the mechanisms mediated by GRs.

For many years, the effects of glucocorticoids on synaptic plasticity and memory were believed to result exclusively from the classical genomic-dependent pathway of GR activation. However, it has recently been shown that many effects of GRs are also mediated by rapid, genomic-independent mechanisms (Groeneweg et al., 2011; Prager & Johnson, 2009).

As mentioned earlier, the genomic action of GRs occurs in the nucleus, where these receptors can directly activate transcription by binding to the GREs in the promoter of target genes (Karst et al., 2000; Prager & Johnson, 2009). However, GRs can control gene expression also by interacting with other transcription factors, including activator protein 1 (AP1), nuclear factor-κB (NF-κB), transcription factor IID (TFIID), signal transducer and activator of transcription 5 (STAT5), and CREB (Sandi, 2004). Studies using DNA microarray or serial analysis of gene expression (SAGE) in cultured hippocampal neurons or in the hippocampus *in vivo* demonstrated that activation of GRs leads to the transcription of various genes, including calcium binding proteins, synaptosomal-associated proteins (SNAPs), neuronal cell-adhesion molecules (NCAMs), dynein, neurofilaments, β-actin, LIM domain kinase 1 (LIMK1) and profilin. These genes have key functions in intracellular signal transduction, metabolism, neuronal structure, synaptic plasticity, and memory, suggesting that they may be target genes regulated by GR in long-term memory formation (Datson, Morsink, Meijer, & de Kloet, 2008; Datson, van der Perk, de Kloet, & Vreugdenhil, 2001; Morsink et al., 2006; Sandi, 2004).

Although GR-mediated transcriptional activation is necessary for long-term synaptic changes in the hippocampus, studies have shown that genomic-independent actions of GRs rapidly control glutamate release and modulate synaptic transmission and plasticity (Groeneweg et al., 2011; Haller, Mikics, & Makara, 2008; Prager & Johnson, 2009; Tasker, Di, & Malcher-Lopes, 2006). In addition, several investigations provided evidence of genomic-independent

Please cite this article in press as: Finsterwald, C., & Alberini, C. M. Stress and glucocorticoid receptor-dependent mechanisms in long-term memory: From adaptive responses to psychopathologies. *Neurobiology of Learning and Memory* (2013), http://dx.doi.org/10.1016/j.nlm.2013.09.017