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Review

Stress modulation of hippocampal activity – Spotlight on the dentate gyrus

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ABSTRACT

The effects of stress on learning and memory are diverse, ranging from impairment to facilitation. Many studies emphasize the major role of the hippocampus, mainly its CA1 and CA3 areas, in the process of memory formation under emotional and stressful conditions. In the current review, we summarize work which suggests that the dentate gyrus (DG) of the hippocampus is likely to play a pivotal role in defining the impact of stress on hippocampal functioning. We describe the effects of stress on long term potentiation (LTP) and local circuit activity in the DG and the role of the amygdala in mediating these effects. As one of the brain regions known to have a high rate of adult neurogenesis, the effects of stress on DG neurogenesis will also be reviewed. Finally, we discuss exposure to stress during juvenility and its influence on the adult DG. The DG is a dynamic structure which is susceptible to stress. Under stressful conditions, its response is variable and complex, much like the behavioral outcomes of such circumstances. It is likely to significantly contribute to the diverse effects of stress on memory formation.

1. Introduction

Stress is not yet a well-defined concept (Koolhaas et al., 2011), but it has long been established that when facing a stressful challenge an organism will make the corresponding physiological/psychological responses in attempting to cope (Chrousos, 2009). Stress may be helpful and prepare an individual for the acute consequences of dangerous or threatening situations but it may also induce long-term negative outcomes (Habib, Gold, & Chrousos, 2001). Altered cardiovascular tone, immune-system suppression and changes of brain functions are often reported as adverse physiological effects of stress in humans and animals. Stress-induced alterations in learning and memory processes are also involved in the pathophysiology of stress-related disorders (de Kloet, Oitzl, & Joels, 1999; McEwen & Sapolsky, 1995).

The hippocampus is a medial temporal lobe structure that is thought to take on various roles: it is crucial for the formation of stable 'declarative' memory (Squire, 1992), it specializes in encoding spatial information (Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999) and it is an important regulator of emotion and particularly of the stress response (Herman, Ostrander, Mueller, & Figueiredo, 2005). The hippocampus contains an extremely high level of corticosteroid receptors (Chao, Choo, & McEwen, 1989; Van Eekelen, Jiang, De Kloet, & Bohn, 1988) and it is therefore particularly susceptible to stress hormones, which typically impair its function (Joels, Krugers, & Karst, 2008). Exposure to stress or stress hormones was shown to affect hippocampal synaptic plasticity, neurochemistry, neurogenesis, neural morphology and cell apoptosis (reviewed in Conrad, 2006, 2008; Herman & Seroogy, 2006; Joëls & Krugers, 2007; Joëls et al., 2004; Lucassen et al., 2006) as well as disrupt hippocampus-dependent memory performance (Conrad, 2009). Although most studies dealing with the effects of stress on hippocampal functioning describe impairments, it should be noted that some studies raise the possibility that under certain conditions stress may positively affect hippocampal functioning (for example, Kirby et al., 2013; Lyons et al., 2010). For instance, intermittent social separations and new pair formations increased hippocampal neurogenesis in squirrel monkey and enhanced hippocampal-dependent spatial learning performance (Lyons et al., 2010).

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While most studies concerned with the effects of stress on hippocampal functioning focused on the CA1 and CA3 fields of the hippocampus proper, the DG received much less attention with regards to this subject. The DG is typically considered to have a key role in the encoding of spatial and contextual information, particularly in pattern separation and novelty detection (Kesner, 2007, 2013; Xavier & Costa, 2009). In recent years, the DG is also increasingly associated with affective regulation and pathophysiology of mood disorders. For instance, in a recent study Kheirbek et al. (2013) showed that elevating the activity in granule cells in the ventral DG (but not the dorsal DG) suppresses innate anxiety. In addition, abundant evidence points to a link between neurogenesis in the DG and exposure to stress and stress hormones. Acute and chronic stress as well as corticosterone treatment typically suppress neurogenesis of DG granule neurons (reviewed in Schoenfeld & Gould, 2012) while treatment with antidepressants can increase the level of granular cells in the DG under certain conditions (David et al., 2009). While evidence for functions of the DG gradually accumulates, many of the findings are still under active debate, particularly those concerning the DG's function in emotional processing.

In this review we summarize studies concerning the effects of stress on DG functioning. We evaluate the effects of stress on neural activity and plasticity, focusing on local circuit activity of DG interneurons and on long term potentiation (LTP). Since the amygdala has a central role in mediating the effects of stress on the DG, we also address the way in which it alters DG functioning under stressful conditions. Next, we address the effects of stress on neurogenesis and speculate their function in regulating the stress response. Finally, we discuss the effects of stress exposure in juvenility and its effects on DG functioning in adulthood.

The review focuses on the DG as an important brain region affected by and involved in response to stress. The focus on the DG is important because its contribution to stress and emotional responses has so far been underestimated. However, it is also important to note that stress affects many brain regions and that in the end it is the circuitry and network activity that is altered by stress and that affects the phenotype. While a spotlight on the special role of the DG in this respect is important, it should be stated that in order to understand the effects of stress on an individual it would be important to "zoom out" again and study the connectivity and function of different brain networks as a whole, but with the DG as an important part of that network view.

2. An overview of DG

The DG region of the hippocampal formation receives the hippocampus's major excitatory input from the cortex and subcortical areas, such as the amygdala. Cortical and subcortical projections converge within the entorhinal cortex which then projects to the DG, thus establishing it as the main gateway of information into the hippocampus.

The DG is composed of three layers: molecular, granular, and polymorphic. The molecular layer is the outermost layer and is relatively cell free. It mainly contains the dendrites from the principal dentate neurons and axons that originate from the perforant path, arising from the entorhinal cortex. The second and main cell layer is the granule cell layer, which is made up largely of densely packed granule cells. The third layer is the polymorphic cell layer or the hilus which contains a number of cell types, in which the most prominent are the mossy cells (Amaral, Scharfman, & Lavenex, 2007).

The principal cells of the hippocampus, the granule cells, are excitatory cells that extend their dendrites through the molecular layer and are covered with spines. The dendrites of granule cells receive input from the entorhinal cortex which represents the majority of excitatory synapses on granule cell dendritic arbors. The output of granule cells is formed by distinctive unmyelinated axons called mossy fibers. They pass through the mossy cells of the polymorphic layer to their final target, the CA3 pyramidal cells of the hippocampus (Amaral et al., 2007).

Another type of excitatory hippocampal cell is the mossy cells which reside in the polymorphic layer. These glutamatergic cells have extensive dendritic arbors within the polymorphic layer and could be activated by granular cells (Scharfman, Kunkel, & Schwartzkroin, 1990), but occasionally their dendrites can also be found in the molecular layer, which suggests that they also receive inputs from the peforant path. The vast majority of mossy cells target DG granular cell dendrites. The axons of mossy cells are also sent to contralateral DG to form commissural projection while some synaptic contacts of mossy cells are also found on dendrites of interneurons in the polymorphoc layer (Ribak, Seress, & Amaral, 1985).

Various interneurons have been identified in the rat hippocampal formation (a detailed overview of the characteristics of the various hippocampal interneurons can be found in Freund & Buzsaki, 1996), most of which are gamma-aminobutyric acid-ergic (GABAergic). These interneurons can further be divided into subtypes according to neuropeptide biomarkers that coexist with GABA, such as parvalbumin, somatostatin, neuropeptide Y and cholecystokinin. Another way to subdivide these interneurons is according to their morphology (basket cell, stellate cell, fusiform cell) and physiological properties (fast or slow-spiking). These interneurons innervate principal cells or other interneurons inside and outside of the DG. In addition, these interneurons also have axon terminals associated with the perforant pathway or the DG commissural pathway (Buckmaster & Schwartzkroin, 1995; Ribak & Seress, 1983; Sik, Penttonen, & Buzsaki, 1997). There is also evidence that commissural fibers from contralateral DG directly activate interneurons of the DG and form feed-forward inhibitory modulation on granule cells (Ribak et al., 1986).

The effects of stress on inhibitory interneuron activity and on the interaction between interneurons and principle neurons will be further discussed in Sections 3.2 and 6 of this review.

3. The effects of stress on DG LTP induction and local circuit activity

3.1. The effects of stress on LTP induction

Exposure to stress causes modifications of plasticity in the hippocampus (Diamond, Fleshner, Ingersoll, & Rose, 1996; Foy, Stanton, Levine, & Thompson, 1987; Garcia, 2002; Kim, Foy, & Thompson, 1996). One such form of plasticity, repeatedly shown to be affected by stress and widely associated with learning and memory processes, is long-term potentiation (LTP) of reactivity to afferent stimulation (Bliss & Lomo, 1973). Many studies have shown that stress affects hippocampal subregions differentially. While Exposure to stress was constantly shown to impair LTP in CA1 field of the hippocampus (Foy et al., 1987; Kavushansky, Vouimba, Cohen, & Richter-Levin, 2006; Kim & Diamond, 2002; Pavlides, Ogawa, Kimura, & McEwen, 1996; Shors, Seib, Levine, & Thompson, 1989), reports about stress effects on LTP in the DG are much less consistent.

Much like CA1 LTP, several studies have shown impairment in DG LTP induction following exposure to both acute and chronic stress (Alfarez et al., 2003; Shors & Dryver, 1994; Wang, Akirav, & Richter-Levin, 2000) or corticosterone (CORT) administration (Pavlides, Watanabe, & McEwen, 1993). For example, by using an unpredictable stress paradigm for 21 days, including immobilization,

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