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Review

The impact from the aftermath of chronic stress on hippocampal structure and function: Is there a recovery?

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ABSTRACT

Chronic stress results in functional and structural changes to the brain and especially the hippocampus. Decades of research have provided insights into the mechanisms by which chronic stress impairs hippocampal-mediated cognition and the corresponding reduction of hippocampal CA3 apical dendritic complexity. Yet, when chronic stress ends and time passes, which we refer to as a "post-stress rest period," hippocampal-mediated spatial memory deficits begin to improve and CA3 apical dendritic arbors increase in complexity. The processes by which the hippocampus improves from a chronically stressed state are not simply the reversal of the mechanisms that produced spatial memory deficits and CA3 apical dendritic retraction. This review will discuss our current understanding of how a chronically stressed hippocampus improves after a post-stress rest period. Untangling the mechanisms that allow for this post-stress plasticity is a critical next step in understanding how to promote resilience in the face of stressors.

1. Introduction

In this article we discuss the growing field of research investigating the ability of the adult rodent brain to display plasticity in the aftermath of chronic stress. The main goal of our review is to elucidate the mechanisms that allow for chronic stress-induced spatial ability and hippocampal CA3 dendritic retraction to show improvements following the end of stress. We also contend that these improvements do not necessarily constitute a "recovery" or a return to baseline functioning, but instead point to the concept that these changes may represent a more resilient phenotype under certain circumstances. Finally, studying the improvements in brain structure and function following the end of chronic stress may have important implications for stress-related mental disorders, and here we highlight major depressive disorder as one disease that can be better understood by investigating the post-stress rest period.

2. Why study chronic stress and its aftermath on the hippocampal structure and function?

Major depressive disorder (MDD) is a multifaceted mental disorder that affects a significant percentage of the population. Depression is one of the leading causes of disability worldwide (W.H. Organization, 2015) with approximately 20% of adults in the United States demonstrating symptomology for MDD (Kessler and Bromet, 2013). The symptoms of MDD include feelings of sadness, emptiness, or hopelessness, loss of interest or pleasure, significant changes in weight or diet, insomnia, psychomotor agitation, fatigue, and feelings of worthlessness; MDD involves drastic changes in affect and cognition (A.P. Association, 2013). Patients with MDD are at risk for other adverse health outcomes with higher than average co-morbidity for diabetes mellitus, heart disease, and stroke (Whooley and Wong, 2013). Furthermore, MDD commonly reoccurs with approximately 80% of patients experiencing at least one recurrent episode of MDD in their lifetime, even after successful remittance (Otte et al., 2016). More striking is that approximately 30% of MDD patients fail to respond to treatments (Rush et al., 2006; Thase et al., 2007; Vos et al., 2004). While various therapies for MDD have existed for decades, the resistance to remission and the frequency of recurrence emphasize the need to identify novel therapies and treatments (Otte et al., 2016).

In preclinical work, MDD is difficult to mimic, due in part to the heterogeneous nature of the disorder. As such, animal models of MDD can be utilized to understand different neurobiological processes underlying specific symptoms. For example, administering chronic stress in rodents is a prevalent model currently utilized to study MDD, due in part to the findings that chronic stress can lead to depressive-like behaviors that can be reversed by antidepressants (Willner, 2005). Depressive-like behaviors assessed in rodents are thought to be a measure of hopelessness or anhedonia. In the forced swim test, the time an animal spends actively swimming versus passively floating in a tube filled

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with water is measured. Chronic stress leads to rodents spending less time actively swimming and more time floating, which is thought to reflect behavioral despair (Cryan et al., 2002; Nestler et al., 2002), although some disagreements with this interpretation exist (Nestler and Hyman, 2010). In the sucrose preference task, rats are given a choice of tap water or sucrose water. While rats tend to prefer sweets, chronically stressed animals will consume less sucrose compared to non-stress animals (Willner et al., 1987). In these tasks, anti-depressant medications can reverse the depressive-like phenotype, providing validity to use chronic stress in rodents as a model for some symptoms of MDD. Often, rodents will be tested on several tasks to obtain a depressive-like index. These are some of the reasons that chronic stress models can be useful in the study of various symptoms of MDD.

The hippocampus is one brain area commonly found to be altered in patients with MDD. The hippocampus is part of the limbic region and is involved in the formation of episodic and declarative memory (Scoville and Milner, 1957). Furthermore, the rich concentration of receptors for the stress hormones, called glucocorticoids (i.e., cortisol in humans, corticosterone in rodents), positions the hippocampus to be a major regulator of the hypothalamic-pituitaryadrenal (HPA) axis (McEwen et al., 1968; Sapolsky et al., 1984), but also makes the hippocampus sensitive to glucocorticoids. For individuals with MDD, the HPA axis is dysregulated (Knorr et al., 2010; Stetler and Miller, 2011) and the hippocampal volume is reduced (McKinnon et al., 2009; Kaymak et al., 2010) with accompanying hippocampal-mediated cognitive impairments (Vythilingam et al., 2004; Gotlib and Joormann, 2010; Trivedi and Greer, 2014). In rodents, chronic stress can produce similar outcomes. These include a dysregulation of the HPA axis (Joels et al., 2004; McEwen, 2007; Jankord and Herman, 2008) leading to a prolonged exposure to stress hormones (Sapolsky et al., 1984; Mizoguchi et al., 2003). Prolonged exposure to chronic stress or stress hormones leads to a reduction in the volume of the hippocampus (Tata and Anderson, 2010), especially through dendritic atrophy of the principle hippocampal neurons in the CA3 region (Conrad et al., 2017; Watanabe et al., 1992; Magarinos and McEwen, 1995a). Moreover, chronic stress produces poor hippocampal-dependent spatial ability (Kim and Diamond, 2002; Conrad, 2006; Conrad, 2010; Wright et al., 2006; Luine et al., 1994; Hoffman et al., 2011; Mika et al., 2012; Ortiz et al., 2014). Collectively, chronic stress in rodents can lead to many similar effects observed in patients with MDD. While no one animal model can capture the full milieu of MDD symptomology, chronic stress rodent models can be used to understand the contribution of changes in the hippocampus to the pathology of MDD.

Historically, chronic stress work has focused on the functional, structural, and molecular changes in the hippocampus of chronically stressed rodents in order to understand the potential changes in cognitive processing from patients with MDD. The preclinical literature derived from chronic stress in rodents has led to many insights about the mechanisms that produce poor hippocampal functioning. We know much about the factors by which chronic stress results in a pruning of dendritic arbors in the hippocampus (Watanabe et al., 1992), an outcome that coincides with spatial learning and memory deficits (Conrad, 2010). Eventually, hippocampal dendritic atrophy manifests, and it requires corticosterone, as hippocampal CA3 apical dendritic retraction occurs following chronic corticosterone administration (Woolley et al., 1990; Watanabe et al., 1992; Sousa et al., 2000; Ortiz et al., 2013) or is prevented by pharmacologically attenuating corticosterone secretion (Magarinos and McEwen, 1995b). In humans, patients who hypersecrete glucocorticoids due to Cushing's Syndrome show reduced hippocampal volumes (Starkman et al., 1992; Starkman, 2013) that appear to increase in volume after cortisol levels are normalized (Starkman et al., 1999). These findings show that chronic stress leads to reduced hippocampal volume and dendritic retraction through the actions of glucocorticoids.

Additional studies have identified important neurochemicals by which glucocorticoids lead to hippocampal dendritic retraction and reduced hippocampal volume. Excitatory pathways are critical because lesioning the main excitatory input into the hippocampus prevents stress-induced hippocampal CA3 dendritic atrophy (Sunanda et al., 1997). Moreover, antagonizing the excitatory NMDA receptor, which is a prominent glutamate receptor in the hippocampus, can also block stress-induced CA3 dendritic retraction (Magarinos and McEwen, 1995b; Christian et al., 2011). These findings corroborate the reports that chronic stress or prolonged corticosterone exposure skews the hippocampal tone towards hyperexcitability by enhancing glutamate neurotransmission (Joels et al., 2004) and increasing extracellular glutamate (Skorzewska et al., 2007) and mRNA for the glutamate transporter (Wood et al., 2004). Along these lines, enhancing hippocampal GABAergic activity via a benzodiazepine can also block chronic stress-induced dendritic retraction (Magarinos et al., 1999). The ability of the GABAergic agonists to block stress-induced dendritic retraction is probably a reflection of the counter-actions in response to the over-excitation from glutamate. Reports support these outcomes as chronic stress decreases the concentration of GABA in the hippocampus (Gronli et al., 2007) and decreases the expression of markers for GABAergic neurons in the hippocampus (Czeh et al., 2005; Milner et al., 2013; Czeh et al., 2015; Csabai et al., 2017). Serotonin is also involved because inhibiting serotonin re-uptake with fluoxetine or tianeptine, an atypical antidepressant, prevents chronic stress-induced hippocampal dendritic retraction (Watanabe et al., 1992; Magarinos et al., 1999; Conrad et al., 1999). Moreover, chronic stress appears to reduce the serotonin transporter expression in the hippocampus (McKittrick et al., 2000). A synopsis of these mechanisms by which chronic stress leads to hippocampal CA3 dendritic retraction is illustrated in Fig. 1.

Neurotrophins also contribute to the dendritic changes observed in the hippocampus in response to chronic stress. Brain derived neurotrophic factor (BDNF), a protein that is important for synaptic, morphological, and cognitive plasticity, impacts hippocampal CA3 dendritic retraction. In BDNF haploinsufficient mice in which BDNF is partially expressed, hippocampal dendritic complexity is reduced in the brains of unstressed mice. Moreover, the CA3 dendritic arbors of these mice are unresponsive to chronic stress, as the dendritic arbors are not further reduced after chronic stress (Magarinos et al., 2011). Interestingly, we observed a similar phenomenon in which hippocampal BDNF expression was downregulated using short-hairpin sequence (Fire et al.,

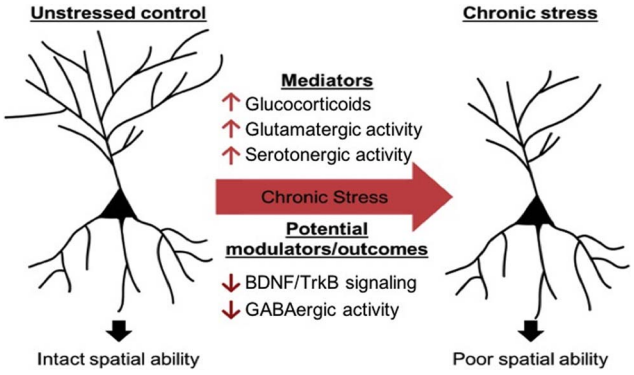

Fig. 1. Mechanisms of chronic stress-induced CA3 apical dendritic retraction and impact on spatial ability. Chronic stress leads to apical dendritic retraction in hippocampal CA3 pyramidal neurons with other subregions being impacted when chronic stress is sufficiently robust or long-lasting. The retraction of apical dendrites on CA3 neurons is thought to contribute to poor hippocampal function, which is seen consistently in response to chronic stress. There are many mediators of CA3 apical dendritic retraction, such as an increase in exposure to the stress hormones glucocorticoids, an increase in glutamatergic activity, and an increase in serotonergic activity. Furthermore, chronic stress leads to hippocampal reductions in BDNF and TrkB signaling and GABAergic activity. As such, these may also be potential modulators of the stress-induced reduction in hippocampal CA3 apical dendritic complexity. In contrast to the robust stress effects on CA3 apical dendrites, basal dendrites of CA3 neurons are largely unaffected by chronic stress and remain complex following most chronic stress paradigms.