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REVIEW

STRESS, ANXIETY, AND DENDRITIC SPINES: WHAT ARE THE CONNECTIONS?

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Abstract—Stressful life events, especially those that induce fear, can produce a state of anxiety that is useful for avoiding similar fearful and potentially dangerous situations in the future. However, they can also lead to exaggerated states, which over time can produce mental illness. These changing states of readiness versus illness are thought to be regulated, at least in part, by alterations in dendritic and synaptic structure within brain regions known to be involved in anxiety. These regions include the amygdala, hippocampus, and prefrontal cortex. In this article, we review the reciprocal relationships between the expression of stress- and anxiety-related behaviors and stress-induced morphological plasticity as detected by changes in dendrites and spines in these three brain regions. We begin by highlighting the acute and chronic effects of stress on synaptic morphology in each area and describe some of the putative mechanisms that have been implicated in these effects. We then discuss the functional consequences of stress-induced structural plasticity focusing on synaptic plasticity as well as cognitive and emotional behaviors. Finally, we consider how these structural changes may contribute to adaptive behaviors as well as maladaptive responses associated with anxiety.

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Key words: synapse, hippocampus, amygdala, prefrontal cortex, plasticity.

Contents

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Abbreviations: BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; BDNF, brain-derived neurotrophic factor; CRH, corticotropin-releasing hormone; HPA, hypothalamic–pituitary–adrenal; LTD, long term depression; LTP, long-term potentiation; mPFC, medial prefrontal cortex; tPA, tissue plasminogen activator.

INTRODUCTION

> ‘‘Patients with agoraphobia, a fear of open places, say they feel silly avoiding a place where they once had a panic attack. But if they are asked what the best response would be if years ago they had been attacked by a tiger at that spot, most quickly realize that a hundred false alarms would be worth a single escape from an attack.’’ (What good is feeling bad? Nesse, The Sciences, 1991).

Anxiety is a complex psychological process that often emerges after stressful life experiences. In some cases it is adaptive, because it prepares the organism for future stressful encounters. However, if prolonged or exaggerated over time, anxiety produces many abnormal and maladaptive thoughts and behaviors. Anxiety disorders are characterized by excessive fear, typically in response to specific objects or situations that do not pose or predict danger (Shin and Liberzon, 2010). They are prevalent in the general population with lifetime estimates at almost 30% (Kessler et al., 2005). Common symptoms of anxiety disorders include cognitive disturbance, rumination, poor concentration, and negative affect (Gualtieri and Morgan, 2008). Anxiety disorders are highly comorbid with depression and are associated with a variety of health problems, which may lead to the overall decrease in the quality of life experienced by anxious individuals (Hoffman et al., 2008). In addition, anxiety disorders represent a major economic burden because they impair performance in the workplace (Hoffman et al., 2008). As such, anxiety disorders are devastating in their personal, societal, and financial costs.

Like all psychiatric disorders, those that involve anxiety are complex, with a range of genetic, epigenetic, and environmental causes or triggers (Yehuda and LeDoux, 2007; McEwen et al., 2012). As noted, stressful life events are a major contributor, and clinical studies

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have consistently shown that traumatic or repeated stress precipitates or exacerbates the feelings and symptoms of anxiety (Pêgo et al., 2010; Shin and Liberzon, 2010). Similarly, one consequence of stress exposure in rodents is heightened anxiety (Cryan and Holmes, 2005; Pêgo et al., 2010). For example, animals exposed to repeated stressful events are less likely to explore a novel environment (Kabbaj et al., 2000). Although it is difficult to exactly reproduce the myriad of symptoms and feelings in humans, those afflicted with social phobia or generalized anxiety disorder, for example, are also reluctant to explore new places and relationships especially if they are currently experiencing stressful interactions in their everyday lives. These avoidant responses can disrupt their daily living to the point where they become even more alone, more dysfunctional, and consequently more anxious.

Many brain regions acting in concert mediate the symptoms of anxiety, both normal and abnormal. However, some regions such as the hippocampus, prefrontal cortex, and amygdala, seem to be preferentially involved (Fig. 1) (Canteras et al., 2010). Each of these areas has been associated with the neurocircuitry of anxiety in humans (Mathew et al., 2008; Shin and Liberzon, 2010; Kim et al., 2011). Laboratory experiments in animal models have confirmed their roles in fear and/or anxiety regulation (LeDoux, 2003; Adhikari et al., 2010; Davis et al., 2010; Fanselow and Dong, 2010). The hippocampus, prefrontal cortex, and amygdala also critically participate in orchestrating the hypothalamic–pituitary–adrenal (HPA) axis response to stress (Ulrich-Lai and Herman, 2009; Radley and Sawchenko, 2011), which can be abnormal in individuals with anxiety (Mathew et al., 2008). In addition, these brain regions are involved in various cognitive processes influenced by stress and associated with anxiety (McLaughlin et al., 2009; Bangasser and Shors, 2010; Campeau et al., 2011).

The mechanisms which govern the immediate response to a stressful event and maintain the state of anxiety over some extended period likely include neuromorphological changes in the hippocampus, prefrontal cortex, and amygdala (Gorman and Docherty, 2010). Neurons in these regions are highly plastic and undergo dramatic transformations often in an activity- and experience-dependent manner (Holtmaat and Svoboda, 2009; Leuner and Gould, 2010). Dendritic branches extend or retract and on these dendrites, small protrusions called spines, emerge, disappear, or change in shape and size. The numbers of spines are thought to reflect the amount of connectivity between neurons and because spines are sites of glutamatergic synapses, they can regulate the amount of excitatory neurotransmission in a particular brain region. Not only can the overall density of spines impact connectivity and neuronal excitability but so can spine stability and morphology – small, thin spines are motile, transient, and form weaker synapses, whereas large, mushroom spines are more stable and form strong synapses with larger postsynaptic densities, more AMPA receptor content, and a larger presynapse (Kasai et al., 2003). Since some of these changes occur on the order of seconds and minutes, they provide a substrate for responding rapidly to the environment and all the potential dangers it can present. Thus, dendrites and spines are crucial components for inducing immediate and long-term changes in synaptic function, synaptic plasticity, and patterns of connectivity (Bosch and Hayashi, in press; Kulkarni and Firestein, 2012; Tavosanis, 2012). In this way, stress-induced structural plasticity may contribute to the expression of adaptive anxiety-related behaviors as well as maladaptive behaviors characteristic of anxiety disorders that can arise in select individuals.

Here, we review the effects of stress on dendrites and dendritic spines in the hippocampus, prefrontal cortex, and amygdala and discuss some of the mediators underlying these effects. We also consider how structural changes may contribute to the expression of normal, presumably adaptive stress-related behavioral functions as well as maladaptive responses associated with anxiety. Together, these findings identify structural plasticity,

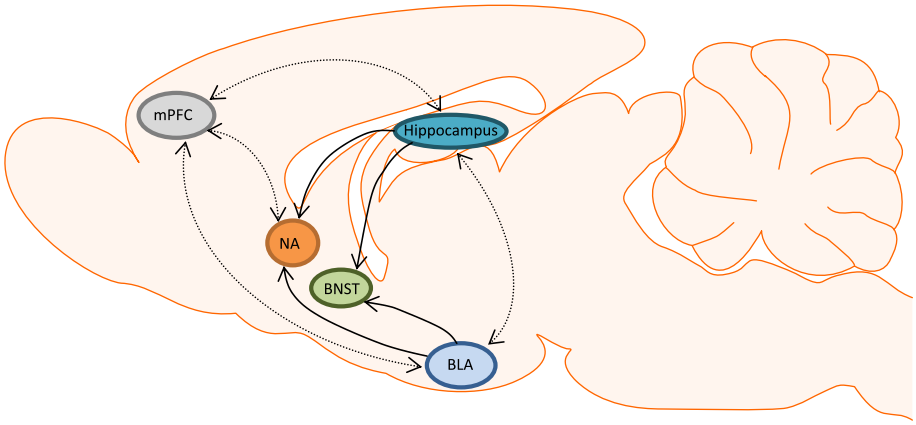

Fig. 1. The neural circuitry affected by stress. A sagittal slice of the rat brain showing the hippocampus, medial prefrontal cortex (mPFC), basolateral amygdala (BLA), bed nucleus of the stria terminalis (BNST), and nucleus accumbens (NA) as well as their direct connections. Neurons in these brain regions undergo structural modifications in response to stressful experience which are thought to contribute to the expression of stress- and anxiety-related behaviors.