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Research article

Spine synapse remodeling in the pathophysiology and treatment of depression

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ABSTRACT

Clinical brain imaging and postmortem studies provide evidence of structural and functional abnormalities of key limbic and cortical structures in depressed patients, suggesting that spine synapse connectivity is altered in depression. Characterization of the cellular determinants underlying these changes in patients are limited, but studies in rodent models demonstrate alterations of dendrite complexity and spine density and function that could contribute to the morphological and functional alterations observed in humans. Rodent studies demonstrate region specific effects in chronic stress models of depression, including reductions in dendrite complexity and spine density in the hippocampus and prefrontal cortex (PFC) but increases in the basolateral amygdala and nucleus accumbens. Alterations of spine synapse connectivity in these regions are thought to contribute to the behavioral symptoms of depression, including disruption of cognition, mood, emotion, motivation, and reward. Studies of the mechanisms underlying these effects demonstrate a role for altered brain derived neurotrophic factor (BDNF) signaling that regulates synaptic protein synthesis. In contrast, there is evidence that chronic antidepressant treatment can block or reverse the spine synapse alterations caused by stress. Notably, the new fast acting antidepressant ketamine, which produces rapid therapeutic actions in treatment resistant MDD patients, rapidly increases spine synapse number in the PFC of rodents and reverses the effects of chronic stress. The rapid synaptic and behavioral actions of ketamine occur via increased BDNF regulation of synaptic protein synthesis. Together these studies provide evidence for a neurotophic and synaptogenic hypothesis of depression and treatment response and indicate that spine synapse connectivity in key cortical and limbic brain regions is critical for control of mood and emotion.

1. Introduction

Major depressive disorder (MDD) is a devastating illness that affects approximately 17% of the population in the United States causing enormous personal and economic consequences [53]. Moreover, the currently available monaminergic antidepressants have significant limitations, including slow onset of action and low response rate [109]. Despite extensive efforts there have been no new therapeutic medications with novel mechanisms, in part due to the heterogeneity and complexity of depression. Therefore, rational drug design is not possible without a more complete understanding of the underlying pathophysiology of depression.

Nevertheless, there has been significant progress from clinical and preclinical studies that have provided evidence that depression is associated with loss of neurotrophic factor support that leads to atrophy of neurons and reduced connectivity [23,24]. Clinical brain imaging and postmortem studies demonstrate structural and functional alterations of several limbic and cortical regions in MDD, including the prefrontal cortex (PFC), hippocampus, cingulate cortex, amygdala, and basal ganglia [75,99]. These studies demonstrate decreased function and atrophy of certain brain regions, including the PFC and hippocampus, but increased function and altered morphology of other regions, including the subcallosal cingulate and amygdala. Altered connectivity of these regions could contribute to the symptoms of depression, in part via reduced function of the PFC (e.g., decreased reaction time and cognitive function), and increased function of the amygdala (loss of control of emotion and mood, and increased fear, anxiety and hypothalamic-pituitary-adrenal axis reactivity). Altered function and connectivity of PFC and the ventral striatum could also underlie reduced motivation and reward in MDD.

The most consistent structural and functional alterations have been observed in the PFC and hippocampus, where reduced volume is inversely correlated with length of illness, time of treatment, and

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severity of depression [22,67]. There is limited evidence from postmortem studies demonstrating decreased neuronal cell body size and atrophy of dendritic processes, although there is one report of decreased synapse number in a small cohort of depressed subjects [47]. Additional postmortem studies are needed to confirm and further characterize the synaptic alterations in MDD as well as related illnesses (e.g., psychotic depression) that could also involve disruption of synaptic connections. However, detailed studies of preclinical models of depression have provided extensive evidence demonstrating that chronic stress causes alterations of the density and function of spine synapses in key limbic and cortical brain regions implicated in depression. Here, we provide a review of this literature, as well the mechanisms underlying the regulation of spine synapses by stress. In addition, we discuss the opposing effects of antidepressant treatments, notably novel rapid acting agents that increase spine synapses in the PFC and the functional consequences of these changes.

2. Spine structure and function

The small protrusions of the dendritic surface referred to as "spines" are the principal site of most cortical excitatory synapses. The existence of spines greatly increases the surface area available for synaptic transmission, allowing for a high density of synaptic connections onto individual dendrites and neurons [84]. In addition to providing a physical substrate for synapse formation, the spine

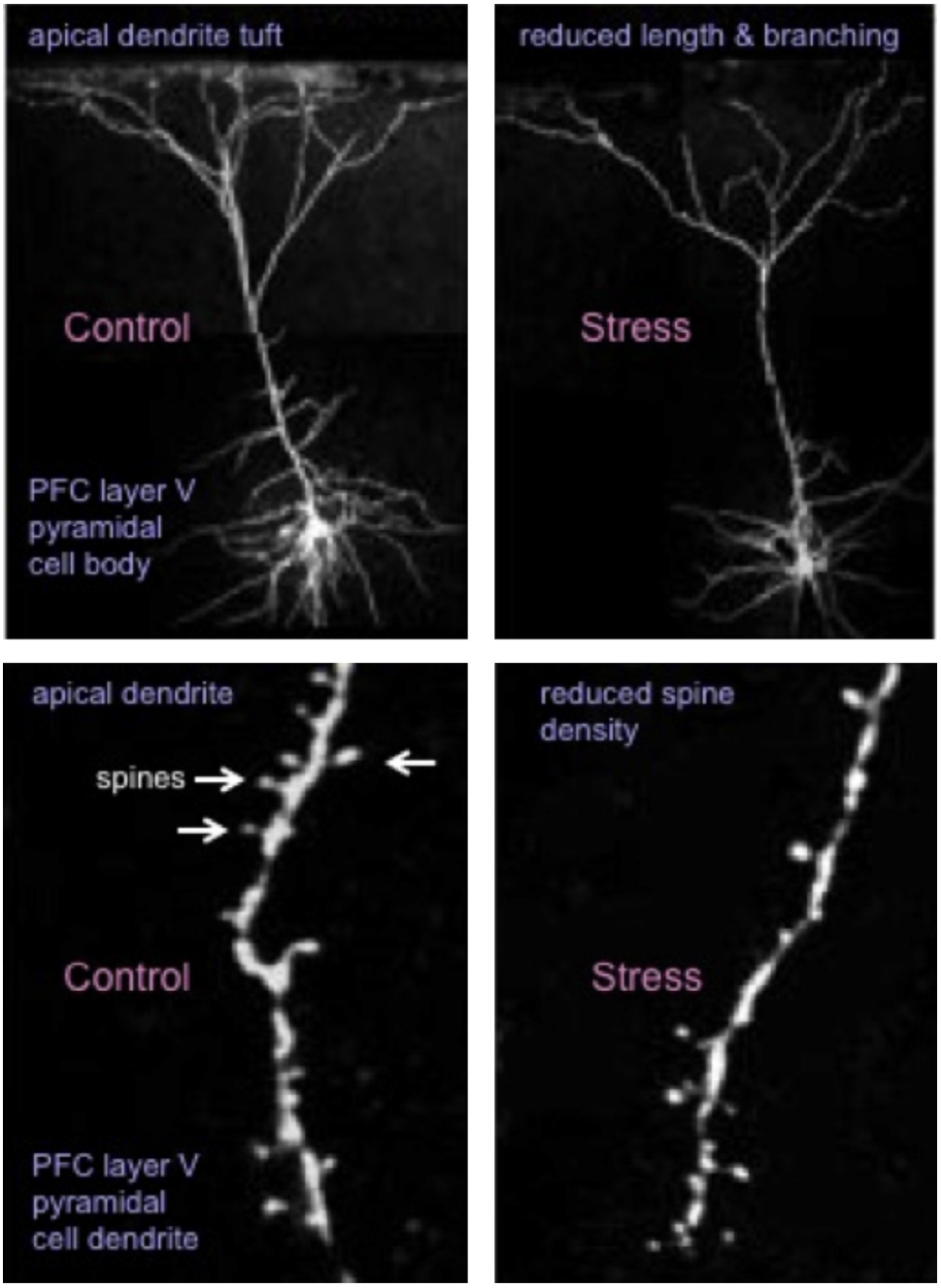

Fig. 1. Chronic stress causes atrophy of layer V pyramidal neurons in the medial PFC.
Shown is the influence of repeated restraint stress (30 min per day for 7 d) on layer V pyramidal neurons in the medial PFC. The upper panels demonstrate that effects of stress on the length and branching of apical dendrites, and the lower panels show the effects of stress on the density of spines on apical dendrites of labeled layer V neurons. Neurobiotin labeled neurons were visualized by two-photon laser scanning miscrocopy (see Liu and Aghajanian [62]).