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BRAIN RESEARCH

Focused Review

Stress-induced dendritic remodeling in the medial prefrontal cortex: Effects of circuit, hormones and rest

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ABSTRACT

The medial prefrontal cortex (mPFC) has been implicated as a site of dysfunction and abnormal morphology in major depressive disorder and post-traumatic stress disorder, two illnesses that can be brought on by exposure to stress. In animal models, stress has long been shown to induce impairments in tasks known to be mediated by the mPFC, and recent work has demonstrated that chronic stress can lead to morphological changes in mPFC pyramidal cells. This review explores the current literature on stress-induced dendritic remodeling in the mPFC, with particular focus on new findings that illuminate modulators of these effects.

1. Introduction

Stressful experiences can precipitate or exacerbate mental illnesses such as major depressive disorder (MDD; Lechin et al., 1996) and post-traumatic stress disorder (PTSD; Turner and Lloyd, 2004), but the mechanisms by which the effects of stress contribute to the development of clinical pathologies are not well understood. Both post-mortem and functional imaging studies of patients with these disorders implicate the medial prefrontal cortex (mPFC) as a site of abnormal structure and function, suggesting a potential vulnerability to stress in this region. Specifically, the brains of suicide victims–who are likely to be depressed (Hovanesian et al., 2009)–are reported to have decreased neuron and glia density compared to healthy controls (Rajkowska et al., 2001), and mPFC activity is suppressed in patients with MDD (Liberzon and Phan, 2003; Pizzagalli et al., 2004). Common symptoms of MDD and PTSD–rumination, poor concentration and negative affect, for example–also suggest mPFC dysfunction (Arnsten, 1998). Together, these findings identify the mPFC as a key player in the manifestation of stress-related mental illnesses, and an understanding of the effects of stress in this region will be critical to our progress toward better treatments.

2. Stress-induced dendritic remodeling in the mPFC

Though the mechanisms by which stress exposure can lead to clinical pathology are not clear, much work has been done in animals in an attempt to identify possible contributing factors. Animal models of chronic stress commonly involve subjecting an animal to daily restraint or immobilization, a regimen that has been reliably shown to activate the hypothalamic–pituitary–adrenal (HPA) axis, induce corticosterone release and cause morphological changes in several brain regions (reviewed in McEwen, 1999). In the rat mPFC, repeated restraint stress can cause retraction of the apical dendritic

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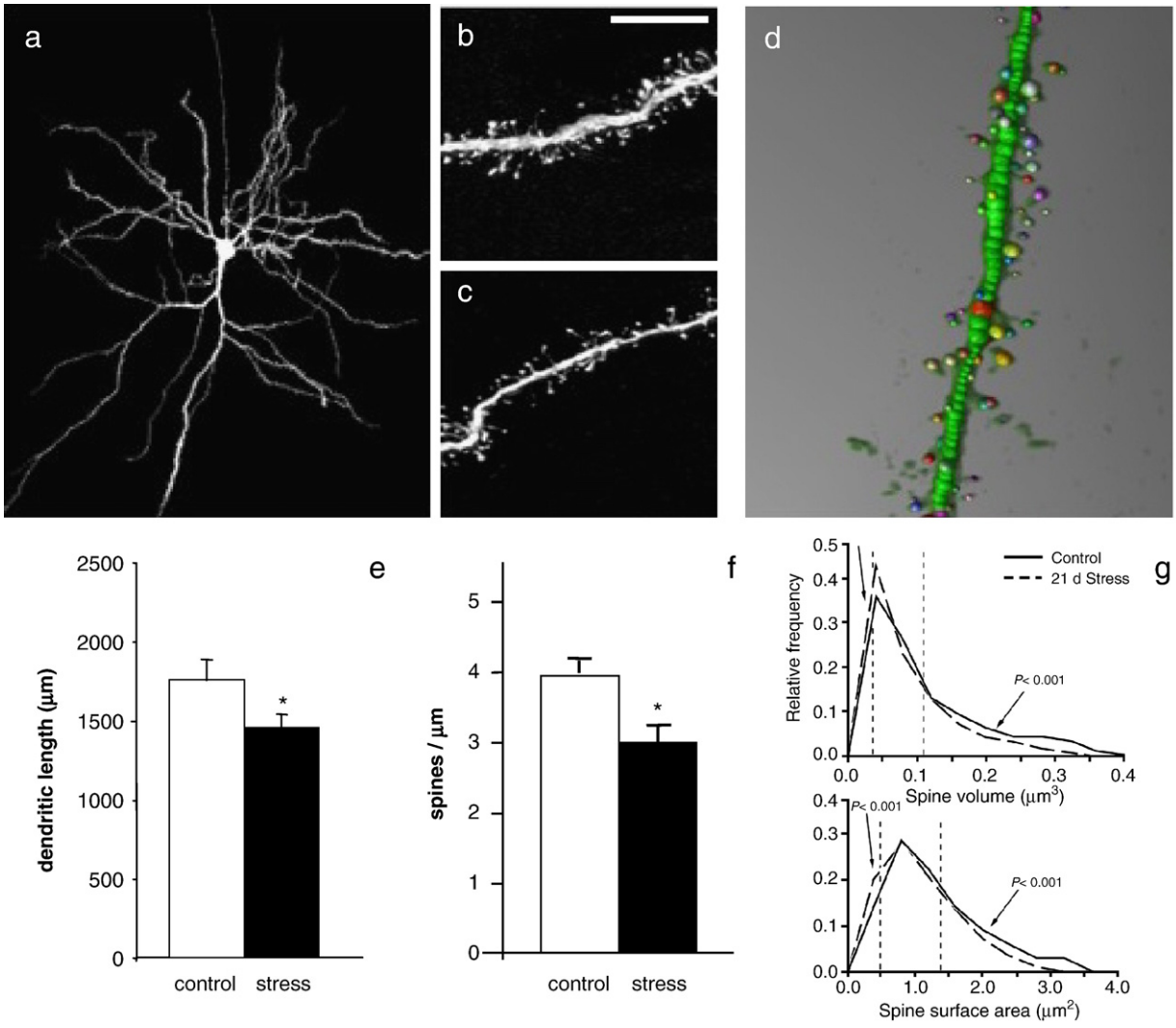

Fig. 1 – Chronic restraint stress causes dendritic remodeling in mPFC dendrites and spines. (a) A layer II/III pyramidal mPFC neuron filled with Lucifer Yellow to allow for dendrite visualization. (b and c) Dendrite segments from control and stress groups, demonstrating spine loss. (d) NeuronStudio software re-construction of a dendritic segment, demonstrating spine size measurements. (e and f) 21 days restraint stress causes significant decrease in total apical dendrite length and in spine density. (g) Chronic restraint stress also causes a shift in spine size, with dendrites exhibiting a smaller percentage of large spines. Adapted from Radley et al. (2004, 2006, 2008). *$p<0.05$.

arbor in layer II/III pyramidal cells, an effect that has been demonstrated in the anterior cingulate (AC), prelimbic (PL; Izquierdo et al., 2006; Radley et al., 2004) and infralimbic (IL; Shansky et al., in press) subregions (Fig. 1). These changes in dendritic length have been shown to be accompanied by impairments in cognitive tasks selectively mediated by the mPFC while sparing non-mPFC-specific abilities (Liston et al., 2006), suggesting that stress-induced remodeling in the mPFC may have distinct functional consequences.

In addition to dendritic length changes, chronic stress has been shown to induce alterations in mPFC spines on the same neuronal populations that exhibit dendritic remodeling. In the AC and PL, spine density is reduced by 16% in chronically stressed animals (Fig. 1), which, when combined with the decrease in dendritic arborization, translates into a 30% loss of spines on each neuron (Radley et al., 2006). Recent data suggest that spine morphology, e.g. size, may be a critical reflection of a capacity for synaptic plasticity (Kasai et al., 2003); thus in addition to an overall spine number, it is important to determine which spine classes are preferentially affected. More specifically, it has been proposed that small spines are highly motile and transient, capable of expansion and consolidation under certain circumstances or retraction, while large spines are viewed as more stable and likely to mediate long-term well established neural networks (Kasai et al., 2003). A recent analysis of spine volume and surface area in the mPFC neurons affected by stress revealed that the spine loss can be accounted for primarily by a reduction in large (>1.0 μm^2 and/or >0.2 μm^3) spines (Radley et al., 2008) (Fig. 1). Since it is unlikely that these large stable spines would retract with stress, this shift in the size profile of spines was interpreted as a reflection of a decreased capacity for the maturation and stabilization of small spines into large stable spines (Radley et al., 2008). This selective decrease in large