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REVIEW

DYNAMIC PLASTICITY: THE ROLE OF GLUCOCORTICOIDS, BRAIN-DERIVED NEUROTROPHIC FACTOR AND OTHER TROPHIC FACTORS

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Abstract—Brain-derived neurotrophic factor (BDNF) is a secreted protein that has been linked to numerous aspects of plasticity in the central nervous system (CNS). Stress-induced remodeling of the hippocampus, prefrontal cortex and amygdala is coincident with changes in the levels of BDNF, which has been shown to act as a trophic factor facilitating the survival of existing and newly born neurons. Initially, hippocampal atrophy after chronic stress was associated with reduced BDNF, leading to the hypothesis that stress-related learning deficits resulted from suppressed hippocampal neurogenesis. However, recent evidence suggests that BDNF also plays a rapid and essential role in regulating synaptic plasticity, providing another mechanism through which BDNF can modulate learning and memory after a stressful event. Numerous reports have shown BDNF levels are highly dynamic in response to stress, and not only vary across brain regions but also fluctuate rapidly, both immediately after a stressor and over the course of a chronic stress paradigm. Yet, BDNF alone is not sufficient to effect many of the changes observed after stress. Glucocorticoids and other molecules have been shown to act in conjunction with BDNF to facilitate both the morphological and molecular changes that occur, particularly changes in spine density and gene expression. This review briefly summarizes the evidence supporting BDNF's role as a trophic factor modulating neuronal survival, and will primarily focus on the interactions between BDNF and other systems within the brain to facilitate synaptic plasticity. This growing body of evidence suggests a more nuanced role for BDNF in stress-related learning and memory, where it acts primarily as a facilitator of plasticity and is dependent upon the coactivation of glucocorticoids and other factors as the determinants of the final cellular response.

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Key words: hippocampus, amygdala, glucocorticoids, BDNF, stress.

Contents

INTRODUCTION

The identification of brain-derived neurotrophic factor (BDNF), a protein isolated from the brain that supports neuronal survival both *in vitro* (Lindsay et al., 1985) and *in vivo* (Hofer and Barde, 1988), was a breakthrough whose impact is continuing to expand. Since it was first purified (Barde et al., 1982), BDNF has accumulated over 10,000 publications as new functions continue to be discovered. This review will focus on the role of BDNF in neuroplasticity in response to stress, and how glucocorticoids (GC) as well as other molecules work in

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Abbreviations: ACTH, adrenocorticotropic hormone; BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; CA, cornu ammonis; CE, central nucleus; CORT, corticosterone; CREB, cAMP response element-binding protein; CRH, corticotrophin-releasing hormone; ERK, extracellular signal-regulated protein kinase; FST, forced swim test; GC, glucocorticoids; GR, glucocorticoid receptor; ir, immunoreactivity; Lcn2, lipocalin-2; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; MR, mineralocorticoid receptor; NMDA, N-methyl-D-aspartic acid; $p75^{NTR}$, p75 neurotrophin receptor; PI3K, phosphoinositide 3-kinase; PFC, prefrontal cortex; PLCγ, phospholipase Cγ; PNNs, peri-neuronal nets; ptrkB, phosphorylated trkb; PVN, paraventricular nucleus of the hypothalamus; SSRIs, selective serotonin reuptake inhibitors; tPA, tissue plasminogen activator; TrkB, tropomyosin-related kinase B; Val66Met, valine to methionine change at position 66; WT, wild type.

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conjunction with BDNF to facilitate changes in neural connectivity.

Chronic stress has numerous pathological effects in males that can vary by brain region, but have been most well-documented in the hippocampus, prefrontal cortex (PFC), and amygdala. In the hippocampus, stress has been associated with decreases in overall size, reduced numbers of new neurons (Gould et al., 1997), such as GABAergic parvalbumin-containing interneurons (Czeh et al., 2005; Hu et al., 2010), reduced dendritic branching, and decreases in spine density [reviewed (McEwen, 1999)]. Similar changes in dendritic branching and spine density have been observed in the PFC [reviewed (Holmes and Wellman, 2009)], whereas in the amygdala, opposite effects are observed, resulting in increases in dendritic length and spine density (Vyas et al., 2002; Mitra et al., 2005). In the hippocampus and amygdala, stress-induced changes can be replicated by the chronic administration of GCs, which mimic the elevation of cortisol that occurs during activation of the hypothalamic/pituitary/adrenal axis in response to stress (McEwen, 1999; Mitra and Sapolsky, 2008). However, recent work has also suggested that elevation of cortisol prior to an acute stress can be protective of stress-induced changes in the amygdala (Rao et al., 2012). Together these results show that the effects of GC elevation can vary depending on brain region, duration of treatment, and relation to other stressors, suggesting that other factors in the brain help to mediate the effects of GCs.

These changes in the hippocampus in response to stress led to the formulation of the ''neurotrophic hypothesis'' of mood disorders, which postulated that depression and anxiety arose from a lack of trophic support in specific brain regions, and by reversing this deficit symptoms could be ameliorated (Duman et al., 1997; Nestler et al., 2002). Research into the neurotrophic hypothesis has focused on BDNF as a primary factor. Initial studies showed reductions in BDNF in the hippocampus after acute and chronic stress that, in the dentate, could be replicated by corticosterone (CORT) administration (Smith et al., 1995b). Studies of post-mortem brain have shown reductions in BDNF in the hippocampus (Dwivedi et al., 2003; Karege et al., 2005; Dunham et al., 2009) and PFC (Karege et al., 2005) of depressed patients. Alternatively, either no change or increases in BDNF have been observed in patients treated with antidepressants (Chen et al., 2001). In rodents, direct infusion of BDNF has been shown to increase neurogenesis in the hippocampus (Scharfman et al., 2005). Further, the administration of antidepressants to rodents can increase BDNF expression in the hippocampus (Nibuya et al., 1995) and prevent stress-induced changes (McEwen et al., 1997). However, work from this lab (Kuroda and McEwen, 1998) and others (Isgor et al., 2004) have not consistently identified reductions in BDNF mRNA after chronic stress, suggesting that the hippocampal atrophy observed cannot simply be explained as decreased neurogenesis resulting from decreased BDNF. These data, as well as more recent studies showing that BDNF levels in CA3 return to baseline after recovery from either an acute or chronic stressor (Lakshminarasimhan and Chattarji, 2012), suggest that hippocampal BDNF levels are highly dynamic. This review seeks to characterize the complex interplay between fluctuating GC and BDNF levels as they relate to structural and functional changes in the brain in response to stress.

LOCALIZATION AND ACTIVATION OF BDNF AND ITS RECEPTORS

BDNF is initially translated as a precursor protein (proBDNF) that is proteolytically cleaved to form mature BDNF (Seidah et al., 1996; Lu, 2003). Mature BDNF functions by binding primarily to tropomyosin-related kinase B (TrkB) receptors to activate several intracellular signaling pathways, including mitogen-activated protein kinase/extracellular signal-regulated protein kinase (MAPK/ERK), phospholipase Cγ (PLCγ), and phosphoinositide 3-kinase (PI3K)(Huang and Reichardt, 2003). ProBDNF preferentially binds the low-affinity p75 neurotrophin receptor ($p75^{NTR}$) to activate a distinct signaling cascade that can have the opposite downstream effects of TrkB (Lee et al., 2001; Woo et al., 2005).

Binding of BDNF to the extracellular domain of TrkB initiates dimerization of the receptor. This dimerization causes autophosphorylation of tyrosine residues at the intracellular kinase domain, thereby inducing activation of the 3 intracellular signaling cascades (MAPK/ERK, PLCγ, and PI3K). Phosphorylation of TrkB can be rapidly induced by antidepressant drugs, and activation of the receptor is believed to be required for the antidepressant-like behavioral effects (Saarelainen et al., 2003). Recent reports have shown that GCs can induce TrkB phosphorylation in neuronal cells, independent of neurotrophin levels (Jeanneteau et al., 2008). However, BDNF and GCs can also regulate the release of corticotrophin-releasing hormone (CRH) (Jeanneteau et al., 2012). These findings, along with others discussed below, suggest a more complex role for the BDNF system, where downstream targets such as TrkB are activated by GCs or other trophic factors independent of ligand.

Both BDNF and TrkB receptor mRNA are highly expressed throughout the brain, even in non-neurogenic regions such as the PFC (Hofer et al., 1990; Klein et al., 1990; Lein et al., 2007). Immunoreactivity (ir) for BDNF is present in both hippocampus and amygdala, with CA3 and dentate gyrus particularly enriched (Conner et al., 1997). Not only was labeling evident in cell bodies, but also in processes where little mRNA had been previously detected, suggesting active transport of BDNF protein within neurons (Conner et al., 1997). Generation of a transgenic mouse model expressing BDNF fused to a HA-tag has facilitated improved visualization of BDNF protein levels using immunohistochemical methods directed at the tag (Yang et al., 2009). Our work with this animal has confirmed that high levels of BDNF-HA-ir are present in the