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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.

Keywords

hippocampus; amygdala; glucocorticoids; BDNF; stress

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 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 C γ (PLC γ), 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, PLC γ , 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 hippocampal mossy fiber pathway (Fig. 1A). Moreover, BDNF-HA-ir is found in hippocampal pyramidal cells (Fig. 1A) and in cell processes in the amygdala (Fig. 1B). Ultrastructural studies have confirmed BDNF is localized to terminals in the central nucleus (CE) of the amygdala (Agassandian et al., 2006).

Within the hippocampus, immunoreactivity for the full length TrkB receptor is in pyramidal and granule cells and in select interneurons (Drake et al., 1999). Ultrastructurally, full-length TrkB-ir is in terminals, glia, and is dense in axon initial segments, suggesting it is extensively involved in receptor trafficking (Fig. 2A–C) (Drake et al., 1999). Immunoreactivity for TrkB phosphorylated at tyrosine 816 (pTrkB) has a similar distribution, but is particularly dense in the CA1 and the subgranular zone of the dentate gyrus (Fig. 1C) (Spencer et al., 2008). Ultrastructurally, pTrkB-ir is prominent in axons and terminals but it is also found in dendritic shafts, spines and glial processes (Fig. 2D–F) (Spencer-Segal et al., 2011). In the amygdala, TrkB-ir is primarily present in CE neurons receiving cortical inputs (Agassandian et al., 2006; Agassandian and Cassell, 2008), and pTrkB is similarly localized (Fig. 1D). In the cortex, TrkB-ir has been associated primarily with parvalbumin-containing inhibitory interneurons (Cellerino et al., 1996; Gorba and Wahle, 1999).

In contrast with the primarily trophic effects of BDNF–TrkB binding, proBDNF binding to p75^{NTR} has been shown to play a role in apoptosis (Casaccia-Bonnet et al., 1996; Frade et al., 1996; Bamji et al., 1998) and can induce long-term depression in the hippocampus (Woo et al., 2005). In the hippocampus and amygdala, p75^{NTR}-ir is strongest in axonal projections of the cholinergic system (Pioro and Cuello, 1990). Subsequent ultrastructural studies have confirmed this finding (Dougherty and Milner, 1999) and also identified p75^{NTR} in dendritic spines of the hippocampus (Woo et al., 2005), suggesting a role in modulating signaling both pre- and post-synaptically.

ProBDNF can also bind a third receptor, sortilin, which forms a high-affinity complex with p75^{NTR} to induce apoptotic signaling (Nykjaer et al., 2004; Teng et al., 2005) and growth cone collapse (Deinhardt et al., 2011). However, the mechanisms underlying p75^{NTR} signaling have yet to be resolved because of its ability to act as a coreceptor for a diverse assortment of ligands and other receptors, such as Nogo receptor (Wang et al., 2002; Mi et al., 2004), Neuropilin-1 (Ben-Zvi et al., 2007), and Eph receptors (Lim et al., 2008), each leading to distinct biological outcomes. While this review will primarily focus on the trophic effects of BDNF signaling through the TrkB receptor, the balance between proBDNF and BDNF in response to stress is an important area of research. One of the proteases able to convert proBDNF to BDNF is plasmin, which is activated by the conversion of plasminogen into plasmin by the serine protease tissue plasminogen activator (tPA) (Lee et al., 2001; Pang et al., 2004). The role of tPA and BDNF in neural plasticity in response to stress will be discussed in more detail in the following section.

TROPHIC INFLUENCE OF GCs IN BRAIN

Coincident with the discovery of BDNF, GCs were also established as trophic factors in the hippocampus. Studies removing circulating GCs by adrenalectomy showed reduced dendritic branching and complexity as well as death of granule neurons of the dentate gyrus as early as three days after the procedure (Gould et al., 1990) and this loss persisted for three to four months in rats (Sloviter et al., 1989). However, cell death and changes in neuronal morphology could be prevented by CORT replacement after adrenalectomy, clearly demonstrating the trophic influence of GCs on the hippocampus (Gould et al., 1990). These findings contrast with studies showing that excess GC administration over extended periods also results in cell death in the hippocampus (Sapolsky et al., 1985; Uno et al., 1989), as well as atrophy of dendritic trees (McEwen, 1999). Taken together, both depleted and excess GC levels result in hippocampal toxicity.

Recently, the trophic effects of GCs have been directly linked to activation of the TrkB receptor. Using acute dexamethasone treatment, Jeanneteau et al. (2008) showed increased levels of pTrkB and glucocorticoid receptor (GR) in neurogenic regions of the hippocampus. GCs can bind both GRs and mineralocorticoid receptors (MR), which are distinguished by their downstream effects, but both serve primarily as transcription factors after activation (Funder, 1997). *In vitro* studies also found that BDNF and dexamethasone had a markedly different time-course of pTrkB activation, where BDNF resulted in immediate activation, and the response to dexamethasone was smaller but persisted over a longer period, and these effects were independent of the release of other neurotrophins (Jeanneteau et al., 2008). Building on these findings, Numakawa et al. (2009) found that GR can be coimmunoprecipitated with TrkB. Both dexamethasone and CORT decreased this TrkB–GR interaction and reduced BDNF-induced glutamate release (Numakawa et al., 2009). The interaction with TrkB required the N-terminal of GR (Numakawa et al., 2009) and transcriptionally deficient GR failed to phosphorylate TrkB (Jeanneteau et al., 2008). Together these studies suggest there are multiple mechanisms of GC mediation of BDNF-signaling, as short term treatments of CORT and dexamethasone failed to effect BDNF-dependent glutamate release (Numakawa et al., 2009), but were sufficient to phosphorylate TrkB (Jeanneteau et al., 2008). Clearly, the interaction of GC and BDNF signaling remains incompletely understood and will be an important area of future research.

IN VIVO REGIONAL AND TEMPORAL VARIATION IN THE BDNF RESPONSE TO ELEVATED GCs RESULTING FROM STRESS

As research into the effects of stress on the brain expanded beyond the hippocampus, it became evident that elevated GC levels can have contrasting effects across brain regions. In

the male rat basolateral amygdala (BLA), chronic restraint stress resulted in dendritic growth and increases in spine density, exactly opposite the changes observed in the hippocampus (Vyas et al., 2002). These changes in the BLA in response to stress are less plastic in comparison to the CA3 of the hippocampus, whose stress-induced changes can be reversed after 21 days of recovery from stress, but are not reversed in the BLA (Vyas et al., 2004). Further, exposure to a single 2-h restraint stress is sufficient to induce changes in spine density of the BLA 10 days later, even though no remodeling is evident after 24 h (Mitra et al., 2005). These effects were believed to be linked to transient elevation of BDNF in BLA, which showed increased mRNA levels 2 h after cued fear conditioning (Rattiner et al., 2004).

Subsequent studies have supported the link between increased BDNF in the BLA in response to stress, and increased dendritic branching and spine density. Mice overexpressing BDNF in forebrain structures showed increased anxiety-like behaviors and increased spine density in the BLA, that could not be further increased by chronic restraint stress (Govindarajan et al., 2006). Most recently, micro-dissection experiments have shown that chronic restraint stress results in a significant elevation of BDNF in the BLA, which is simultaneously decreased in CA3 of the hippocampus (Lakshminarasimhan and Chattarji, 2012). Further, after recovery from both an acute and chronic restraint stressor, BDNF levels in CA3 returned to baseline, whereas levels of BDNF remained elevated in the BLA (Lakshminarasimhan and Chattarji, 2012). This parallels data showing that a single CORT injection is sufficient to induce hypertrophy in the BLA (Mitra and Sapolsky, 2008). However, elevation of GCs does not always mirror the effects of stress in the BLA, as treatment with CORT in the drinking water (rather than injection) prior to an acute stressor, prevented the effects of the acute stress in the BLA, suggesting that this region is highly sensitive to the duration and level of GC elevation (Rao et al., 2012). These studies collectively demonstrate that the directionality and temporal regulation of BDNF in response to elevated GCs may be unique in each brain region. Table 1 provides a summary of BDNF changes induced by different stress paradigms in the hippocampus and amygdala.

In the hypothalamus, a region rich in GRs and essential for neural regulation of the endocrine system, BDNF is increased in response to stress (Smith et al., 1995a) and plays a modulatory role in CRH homeostasis (Jeanneteau et al., 2012). Conditional genetic deletion of GR from the paraventricular nucleus (PVN) resulted in an elevation of CRH, BDNF protein levels, and pTrkB labeling. Conversely, genetic overexpression of BDNF in the PVN increased CRH levels, but not total CORT. The authors propose a model in which BDNF is able to induce CRH expression through cAMP response element-binding protein (CREB) signaling and activation of GR signaling deactivates the CREB-mediated induction of CRH.

Changes in BDNF levels after acute and chronic restraint stress in the hippocampus have been the subject of numerous studies that have revealed its regulation is more complicated than first hypothesized. Initial evidence showed reductions in BDNF mRNA in both dentate gyrus and CA3 of the rat after a single stress or 7 days of chronic stress (Smith et al., 1995b; Ueyama et al., 1997). Interestingly, CORT administration was able to replicate this effect in the dentate gyrus, but not CA3; adrenalectomy failed to prevent stress-induced changes in BDNF in dentate, but did block stress-induced changes in CA3 (Smith et al., 1995b). Shortly after this discovery, other labs failed to find a difference in BDNF after a 21-day restraint stress in rats, suggesting that the timing of the stress is important (Kuroda and McEwen, 1998).

Marmigere et al. (2003) showed a rapid elevation of BDNF mRNA in response to an acute restraint stress that peaked at 1 h after stress exposure, with protein levels peaking slightly later at 3 h. They report BDNF mRNA levels subsequently drop below basal levels 2 h after

stress onset, consistent with initial observations by Smith et al. (1995b), and suggesting a bi-phasic response of BDNF levels after stress. CORT levels in these rats were significantly elevated within 15 min of stress onset and remained high for the following 5 h. Murakami et al. (2005) expanded this finding by showing that BDNF is still decreased 6 h after stress onset, but remains significantly depressed 24 h after stress. Further, they show that when animals are chronically restrained and assayed immediately after stress, BDNF reductions peak after 2 weeks of treatment, but by 3 weeks are not significantly different from control in the dentate.

However, when male rats are collected 24 h after their final restraint session, no differences in BDNF mRNA levels were observed despite undergoing 3 weeks of chronic restraint (Murakami et al., 2005), replicating the findings from Kuroda and McEwen (1998). Subjecting male rats to a more severe stress paradigm, using chronic *variable* physical and social stressors for 28 days, still produced no differences in BDNF mRNA in the hippocampus when assayed 24 h after the final stressor (Isgor et al., 2004). This suggests there may also be a bi-phasic response of BDNF levels over the course of a chronic stress paradigm, as BDNF levels were higher after 3 weeks of stress, than at 2 weeks. Additionally, hippocampal BDNF levels remain highly responsive, as levels return to nearly those of controls within 24 h. Recently, rats subjected to 3 weeks chronic restraint showed a completely inverted BDNF response immediately following the final stress, where chronically stressed animals had elevated baseline BDNF levels, but subjecting them to the stressor immediately decreased BDNF to below basal levels (Naert et al., 2011). In this study, chronically stressed animals had basally elevated CORT levels, and showed an increased CORT response over the first hour of stress onset compared with controls. This suggests that an elevation of CORT levels may facilitate BDNF expression to a point, beyond which too much CORT (or elevated CORT for too long) can suppress BDNF expression.

In transgenic mouse models, BDNF overexpression in the hippocampus can increase dendritic complexity (Tolwani et al., 2002) and prevent stress-induced hippocampal atrophy and decreases immobility time in the forced swim test (FST) (Govindarajan et al., 2006). While BDNF-overexpressing mice had lower basal CORT level, there was no difference in the CORT response to stress across genotypes (Govindarajan et al., 2006). Conversely, selective deletion of BDNF from the forebrain structures resulted in a thinner cortex in adulthood (Gorski et al., 2003b), but no difference in pyramidal cell spine density (Hill et al., 2005). Conditional deletion mice were impaired on some learning tasks and showed deficiencies in long term potentiation (LTP) (Monteggia et al., 2004), but had no change in anxiety-like behaviors (Gorski et al., 2003a). Similarly, mice haploinsufficient for BDNF (BDNF+/-) do not show a depression-like phenotype (MacQueen et al., 2001; Chourbaji et al., 2004), although exposure to a mild stress (saline injections) increased immobility time in FST, suggesting deficient BDNF levels may increase susceptibility to depressive-like behavior (Advani et al., 2009).

BDNF+/-'s showed decreased BDNF protein in the hippocampus by ELISA, decreased hippocampal volume, and decreased dendritic branching that cannot be further reduced by chronic restraint stress (Magarinos et al., 2011). BDNF+/-'s also were insensitive to stress-related changes in spine type in CA3 and CA1, suggesting that genetically low BDNF levels, which may have been further suppressed by chronic stress, produced conditions insufficient for spine and dendritic remodeling. Basal CORT levels were not different between WT and BDNF+/-, and 24 h after the end of chronic restraint, levels were also not different between genotypes and there was no significant effect of stress on CORT (Magarinos et al., 2011). Interestingly, a non-significant increase in BDNF protein was observed in WT mice 24 h after the end of chronic restraint. Other studies have shown that

administration of CORT to mice resulted in decreased hippocampal BDNF, increased immobility time in the FST, and decreased progressive ratio responding (a learning task), but direct infusion of BDNF could rescue both behavioral phenotypes (Gourley et al., 2008). Surprisingly, BDNF infusion to animals also significantly reduced progressive ratio responding, suggesting an inverted U-effect on responding, where too much BDNF can be as detrimental as too little (Gourley et al., 2008). This parallels findings from BDNF^{+/-}, where too little BDNF prevents stress from inducing any hippocampal remodeling. Taken together, these studies suggest that there may be both a floor and ceiling to BDNF's ability to regulate hippocampal plasticity.

Most recently, transgenic mice carrying a single-nucleotide polymorphism in the prodomain of BDNF, which causes a valine to methionine change at position 66 (Val66Met), were found to have increased stress reactivity (Yu et al., 2012). The Val66Met mutation has been associated in humans with an increased risk of depression and anxiety-related disorders (Sen et al., 2003; Verhagen et al., 2010) and results in a decrease in activity-dependent BDNF secretion (Egan et al., 2003; Chen et al., 2004). No basal difference in CORT was observed between WT and Val66Mets, but after 7 days of 2 h chronic restraint stress, Val66Mets showed potentiated CORT levels that were significantly higher than equally stressed WT mice when measured immediately at the end of stress (Yu et al., 2012). BDNF mRNA levels were equally reduced by stress, and protein levels were decreased basally in Val66Mets and still significantly reduced by stress in the hippocampus. Interestingly, the greatest differential changes in mRNA and protein levels by genotype were observed in the amygdala and PFC, where stress respectively increased and decreased BDNF more in the heterozygous mice. The amygdala and PFC also showed significant changes in spine density in stressed Val66Mets. This increased plasticity of the Val66Mets in the PFC, where the genotype results in reduced protein levels that are further depressed by stress, is counterintuitive with results from the BDNF^{+/-} in the hippocampus, which showed decreased plasticity in the presence of suppressed BDNF levels. Studies from these mice again demonstrate how the response to BDNF is highly variable across brain regions. The stress-effects on the Val66Met mice were insensitive to fluoxetine (Bath et al., 2012b; Yu et al., 2012), but did respond to desipramine (Yu et al., 2012) demonstrating an essential role for BDNF as a modulator of neurogenesis that is also dependent on interactions with other neurotransmitter systems (discussed in the next section).

Chronic stress of male Val66Met heterozygotes worsened performance on several measures of depression, anxiety, and learning and memory, again suggesting that decreased BDNF release increases sensitivity to environmental stressors (Yu et al., 2012). Additionally, female mice homozygous for the Met mutation showed increased anxiety-like behavior, that fluctuated over the estrous cycle, highlighting how the effects of BDNF also depend on the levels of other steroid hormones such as estrogen (Bath et al., 2012a) (*cross-reference this issue*).

Data from this lab support a highly dynamic response of BDNF to GCs. Acute restraint stress in mice was found to induce a rapid increase in BDNF mRNA 1 h after stress in the hippocampus (unpublished), replicating effects observed in rats (Marmigere et al., 2003). Both chronic restraint stress and chronic CORT administration induced elevated levels of BDNF mRNA when assayed 24 h after the end of chronic restraint (unpublished), mimicking results based on protein levels in mice (Magarinos et al., 2011).

SYNAPTIC PLASTICITY REQUIRES GC, BDNF AND OTHER MODULATORS

Direct evidence has emerged demonstrating an essential role for GCs in spine remodeling and plasticity *in vivo*. Using transcranial two-photon live imaging of the cortex, Liston and

Gan (2011), showed that CORT injections enhance spine turnover in multiple cortical regions and either dexamethasone suppression (Fig. 3A–C) or use of CORT antagonists (Fig. 3D, E) can block spine remodeling. However, while short-term CORT treatments enhanced spine dynamics, chronic CORT exposure disrupted established spines (Liston and Gan, 2011), consistent with the negative effects of chronic stress on learning and memory (Luine et al., 1994). However, GCs and BDNF cannot function alone as modulators of plasticity. New research demonstrates how their effects are dependent on signals from neurotransmitters and intracellular molecules to regulate plasticity.

Glutamate and GABA system

Numerous studies have established BDNF as important for glutamatergic and GABAergic synaptic maturation and LTP in response to neuronal activity (reviewed (Gottmann et al., 2009). Several recent papers have highlighted a role for GCs alongside BDNF in synaptic modulation as a means to enhance learning and memory.

In pyramidal neurons of the PFC, acute stress has been found to enhance glutamatergic transmission and increase surface expression of N-methyl-D-aspartic acid (NMDA) receptor subunits through activation of GR (Yuen et al., 2009). A single acute stress actually improved performance in working memory tasks in rats, and these behavioral and electrophysiological effects could be blocked by use of a GR antagonist (Yuen et al., 2009). Subsequent studies found that *in vitro* CORT was also able to increase surface expression of NMDA and AMPA receptor subunits in dissociated PFC neurons and potentiated currents in slice culture (Yuen et al., 2011). This GC-mediated enhancement of NMDA and AMPA currents was found to depend on serum- and glucocorticoid-inducible kinase, an immediate early gene induced by GCs, and activation of Rab4, a small GTPase involved in membrane trafficking (Yuen et al., 2011).

The visual system has long been used to study neural plasticity, where early in life it is highly dynamic, but plasticity is lost over the course of development [reviewed (Hensch, 2005)]. This shift has been attributed to changes in NMDA receptor subunits (Erisir and Harris, 2003), activity of the CREB system (Pham et al., 1999), consolidation of perineuronal nets (PNNs) (Pizzorusso et al., 2002), and particularly BDNF-dependent maturation of the intracortical inhibitory circuits (Hensch et al., 1998; Huang et al., 1999; Berghuis et al., 2004). Recently, increases in the number of BDNF-ir positive cells have been identified in the visual cortex after recovery from amblyopia, which can be enhanced by an enriched environment (Sale et al., 2007). There was a coincident decrease in the density of PNNs and GABA levels in the visual cortex, suggesting that for plasticity to occur, not only does BDNF increase, but GABA levels and PNN density decrease. PNNs have also been implicated in the consolidation of new fear memories in the amygdala, where chemical treatment causing the degradation of PNNs left newly acquired memories susceptible to loss (Gogolla et al., 2009), however, it remains unknown how BDNF and GCs effect PNNs.

Transplantation of embryonic GABAergic interneurons into the visual cortex after the end of the critical periods can restore plasticity (Southwell et al., 2010). The timing of these experiments suggests that there are intrinsic developmental programs that the interneurons can still execute upon transplantation (Southwell et al., 2010). However the extent to which these experiments change local BDNF and GC levels remain unknown. Most recently, elevation of CORT levels, either by its addition to the drinking water or through food restriction, was found to facilitate the restoration of plasticity in the adult visual cortex (Spolidoro et al., 2011). The effect of food restriction could be blocked by the administration of diazepam (resulting in an elevation of GABA levels). However, BDNF and PNN-density levels were found to be unchanged with food restriction (Spolidoro et al., 2011). When

considered with in vitro observations that elevated GCs result in increased pTrkB independent of neurotrophin levels (Jeanneteau et al., 2008), these studies suggest the possibility that GCs may be activating the BDNF pathway, independent of any change in BDNF ligand levels. Future research will be necessary to unravel the dynamic interplay between the GABAergic system, BDNF, and GCs in the maintenance of neural plasticity.

Selective serotonin reuptake inhibitors (SSRIs)

While SSRIs have been shown to increase BDNF in rodents (Nibuya et al., 1995), they may also directly facilitate plasticity. Chronic treatment with a commonly used SSRI, fluoxetine, was able to restore plasticity in the adult visual cortex, after the critical period when ocular dominance is established (Maya Vetencourt et al., 2008). Similar to work discussed earlier, BDNF was increased and GABA was decreased in the visual cortex, and increasing GABA with diazepam was able to block the effect of fluoxetine (Maya Vetencourt et al., 2008). However, the animal model literature has produced mixed results on the effectiveness of SSRIs in restoring plasticity. Previous work has shown that fluoxetine was unable to improve motor performance in rats with focal ischemic lesions after 4 weeks of treatment (Windle and Corbett, 2005). Despite these findings from animal models, clinical trials evaluating neurological improvement after stroke with either fluoxetine (Dam et al., 1996; Pariente et al., 2001) or citalopram (Zittel et al., 2008; Acler et al., 2009) all showed some improvement in motor ability. The largest and most recent randomized placebo-controlled trial with stroke victims found a significant increase in motor skills performance in the fluoxetine group 90 days after beginning treatment, with no differences evident at 30 days (Chollet et al., 2011). Despite these compelling clinical outcomes, a study of the SSRI paroxetine in healthy individuals showed that a single dose of SSRI produced hyperexcitability of the motor cortex, whereas chronic treatment produced the opposite effect (Gerdelat-Mas et al., 2005). Clearly, the SSRIs, which can function as trophic factors supporting neurogenesis and as drugs that can acutely impact brain neurochemistry, serve as powerful regulators of plasticity, likely through BDNF, but more research is necessary to completely understand their mechanisms of action.

tPA

Another molecule identified as important in neural plasticity after stress is tPA, a serine protease that is able to breakdown blood clots, and therefore is widely used clinically after certain strokes. At the molecular level, tPA converts the inactive zymogen plasminogen in its active form, plasmin, by proteolytic cleavage (Plow et al., 1995). Plasmin is able to cleave both proBDNF and pro-nerve growth factor (NGF) into their mature form, thus tPA is likely to play a role in the balance between pro- and mature BDNF (Lee et al., 2001). Initially, tPA was identified as a regulator of synaptic plasticity in late LTP in the hippocampal mossy fiber pathway (Baranes et al., 1998). Building on this work, Pang et al., (2004) showed that cleavage of proBDNF by plasmin was required for hippocampal LTP. A link to GC-dependent plasticity was established when tPA was found to be up-regulated in the amygdala after an acute restraint stress, but not in the hippocampus (Pawlak et al., 2003). This increase in tPA peaked 30 min after the beginning of stress, similar to the peak in CORT levels (Pawlak et al., 2003). Additionally, tPA knockout mice (tPA^{-/-}) showed no stress-induced anxiety like behaviors (Pawlak et al., 2003). Subsequent studies showed that this increase in amygdala tPA could be directly stimulated by CRH, and tPA^{-/-} mice showed deficient c-fos induction in the amygdala, but not in PVN (Matys et al., 2004). Interestingly, tPA^{-/-} exhibit normal CORT elevation in response to CRH, but CORT levels remain elevated in these mice after 2 h, during which time the WT levels returned to baseline (Matys et al., 2004). Morphological characterization of dendritic spine in the amygdala showed that the response to chronic stress was highly specific, with spine density decreased in the medial amygdala, but increased in the BLA (Bennur et al., 2007). In tPA^{-/-}

– mice, the stress-induced spine reduction was attenuated in the medial amygdala, but the response was unchanged in the BLA (Bennur et al., 2007).

While a single acute stress was not sufficient to induce tPA expression in the hippocampus (Pawlak et al., 2003), chronically stressed tPA^{-/-} appeared resistant to the stress-induced impairment of spatial learning and down-regulation of spines in CA1 (Pawlak et al., 2005). Further, both the tPA^{-/-} and the plasminogen knockout mice (Plg^{-/-}) were resistant to the stress-induced decrease in NMDA receptor subunits after chronic stress (Pawlak et al., 2005), suggesting that tPA does in fact play a role in plasticity resulting from chronic stress in the hippocampus. Interestingly, no difference was observed in BDNF, GAD65 or GABA_B receptor levels in the chronically stressed WT mice, further supporting the concept that the mechanisms of BDNF and GC-dependent plasticity may vary by brain region.

Studies using prenatal or early life stress paradigms have also found differences in the balance between pro-and mature BDNF across brain regions. Decreases in the mature BDNF, but not the pro-form were observed in the hippocampus and striatum of maternally separated pups, whereas proBDNF was increased in the ventral tegmental area, but no significant difference in either form was identified in the amygdala (Lippmann et al., 2007). Further, sex-specific differences in the response of BDNF have been identified, where prenatal restraint stress failed to change BDNF levels in female rats in the hippocampus, whereas prenatally stressed male rats had an elevation of both mature and pro-BDNF (Zuena et al., 2008). The BDNF response to prenatal stress can also vary by genetic background among male rats, as Fischer rats showed no change in BDNF in response to prenatal stress, whereas Sprague–Dawley and Lewis rats had significantly reduced proBDNF in the hippocampus after prenatal stress (Neeley et al., 2011). Lewis and Sprague–Dawley rats also showed significantly decreased levels of plasminogen mRNA after prenatal stress, suggesting tPA activity might be an important mechanism underlying the BDNF ratio in these strains (Neeley et al., 2011). Building on these findings, Yeh et al. (2012) showed that prenatal restraint stress inhibited the induction of LTP in CA1 of the hippocampus in 5 week old rats, but did not change dendritic morphology. Pro-BDNF levels were significantly higher in CA1, and there was a corresponding reduction in mature BDNF (Yeh et al., 2012). This shift in BDNF isoform levels was coincident with a significant decrease in tPA activity, again supporting a role for tPA in neural plasticity. Interestingly, no differences in LTP, BDNF levels, or tPA activity were observed by 8 weeks of age, suggesting that these early-life differences due to prenatal stress are transient and resolve by adulthood (Yeh et al., 2012).

Lipocalin-2

One of the newest molecules to be associated with synaptic plasticity in the hippocampus is lipocalin-2 (Lcn2). First identified over 15 years ago as a secreted protein inducible by the GC, dexamethasone (Liu and Nilsen-Hamilton, 1995), Lcn2 was recently shown to be up-regulated in the hippocampus after 3 days of restraint stress (Mucha et al., 2011). Interestingly, this short period of chronic restraint produced an increase in spine density in both WT and Lcn2 knockout mice, which showed basal increases in dendritic spine density. However, *in vitro* application of Lcn2 to hippocampal neuronal cultures resulted in a decrease in spine density. These findings suggest a complicated model, where Lcn2 may be up-regulated in stress as an attempt to maintain spine homeostasis and down regulates spines by modulating spine type. *In vitro*, Lcn2 increased thin and filopodia-like spines at the expense of mushroom spines, whereas loss of Lcn2 *in vivo* led to a large increase in mushroom spines in response to stress (Mucha et al., 2011). While all the details of this mechanism remain to be elucidated, Lcn2 is likely to remain an important target of translational researchers, given the observation of increased stress-induced anxiety-like behaviors in Lcn2 KO mice. Of particular importance will be studying Lcn2's effects in

other brain regions, such as the PFC and amygdala, and how it can effect spines over longer stress paradigms known to decrease spine density (Chattarji, 2011).

FUTURE DIRECTIONS

The research described above demonstrates the importance of other molecules acting together with BDNF to modulate neural plasticity, yet the mechanisms underlying how they each orchestrate changes in the brain's structure and function are far from fully described. Of particular importance going forward will be a more detailed analysis of the time-course and mechanisms of GC–BDNF actions, as recent work has suggested GCs are positioned to mediate rapid actions on TrkB (Johnson et al., 2005), similar to estrogen receptors (Mitterling et al., 2010). Additionally, understanding the mechanisms underlying the activation of TrkB receptors by GCs is incomplete (Jeanneteau et al., 2008), but highlights how GC may be neuroprotective in certain biological contexts.

Further, if rapid oscillations in GC and BDNF levels are a natural aspect of brain biology, how do changes to this rhythm impact cellular function and subsequent behavior? GC levels are known to rapidly oscillate with circadian rhythms (De Kloet et al., 1998) and manipulation of GC levels has a rapid effect on spine morphology (Liston and Gan, 2011); however, the extent to which the natural oscillations in GC levels effect spine turnover remain unknown. Most recently, GCs have been implicated in post-traumatic stress disorder-like memory impairment and changes in neural function (Kaouane et al., 2012). The extent to which morphological changes contribute to these behavioral effects remains to be explored. Finally, the ability of GCs to restore plasticity after critical periods suggests that GCs and BDNF can unlock molecular mechanisms that were silenced during the normal progression of development (Spolidoro et al., 2011). The nature of the genomic or possibly epigenetic changes that occur to facilitate this remains unknown.

Finally, while extensive work has been done with genetic knockouts and overexpressing mice to shift the system to one extreme or the other, more valuable information about GC–BDNF interactions can also be gained through subtle manipulations of GC levels using various stressors in combination with translationally relevant genetic models, such as the BDNF Val66Met mouse. These efforts are well underway, and the molecular mechanisms underlying neural plasticity in response to GCs and BDNF are certain to get more complicated as new discoveries are made.

SUMMARY

This review summarizes how neural plasticity in response to stress involves not only the elevation of GCs, but requires BDNF and other molecules to induce numerous physiological and morphological changes in neurons. BDNF and its receptors are localized to regions of the brain that are the most dynamic in response to stress, both at the gross anatomical level in the hippocampus and amygdala, and at the ultrastructural level in either presynaptic terminals or postsynaptic dendritic shafts and spines. Further, GCs may serve as their own trophic factors by directly activating the BDNF receptors system through TrkB. Changes in BDNF levels are not only dependent on the type of stress (acute or chronic), but also highly temporally variable and differentially responsive across brain regions. Finally, changes in BDNF alone are often not sufficient to effect neural remodeling. Neurotransmitters and other proteins act together with BDNF to modulate the cellular response to stress.

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Abbreviations

ACTH	adrenocorticotrophic 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 C γ
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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Fig. 1. BDNF-HA and pTrkB immunoreactivity in hippocampus and amygdala. BDNF-HA protein levels appear highest in the CA3 and dentate gyrus of the hippocampus, with significant staining still evident in CA1 (A). In the amygdala, labeling is evident in cell bodies of the BLA and process of the central nucleus (B). pTrkB labeling appears throughout the hippocampus, and is highly enriched in the central nucleus of the amygdala (C,D). BLA = basolateral amygdala, CA1 = cornu ammonis 1, CA3 = cornu ammonis 3, DG = dentate gyrus, Ce = central nucleus, marker bars = 200 μ m.

Fig. 2.

TrkB and pTrkB ultrastructural localization in CA1 of Hippocampus. Axon terminals (A), glial cells (B), and the axon initial segment (C) are enriched in TrkB labeling. pTrk is also present in dendritic spines (D), and tends to localize near mitochondria in terminals (E) and dendrites (F). uD = unlabeled dendrite, T = terminal, gf = glial filaments, T = unlabeled terminal, m = mitochondria, D = dendrite, uS = unlabeled synapse, ssv = small synaptic vesicles, Marker bar = 500 nm.

Fig. 3.

Glucocorticoids regulate spine remodeling *in vivo*. Schematic illustrating how low doses of dexamethasone, which do not penetrate the blood–brain barrier, inhibit the anterior pituitary, reducing the production of adrenocorticotrophic hormone (ACTH) and thereby suppressing CORT release from the adrenal gland (A). Treatment with dexamethasone for 3 days reduced spine turnover in the cortex, but this could be restored by exogenous administration of CORT in a dose-dependent manner (B). One day of dexamethasone treatment was sufficient to almost completely suppress spine turnover (C). CORT binds to glucocorticoid or mineralocorticoid receptors (GR and MR). Antagonists to these receptors were able to block spine formation in spite of exogenous CORT administration (D). Interestingly, only MR antagonist reduced spine elimination, whereas GR antagonists showed no effect (E). Reprinted with permission from Liston and Gan (2011).

Table 1

Summary of stress experiments examining BDNF levels in amygdala and hippocampus. Several groups have shown that stress increases BDNF mRNA and protein levels in the amygdala, whereas stress generally decreases BDNF in the hippocampus. However, numerous groups have failed to find a difference in BDNF mRNA and protein in the hippocampus after chronic stress, particularly when assayed 24 h after the end of the stress paradigm, suggesting BDNF levels in the hippocampus are highly dynamic in response to stress. Further, the type, severity and duration of the chronic stress may modulate the BDNF response

Brain region	Stress duration	Type of stress	Assay endpoint	Protein or mRNA	Direction of BDNF response	Species	Citation
Amygdala	Acute	FearCond.	2 h after	mRNA-in situ	Up	Rat	Rattiner et al., (2004)
	24 h	Restraint	24 h or 10 days	Protein	Up	Rat	Lakshminarasimhan and Chattarji (2012)
Hippocampus	Chronic	Restraint	24 h	Protein ELISA	Up-persists 21 days	Rat	Lakshminarasimhan and Chattarji (2012)
	7 days	Restraint	Immediate	Protein and mRNA	Up	V66 M mouse	Yu et al. (2012)
	Acute	Restraint	Immediate	mRNA-in situ	Down	Rat	Smith et al., (1995b)
	8 h	Restraint	Immediate	mRNA-in situ	Down	Rat	Ueyama et al. (1997)
	Time course	Restraint	Immediate	mRNA and Protein	Up, then down	Rat	Marmigere et al. (2003)
	6 h	Restraint	Immediate	mRNA	Down	Rat	Murakami et al., (2005)
	6 h	Restraint	24 h	mRNA	Down	Rat	Murakami et al., (2005)
	Chronic	Restraint	Immediate	mRNA-in situ	Down	Rat	Smith et al., (1995b)
	7 days	Restraint	24 h	mRNA-in situ	Down	Rat	Smith et al., (1995b)
	21 days	Restraint	24 h	mRNA	No difference	Rat	Kuroda and McEwen (1998)
	28 days	Variable and Social	24 h	mRNA-in situ	No difference	Rat	Isgor et al. (2004)
	1, 2, & 3 weeks	Restraint	Immediate	mRNA	Down	Rat	Murakami et al., (2005)
	1, 2, & 3 weeks	Restraint	24 h	mRNA	No Difference	Rat	Murakami et al., 2005
	14 days	CORT	6 days	Protein ELISA	Down	Mouse	Gourley et al. (2008)
	21 days	Restraint	Immediate	Protein ELISA	Down	Rat	Naert et al. (2011)
	21 days	Restraint	24 h	Protein ELISA	No difference	BDNF+/- mouse	Magarinos et al. (2011)
	7 days	Restraint	Immediate	Protein and mRNA	Down	V66 M mouse	Yu et al. (2012)
	10 days	Restraint	24 h	Protein ELISA	Down-does not persist	Rat	Lakshminarasimhan and Chattarji (2012)