

CHAPTER

13

c0065 Stress Responsiveness of BDNF/TrkB Signaling in the Neuroendocrine System and Future Implications

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KEY POINTS

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- Functions of BDNF/TrkB signaling are essential for regulation of neuronal plasticity genes and the recovery process of depression-like behaviors typically induced by antidepressants.
- BDNF has synergistic actions with GCs in the HPA axis via a positive feedback loop.
- Disruption of either pathway can be maladaptive:
 - loss of resilience
 - development of stress-related pathologies
 - increased resistance to antidepressants
- The use of animal models provides a comparable approach of elucidating the mechanisms that lead to vulnerability and adaptability to depression in humans.

- The responses of both sexes to stress are biologically different. u0110
 - More gender studies in mood-related disorders would positively impact clinical use of preclinical research. u0115
- Use of small molecule TrkB receptor antagonists and/or agonists in stress pathology research may have important implications for preclinical resilience and vulnerability studies with potential clinical relevance: u0120
 - Capability to cross the blood-brain barrier. u0125
 - Induction of stronger effects than direct BDNF inhibition. u0130
- Requirements to understand an organism's stress-context detecting function and the state-dependent nature (i.e., resilient vs vulnerable) of an individual in responding to stress exposure. u0135

- u0140 • TrkB signaling in individuals susceptible to stress-related anxiety and depression may have clinical significance as a therapeutic strategy for attenuating or treating stress-related disorders.
- u0145 • TrkB inhibition may enhance anxiety in individuals under normal/low stress/unchallenged conditions leading to discrete biochemical changes in interconnected structures, such as the PVN and VTA.

INTRODUCTION

s0010

p0165 The subjective term “stress” was coined by Hans Selye¹ in 1936 to describe the “nonspecific response of the body to any demand.” Central to this concept are the responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system, of which the end product of the former is glucocorticoids (GCs, cortisol in humans and corticosterone in rodents), in fostering adaptation or vulnerability to present and future stressors. As it relates to the human condition, stress has been used to describe a variety of reactions to human experiences, suggesting a disruption or disturbance of the internal homeostasis with a psychological component. Stress exposure to a certain extent can be beneficial in motivating people; increasing productivity, attention, and memory; and enhancing resilience to future stressors. In contrast, chronic and unrelieved stress exposure can lead to hyper activation of the HPA axis and abnormal secretion of GCs, playing a role in the onset and development of pathological states, such as depression and other psychological disorders.

p0170 Recent advances in translational animal and human research address the delicate functional balance in the adaptive changes required to protect a system and the vulnerability that may lead to permanent damage. Adrenal steroids represent one of many systems that mediate this balance,² such that regulation of synaptic and morphological plasticity may be stressor specific. Short-lived stress exposure may suppress plasticity mechanisms in the hippocampus, leading to cognitive impairments in learning and memory and inducing dendritic atrophy in CA3 pyramidal layers^{2, 3}; however, these changes in morphology and function are reversible. In contrast, it is unclear whether the impact of prolonged or chronic stressors is reversible or whether the system will adopt a new activation threshold and perform at suboptimal levels. The latter may mount dysfunctional physiological responses, such as those noted in subjects with posttraumatic stress disorder.⁴ In this context, stressor-specific neuroendocrine responses observed in response to acute or chronic stress exposure have supported complex system interplay.

p0175 It has been proposed that long-term adaptations are necessary to the therapeutic actions of chronic treatments,

including cognitive behavioral therapy and synergistic nonpharmacological/pharmacological options. Among such adaptations, the regulation of neurotrophins, such as brain-derived neurotrophic factor (BDNF) in both pre-synaptic and postsynaptic mechanisms, has led to the neurotrophic hypothesis of depression.⁵ The hypothesis proposes that depression is a consequence of decreased neurotrophic support, which leads to neuronal atrophy, reduced hippocampal neurogenesis and loss of glia that may be blocked or reversed with the use of antidepressant treatment,⁶ and thus may represent a critical mechanism underlying the efficacy of antidepressants. Antidepressant treatments are reported to elevate adaptive responses of neuronal systems and activity-dependent BDNF expression, gradually improving network function and mood.⁷ Although antidepressants restore BDNF actions and improve recovery, the ligand is among a series of identified mediators of anxiety and depression. Indeed, attenuated BDNF levels in the hippocampus plays a role in the behavioral dysfunctions consistent with serotonergic abnormalities^{8, 9} and trophic effects on noradrenergic neurons,^{10, 11} particularly suited to disorders developing from stress exposure.¹⁰ Notably the neurotrophic hypothesis of depression appears validated only in consideration with the relationship to hippocampal function. As such an increasing number of studies addressing the differential stress response of BDNF expression within the brain’s reward and stress systems have provided inconsistent findings. Thus, while BDNF signaling within the hippocampus, amygdala and prefrontal cortex acts to promote antidepressant phenotype¹² and is downregulated by stress, increased BDNF in the hypothalamus, and ventral tegmental area—nucleus accumbens (VTA-NAc) pathway induces susceptibility to a depression phenotype.^{13–16} Furthermore, measurements of BDNF are not uniformly patterned between brain regions. Such findings have led to a growing need to revisit and reassess the hypothesis (see reviews on this topic^{17, 18}). Thus the process of plasticity may be site-specific or extend across cortical areas, coordinating, monitoring, and calibrating behavioral and physiological responses to stress.¹⁹

This chapter presents an overview of the interplay p0180 between BDNF, GCs, and their respective receptors in the brain that act upon improving resilience/adaptability or triggering stress-related psychiatric diseases. The basic regulation and function of BDNF, its mechanistic interaction with GCs within the HPA axis system, the differential stress-related responses of particular regions within the brain’s stress and reward systems, and BDNF’s functional discrepancy between sexes will be discussed. Presentation of the BDNF^{Val66Met} polymorphism in relation to stress is reported elsewhere.²⁰ The chapter concludes with a translational perspective of the current knowledge of BDNF and its primary receptor as potential

drug targets to modulate the response to mood disorders and stress-related pathophysiology.

s0015

AN OVERVIEW OF REGULATORY ACTIONS OF BDNF

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Neurotrophins are among the many growth factors that are widely studied as genuine molecular mediators of synaptic development and plasticity in the adult central (CNS) and peripheral (PNS) nervous systems. This family of growth factors includes nerve growth factor (NGF),²¹ BDNF,²² as well as neurotrophin-3 (NT-3),²³ and neurotrophin-4/5 (NT-4/5).^{24, 25} They are secreted by neurons in both a constitutive (i.e., Ca²⁺-independent) and activity-dependent (i.e., Ca²⁺-dependent) manner.^{26–29} Among such neurotrophins, BDNF, a highly conserved protein, exerts diverse effects on inhibited apoptosis of developing neurons, neuronal differentiation, synapse formation, maturation, and function throughout the CNS and PNS, and underlies memory and learning processes.^{30–32} In addition, it acts as a mediator of behavioral interactions between an organism and its external environment.³³ Changes in transcription of neurotrophins can cause long-term alterations in the functionality of adult neurons and may contribute to delayed changes observed in therapeutic actions of antidepressant treatments.¹⁰

p0190

The 14kDa neurotrophin BDNF was first isolated in 1982 when it was purified from mammalian pig brain and shown to support the survival of a subpopulation of dorsal root ganglion cultured neurons from 10-day-old chick embryos.²² Initial synthesis occurs in subregions of the hypothalamus, for example, lateral hypothalamus, paraventricular nucleus (PVN), and ventro- and dorsomedial hypothalamic nuclei.³⁴ Furthermore, high levels are observed in the hippocampus, amygdala, and cortex of the developing and mature mammalian CNS.^{35–38} BDNF is translated as a precursor protein, proBDNF, which is then cleaved in the cytoplasm by endoproteases or in the extracellular matrix by plasmin or matrix metalloproteinases to yield a N-terminal prodomain and a C-terminal protein, mature BDNF (mBDNF).^{39, 40} Considered the biologically active form, mBDNF signals via its high-affinity transmembrane receptor tyrosine-related kinase B (TrkB), while both pro-BDNF and mBDNF can bind to and activate the proteolysis and apoptosis promoter, pan 75 neurotrophin receptor [p75^{NTR}, a member of the tumor necrosis factor family (TNF-CD40-Fas receptor family)], resulting in activation of apoptotic signaling cascades with opposite modulatory effects on neuronal survival, growth cones responses to inhibitory axon-guidance molecules, and synaptic plasticity.^{10, 41} Lack of p75^{NTR} or pro-BDNF/BDNF is shown to enhance memory in an inhibitory avoidance task.⁴¹ Conversely, elevated

p75^{NTR} expression in the CNS has been reported following ischemia,⁴² traumatic injury,⁴³ and stress,⁴⁴ suggesting that p75^{NTR} activation plays a role in mediation of cell death and functional impairments. In contrast, BDNF's activation of TrkB receptors has beneficial effects on cell survival and synaptic transmission, regulation of gene expression, ion channel function, and morphogenesis, which promote neuronal protection and the recovery process of depression-like behaviors typically induced by antidepressant drugs.¹¹ Furthermore, BDNF binding to TrkB is shown to induce the expression of nuclear factor-κB (NF-κB), a transcription factor that is closely involved in the expression of pro- and antiapoptotic genes and in adaptive immune responses in psychiatric and neurodegenerative diseases, although modulatory pathways remain to be elucidated (Fig. 13.1).⁴⁰

BDNF expression is driven by a coordinated activation of transcription factors. Accordingly, membrane depolarization by high potassium (K⁺) triggers Ca²⁺ influx via L-type voltage gated Ca²⁺ channels (VGCCs), and N-methyl-D-aspartate (NMDA)-type glutamate receptors promotes phosphorylation of cyclic AMP (cAMP) response element binding protein (CREB) and the binding of transcription factors such as Ca²⁺ response factor (CaRF) inducing BDNF transcription, mRNA expression, and protein secretion.^{26, 32, 45–47} Coexpression of BDNF and TrkB in neurons and vasculature of the CNS suggest that BDNF acts as paracrine (local action on nearby cells) or autocrine (direct action on the cell in which it was produced) factors to modulate function.^{28, 48, 49}

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INTERACTION OF BDNF AND GCs WITHIN THE NEUROENDOCRINE SYSTEM

s0020

Normal HPA axis activity is important for the regulation of internal homeostasis and survival during times of homeostatic disruption, that is, stress. Activation of the HPA axis is facilitated through anatomical connections between brain regions such as the amygdala, hypothalamus, and hippocampus (Fig. 13.2A). Within minutes of stressor onset, amygdala activation triggers the release of corticotropin-releasing hormone (CRH) in the PVN of the hypothalamus, followed by the induced secretion of adrenocorticotrophic hormone from the anterior lobe of the pituitary gland by the hypothalamus, and the subsequent stimulated synthesis and secretion of GCs by the adrenal gland. To dampen excess activation of the HPA axis and terminate the stress response, GCs bind to two types of nuclear receptors that act as transcriptional regulators, Type I mineralocorticoid receptors (MR) and Type II glucocorticoid receptors (GR).^{50, 51} GR, exhibiting highest density in the PVN and in limbic regions that modulate PVN function, is also localized in various

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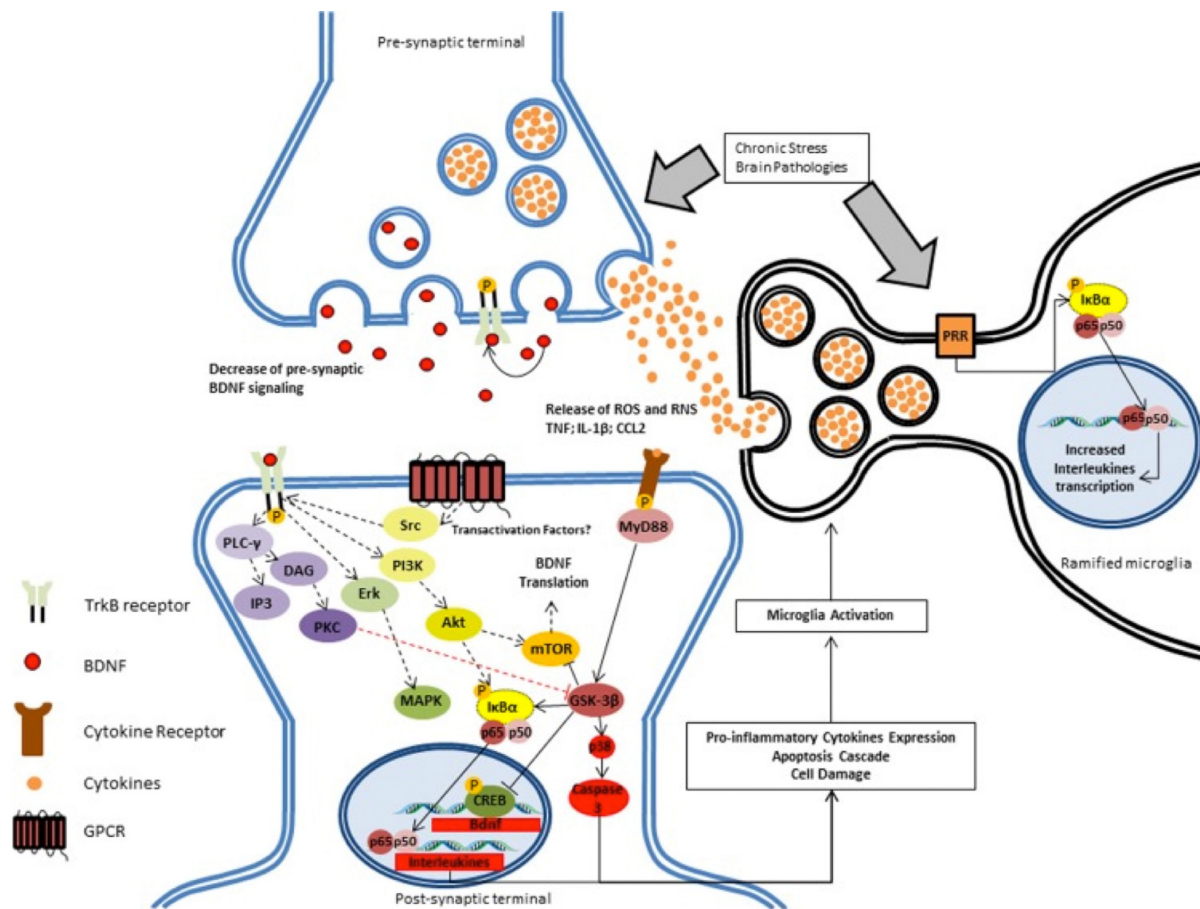


FIGURE 13.1 BDNF response after inflammatory brain pathogenicity. In chronically stressful situations, such as brain pathologies, there is an induction of NF- κ B-dependent proinflammatory activation of microglia after induction of the pattern recognition receptor (PRR) by the challenge (e.g., stress or pathology). Proinflammatory cytokines, especially IL-1, can directly bind microglial cells, which result in induction of the expression and release of several mediators, most of which are neurotoxic, including reactive oxygen (ROS) and nitrogen species (RNS), proinflammatory cytokines (such as tumor necrosis factor), and chemokines (such as CC-chemokine ligand 2, CCL2; also known as MCP1). Additionally, there is a decrease of BDNF signaling in the synaptic cleft, further reducing BDNF-dependent survival-related signaling (black dashed lines) and inhibition of apoptotic pathways, such as glycogen synthase kinase 3-beta (GSK-3; red dashed line). Such factors will lead to an increase of NF- κ B complex binding to genes that express proinflammatory cytokines (e.g., interleukin 1- β , IL-6, IL-8, and TNF). The effect of transactivation factors on the BDNF-independent maintenance of TrkB is not clear yet. Adapted and reprinted with permission from Lima Giacobbo B, Doorduyn J, Klein HC, Dierckx RAJO, Bromberg E, de Vries EFJ. Brain-derived neurotrophic factor in brain disorders—focus on neuroinflammation. *Mol Neurobiol.* 2019;56:3295–3312. <https://doi.org/10.1007/s12035-018-1283-6>.

stress-responsive brain regions, whereas MR has a more restrictive binding pattern in the brain and is suggested to regulate the HPA axis during basal periods of secretion.^{52, 53} Research suggests that the immediate, adaptive responses to physical or emotional stressors have some specificity toward the different classes of stressors that generate them,⁵¹ e.g., processive (requiring interpretation by higher brain structures with respect to previous experience) or systemic (physiologic threat).⁵⁴ Thus, the outcome of the stress system in response to GCs depends on the severity, duration and context of the stressor, the age of exposure, sex of the organism, species,

glucocorticoid circadian variation, and the hypo- or hyperresponsiveness of the HPA axis.^{55–59}

The interplay between GCs and BDNF/TrkB-mediated signaling has been proposed,^{20, 60, 61} associating GCs and BDNF with the pathophysiology of depression. BDNF plays a putative role in the regulation of the brain's stress and reward systems and is considered a stress-responsive intercellular messenger in HPA axis activity.^{37, 62, 63} The neurotrophin is reported to balance the ability of GCs to influence CRH expression within the PVN via a unique mechanism involving CREB and its coactivator protein, CRTC2,⁶³ while elevations in

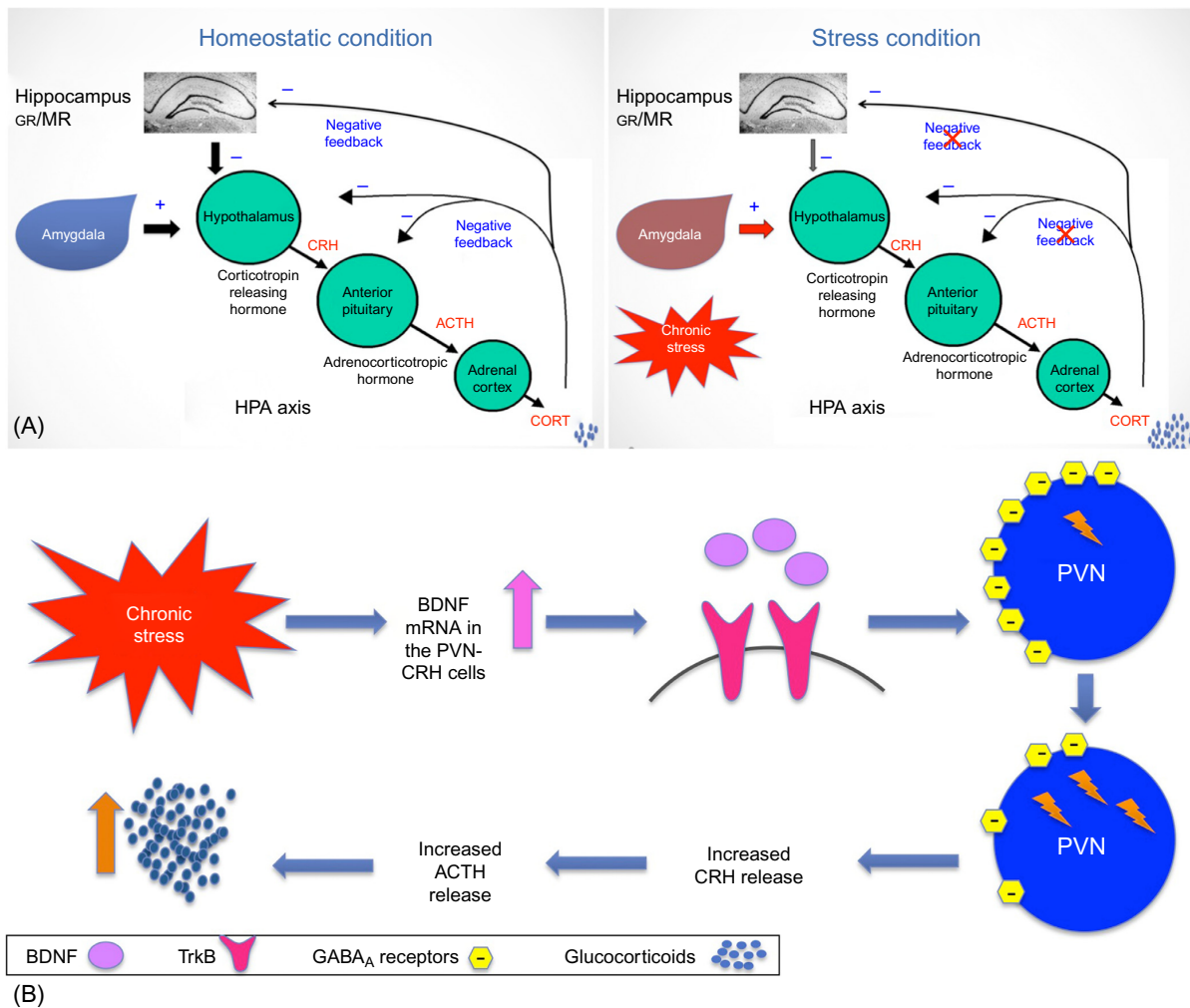


FIGURE 13.2 HPA axis—homeostatic and stress conditions. (A) In a homeostatic condition, activation of the amygdala promotes the eventual release of glucocorticoids (CORT) through the HPA axis, and subsequently glucocorticoids feedback at the level of the hippocampus, hypothalamus, and pituitary to dampen excess activation of the HPA axis. In a chronic stress condition, inappropriate activation of the amygdala extensively stimulates the HPA axis, resulting in high levels of CORT. Prolonged exposure may weaken or disrupt the negative feedback, leading to neuronal loss and morphological atrophy in the hippocampus. (B) Chronic stress may trigger dysregulated functioning of glucocorticoid receptors in the PVN, which in turn increases BDNF mRNA in the region. BDNF then binds to and activates postsynaptic TrkB receptors, thereby reducing the surface expression of inhibitory GABA_A receptor clusters in the PVN. This may increase the firing rate of PVN neurons involved in the stress response and trigger the cascade and dysregulation of the HPA axis when the stressor persists.

levels of GCs downregulate BDNF synthesis, during stress, which inhibits dendritic spine density, neurogenesis, and long-term potentiation (LTP), subsequently impairing synaptic plasticity.^{62–64} However, GR phosphorylation at BDNF-sensitive sites is necessary to reverse the impact on structural remodeling and neuroplasticity induced by chronic unpredictable stress. Low levels of BDNF are shown to increase GR desensitization and stress vulnerability, whereas higher levels of BDNF prime GR-mediated signaling, possibly via activation of a TrkB-mitogen-activated protein kinase pathway when

paired with the deactivation of a GR-protein phosphatase 5 pathway, and is therefore shown to promote functional attributes required for adaptive plasticity of neurons to stress and response to antidepressants.⁶⁵ Of note an impairment of GR functions in the PVN upregulates BDNF levels, triggering a gradual increase in CRH expression, and subsequent disinhibition of the HPA axis (Fig. 13.2B).^{62, 63} CRH expression is also increased by overexpression of BDNF in the PVN, whereas reduced expression of BDNF or TrkB downregulates CRH.⁶³ Interestingly the colocalization of TrkB and GR in both the

cortex and hippocampus⁶⁶ suggests that elicitation of BDNF-independent effects by TrkB may be achieved via interaction with other effectors, as demonstrated through the activation of TrkB in the hippocampus with the synthetic GCs dexamethasone, which is shown to promote TrkB activation and cell survival in neurons deprived of trophic support via a mechanism of genomic GR actions.⁶⁷ In addition, BDNF heterozygous (^{+/-}) mice also show increased phosphorylation of TrkB, despite a 50% decrease in brain BDNF mRNA and protein levels.^{68, 69} These suggest that there are compensatory mechanisms that are involved following the loss of BDNF, either via stress exposure or other means (e.g., adenosine-induced transactivation).⁷⁰ Thus the synergistic actions of BDNF and glucocorticoids, via a positive feedback loop, are necessary to prime the activation of GR's genomic response and promote neuronal plasticity, which would mean that disruption of either pathway could lead to an abnormal responsiveness to stressors and trigger the development of stress-related psychiatric diseases, loss of resilience, and increase resistance to antidepressants. Such molecular link between the BDNF and glucocorticoid systems highlights their importance in neuronal integrity and stress-associated pathophysiology in the nervous system.

s0025 **Stress Differentially Regulates BDNF Action in the Brain's Stress System: PVN and Hippocampus**

s0030 **PVN**

p0210 Activity-dependent upregulation of BDNF in PVN neurons may be set off by excitatory inputs from other brain regions projecting to the PVN and is suggested to lead to a positive feedback mechanism in the PVN to further increase neuronal activity and activity-dependent BDNF synthesis by paracrine/autocrine mechanisms.⁷¹ The PVN receives afferent inhibitory GABAergic projections mainly from local hypothalamic sources, and manipulations that decrease GABA's tight regulation on CRH cells^{72, 73} increase levels of circulating GCs and can initiate HPA axis reactivity post stress.⁷⁴ Similarly, signaling of the excitatory neurotransmitter, glutamate, exerts a regulatory influence on HPA axis response to stress.⁷⁵ Elevated BDNF levels may facilitate glutamate neurotransmission at glutamatergic synapses by increasing the open probability of NMDA receptors⁷⁶ and diminish GABA_A receptor-mediated inhibition by blocking surface expression of GABA_A receptors (e.g., subunits $\beta 1$ and $\beta 2$) through modulation of the electrochemical chloride gradient.⁷⁷ Effects of the latter can be reversed by prior administration of the TrkB receptor antagonist, K252A.⁷⁸ Subtle changes in the balance of GABA and glutamate alter BDNF expression affecting synaptic

transmission and neuronal development. Antidepressant properties of TrkB receptor blockade are also partly attributable to inhibition of stress-induced BDNF effects in the PVN.

Hippocampus

Elevations in BDNF expression in the hippocampus are suggested to reinstate feedback inhibition of the HPA axis in response to antidepressant treatment, such that BDNF and TrkB are implicated in the structural and functional aspects of the adaptive response of hippocampal neurons to stress.⁷⁹ Conversely, heightened GR levels following HPA axis hyperactivity have been linked to BDNF downregulation,⁸⁰ resulting in atrophy of limbic structures implicated in depression.⁴ It is well established that antidepressant therapy exerts beneficial actions on the HPA axis, including blockade of corticosterone-mediated decrease in BDNF expression.^{81, 82} Accordingly, increased BDNF and TrkB expression, as well as CREB protein, are observed in patients treated with antidepressants at the time of death, compared with non-treated subjects, while reduced expression of BDNF and TrkB has been characterized in the postmortem hippocampus and prefrontal cortex (PFC) of suicide victims.^{83, 84} Furthermore, BDNF expression is differentially affected at the hippocampus and amygdala, exhibiting a temporal profile. For example, relative to delayed recovery effects observed in the rat amygdala [i.e., enhanced dendritic arborization in the pyramidal and stellate neurons of the basolateral amygdala (BLA)] at least for 21 days following chronic immobilization stress, a more rapid reinstatement of normal morphology at the hippocampal CA3 layer was noted in the same period.^{85, 86} Such region-specific adaptive responses of an organism may consist of a variety of refinements by BDNF in the morphology and function of neurons that can lead to strengthening or weakening of synapses, which may alter presynaptic neurotransmitter release and postsynaptic neuron responsiveness via a TrkB phosphorylation-dependent pathway.

BDNF Signaling in the Reward System and Depression Susceptibility: VTA-NAc Pathway

BDNF/TrkB signaling in the mesolimbic dopamine pathway (composed of the dopaminergic neurons projecting from the VTA to the NAc) can predict susceptibility in disorders implicating stress as a predisposing factor.⁸⁷ An excellent review of the brain reward circuitry ranging from involvement of dopaminergic, GABAergic, glutamatergic, and neurotrophic factors to transcriptional and genetic mechanisms in mood disorders has been put forth.⁸⁷ As stated, BDNF-containing projections to the NAc originate from the VTA and PFC. Following

external stimulus (e.g., chronic stress) that increases susceptibility, BDNF/TrkB release, and signaling is reported increased in the NAc not only from the VTA but also via further priming of BDNF signaling cascades through epigenetic modifications, causing a maladaptive response that involves increased phosphorylation and enhanced activity of downstream signaling mediators, including CREB.⁸⁷ Studies suggest that promotion of BDNF-TrkB-CREB signaling and downstream cascades of BDNF in the NAc can increase susceptibility to chronic social defeat stress. This effect is thought mediated via repressive histone methylation (G9a) in the NAc⁸⁸ and support altered BDNF signaling as a factor mediating individual predisposition to mood disorders upon stress exposure. Furthermore, BDNF infusion into the NAc triggers prodepressant effects, whereas inhibition of its action (e.g., via adenoassociated viral infection of dominant-negative receptor TrkB-T1,¹⁴ adenovirus TrkB receptor knock-down in the NAc shell,⁸⁹ or via systemic or brain-region specific administration of the TrkB receptor antagonist ANA-12 in stress conditions^{90–93}) promotes antidepressant and reduces anxiety-like effects. Such inhibitory action is observed to prevent stress-induced increase in delta FosB expression at the NAc and increased BDNF and type 1 glutamate (GluA1) receptor expression at the VTA.⁸⁹ Thus the impact of internal states, brain region- and context-specific actions of BDNF/TrkB signaling in the attenuation of stress-induced mood disorders, and active maintenance of homeostasis within the reward circuitry warrants further examination.

and enhance hedonic capacity,⁹⁹ suggesting that estradiol administration may have beneficial effects in stress conditions. Human studies have reported reduced PFC BDNF levels in the postmortem brains of depressed females, but not males, who died by suicide, whereas within the hippocampus, brain samples of postmortem depressed males, but not females, showed significant attenuations in BDNF levels.¹⁰⁰ These studies suggest that BDNF effects are also species and brain region specific.

Of note, there exists a developmental shift in pro- to mBDNF across adolescence that is different between sexes and is reported to cooccur within a developmental window of risk for neurodevelopmental disorders.^{20, 101} Adolescence is characterized by important hormonal changes and brain maturation, and although the capacity for resilience is increased in young relative to older age, there are also increased chances of vulnerability to adverse environmental stimuli and internal perturbations at this developmental stage, leading to subsequent stress dysregulation. During puberty, maturity of the stress system occurs as a crosstalk between gonadal and adrenal axes.¹⁰² In males the influence of testosterone may lead to a blunted effect on HPA axis stress reactivity, impacting the GABAergic inhibitory tone of the PVN, whereas in females, cyclicity of progesterone and estrogen affect sensitivity of glucocorticoid-mediated negative feedback mechanisms, exerting a stimulatory influence on HPA function and modulation of dopaminergic activity, an action mainly achieved through estrogen receptors (ER) activation at the PVN, of which ER β is the predominant isoform, exerting inhibitory actions on the HPA axis, while ER α is found in stress-responsive areas such as the bed nucleus of the stria terminalis and the peri-PVN that provide indirect GABA inhibitory input to the PVN.^{103, 104}

Sex hormones also regulate activities of BDNF, such contention being substantiated by gender-specific differences in stress responses across the lifespan. The *BDNF* gene contains a putative estrogen-response element, increasing sensitivity of BDNF expression to estrogen fluctuations.¹⁰⁵ Thus BDNF-estrogen interactions may induce similar effects as stress exposure during critical periods of development, contributing to variations in adult phenotypes. We refer the reader to a few recent reviews,^{20, 102, 106, 107} alluding to the organizational and activational influence of gonadal hormones (e.g., androgens in males and estrogens in females) and sex chromosome genes in guiding brain plasticity in the crucial regulatory regions of the mesolimbic circuitry. Females have earlier onset of puberty; therefore the testing of females at the same age as males is not representative of the age of psychological development. Accordingly, greater attention to the phase and timing of puberty in animal research may increase the comparable relevance of the work to human studies. The adoption of standardized experimental procedures recently received strong support from research reporting a distinguished

s0045 **BDNF's FUNCTIONAL DISCREPANCY
ACROSS SEXES: CROSSTALK WITH
HORMONES AND STEROID RECEPTORS**

p0225 Functional heterogeneity in males and females with regard to steroid receptors may impact negative feedback of the stress circuitry and sensitivity to hormone secretion, thereby promoting sex biases in stress pathology or coping responses. Animal studies that assess the sex-specific functional differences in BDNF/TrkB signaling are crucial in understanding fundamental mechanisms at play that mediate these differential physiological responses triggered by stress-inducing stimuli. For instance, BDNF content within the hippocampus, amygdala, cortex, and ventromedial hypothalamus is elevated in female rats relative to males after exposure to stress or environmental enrichment,^{94–97} and this may be related to the excitatory effect of elevated BDNF levels in the hypothalamus to activate and recruit PVN CRH neurons.⁶² The opposite is detected in female mice compared with male mice.⁹⁸ Interestingly, higher BDNF expression in the PFC of ovariectomized female stress mice treated with estradiol is shown to alleviate behavioral despair

influence of circadian rhythms in men and women on plasma BDNF levels, of which further assessments may reveal impairments related to disease states.¹⁰⁸ Taken together, emphasis is on the need to include sex as a variable in animal studies of anxiety and depression, as women show higher incidences of depression and comorbidities than men, and changes in hormones and neuroplasticity are sex-related.

s0050 **DISEASE-RELATED THERAPEUTIC EFFICACY OF TrkB AGONISTS AND ANTAGONISTS**

p0240 At present, depression remains the best-characterized pathology linked with BDNF, and stress is considered a major risk factor for this disease. However, as much as the prophylactic and therapeutic effects of neurotrophins administration have been noted in preclinical studies, applications in clinical contexts have not yielded improvements.¹⁰⁹ BDNF has a poor pharmacokinetic profile that greatly limits its therapeutic potential.¹¹⁰ Thus the development of small molecule TrkB agonists^{110, 111} and antagonists,⁹² or TrkB transactivation by ligands of G-protein coupled receptors, such as GCs,¹¹² provide an alternative therapeutic strategy to BDNF-related disorders. For instance the TrkB agonist, 7,8-dihydroxyflavone (7,8-DHF), which penetrates the blood brain barrier, induces neurotrophic effects on in vitro excitotoxic processes¹¹³ and has been shown to protect neurons from apoptosis in a TrkB-dependent manner, robustly mimicking BDNF's biochemical and physiological actions.¹¹⁰ Such flavonoid-based agonists are considered as promising compounds to improve neuroprotection.¹⁰⁹ As for the small molecule TrkB antagonist, ANA-12, it demonstrates a 2-site mode of action, blocking activation by BDNF noncompetitively in high (specific to neurons) and low (TrkB only-expressing cells) affinity sites, also showing selective TrkB receptor binding and inhibition of downstream processes without altering TrkA and TrkC functions.⁹² Preclinical studies report that systemic administration of ANA-12 enhanced TrkB phosphorylation in the NAc of learned helplessness rats,¹¹⁴ and reduced METH-induced depression-like behavior and dopamine release,¹¹⁵ but showed no effects on BDNF amounts, being unable to increase levels of BDNF protein.⁹³ Furthermore, ANA-12 bilateral infusion into the NAc shell of $\alpha 7$ subtype of nicotinic acetylcholine receptor knockout mice (a rat model of inflammation/depression implicated in schizophrenia) induced a rapid antidepressant effect through increased normalization of synaptogenesis and reduced depressive-like behaviors/anhedonia in the forced swim, tail suspension, and sucrose preference tests.¹¹⁶ These effects were not observed with 7,8-DHF or the selective serotonin reuptake inhibitor, fluoxetine. In another study, Shirayama

and colleagues¹¹⁴ showed that acute bilateral infusion of 7,8-DHF, but not ANA-12, into the infralimbic mPFC and hippocampus (i.e., CA3 and dentate gyrus) promoted antidepressant effects in learned helplessness rats. These findings indicate that TrkB activation in the mPFC and hippocampus, and TrkB antagonism at the NAc, promote antidepressant effects and normalizes alterations in BDNF/TrkB signaling. Both ANA-12 and 7,8-DHF remain to surpass preclinical status, thus more studies on their impact in various disease states that have aberrant receptor stability and function are warranted. To our knowledge, there is no data available concerning diffusion profile of ANA-12 or any other molecules of similar size and injection volume. Furthermore a detailed comparison of metabolic rates in brain and periphery following systemic and direct infusion of small molecule TrkB antagonists, and agonists would be a valuable addition to the existing literature and would further aid in replicable and comparable studies aiming for a move from preclinical to clinical applications.

THE PUZZLE OF TrkB ISOFORMS AND FUNCTIONAL IMPACT

s0055

p0245 BDNF and activation of TrkB signaling pathways are important for the control of developmental processes. However, the presence of TrkB receptor isoforms [TrkB full length (TrkB.FL) and the truncated form (TrkB.T1)] suggests that each isoform operates on multiple enzymatic and kinase pathways (Fig. 13.3), highlighting additional mechanisms that influence a plethora of neurotrophin-induced signaling molecules.^{117, 118} The isoform signature on discrete functional changes upon TrkB receptor activation has only emerged in the last decade. To date, there is still a need to elucidate the complex function of TrkB isoforms on BDNF actions in the CNS with relation to neurological disorders and stress pathology, as available reports are limited and findings can be inconsistent. An excellent review by Tejada and Diaz-Guerra¹⁰⁹ discussed the relevance of combining actions geared at both BDNF and TrkB targets to enhance neurotrophic signaling and further characterize aberrant BDNF/TrkB signaling. BDNF exerts trophic effects via phosphorylation of TrkB.FL, effecting downstream signaling cascades. However, it may also promote cell death via binding with P75^{NTR},¹¹⁹ especially when TrkB.FL is downregulated or not active, or when phosphorylation of TrkB.FL is combined with upregulation of TrkB.T1.^{117, 120, 121} In the postmortem brains of suicide victims with previous history of major depression, BDNF levels, and that of TrkB.FL and TrkB.T1 are reduced in the PFC,¹²²⁻¹²⁴ similar to effects observed in Methylmercury-exposed wild-type mice, which also extended to increased anxiety and depression

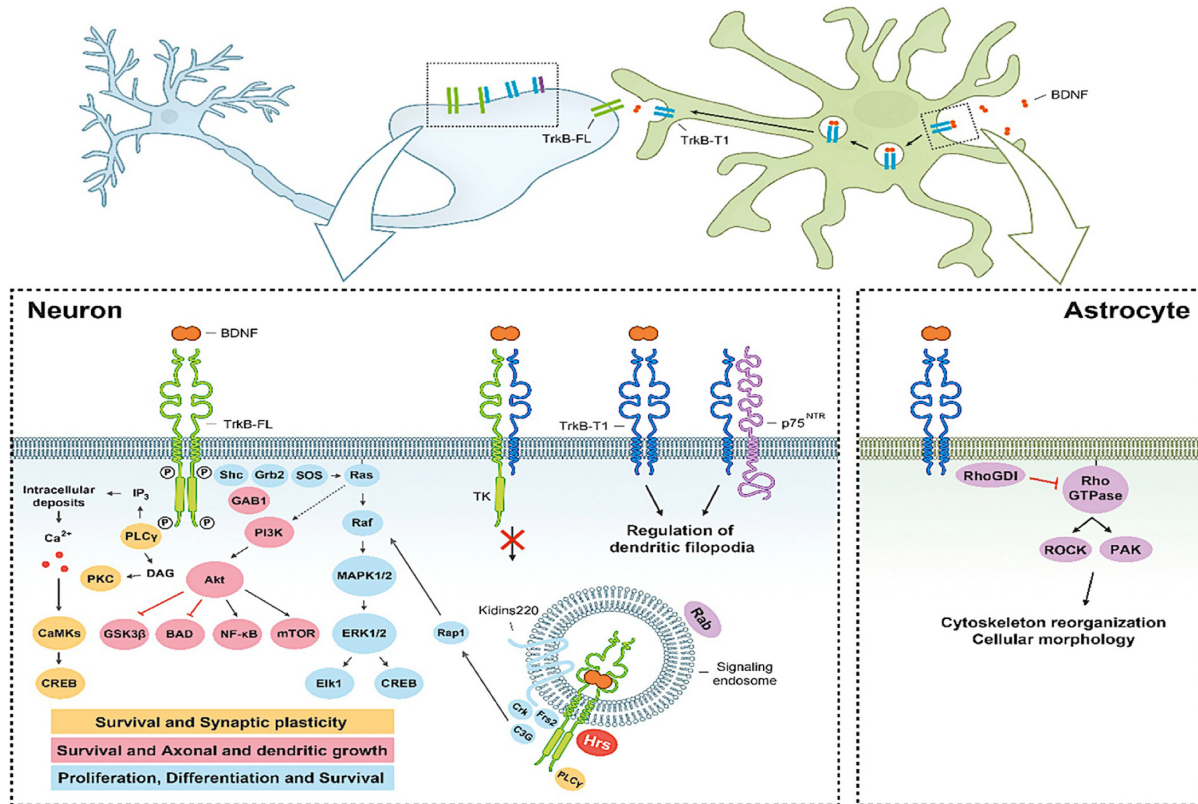


FIGURE 13.3 Function of BDNF/TrkB signaling in the CNS. BDNF binding to TrkB-FL in neurons (*left diagram*) induces receptor homodimerization and activation, triggering three main signaling pathways: MAPK/ERK (*blue*), PI3K (*pink*), and PLC γ (*yellow*), which regulate several processes central to neuronal function. The ligand-receptor complex can internalize and continue functioning in signaling endosomes. Alternatively, TrkB-T1 can form heterodimers with TrkB-FL and block its transduction cascades. TrkB-T1 is also involved in the regulation of local BDNF concentration (*upper diagram*) and cell morphology, both in neurons and astrocytes (respectively, *left and right diagrams*). P, phosphorylation sites important for receptor activation. Adapted and reprinted with permission from Tejada GS, M. Díaz-Guerra M. Integral characterization of defective BDNF/TrkB signaling in neurological and psychiatric disorders leads the way to new therapies. *Int J Mol Sci.* 2017;18:268. <https://doi.org/10.3390/ijms18020268>.

behavior.¹²⁵ Overexpression of hippocampal TrkB.FL in transgenic mice through activation of the TrkB-phospholipase C γ pathway reduced anxiety¹²⁶ and protected against memory deficits and depression behavior.¹²⁵ However, excess TrkB.FL activation has been reported in the induction of epilepsy and destruction of hippocampal neurons,¹²⁷ triggered by heightened and aberrant neuronal excitability. In contrast, overexpression of TrkB.T1 significantly inhibited TrkB.FL signaling through a dominant-negative mechanism,^{120, 128} a phenomenon observed particularly in the PFC of female schizophrenic subjects,¹²⁹ and is shown to affect dendritic morphology.¹³⁰ Interestingly, TrkB.T1 deficiency in mice did not significantly impact global brain development and function but was reported to increase anxiety and induce morphological changes in neurite length and complexity in the BLA.¹³¹ As such, attenuated TrkB.FL is reported to impair E3 ligase c-Cbl-induced stabilization by ubiquitination, whereas diminished TrkB.T1 increased

Has-miR-185, a regulator of the truncated TrkB isoform.^{123, 124} The predominance of TrkB.T1 signaling in the adult brain highlights the need to investigate its dynamic physiological function in vivo and suggests that therapies aimed at ameliorating neurotrophin deficits may consider blocking excessive truncated TrkB function as a means to properly regulate BDNF/TrkB signaling. Possibility has been evoked that the disease process may compromise the TrkB receptor isoforms' properties, which could invalidate or increase difficulty in the study of these biological systems as available markers may not correctly grasp the mechanisms involved at the molecular and systems levels. As such, increasing requirements for effective therapeutic compounds targeting TrkB signaling and its downstream cascades is warranted in disease states that can promote excitotoxicity, especially when used in synergy with drugs having upstream actions, in order to attain balance of TrkB.FL/TrkB.T1 isoform relative levels.¹⁰⁹

FUTURE PERSPECTIVE

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Plasticity-related processes are shown more relevant in the efficacy of antidepressant therapeutic means and in improving cognitive function. Although inhibiting BDNF signaling may not lead to depressive phenotype, attenuation of stress-induced mood disorders may be achieved via selective antagonism or agonism of BDNF actions following regulation of differential expression of TrkB receptors in stress or reward regions of the brain and within areas of the PNS. At this juncture, studies that assess the mechanistic and molecular components of BDNF/TrkB signaling in enhancing adaptive capabilities and attenuating damaging responses are necessary, but they only touch the surface of a very complex system. This complexity is related to a great diversity of biological systems that are activated and regulated by TrkB receptors and their downstream signaling pathways, as well as the distinct roles of cell surface signaling by BDNF-bound TrkB receptors and endosomes that bind and internalize BDNF/TrkB complexes.¹⁰⁹ Besides pharmaceutical interventions and behavioral observations, many approaches to reduce the impact of chronic and repeated stress exposure, such as implementing changes in lifestyle, reprogramming deleterious personal belief systems, improving government policies geared toward a more health-conscious society, considering the context of experiences across the lifespan, and reducing stress burden at the individual level would have a huge influence on modulating the prevalence of disease states. Despite an overwhelming amount of research on BDNF/TrkB signaling in stress and treatment strategies, more research geared toward a clinical approach is required to elucidate aberrant neurotrophic signaling in mood disorders. This is especially important, as the translational perspective of BDNF-related preclinical research in the pathogenesis and facilitation of depression and anxiety in humans remains controversial.

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Non-Print Items

Abstract

The extensive literature on stress effects support that chronic and repeated stress exposure can lead to dysregulation of the hypothalamic–pituitary–adrenal axis, cause a gradual decrease in its activity, or facilitate axis responses to subsequent stressors, thereby influencing active coping mechanisms and the ability to prevent allostatic load on the brain. Despite the large number of studies establishing the crosstalk between the plasticity-related neurotrophin brain-derived neurotrophic factor (BDNF) and the stress hormone glucocorticoids (GCs) in the pathophysiology of depression, a lack of information exists with respect to sex differences and the translational perspective of BDNF signaling as a potential drug target in modulating stress-related psychiatric diseases. Thus understanding the network of interconnected structures within the brain's stress and reward systems may further highlight the mechanistic relationship between BDNF and GCs in stress adaptation and susceptibility and may provide avenues for clinical relevance in attenuating the deleterious effects of stress exposure.

Keywords: Brain-derived neurotrophic factor, Tyrosine-related kinase B, HPA axis, Glucocorticoids, stress, Depression, Sex-specific differences