Proteolytic Control of Neurotrophin Signaling in Activity-Dependent Brain Plasticity: Relevance to Compulsive-Like Behavior

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Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Neural plasticity depends not only on the abundance of neurotrophic factors but also on their molecular processing, receptor preference, cellular localization, and temporal pattern of release. Brain-derived neurotrophic factor (BDNF) represents a particularly important example because its precursor, proBDNF, and mature form can engage distinct receptor systems and promote functionally divergent effects on synaptic strength, neuronal remodeling, and behavioral adaptation. Emerging evidence indicates that intracellular proprotein convertases and extracellular proteolytic systems regulate the balance between these forms, thereby creating a molecular checkpoint capable of translating neuronal activity into persistent circuit modification. This mechanism may be especially relevant to disorders characterized by behavioral rigidity and impaired adaptive control, including obsessive-compulsive disorder and related compulsive phenotypes. Physical exercise produces widespread activity-dependent changes in BDNF synthesis, neurotrophin signaling, monoaminergic transmission, cellular metabolism, and synaptic remodeling. Pharmacological enhancement of serotonergic signaling can similarly recruit delayed neuroplastic mechanisms extending beyond acute serotonin-transporter inhibition. The convergence of these interventions on neurotrophin-dependent signaling therefore provides a biologically plausible framework for understanding how apparently different therapeutic manipulations may influence repetitive or inflexible behavior. This review examines the physiology of precursor-to-mature neurotrophin processing, its relationship with BDNF receptor signaling, exercise-induced plasticity, serotonergic modulation, and rodent models of compulsive-like behavior. Particular emphasis is placed on unresolved questions concerning regional specificity, temporal dynamics, proteolytic regulation, and the interpretation of behavioral endpoints. A neurotrophin-maturation perspective may provide an important bridge between molecular plasticity and systems-level behavioral flexibility.

Keywords: neuroplasticity, BDNF, proteolytic processing, compulsive behavior

Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent intrusive thoughts and repetitive behaviors that become difficult to suppress despite their adverse functional consequences. Although serotonin reuptake inhibitors remain a major pharmacological treatment, contemporary neurobiology does not support a purely serotonergic explanation of OCD. Instead, the disorder is increasingly regarded as a systems-level disturbance involving corticostriatal-thalamo-cortical circuitry, glutamatergic and dopaminergic modulation, altered habit formation, impaired inhibitory control, and deficient flexibility between goal-directed and repetitive behavioral programs. These observations suggest that successful treatment may require gradual modification of circuit function rather than simple correction of a single neurotransmitter concentration. [1]

One mechanism capable of linking neurotransmitter signaling to longer-lasting circuit reorganization is neurotrophin-dependent plasticity. Brain-derived neurotrophic factor regulates dendritic structure, synaptic efficacy, neuronal survival, neurotransmitter phenotype, and experience-dependent remodeling throughout the central nervous system. Importantly, BDNF biology is more complex than a simple relationship between higher BDNF concentration and improved neuronal function. BDNF is synthesized initially as pre-proBDNF and subsequently as proBDNF, after which proteolytic processing determines the relative availability of precursor and mature forms with different receptor preferences and physiological consequences. [2]

The distinction between proBDNF and mature BDNF is therefore potentially important in conditions characterized by persistent maladaptive behavioral patterns. Mature BDNF predominantly activates tropomyosin receptor kinase B (TrkB), promoting pathways related to synaptic potentiation, neuronal survival, dendritic development, and adaptive remodeling. In contrast, proBDNF can signal through p75 neurotrophin receptor and sortilin-containing complexes, favoring processes such as synaptic weakening, dendritic simplification, and long-term depression under particular conditions. The functional state of a circuit may consequently depend not only on total BDNF expression but also on how efficiently precursor BDNF is processed. [3]

The aim of this review is to examine proteolytic regulation of neurotrophin signaling as an underexplored physiological interface between activity-dependent plasticity and compulsive-like behavior. Particular attention is given to exercise and serotonergic modulation because both interventions produce delayed changes in BDNF-related signaling and neuronal plasticity. The principal research gap is that most behavioral neuroscience studies measure total BDNF without simultaneously assessing precursor BDNF, mature BDNF, or the enzymes responsible for their interconversion. Consequently, an important mechanistic layer linking treatment exposure to behavioral adaptation may remain undetected. [4]

2. BDNF Maturation as a Physiological Plasticity Switch

BDNF is synthesized in the endoplasmic reticulum as pre-proBDNF. Removal of the signal peptide generates proBDNF, which subsequently enters regulated and constitutive secretory pathways. Intracellular cleavage can occur within the trans-Golgi network or secretory vesicles through subtilisin-like proprotein convertases, including furin and related enzymes. Alternatively, proBDNF may be secreted and subsequently cleaved extracellularly by proteases such as plasmin and selected matrix metalloproteinases. These parallel routes allow neuronal activity, intracellular trafficking, extracellular protease activity, and cellular metabolic state to influence the final ratio of precursor to mature neurotrophin. [5]

Classical biochemical studies demonstrated that mammalian proprotein convertases are capable of processing neurotrophin precursors, establishing the fundamental concept that neurotrophin maturation is enzymatically regulated rather than constitutive. Furin is widely distributed and cycles through the trans-Golgi network, endosomal compartments, and cell surface, placing it strategically within the secretory apparatus. Because neuronal activation alters secretory trafficking and protein processing, changes in convertase activity could theoretically modify the biological effect of a given amount of newly synthesized BDNF without requiring a proportional change in BDNF gene transcription. [6]

The physiological importance of this distinction is supported by evidence that proBDNF and mature BDNF have opposing effects on synaptic structure. Cleavage-resistant proBDNF models demonstrate reduced dendritic complexity, decreased spine density, impaired basal synaptic transmission, reduced long-term potentiation, and enhancement of long-term depression. These observations show that precursor accumulation cannot be considered biologically inert. Rather, incomplete neurotrophin maturation can shift the direction of synaptic remodeling and potentially bias neural networks toward reduced flexibility. [7]

Proteolytic processing also appears temporally organized during memory-related plasticity. Experimental studies of late-phase long-term potentiation have shown that extracellular and intracellular cleavage mechanisms can contribute at different stages. Early phases may use extracellular processing of secreted precursor, whereas maintenance of long-lasting potentiation can depend on newly synthesized neurotrophin undergoing intracellular processing. This temporal division suggests that proteolytic machinery participates not merely in neurotrophin production but in determining when plastic changes are initiated and stabilized. [8]

3. Neurotrophin Signaling and the Physiology of Behavioral Flexibility

Mature BDNF binding to TrkB activates several intracellular cascades, including phosphatidylinositol-3-kinase/Akt, Ras–mitogen-activated protein kinase, and phospholipase C-γ pathways. These pathways influence protein synthesis, cytoskeletal remodeling, synaptic receptor trafficking, neuronal excitability, and transcriptional regulators such as cAMP response element-binding protein. Such processes are essential for converting transient changes in neural activity into persistent alterations in synaptic organization. In networks controlling action selection, reinforcement learning, and response inhibition, these mechanisms can influence whether previously learned behavioral sequences remain rigid or become susceptible to modification. [9]

Compulsive behavior has been linked to abnormal balance between goal-directed and habitual action-control systems. Cortical regions including orbitofrontal, medial prefrontal, and anterior cingulate territories interact with dorsal and ventral striatal compartments through recurrent loops involving globus pallidus, substantia nigra, and thalamus. Excessive stabilization of specific action sequences or deficient updating of expected outcomes may contribute to repetitive behavior. Neurotrophin signaling is relevant because synaptic reweighting within these networks is necessary for reversal learning, extinction, inhibitory control, and adaptive responses to changing environmental contingencies. [10]

Clinical observations also provide indirect support for altered neurotrophic regulation in OCD. Peripheral BDNF measurements cannot be assumed to represent brain concentrations, yet drug-naïve OCD cohorts have shown alterations in circulating BDNF compared with healthy participants. The significance of peripheral findings remains uncertain because platelet release, exercise status, metabolic factors, circadian variation, and assay methodology influence serum measurements. Nevertheless, such observations have encouraged investigation of neuroplastic mechanisms beyond classical neurotransmitter hypotheses. [11]

4. Exercise as an Activity-Dependent Modulator of Neurotrophin Biology

Physical exercise provides one of the strongest physiological stimuli for activity-dependent neural adaptation. Exercise increases cerebral perfusion, metabolic substrate utilization, vascular signaling, neuronal firing, peripheral myokine production, and multiple neurotrophic pathways. In experimental animals, voluntary running and treadmill training can increase BDNF transcription and activate downstream TrkB-related signaling in several brain regions. Importantly, the response varies with exercise mode, duration, intensity, stress exposure, age, sex, and the brain region examined. Thus, exercise should be regarded as a multidimensional physiological stimulus rather than a unitary intervention. [12]

Experimental evidence demonstrates that exercise can alter the molecular forms of BDNF rather than simply total protein concentration. In rats subjected to treadmill exercise, increases in mature BDNF have been observed in cortical tissue, with mature BDNF showing relationships with synaptophysin expression. Such findings are particularly informative because assays of total BDNF may obscure

biologically meaningful differences between proBDNF accumulation and successful generation of mature protein. This methodological issue is central to investigations attempting to connect exercise with functional neuroplasticity. [13]

Exercise-induced BDNF signaling activates downstream pathways involved in cellular survival and synaptic remodeling. Voluntary physical activity has been associated with increased activity of PI3K, Akt, Trk-related signaling, and CREB in the rodent hippocampus. These pathways can modify transcription, mitochondrial function, synaptic protein expression, and neuronal resistance to metabolic stress. Consequently, exercise-induced improvement in behavioral flexibility may emerge from coordinated molecular adaptations rather than from a single increase in BDNF concentration. [14]

Exercise also influences monoamine systems that interact bidirectionally with neurotrophin signaling. Chronic aerobic training has been shown to modify serotonin metabolism within cortical and subcortical regions of rodents, while long-term exercise can affect serotonin transporter expression, serotonin receptors, and BDNF simultaneously. BDNF contributes to serotonergic neuronal development and function, whereas serotonergic activity can regulate BDNF expression. This reciprocal relationship provides a mechanistic basis for convergence between physical activity and pharmacological serotonergic manipulation. [15]

5. Serotonergic Pharmacotherapy Beyond Acute Transporter Blockade

Selective serotonin reuptake inhibitors increase extracellular serotonin relatively rapidly, yet clinically meaningful improvement in compulsive symptoms generally requires prolonged administration. This temporal discrepancy suggests that downstream adaptations are essential to therapeutic action. Chronic serotonergic treatment alters receptor sensitivity, intracellular signaling, gene transcription, synaptic protein expression, and neurotrophic pathways. Therefore, the acute increase in serotonin availability should be regarded as an initiating event rather than the complete mechanism responsible for behavioral improvement. [16]

Fluoxetine provides an extensively studied example. Chronic administration can increase BDNF expression in selected cortical and mesocorticolimbic regions, and repeated exposure has been associated with persistent changes in medial prefrontal dendritic complexity, spine density, and BDNF/TrkB expression. Such findings are important for compulsivity because prefrontal cortical regions participate in behavioral inhibition, outcome evaluation, and top-down regulation of striatal action selection. Neuroplastic changes in these regions could therefore contribute to delayed therapeutic modification of rigid behavior. [17]

Evidence additionally suggests that some plasticity-promoting effects of fluoxetine are not explained exclusively by serotonin-transporter blockade. Experimental studies have demonstrated activation of BDNF/TrkB-associated signaling in cellular and animal models even under conditions that reduce the contribution of the serotonin transporter. More recent work has proposed direct interaction between antidepressant drugs and the transmembrane domain of TrkB, facilitating receptor localization and responsiveness to endogenous BDNF. These findings broaden the conventional monoamine hypothesis and place neurotrophic signaling closer to the center of long-term antidepressant-induced plasticity. [18]

6. Convergence of Physical Activity and Pharmacological Plasticity

A particularly relevant observation is that exercise and antidepressant treatment can produce additive or potentiating effects on BDNF transcription. In rodent hippocampus, combined physical activity and antidepressant exposure has increased specific BDNF transcripts more strongly or rapidly than either intervention alone. Although these experiments were not designed specifically as models of OCD, they demonstrate a general biological principle: behaviorally induced neuronal activation and pharmacologically initiated monoaminergic signaling can converge on common transcriptional and plasticity machinery. [19]

The important unanswered question is whether such convergence occurs only at BDNF transcription or extends to precursor processing. Increased synthesis of proBDNF would not necessarily produce an equivalent increase in mature BDNF if intracellular convertase capacity, vesicular trafficking, extracellular proteolysis, or receptor availability became limiting. Accordingly, simultaneous

measurement of BDNF mRNA, proBDNF, mature BDNF, relevant processing enzymes, TrkB phosphorylation, and p75NTR signaling could distinguish enhanced synthesis from enhanced biological maturation. This distinction may substantially improve mechanistic interpretation of intervention studies. [5]

Proteolytic regulation may also offer a mechanism through which exercise intensity influences neural outcomes. Moderate activity can enhance adaptive neuroplastic pathways, whereas excessively intense forced exercise may activate glucocorticoid and oxidative stress responses capable of modifying BDNF expression and protease regulation. In animal experiments, voluntary wheel running and forced treadmill exercise are therefore not physiologically interchangeable. Stress generated by forced exercise can itself alter corticostriatal function, serotonin signaling, and repetitive behavior, creating important confounds when exercise is used as an experimental treatment. [20]

7. Relevance to Rodent Compulsive-Like Behavior

No rodent model reproduces the subjective obsessions that define human OCD; preclinical models instead capture selected dimensions such as repetitive responding, excessive checking, behavioral persistence, stereotypy, or resistance to changing contingencies. Frequently used paradigms include marble burying, quinpirole-induced checking, signal attenuation, spontaneous stereotypy in deer mice, and pharmacologically altered alternation behavior. Each differs in face, construct, and predictive validity, making it inappropriate to equate suppression of one repetitive behavior automatically with an anti-OCD effect. [21]

Marble burying is widely used because it is technically straightforward and sensitive to serotonergic drugs, but its interpretation remains controversial. Burying is part of normal rodent behavioral repertoires, and reductions can arise from anxiolysis, altered exploration, sedation, motor impairment, or changes in neophobia rather than specific suppression of compulsivity. Appropriate locomotor controls and complementary behavioral tests are therefore essential when relating molecular findings to a compulsive-like phenotype. [22]

Quinpirole sensitization offers a different approach by producing persistent, ritualized checking behavior after repeated D2/D3 receptor stimulation. The model emphasizes dopaminergic and corticostriatal components of compulsivity and can reveal interactions among dopamine, serotonin, and plasticity mechanisms. Because repeated treatment is necessary for the checking phenotype to develop, the model may be particularly useful for investigating gradual molecular remodeling rather than acute suppression of repetitive behavior. [23]

An optimal experimental strategy would therefore connect biochemical findings with more than one behavioral domain. Measures of repetitive behavior could be combined with open-field locomotion, anxiety-related behavior, reversal learning, spontaneous alternation, or an operant measure of behavioral flexibility. If an intervention changes both the molecular balance between precursor and mature neurotrophin and a specific measure of behavioral rigidity without producing nonspecific motor suppression, the mechanistic inference becomes substantially stronger. [21]

8. Methodological Considerations for Studying Neurotrophin Processing

Tissue selection is crucial. OCD-relevant physiology is centered primarily on frontal cortical–striatal circuits, whereas much of the exercise-BDNF literature is based on hippocampal measurements. Although the hippocampus remains useful for confirming a systemic plasticity response, the orbitofrontal or medial prefrontal cortex and striatum provide greater mechanistic proximity to compulsive behavior. Region-specific analysis may reveal opposing responses that disappear when whole-brain homogenates are examined. [10]

Protein methodology requires similar precision. Commercial BDNF assays often quantify total immunoreactivity and may not reliably discriminate precursor from mature forms. Western blotting with appropriately validated antibodies, accompanied where possible by orthogonal assays, is preferable when the central hypothesis concerns neurotrophin maturation. Measurement of a processing enzyme alone is also insufficient because protein abundance does not establish enzymatic activity. Downstream indicators such as the proBDNF ratio and TrkB activation help determine whether changes in processing

machinery are functionally meaningful. [13]

Timing represents another major variable. Acute exercise can activate neurotrophic signaling within hours, whereas chronic exercise produces transcriptional and structural adaptations. Similarly, acute serotonin-transporter blockade differs fundamentally from chronic pharmacological treatment. Sampling immediately after the final exercise session may therefore measure acute activity-dependent changes, whereas sampling after a defined recovery period may better capture sustained adaptation. A time-course design is especially valuable when linking proteolytic processing to behavior. [19]

Sex should also be considered as a biological variable. Gonadal hormones influence BDNF expression, serotonergic transmission, stress responsiveness, and exercise adaptation. Female rodents may display estrous-cycle-associated variability, but exclusion of females prevents determination of whether a proposed mechanism is sexually dimorphic. Balanced experimental designs or carefully controlled sex-specific studies would strengthen translational relevance. [24]

9. Translational Implications and Research Gap

Clinical evidence for exercise as an adjunctive intervention in OCD remains preliminary. Systematic reviews suggest encouraging reductions in symptom severity in several small studies, but randomized evidence is limited and susceptible to methodological concerns. Exercise should therefore not be framed as an established replacement for exposure-based psychotherapy or evidence-based pharmacotherapy. Its more defensible role at present is as a physiologically plausible adjunct whose molecular effects may help identify mechanisms of treatment responsiveness and residual symptom reduction. [25]

A major opportunity lies in shifting the field from measuring neurotrophin quantity to measuring neurotrophin processing. If behavioral rigidity reflects deficient capacity for adaptive circuit remodeling, then interventions might influence behavior by altering the balance between plasticity-promoting and plasticity-restricting neurotrophin signals. Demonstrating such a relationship would require coordinated assessment of proteolytic processing, receptor activation, region-specific signaling, and behavior rather than reliance on a single molecular endpoint. [2]

Future studies should also test whether combined interventions produce additive, synergistic, or merely overlapping effects. A factorial design containing control, exercise, pharmacological, and combined-treatment groups can distinguish these possibilities. Statistical interaction testing is particularly important because a combined group showing the largest numerical effect does not itself prove synergy. Linking interaction effects to precursor BDNF ratios and circuit-relevant behavior would provide substantially stronger mechanistic evidence. [19]

10. Conclusion

Neurotrophin maturation represents a physiologically meaningful but insufficiently examined level of neural plasticity. The balance between proBDNF and mature BDNF can determine the direction of synaptic remodeling, while intracellular and extracellular proteolytic systems provide regulatory checkpoints linking neuronal activity to long-lasting structural and functional adaptation. Exercise and serotonergic pharmacotherapy both influence BDNF-related signaling through partly overlapping mechanisms, creating a plausible molecular interface through which they may alter behavioral flexibility. In compulsive-like states, examining neurotrophin processing alongside corticostriatal behavior may therefore reveal mechanisms that remain invisible when only total BDNF or neurotransmitter concentration is measured.

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