

BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders

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Brain-derived neurotrophic factor (BDNF) and serotonin (5-hydroxytryptamine, 5-HT) are known to regulate synaptic plasticity, neurogenesis and neuronal survival in the adult brain. These two signals co-regulate one another such that 5-HT stimulates the expression of BDNF, and BDNF enhances the growth and survival of 5-HT neurons. Impaired 5-HT and BDNF signaling is central to depression and anxiety disorders, but could also play important roles in the pathogenesis of several age-related disorders, including insulin resistance syndrome, Alzheimer's disease and Huntington's disease. Enhancement of BDNF signaling may be a key mechanism whereby cognitive stimulation, exercise, dietary restriction and antidepressant drugs preserve brain function during aging. Behavioral and pharmacological manipulations that enhance 5-HT and BDNF signaling could help promote healthy brain aging.

Intercellular and intracellular signaling pathways that sculpt neuronal circuits during brain development also serve fundamental roles in regulating synaptic plasticity and cell survival in the adult brain. Neurotrophic factors and neurotransmitters are two major classes of intercellular signals that mediate such adaptive neuroplasticity throughout life. The numbers of neurotrophic factors and neurotransmitters, and the signal transduction pathways they activate, are diverse and, in many cases, are restricted to particular populations of neurons within the brain. However, recent research has identified brain-derived neurotrophic factor (BDNF) and serotonin (5-hydroxytryptamine, 5-HT) as two prominent signals that act in concert to regulate aspects of neural plasticity in multiple brain regions. It appears that these could become compromised in aging and age-related neurodegenerative disorders. The preservation of these signaling pathways therefore might be crucial for maintenance of neural plasticity and disease resistance during aging. In this article, we present a viewpoint in which 5-HT and BDNF signaling act cooperatively to engage molecular changes in neurons that allow the brain to respond adaptively to environmental demands during aging, thereby ensuring successful (disease-free) brain aging.

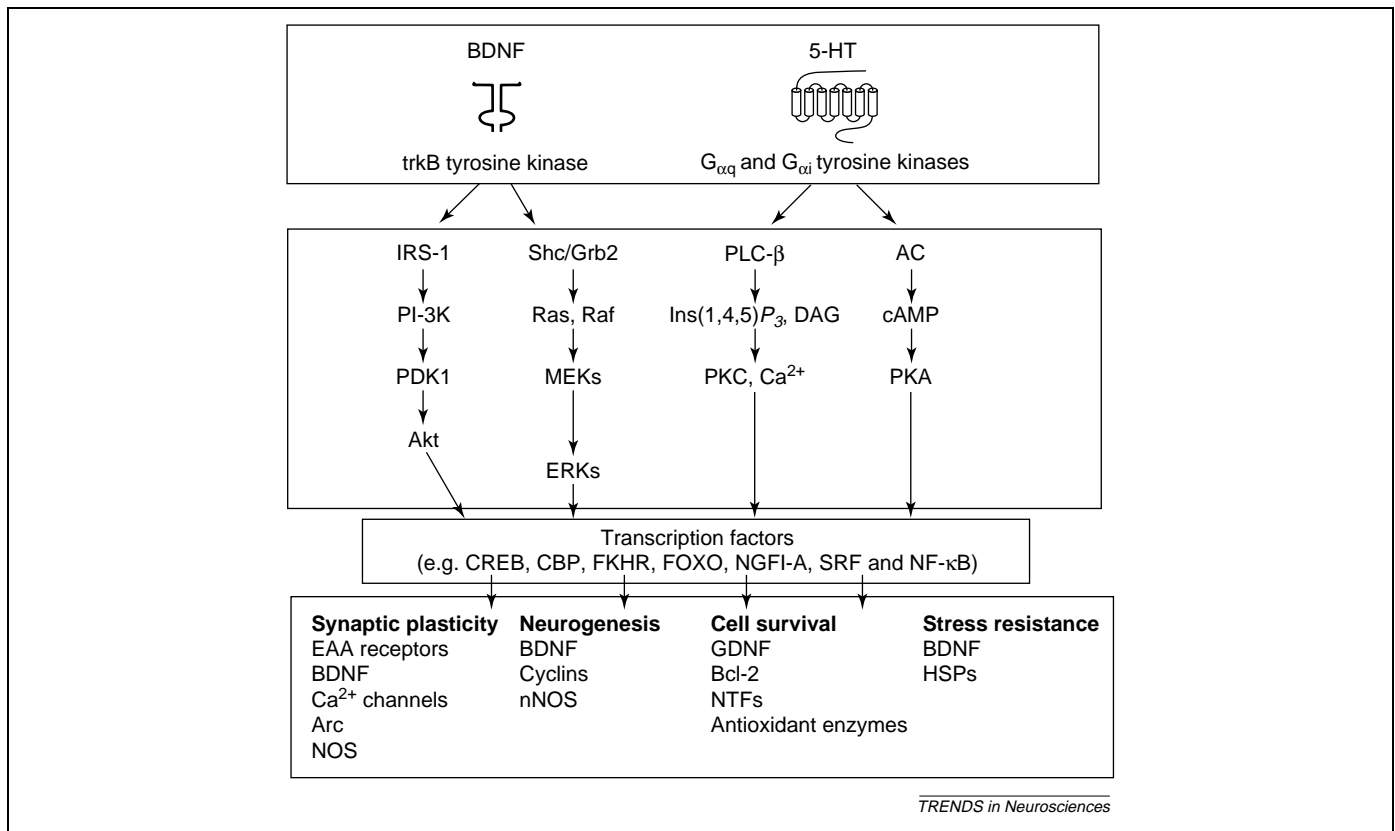
Roles of BDNF and 5-HT in neuronal plasticity and survival

BDNF, a member of the neurotrophin family, activates a high-affinity cell surface receptor (trkB) that is coupled to activation of phosphatidylinositol-3-kinase and protein kinase B (Akt) (Figure 1). By promoting neurogenesis, synaptic plasticity and cell survival, BDNF plays a pivotal role in the development and plasticity of the brain. During development of the cerebral cortex and hippocampus, BDNF induces the differentiation of neural stem cells into neurons and promotes the survival of newly generated neurons [1–3]. BDNF signaling at synapses enhances long-term potentiation (LTP), a process of synaptic strengthening associated with learning and memory; the effect of BDNF on LTP is apparently mediated by cAMP-response-element-binding protein (CREB), which regulates the expression of genes involved in LTP and memory formation [4]. Levels of BDNF are increased in the hippocampus of rats during and after performance of a spatial learning task (a radial-arm maze), and both acquisition and maintenance of spatial memory are impaired when BDNF levels are decreased using antisense methods [5]. In rats that had previously acquired spatial memory by extensive training, suppression of BDNF expression impaired both reference and working memory [5]. Another study showed that mice lacking one copy of the BDNF gene exhibit impaired spatial learning in the Morris water maze [6]. BDNF also plays an important role in preventing death of neurons during development, and promotes cell survival during stressful conditions such as ischemia and trauma in the adult brain [7].

5-HT is produced by neurons located in the brainstem raphe nucleus; the axons of these 5-HT neurons innervate multiple cortical and subcortical brain regions to regulate an array of behaviors including sensorimotor control, cognition and mood [8]. There are seven different subtypes of 5-HT receptor, some of which activate GTP-binding proteins that are coupled either positively or negatively to the adenylate cyclase–cAMP signaling pathway, whereas other 5-HT receptors activate phospholipase C, resulting the production of inositol (1,4,5)-trisphosphate and diacylglycerol (Figure 1). In addition to modulating synaptic function in the adult brain, 5-HT controls important functions in brain development where it regulates neurite outgrowth, synaptogenesis and cell survival [9]. Studies of

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Figure 1. Signal transduction pathways by which brain-derived neurotrophic factor (BDNF) and serotonin (5-hydroxytryptamine, 5-HT) regulate neuronal plasticity and cell survival. BDNF binds to its high-affinity receptor tyrosine kinase trkB resulting in the recruitment of proteins that activate two different signal transduction cascades. One cascade involves sequential activation of insulin receptor substrate-1 (IRS-1), phosphatidylinositol-3-kinase (PI-3K), 3-phosphoinositide-dependent protein kinase-1 (PDK1) and protein kinase B (Akt). The other involves activation of Shc/Grb2, Ras, Raf, mitogen-activated protein kinase kinases (MEKs) and extracellular signal regulated kinases (ERKs). 5-HT activates seven-transmembrane-domain receptors which, depending on the specific subtype of 5-HT receptor, are coupled to different GTP-binding proteins (e.g. G_{αq} and G_{αi} tyrosine kinases). Two major pathways activated by 5-HT are one involving adenylate cyclase (AC), cAMP and protein kinase A (PKA), and another involving phospholipase Cβ (PLC-β), inositol (1,4,5)-trisphosphate [Ins(1,4,5)P₃], diacylglycerol (DAG) and protein kinase C (PKC). The BDNF and 5-HT signaling pathways activate one or more transcription factors that regulate expression of genes encoding proteins involved in neural plasticity, stress resistance and cell survival. Such transcription factors include cAMP-response-element-binding protein (CREB) and CREB-binding protein (CBP), forkhead transcription factors of the FOXO family (e.g. FKHR and FOXO), nerve growth factor-inducible factor A (NGFI-A), serum response factor (SRF) and nuclear factor kappa B (NF-κB). Proteins that mediate beneficial neuronal responses to BDNF and 5-HT include excitatory amino acid receptors (EAA receptors), activity-regulated cytoskeleton-associated protein (Arc), neuronal nitric oxide synthase (nNOS), cyclins, Bcl-2 family members, glial-cell-line-derived neurotrophic factor (GDNF), BDNF itself, other neurotrophic factor (NTFs), antioxidant enzymes, and heat-shock proteins (HSPs). Although the pathways shown in this diagram all result in changes in gene transcription, both BDNF and 5-HT can also exert rapid transcription-independent effects on neurons and glial cells. For example, BDNF can trigger depolarization of neurons by activating the Na(V)1.9 channel [70], and can induce Ca²⁺ release from the endoplasmic reticulum of glia via a pathway activated by a truncated trkB receptor [71].

rodents in which 5-HT signaling has been altered using pharmacological or genetic manipulations have provided convincing evidence that 5-HT is involved in learning and memory, although its effects on cognitive function depend on which subtype of 5-HT receptor is activated. For example, activation of 5-HT_{1A} receptors can impair learning and memory whereas 5-HT_{2A} and 5-HT_{2C} receptors facilitate memory formation [10]. A role for 5-HT in neurogenesis has been suggested by studies showing that serotonin-selective reuptake inhibitor (SSRI) antidepressants can stimulate adult hippocampal neurogenesis [11]. 5-HT can also promote the survival of neurons in the adult brain, as demonstrated by the abilities of a 5-HT receptor agonist and SSRI to protect neurons against excitotoxic and ischemic injury in animal models [12,13]. There are therefore several commonalities of function in the CNS for BDNF and 5-HT in terms of their effects on synaptic plasticity, neurogenesis and cell survival.

Illustrating this point, 5-HT and BDNF often function in a cooperative manner to regulate neuronal plasticity and survival. Activation of 5-HT receptors coupled to

cAMP production and CREB activation can induce transcription of the BDNF gene (Figure 1). Conversely, BDNF can stimulate the growth and sprouting of 5-HT neuron axons innervating the cerebral cortex, thereby presumably increasing the number of 5-HT synapses in this brain region [14]. 5-HT and BDNF often activate sets of genes that serve complementary functions in neuronal plasticity and survival (Figure 1). For example, SSRIs induce expression of the activity-regulated cytoskeletal-associated protein Arc, an effector immediate-early gene that has been implicated in LTP and other forms of neuroplasticity, suggesting a potential mechanism whereby 5-HT facilitates learning and memory [15]. Early postnatal handling of rat pups increased expression of nerve growth factor-inducible factor A (NGFI-A) and activator protein-2 (AP-2), two plasticity-associated transcription factors induced by 5-HT and cAMP [16]. Effects of BDNF on neuronal survival, synaptic plasticity and neurogenesis seem to be mediated by signal transduction pathways involving Ca²⁺/calmodulin, Akt kinase and mitogen-activated protein (MAP) kinases [17–19]. Gene targets of these BDNF

signaling pathways include the anti-apoptotic protein Bcl-2 [20], NMDA glutamate receptor subunits [21] and neuronal nitric oxide synthase [3].

BDNF and 5-HT in brain aging and neurodegenerative disorders

Aging

Aging itself appears to be associated with decreased BDNF signaling in the brain. Amounts of BDNF protein in hippocampal pyramidal neurons and dentate granule cells are decreased during aging in monkeys [22]. Basal levels and maze-training-induced increases in BDNF expression were both significantly lower in hippocampal neurons of rats with age-related impairment in learning and memory than in rats of the same age with normal learning and memory function [23]. The reduced BDNF levels during aging might be due to impaired CREB-mediated transcription of the BDNF gene because levels of CREB DNA-binding activity were significantly decreased in several different regions of aged rats compared with young adult rats [24]. In addition, CREB protein levels were decreased in neurons in the cerebral cortex and hippocampus of aged rats [25]. Conditional knockout of BDNF in the cerebral cortex of mice did not affect the number of striatal neurons during development, but resulted in loss of striatal neurons during aging [26]. The ability of stress to upregulate BDNF expression in the striatum is also compromised in aging, consistent with a contribution of impaired neurotrophic signaling in the age-related increase in susceptibility of the brain to neurodegenerative disorders [27].

As with BDNF, levels of 5-HT are decreased in the brains of rats during aging. Treatment of aged rats with the antioxidant α -lipoic acid increases 5-HT levels, suggesting that 5-HT depletion during aging might be due to oxidative stress [28]. Patients with major depression appear to have a generalized increase in oxidative stress as indicated by increased serum levels of lipid peroxidation products and superoxide dismutase and decreased levels of ascorbate. This aberrantly high oxidative stress is, however, reversed when patients are treated with an SSRI [29]. 5-HT signaling in the brain might therefore be able to suppress age-related increases in oxidative stress. Positron emission tomography imaging of glucose metabolism in the brains of young and old control subjects and subjects treated with the SSRI citalopram suggest that age-related loss of 5-HT innervation of the cerebral cortex can be compensated for by the antidepressant in some brain regions [30]. Other findings suggest that 5-HT and BDNF cooperate to suppress age-related functional deficits in the brain. For example, 5-HT could facilitate learning and memory during aging by stimulating the expression of BDNF and by interacting with the cholinergic system [31].

Alzheimer's disease

BDNF expression is decreased in samples of hippocampal tissue from Alzheimer's disease (AD) patients compared with age-matched control subjects [32]. Levels of trkB protein are also decreased in the temporal and frontal cortex of AD patients [33]. CREB signaling is impaired in AD [34], and by exposure of neurons to subtoxic amounts

of the β -amyloid peptide $A\beta_{1-42}$ [35]. Collectively, these findings suggest that $A\beta$ might compromise BDNF production and signaling, which could contribute to synaptic dysfunction and neuronal degeneration in AD. AD patients also exhibit degeneration of serotonergic neurons, which results in a severe CNS functional 5-HT deficit [36]. Reduced 5-HT levels and increased 5-HT_{1A} receptor levels are markers for accelerated cognitive decline in AD [37]. Activation of 5-HT_{1A} autoreceptors results in decreased levels of synaptic 5-HT, and 5-HT_{1A} receptor antagonists can enhance cognition and could be beneficial in the treatment of AD [38]. Thus, the available evidence suggests that abnormalities in 5-HT signaling pathways contribute to the pathogenesis of AD.

Huntington's disease

Evidence has emerged recently that links alterations in BDNF and 5-HT signaling to Huntington's disease (HD). HD involves the progressive degeneration of striatal and cortical neurons, and is caused by CAG repeat expansions in the huntingtin gene resulting in a huntingtin protein with expanded polyglutamine repeats. HD patients and huntingtin mutant transgenic mice exhibit reduced levels of BDNF in vulnerable regions of their brains [39,40]. BDNF levels can be normalized, and the course of the disease retarded, in HD mice maintained on dietary restriction [40], an intervention that enhances neuronal plasticity and protects neurons against oxidative and metabolic insults [41]. Environmental enrichment also increases BDNF levels and ameliorates motor dysfunction in HD mice [42]. HD mice exhibit reduced levels of 5-HT in the striatum; treatment of these mice with the SSRI paroxetine can elevate levels of both 5-HT and BDNF and so retard disease onset and progression, suggesting roles for impaired 5-HT and BDNF signaling in HD [43]. The mechanism(s) responsible for 5-HT and BDNF deficits in HD are not known, but recent findings suggest that mutant huntingtin can impair CREB-binding-protein-mediated transcription [44].

Lifestyle and healthy aging: involvement of the dynamic duo

It is well known that diet and exercise influence the risk of major age-related disorders, including cardiovascular and cerebrovascular diseases and diabetes. Data from epidemiological and animal studies indicate that dietary restriction (reduced meal size and/or frequency) [41,45] and exercise [46,47] might also promote healthy brain aging. In addition, cognitive stimulation might also reduce the risk of AD [48]. Considerable evidence from animal studies suggests a role for BDNF signaling in the beneficial effects of dietary restriction, exercise and cognitive stimulation on brain aging. When rats or mice are maintained on an intermittent fasting dietary restriction regimen, levels of BDNF are increased in several brain regions including the hippocampus, cerebral cortex and striatum [1,49]. Rodents provided access to a running wheel [50] or housed in cognitively stimulating environments [51] also exhibit increased levels of BDNF in several regions of their brains. Evidence that dietary and behavioral factors that enhance neuronal plasticity

and protect against age-related neurodegeneration can also increase brain BDNF production begs the question of whether BDNF signaling mediates the beneficial effects of these factors. Evidence supporting a pivotal role for BDNF comes from studies of rodents in which BDNF levels or activity were selectively decreased or increased. For example, the ability of dietary restriction to enhance hippocampal neurogenesis was significantly attenuated in BDNF heterozygous knockout mice [1], and infusion of a BDNF-blocking antibody into the lateral ventricles of mice abrogated the ability of dietary restriction to protect hippocampal neurons against excitotoxic injury [49].

The mechanism(s) by which the different dietary and behavioral interventions exert their effects on neuronal plasticity and disease susceptibility are not yet fully understood. However, a working model is suggested in which different aspects of a healthy lifestyle converge on BDNF signaling (Figure 2). In the case of cognitive stimulation, it is likely that the increased activity at glutamatergic synapses stimulates CREB activity and transcription of the BDNF gene [52]. In the cases of exercise and dietary restriction, there could be a key role for 5-HT signaling in the increased production of BDNF. As evidence, it has been reported that exercise training increases 5-HT turnover in the cerebral cortex [53] and that 5-HT receptor antagonists can modify the ability of exercise to upregulate BDNF expression [54]. CREB is probably required for this, as BDNF expression is not responsive to SSRI treatment in CREB-deficient mice [55]. Exercise following traumatic brain injury resulted in increased levels of BDNF and improved recovery of

cognitive function in rats [56]. Cognitive function is also improved by SSRI treatment in patients with traumatic brain injury [57], suggesting roles for both BDNF and 5-HT in enhancing the ability of the brain to recover from severe stress. Dietary restriction might also exert beneficial effects by cooperative interactions of 5-HT and BDNF because levels of 5-HT and BDNF are decreased in parallel in the striatum of HD mice, and both intermittent fasting and SSRIs increase BDNF levels and retard disease onset and progression in those mice [40,43]. BDNF and 5-HT thus seem vital in the response of the brain to injury and disease.

Recent findings have shown that, in addition to their adverse effects on the cardiovascular and immune systems, chronic uncontrollable stressors can have detrimental effects on the brain, such as impaired synaptic plasticity and neurogenesis, and increased vulnerability of neurons to oxidative, metabolic and excitotoxic injury [58]. Impairment of BDNF and 5-HT signaling could contribute to the detrimental effects of uncontrollable stress on the brain. Studies of rodents have shown that inescapable stressors cause a pronounced decrease in BDNF levels in the hippocampus and other brain regions, and that SSRI can alleviate the stress-induced decrease in BDNF levels [59]. Stress can also decrease 5-HT signaling, as demonstrated in studies of the effects of chronic social stress on 5-HT indices in the prefrontal cortex of monkeys [60]. Exercise [61], cognitive stimulation [62] and dietary restriction [63] can counteract stress-induced decreases in BDNF expression, consistent with a role for BDNF signaling in the ability of these three lifestyle factors to protect neurons against age-related neuronal degeneration.

Finally, emerging evidence suggests that beneficial effects of 5-HT and BDNF signaling, in regard to successful aging, extend beyond the brain. Insulin resistance syndrome is a major risk factor for diabetes and cardiovascular disease. Mice with reduced BDNF levels are typically obese and exhibit insulin resistance; intermittent fasting increases BDNF levels and improves glucose regulation in those mice [63]. Conditional deletion of BDNF in the brains of postnatal mice results in perturbed energy metabolism and obesity [64], whereas intracerebroventricular administration of BDNF increases peripheral insulin sensitivity [65], suggesting that BDNF signaling in the brain can exert an anti-diabetic action. Consistent with the latter findings, and in line with the cooperative interactions of the dynamic duo, patients with clinical depression (who one would expect to have reduced 5-HT and BDNF levels in their brains) exhibit insulin resistance that can be normalized when they are treated with an SSRI [66]. Dietary restriction enhances BDNF signaling in multiple brain regions, increases insulin sensitivity, reduces blood pressure and improves cardiovascular stress adaptation in rodents [1,49,67,68]. Although increasing evidence suggests that BDNF and 5-HT signaling in the brain can enhance peripheral insulin sensitivity [63–65,69], roles for this dynamic duo in other health benefits of exercise and dietary restriction remain to be established. Nevertheless, BDNF and 5-HT signaling pathways seem to be attractive targets for interventions in aging and age-related disease.

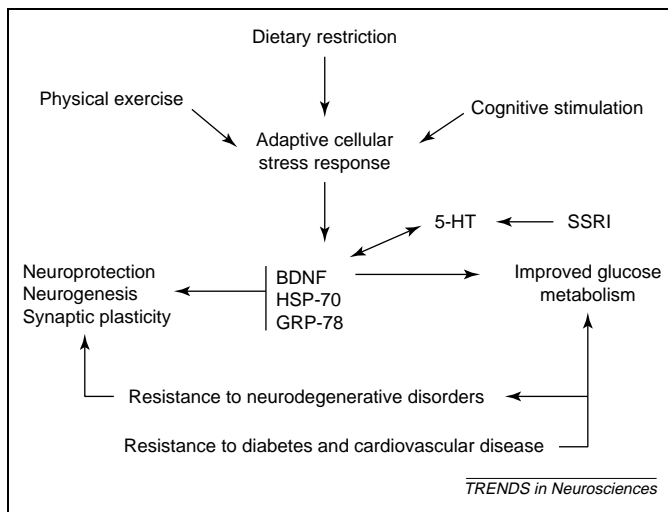


Figure 2. Brain-derived neurotrophic factor (BDNF) and serotonin (5-hydroxytryptamine, 5-HT) mediate beneficial effects of different lifestyle factors on the aging brain. Exercise, dietary restriction and cognitive stimulation all increase the expression of BDNF in multiple brain regions; the upregulation of BDNF can be considered as an adaptive response to the mild stress associated with each lifestyle factor. BDNF and 5-HT act cooperatively such that BDNF enhances 5-HT signaling and 5-HT, in turn, stimulates the production of BDNF. Antidepressants that act by inhibiting 5-HT reuptake (selective serotonin reuptake inhibitors, SSRI) stimulate BDNF production. Beneficial effects of the lifestyle factors and SSRI that are mediated by BDNF [and downstream factors such as heat-shock protein (HSP)-70 and glucose-regulated protein (GRP)-78] include resistance of neurons to age-related oxidative and metabolic stress, stimulation of neurogenesis and enhancement of synaptic plasticity. BDNF can also increase resistance to neurodegenerative disorders, diabetes and cardiovascular diseases via improved glucose metabolism. In these ways, BDNF and 5-HT signaling could promote healthy aging and protect the brain against age-related neurodegenerative disorders.

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