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Neurotrophins as Mediators of Drug Effects on Mood, Addiction, and Neuroprotection

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Abstract

The induction of synthesis or release of endogenous neurotrophic factors in the brain by low-molecular-weight drugs could be a feasible alternative for the direct administration of neurotrophic factors for the treatment of central nervous system disorders. Recent data suggest that several drugs already in clinical use increase the synthesis, release, or signaling of neurotrophins. Antidepressant drugs increase the synthesis and signaling of brain-derived neurotrophic factor (BDNF), and BDNF signaling appears to be both sufficient and necessary for the antidepressant-induced behavioral effects. Furthermore, neurotrophins and other neurotrophic factors play a role in the acute and chronic responses produced by addictive drugs. Moreover, several neuroprotective drugs influence neurotrophin synthesis or signaling, although the significance of these effects is still unclear. These findings reveal a wider role for neurotrophic factors in drug action than has previously been expected, and they suggest that neurotrophin-induced trophic responses in neuronal connectivity and plasticity may be involved in the mechanism of action of several classes of CNS drugs. Improved assay systems are needed for the systematic screening of the effects of putative neuroprotective drugs on the synthesis, release, and signaling of neurotrophic factors, and for the evaluation of the functional role of these factors in the action of novel drug candidates.

Index Entries: BDNF; NGF; antidepressants; morphine; neurodegeneration; plasticity.

Introduction

The central nervous system (CNS) consists of interconnected neural networks, which are believed to form the basis of neuronal function, including thinking, learning, and emotionality. These networks are laid down under genetic instructions, but are fine-tuned during development in a process that requires interaction with the environment. The disruption of these interacting networks has been proposed to underlie several neurodegenerative and psychiatric disorders. Restoration of the disrupted neuronal connections would in this case constitute an optimal, and even curative, therapy for

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CNS disorders. Molecules that are involved in the development and maintenance of synaptic connections in brain are therefore seen as promising candidates for neuroprotective or restorative drugs *(1–5).*

The neurotrophins nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4) play a critical role in activity-dependent neuronal organization during development *(6,7).* In the adult brain, neurotrophins—in particular, BDNF—are involved in learning and memory *(6),* but they can also support the survival and regenerative sprouting of damaged neurons in the brain *(8–10).* These findings have raised considerable interest in neurotrophins as treatments for neurodegenerative disorders. Importantly, a polymorphism in the BDNF gene, which reduces activity-stimulated BDNF release *(11),* has been linked to familial Alzheimer's disease *(12–14)* and bipolar disorder *(15,16).* These recent data indicate that the impaired regulation of BDNF release and signaling may also play a role in human disorders and suggest that treatment strategies that aim at increased neurotrophin signaling may represent more than just symptomatic therapies for many neurodegenerative disorders.

The outcome of the clinical trials in which various neurotrophic factors have been tested for different neurodegenerative disorders have been disappointing *(1,4).* Neurotrophins as relatively large proteins do not pass through the blood-brain barrier *(17)* and the poor outcome of clinical trials has, at least partially, been due to the inability of subcutaneously administered neurotrophins to effectively reach their target neurons. Several different methods have been introduced to circumvent the inability of neurotrophins to penetrate through the blood-brain barrier (for review, *see* ref. *18*). Neurotrophins have been coupled to molecules that would help to transfer them inside the barrier *(18–20),* or they have been introduced into cells, such as T lymphocytes, that are supposed to penetrate from the peripheral side of the barrier to inside *(21).* However, with the possible exception of the transferrin-receptor-coupled NGF *(19,22),* there is little evidence that the carrier-coupled neurotrophins would penetrate to the brain in sufficient amounts. Another strategy has been to search for small-molecule agonists or the activators of neurotrophin receptors (for review, *see* ref. *18*). Although a number of such molecules have been introduced to clinical trials, none of them have so far been used in clinics.

An alternative to the administration of neurotrophins or their agonists is to use small blood-brain-barrier-penetrating molecules, which stimulate the production and release of neurotrophins in their natural site of synthesis in the brain *(23).* Apart from circumventing the blood-brain barrier problem, this strategy also restricts the action of neurotrophic effects to the sites of their natural production, which is likely to produce fewer side effects as compared with injections or agonist treatments, both of which would flood the entire CNS with the drug.

The first drugs that were shown to be able to increase the synthesis of the mRNA and protein for NGF and BDNF in the cortex, hippocampus, and other brain areas were agonists of AMPA-type glutamate receptors, such as kainic acid *(24–26).* It was further observed that the induction of NGF and BDNF mRNA with similar, although not identical, distribution as produced by kainic acid could be induced by the cholinergic muscarine-receptor agonist pilocarpine *(27).* The fact that both of these drug classes produce seizures has prevented their use in clinical medicine. However, recent evidence suggests that several classes of CNS drugs, many of which have been clinically used for decades or even centuries, appear to at least partially act by stimulating the production and release of endogenous neurotrophins in the brain. This review discusses the recent findings about the role of endogenous neurotrophins in the action of several drug classes and the implication of these observations for the use of neurotrophin-stimulating drugs.

Antidepressants

Antidepressants were serendipitously found almost five decades ago to alleviate symptoms

of depression or, especially in the case of lithium, also mania. Subsequently, the major classes of antidepressant drugs were found to influence the serotonergic and noradrenergic neurotransmission *(28–33).* One of the distinctive features of these drugs has been the fact that their therapeutic effect develops slowly, over the first weeks or months of continuous treatment *(33).* This fact has been difficult to reconcile with the known effects of antidepressants on the monoaminergic system. Observations that severe depression is associated with reduced volume of gray matter in certain brain areas, and that this reduction can be at least partially reversed by an effective antidepressive treatment, have suggested that depression—at least in its severe form—may be a reversible neurodegenerative disorder *(34–36).* Clinically effective antidepressant action may require restoration of synaptic connections, which might explain the time delay in the therapeutic effect *(37).* This possibility suggests that antidepressants do not only correct the chemical balance of the monoaminergic system, but may also act through trophic effects on synaptic connectivity.

The observation that seizures, including those induced by electroconvulsive shock treatment (ECT), the most effective known antidepressant therapy, strongly induced neurotrophin synthesis and release *(24,26,38,39–43)* suggested that neurotrophins might play a role in the mechanism of antidepressant effect *(28,29)* (Table 1). This idea was further supported by the observation that chronic, but not acute, antidepressant treatment produced a modest but significant increases in BDNF mRNA levels in the rodent hippocampus *(40,44,45)* and that hippocampal BDNF levels were increased in the postmortem brain samples of depressed patients treated with antidepressants when compared to nontreated depressed patients *(46)* (Table 1). The increase in BDNF mRNA levels produced by the ECT is much higher and more widespread than that produced by antidepressants, which may explain the better clinical efficacy of ECT over the drug treatments. We recently reported that antidepressants acutely as well as chronically stimulate the autophosphorylation of the BDNF receptor trkB, which suggests that antidepressants stimulate local BDNF release in the brain *(47)* (Table 1). A similar increase in trkB autophosphorylation was recently reported in response to lithium treatment *(48).* These data suggest that antidepressant drugs induce the production and release of BDNF in the rodent, and probably also in the human, brain.

Importantly, recent data suggest not only that the increased BDNF synthesis and release are produced by antidepressants, but also that the endogenous BDNF mediates the clinical antidepressant effects of these drugs. Infusion of BDNF (and NT-3) into the rat brain-stem area or hippocampus *(49,50)* produces behavioral effects similar to those observed after antidepressant administration; comparable behavior effects have been observed in transgenic mice with increased activity of the BDNF receptor trkB in brain (Võikar and Castrén, unpublished observations), which suggests that BDNF or trkB activation alone can produce an antidepressant effect. Interestingly, infusion of BDNF into the projection from the ventral tegmental area to the nucleus accumbens produces depression-like behavioral effects *(51),* which indicates that BDNF in some brain areas might play a role in the development of depression, while in other areas it has an antidepressant action. Most importantly, transgenic mice with reduced trkB signaling as well as heterozygous BDNF knockout mice ($BDNF^{+/-}$) with reduced brain BDNF levels are insensitive to behavioral effects of antidepressants *(47)* (Table 1). Taken together, these data suggest that neurotrophins are sufficient and necessary for the antidepressant-produced behavioral effects in rodents. They also suggest an exciting possibility that the neurotrophin release in response to antidepressants may initiate a trophic process, perhaps involving sprouting of serotonergic fibers *(9,10),* which gradually leads to the slowly developing clinical antidepressant effect *(37).*

It is of interest to note that not only are antidepressants used for the treatment of depression, but they also show a relatively wide

Table 1
The Effects of Antidepressant and Electroconvulsive Shock Treatments (ECT) on BDNF, trkB and CREB Expression and Phosphorylation in Brain.

	Antidepressant treatment			
	Acute	Chronic	ECT	Chronic stress
BDNF mRNA	– *(40)*	↑ *(40,44,45,106–108)*	↑ *(40,41,109)*	↓ *(106,110,111)*
BDNF protein	– *(47)*	↑ *(46)*	ND	ND
trkB mRNA	– *(40)*	↑ *(40)*	↑ *(40)*	↑ *(112)*
phospho-trkB	↑ *(47)*	↑ *(47)*	ND	ND
CREB mRNA	– *(113)*	↑ *(113)*	ND	ND
phospho-CREB	↑ *(47)*	↑ *(47,114)*	↑ *(115)*	ND

(–), no effect; ↑, increase; ↓, decrease; ND, not determined.

spectrum of effects on multiple CNS disorders, including chronic pain, phobia, obsessive-compulsive disorders, bulimia, and premenstrual syndrome, among others *(33).* Furthermore, in all these conditions, as in depression, long-term drug administration is required for clinical efficacy. As neurotrophins, particularly BDNF, have been implicated in the pathophysiology of chronic pain *(52),* it is possible that the ability of antidepressants to induce BDNF release would also play a role in their antinociceptive action and perhaps also in other conditions where antidepressants have been show to be effective.

There is evidence to suggest that neurotrophins are involved not only in the antidepressant effect, but also in the pathophysiology of depression. Chronic stress, which is known to predispose to depression, reduces BDNF mRNA levels in the hippocampus, an effect that can be counteracted by antidepressant treatment *(53).* Furthermore, conditional BDNF knockout mice show an anxiety-like phenotype *(54)* and $BDNF^{+/-}$ mice show aggressiveness and other behavioral effects, which are responsive to antidepressant treatment *(55).* Conversely, mice that overexpress trkB receptor in the cortex and hippocampus show reduced anxiety in elevated-plus maze and related tests *(56).* Finally, a single-nucleotide polymorphism in the coding region of human BDNF gene, which influences activity-dependent BDNF release *(11),* was recently shown to be linked to hereditary bipolar affective disorder *(15,16)* and anxiety *(57).*

Addictive Drugs

The activity of dopaminergic neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens is considered central in the rewarding effects of drugs of abuse. Chronic administration of addictive drugs, such as morphine and cocaine, produce long-lasting plastic changes in synaptic function and signal transduction in dopaminergic and noradrenergic neurons, involving particularly cAMP signaling and tyrosine hydroxylase activity *(58,59).* Although these biochemical adaptations persist for days or even weeks after the cessation of addictive drug administration, none of them is as long-lived as the behavioral changes related to addiction and relapse. Nestler has pointed out that there are interesting similarities between the effects of addictive drugs and learning processes *(60).* For example, a single dose of cocaine given to a mouse produces the long-term potentiation in dopaminergic neurons in the substantia nigra *(61,62).* Interestingly, chronic morphine administration

Table 2
The Effects of Addictive Drugs Morphine and Cocaine on Neurotrophins and trkB Receptor in Brain.

	Morphine	Cocaine	Withdrawal
BDNF mRNA	↑ *(72)*	– *(40,116)*	↑ *(72)*
NT-3 mRNA	↑ *(72)*	ND	↓ *(72)*
trkB mRNA	*(72)*	– *(40)*	↑ *(72)*
phospho-trkB	↑ *(77)*	ND	ND
NT-4 release	↑ *(77)*	ND	ND
GDNF	– *(76)*	↑ *(115)*	ND
Phospho-ret	↓ *(76)*	↓ *(76)*	ND

(–), no effect; ↑, increase; ↓, decrease; ND, not determined.

has been shown to produce morphological changes in the mesolimbic dopamine neurons *(63)*, which suggests that changes in the structure of neuronal networks may be induced by addictive drugs. It is currently unknown whether these changes in the structure and function of synaptic connections are sufficiently long-lasting to be able to explain the nearly permanent behavioral changes produced by the repeated administration of addictive drugs.

The pioneering studies of Eric Nestler and his coworkers have revealed a role for the neurotrophic factors in the mechanism of action of the addictive drugs *(64–66)* (Table 2). BDNF is known to produce trophic and morphological changes in dopaminergic neurons both in vitro and in vivo *(67–71)*. Chronic morphine treatment induced a modest increase in the BDNF and NT-3 mRNA levels in (apparently) noradrenergic neurons in the locus coeruleus but did not influence the mRNA levels of BDNF, NT-3, or their receptors trkB and trkC in the dopaminergic neurons in the VTA *(72)* (Table 2). However, withdrawal from chronic opioid treatment rapidly increased BDNF and trkB mRNA levels in the LC; trkB mRNA was increased also in the VTA by morphine withdrawal *(72)* (Table 2). The injection of BDNF into the VTA prevents many of the adaptational and morphological changes observed in dopaminergic neurons after chronic morphine or cocaine administration *(63,65,73)*. Furthermore, BDNF infusion produced a long-lasting enhancement of locomotor stimulation and conditioned reward produced by cocaine, and behavioral sensitization to cocaine was delayed in $BDNF^{+/-}$ mice *(74)*. Recently, the analysis of mice with a conditional neuron-specific deletion of BDNF revealed a critical role for BDNF in the neuronal adaptations to chronic opiate treatment in the LC: chronic morphine produced a downregulation of the cAMP-mediated excitation in BDNF-null mice, while a normal sensitization of the cAMP system was observed in wild-type mice *(75)*. Furthermore, BDNF-null mice failed to upregulate tyrosine hydroxylase levels in the LC region in the response to chronic morphine *(75)*. Interestingly, glial cell line-derived neurotrophin factor (GDNF), a member of another family of neurotrophic factors, was shown to block the biochemical adaptations after chronic morphine and cocaine administration and the phosphorylation of the GDNF receptor c-ret was reduced (indicating reduced GDNF release) in the VTA of rats chronically treated with cocaine *(76)* (Table 2). These exciting observations suggest that BDNF and GDNF may play reciprocal roles in the cellular adaptations to chronic treatment with addictive

drugs and in the development of addiction: BDNF promotes or mediates cellular adaptations, while GDNF opposes them.

Recent reports suggest that another neurotrophin, NT-4, plays an important role in the acute effects of opioids, as well as in the development of tolerance to repeated morphine administration. Lucas et al. *(77)* found that the analgesic effects of morphine were attenuated in the NT-4$^{-/-}$ mice, which otherwise show a normal nociception. A similar kind of partial resistance to morphine was observed in mice overexpressing the dominant-negative trkB isoform *(77).* Furthermore, morphine increased NT-4 release and trkB autophosphorylation in the brain-stem region, indicating that morphine-induced NT-4 release sensitizes the opioid receptor system to morphine *(77).* Interestingly, a very recent report indicates that NT-4$^{-/-}$ mice develop a tolerance to morphine significantly slower than wild-type mice do *(78),* which further suggests an interrelationship between NT-4 and the opiate signaling. Taken together, these data suggest that two different neurotrophins, BDNF and NT-4, both of which activate the same receptor trkB, play distinct, but perhaps partially overlapping, roles in different phases of opioid actions.

Neuroprotective Drugs

Several clinically used neuroprotective drugs have been shown to induce the production or release of neurotrophins in the CNS or peripheral tissues, which might render them attractive alternatives to the therapy involving direct neurotrophin administration. However, direct evidence that this increase in neurotrophin synthesis or release plays any critical role in the neuroprotective effect of these drugs is largely lacking.

Riluzole is clinically used to treat amyotrophic lateral sclerosis, and it shows neuroprotective properties in animal models of Parkinson's and Huntington's diseases *(79).* It has been suggested that riluzole produces these effects by inhibiting voltage-sensitive Ca^{2+} channels, thereby reducing glutamate release in the brain *(79).* Riluzole has been shown to increase the synthesis and secretion of NGF, BDNF, and GDNF in cultured mouse astrocytes *(80).* Furthermore, long-term riluzole administration produces a persistent increase in BDNF levels in rat hippocampus and cortex in vivo, and this effect correlates with increased hippocampal granule cell proliferation *(81).* It would be important to investigate neuroprotective effects of riluzole in animal models, where neurotrophin signaling has been reduced, to reveal whether the regulation of neurotrophin synthesis and release by this drug plays any direct role in neuroprotection.

Memantine is an uncompetitive NMDA-receptor antagonist, which is used in clinics for Alzheimer's disease *(82).* The mechanism of the beneficial clinical effect of memantine is unclear, but neuroprotective effects due to the antagonism of NMDA receptors have been suggested to be involved *(82).* Memantine was recently reported to increase the levels of BDNF and trkB mRNA, as well as BDNF protein, in several rat brain areas *(83).* However, it is currently unclear whether increased BDNF levels play a role in the neuroprotective effect of memantine.

Low-molecular-weight drugs that positively modulate the AMPA receptor function have recently been suggested as drugs for neurodegenerative disorders and memory problems. Since the activation of AMPA and kainate-type glutamate receptors is known to increase the synthesis and release of BDNF and NGF in the brain *(24–26),* it is possible that increased neurotrophin signaling might play a role in the mechanism of action of drugs of this type. Indeed, several distinct potentiators of AMPA receptor function have been found to increase BDNF mRNA levels in neurons both in vitro and in vivo *(84–87).* However, it is still unclear to which extent this increased neurotrophin production and release plays a role in the neuroprotective and memory-enhancing action of these drugs.

Guillin and coworkers, in an elegant report, recently showed that behavioral sensitization to repeated administration of the dopamine pre-

cursor L-dopa, the drug of choice for Parkinson's disease, is mediated by the increased production and release of BDNF from corticostriatal neurons *(88).* These data suggest that L-dopa, which is converted to dopamine in the brain, increases BDNF release in the brain. It is possible that BDNF contributes to not only to the behavioral sensitization, but also to the clinically beneficial effects of L-dopa in Parkinsonian patients. Furthermore, dopamine, as well as the dopamine-receptor agonist apomorphine, has been shown to increase BDNF and NGF synthesis in cultured astrocytes *(89,90)*

Selegiline (L-deprenyl) is clinically used to treat Parkinson's disease *(91).* It was originally found to act as a relatively selective inhibitor of monoamine oxidase B *(91),* but it has been suggested that at least some of the neuroprotective effects of selegiline are independent of the MAO inhibition *(92).* Selegiline has been shown to stimulate the synthesis of NGF, BDNF, and GDNF in cultured astrocytes *(93).* However, although selegiline appears to have a neurotrophic-type effect on cultured dopaminergic neurons, this effect is qualitatively and quantitatively different from that produced by BDNF *(71),* which suggests that the neurotrophic effects of selegiline are not mediated by the increased BDNF release. Finally, there is no evidence that increased production of neurotrophins would play a role in the neuroprotective effects of selegiline in vivo.

Taken together, these observations suggest that several drugs with neuroprotective activity increase the production, release, or signaling of endogenous neurotrophins in brain. It will be important to systematically examine what role, if any, neurotrophins play in the action of these drugs. The elucidation of the role of neurotrophins might help to develop new assay systems for the screening of novel neuroprotective drugs.

Other Drugs

Yohimbine, an antagonist of noradrenergic α2 receptors, has been shown to increase BDNF release and trkB autophosphorylation in rat brains *(42).* α2 adrenoreceptors are predominantly located in the presynaptic terminals of noradrenergic neurons, where they control norepinephrine release. Antagonists of these receptors, such as yohimbine, are known to increase norepinephrine release in the cortex. Because BDNF is expressed in noradrenergic neurons *(94)* and anterogradely transported to nerve endings *(95),* the source of yohimbine-induced BDNF release is probably noradrenergic terminals *(42).* A number of newer, more specific α2-receptor antagonists have been developed and it would be interesting to investigate whether they share the ability of yohimbine to increase BDNF release in the cortex.

NGF and BDNF production is increased by 4-methylcatechol in cultured hippocampal neurons and cultured astrocytes *(96).* Furthermore, the intraventricular injection of 4-methylcathecol increases BDNF mRNA and protein in rat brains *(96).* A major problem of 4-methylcatechol is that it does not pass through the blood-brain barrier. However, when injected peripherally into newborn rats, 4-methylcatechol increased brain BDNF content *(96),* which indicates that it might be useful in conditions where the blood-brain barrier is partially damaged.

Estrogen is known to have a variety of effects on mood, attention, and cognition. In addition, estrogen has been show to possess neuroprotective and neurotrophic effects in the brain *(97,98).* Estrogen regulates BDNF expression during brain development *(99)* as well as in adults *(100),* and it has been suggested that the neurotrophic effects of estrogen are at least partially mediated by BDNF in the brain *(101,102).* Because there is evidence that the neuroprotective effects of estrogen are at least partially independent of its nuclear estrogen receptor activity *(97,98),* it is possible that estrogen derivatives devoid of reproductive effects might be developed as drugs that indirectly regulate neurotrophin activity in the brain.

Immunophilin ligands have been shown to produce neurotrophic and neuroprotective effects in vitro and in vivo *(103,104).* Tanaka et

al. *(105)* recently reported that the immunosuppressive as well as nonimmunosuppressive immunophilin ligands increase brain concentrations of BDNF and GDNF, suggesting that at least part of the neurotrophic effects of immunophilin ligands might be mediated by the neurotrophic factors.

Conclusions

Recent observations reviewed here suggest that several drugs that have for a long time been used in clinics for various CNS disorders are able to stimulate the synthesis or release of neurotrophins and other neurotrophic factors in brain. For most of these drugs it is still unclear which part, if any, of their clinical action can be explained by their ability to stimulate neurotrophic systems. However, for certain drugs, particularly antidepressants, several lines of converging evidence are pointing toward a critical role of neurotrophins in their mechanism of action. It is worth noticing that the therapeutic (or addictive) effects of many of the drugs discussed here develop slowly and require days or weeks of treatment. This, together with the involvement of neurotrophic molecules, suggests that trophic and developmental processes, such as neuronal survival, connectivity, synaptogenesis, and plasticity, may be indirectly influenced by drug treatments and may represent the actual mechanisms by which many classes of CNS drugs bring about their clinically relevant effects *(37)*. Since these trophic processes are typically regulated by use-dependent neuronal activity, the neurotrophic concept of drug action discussed above might provide a novel rational framework for the combination of pharmacological and non-drug therapies, such as rehabilitation and psychotherapy, as a means toward the optimal treatment of CNS disorders.

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