

EXPERT REVIEW

Neuronal plasticity and neurotrophic factors in drug responses

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Neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF) and other members of the neurotrophin family, are central mediators of the activity-dependent plasticity through which environmental experiences, such as sensory information are translated into the structure and function of neuronal networks. Synthesis, release and action of BDNF is regulated by neuronal activity and BDNF in turn leads to trophic effects such as formation, stabilization and potentiation of synapses through its high-affinity TrkB receptors. Several clinically available drugs activate neurotrophin signaling and neuronal plasticity. In particular, antidepressant drugs rapidly activate TrkB signaling and gradually increase BDNF expression, and the behavioral effects of antidepressants are mediated by and dependent on BDNF signaling through TrkB at least in rodents. These findings indicate that antidepressants, widely used drugs, effectively act as TrkB activators. They further imply that neuronal plasticity is a central mechanism in the action of antidepressant drugs. Indeed, it was recently discovered that antidepressants reactivate a state of plasticity in the adult cerebral cortex that closely resembles the enhanced plasticity normally observed during postnatal critical periods. This state of induced plasticity, known as iPlasticity, allows environmental stimuli to beneficially reorganize networks abnormally wired during early life. iPlasticity has been observed in cortical as well as subcortical networks and is induced by several pharmacological and non-pharmacological treatments. iPlasticity is a new pharmacological principle where drug treatment and rehabilitation cooperate; the drug acts permissively to enhance plasticity and rehabilitation provides activity to guide the appropriate wiring of the plastic network. Optimization of iPlastic drug treatment with novel means of rehabilitation may help improve the efficacy of available drug treatments and expand the use of currently existing drugs into new indications.

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INTRODUCTION

Neuronal plasticity is a process through which external and internal environment of an individual gradually becomes represented in neuronal structure and function during development and through learning. Although gross connectivity develops through genetically governed guidance, fine-tuning takes place through experience and activity-dependent plasticity, where neurons and connections that actively participate in network function are selected for stabilization and strengthened, whereas inactive contacts are weakened or eliminated.^{1–3}

Neuronal plasticity does not only involve trophic processes such as neurogenesis and synaptogenesis but also includes atrophic processes, such as the elimination of inactive neurons and neuronal contacts. Although it is often thought that loss of neurons or synapses is harmful, elimination of connections that do not mediate useful information is, in fact, necessary for the optimal signal-to-noise ratio within the nervous system.^{1,2} Indeed, most of the neurons and synapses formed during development are wiped out by adulthood.^{1,2} Therefore, plasticity in itself does not have any particular direction; it is the experience-dependent activity within the neuronal network that determines which of the connections are strengthened and maintained and which ones are eliminated. Therefore, plasticity is adaptive when it is guided by beneficial environmental stimuli, but it can also be maladaptive, if the guiding experiences are adverse.

Neuronal plasticity is heightened during critical periods of postnatal development, which allows an efficient experience-driven fine-tuning of developing networks.⁴ After the closure of

critical periods, neuronal plasticity and changes in network structure are more restricted. However, recent data indicate that several drugs used for the treatment of neuropsychiatric disorders can directly influence the plasticity and reactivate a critical period-like plasticity in the adult brain, a process known as induced plasticity (iPlasticity).^{5–8}

To be translated into neuronal structure and function, neuronal activity needs molecular mediators⁹ and neurotrophic factors are prime candidates for mediators between neuronal activity and plasticity.^{10,11} In this review, we will first introduce the role of the neurotrophin family and especially of BDNF as a mediator of plasticity and drug effects. We will then discuss the role of neuronal plasticity in the mechanisms of action of drugs acting on the brain. Finally, we will review recent evidence that developmental-like plasticity, iPlasticity, can be activated in the adult brain and argue that iPlastic drugs should be combined with training, rehabilitation or psychotherapy to facilitate treatment outcome. For the role of other neurotrophic factors in neuronal plasticity, especially the family members of the glial cell line-derived neurotrophic factor, fibroblast growth factor and insulin-like growth factor, we refer to recent review articles.^{12–14}

NEUROTROPHINS IN PLASTICITY

The first neurotrophic factors, nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) were discovered through their ability to support the survival of neurons and neurites during development;^{15–17} other members of the

neurotrophin family, neurotrophin-3 (NT-3)^{18–20} and neurotrophin-4 (NT-4)^{21–23} were then identified through sequence similarity to NGF and BDNF.

Neurotrophins act by binding to two types of receptors, Trk-family members^{24–27} and the p75 neurotrophin receptor (p75NTR).^{28–31} NGF binds to TrkA, BDNF and NT-4 to TrkB and NT-3 interacts mainly with TrkC receptors, whereas all neurotrophin family members bind to the p75NTR.³² Recent evidence suggests that mature forms of neurotrophins predominantly bind to Trk receptors to promote neuronal survival and plasticity, whereas intracellularly generated pro-forms of neurotrophins preferentially interact with the p75NTR to increase cell death and eliminate synapses.^{33,34}

In the peripheral nervous system, neurotrophic factors are constitutively released in minute amounts by the target cells to regulate survival and process outgrowth of developing neurons. To act as a mediator of activity-dependent plasticity in the central nervous system, neurotrophins need to be released and to act in an activity-dependent manner.^{10,35,36} Levi-Montalcini and co-workers first found that hypothalamic *Ngf* mRNA levels in mice were regulated by behavioral activity, namely aggression, indicating the role for neurotrophins in the regulation of behavior.³⁷ At the same time, Gall and co-workers showed that *Ngf* mRNA was regulated by neuronal activity induced by seizures.³⁸ A similar activity-dependent regulation was observed for *Bdnf* mRNA,^{39–41} and subsequent studies showed that synthesis and release of BDNF and NGF, but not those of NT-3 and NT-4, are regulated by activity.⁹ Furthermore, TrkB, which is mostly localized within vesicles inside the cell, is translocated to plasma membrane through neuronal activity.^{42,43} These data are consistent with a central role of neurotrophins as mediators of activity-dependent plasticity^{9,10} (Figure 1).

The first functional evidence for the role of neurotrophins in plasticity was obtained in the visual cortex, a classical model for developmental plasticity, when Maffei and colleagues showed that NGF prevents the effects of monocular deprivation (MD) during the critical period of visual development^{44,45} (for a review, see refs 46,47). These findings led the authors to propose an influential hypothesis that thalamic axons reaching the visual cortex compete for access to a neurotrophic factor that is regulated by activity.⁴⁴ The observation that BDNF synthesis in the visual cortex is regulated by visual stimulation made BDNF the prime candidate for this activity-dependent regulated factor.⁴⁸ Indeed, the presence of an excess of the TrkB ligands, BDNF and NT-4, prevented ocular column segregation during development,^{49–52} which is consistent with such a role. These studies demonstrate that neurotrophins are critical regulators of neuronal plasticity in the developing visual cortex,⁵³ they also established visual cortex as an excellent model for studying the role of neurotrophic factors in neuronal plasticity (Figure 2).

NGF and BDNF promote the outgrowth of axons and dendrites and increase synapse formation.^{54–57} The effect of BDNF on dendritic branching is dependent on neuronal activity,⁵⁶ which again is consistent with the role of BDNF in activity-dependent plasticity.

BDNF also regulates synaptic plasticity. Long-term potentiation (LTP) is a widely used model of synaptic plasticity and BDNF has been demonstrated to be a critical regulator of the late, protein synthesis-dependent stage of LTP.^{9,58,59} High-frequency stimulation that induces LTP increases BDNF production.^{60,61} Furthermore, BDNF increases neurotransmitter release,⁶² promotes synaptic transmission and LTP *in vitro*^{63–65} as well as *in vivo*.^{66–69} Mice deficient of BDNF fail to show LTP,^{70,71} which can be rescued by exogenous BDNF administration.^{71–73} Similar findings have been found in mice carrying the Val66Met mutation in the *Bdnf* gene,⁷⁴ which corresponds to a common human *BDNF* gene polymorphism that alters the amino acid valine to methionine in the position 66 of the BDNF pro-region, leading to impaired

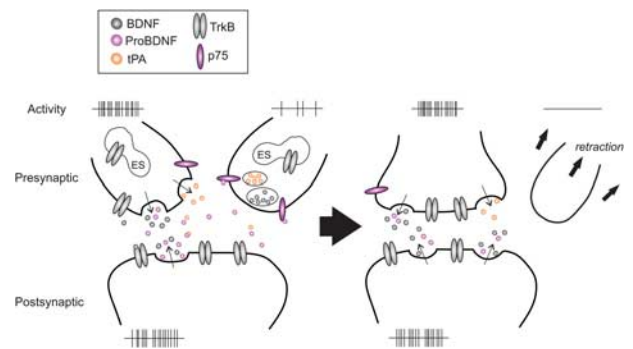


Figure 1. Neurotrophins as regulators of activity-dependent plasticity. Neurotrophins and their pro-forms mediate synaptic strengthening and dendritic retraction, respectively. This dual action is regulated by neuronal activity that controls the expression and secretion of BDNF, cleavage of proBDNF and plasma membrane translocation of TrkB receptors. BDNF binds to TrkB receptors to mediate neuronal survival and stabilization, whereas proBDNF binds with a higher affinity to p75NTRs that in the absence of Trk receptors promote apoptosis, dendritic retraction and synaptic depression, allowing differential responses in neurons depending on their activity state. When two axons are competing for the innervation of the same target neuron, the functional connection eventually forms between the two active neurons and the less active neuron retracts. Neuronal activity promotes the release of BDNF and proBDNF as well as tPA, which promotes extracellular cleavage of proBDNF to BDNF. In addition, TrkB receptors that normally reside inside the cell are inserted to the plasma membrane in the active neurons. This allows BDNF to mediate survival promoting and synapse strengthening signals in the active neurons. In the less active neuron, TrkB receptors or tPA are not available; however, p75NTR is expressed and the proBDNF released from the active neighbor or the target cell promotes atrophic signals. These effects result in activity-dependent selection of neuronal connectivity. BDNF, brain-derived neurotrophic factor; ES, endoplasmic system; p75, p75 neurotrophin receptor; proBDNF, pro-form of BDNF; tPA, tissue plasminogen activator; TrkB, tropomyosin receptor kinase.

activity-dependent BDNF release.⁷⁵ Consistent with this, direct current stimulation promotes learning in homozygous BDNF Val66Val subjects, but not in Met allele carriers, both in humans and mice.⁷⁶ However, since long-term manipulations, such as transgenic mice, can have major effects on glutamate release and other basic synaptic properties that in turn alter the threshold for LTP and other forms of synaptic plasticity, it is not always clear whether the effects of neurotrophins on neuronal or synaptic plasticity are instructive or permissive.^{59,77}

Mice deficient in TrkB also show blunted LTP and deficient learning.^{58,78} These effects appear to be specifically mediated by signaling through the phospholipase C γ signaling pathway, since deletion of the tyrosine residue in TrkB mediating this signaling disrupts LTP.⁷⁹ Furthermore, overexpression of TrkB occludes LTP in the hippocampal CA1 area, which is consistent with a critical role for TrkB signaling in LTP.⁸⁰

As noted above, plasticity is not only a trophic effect but also includes atrophic processes such as apoptosis, axonal retraction, dendritic pruning, synapse loss and long-term depression. Interestingly, genes for neurotrophins produce mediators of both of these functions. Although mature forms of neurotrophins activate Trk family receptors to promote trophic effects, pro-forms of neurotrophins bind to and activate the p75NTR to induce atrophic effects.^{31,33,81} p75NTR is widely expressed in cortical and hippocampal neurons during early development, but its expression is reduced during the first postnatal weeks; however, there is evidence that p75NTR is re-expressed in the cortex and hippocampus after injury.^{31,82,83} In addition, the BDNF pro-peptide

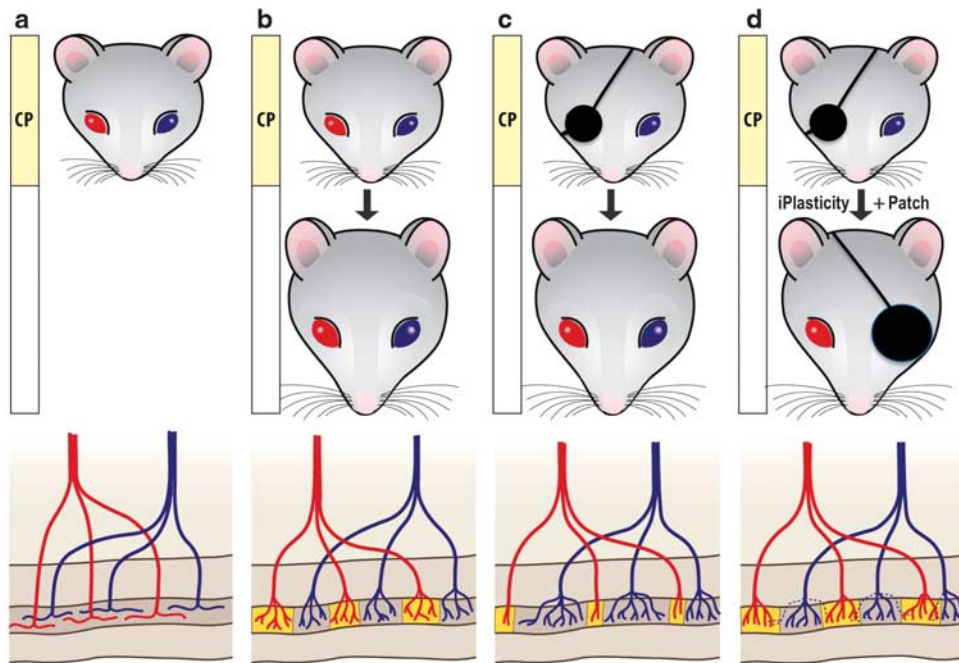


Figure 2. iPlasticity in the adult visual cortex. Development of the ocular dominance (OD) and its response to monocular deprivation in the mammalian visual cortex is probably the best-characterized model of neuronal network development in the cerebral cortex. (a) During early life, thalamic inputs representing each eye diffusely innervate the entire visual cortex, but (b) during the CP of early postnatal life, visual inputs from each eye segregate into alternating eye-specific regions in the primary visual cortex, called OD columns, such that each column becomes predominant innervated by one eye only. (c) If vision of one eye is blocked (MD) during the critical period, the more active inputs of the open eye take over the visual cortex through an activity-dependent competition involving BDNF signaling, and the closed eye loses its connectivity (see Figure 1), thereby becoming poor in vision, or amblyopic. Vision of the amblyopic eye can be recovered if normal vision is restored during the critical period and the use of the weaker eye is encouraged by patching the better eye, but if MD extends beyond the end of the critical period, amblyopia becomes permanent and cannot be revised by patching. (d) However, vision of an amblyopic eye can be restored in adulthood if eye patching is combined with a treatment that induces iPlasticity, such as fluoxetine or environmental enrichment (see Table 1). iPlasticity promotes functional recovery also in other brain areas where abnormal environment has led to miswiring of developing networks. Modified with permission from Elsevier Ltd from Castrén and Hen.³ BDNF, brain-derived neurotrophic factor; CP, critical period; MD, monocular deprivation.

that is released from pro-BDNF has recently been shown to possess biological effects on its own.^{84,85} Pro-neurotrophins induce apoptosis in the absence of Trk receptors via interaction between sortilin and p75NTR.^{33,82,86,87} Pro-BDNF binding to p75NTR has also been shown to induce pruning of axons and dendrites^{85,88–91} and promote long-term depression.^{92–94} There is evidence that the release of these competing signals derived from a single pro-neurotrophin is effectively utilized by neurons competing for target innervation to promote their own growth while inhibiting that of competing neighbors^{81,95–98} (Figure 1).

NEUROTROPHINS AND PLASTICITY IN DRUG RESPONSES

Since the discovery of BDNF and its receptor TrkB, efforts have been made to use BDNF as a therapeutic agent for neuropsychiatric disorders or to develop small-molecule pharmaceuticals that could increase the production of BDNF or activate TrkB in brain (for review, see refs 99,100), and these efforts are still ongoing.¹⁰¹ It is, therefore, remarkable that there actually are safe and widely used drugs already in market that increase the production of BDNF or the activation of TrkB in brain. In particular, the effects of antidepressant drugs on BDNF synthesis and TrkB signaling have been well-characterized,^{102–105} yet these effects have been largely ignored by the pharmaceutical industry and clinical development. Given the meager outcome of the efforts to develop BDNF mimetics or TrkB agonists, one cannot escape contemplating that many of the scientists involved in these efforts ended up being treated with the very drugs they failed to discover.

Antidepressants activate BDNF signaling

Duman and co-workers were the first to observe that antidepressant drugs acting through diverse mechanisms increased *Bdnf* mRNA expression in the rat hippocampus.¹⁰⁶ Later, multiple studies reported that chronic antidepressant treatment increases *Bdnf* mRNA expression^{107–109} and triggers upregulation of genes associated with BDNF-induced plasticity.^{110–112} The antidepressant-induced increase in *Bdnf* mRNA expression can be further potentiated if the drug treatment is combined with voluntary exercise.¹¹³ Moreover, chronic antidepressant treatment can prevent the downregulation of *Bdnf* mRNA expression caused by stress.^{106,109,113} In addition, BDNF protein levels as well as the expression of genes associated with BDNF-induced plasticity are increased after chronic antidepressant treatment.^{112,114} Acute antidepressant treatment, however, does not regulate BDNF expression.^{106,114–117} Studies on human subjects support the findings in rodents; BDNF expression is increased in post-mortem samples of the hippocampus of depressed patients on antidepressant medication at the time of death.¹¹⁸ Furthermore, electroconvulsive shock treatment increases brain and serum BDNF levels in rats and depressed patients, respectively.^{106,119} Conversely, BDNF and TrkB mRNA and protein levels are decreased in the frontal cortex and hippocampus of suicide victims when compared with controls.¹²⁰

Genetic studies have demonstrated that BDNF signaling is required for the behavioral effects of antidepressant drugs.¹⁰⁵ In BDNF heterozygous knockout mice and BDNF conditional knockout mice, the behavioral response to antidepressant drugs in the

forced swim test is abolished.^{105,115,121} Moreover, after chronic mild stress, BDNF heterozygous knockout mice did not respond to chronic imipramine treatment in the novelty suppressed feeding test.¹²² On the other hand, administration of BDNF directly into the midbrain region¹²³ or hippocampus is sufficient to induce antidepressant-like behavior and neurogenesis.^{69,124}

The increase in BDNF expression takes several days of antidepressant treatment to develop, but a single acute administration of many different antidepressants rapidly increases the phosphorylation of TrkB.^{115–117} This delayed increase in BDNF expression may be mediated by TrkB activation, since BDNF is known to regulate its own expression through TrkB.^{125,126} Antidepressants increase TrkB phosphorylation at the phospholipase C γ -binding site (Y816), but not at the Shc-binding tyrosine (Y515) and the phosphorylation takes place independent of BDNF,¹¹⁷ indicating TrkB transactivation. Interestingly, fluoxetine activates TrkB receptor similarly in wild-type mice and mice lacking the serotonin transporter, the main target of fluoxetine.¹¹⁷ TrkB receptor overexpression, which results in increased TrkB signaling, is sufficient to produce antidepressant-like behavioral effect in the forced swim test.¹²⁷ Intact TrkB signaling is required for the behavioral effects of antidepressant drugs, since mice overexpressing the dominant-negative truncated form of the TrkB receptor do not respond to antidepressant drugs in the forced swim test.¹¹⁵ Moreover, the behavioral effects of chronic antidepressant treatment were blunted in mice lacking TrkB in the newly born hippocampal neurons.¹²⁸ In addition to activating TrkB receptor signaling, chronic treatment with antidepressant drugs increases *Trkb* mRNA expression.¹⁰⁶

Chronic stress is an important precipitating factor for depression and has been shown to induce atrophic changes in dendritic complexity and thus affect neuronal network function. Interestingly in animal models, antidepressant treatment during the chronic stress paradigm can counteract the effects of stress on dendritic spines via a mechanism that includes regulation of glucocorticoid receptor phosphorylation by BDNF.¹²⁹ Specifically, BDNF through TrkB activation regulates the functional consequences of the glucocorticoid receptor activation following stress.¹³⁰

Taken together, these data convincingly demonstrate that antidepressant drugs activate TrkB signaling and subsequently increase BDNF levels in brain, and that BDNF signaling is critical for the behavioral effects of antidepressants. Therefore, effective TrkB agonists exist and are therapeutically used by millions of patients.

Antidepressants and neuronal plasticity

The finding that BDNF expression is increased by antidepressants was the trigger for the hypothesis that neuronal plasticity is involved in the antidepressant drug action.¹⁰² Since then, several lines of data indicate that antidepressant drugs activate and act through neuronal plasticity.³ Neurogenesis in adult animals is restricted to the subventricular zone of lateral ventricles and to the dentate gyrus of the hippocampus.¹³¹ Hippocampal neurogenesis is sensitive to a variety of environmental stimuli, including exercise, enrichment and antidepressant treatment.¹³¹ Essentially all antidepressant drugs increase hippocampal neurogenesis after ~2 weeks of treatment in rodents^{132–135} and neurogenesis appears to be required for many, although not all the behavioral effects of antidepressant drugs.^{133,136,137} The effects of antidepressants on neurogenesis are dependent on the intact BDNF signaling through TrkB.^{128,138}

In addition to hippocampal neurogenesis, antidepressants increase remodeling of axons and dendrites in the hippocampus^{110,139} as well as in the prefrontal cortex.¹³⁷ Antidepressants also increase synaptogenesis apparently by increasing spine turnover.^{137,140,141} Furthermore, antidepressants promote LTP in the hippocampus, cortex and amygdala^{5,139,142,143}

and propagation of signals through hippocampal circuitry.^{144,145} Although the effects of antidepressants on dendritic remodeling in the dentate gyrus are associated with ongoing neurogenesis,¹³⁹ in other parts of the hippocampus and in the prefrontal cortex these effects are independent of neurogenesis.¹³⁷

Ketamine

Ketamine has recently received a lot of attention as a rapid-acting antidepressant drug¹⁴⁶ (for a review, see ref. 147). A single dose of ketamine alleviates depression within an hour, but the effect lasts for a week or more, even though the half-life of ketamine and its metabolites is only a few hours.^{146,147} This temporal discrepancy between the effects and kinetics of ketamine suggests that neuronal plasticity may be behind the long-lasting effects.¹⁴⁸ Indeed, ketamine promotes synaptogenesis in the rodent prefrontal cortex.^{148,149} Ketamine has also been reported to promote hippocampal neurogenesis,^{150,151} but neurogenesis does not appear to be necessary for the antidepressant effects of this drug.¹⁵¹

BDNF and TrkB have been linked to the mechanism of the antidepressant actions of ketamine.^{103,148} BDNF Val66Met polymorphism can affect the responsiveness to ketamine in humans and rodents. The ability of ketamine to induce dendritic spine formation was abolished in BDNF Met66Met mice and the mice failed to respond to ketamine in FST.¹⁵² Depressed human patients carrying the met allele did not respond to ketamine as effectively as the Val66Val carriers.¹⁵³ These results suggest that the activity-dependent secretion, which is impaired in BDNF Met carriers, is involved in the mechanism of ketamine action. In cultured neurons, ketamine stimulation indeed increases BDNF secretion.¹⁵⁴

The ketamine metabolite, (2R,6R)-hydroxynorketamine (HNK), can reproduce the behavioral effects of ketamine in animal models,¹⁵⁵ although it does not bind to NMDA receptors that are thought to be the main targets mediating the effects of ketamine. Instead, (2R,6R)-HNK increases AMPA-mediated currents and BDNF expression. The NMDA receptor-independent actions of (2R,6R)-HNK suggest that mechanisms other than NMDA antagonism, such as the effects mediated by BDNF and TrkB, can be crucial in the antidepressant effects of ketamine. This hypothesis is supported by findings from Autry *et al.*¹⁵⁶ that a single ketamine injection rapidly increases the TrkB receptor activation and the translation of BDNF via eukaryotic elongation factor 2 in the mouse hippocampus, effects that are also seen after chronic fluoxetine treatment.¹⁵⁷ Furthermore, the antidepressant-like behavioral effects of ketamine were lost in mice lacking BDNF or TrkB or if BDNF function blocking antibody was infused into the medial prefrontal cortex of rats.^{154,156} In BDNF heterozygous knockout mice, however, the response to ketamine in FST is preserved, suggesting that ketamine is able to produce antidepressant effects in situations where BDNF expression is reduced but not completely lost.¹⁵⁸

Fingolimod

Fingolimod is a sphingosine-1-phosphate receptor modulator that is clinically used for multiple sclerosis, but it has been suggested for the treatment of several neurological disorders, including Huntington's disease and Rett syndrome, where BDNF signaling has been implicated.¹⁵⁹ Indeed, fingolimod increases BDNF levels in cultured neurons and in brain and rescues reduced BDNF levels in the brain of Rett syndrome model mice.¹⁶⁰ In addition, fingolimod has been shown to improve memory and prevent the upregulation of p75NTR in Huntington's disease model mice.¹⁶¹ Finally, fingolimod has antidepressant-like effects,¹⁶² which is consistent with the critical role of BDNF signaling in the antidepressant drug action.

Table 1. iPlastic drugs

Drug	Administration	Assay	Species	Role of BDNF	Ref
Chondroitinase	Intracortical	VC	R	?	188
		FC	M	?	190
		SC	R	?	189
Fluoxetine	p.o.	VC	R, M	+	5,141
		FC	M	+	143
		DG	M	?	6
		SC	R	?	191
AChEI		VC	M	?	192
HDACI	i.p.	VC	R	?	193–195
		AC	M	?	196
		AC	H	?	197
IGF-1	Intracortical	VC	R	?	198

Abbreviations: AC, auditory cortex; AChEI, acetylcholinesterase inhibitor; BDNF, brain-derived neurotrophic factor; DG, dentate gyrus; FC, fear conditioning, H, human; HDACI, histone deacetylase inhibitor; IGF-1, insulin-like growth factor-1; i.p., intraperitoneal; M, mouse; p.o., peroral; R, rat; SC spinal cord lesion; VC, visual cortex.

Drug-induced Trk receptor transactivation

TrkB receptors can be activated independently of BDNF via transactivation through other receptors. TrkB receptor appears to mediate, in particular, the neuronal survival promoting effects of compounds able to transactivate TrkB.¹⁶³ For example, the adenosine A2 and PACAP receptors that belong to the family of G-protein-coupled receptors can transactivate Trk receptors.^{164,165} *In vivo*, the effects of adenosine 2A receptor agonists on survival of motoneurons were mediated via TrkB receptor transactivation.¹⁶⁶ In addition to transactivation via G-protein-coupled receptors, TrkB receptor activation and signaling can be induced by glucocorticoids, for example dexamethasone, to mediate their effects on neuronal survival.¹⁶⁷

Drugs of abuse

Drugs of abuse produce long-lasting memories, typically persisting for life and neuronal plasticity has been for a long time implicated in the formation and maintenance of these memories (for a thorough discussion of this area, see refs 168–170). The first evidence for long-term plastic changes in response to an addictive drug was observed in the dopaminergic neurons originating from the ventral tegmental area and forming synapses in the nucleus accumbens (NAc). A single cocaine administration induced an LTP in this synapse that was observed 24 h after the cocaine administration but no longer at 1 week after.¹⁷¹ Repeated cocaine injections also induce production of new synapses in the excitatory projections to NAc, which remain silent expressing only NMDA receptors and having no AMPA-receptor mediated currents.¹⁷² Subsequently, during withdrawal, AMPA-receptors are gradually recruited to these silent synapses, which converts them to mature synaptic contacts.¹⁷³

The role of neurotrophins in addiction has been extensively studied, particularly by Nestler and co-workers.¹⁷⁴ BDNF is expressed in dopamine neurons as well as in excitatory neurons projecting to the NAc and TrkB is expressed in both dopamine D1 and D2 receptor expressing neurons in the NAc.^{174,175} Expression of both BDNF and TrkB is increased by cocaine exposure^{176,177} and inhibition of BDNF-TrkB signaling reduces the rewarding effects of cocaine.¹⁷⁷ Interestingly, TrkB signaling within the D2-expressing NAc neurons promotes reward to cocaine, whereas TrkB in the D1 neurons suppresses it.¹⁷⁵ In contrast, chronic morphine administration reduces BDNF expression in the ventral tegmental area and suppression of BDNF signaling in the NAc promotes morphine reward.¹⁷⁸ Therefore, BDNF as well as other neurotrophic factors (for a review of the role of glial cell line-derived neurotrophic

factor, see ref. 179) have a critical, though complex, role in the neuronal plasticity leading to addiction.

It has been proposed that addictive drugs of abuse 'hijack' a process of neuronal plasticity that normally takes place during development. Nestler and co-workers have proposed a neural rejuvenation hypothesis of addiction, which suggests that repeated exposure to cocaine reactivates developmental processes that normally occur in the juvenile brain.¹⁷⁰ It will be important to explore whether rejuvenation and iPlasticity in fact represent a common mechanism through which developmental plasticity is activated in the adult brain through drugs or experiences to promote adaptive or maladaptive plasticity.

ROLE OF IPLASTICITY IN DRUG RESPONSES

Plasticity is adaptation of the nervous system to environmental experiences, and since exposure to a drug is an experience, it is to be expected that drugs acting on the nervous system involve plasticity. However, recent evidence suggests that central processes of developmental plasticity, such as critical periods, neurogenesis and synaptic plasticity, can be direct targets of drug treatments.

Postnatal critical or sensitive periods are phases of heightened neuronal plasticity during which a certain network is particularly sensitive to environmental input and experiences have a large impact on the subsequent structure and function of the network.⁴ A classical experimental set-up for the investigation of critical periods is the development of the mammalian visual cortex^{4,180} (Figure 2). In this process a perfectly healthy eye that has grown its projections to the visual cortex normally, may lose its connectivity and become permanently deficient only because it is deprived of activation during the critical period. Critical periods are ubiquitous and also govern the development of, for example, motor learning, language and social interactions.^{181–183} Therefore, abnormal experiences during early life can guide maladaptive wiring of many cortical networks, including those governing social interactions, and this wiring becomes permanent after the closure of the corresponding critical period, impeding normal adaptation of the network function. Critical periods typically have a relatively well-defined boundaries and it is known that GABA-mediated signaling as well as BDNF are central regulators of the opening and closure of these boundaries.^{4,184,185} Drugs acting on GABA receptors, such as benzodiazepines and anesthetics, are occasionally used in children and adolescents, but so far very little is known about the impact of these drug treatments on the opening and closure of critical periods, a field that clearly would benefit from more attention.

iPlasticity: induced critical period-like plasticity in the adult brain

It had been considered that once closed, critical periods remain closed. However, recent evidence has demonstrated that it is possible to reactivate a state of plasticity in the adult cerebral cortex closely resembling that observed at the peak of postnatal critical periods.^{3,7,104,186} This iPlasticity creates a window of opportunity for better rewiring of abnormally connected or injured neuronal networks, which has obvious potential in the treatment of neuronal trauma and psychiatric disorders (Figure 2). Furthermore, since natural critical periods coincide with a period of brain growth when many experimental procedures such as brain imaging are complicated, iPlasticity that can be induced in the adult brain facilitates investigations of the molecular and cellular mechanisms of enhanced plasticity.

The first chemical treatment that was shown to induce critical period-like plasticity in the adult brain was the enzyme chondroitinase ABC (ChABC) that, upon intracerebral infusion, degrades perineuronal nets, extracellular matrix structures preferentially encasing parvalbumin-expressing interneurons.¹⁸⁷

Intracerebral infusion of ChABC was shown to reactivate a critical period-like ocular dominance (OD) plasticity after MD in the rat visual cortex.¹⁸⁸ Degradation of perineuronal nets has been shown to reactivate early life-like plasticity also in the spinal cord and fear circuitry.^{189,190} Subsequently, several pharmacological treatments (Table 1) and environmental manipulations,^{7,199–201} as well as genetic means, have been used to induce iPlasticity in several model systems and also in humans.¹⁸⁶ Clearly, iPlasticity is an increasingly recognized pharmacological principle with a wide range of potential applications.

iPlasticity induced by antidepressant drugs

Intracortical infusion of ChABC is an invasive procedure and not feasible for human use. However, recent findings have shown that the antidepressant fluoxetine activates iPlasticity in the adult rat visual cortex in a manner very similar to that found at the peak of the natural critical period and to that produced by ChABC or enriched environment.^{5,104,141} During chronic treatment by fluoxetine, critical period-like plasticity is reactivated and MD induces a shift in OD in the visual cortex of adult rats⁵ (Figure 2). Further, in rats rendered amblyopic through MD from early life onwards, opening of the weak eye and patching of the healthy eye in adulthood restores vision to the amblyopic eye only when fluoxetine is given during the patching procedure.⁵ BDNF levels are increased by fluoxetine in the visual cortex and BDNF signaling through TrkB is required for iPlasticity. Furthermore, fluoxetine reduces intracortical inhibition and diazepam that potentiates GABA-mediated inhibition, prevents its effects on visual plasticity.⁵ Finally, serotonin through 5HT1A receptors is involved in iPlasticity.¹⁹³ Fluoxetine has also been shown to produce enhanced structural plasticity in the mouse visual cortex, promoting turnover of synaptic sites.¹⁴¹ Essentially all antidepressant drugs increase TrkB signaling in brain,¹¹⁶ but it is not clear whether iPlasticity is produced by other antidepressants than fluoxetine. However, preliminary data show that tianeptine, an antidepressant that does not inhibit monoamine reuptake,²⁰² readily reactivates OD plasticity in the adult rat visual cortex (JF Maya-Vetencourt, A Cattaneo and E Castrén, unpublished), which suggests that iPlasticity might be induced by other antidepressant drugs as well. It should be emphasized that fluoxetine treatment alone has no effects on the vision in rats; the effects on visual acuity only become apparent when the promoted plasticity is combined with a manipulation (such as MD) that produces a new pattern of activity within the plastic networks.⁵

iPlasticity produced by fluoxetine is not restricted to the visual cortex. Chronic peroral fluoxetine exposure induces markers of critical period-like plasticity and promotes LTP in the amygdala, which is indicative of iPlasticity.^{143,203} These effects also reactivate the ability to suppress fearful memories when fluoxetine treatment is combined with extinction training.¹⁴³ Similar iPlastic effects have also been shown after injection of ChABC into the amygdala in adult mice.¹⁹⁰ As was the case for iPlasticity in the visual cortex, the effects of fluoxetine on fear extinction were also dependent on BDNF signaling and were apparent only when fluoxetine treatment was combined with rehabilitation, in this case extinction training.¹⁴³ Taken together, iPlasticity may constitute a neurobiological basis for the observation that the combination of antidepressant treatment and psychotherapy works better than either treatment alone.¹⁴³

In the adult hippocampal dentate gyrus, fluoxetine reverts the molecular and functional properties of granule neurons to an immature state, a phenomenon coined dematuration.^{6,204} Although dematuration coincides with iPlasticity in other cortical regions, it is currently unclear whether these two phenomena share the same molecular and cellular background.

Fluoxetine has recently been found to promote recovery from stroke and from brain trauma.^{205–207} It is possible that iPlasticity

has a significant role in these actions. In rats, iPlasticity induced either by ChABC or fluoxetine improves recovery from spinal cord lesion.^{189,191} If iPlasticity was the underlying mechanism, fluoxetine (promoting plasticity) and rehabilitation (guiding plasticity by activity) together should produce an even better response than either treatment alone; this should be taken into consideration in patient care and in the design of future clinical trials.

Taken together, these data demonstrate that a safe and widely used drug fluoxetine can reactivate critical period-like plasticity in many cortical regions and promote recovery of vision in an amblyopic eye in adult rodents, but whether similar effects are produced in humans is not clear. Normann and co-workers showed that a 3-week treatment with the antidepressant sertraline increases visually evoked potentials in response to a strong visual stimulation in healthy humans,²⁰⁸ which is reminiscent of the increased LTP produced by fluoxetine in rats,⁵ indicating that antidepressants influence human visual cortex. However, in a recent clinical trial in amblyopic patients, fluoxetine and placebo were equally effective in improving the acuity of the amblyopic eye when given together with a daily eye patching and a computer game-based training of the weaker eye (H Huttunen, M Palva, L Lindberg, S Palva, V Saarela, J Liinamaa, E Karvonen, M-L Latvala, S Booms, E Castrén and H Uusitalo, unpublished observations). Therefore, it remains unclear to what extent iPlasticity contributes to the clinical effects of antidepressant drugs in humans.

iPlasticity induced by other drug treatments

Experiences have long-lasting effects on gene expression through the epigenetic regulation of chromatin structure and DNA methylation.^{209,210} Histone acetylation is one of the key epigenetic mechanisms promoting the open chromatin state and regulating gene expression. Histone acetylation can be increased by inhibitors of histone deacetylase (HDAC) and several drugs in clinical use act as HDAC inhibitors.²⁰⁹ Since activity-dependent plasticity requires changes in gene expression and protein synthesis, HDAC inhibitors might activate iPlasticity. Indeed, HDAC inhibition increases the expression of plasticity-related factors and promotes OD plasticity in the visual cortex.^{193–195} Treatment with the HDAC inhibitor valproate also reactivates the plasticity related to music preference in mice through activation of plasticity in a network including the prefrontal cortex.¹⁹⁶ Interestingly, valproate promotes auditory pitch recognition in human volunteers;¹⁹⁷ since development of perfect pitch has a postnatal critical period, this finding is consistent with valproate-activated iPlasticity in the auditory pitch circuitry in humans.

Cholinergic innervation has been known for a long time to regulate critical period plasticity.²¹¹ The cholinesterase inhibitor physostigmine was recently demonstrated to induce OD plasticity in the adult mouse visual cortex and to reverse amblyopia in adulthood when given together with patching of the better eye,¹⁹² suggesting that cholinesterase inhibitors induce iPlasticity. Since physostigmine has side effects, it would be important to investigate whether other cholinesterase inhibitors with fewer side effects, such as donepezil, which is widely used for dementia, also activate iPlasticity. Indeed, a clinical trial is ongoing to test whether donepezil together with patching of the better eye can be used for the treatment of residual amblyopia after the closure of the natural critical period in humans (<https://clinicaltrials.gov/ct2/show/NCT01584076>).

Finally, it should be kept in mind that iPlasticity can also be achieved in the visual cortex with purely environmental manipulations, such as environmental enrichment or food restriction.^{7,199–201} iPlasticity induced by fluoxetine and enriched environment closely resemble each other and they both share electrophysiological properties with the naturally occurring critical period. iPlasticity induced by cortical injection of IGF-1 was occluded by the simultaneous exposure to enriched environment;

one explanation of this finding is that both treatments share the same core mechanisms.¹⁹⁸ However, iPlasticity induced by calorie restriction is not dependent on BDNF.²⁰¹ Plasticity induced by transcranial magnetic stimulation is more pronounced in BDNF Val66Val subjects than in Met allele carriers, suggesting that iPlasticity may also be involved in the TMS-induced plasticity.²¹² Clearly, more information is needed about the cellular and molecular mechanisms that govern iPlasticity and to which extent these mechanisms recapitulate those in play during the natural critical periods. Nevertheless, the fact that critical periods are ubiquitous suggests that iPlasticity could be beneficial in the treatment of many neurological and psychiatric disorders, especially when combined with rehabilitation.¹⁰⁴

CONCLUSIONS

Neurotrophins are regulated by several classes of drugs used in clinical practice. Many of these drugs also induce iPlasticity, a newly recognized pharmacological principle where drugs can be used to directly promote neuronal plasticity. If iPlasticity is induced by drugs that are consumed by millions of people, why has it not been recognized before? One possibility is that iPlasticity is a central mechanism producing the expected clinical effects these drugs, such as mood recovery in the case of antidepressants.¹⁰⁴ The disorders being treated by iPlastic drugs, such as depression, may also themselves restrict neuronal plasticity and thereby limit the observable plastic effects. Another potential reason is that although iPlasticity has now been recognized in several species of experimental animals, iPlasticity may not take place in the human brain. Finally, it must be emphasized that iPlastic drugs need to be combined with rehabilitation to guide the plastic networks towards a new function. Such rehabilitation may not be a prominent component of current treatment strategies, but with the advent of smart phones and virtual reality, it is possible to design novel and inexpensive rehabilitation programs that combined with iPlasticity may significantly potentiate the effects of currently available drugs. Such combinations of iPlasticity and rehabilitation could also extend the utility of available drugs into new clinical indications and might have a significant impact on the recovery from, for example, neurological insults. There is already evidence for this.²⁰⁷

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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