Cell and Tissue Research (2019) 377:115–124
https://doi.org/10.1007/s00441-018-02985-6

REVIEW

TrkB neurotrophin receptor at the core of antidepressant effects, but how?

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Received: 15 October 2018 / Accepted: 14 December 2018 / Published online: 12 January 2019

Abstract

The role of brain-derived neurotrophic factor (BDNF) and its receptor TrkB has been studied in the context of mood disorders and their treatments for a couple of decades. Pharmacologically diverse antidepressant drugs increase the synthesis of BDNF in the cortex (and some subcortical structures) and this effect accounts for their ability to facilitate neurotrophic processes eventually leading into heightened plasticity within the cortex. Induction of BDNF-TrkB signaling has also been associated with the mechanism of action of ketamine and more recently with some other anesthetics, even with ones not thought to possess antidepressant potential. Notably, both ketamine and conventional antidepressants activate TrkB receptor and its downstream signaling rapidly within the same time scale in the brain while electroconvulsive therapy (ECT), among the most potent inducers of BDNF, has not been unequivocally shown to produce such acute effects on TrkB. The ability of antidepressants to regulate TrkB signaling is developmentally regulated and requires an intact central nervous system. The purpose of this review is to highlight and discuss some of these peculiarities associated with the effects of ketamine and classical antidepressants and BDNF on TrkB signaling.

Keywords Antidepressant · Electroconvulsive therapy · Nitrous oxide · Transactivation · Anesthesia

Introduction

The therapeutic effects of chemically induced seizures against neuropsychiatric disorders, most notably schizophrenia and severe depression, provided a rational basis for the development of electroconvulsive therapy (ECT) (Payne and Prudic 2009). Since its initial clinical implementation in 1938, the antidepressant effects of ECT have been well documented. The first antidepressant drugs, a chlorpromazine derivative imipramine and an isoniazid derivative iproniazid, were discovered in the 1950s. Their pharmacological mode of action was soon traced down to facilitation of monoaminergic tone, which rationalized the subsequent development of pharmacologically similar compounds. Of these drugs, the serotonin/norepinephrine selective reuptake inhibitors are the first-line medications in the treatment of depression today. However, overall remission rates to these medications are low and there is a delayed onset before the effects on the core symptoms of depression become evident (Fava 2003). The relatively recent discovery of the rapid antidepressant effects of ketamine, an *N*-methyl-*D*-aspartate (NMDA) receptor antagonist (Berman et al. 2000; Aan Het Rot et al. 2012), has generated huge enthusiasm to develop novel antidepressants with better efficacy and a faster onset of therapeutic action. While there is little doubt on the antidepressant effects of ketamine, the precise neurobiological basis of its therapeutic actions—as with classical antidepressants and ECT—remains to be unknown. Emerging experimental data however suggest that induction of intrinsic regenerative and neurotrophic mechanisms and subsequent facilitation of synaptic plasticity significantly contribute to antidepressant effects (Castrén and Rantamäki 2010; Duman and Aghajanian 2012; Castrén and Hen 2013). It is increasingly recognized that upregulation of brain-derived neurotrophic factor (BDNF) synthesis and release and activation of its neurotrophin receptor tropomyosin-related kinase B (TrkB) are at the core of these alterations, as reviewed elsewhere (Duman and Monteggia 2006; Rantamäki and Castrén 2008; Castrén and Rantamäki 2010; Duman and Aghajanian 2012; Castrén and Hen 2013). Less attention has been put on

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some of the discrepancies and obscurities related to the effects of antidepressants on TrkB. Before highlighting and discussing these, it is important to introduce some of the basic principles of BDNF-TrkB signaling machinery.

An overview of BDNF-TrkB signaling

BDNF belongs to the neurotrophin family of neurotrophic factors (Barde et al. 1982). Neurotrophins are ~ 14-kDa glycoproteins that support the survival and differentiation of specific neuronal populations in the peripheral nervous system during development (Huang and Reichardt 2001). In the developing brain, BDNF regulates the differentiation, maturation and function of many neuronal subtypes, especially the GABAergic (γ-aminobutyric acid) interneurons (Huang et al. 1999). BDNF is the most widely expressed neurotrophin in the adult brain wherein the most prominent expression is observed at the level of the hippocampus and cerebral cortex. BDNF is, however, also found, e.g., in the blood that is thought to arise mainly from circulating platelets (Rosenfeld et al. 1995; Chacón-Fernández et al. 2016). The levels of BDNF in the human serum are in fact very high (~ 5–25 ng/ml; see below). The levels of BDNF in the mouse serum are instead low or undetectable (Chacón-Fernández et al. 2016).

Among neurotrophins, the role of BDNF in regulating synaptogenesis and synaptic plasticity (e.g., long-term potentiation (LTP)) in the developing and adult central nervous system has been best characterized (Thoenen 1995; Hensch 2005; Park and Poo 2013). These effects of BDNF have been associated with the ability of neuronal activity to regulate the expression, process and release of BDNF. While robust neuronal excitation, such as generalized seizures (Isackson et al. 1991), produces prominent increase in BDNF synthesis, physiological stimuli such as light (at the level of visual cortex) (Castrén et al. 1992) and physical exercise (Neeper et al. 1995) also increase *bdnf* mRNA levels in the adult hippocampus and cortex. Like the other so-called immediate-early genes (e.g., *c-fos*, *arc*, *zif-268*), the *bdnf* gene is rapidly but transiently activated in response to various stimuli.

The *bdnf* gene structure is complex and due to alternative splicing, numerous mRNA transcripts can be made (Aid et al. 2007; Pruunsild et al. 2007). These transcripts are, however, translated and processed into identical pro-BDNF protein that is further enzymatically processed into mature protein within or outside the cell (note: the protein sequence of the mature BDNF is essentially identical among humans and mice). LTP-inducing paradigms have been shown to increase *bdnf* mRNA (Castrén et al. 1993) and concomitant release of pro-BDNF and tissue plasminogen activator (tPA) from neurons resulting in plasmin-mediated cleavage of pro-BDNF within activated synapses in vitro (Pang et al. 2004). Without such conversion, the levels of pro-BDNF may increase extracellularly allowing it to bind to the $p75^{NTR}$, a member of the TNF family of receptors, whose activation has been associated with opposing effects on neuronal structure and synaptic plasticity as seen with BDNF (Teng et al. 2005; Woo et al. 2005). To which extend this pro-BDNF $p75^{NTR}$ signaling axis influences brain function under physiological context in vivo is unclear, especially in the adult brain where the levels of pro-BDNF are low (Matsumoto et al. 2008) and $p75^{NTR}$ expression is largely confined in the cholinergic neurons of the basal forebrain.

The neurotrophic and neuroplastic effects of BDNF are mainly mediated by the TrkB receptor (Klein et al. 1991; Barbacid 1994; Huang and Reichardt 2001). Full-length TrkB receptors are ~ 145-kDa membrane bound glycoproteins (core protein ~ 93 kDa) that bind with high affinity to BDNF and a lesser extent to NT-3 (neurotrophin-3) and NT-4. TrkB receptors exist also as truncated forms that lack the majority of the intracellular domain while the extracellular domain is identical with the full-length receptors (Middlemas et al. 1991). These receptors act as BDNF scavengers or dominant-negative regulators of the full-length TrkB (Eide et al. 1996; Saarelainen et al. 2000), although the biological role of these receptors appears more complex (Fenner 2012). Upon binding to BDNF, TrkB receptors dimerize and transphosphorylate each other within the autophosphorylation loop (Y705/6) (Fig. 1). These posttranslational modifications further launch phosphorylation of other tyrosine residues that serve as docking sites for adaptor proteins that set off complex intracellular signaling cascades (Huang and Reichardt 2001). Phosphorylation of the Shc binding site (Y515) ultimately regulates protein kinase B (AKT) and mitogen-activated protein kinase (MAPK) pathways that are important regulators of cell survival and neuronal differentiation. AKT regulates a number of apoptotic and survival mechanisms and is also an important regulator of mTor (mammalian target of rapamycin) and GSK3β (glycogen synthase 3β) (Kim et al. 2001; Beurel et al. 2015; Hermida et al. 2017). GSK3β is a promiscuous serine-threonine kinase that regulates a wide variety of cellular functions including metabolism and differentiation (Beurel et al. 2015; Hermida et al. 2017). Phosphorylated Y816 serves as a docking site for the phospholipase-Cγ1 (PLCγ1) that upregulates $[Ca^{2+}]_i$ levels and thereby activation of, e.g., calcium/calmodulin kinase pathway. This pathway and MAPK ultimately regulate gene expression via transcription factor CREB (cAMP response element binding protein) (Finkbeiner et al. 1997). Activation of the PLCγ1 pathway has been shown to be particularly important for TrkB-induced synaptic plasticity (Minichiello et al. 1999, 2002). Direct application of BDNF (> 1–5 ng/ml) into cultured neurons readily phosphorylates Y705/6, Y515 and Y816 residues in TrkB (note: since Trk receptors share close similarity within their tyrosine kinase domains and the PLCγ1 binding sites, it is difficult to develop antibodies that specifically detect TrkB phosphorylation on these sites).

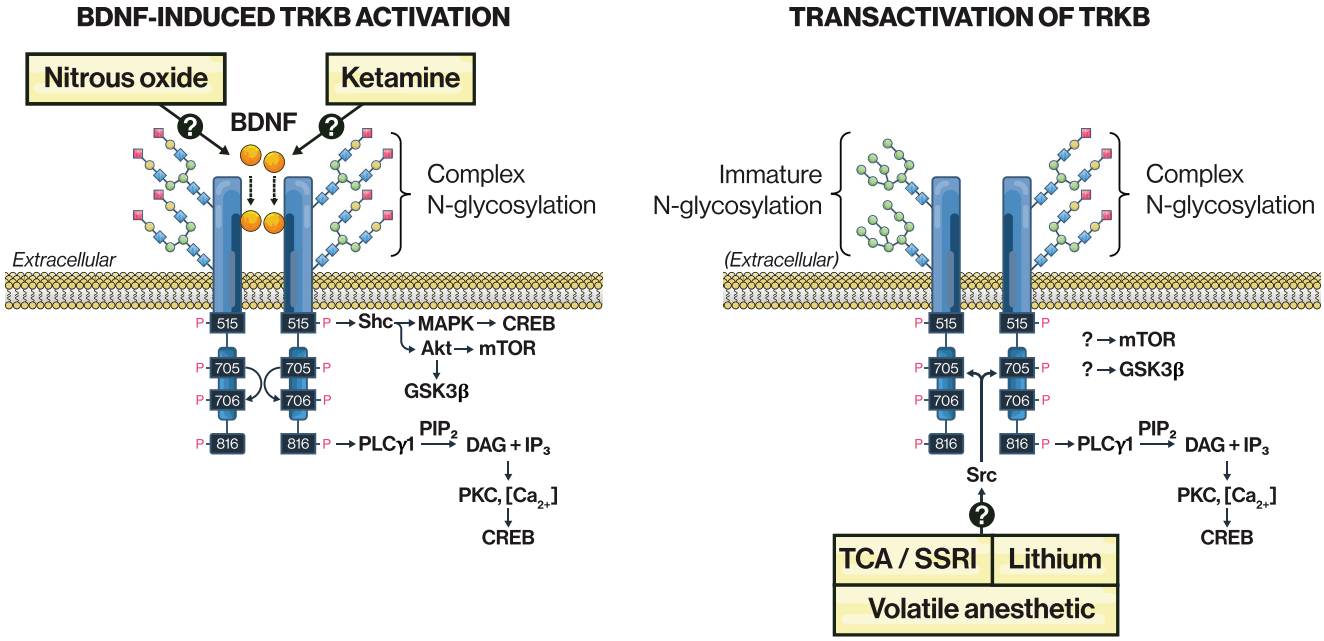

Fig. 1 Effects of BDNF and antidepressants on TrkB receptor signaling. Upon BDNF binding, TrkB receptors dimerize at the cell surface leading to transphosphorylation of the autophosphorylation loops (Y705/6) and phosphorylation of tyrosine residues 515 and 816 that set fourth MAPK/Akt and PLCγ1 signaling cascades, respectively. Monoaminergic antidepressants and isoflurane anesthesia increase phosphorylation of Y705/6 and Y816 within TrkB while leaving Y515 unaffected. Unlike BDNF, these drugs appear to (trans)activate TrkB receptors (immaturely glycosylated) residing also in intracellular compartments. BDNF, brain-derived neurotrophic factor; MW, molecular weight; MAPK, mitogen-activated protein kinase; CREB, cAMP response element binding protein; Akt, protein kinase B; mTor, mammalian target of rapamycin; PLCγ1, phospholipase Cγ1; GSK3β, glycogen synthase kinase 3β; DAG, diacylglycerol; PKC, protein kinase C; IP3, inositol triphosphate; PIP2, phosphatidylinositol 4,5-bisphosphate; TCA, tricyclic antidepressant; SSRI, serotonin-selective reuptake inhibitor

Despite the indisputable effects of BDNF on neuronal function and behavior in the brains of adult animals (incl. intracerebral applications of BDNF; see, e.g., Siuciak et al. 1994, 1996, 1997; Mamounas et al. 1995) BDNF-TrkB signaling seems to undergo significant developmental-dependent changes (Fig. 2). First, in contrast to adult animals, seizures produce negligible effects on hippocampal *bdnf* mRNA when delivered during early postnatal development (< P14) (Dugich-Djordjevic et al. 1992). Moreover, while BDNF strongly phosphorylates TrkB receptors in cultured neurons and in ex vivo preparations of an early postnatal brain, the responsiveness of TrkB to BDNF drastically reduces in a more mature brain. At around the third postnatal week and thereafter, an application of BDNF produces only minor effects on TrkB phosphorylation (Knüsel et al. 1994; Di Lieto et al. 2012). This intriguing phenomenon is unrelated to the gradual increase of dominant-negative truncated TrkB receptors during postnatal development (Di Lieto et al. 2012). Indeed, an essentially similar developmentally regulated reduced responsiveness of TrkA (no truncated receptors) to nerve growth factor (NGF) is observed (Knüsel et al. 1994). Moreover, basal TrkB phosphorylation levels are strongly reduced in the hippocampus of Bdnf-deficient mice during early development, while no baseline difference is seen in adult mice (Di Lieto et al. 2012). The neurobiological basis of these developmental-dependent changes in BDNF-TrkB signaling remains poorly known. For example, $p75^{NTR}$ and SorCS2 receptors, family members of vacuolar protein sorting 10 (VPS10) domain-containing receptor proteins, have been shown to facilitate the responsiveness of TrkB to BDNF (Berg et al. 1991; Glerup et al. 2016). In the absence of SorCS2, the ability of BDNF to induce TrkB signaling, LTP and neurotrophic effects is essentially abolished (Glerup et al. 2016).

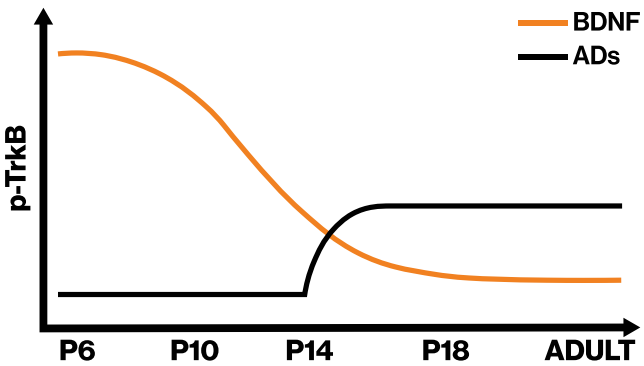

Fig. 2 Contrasting developmental-dependent effects of BDNF and antidepressants on TrkB. The ability of BDNF to activate TrkB gradually reduces during early postnatal development in rodents. At around 2 weeks of age, BDNF brings negligible effects on TrkB while systemic administrations of antidepressants begin to bring their effects on TrkB signaling. ADs, antidepressants; BDNF, brain-derived neurotrophic factor; P, postnatal day; p-TrkB, TrkB phosphorylation

The complexity of Trk(B) signaling is further highlighted by transactivation mechanism. At least glucocorticoids, zinc,

H_2O_2, adenosine and pituitary adenylate cyclase–activating polypeptide (PACAP) can phosphorylate and activate Trk receptors independently of neurotrophins (Lee and Chao 2001; Lee et al. 2002; Huang et al. 2008; Jeanneteau et al. 2008; Huang and McNamara 2010, 2012). Notably, such transactivation seems to appear also in intracellular compartments, as evidenced by the phosphorylation of low molecular weight Trk receptors presumably corresponding to immaturely glycosylated forms of the receptor (Rajagopal et al. 2004). While most transactivation mechanisms have been studied in cultured cells, zinc is shown to activate TrkB also when administered systemically in adult mice (Huang et al. 2008). The effect of zinc and H_2O_2 on TrkB signaling also becomes evident rapidly while it takes a few hours for the other transactivators to bring similar effects in vitro. Src family kinases have been implicated in Trk transaction (Lee and Chao 2001; Huang and McNamara 2010) while other mechanisms may also be involved.

Pharmacologically diverse antidepressant drugs target TrkB receptors, but how?

Since the important scientific discoveries demonstrating the effects of stress and antidepressants on *bdnf* mRNA levels in the early 1990s (Smith et al. 1995; Nibuya et al. 1995), the role of BDNF has been thoroughly studied in the context of mood disorders and their treatments (Duman and Monteggia 2006; Castrén and Hen 2013). The opposing effects of stress (reduction) and classical antidepressant drugs (increase) on *bdnf* synthesis in the hippocampus and cortex have been repeatedly reported. Notably however, induction of *bdnf* synthesis is by no means restricted to pharmacological agents carrying antidepressant effects. The effects of classical antidepressant on *bdnf* mRNA levels emerge gradually within the time course of a few weeks, which corresponds with the delayed onset of therapeutic actions of these medications (Nibuya et al. 1995). Changes in *bdnf* mRNA have been, however, also reported already after a single treatment of monoaminergic antidepressants by some groups (e.g., Zetterström et al. 1999). Changes in BDNF protein have been reported less consistently, indicating that the total tissue levels of BDNF are relatively stable and BDNF is synthesized and released on demand in active synapses. Only minute amounts of BDNF are released upon activation, making the investigation of the neuronal release of BDNF challenging (Balkowiec and Katz 2002), especially in in vivo settings.

In an (initial; see below) attempt to indirectly investigate the effects of antidepressants on BDNF release, Dr. Castrén and colleagues—including myself—assayed TrkB phosphorylation levels in the brain lysates of mice subjected to antidepressant treatments (Fig. 1). Both imipramine (tricyclic) and fluoxetine (serotonin-selective reuptake inhibitor) induce TrkB phosphorylation and phosphorylation of CREB in the adult rodent cortex within an hour after a single systemic injection (Saarelainen et al. 2003). These findings were later confirmed and extended using a battery of pharmacologically distinct antidepressant drugs (Rantamäki et al. 2007) and with lithium (Rantamäki et al. 2006). Classical antidepressants activate TrkB in various brain areas, including the hippocampus, striatum, visual cortex and cerebellum (Saarelainen et al. 2003; Rantamäki et al. 2007, 2011) (Rantamäki, unpublished). Notably, antidepressants preferentially increase the phosphorylation of the autophosphorylation loop (Y705/6) and the PLCγ1 site while leaving the phosphorylation of the Shc binding site mostly unaffected (Saarelainen et al. 2003; Rantamäki et al. 2007, 2011; Di Lieto et al. 2012), although amitriptyline has been shown to phosphorylate all sites (Aonurm-Helm et al. 2015). Indeed, phosphorylation of AKT and MAPK remains unchanged (or even reduced) after acute antidepressant treatments (Rantamäki et al. 2007; Di Lieto et al. 2012).

Phospho-TrkB antibodies recognize ~ 100–110-kDa band in brain lysates obtained from antidepressant-treated mice (Saarelainen et al. 2003; Rantamäki et al. 2011). This protein may represent the immaturely glycosylated form of the receptor that is often observed when Trk receptors are transactivated independently by BDNF (see above) (Fig. 1). To support this idea, we have shown that imipramine activates TrkB receptors also in the hippocampus of forebrain-specific conditional BDNF knockout mice (Rantamäki et al. 2011). Moreover, the ability of antidepressants to activate TrkB is developmentally regulated (Di Lieto et al. 2012). A significant effect is seen in around a 2-week-old mouse and thereafter. This developmental time window corresponds with the differential responsiveness of TrkB to BDNF (discussed above) (Fig. 2). In fact, antidepressants have no effect on TrkB phosphorylation in culture neurons derived from embryonic rat brain or in cell lines (Rantamäki et al. 2011), although amitriptyline may again be an exception (Jang et al. 2009). All in all, the precise mechanism how antidepressants (trans)activate TrkB remains to be discovered but an intact and mature central nervous system seems to be required.

Differential effects of electroconvulsive shock and anesthesia on TrkB

The therapeutic effects of ECT become evident faster than those of conventional antidepressants (Segman et al. 1995), yet reduction of symptoms after a single ECT treatment is only seldom reported (Rich 1984; Thomas and Kellner 2003; Fligelman et al. 2016). An electric current leading into a short epileptiform electroencephalogram (EEG) activity is delivered during ECT under light anesthesia but how this "seizure" leads into a remedy remains a mystery.

Electroconvulsive shock (ECS; an animal model of ECT)—and seizures in general—increases *bdnf* mRNA levels (and other immediate early genes) in the adult rodent cortex and hippocampus. The effects appear faster and are in magnitude greater than those observed after classical antidepressants (Nibuya et al. 1995). Indeed, ECS, especially when delivered repeatedly during a course of several days or weeks, increases BDNF protein levels (Altar et al. 2003; Hansen et al. 2007; Segawa et al. 2013; Neyazi et al. 2018). To nail down the putative involvement of TrkB signaling, we investigated the effects of ECS on TrkB phosphorylation. Unexpectedly however, TrkB phosphorylation levels were reduced after a single ECS treatment (Hansen et al. 2007). Lack of effects on TrkB was also seen with repeated ECS treatment paradigm, even if BDNF protein levels were concomitantly increased in the same samples (Hansen et al. 2007). Since these early attempts, there has been little interest to investigate the effects of ECS on TrkB activation, although one recent study showed increased TrkB phosphorylation following repeated administration of ECS (Enomoto et al. 2017). Notably, brain samples were collected for analyses 4 h after the last ECS in this study. Pharmacologically induced seizures on the other hand have been more consistently shown to lead into increased TrkB phosphorylation in the adult hippocampus and cortex (Aloyz et al. 1999; Binder et al. 1999; He et al. 2002, 2004). Here too, the involvement of BDNF is however unclear as seizure-induced phosphorylation of TrkB in the hippocampus is readily also seen in conditional $Bdnf^{-/-}$ (synapsin-cre) mice (He et al. 2004).

A postictal emergence electroencephalogram (EEG) burst suppression pattern has been associated with the efficacy and onset-of-action of ECT (Sackeim et al. 1993; Nobler et al. 1993; Tadler and Mickey 2018). This encouraged clinical investigations to test whether deep burst-suppressing isoflurane anesthesia can ameliorate depressive symptoms with partially promising outcomes (Langer et al. 1985, 1995). This prompted us recently to investigate the effects of isoflurane on TrkB signaling in rodents. Isoflurane, at anesthetic doses, increased TrkB phosphorylation and phosphorylation of CREB within minutes in the adult prefrontal cortex and hippocampus while BDNF levels (mRNA and protein) remained unchanged (Antila et al. 2017; Theilmann et al. 2019). Remarkably, a single and brief isoflurane anesthesia produced antidepressant-like behavioral responses and facilitation of LTP several hours or a day later after the treatment (Antila et al. 2017). Antidepressant-like behavioral effects of isoflurane have been recently reported also by others (Brown et al. 2018). Similarly with the classical antidepressants, isoflurane regulates TrkB activation also in Bdnf-deficient mice (Antila et al. 2017) and the effects seem restricted to adult animals (Rantamäki et al., unpublished). Halothane, a closely related volatile anesthetic, is reported to have no antidepressant-like effects (Brown et al. 2018), although it does regulate TrkB signaling at anesthetic doses (Antila et al. 2017). It should be noted that of all the tested pharmacological manipulations so far, deep anesthesia is clearly one of the most potent and reliable means of inducing TrkB phosphorylation in the adult rodent brain (Theilmann et al. 2019). Moreover, we recently showed that medetomidine, a hypnotic-sedative drug, readily activates TrkB signaling although it did not bring antidepressant-like behavioral responses (Kohtala et al. 2018). Notably, as in the case of monoaminergic antidepressants and lithium, the effects of isoflurane on TrkB signaling follow closely the pharmacokinetic profile of the drug (Antila et al. 2017) (Fig. 3).

Rapid-acting antidepressants also act through TrkB: is the mechanism different from other antidepressants?

Ketamine is a widely used intravenous analgesic-anesthetic agent. At low subanesthetic doses (≤ 0.3 mg/kg IV), ketamine possesses marked analgesic properties with negligible effects on consciousness and cognition. Ketamine produces dose-dependent psychotomimetic effects, sedation and ultimately dissociative anesthesia (≥ 1.0 mg/kg, IV). Importantly, the antidepressant effects of ketamine become evident already at subanesthetic doses (Berman et al. 2000). A slow IV infusion of 0.5 mg/kg is routinely delivered in psychiatric practice but the optimal dose-window for its antidepressant effects remains to be determined and is likely specific for a given patient (Aan Het Rot et al. 2012). Anyhow, it is obvious that deep burst-suppressing EEG (c.f. isoflurane) is not essential for ketamine's antidepressant effects.

The molecular mechanisms underlying the antidepressant effects of ketamine have been extensively studied in animal models. In most reports, ketamine has been injected intraperitoneally at a dose range of 3–10 mg/kg, while few studies indicate that ketamine might induce antidepressant-like behavioral responses also at higher doses and when administered intravenously (Browne and Lucki 2013). Somewhat similarly with ECS, subanesthetic treatment of ketamine increases glutamate release and cortical excitability. Here, the inhibition of NMDA-R and release of the tonic inhibition of GABAergic interneurons on glutamatergic neurons have been proposed as one putative mechanism (Duman and Aghajanian 2012). While also blocking the NMDA-R on glutamatergic neurons, released glutamate binds and activates preferentially postsynaptic AMPA-Rs (amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors). Indeed, AMPA-R blockade abolishes antidepressant effects of ketamine in animal models (Maeng et al. 2008). Ketamine and positive allosteric modulators of AMPA-Rs upregulate immediate early gene expression, including the *bdnf*. Moreover, ketamine has been shown to increase local translation of BDNF and activation of

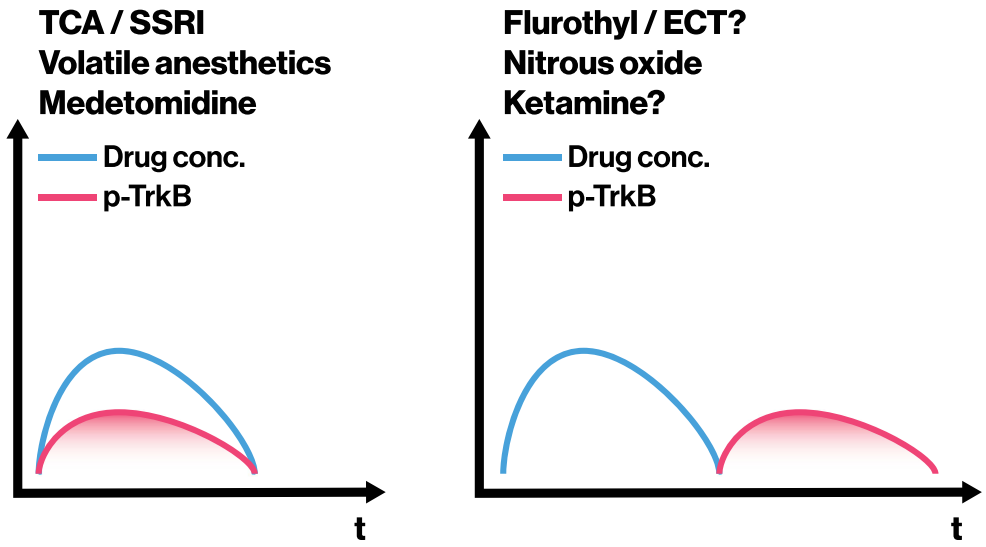

Fig. 3 Drug-induced TrkB phosphorylation in vivo—under drug influence or upon drug withdrawal? Monoaminergic antidepressants, volatile anesthetic and medetomidine rapidly increase TrkB phosphorylation during the peak of pharmacological effect. Most clinically effective rapid-acting antidepressants (e.g., subanesthetic ketamine, nitrous oxide) are thought to regulate TrkB signaling after the peak of pharmacological effect. p-TrkB, TrkB phosphorylation; TCA, tricyclic antidepressant; SSRI, serotonin-selective reuptake inhibitor; ECT, electroconvulsive therapy

TrkB receptor in the rodent prefrontal cortex and hippocampus (Autry et al. 2011; Monteggia et al. 2013; Yang et al. 2015, 2016; Carreno et al. 2016; Sun et al. 2016; Dong et al. 2017; Ma et al. 2017) (Fig. 1). Ketamine also stimulates BDNF release in neuronal cultures (Lepack et al. 2016). To my knowledge however, the ability of ketamine to regulate TrkB phosphorylation in Bdnf-deficient mice has not been yet studied. Moreover, the dose-dependent effects of ketamine on TrkB have not been thoroughly examined in vivo or in vitro.

Among putative intracellular signaling events downstream of TrkB, activation of MAPK, activation of mTor (mammalian target of rapamycin) (and its target p70S6 kinase) and inhibition of GSK3β (glycogen synthase 3β) have been intimately connected with ketamine's antidepressant effects in animal models (Li et al. 2010; Beurel et al. 2011). Ketamine regulates MAPK signaling even in cultured neurons (Lepack et al. 2016). Activation of mTor pathway is thought to underlie ketamine's rapid changes on synaptogenesis (Li et al. 2010). These acute molecular changes are however not specific for ketamine. For example, isoflurane anesthesia produces very similar changes on mTor and GSK3β (Kohtala et al. 2016; Leikas et al. 2017; Antila et al. 2017), without significant effects on synaptogenesis in adult rodents (De Roo et al. 2009; Antila et al. 2017). Notably, isoflurane, as also several other general anesthetics (including ketamine), has been shown to increase synaptogenesis during early postnatal development during a time window when BDNF's ability to activate TrkB is strongly reduced (De Roo et al. 2009; Briner et al. 2010, 2011).

Nitrous oxide (N_2O), another NMDA-R blocker and a dissociative anesthetic, has been recently shown to produce rapid antidepressant effects in a subset of patients (Nagele et al. 2015). We revealed that N_2O readily regulates Bdnf synthesis while TrkB signaling remains unchanged during gas administration (Kohtala et al. 2018). Importantly, TrkB signaling is set on only upon gas withdrawal (eliminated within minutes) during a brain state dominated by slow EEG oscillations (Kohtala et al. 2018). Subanesthetic ketamine and flurothyl (a volatile convulsant analogous to ECT) produce very similar EEG effects after the acute pharmacological effects on cortical excitation fade (Kohtala et al. 2018). The exact adaptive mechanism that is induced in response to N_2O exposure (and other rapid-acting antidepressants) (Autry et al. 2011; Ly et al. 2018) responsible for the facilitation of TrkB signaling upon drug withdrawal (Fig. 3) remains under intense study in my lab.

Conclusions

Essentially, all treatments carrying antidepressant potential have the ability to rapidly—within an hour—regulate TrkB receptor signaling and this effect seems to be at the core of the neurotrophic and neuroplastic alterations set forth by these treatments. While this effect has not yet unequivocally demonstrated with ECT (or ECS), our recent study with the volatile convulsant flurothyl supports a notion that convulsive therapies also facilitate TrkB signaling but only after the epileptiform activity has dissipated when the brain goes into "a silent mode," a phenomenon thought to predict the efficacy and onset of action of ECT. TrkB signaling is, however, facilitated also by a number of agents not carrying antidepressant effects (Autio et al. 2011; Koskimäki et al. 2014; Antila et al. 2017; Kohtala et al. 2018) pointing out that TrkB activation per se is not

sufficient in antidepressant responses. Future efforts are thus needed to identify the specific neurobiological basis of how antidepressants, both conventional and rapid-acting and both clinically established and putative novel agents effective in animal models, target TrkB signaling (Figs. 1, 2 and 3).

Acknowledgements M. Sci. Okko Alitalo is thanked for helping with their preparation of the figures. I wish to thank all the members of my lab for the support.

Funding information Open access funding provided by the University of Helsinki including Helsinki University Central Hospital. This study has been supported by the Academy of Finland (grants 276333 and 305195).

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