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Antidepressant drug action — From rapid changes on network function to network rewiring

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ABSTRACT

There has been significant recent progress in understanding the neurobiological mechanisms of antidepressant treatments. The delayed-onset of action of monoamine-based antidepressant drugs have been associated to their ability to slowly increase synaptic plasticity and neuronal excitability via altering neurotrophic signaling (synthesis of BDNF and activation of its receptor TrkB), dematuration of GABAergic interneurons and inhibition of "breaks of plasticity". On the other hand, antidepressants rapidly regulate emotional processing that – with the help of heightened plasticity and appropriate rehabilitation – gradually lead to significant changes on functional neuronal connectivity and clinical recovery. Moreover, the discovery of rapid-acting antidepressants, most notably ketamine, has inspired interest for novel antidepressant developments with better efficacy and faster onset of action. Therapeutic effects of rapid-acting antidepressants have been linked with their ability to rapidly regulate neuronal excitability and thereby increase synaptic translation and release of BDNF, activation of the TrkB–mTOR–p70S6k signaling pathway and increased synaptogenesis within the prefrontal cortex. Thus, alterations in TrkB signaling, synaptic plasticity and neuronal excitability are shared neurobiological phenomena implicated in antidepressant responses produced by both gradually and rapid acting antidepressants. However, regardless of antidepressant, their therapeutic effects are not permanent which suggests that their effects on neuronal connectivity and network function remain unstable and vulnerable for psychosocial challenges.

1. Introduction

Major depression is a highly disabling psychiatric disorder and among the biggest contributors to the disease burden worldwide (Kessler et al., 2003; Olesen et al., 2012). Due to multifactorial nature and heterogeneous symptomatology the precise etiology of this debilitating disorder remains poorly understood. However, among precipitating factors chronic stress and psychosocial trauma are prevalent determinants (Liu and Alloy, 2010). In particular, early-life adverse events increase the vulnerability to stress and facilitate the development of major depression later in life (Heim and Nemeroff, 2001). Yet, not all individuals react to stress similarly; for example genetic vulnerability, epigenetic factors, personal trait, previous experiences and personal development, and environmental factors play a role in the susceptibility to depressive illness.

Several brain structures and neurocircuits are affected in major depression. In particular, depressive states are associated with altered activity and neuronal connectivity (e.g. due to spine loss, neuronal atrophy) within and between prefrontal and limbic structures, which are thought to contribute to cognitive and emotional deficits (anhedonia, negative affect), attention biases and impaired decision-making (Arnsten, 2009; Koenigs and Grafman, 2009; Price and Drevets, 2012). Reduced neurotrophin support, especially deficient BDNF (brain-derived neurotrophic factor) synthesis and signaling of its receptor TrkB, is linked with the atrophic alterations associated with stress and depression (Castrén et al., 2007; Duman and Aghajanian, 2012; Duman et al., 1997). Neurobiological basis of altered activity of brain neurocircuits remain less understood, but abnormal function and/or expression of ion channels that regulate intrinsic neuronal excitability have been suggested to play a role (Arnsten, 2009).

The standard treatment for major depression is pharmacotherapy. However, commonly used antidepressants, such as selective serotonin (5-HT) reuptake inhibitor (SSRI) fluoxetine, have a delayed onset of action and significant number of patients responds inadequately or not at all to these medications (Fava, 2003). These drugs acutely elevate extrasynaptic monoamine levels but weeks of treatment are required

Abbreviations: 5-HT, serotonin; AMPA, amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; DBS, deep brain stimulation; ECS, electroconvulsive shock; ECT, electroconvulsive therapy; GABA, gamma-aminobutyric acid; mTOR, mammalian target of rapamycin; NMDA, *N*-methyl-*D*-aspartate; LTP, long-term potentiation; NA, noradrenaline; SNRI, serotonin and noradrenaline reuptake inhibitor; PNN, perineuronal net; PTSD, post-traumatic stress disorder; REDD1, regulated in development and DNA damage responses 1; SSRI, selective serotonin reuptake inhibitor; TrkB, tropomyosin-related kinase B.

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before the core symptoms of depression (anhedonia, depressed mood) will be ameliorated. This discrepancy between antidepressant-induced acute neurochemical effects and clinical efficacy has puzzled the researchers for several decades and steered the development of neuroadaptative theories. On the other hand, emerging evidence support a hypothesis that antidepressants rapidly initiate functional alterations within brain neurocircuits, which *gradually* lead to a more significant and sustained therapeutic effect (see below) (Fig. 1). Besides depression, these monoamine-based drugs show therapeutic efficacy against several other nervous system disorders, such as neuropathic pain, anxiety and eating disorders. This wide indication spectrum adds another unsolved characteristic associated with the use of antidepressants. Importantly, regardless of indication the therapeutic effects of these drugs are observed more clearly with a significant delay.

After launching the electroconvulsive therapy (ECT; in 1930s) and serendipitous discovery of monoamine-based antidepressants (in 1950s), there has been considerable delay in finding truly novel antidepressant treatments. Indeed, essentially all antidepressant drugs recently entered into the clinical markets are based on the basic pharmacological principle (monoamine theory) of the first antidepressant drugs (e.g. 5-HT and noradrenaline (NA) reuptake inhibitor (SNRI) duloxetine). Importantly however, NMDA (*N*-methyl-*D*-aspartate) receptor blocker ketamine has received strong attention during the past 10 years as a novel rapid-acting antidepressant (Duman and Aghajanian, 2012). Although, some of the pharmacological actions strongly limit the therapeutic use of ketamine, understanding of the mechanisms governing its antidepressant actions is essential for novel rapid-acting and more effective antidepressant developments.

In this review we will present some of the early groundbreaking findings and more recent scientific discoveries that provide important insights into the neurobiological actions of classical antidepressants and rapid-acting antidepressants, particularly ketamine.

2. From neurotrophin hypothesis

The pioneering work by Dr. Ronald Duman and colleagues showing that monoamine based antidepressants and electroconvulsive shock (ECS; model of ECT) gradually increase BDNF synthesis in the hippocampus and cortex (Nibuya et al., 1995) turned the attention to slowly developing plastic changes as important mediators of antidepressant action (Duman et al., 1997). Antidepressant-induced

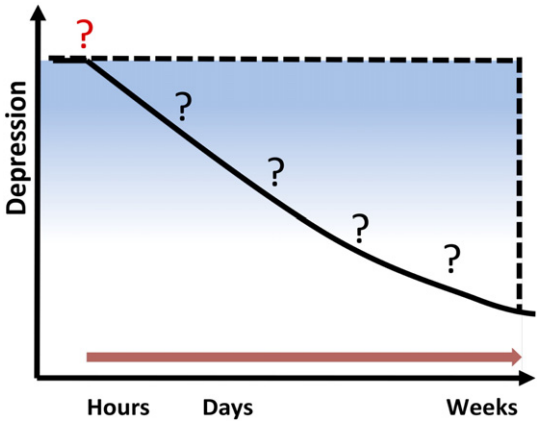

Fig. 1. Two models depicting delayed-onset action of antidepressants. In scientific literature (—) the effects of antidepressants are often described as "on–off" phenomenon where the acute pharmacological effects (?) of antidepressants is followed by a period of "silence" before the adaptive alterations leading to therapeutic effects become evident. Clinical situation (⎯) is more dynamic: antidepressants gradually improve depression symptomatology, albeit weeks of treatment are required before the core symptoms of depression, anhedonia and depressed mood are ameliorated. Changes occurring between (?) the onset of treatment and significant effects of mood are equally important or even essential for recovery. Red arrow = antidepressant treatment.

BDNF synthesis was further linked with the facilitated monoaminergic neurotransmission, in particular with cyclic AMP signaling and subsequent activation of transcription factor CREB (cAMP related element binding protein) (Blendy, 2006; Chen et al., 2001; Duman et al., 1997; Nibuya et al., 1996). Interestingly, the ability of antidepressants to facilitate BDNF synthesis through CREB is not directly linked with their ability to increase the signaling of TrkB, the primary receptor of BDNF. Indeed, antidepressants activate TrkB signaling already within an hour of a single treatment (Rantamäki et al., 2006, 2007; Saarelainen et al., 2003) and this effect appear to be independent of both monoamines and BDNF (Rantamäki et al., 2011). All in all, the precise molecular mechanism underlying antidepressant-induced rapid TrkB activation remains obscure (Di Lieto et al., 2012; Rantamäki et al., 2011) and awaits further investigations. Equally important, the specific cellular population(s) showing most prominent changes in TrkB signaling after antidepressant administration remains unidentified. Yet, these findings importantly show that the induction of plastic signaling is very rapid and does not coincide with the therapeutic delay of monoamine-based antidepressants (Fig. 2). Notably, since TrkB signaling positively regulates *Bdnf* gene expression (Saarelainen et al., 2001), BDNF-independent rapid TrkB transactivation may lead to increased BDNF synthesis, which subsequently activate its cognate receptor during prolonged treatment (Rantamäki et al., 2007) (Fig. 3). However, in contrast with BDNF-induced TrkB phosphorylation and activation, both acute and chronic antidepressant treatment produce intriguing site-specific phosphorylation changes on TrkB (Di Lieto et al., 2012; Rantamäki et al., 2007, 2011; Saarelainen et al., 2003), favoring predominant transactivation mechanism regardless of the duration of antidepressant administration.

Subsequent studies showed that prolonged antidepressant drug treatment enhances (or reverses stress-induced abnormalities therein) several cellular and functional level changes associated with neuronal plasticity such as hippocampal neurogenesis (Malberg et al., 2000), synaptogenesis (Hajszan et al., 2005, 2009), changes in synaptic efficacy/strength (long-term potentiation, LTP) and neuronal excitability (Chen et al., 2011; Rocher et al., 2004) (Fig. 2). Most importantly, enhanced BDNF–TrkB signaling appears necessary for antidepressant-like actions in rodents (Deltheil et al., 2008; Monteggia et al., 2007; Saarelainen et al., 2003). Since increased BDNF–TrkB signaling has been also suggested to be sufficient for antidepressant actions (Koponen et al., 2005; Saarelainen et al., 2003; Shirayama et al., 2002; Siuciak et al., 1997), there has been considerable recent interest in finding novel antidepressant-like drugs targeting the TrkB receptor (Liu et al., 2010; Obianyo and Ye, 2013). However, it is important to note that the behavioral outcome of increased BDNF signaling critically depends on specific brain area and neurocircuit. For example, mesolimbic BDNF signaling is importantly regulating (mal)adaptive behavioral responses to chronic social defeat stress and addictive substances (Berton et al., 2006; Hall et al., 2003; Lu et al., 2004; Wang et al., 2013). Moreover, BDNF signaling regulates homeostatic functions within the hypothalamus (Takei et al., 2014) and synaptic connectivity (Park and Poo, 2013) of several other brain neurocircuits as well, especially during development. Thus, BDNF–TrkB signaling importantly regulates synaptic plasticity and connectivity in many, if not most, neuronal networks but the network function itself and plasticity within the network determines the ultimate outcome. Therefore, direct activation of essentially all TrkB receptors (i.e. using TrkB specific agonists) within the brain may not be therapeutically rational (Zhang et al., 2014). Notably however, although currently used monoamine-based antidepressants do not act as direct TrkB agonists, they do activate TrkB in various brain areas (Rantamäki et al., 2011).

3. To network hypothesis

Researchers have recently started to investigate the ultimate functional consequence of antidepressant-induced synaptic plasticity.

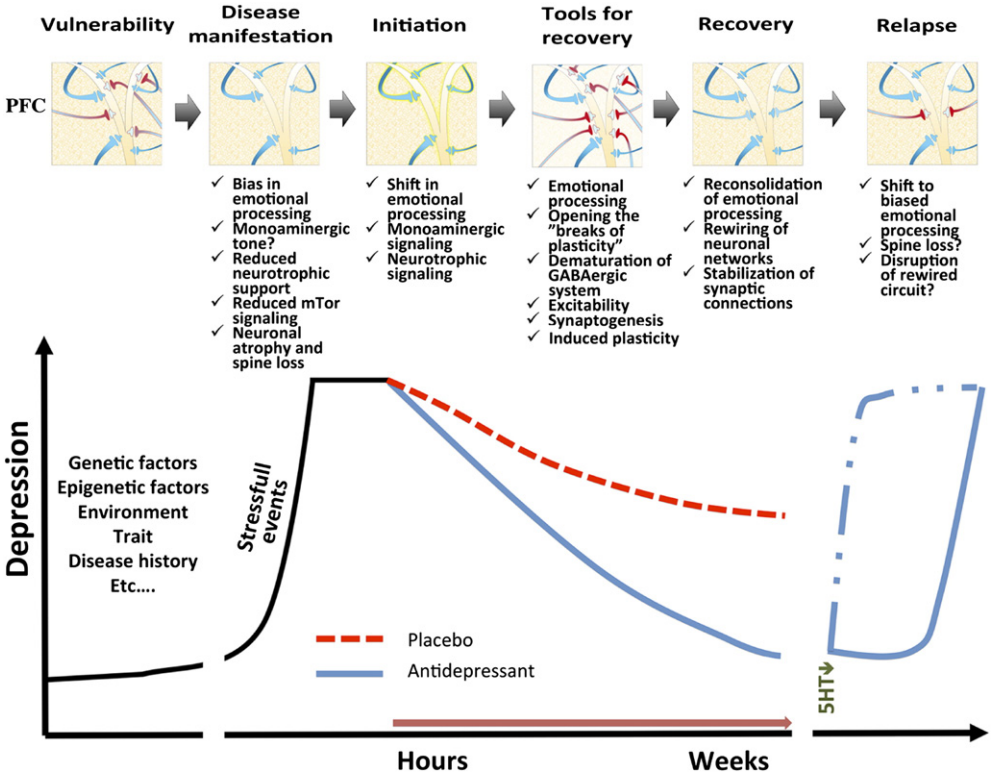

Fig. 2. "Roadmap" of depression, recovery and relapse at the level of prefrontal cortex. I) Vulnerability. Several genetic, epigenetic, environmental and developmental factors make individual susceptible for depression later in life. II) Disease manifestation. Strong psychosocial stress often precipitate depression episode through altering neurotrophic signaling and producing aberrant changes in neuronal connectivity (e.g. loss of unstable spines, marked with red color) and in network function (abnormal emotional processing) within the prefrontal circuits. III) Initiation. Antidepressants facilitate monoaminergic signaling (spines glow in yellow) and thereby regulate rapid changes in emotional processing. Notably, antidepressants begin to activate plastic neurotrophic signaling already at this stage. IV) Tools for recovery. Antidepressant treatment gradually increases synaptic plasticity by increasing BDNF synthesis, synaptogenesis (newly formed, but still unstable, spines marked with red color), facilitating synaptic strength and excitability and by removing "brakes of plasticity". V) Recovery and reconsolidation. Induced plasticity allows rewiring of neuronal connections. The rewiring and selection of appropriate synaptic connections is guided by the network itself (e.g. emotional processing) and/or external cues (e.g. rehabilitation). Note that the relative efficacy of antidepressant drug (——) compared to placebo (– – –) increase by time. VI) Remission. Monoamine depletion (**5-HT**↓; — -- —) and drug discontinuation lead to rapid and gradual re-emergence of depressive symptoms, respectively. Schematic presentation of proposed alterations in prefrontal (PFC) connectively during different stages are depicted above. Red arrow = antidepressant treatment.

Indeed, neuronal wiring and selection of synaptic connections is inherently active process that is determined by the network function itself and environmental stimuli (Hensch, 2005). This process is best understood in early life heightened plasticity stages (i.e. sensitive periods) when the neuronal networks are initially formed ("programmed") and consolidated ("hard-wired") by the guidance of environmental cues (Hensch, 2005). Importantly, adverse conditions early in life may thus produce long-lasting sustainable alterations within the network that make the individual susceptible to specific brain disorders later in life (Castrén et al., 2012) (Fig. 2). Formation of perineuronal nets (PNN) and emergence of other "breaks of plasticity" and maturation of GABAergic inhibition are important neurobiological mechanisms underlying the closure of these sensitive periods (Hensch, 2005).

Recent evidence suggests that chronic antidepressant treatment produce "dematuration" of GABAergic interneurons, removal of the "breaks of plasticity" and reduced inhibition within certain brain neurocircuits (Chen et al., 2011; Karpova et al., 2011; Kobayashi et al., 2010; Maya Vetencourt et al., 2008; Ohira et al., 2013). Most importantly, this reopening of juvenile-type of plasticity strongly facilitates the reorganization of synaptic connections guided by the environmental stimuli or functional therapy (Fig. 2). Specifically, combination of fluoxetine with active rehabilitation – but neither alone – completely recovers developmental amblyopia (so called lazy eye; i.e. vision of one eye strongly and persistently reduced due to improper visual input during the sensitive period) in adult rats (Maya Vetencourt et al., 2008). These findings are pretty remarkable since the condition has been considered incurable after the termination of sensitive period in the visual cortex. In order to test the similar concept – reinstatement of juvenile-type of plasticity – can be similarly induced with antidepressants in mood-related neuronal networks, Dr. Eero Castrén and collegues recently investigated the impact of the antidepressant treatment on plasticity within the fear circuits of amygdala. Pathophysiological fear learning against safe situations and fear generalization (e.g. post-traumatic stress disorder, PTSD) can be overcome by active desensitization process during juvenile period but not effectively in adulthood. Importantly, combination of extinction training (a model of exposure therapy) with fluoxetine, but neither alone, induced a sustained loss of conditioned fear memory in adult mice (Karpova et al., 2011). These exciting findings are in line with the network hypothesis of antidepressant action (Castrén, 2005): antidepressants are *not therapeutical* per se but they *merely* produce a plastic state – heightened adaptability – in the brain that significantly *facilitates* the impact of rehabilitation (Castrén and Hen, 2013; Castrén and Rantamäki, 2010).

Although the network theory of antidepressant action is still in its infancy and needs further experimental and especially clinical investigations, it already helps to understand many of the intriguing characteristics associated with the use of classical antidepressants. The formation of plastic state and rewiring of neuronal connections inevitably takes time (delayed onset of action) and lack of rehabilitation may, at least partially, underlie the inefficacy associated with the use of medication (treatment-resistance/lack of efficacy). Moreover, drug-induced plasticity appears to be not restricted in mood-related neurocircuits but rather act in many levels (therapeutic effects against several nervous system disorders).

The true therapeutic potential of drug-induced plasticity and combination of functional rehabilitation in nervous system disorders remains to be investigated. It is important to note however that combination of fluoxetine with rehabilitation promotes recovery in ischemic stroke patients devoid of psychiatric illness such as depression (Chollet et al., 2011). On the other hand, if the appropriate environment is critical for recovery, what happens in inappropriate environmental conditions? Interestingly enough, monocular deprivation ("inappropriate environment") in adult animals chronically treated with fluoxetine produced the shift in ocular dominance in favor of the open eye and poor vision of the visually deprived eye (amblyopia) (Maya Vetencourt et al., 2008). All in all, the neurobiological mechanisms of antidepressants appear to be much more complex than originally thought and the specific context of which they are used seem to have significant role in determining the ultimate functional outcome. It should be thus much more closely examined the outcomes of antidepressant use in different clinical contexts (e.g. correlation of clinical efficacy with patient diaries, adverse environment).

On the other hand, the therapeutic effects of antidepressants are not permanent and re-emergence of symptoms after the discontinuation of effective antidepressant treatment is frequently observed. Consequently, months of "steady-state" antidepressant treatments are commonly used — and they appear effective (Shelton, 2004). Moreover, 5-HT depletion rapidly produces relapse in depressive patients under effective SSRI medication (Delgado et al., 1990). Therefore, antidepressant treatments do not target the core of depression pathology but rather produce beneficial functional and morphological alterations in brain neurocircuits that remain vulnerable and are readily subjected to remodifications (Fig. 2). Since sustained drug treatment is effective, does the network become more depended on serotonergic transmission? It will be very important to investigate the stability of neuronal connections rewired during antidepressant treatment in adulthood.

4. Rapid alterations in network function — emotional processing

Although antidepressants alleviate depressed mood slowly, they certainly do something during the very early stages of treatment. The lag-time associated with antidepressants is often misinterpreted as an on–off phenomenon, i.e. clinical effects of the drugs appear *only* after several weeks of treatment (Fig. 1). It is important to note however, that the relative efficacy of antidepressant drug compared to placebo increase by time and slight reduction of some of the symptoms is often observed already during the first week of treatment (Taylor et al., 2006). Thus, antidepressants *gradually* reduce symptoms but the significant clinical effect become more obvious only after exceeding certain (patient-specific) threshold. More intriguingly, accumulating clinical data indicates that antidepressant drugs rapidly regulate information processing in neurocircuits implicated in depression (Harmer et al., 2009). Depressive patients have biased emotional processing towards negative emotions (Beck, 2008; Bouhuys et al., 1999; Bradley and Mathews, 1983; Gur et al., 1992), and this functional abnormality is thought to underlie and even maintain depressive states. In healthy controls, acute antidepressant treatment shift emotional processing towards the positive domain (Browning et al., 2007; Harmer et al., 2003). On the other hand, fearful face recognition and startle responses (e.g. eye-blink response to emotional stimuli) are facilitated by acute, but attenuated by prolonged treatment of antidepressants, although amygdala show sustained reduced responses to fearful and aversive stimuli (Browning et al., 2007; Harmer et al., 2003, 2004, 2006; Rawlings et al., 2010; Windischberger et al., 2010). Chronic antidepressant treatment also improves social problem solving behavior and reduces submissive behavior (Knutson et al., 1998; Raleigh et al., 1991; Tse and Bond, 2002), which is commonly observed in depressed people. In summary, the early effects of antidepressants on the processing of positive emotional stimuli are maintained whereas continuous treatment bring beneficial effects on threat processing and behaviour in general (Harmer and Cowen, 2013). Most importantly, similar observations (shift towards positive emotional processing, attenuated amygdala responses to threat stimuli) have been observed in depressed patients (Harmer et al., 2003), although most studies have focused on prolonged drug administration and thus the rapidity of the responses awaits further clarifications. Effects of antidepressants on emotional processing appear to be regulated by increased monoaminergic tone (Booij and Van der Does, 2011; Harmer and Cowen, 2013), which directly links the primary pharmacological mechanism of antidepressants on these responses.

Based on emotional processing theory of antidepressant action, initial shift in emotional processing leads to gradual positive changes in social reinforcement and mood (Fig. 2) (Harmer and Cowen, 2013). This psychological reconsolidation may be further facilitated – or even depend on – by enhanced synaptic plasticity (see above). Thus, the network theory and emotional processing theory are not mutually exclusive but complementary: both theories link antidepressant action with cognitive or behavioral theories of depression.

Further efforts have been put to investigate the network-level functional correlates that could help to better explain the emotional and network theories of antidepressant actions. These brain-imaging studies have shown that depressed patients show abnormal resting state functional connectivity – measured as temporally linked activity between neuronal networks – in specific brain circuits within and between prefrontal and limbic structures (Anand et al., 2005; Greicius et al., 2007; Lui et al., 2011; Perrin et al., 2012; Sheline et al., 2010; Veer et al., 2010; Wang et al., 2015). Most notably, increased functional connectivity between dorsomedial prefrontal cortex (termed dorsal nexus) and many of its target areas are highly associated with depressive states and are thought to underlie rumination (i.e. compulsive attention on the symptoms of distress and potential negative consequences) (Sheline et al., 2010). Importantly, clinically effective antidepressant treatments (antidepressant drugs, ECT) normalize this hyperactivity (Perrin et al., 2012; Wang et al., 2015). Interestingly, and strictly in line with the emotional processing and network theories of antidepressant action, antidepressants alter functional neuronal connectivity also in healthy volunteers (McCabe and Mishor, 2011; McCabe et al., 2011; van Wingen et al., 2013). Further studies are needed to understand the precise neurobiological basis of antidepressant-induced functional neuronal connectivity, how quickly it appears and how stable it is. One caveat is that such scientific questions can be currently investigated in animals only under anesthesia, which in its self may alter neuronal connectivity or modify the responses produced by antidepressants. In clinical practice however, functional brain imaging techniques are becoming more and more valuable tools to predict and correlate therapeutic responses in patients.

5. Towards rapid-acting antidepressant drugs

Since slowly developing functional and morphological changes likely precede depressive episodes, it is very conceivable that such adaptive alterations cannot be recovered quickly. Importantly however, some treatments show superior rapidity over commonly used antidepressants to ameliorate depressive symptoms. Intriguingly, all these rapid-acting antidepressants, including sleep deprivation (Giedke and Schwärzler, 2002) and ECT (Payne and Prudic, 2009), strongly and rapidly regulate inhibition-excitation balance and thereby neuronal excitability in the brain. ECT remains as the treatment of choice for drug-refractory depressive patients and when fast relief of symptoms is needed (e.g. suicidal ideation). Although currently delivered under general anesthesia, ECT remains stigmatized and its use may lead to side effects such as cognitive impairment (Payne and Prudic, 2009). Moreover, despite its long therapeutic use, the precise neurobiological mechanism governing the antidepressant effects of ECT remain obscure, although BDNF signaling is considered to play important role (Taylor, 2008). Interestingly enough, the therapeutic effect of ECT is associated with post-seizure neuronal inhibition (evident as burst suppression in the

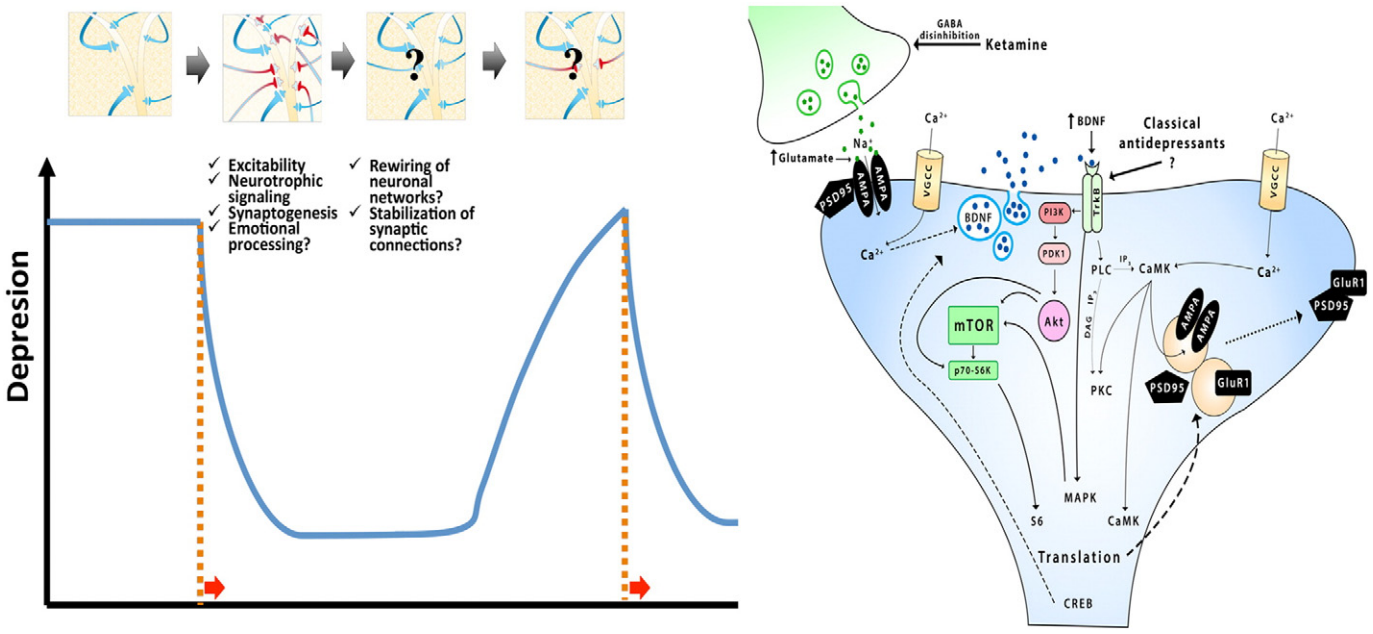

Fig. 3. Neurobiological mechanisms and effects of rapid acting antidepressant ketamine. A single ketamine treatment induces rapid changes in cortical excitability through blocking inhibitory GABAergic interneurons (not shown) and subsequent activation of AMPA receptor signaling in glutamatergic neurons. Increased AMPA receptor signaling lead to synaptic translation and release of neurotrophin BDNF, which further induces TrkB–mTOR–p70S6k signaling pathway, facilitation of synaptic plasticity, increase in synaptic proteins (PSD95, GluR1) and synaptogenesis. Notably, classical antidepressants also acutely increase TrkB receptor signaling and phosphorylation of CREB with an unknown mechanism. Depressive symptoms re-emerge within days after ketamine treatment. Neurobiological correlates (?) for the transient therapeutic effects of ketamine remain unknown. Red arrow = ketamine.

electroencephalogram (EEG)) (Perera et al., 2004), although to our knowledge no experimental studies examining rodent models of ECT have specifically followed along with this phenomenon.

Recent studies demonstrate that ketamine, a dissociative anesthetic, produces antidepressant actions. Compared to classical antidepressant drugs, ketamine does not only act on a novel pharmacological target (the NMDA receptor), its antidepressant effects also appear very rapidly – within few hours – after a single treatment (Fig. 3). The therapeutic effect of a single ketamine treatment also sustains for several days — thus long after the drug has been removed from the brain. Antidepressant effects of ketamine have been mostly studied and shown in treatment-resistant depressive patients, even in patients that do not respond to ECT (Berman et al., 2000; O'Leary et al., 2015; Zarate et al., 2006). Ketamine is effective already at subanesthetic doses, however researchers have recently got interested whether anesthetic doses of ketamine would produce more sustained effects (Okamoto et al., 2010).

Antidepressant-like effects of a single ketamine administration has also been observed in rodents (Li et al., 2010; Lindholm et al., 2012). Experimental data suggest that the antidepressant effects of ketamine are mediated by rapid regulation of inhibition-excitation balance (increased cortical excitability) (Cornwell et al., 2012; Di Lazzaro et al., 2003), fast synaptic translation and the release of BDNF in the prefrontal cortex that further leads to increased signaling of the TrkB–mTOR–p70S6k pathway, facilitation of synaptic plasticity and alterations in dendritic spine dynamics (Autry et al., 2011; Li et al., 2010; Maeng et al., 2008) (Fig. 3). Indeed, the magnitude of therapeutic response to ketamine varies between patients, a phenomenon recently associated with the differential alterations in BDNF homeostasis and *Bdnf* gene polymorphism (Haile et al., 2014; Laje et al., 2012). The potential role of mTOR pathway in the pathophysiology of depression has been recently strengthened by observations demonstrating increased expression and signaling of REDD1 (regulated in development and DNA damage responses 1), a negative regulator of mTOR, in depressive patients and animals subjected to chronic stress (Ota et al., 2014). Interestingly, REDD1 expression in the prefrontal cortex is also sufficient to produce anxiodepressive phenotype and dendritic spine loss reminiscent with chronic stress (Ota et al., 2014). Moreover, the levels of mTOR and its downstream kinase p70S6k are reduced in the prefrontal cortex of depressive patients (Jernigan et al., 2011).

The discovery of rapid acting effects of ketamine has strongly increased the interest towards novel faster acting antidepressant developments (Duman and Aghajanian, 2012; Zarate et al., 2013). Intriguingly, antimuscarinic agent scopolamine have been also shown to produce rapid antidepressant effects (Furey and Drevets, 2006) and, similarly with ketamine, increased glutamatergic transmission, mTOR signaling and synaptogenesis have been associated with these responses (Voleti et al., 2013). Moreover, burst-suppressing anesthesia (see above) has been shown to produce antidepressant effects comparable to those of ECT, without affecting cognitive performance (Langer et al., 1995). More importantly, antidepressant effects of isoflurane seem to appear already after the first treatment episode (Langer et al., 1995). A recent clinical study supports the hypothesis that isoflurane possess antidepressant effects (Weeks et al., 2013), however, this study did not specifically look the rapidity of these responses. Yet, differential therapeutic responses in patients (Greenberg et al., 1987; Langer et al., 1995) and unknown neurobiological basis have strongly reduced the interest to further evaluate anesthesia as a potential (and intriguing) substitute of ECT. Thus, better understanding of the mechanisms underlying antidepressant actions of isoflurane in experimental animals is needed.

The antidepressant effects of ketamine appear within few hours, a time window where environmental guided rewiring of synaptic connections may not yet take place, although ketamine rapidly increases synaptic markers and regulates the formation of functional excitatory synapses (Li et al., 2010). Whether these new synaptic contacts bring about physiological changes in neuronal connectivity or merely produce "noise" that beneficially alters existing network function remains unknown. Interestingly, hyper- and hypoactivity within specific prefrontal circuitries have been associated with depression. Local deep brain stimulation (DBS) and effective antidepressant treatment normalize these alterations (Mayberg et al., 2005). Moreover, optogenetic and electrical stimulations of the specific prefrontal

circuitries can induce either antidepressant-like or depression-like behavioral responses in rodents (Barthas et al., 2015; Hamani et al., 2010a,b, 2012). These studies clearly demonstrate that the mood-related circuits can be effectively and rapidly regulated which is directly reflected in behavior. In line with these findings, functional connectivity within mood-related neuronal circuits are facilitated already during an acute ketamine administration in rats (Gass et al., 2014), whereas blunting of functional connectivity – as observed after repeated treatment of classical antidepressants – is observed 24 h after the treatment in humans (healthy volunteers) (Scheidegger et al., 2012), a time window associated with most significant antidepressant effect of ketamine.

Importantly, similarly with classical antidepressants, the therapeutic effects of ketamine gradually disappear (Murrough et al., 2013). New dose will be effective however repeated administration (cf. ECT) of psychoactive substance with strong abuse potential is warranted. It remains to be investigated how transient and stable effects ketamine produces on neuronal connectivity and network function and whether the circuits could be stabilized through rehabilitation. Notably, prefrontal circuitries are particularly vulnerable for environmental challenges (Izquierdo et al., 2006). Moreover, since monoaminergic antidepressants and ketamine produce qualitative and quantitatively different changes on synaptic plasticity, their combined use should be examined.

6. Conclusions

There has been important recent progress in understanding the neurobiological mechanisms of classical antidepressants and rapid-acting antidepressant ketamine (Figs. 2–3). Monoamine based antidepressants rapidly regulate emotional processing and TrkB neurotrophin signaling. Continued antidepressant treatment further produces heightened plasticity that allows rewiring and efficient reconsolidation of neuronal connections guided by intrinsic and extrinsic cues. These findings help to explain (and substantiate) the superior therapeutic efficacy of combined use of pharmacotherapy and functional rehabilitation but also raises critical thinking about the potential impact of such heighted plasticity in undesired environmental conditions.

Increased neuronal excitability, activation of TrkB–mTOR–p70S6k signaling and increase in cortical synaptogenesis are implicated in the antidepressant actions of ketamine. Thus, induced plasticity through TrkB signaling is implicated in the mechanisms of action of both gradually acting and rapid-acting antidepressant drugs. However their mechanisms and effects on TrkB receptor differ (Autry et al., 2011; Di Lieto et al., 2012; Rantamäki et al., 2011) which leads to qualitatively, quantitatively and spatially differential, yet largely unknown, downstream signaling events and functional consequences.

Regardless of antidepressant, their therapeutic effects are often not permanent. Consequently, antidepressant treatments do not target the core of depression pathology but produce beneficial functional and morphological alterations in brain neurocircuits that are readily subjected to remodifications. Better understanding of the acute and long-lasting neurobiological effects of diverse antidepressant treatments on neuronal connectivity and function will lead to more effective therapeutic approaches against major depression and other nervous system disorders that benefit from induced plasticity.

Author contribution

T.R. and I.Y. wrote the paper.

Conflict of interests

T.R. have received research support from Orion Pharma, Hermo Pharma and Ono Pharmaceuticals.

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