

Review

Environmental and pharmacological modulations of cellular plasticity: Role in the pathophysiology and treatment of depression

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ARTICLE INFO

Article history:

Received 19 January 2012

Revised 5 April 2012

Accepted 31 May 2012

Available online 9 June 2012

Keywords:

Major depressive disorder

Stress

Animal models

Antidepressants

Exercise

Omega-3 fatty acids

Early life stress

ABSTRACT

Atrophy of neurons and gross structural alterations of limbic brain regions, including the prefrontal cortex (PFC) and hippocampus, have been reported in brain imaging and postmortem studies of depressed patients. Preclinical findings have suggested that prolonged negative stress can induce changes comparable to those seen in major depressive disorder (MDD), through dendritic retraction and decreased spine density in PFC and hippocampal CA3 pyramidal neurons. Interestingly, recent studies have suggested that environmental and pharmacological manipulations, including antidepressant medication, exercise, and diet, can block or even reverse many of the molecular changes induced by stress, providing a clear link between these factors and susceptibility to MDD. In this review, we will discuss the environmental and pharmacological factors, as well as the contribution of genetic polymorphisms, involved in the regulation of neuronal morphology and plasticity in MDD and preclinical stress models. In particular, we will highlight the pro-depressive changes incurred by stress and the reversal of these changes by antidepressants, exercise, and diet.

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Introduction

Major depressive disorder (MDD) is a recurring psychiatric illness that affects up to 17% of the American population, and can be severely debilitating, affecting sleep, work, social relationships, and appetite

(Kessler et al., 2005). Both clinical and pre-clinical studies have revealed that prolonged stress can lead to depressive symptoms that are associated with atrophy of neurons and related behavioral alterations in limbic brain areas, most notably the prefrontal cortex (PFC) and hippocampus. For example, postmortem findings show cell atrophy and decreased volume of the PFC in MDD patients (Drevets et al., 1997; Rajkowska et al., 1999). Further, a recent meta-analysis of imaging studies revealed that lower gray matter volumes are seen in cortical limbic structures (dorsal frontomedial

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Available online on ScienceDirect (www.sciencedirect.com).

and paracingulate cortex) of MDD patients, in parallel with increases in glucose metabolism in related cortical regions (subgenual and pregenual anterior cingulate) (Sacher et al., 2011). Consistent with this, morphological and morphometric analyses of the hippocampus in depressed patients show reduced volume, gray matter, and neuro-pil (Bremner et al., 2000; Campbell et al., 2004; McKinnon et al., 2009; Sheline et al., 1996; Stockmeier et al., 2004). The amygdala is another limbic structure that undergoes structural alterations, although in this case amygdala neurons undergo a hypertrophy in response to repeated stress that could contribute to anxiety and certain emotional symptoms of depression (see Roozendaal et al., 2009 for a review of the role of the amygdala in stress).

Understanding the mechanisms by which these structural and morphological changes arise could provide insight into the biological basis of MDD. Importantly, recent work has shown that these changes are not permanent and that these structural alterations can be altered bi-directionally through environmental and pharmacological influences. Here, we provide an overview of the morphological changes in rodent models of stress and MDD, and the influence of environmental, pharmacological, and genetic factors. This work provides a framework for understanding the impact of lifetime exposure to environmental factors in the context of genetic susceptibility or resilience to depression and will lead to updated recommendations for healthy emotional preventative lifestyles and new therapeutic interventions.

Structural and neurotrophic deficits caused by chronic stress and depression

Stress, defined as an alteration of normal homeostasis (Selye, 1936), is a strong environmental factor that can have a wide range of effects on multiple organ systems, including depression. Consistent with this, chronic stress is commonly used as an animal model of depression. Preclinical studies demonstrate that chronic stress causes dendritic retraction and decreased spine density in PFC pyramidal neurons (layer II/III and layer V) and hippocampal CA3 pyramidal neurons following repeated stress (Izquierdo et al., 2006; McEwen, 1999; Radley et al., 2004, 2006; Shansky et al., 2009; Sousa et al., 2000). Reductions of spine density and length are observed at both the distal and proximal segments of the apical tuft, and can be measured by reduction in expression of synaptic proteins (Li et al., 2011). These cellular alterations may contribute to the reduced volume of PFC and hippocampus reported in brain imaging studies, and to the cognitive and emotional deficits observed in depressed patients (Drevets et al., 1997; McEwen, 2007; Sacher et al., 2011; Sheline et al., 2003).

Chronic stress is one of the better rodent models of depression, resulting in structural alterations as well as behavioral anhedonia, a core symptom of depression (Willner, 1997). Anhedonia and behavioral despair, the latter typically assessed in the forced swim test, are also reversed by antidepressant treatment, providing a level of construct validity. However, it is difficult to interpret the meaning of behavioral despair in these models and to model other aspects of depression that are evaluated by verbal assessment in humans. In addition, the heterogeneous nature of MDD makes it difficult to accurately model all aspects of depression at behavioral, as well as molecular and cellular levels. Nevertheless, when used with an understanding of the limitations, the chronic stress model can provide powerful information on the underlying molecular and cellular determinants of depression and the circuitry controlling complex stress-related behaviors.

One mechanism that may mediate the cellular alterations observed following chronic stress is altered expression of neurotrophic factors. Neurotrophic factors are important for growth and survival during neuronal development but continue to play a critical role in the survival and function of neurons in the adult brain (McAllister, 2002). Here we discuss some of the factors best-characterized for their roles in stress and depression, including brain derived neurotrophic

factor (BDNF), vascular endothelial growth factor (VEGF), VGF (non-acronym), and insulin-like growth factor (IGF)-1.

Stress decreases neurotrophic factor expression and signaling

BDNF

Perhaps the most studied neurotrophic factor in stress and MDD is BDNF (Castrén et al., 2007; Duman and Monteggia, 2006; Monteggia, 2007). BDNF levels are decreased in cortical and hippocampal regions of postmortem brains of depressed subjects relative to controls (Chen et al., 2001; Dwivedi et al., 2003; Karege et al., 2005). Interestingly, levels of BDNF in blood correlate with that in brain tissue, and are decreased in depressed patients relative to controls (Bocchio-Chiavetto et al., 2010; Brunoni et al., 2008; Karege et al., 2005; Klein et al., 2011; Sen et al., 2008; Shimizu et al., 2003). However, BDNF is also expressed in many peripheral tissues, and the source of BDNF that contributes to altered levels in blood of MDD patients, as well as the underlying mechanisms, requires further investigation (Schmidt et al., 2011).

Further supporting a role of BDNF in MDD is evidence that this neurotrophic factor is decreased in animal models of chronic stress (Duman, 2004b; Murakami et al., 2005). Moreover, applications of recombinant BDNF (i.e., i.c.v., intra-hippocampus, or intra-midbrain) have antidepressant and anxiolytic effects in behavioral models. These effects include increased mobility in the forced swim test, increased escape in the learned helplessness test, increased sucrose consumption in the chronic unpredictable stress (CUS) paradigm, decreased latency in the novelty induced hypophagia test, and increased time spent in the open arms of an elevated plus maze (Schmidt and Duman, 2010; Shirayama et al., 2002; Siuciak et al., 1997).

In contrast, deletion of BDNF blocks the behavioral effects of antidepressants in several of these models, including the forced swim test and learned helplessness model (Duman and Monteggia, 2006; Monteggia et al., 2004). Consistent with this, constitutive heterozygous (+/−) deletion of BDNF (homozygous deletion mutants are lethal) results in neuronal atrophy in the hippocampus and PFC (Chen et al., 2006; Magariños et al., 2011), which may contribute to blockade of antidepressant responses. Interestingly, most studies have shown that the deletion of BDNF alone is not sufficient to cause depressive behavior in rodents, but instead increases susceptibility to depressive effects (Duman et al., 2007; Martinowich et al., 2007). A recent study, however, has shown that short hairpin RNA (shRNA) knockdown of BDNF in the hippocampus is sufficient to cause depressive behaviors, suggesting that perhaps BDNF plays a specific regional role in the etiology of depression (Taliaz et al., 2010). The discrepancy between this and previous approaches that do not target a specific brain region could be due to selective knockdown in the hippocampus, as BDNF in the mesolimbic dopamine circuit produces opposing depressive actions (Krishnan and Nestler, 2008). Taken together, these preclinical studies demonstrate a requirement for BDNF in the actions of antidepressants and implicate BDNF deficits as a risk factor that contributes to neuronal atrophy and is associated with depressive symptoms.

The expression of BDNF is induced by activation of the cyclic AMP (cAMP) and Ca²⁺/calmodulin (CAM) signaling cascades, activation of cAMP- and CAM-dependent protein kinases (PKA and CAMK, respectively), and the cAMP response element binding protein (CREB) (Greer and Greenberg, 2008; Nestler et al., 2002). BDNF also has numerous downstream molecular effectors (Fig. 1). BDNF activates TrkB, which can stimulate the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)-Akt signaling pathways. Based on the significant role of BDNF in depression and treatment response, it is not surprising that MAPK signaling is similarly required for the behavioral effects of antidepressant action (Duman et al., 2007). Consistent with this, recent studies have shown that MAPK signaling is decreased in postmortem brains of depressed

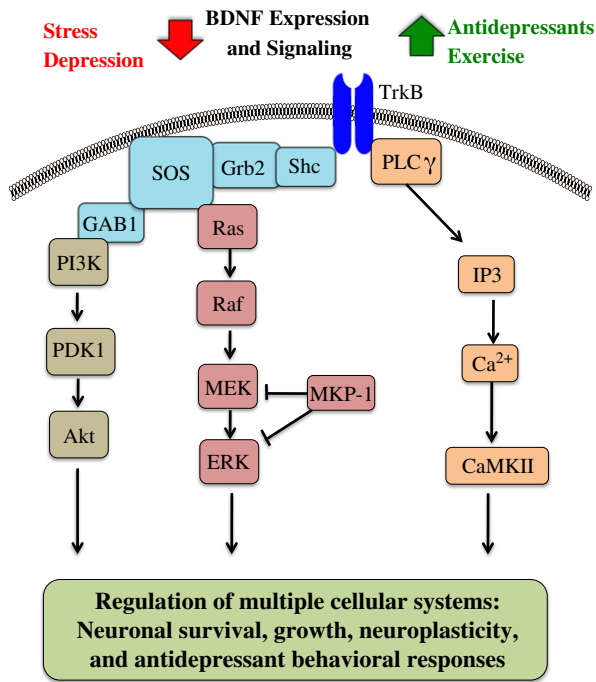


Fig. 1. BDNF signaling pathways and opposing effects of stress, depression, exercise and antidepressants. BDNF binds to the TrkB receptor, resulting in autophosphorylation of tyrosine residues. These sites then interact to activate the MAPK, CaMKII, and PI3K signaling cascades. These pathways ultimately regulate multiple cellular systems, including neuronal survival, growth, and neuroplasticity, which can lead to alterations in antidepressant behavioral responses. Stress and depression decrease activation of these pathways, while antidepressants and exercise increase activation of these pathways. Abbreviations: BDNF, brain derived neurotrophic factor; TrkB, tropomyosin-related kinase B; MAPK, mitogen-activated protein kinase; CaMKII, calmodulin-dependent protein kinase; PI3K, phosphatidylinositol 3-kinase; Grb2, growth factor receptor-bound protein 2; GAB1, Grb2-associated binder-1; SOS, son of sevenless; Shc, Src homology 2-domain containing adaptor protein; PLC γ , phospholipase C- γ ; ERK, extracellular signal-regulated kinase; MEK, MAP/ERK kinase; MKP-1, MAP kinase phosphatase 1; PDK1, phosphoinositide dependent kinase 1; Akt, serine threonine kinase or protein kinase B; IP3, inositol triphosphate. Figure adapted from [Duman and Voleti \(2012\)](#).

subjects and that MAPK phosphatase-1 (MKP-1), which negatively regulates the MAPK signaling pathway, is increased in the hippocampus of depressed subjects ([Duric et al., 2010](#); [Dwivedi et al., 2006, 2007](#)). Induction of MKP-1 using a viral expression approach produces stress-like behaviors in the absence of stress in rodents, while MKP-1 deletion creates a state of resilience to chronic stress exposure ([Duric et al., 2010](#)). Taken together, these studies elucidate some of the downstream signaling mechanisms by which BDNF can underlie depression behaviors, although additional studies are needed to further elucidate the complex signaling pathways that contribute to the actions of BDNF.

Interestingly, a human functional genetic variant of BDNF, the Val66Met single nucleotide polymorphism (SNP), has provided further evidence for a role for BDNF in MDD. The BDNF Met polymorphism results in decreased activity-dependent release of BDNF by decreasing the processing and targeting of mature BDNF to dendrites and synapses ([Chen et al., 2004](#); [Chiaruttini et al., 2009](#); [Egan et al., 2003](#)). Carriers of the BDNF Met allele have decreased hippocampal volume and display cognitive deficits compared to the Val allele ([Bueller et al., 2006](#); [Egan et al., 2003](#); [Hariri et al., 2003](#); [Pezawas et al., 2004](#); [Szeszko et al., 2005](#)). Although there is no direct association of the BDNF Met allele with depression ([Verhagen et al., 2010](#)), there are reports that early life stress or trauma increases the vulnerability to depressive phenotypes in BDNF Met carriers ([Gatt et al., 2009](#)) ([Fig. 2](#)).

Studies of the Met allele in rodents provide similar evidence for structural and functional alterations. Mice with a knock in of the

BDNF Met allele exhibit atrophy of pyramidal neurons in the hippocampus and PFC ([Chen et al., 2006](#); [Liu et al., 2011](#)). BDNF Met knock in mice also display decreased density of spines, decreased number of large diameter “mushroom” or mature spines, and a reduction in excitatory postsynaptic currents in the PFC ([Liu et al., 2011](#)). Similar reductions in dendrite length and branching have been observed in constitutive BDNF heterozygous mutant mice that express one half the normal complement of BDNF ([Chen et al., 2006](#); [Magariños et al., 2011](#)). These effects of the BDNF Met allele, as well as constitutive BDNF heterozygous deletion mutant mice, are reminiscent of the atrophy of neurons in the PFC and hippocampus caused by chronic stress.

VEGF

Although VEGF was first characterized in and is best known for its effects on endothelial cell proliferation and angiogenesis, it is also expressed in brain and influences neurite outgrowth and maturation during development ([Fournier and Duman, 2011](#)). Studies in humans suggest that a VEGF polymorphism, VEGF2578C/A, which leads to lower circulating levels of VEGF ([Lambrechts et al., 2003](#)), is linked to treatment-resistant depression ([Viikki et al., 2010](#)). In parallel, CUS in rodents decreases expression of VEGF in the granule cell layer and hilar regions of the hippocampus, providing evidence that disruption of this factor could also contribute to the structural and behavioral deficits caused by stress ([Bergström et al., 2008](#); [Heine et al., 2005](#)).

Stress and neurogenesis

One of the functional consequences of alterations in neurotrophic factors is regulation of neurogenesis. Neurogenesis not only occurs during early postnatal development, but also continues in certain neurogenic zones in the adult, notably the dentate gyrus of hippocampus and subventricular zone. Different types of stress, including CUS, intruder stress, predator stress, and footshock stress, all decrease the number of newborn neurons in the granule cell layer of the adult hippocampus ([Drew and Hen, 2007](#); [Duman, 2004a](#); [McEwen, 1999](#)). Interestingly, the loss of new neurons is not sufficient to produce depressive behaviors ([Drew and Hen, 2007](#); [Sahay and Hen, 2007](#)), but a recent study demonstrates that new neurons are necessary for proper control of endocrine and behavioral responses to stress ([Snyder et al., 2011](#)). Consistent with the effects of stress on BDNF and its role in depression, there is strong evidence that BDNF also contributes to the regulation of neurogenesis. For example, central or peripheral BDNF administration increases adult hippocampal neurogenesis ([Schmidt and Duman, 2010](#)). In contrast, conditional deletion of TrkB in hippocampal neural progenitor cells leads to impaired proliferation and neurogenesis ([Li et al., 2008](#)). Similarly, BDNF +/- mice have decreased basal proliferation ([Lee et al., 2002a](#)), and both BDNF +/- and dominant negative TrkB over expressing mice show impaired long-term survival of newborn neurons ([Sairanen et al., 2005](#)).

Taken together, these findings demonstrate that chronic stress serves as a valid model for depression-related alterations: many of the same structural and cellular changes are observed in depression and chronic stress, and there is evidence that the same trophic factors and signaling pathways may be involved in humans and animal models. Although we have focused on the role of neurotrophic factors, there are a number of other factors and systems that have also been implicated in depression that will not be discussed due to space limitations. This includes recent work demonstrating alterations of the GABA neurotransmitter system in depressed patients (see [Sanacora, 2010](#) for a review).

Early life stress and maternal care

In addition to stress in adulthood, early postnatal or adolescent stress, as well as maternal care, can have major consequences on

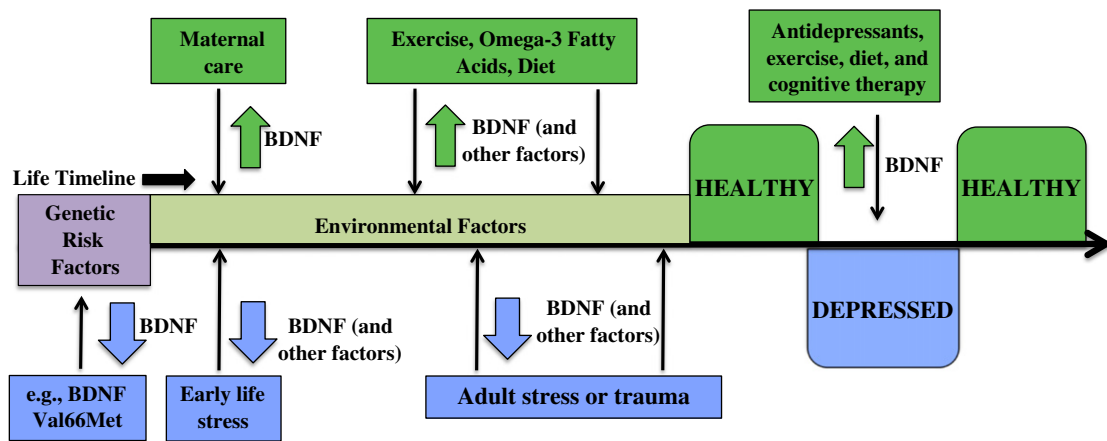


Fig. 2. Life timeline of genetic and environmental modulations of healthy emotional state or depression by BDNF and other neurotrophic factors. Genetic risk factors and stress can exacerbate depressive symptoms, while antidepressants, exercise, and diet may ameliorate depressive symptoms, in part, through the action of neurotrophic factors. This up- or down-regulation of BDNF by these environmental factors can shift the balance from depressed to healthy, and vice versa. Abbreviations: BDNF, brain derived neurotrophic factor.

neuronal function and behavior in the adult. Studies have shown that individuals with a history of childhood abuse are more likely to develop depression or other stress-related illnesses (e.g., PTSD) in adulthood (Felitti et al., 1998; Heim and Binder, 2011; Mullen et al., 1996; Wilkinson and Goodyer, 2011). In support of this, preclinical studies have shown that exposure to early life stress, such as prolonged daily maternal separation, is associated with increased emotionality and stress-responsiveness (Heim and Nemeroff, 1999; Meaney, 2001). At the neural level, these effects are associated with alterations in the activity of the HPA axis. Maternal separation stress is associated with decreases in the levels of glucocorticoid receptors, which bind the stress hormone corticosterone and provides negative feedback on further activity of the HPA axis. These changes persist into adulthood and are associated with increased corticosterone release and changes in emotional behavior (Anisman et al., 1998).

BDNF expression can also be altered by early life stress or variations on maternal care (Fig. 2). Maternal separation (24 h) on postnatal day 9 in rats can lead to reduced BDNF (Roceri et al., 2004), while high levels of maternal care, measured by licking and grooming behavior, increase hippocampal BDNF (Liu et al., 2000). These alterations in BDNF expression can ultimately affect synaptic development and behavior in the adult.

Further, studies have found that cell proliferation and number of immature neurons are decreased in the dentate gyrus of adult rats that have undergone maternal separation as pups (Mirescu et al., 2004). This effect can be localized to the ventral, but not dorsal, hippocampus, the former being associated with circuitry underlying anxiety (Hulshof et al., 2011). Moreover, the reduction in cell proliferation can be reversed by decreasing corticosterone levels, supporting the hypothesis that early life stress causes hypersensitivity to glucocorticoids and decreases structural plasticity in adults (Mirescu et al., 2004). Animals subjected to maternal separation also show increased anxiety- and depression-like behaviors in adulthood (George et al., 2010; Lee et al., 2007; Wei et al., 2010). As an example, rat pups that have been subjected to prolonged maternal separation exhibit altered emotional responses, including an unwillingness to explore an open field, feed in a novel environment, or interact socially (Caldji et al., 2000).

Interestingly, recent studies have identified genetic polymorphisms that can increase the susceptibility to depression in the human population. This helps to account for the fact that although child abuse is a major risk factor for the development of depression during the lifetime, not all abused children become depressed (Charney and Manji, 2004; Heim and Nemeroff, 2001). For example, in a cross-sectional study of individuals with lifetime MDD, patients that have the BDNF Val66Met

polymorphism show a greater susceptibility to depression later in life following childhood abuse, compared to those with intact BDNF release (Elzinga et al., 2011) (Fig. 2).

Another genetic risk factor is the serotonin transporter gene, 5-HTTLPR, polymorphism. This polymorphism confers susceptibility to depression in individuals subjected to early life stress (Caspi et al., 2003; Eley et al., 2004; Kaufman et al., 2004; Kendler, 2005; Risch et al., 2009; Uher et al., 2011). In addition, there is a three-way interaction of the 5-HTTLPR and the BDNF Val66Met polymorphism with childhood adversity (Grabe et al., 2012; Kaufman et al., 2006; Nederhof et al., 2010; Wichers et al., 2008), suggesting that the BDNF and 5-HT systems work in concert to influence susceptibility to mood disorders. Possible interactions of these systems have been demonstrated in pharmacological studies, showing that BDNF expression is up-regulated by chronic administration of a selective serotonin reuptake inhibitor (SSRI) (Chen et al., 2001).

Collectively, these findings suggest that exposure to early life stress can lead to long-term effects on neuroplasticity in neural circuits that control emotion, which, in turn, can have a profound influence on susceptibility to depression in adulthood.

Antidepressants, neurotrophic factors, and neurogenesis

Pharmacological antidepressants, including SSRI and norepinephrine selective reuptake inhibitors, monoamine oxidase inhibitors, and atypical antidepressants, have many effects that are the opposite to those of stress and depression that have been discussed thus far. Clinical studies demonstrate that levels of BDNF and new cell birth are increased in the hippocampus of those patients treated with antidepressants at the time of death (Boldrini et al., 2009; Chen et al., 2001). Similarly, serum BDNF levels (Gervasoni et al., 2005) and hippocampal volume (Sheline et al., 2003; Vermetten et al., 2003) are partially restored in depressed patients receiving antidepressant treatment.

These findings have been corroborated in preclinical studies. Antidepressant administration in rats increases the expression of BDNF in the hippocampus and PFC (Baj et al., 2012; Duman, 2004b; Krishnan and Nestler, 2008; Monteggia, 2007; Nibuya et al., 1995, 1996) and increases neurogenesis in the adult hippocampus (Duman, 2004b; Duman and Monteggia, 2006; Samuels and Hen, 2011). Up-regulation of BDNF, as well as induction of neurogenesis, is seen after chronic, but not acute, antidepressant administration, consistent with the time course for the therapeutic action of these agents (Duman, 2005).

In addition, VEGF and IGF-1, growth factors known to increase neurogenesis in the adult hippocampus (Duman, 2004b; Sairanen

et al., 2005), produce antidepressant effects in behavioral models when infused into the brain (Duman et al., 2009; Warner-Schmidt and Duman, 2007). In contrast, blockade of VEGF signaling prevents the behavioral actions of antidepressants (Duman et al., 2008; Warner-Schmidt and Duman, 2007). Blockade of neurogenesis blocks the behavioral actions of antidepressants in certain behavioral models (David et al., 2009; Santarelli et al., 2003), suggesting that increased neurogenesis could contribute to the antidepressant effects of trophic factors. Further, deletion of TrkB blocks antidepressant induction of neurogenesis (Li et al., 2008), supporting a role for BDNF or a related neurotrophic factor in these actions.

The requirement for chronic administration of traditional antidepressants suggests that alterations of intracellular signaling pathways and long-term gene expression may underlie the mechanisms of antidepressant action. Chronic, but not acute, administration of both 5-HT and norepinephrine selective reuptake inhibitors increases cAMP-CREB signaling, which subsequently increases the expression of BDNF (Duman and Monteggia, 2006; Nibuya et al., 1996). In addition, MAPK signaling is required for the behavioral actions of traditional antidepressants, whereby blockade of MAPK signaling prevents behavioral antidepressant action (Duman et al., 2007). The glycogen synthase kinase-3 (GSK-3) signaling pathway, which leads to activation of transcription factors promoting cell cycle arrest and apoptosis, has also been linked to mood disorders and is inhibited by the mood stabilizer, lithium, suggesting its role in the regulation of depressive behaviors (Voleti and Duman, 2011). This is just a partial list of the signaling pathways that have been implicated in the actions of traditional antidepressant treatments (Krishnan and Nestler, 2008; Martinowich et al., 2007; Voleti and Duman, 2011).

Rapid acting antidepressant: NMDA receptor antagonists

Traditional antidepressants take 6–8 weeks to produce a therapeutic response, but recent clinical studies have reported that ketamine, an NMDA receptor antagonist, produces antidepressant effects within hours (Berman et al., 2000; Liebrenz et al., 2007; Zarate et al., 2006). Further, the rapid antidepressant actions of ketamine are observed in treatment-resistant patients (i.e., failed two or more typical antidepressants), addressing another major unmet need (improved therapeutic efficacy). These findings represent a major advance for the treatment of depression, identifying a rapid, efficacious therapeutic agent with a completely novel mechanism of action.

Preclinical studies demonstrate that ketamine produces a rapid induction of synaptic protein synthesis, spine density and maturation (Li et al., 2010). These effects are mediated by activation of the mammalian target of rapamycin (mTOR) signaling system (Li et al., 2010), which controls synaptic protein synthesis in dendrites (Hoeffler and Klann, 2010). The rapid synaptic and behavioral actions of ketamine are blocked by rapamycin, a selective inhibitor of mTOR signaling (Koike et al., 2011; Li et al., 2010). In addition, a single dose of ketamine can reverse the reduction in spine density and function caused by chronic stress exposure in a rapamycin-sensitive manner (Li et al., 2011). A possible role for mTOR in depression is supported by a recent postmortem study which reports that mTOR signaling is decreased in the PFC of depressed subjects (Jernigan et al., 2011).

The induction of mTOR and synaptogenesis is thought to occur via increased glutamate-AMPA transmission leading to release of BDNF and related downstream signaling (Hoeffler and Klann, 2010; Jourdi et al., 2009; Slipczuk et al., 2009; Takei et al., 2004) (Fig. 3). Notably, the synaptic and behavioral actions of ketamine are blocked in BDNF conditional deletion mutant mice (Autry et al., 2011) and in BDNF Met knock in mice (Liu et al., 2011). Although Autry et al. (2011) did not observe a role for mTOR, this may be explained by methodological differences (behavior in the forced swim test was examined 30 min after ketamine instead of 2 h or longer, when the

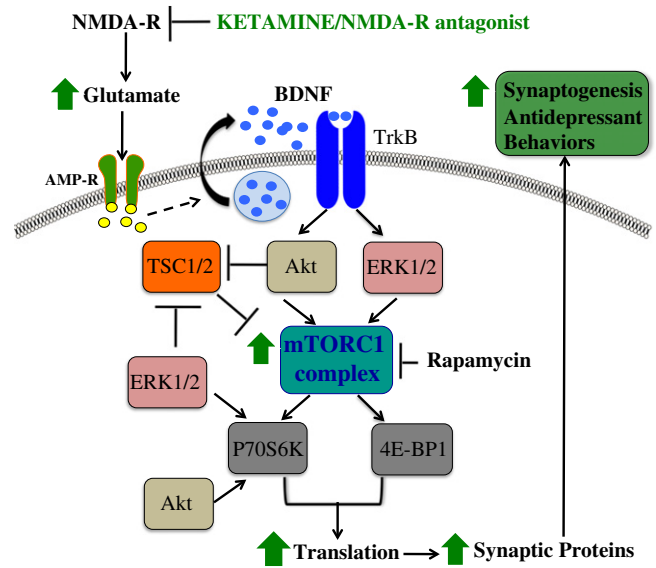


Fig. 3. Pathways mediating the regulation of the mTOR signaling cascade by novel rapid-acting antidepressants. Ketamine, an NMDA receptor antagonist, rapidly stimulates glutamate transmission and AMPA receptor activation, leading to activity-dependent release of BDNF. This leads to phosphorylation of ERK and Akt, subsequently regulating mTOR signaling. This can lead, through regulation of P70S6K and 4E-BP1, to increased translation and increased synaptic proteins, which contributes to increased synaptogenesis and antidepressant behaviors. Abbreviations: BDNF, brain derived neurotrophic factor; TrkB, tropomyosin-related kinase B; mTOR, mammalian target of rapamycin; NMDA, N-methyl-D-aspartic acid; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; ERK, extracellular signal-regulated kinase; Akt, serine threonine kinase or protein kinase B; P70S6K, P70 ribosomal protein S6 kinase; 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; TSC, tuberous sclerosis complex.

Figure adapted from Duman and Voleti (2012).

therapeutic response is observed in depressed patients, see Zarate et al. (2006)). The 30 min time point is also problematic as this is when levels of glutamate are increased and the psychotomimetic effects of ketamine are observed (Berman et al., 2000; Moghaddam et al., 1997; Zarate et al., 2006).

Additional evidence has suggested that GSK-3 may also play a role in mediating the effects of ketamine. Specifically, Beurel et al. (2011) found that ketamine increases the phosphorylation of GSK-3, and that blockade of this phosphorylation prevents the action of ketamine. Similar to the activation of mTOR signaling, induction of phospho-GSK-3 may be mediated by Akt, which is a negative regulator of GSK-3 and is activated by ketamine (Beurel et al., 2011; Duman et al., 2011).

Due to the abuse potential of ketamine, recent work has begun to explore other targets that may have fast-acting antidepressant actions similar to ketamine. For example, inhibition of presynaptic metabotropic glutamate receptor 2/3 (mGluR2/3) or activation of metabotropic glutamate receptor 7 (mGluR7), both of which regulate glutamate release and subsequently the postsynaptic AMPA receptors, can similarly produce antidepressant effects (Bradley et al., 2012; Dwyer et al., 2011; Koike et al., 2011). Moreover, the effects of mGluR2/3 antagonists are also dependent on mTOR signaling, providing further evidence of the potential to produce rapid antidepressant effects (Dwyer et al., 2011; Koike et al., 2011).

Studies of the actions of typical and novel rapid acting antidepressants have provided insight into the cellular and molecular mechanisms underlying these agents and to depression, and further validate the chronic stress model. These studies also demonstrate how typical antidepressant medications provide a pharmacological approach to alleviate depressive symptoms, albeit with limitations, some of which may be addressed with novel ketamine-like agents.

Exercise, neurotrophic factors, and neurogenesis

The stress effects discussed thus far have focused on uncontrollable stressors, be it chronic stress during adulthood or maternal separation during early life, which are perceived as negative or aversive. However, it has become increasingly clear that different types of stress result in different outcomes. In addition to these negative stressors, recent studies have examined the influence of controllable stress. Here, we define stress as “controllable” if the person or animal is able to terminate the stressor at any given time. The differences between uncontrollable and controllable stress have been described for decades, starting with the learned helplessness experiments. In this paradigm, one rat can behaviorally terminate tail shocks (controllable stress) while another yoked rat cannot (uncontrollable stress), with each rat receiving identical shocks (Seligman and Beagley, 1975). In rats that received uncontrollable, but not controllable stress, impaired escape learning and exaggerated fear conditioning are observed (Maier and Watkins, 2005).

One particular type of controllable stress is voluntary exercise. Voluntary exercise is considered to be a type of stress due to activation of the sympathetic nervous system, leading to epinephrine production and regulation of hypothalamic–pituitary–adrenal (HPA) axis and increased glucocorticoid production (Droste et al., 2007; Makatsori et al., 2003). Interestingly, exercise exerts downstream effects that are in the opposite direction from that of the uncontrollable stressors described above. For example, in clinical studies, exercise has been found to be beneficial for reducing depressive symptoms in mild to moderately depressed patients (Babyak et al., 2000; Dunn et al., 2005; Herring et al., 2012).

Preclinical studies have extended this research to further elucidate the molecular and cellular mechanisms underlying the effect of exercise on depression. Wheel running is most often used as a form of voluntary exercise in animal studies (Stranahan et al., 2008). Exercise is a positive reinforcer for rats: they will bar press for access to a running wheel and can even develop conditioned place preference to environments previously paired to a running wheel (Belke and Wagner, 2005; Iversen, 1993). Using the wheel-running exercise paradigm, preclinical studies have also reported an antidepressant effect of exercise. For example, rodents given chronic free access to a running wheel show antidepressant-like effects in learned helplessness, forced swim test, and tail suspension test relative to sedentary controls (Bjørnebekk et al., 2005; Dishman et al., 1997; Duman et al., 2008; Greenwood et al., 2003, 2005).

Exercise may alter the same neurotrophic factors and signaling pathways as antidepressant drug treatment. Chronic exercise increases BDNF expression and phosphorylated MAPK in the hippocampus and cerebral cortex (Adlard and Cotman, 2004; Chen and Russo-Neustadt, 2009; Duman et al., 2008; Russo-Neustadt et al., 1999, 2000), similar to the actions of antidepressants (Baj et al., 2012). Further, the antidepressant effects of exercise in the forced swim test are abolished in mice heterozygous for BDNF deletion (Duman et al., 2008). Consistent with this, blockade of MAPK using PD184161 prevents the antidepressant actions of exercise following forced swim test in wild-type mice (Duman et al., 2008). The antidepressant effects of exercise may depend on post-translational processing of BDNF. Specifically, Sartori et al. (2011) found that voluntary exercise on a running wheel increases levels of mature BDNF protein levels and increases levels of mRNA of the proBDNF proteolytic cleavage-related genes p11 and tPA, with no differences in precursor or truncated forms of BDNF.

Further, voluntary running can even prevent acute and chronic stress-induced alterations in depressive behavior and decreases in BDNF (Adlard and Cotman, 2004; Zheng et al., 2006). Exercise protects against decreases in hippocampal glucocorticoid receptors in response to CUS (Zheng et al., 2006) and prevents decreases in BDNF levels in immobilization stress-exposed animals (Adlard and Cotman, 2004). It is thought that these exercise-induced alterations in BDNF

exert their actions, at least in part, through increased neurogenesis (Erickson et al., 2011; Lafenêtre et al., 2010), as exercise increases neurogenesis in the granule cell layer of the adult hippocampus (van Praag et al., 1999).

Exercise also up regulates other neurotrophic factors that are increased by antidepressant treatment and have been shown to have antidepressant effects in rodent models, including IGF-1 (Trejo et al., 2001). IGF-1 uptake in the hippocampus is stimulated by exercise (Trejo et al., 2001), and peripheral blockade of IGF-1 blocks the exercise-induced antidepressant effects on both hippocampal neurogenesis and in the forced swim test. These data suggest that IGF-1 is required for the antidepressant effects of exercise (Duman et al., 2009; Trejo et al., 2001, 2008). There is evidence that IGF-1 differentially regulates neurogenesis depending on the differentiation state of new neurons, suggesting that the response of proliferating precursors and post mitotic immature neurons to exercise is dependent on IGF-1 (Llorens-Martín et al., 2010).

VEGF is also thought to play a role in the mediation of the antidepressant effects of exercise. Blockade of peripheral VEGF prevents exercise-induced antidepressant effects, including behavioral and neurogenic responses, as well as alterations in blood vessel density in the hippocampus (Fabel et al., 2003; Kiuchi et al., 2012). Early studies were unable to find alterations in VEGF expression in the hippocampus following running in mice, concluding that VEGF was induced in the peripheral vasculature and transported into the brain where it produces central effects, including increased hippocampal neurogenesis (Fabel et al., 2003). However, a more recent study using a VEGF-luciferase reporter mouse found that exercise increases VEGF transcription, mRNA and protein levels in the hippocampus (Tang et al., 2010).

VGF (nonacronym) is a nerve growth factor that is regulated in the hippocampus by exercise at both the mRNA and protein levels (Hunsberger et al., 2007). Originally studied for its roles in energy metabolism (Hahm et al., 1999) and synaptic plasticity (Alder et al., 2003), a recent finding that VGF is also involved in mood regulation has opened up a new avenue of research on this peptide. Administration of a VGF-derived peptide into the brain produces antidepressant effects in mice, and heterozygous VGF deletion mutant mice do not show the exercise-induced antidepressant responses that are observed in wild-type mice (Hunsberger et al., 2007). VGF also promotes proliferation of hippocampal neurons (Thakker-Varia et al., 2007), providing a potential cellular mechanism for the antidepressant-like effects of VGF and exercise. Taken together, these data suggest that VGF also contributes to the antidepressant actions of exercise.

Recent data have also suggested a role for endocannabinoids in mediating the antidepressant effects of exercise (Gorzalka and Hill, 2011; Sparling et al., 2003). In humans, acute exercise increases plasma endocannabinoid levels (Sparling et al., 2003), and preclinical studies report that chronic exercise increases levels of endocannabinoid and the cannabinoid 1 receptor in the hippocampus (Hill et al., 2010; Wolf et al., 2010). Endocannabinoid signaling can also modulate exercise-induced neurogenesis (Hill et al., 2010; Wolf et al., 2010), demonstrating a downstream cellular mechanism that could underlie the antidepressant actions of this interesting neuronal signaling system.

Exercise also influences synaptic plasticity and structure. Long-term potentiation (LTP) is increased in the dentate gyrus both in vitro and in vivo in rodents given access to running (Farmer et al., 2004; van Praag et al., 1999). Further, exercise increases spine density in hippocampal area CA1, the dentate gyrus, and entorhinal cortex layer III (Redila and Christie, 2006; Stranahan et al., 2007), and accelerates neuronal maturation (Zhao et al., 2006).

Taken together, these results suggest that functional antidepressant responses that result from exercise occur via a combination of neurotrophic/growth factor systems and related signaling pathway alterations, and that subsequent increases in hippocampal neurogenesis

and alterations in synaptic plasticity and structure may underlie these effects.

Diet, neurotrophic and neurogenic responses

Dietary restriction

Dietary restriction was first discovered to increase lifespan in a wide range of organisms (Roth et al., 2000; Weindruch et al., 1979), and since then has been studied for other beneficial effects, including reduction in aging-associated illnesses and improved response to stress (Mattson, 2005; Mattson et al., 2004b). In the brain, caloric restriction has similarly beneficial effects, including increased BDNF expression and increased hippocampal neurogenesis via increased survival of newborn neurons (Duan et al., 2001; Lee et al., 2002b; Mattson et al., 2004a). However, these effects are dependent on age and duration of food restriction. One study found that adolescent rats that are food-restricted for 5 weeks starting at postnatal day 28 show significantly increased depressive and anxiety-like behaviors and aberrant serotonergic activity (Jahng et al., 2007). Similarly, another study has suggested that cyclic caloric restriction combined with periods of palatable foods (i.e. binge eating) results in aberrant monoamine activity in limbic regions and increases levels of pro-depressive and anxiety behaviors (Chandler-Laney et al., 2007). Thus, dietary restriction can play both a positive and negative role in depressive behaviors, depending on the developmental stage and context of restriction, possibly through alterations of BDNF and other signaling pathways.

Omega-3 polyunsaturated fatty acids

Omega-3 polyunsaturated fatty acids are the most widely used non-vitamin supplement in the United States (Barnes et al., 2008), and recent epidemiological and clinical studies have suggested that they may have antidepressant actions. In the nervous system, one out of every three fatty acids belongs to the omega-3 fatty acids group, which makes up an essential component of the CNS membrane phospholipid-acyl chains (Bouurre et al., 1991). Omega-3 fatty acids are often ingested as docosahexaenoic acid (DHA) and eicosapentenoic acid (EPA), which are long-chain polyunsaturated fatty acids found in fish and marine sources. Interest in the antidepressant actions of omega-3 fatty acids was first sparked when a cross-national study found that there was a correlation between fish consumption and lower annual prevalence of MDD (Hibbeln, 1998). Follow-up studies have found that depressed patients have significantly lower red blood cell omega-3 levels in erythrocyte membranes and plasma as compared to non-depressed patients (Freeman, 2006), and there appears to be a correlation between omega-3 fatty acid intake and corticolimbic brain matter volume (Conklin et al., 2007).

Although clinical studies have also suggested a role for omega-3 fatty acids in depression, results have been somewhat mixed (Grenyer et al., 2007; Hakkarainen et al., 2004; Lespérance et al., 2011; Marangell et al., 2003; Mischoulon and Fava, 2000; Nemets et al., 2002; Rees et al., 2008; Rocha Araujo et al., 2010; Su et al., 2003). Some of the variability may be attributable to methodological differences, including the type of omega-3 fatty acids and dosing schedule, as one meta-analysis found that EPA, but not DHA, may play a role in antidepressant action (Martins, 2009). Additionally, in most of the studies, the omega-3 fatty acids were used in conjunction with antidepressant treatment, and thus it remains unclear whether omega-3 fatty acids are effective independently. A recent study suggests that omega-3 fatty acid supplementation started concurrently with SSRI treatment can enhance the SSRI's effectiveness as compared to placebo supplement (Gertsik et al., 2012). However, it remains to be seen whether supplementation is effective in all or only in a subpopulation of patients with a low baseline level of

omega-3 fatty acids, and if supplements have independent antidepressant effects.

Preclinical work has proposed several mechanisms by which omega-3 fatty acids may play an antidepressant role, many of which are similar to the effects of pharmacological antidepressants. Consistent with the clinical data, omega-3 fatty acid deprivation in rats for 15 weeks results in a pro-depressive phenotype, as measured by increased immobility time on the forced swim test (DeMar et al., 2006) and decreased BDNF levels in the frontal cortex (Rao et al., 2007). Further, CREB protein DNA-binding activity and nuclear phosphorylated MAPK levels are also reduced with omega-3 deprivation, possibly underlying the reduction of BDNF levels (Rao et al., 2007). Conversely, omega-3 fatty acid supplementation results in an antidepressant effect in forced swim test and increased BDNF levels in the cortex and hippocampus (Vines et al., 2011). Similarly, in rat primary cortical astrocytes, omega-3 supplementation increases BDNF levels (Rao et al., 2007). Other studies have shown that omega-3 fatty acid supplementation can actually reverse the effect of chronic restraint stress on plasma corticosterone levels (Ferraz et al., 2011).

At a cellular level, omega-3 fatty acids may oppose the actions of stress by increasing neurite growth and dendritic arborization. Both in vitro and in vivo studies have shown that low levels of DHA result in decreased neurite length and dendritic arborization (Calderon and Kim, 2004; Dagai et al., 2009), and that this effect can be rescued by DHA supplementation (Calderon and Kim, 2004). Further, administration of omega-3 fatty acids increases hippocampal volume, synaptophysin expression, and newborn cells in rodents, effects that are similar to the actions of antidepressants (Venna et al., 2009).

Although we have focused on the effects of omega-3 fatty acids on neurotrophic factor levels and dendrite arborization, another potential mechanism of antidepressant action is via regulation of proinflammatory cytokines, which are reported to be elevated in certain depressed patient populations (James and Cleland, 1997). Moreover, despite the evidence suggesting a role of omega-3 fatty acids in modulating depressive behaviors, it is important to keep in mind that these findings have been mixed, in both clinical and preclinical studies (Carlezon et al., 2005; Huang et al., 2008; Naliwaiko et al., 2004). Additional clinical and preclinical studies are required to further elucidate the effects of this and other dietary supplements on cellular and behavioral determinants of stress and depression.

Summary and conclusions

It has become increasingly clear that changes observed in MDD patients are the result of a number of environmental factors. Here, we have highlighted behavioral, cellular and morphological changes in models of MDD that are influenced by genetic and environmental factors, as well as pharmacological agents. Through the action of BDNF and other neurotrophic factors, genetic polymorphisms and stress (early and late life) can lead to neuronal atrophy and decreased neurogenesis, while maternal care, exercise, diet, and antidepressants can produce the opposite effects (Fig. 2). Importantly, this evidence suggests that exercise and diet, two factors that can be controlled throughout life, can alter fundamental aspects of neuronal signaling and neurogenesis that are required for mental health. Although further studies will be necessary to obtain a comprehensive understanding of the mechanisms by which the environment can influence depression and mental health, the findings presented here demonstrate the importance of counteracting the inevitable exposure to stress in everyday life. One effective approach for improved mental health may include implementing policies that make recommendations to promote exercise and proper diet. Taken together, this review has presented an array of evidence demonstrating that environment can play an important role in altering neuroplasticity related to depressive behaviors, and suggests that understanding the complex interactions between stress, environment,

and depression, can contribute to better treatments for MDD and other stress-related mood disorders.

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