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Remodeling of axo-spinous synapses in the pathophysiology and treatment of depression

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Abstract

Dendritic spines provide a compartment for assembly and functional organization of synaptic machinery that plays a fundamental role in neuronal communication and neuroplasticity. Studies in humans as well as in animal models have demonstrated abnormal spine architecture in several psychiatric disorders, including depression and other stress related illnesses. The negative impact of stress on the density and organization of spines is thought to contribute to the behavioral deficits caused by stress exposure. Moreover, there is now evidence that medication-induced recovery involves changes in synaptic plasticity and dendrite morphology, including increased expression of pre- and postsynaptic plasticity related proteins, as well as the density and function of axo-spinous synapses. Here we review the evidence from brain imaging and postmortem studies demonstrating that depression is accompanied by structural and functional alterations of cortical and limbic brain regions, including the prefrontal cortex, hippocampus and amygdala. In addition, we present more direct evidence from basic research studies that exposure to stress alters spine morphology, function and plasticity and that antidepressants, particularly new rapid acting agents, reverse these effects. Elucidation of the signaling pathways and molecular mechanisms that control spine synapse assembly and plasticity will contribute to a better understanding of the pathophysiology of depression and development of novel, more effective therapeutic agents.

1. Introduction

Spines are small actin-rich protrusions located on neuronal dendrites. These spines receive the majority of excitatory synaptic input in the central nervous system and are responsible for neural processing of information. While the majority of spines in the adult brain are relatively stable, there is also a population of dynamic spines that provide a structural and biochemical compartment capable of undergoing rapid morphological and functional changes (Holtmaat et al., 2005, Alvarez and Sabatini, 2007). This pool of flexible spines enables fast adaptive responses that are required for higher brain function and processing of stimuli. Plasticity refers not only to changes in cytoskeletal architecture that is required for stabilization and destabilization of dendritic spine structure but also to regulation of pre- and postsynaptic proteins and ion channels that control physiological responses (Fukazawa et al., 2003).

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Aberrant spine morphology has been observed in a number of neurological disorders, including mental retardation (Kaufmann and Moser, 2000, Segal et al., 2003, Grossman et al., 2006), autism (Minshew and Williams, 2007, Hutsler and Zhang, 2010), Down and Rett syndromes (Kaufmann and Moser, 2000, Boda et al., 2004), and Alzheimer disease (Kao et al., 2010). In addition, it is now clear that dysfunction of spines plays a critical role in psychiatric illnesses, including schizophrenia and major depressive disorder (MDD) (Roberts et al., 1996, Lin and Koleske, 2010). Strong evidence of altered spine morphology and function in MDD is also provided by preclinical studies of stress and depression (McEwen, 2008, Pittenger and Duman, 2008, McEwen and Gianaros, 2011).

Synaptic activation can lead to spine plasticity via the insertion of glutamate receptors and spine enlargement, followed by reorganization of the postsynaptic density, which in turn strengthens synaptic connections (Matsuzaki et al., 2001). Such long-lasting changes in the strength and architecture of axo-spinous synapses have been characterized in a cellular model of learning and memory, long-term potentiation (LTP) and opposing processes, including reduced synaptic activity and spine pruning, in long-term depression (LTD) (Matsuzaki et al., 2004, Segal, 2005, Harvey and Svoboda, 2007, Tanaka et al., 2008). Neurotrophic factors, such as BDNF, are required for neuronal development and survival, but are also critical mediators of synaptic plasticity and LTP. This plasticity may occur via reorganization of the actin cytoskeleton within the spine (Rex et al., 2007), and is blocked by inhibition of actin polymerization (Krucker et al., 2000, Ackermann and Matus, 2003, Fukazawa et al., 2003).

Here we review basic research and clinical evidence in support of the hypothesis that disruption of axo-spinous synapses in cortical and limbic brain regions that control mood and cognition contributes to depression. In addition, we review the evidence that antidepressants can block or reverse these effects, at least in part by increasing synaptic plasticity and signaling pathways that control neurotrophic function, glutamate receptor insertion, and synapse stability. Finally, we discuss recent evidence that a fast-acting antidepressant, ketamine, rapidly increases spine density and function in limbic brain regions and that the behavioral effects of ketamine require synaptic protein synthesis and spine formation. This hypothesis is discussed in the context of current theories of MDD, including the monoamine and neurotrophic hypotheses, as typical antidepressants that regulate synaptic monoamines influence synaptogenesis and trophic factors are required for this process.

2. Depression is associated with structural alterations of cortical and limbic brain regions

There has been a significant effort to identify the neurobiological basis of mood disorders, including extensive brain imaging and postmortem studies of MDD, posttraumatic stress disorder (PTSD), and bipolar disorder (BD). Here we review the evidence demonstrating alterations at the gross structural and cellular levels in these disorders, as well as the functional consequences of these changes. Although studies of spine number and morphology are still being conducted, the human imaging and postmortem studies combined with the results of preclinical models of stress and depression (see later sections), provide strong evidence that mood disorders are characterized by structural alterations, including axo-spinous synapse abnormalities.

Volumetric studies of limbic brain regions in depression

A number of magnetic resonance imaging (MRI) studies have reported that mood disorders are characterized by altered size of cortical and limbic brain regions, including the PFC,

hippocampus and the amygdala (Rigucci et al., 2010). In MDD and BD, reductions in tissue volume have been found in orbital, medial and ventrolateral PFC, and these changes may be attributed, in part, to a reduced number of neurons and glial cell types (Rajkowska et al., 1999, Cotter et al., 2001, Cotter et al., 2002, Stockmeier et al., 2004). Further highlighting the relevance of these changes, a recent study has reported that the reduction of PFC volume is more severe in patients with chronic depression as compared to those with sustained remission (Salvadore et al., 2011). Stress exposure may contribute to the development of MDD and other psychiatric illnesses (Lechin et al., 1996, Turner and Lloyd, 2004), providing the rationale for the development of preclinical models of depression discussed later in this review.

Similar to PFC, hippocampal volume is decreased in MDD patients. MRI studies have demonstrated that these hippocampal changes can be lateral or unilateral (Videbech and Ravnkilde, 2004, McKinnon et al., 2009, MacQueen and Frodl, 2011), and that they correlate with memory deficits in depressed patients (Hickie et al., 2005). There are also negative studies of altered hippocampal volume, which could be due to the heterogeneity of depression, as well as length of illness, age, and medication status (McKinnon et al., 2009, Price and Drevets, 2012). More recent studies have also begun to examine structural alterations of specific subregions of hippocampus that could provide more discrete evidence of structural changes (Maller et al., 2007, Malykhin et al., 2010).

Volumetric studies of the amygdala, a brain center involved in control of emotion, anxiety and fear in mood disorders, have led to variable results. In general, studies of first episode or short duration of illness report increased volume of the amygdala (Frodl et al., 2002, Lange and Irle, 2004), whereas reports have been negative in cases of long duration MDD (Caetano et al., 2004, Hastings et al., 2004). In addition, a recent study of non-medicated BD patients has reported a reduction of amygdala volume, while an increase in the volume of the amygdala was found in patients that were treated with a mood stabilizer (Savitz et al., 2010).

Functional alterations associated with structural changes in depression

The structural alterations of these brain regions are also accompanied by abnormal function and information processing in MDD patients. The PFC is involved in the regulation of mood and emotion (Bremner et al., 2002, Price and Drevets, 2012), and functional MRI (fMRI) studies have reported lower activity levels of the PFC in depressed patients (Liberzon and Phan, 2003). Reduced activity of medial PFC results in decreased inhibitory control of amygdala (Drevets, 2003) (Figure 1), which contributes to disturbances in perception of emotional cues and associated memories (LaBar and Cabeza, 2006). The development of depression is also accompanied by decreased blood flow and metabolism in orbitofrontal cortex (OFC) and as a result, decreased PFC activity (Mayberg et al., 1999, Bremner et al., 2002). fMRI studies of cognitive-affective interplay between dorsal and rostral anterior cingulate cortex in MDD show enhanced functional connectivity between these two regions, which again would result in decreased inhibitory control over amygdala (Pizzagalli, 2011).

Reductions of hippocampal volume, which have also been implicated in the regulation of mood and memory, may be attributed to high levels of circulating cortisol and dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in MDD patients (Sapolsky, 2000, MacQueen and Frodl, 2011). Disrupted hippocampal function leads to dysregulation of firing within other regions, including the ventral tegmental area (VTA), which could contribute to anhedonia (Warner-Schmidt and Duman, 2006). Associative memory, a key, hippocampus-dependent process, is decreased in MDD patients (Dalgleish et al., 2007), although there is no direct evidence linking decreased hippocampal volume to altered function. There have also been reports that hippocampal volume is not correlated with MDD severity, but these may be attributed to differences in MDD sample size, age of patients and

number of depressive episodes (MacQueen and Frodl, 2011). Further studies are required to characterize the exact functional correlates of altered hippocampal morphology in MDD.

Neuroimaging studies have also reported disrupted functional correlates of the amygdala in MDD patients (Sheline et al., 2001, Siegle et al., 2002), including abnormally elevated glucose metabolism (Drevets et al., 2008). Together with elevated levels of cortisol and noradrenaline, disrupted amygdala activity may affect processing of emotional stimuli (Drevets, 2001). For example, depressed patients show abnormally exaggerated amygdala responses to sad words and faces (Phillips et al., 2008). Interestingly, it has also been shown that antidepressant treatment can normalize amygdala metabolism (Drevets et al., 2002).

3. Postmortem studies of depression

Altered neuronal and glial morphology in depression

Postmortem studies of MDD subjects have begun to characterize the cellular alterations that could explain the volumetric changes observed in brain imaging studies, including changes in the number and shape of specific neuronal and glial cell populations. Early studies reported that cortical thickness, as well as neuronal density and mean size of neuronal cell bodies, are decreased in MDD subjects, particularly in layers II-IV of OFC and the dorsolateral PFC (Rajkowska et al., 1999). Similar findings are reported for older MDD subjects, where a 30% reduction in the density of pyramidal neurons was found, especially in layers III and V of OFC, with no difference in the density of nonpyramidal cells (Rajkowska et al., 2005). There are reports that the size and number of GABAergic neurons are decreased in MDD subjects, specifically in the dorsolateral PFC (Rajkowska et al., 2007) and occipital cortex (Maciag et al., 2010). These findings are consistent with magnetic resonance spectroscopy imaging studies reporting decreased levels of GABA in depressed patients (Sanacora et al., 2004, Hasler et al., 2007).

Postmortem studies of hippocampus have reported an increased number of pyramidal neurons and granule cells, although this was attributed to an increased packing density and reduced hippocampal volume (Stockmeier et al., 2004). This interpretation is supported by the finding of a significant reduction in the average size of pyramidal neurons and a trend for reduced size of granule neurons in MDD subjects (Cotter et al., 2002), suggesting that the length and complexity of neuronal processes are decreased. Such changes in the cell size and processes may be related to reduced expression of BDNF in depression (Duman et al., 1999, Dwivedi et al., 2003). Studies of amygdala have thus far not reported alterations of the density of neurons, but have found a reduction in the number of glial cells, specifically oligodendrocytes, in MDD and BD patients compared to controls (Bowley et al., 2002).

Decreased glial number and density, as well as decreased expression of glial markers, have also been reported in OFC in MDD subjects (Ongur et al., 1998, Cotter et al., 2001). This includes decreased levels of markers for astrocytes (Miguel-Hidalgo et al., 2010), which are responsible for the recycling of synaptic glutamate, thereby possibly underlying changes in glutamate transmission reported in depression (Popoli et al., 2011). The density of glial cells in the CA1, CA3, and dentate gyrus cell layers of the hippocampus show a 30–35% increase in MDD (Stockmeier et al., 2004, Hercher et al., 2009). Increased packing density of glia and neurons may contribute to the reduction of hippocampal volume in MDD. Finally, a recent study examining white matter changes in PFC of depressed subjects reported a reduction of the number and number of oligodendrocytes, which may affect myelination, thereby resulting in abnormalities in neuronal transmission (Tham et al., 2011).

Evidence of decreased spine number and neuroplasticity related signaling

A reduction of neuronal cell body size in PFC of MDD subjects is consistent with the possibility of decreased length and complexity of dendrites, as well as spine number, although there have been very few studies that directly measure these processes in MDD subjects. One study reports a reduction in the length of pyramidal cell apical dendrites of the subiculum as well as spine density in a small sample of MDD subjects, as well as a small cohort of schizophrenic subjects (Rosoklija et al., 2000). We have recently reported that there is a decrease in the number of synapses, determined by electron microscopy, in the dorsal lateral PFC of a small cohort of MDD subjects, and a corresponding decrease in several synapse-related proteins (Kang et al., 2012). There are a number of studies using markers of spines and synaptic proteins, which serve as an indirect measure of synaptic changes in depression. A very recent postmortem study reported a reduction in MAP-2 immunoreactivity in neuronal dendrites and decreased synaptopodin labeling of spines in the hippocampus, demonstrating an inverse relation with anxiety and depression (Soetanto et al., 2010).

Indirect evidence of altered spine structure and physiology is provided by studies of glutamate receptors that populate axo-spinous synapses. This work demonstrates a reduction in the expression of AMPA receptor subunits GluR1 and GluR3, NMDA receptor subunits NR2A and NR2B and kainate receptor subunit GluR5 in the medial temporal lobe, a region involved in long-term declarative memory, in depressed subjects (Beneyto et al., 2007). However, another study reported that AMPA receptor binding levels are increased in the anterior cingulate cortex, but not in the dorsolateral PFC of MDD subjects (Gibbons et al., 2011). This discrepancy could be related to the specific subregions examined, as well as differences in levels of receptor expression vs. binding. Levels of glutamate are elevated in postmortem forebrain tissue of MDD and BD subjects (Hashimoto et al., 2007), although it is difficult to assess the impact of this change on tissue glutamate levels.

There are several intracellular signaling pathways altered in MDD that also play an important role in the regulation of neuronal plasticity (Chen and Manji, 2006). Among them, the MAPK/ERK signaling pathway is known to be involved in the pathophysiology and treatment of MDD (Duman et al., 2007) (Figure 2). Components of the extracellular-regulated protein kinase (ERK) pathway, including MEK1, MEK2, and Rap1, are decreased in frontal cortex of MDD as well as schizophrenia subjects (Yuan et al., 2010). Levels of the cAMP response element-binding protein (CREB), a transcription factor downstream of ERK, as well as cAMP and Ca^{2+} signaling, are also decreased in MDD (Yuan et al., 2010). Similar decreases in ERK1/2, ERK5, MEK1, and CREB are reported in the hippocampus of suicide victims (Dwivedi et al., 2007, Dwivedi et al., 2009). Rap1, a small Ras-like GTPase, is involved in regulation of spatial memory as well as LTP, coupling cAMP signaling to p42/p44 MAPK and is known to induce removal of surface GluR2/3 containing AMPA receptors (Morozov et al., 2003, Fu et al., 2007). Similar reductions of Rap1 activity were described in PFC and hippocampus of depressed suicidal victims (Dwivedi et al., 2006). Moreover, another report found that a polymorphism of disrupted-in-schizophrenia (DISC-1) (Ser704Cys) is associated with lower ERK activity, reduced gray matter volume, and higher risk for developing MDD (Hashimoto et al., 2006). MAPK-phosphatase 1 (MKP-1), a negative regulator of the MAPK pathway is increased in the hippocampus of MDD subjects (Duric et al., 2010), and viral expression of MKP-1 is sufficient to cause depressive behaviors in rodent models (77). Assuming that ERK signaling is involved in regulation of synaptic plasticity these data suggest that the reduction of ERK signaling in MDD could contribute to a decrease in the density and function of axo-spinous synapses, although further studies are needed to test this hypothesis.

4. Influence of stress on spine and dendrite remodeling: preclinical studies

Rodent models of stress

Stress can precipitate or exacerbate depression, and rodent stress models have been developed to better understand the molecular and cellular mechanisms involved in the pathogenesis of MDD. These paradigms can be divided into acute models such as the forced swim test (FST) and tail suspension test (TST), subchronic models such as inescapable stress (IES)/learned helplessness (LH), and chronic stress models, including chronic social defeat stress (CSDS), chronic restraint stress (CRS) and chronic unpredictable stress (CUS). The acute stress models are primarily used for antidepressant drug screening and have reasonably good predictive validity, although the acute response is inconsistent with the long-term treatment that is required for a therapeutic response in MDD patients. Chronic stress paradigms have predictive, as well as face and construct validity (e.g., CUS causes anhedonia, a core symptom of depression) and as such are better suited for studies of the neurobiology of stress related disorders (Willner, 2005, Nestler and Hyman, 2010). These models also require chronic treatment to produce an antidepressant response, consistent with the therapeutic time course, and therefore have greater level of predictive validity.

Effects of stress on hippocampal neurons

The first studies to demonstrate that stress can cause atrophy or rearrangement of neuronal processes were conducted on the hippocampus, and have consistently reported atrophy of pyramidal cell dendrites (McEwen, 2008, McEwen and Gianaros, 2011) (Figure 1). Exposure to CRS for 21 days results in decreased branch number and length of CA3 pyramidal dendrites (Magarinos et al., 1997). The remodeling of hippocampal CA3 dendrites is also observed after chronic (21 d) glucocorticoid administration (Woolley et al., 1990) and is dependent on the corticotropin-releasing factor (CRF) and its receptor ($CRFR_1$) (Chen et al., 2008b), demonstrating a role for activation of the HPA axis in the effects of stress. These effects of stress and corticosterone are limited to apical dendrites as no changes are observed in basilar dendrites of CA3 pyramidal neurons. Exposure to CRS also influences presynaptic terminals, demonstrated by a decrease in levels of endosome-like structures that are involved in neurotransmitter processing and release (Stewart et al., 2005). CRS is reported to cause a significant reduction of spine number in the CA1 pyramidal cell layer of the hippocampus (Donohue et al., 2006). Other studies have reported no change in CA3 (Chen et al., 2008b) or even an increase in the number of synaptic spines on apical and basal dendrites in CA3 pyramidal cells after CRS (Sunanda et al., 1995). The possible reasons for these discrepancies include the type and length of stress, the species (mouse vs. rat vs. tree shrew), and methods for analysis of spines.

IES/LH stress, a subchronic model, causes persistent loss of synapses (determined by electron microscopic analysis) in CA1, CA3 and dentate gyrus cell layers of the hippocampus (Hajszan et al., 2009). Similar effects are observed after a single injection of corticosterone. Moreover, synaptic loss is associated with a deficit in active avoidance behavior, a measure of helplessness (Hajszan et al., 2009). Prenatal stress (PS) is also reported to induce sex-specific reductions in dendritic arborization and spine density in the hippocampus that could be reversed with neonatal handling (Bock et al., 2011). The effects of PS on dendritic plasticity are further discussed below.

Effects of stress on PFC neurons

Exposure to chronic stress or high levels of glucocorticoids leads to abnormalities of the apical dendrites of pyramidal neurons in the anterior cingulate (AC), the prelimbic (PL), and infralimbic (IL) regions of the rat PFC (Izquierdo et al., 2006, Liston et al., 2006, Radley et al., 2006) (Figure 1). However, there is a subpopulation of IL neurons projecting to

basolateral amygdala (BLA) that are resistant to changes in dendrite remodeling caused by chronic stress (Shansky and Morrison, 2009). CRS induces a retraction of apical dendrites in rat medial PFC that can be reversed by blockade of NMDA receptors (Martin and Wellman, 2011), again suggesting a role for these glutamate receptors in dendrite degeneration (Figure 1). Automated 3D morphometric analysis of spine volume, length and surface area in layer II/III pyramidal neurons of the medial PFC of rat reveal a shift from large to small spines after stress (Radley et al., 2008). In addition, repeated stress causes a reduction of spine volume and surface area, especially in distal apical dendrites. Another study reports that chronic stress causes atrophy of pyramidal neurons in prelimbic and infralimbic subregions of rat medial PFC, reducing apical branch number and length in layer II/III pyramidal neurons, as opposed to hypertrophy of the sensorimotor striatum, with no effect on the spine density (Dias-Ferreira et al., 2009). Together these findings indicate that repeated stress decreases or inhibits synaptic spine maturation and stabilization and decreases dendrite complexity in the PFC. These structural alterations are associated with modified responses in behaviors controlled by the PFC circuits (e.g., decision making) (Dias-Ferreira et al., 2009).

Effects of stress on amygdala neurons

In rats, atrophy of hippocampal neurons in response to chronic stress is associated with, and may contribute to increased dendrite branching in principal cells of the amygdala (Vyas et al., 2003, Vyas et al., 2004, Vyas et al., 2006). Similarly, glucocorticoid exposure enhances the excitability of the principal neurons of the amygdala (Duvarci and Pare, 2007). Chronic stress is known to affect dendrite architecture and spine density of interneurons in the medial (Bennur et al., 2007) and basolateral amygdala (Vyas et al., 2002, Vyas et al., 2006). A recent study shows that CRS decreases dendrite arborization of interneurons of the lateral and basolateral amygdala in mice, without affecting spine density (Gilabert-Juan et al., 2011). In contrast, immobilization stress increases spine density and dendrite complexity in basolateral amygdala neurons (Vyas et al., 2002), effects that could contribute to increased neuronal activity, as well as increased stress related behaviors. The molecular mechanisms underlying the alterations of amygdala in response to stress have not been fully identified, but there is evidence that the serine protease tissue-plasminogen activator (tPA) is increased in response to stress and contributes to the structural plasticity in central and lateral amygdala neurons (Pawlak et al., 2003). Together, this evidence suggests that stress exposure increases dendrite complexity, and thereby contributes to the hyperactivity of amygdala neurons (Figure 1).

Effects of stress on synaptic signaling

The role of glutamate transmission and intracellular signaling pathways in the remodeling of axo-spinous synapses and dendrites has also been examined. Chronic mild stress (CMS), a form of CUS, has been shown to influence the expression of synaptic proteins such as synapsin 1 and the glutamate transporter 1 (VGLUT1), resulting in altered glutamate release and thus contributing to disruption of synaptic transmission and impaired LTP (Fremeau et al., 2004, Tordera et al., 2007, Balschun et al., 2010). LTP in the CA1 pyramidal cell layer of hippocampus requires synaptic delivery of AMPA receptors in an activity-dependent manner (Citri and Malenka, 2008) (Figure 2). A single dose of corticosterone induces lateral diffusion of the AMPA receptor subunits GluR1 and GluR2 in cultures of hippocampal neurons (Groc et al., 2008). In addition, corticosterone exposure potentiates the delivery of GluR2 to the synaptic membrane after chemical-induction of LTP. These results are consistent with the reports that AMPA- and NMDA-mediated transmission in PFC pyramidal neurons is increased by acute stress, which thereby enhances working memory (Yuen et al., 2011).

In contrast to acute exposure, repeated stress suppresses synaptic expression of AMPA and NMDA receptors in the PFC, impairing object recognition memory (Popoli et al., 2011). Chronic exposure to corticosterone also decreases cortical levels of NR2B and GluR2/3, which may contribute to deficits in fear extinction (Gourley et al., 2009). Decreased levels of synaptic vesicle proteins (i.e., synaptophysin and synaptotagmin) have also been reported in stress paradigms (Thome et al., 2001). These reductions in levels of presynaptic proteins could be related to changes in the number and/or structure of synapses and thereby the behavioral deficits, such as anhedonia and helplessness in models of depression (Duman and Monteggia, 2006). Finally, it is worth noting that the MAP kinase signaling pathway involved in the pathophysiology of depression and antidepressant response (Duman et al., 2007), is also required for sustained growth of dendritic spines (Patterson and Yasuda, 2011) (Figure 2).

Role of BDNF in the regulation of dendrites and spines

BDNF and other neurotrophic factors promote the development of new axo-spinous synapses and dendrite branching (Xie et al., 2007), contributing to the regulation of neuronal differentiation and modulation of synaptic transmission (Patterson et al., 1996) (Figure 2). In addition, mutant mice lacking the primary BDNF receptor, TrkB show a reduction in spine number in hippocampus (von Bohlen und Halbach et al., 2006a). The influence of BDNF on spine and dendrite morphology has also been examined using mutant mice with a knock in of a common human single nucleotide polymorphism of the BDNF gene (Val66Met). The Met allele, which is found in 25 to 30 percent of the human population decreases the processing and release of BDNF and is associated with decreased hippocampal volume in humans (*44, 45*). BDNF Met knock in mice show a reduction of hippocampal volume and dendrite arborization in dentate gyrus granule neurons (Chen et al., 2006). Mice with half the normal complement of BDNF (heterozygous deletion mutants) display dendrite deficits similar to the BDNF Met mice (Chen et al., 2006, Magarinos et al., 2011) and there is no further atrophy of hippocampal neurons in response to CRS exposure (Magarinos et al., 2011), suggesting that the effect of stress is occluded. Moreover, studies of PFC demonstrate that BDNF Met mice have decreased dendrite length and spine head diameter of layer V pyramidal neurons (Liu et al., 2011a). These morphological changes are accompanied by reduced serotonin (5-HT) and hypocretin (Hcrt) stimulated excitatory postsynaptic currents (EPSCs) (Liu et al., 2011a), and by increased anxiety and reduced responses to antidepressants (Chen et al., 2006).

These studies suggest that reduced spine number and dendrite complexity could contribute to the decreased hippocampal and PFC volumes and altered cognition in human subjects carrying the Met allele, including psychiatric normal as well as MDD and BD patients (Chepenik et al., 2009, Tsai et al., 2010, Hajek et al., 2011). There is also a report that early life stress or trauma increases the risk for depression and cognitive dysfunction in subjects carrying the Met allele (Gatt, 2009). However, carriers of the Val allele are reported to have a higher incidence of depression and lower antidepressant response rates than Met carriers (Tsai, 2010), indicating a complex relationship between the BDNF Val/Met polymorphism and environmental factors, as well as other gene polymorphisms. These findings also suggest that the reductions in levels of BDNF reported in depressed subjects (Nestler et al., 2002, Sen et al., 2008) could contribute to the structural and behavioral symptoms of depression.

Effects of perinatal stress on dendritic spines

Exposure to stress during the perinatal period, either in utero or the early postnatal period, also impacts brain physiology and behavior of the newborn (Frye et al., 2011, Dunkel Schetter and Tanner, 2012). Stress experienced by the mother during pregnancy affects the

development of brain circuitry in the progeny and increases the risk of neuropsychiatric disorders, such as schizophrenia, autism, anxiety and depression (Bertram and Hanson, 2002, Huizink et al., 2004, King, 2011). Chronic stress and depression during pregnancy may result in preterm birth and lower body weight (Dunkel Schetter and Tanner, 2012), which in turn may lead to impaired emotional and cognitive behaviors, as has been observed in school-age children (Talge et al., 2010, Kerstjens et al., 2011). Moreover, a recent study shows that preterm infants exhibit abnormalities in cortical volume, compared to antenatal matched controls (Lodygensky et al., 2010). Another study reports increased incidence of preterm birth and neurodevelopmental disorders in offspring of women deployed to a combat zone while pregnant (Ryan et al., 2011).

The effects of prenatal stress (PNS) can also be observed in preclinical animal models where cortico-limbic brain areas are particularly sensitive. In rats, physical restraint during pregnancy increases CA1 and decreases CA3 dendritic spine densities in pre-adolescent male offspring, with reductions in spine density of both CA1 and CA3 hippocampal regions in adult PNS offspring (Martinez-Tellez et al., 2009). Female progeny are especially sensitive to PNS, with single PNS exposure during gestational day 18 (GD18) causing a reduction in the volume of dendate gyrus in adult females but not males (Schmitz et al., 2002). Interestingly, prenatal bystander stress, where the pregnant mother is not subjected to stress but observes and is housed with another stressed female, alters the number of neurons and glia in the medial PFC, OFC, and CA1 of hippocampus, as well as the dendritic arbor complexity and spine density in the progeny (Mychasiuk et al., 2011). In addition to these morphological changes, female offspring exposed to PNS show decreased neurogenesis (Koehl et al., 2009). PNS exposure of rats leads to an enlarged amygdala volume in adulthood (Salm et al., 2004) and may also cause dysregulation in BDNF in adult rats that could contribute to alterations of dendrite and spine morphology (discussed above in a separate paragraph) (Fumagalli et al., 2004).

PNS exposure between GD 12 to 16 has also been shown to increase spine density in the nucleus accumbens with a decrease in medial prefrontal cortex (mPFC) and no changes in OFC (Muhammad and Kolb, 2011b). A similar remodeling in spine density was found in layer II/III pyramidal neurons in dorsal anterior cingulate (ACd), a limbic region involved in attention, and OFC in male and female PNS offspring. In contrast to males, the reduction in spine density in females was not accompanied by dendritic atrophy (Murmu et al., 2006).

A recent PNS study has reported additional sexually dimorphic changes in neuronal counts in OFC, CA1 and mPFC that are accompanied by fluctuations in spine density (Mychasiuk et al., 2012). Male offspring of mothers exposed to PNS show reduced spine density in OFC and CA1 and increased dendritic spine number in mPFC, whereas female progeny have reduced spines in mPFC and CA1, but increases in OFC (Mychasiuk et al., 2012). This study also reports that males have fewer, whereas females have more neurons compared to same-sex controls (Mychasiuk et al., 2012). Moreover, PNS causes a lifespan reduction in neurogenesis accompanied by impairments in hippocampal-dependent spatial tasks (Lemaire et al., 2000, Odagiri et al., 2008), with passive avoidance being especially affected in female PNS progeny (Gue et al., 2004). Similar effects of PNS exposure on neurogenesis have been reported in rhesus monkeys (Coe et al., 2003).

Neonatal maternal separation (MS) stress also decreases dendritic spine density on basal dendrites of layer II/III and V pyramidal neurons in the ACd during a specific developmental time window (the stress hypo-responsive period characterized by low basal levels of stress hormones as well as reduced responsiveness to stressors between postnatal days 5–7) (Bock et al., 2005, Gos et al., 2008). Interestingly, MS elevates anxiety-like

behavior in male rats but not in females, and is accompanied by increased spine density in NAc and PFC neurons (Muhammad and Kolb, 2011a).

Chronic mild stress during the postnatal period can decrease the density of mPFC spines, especially the more stable mushroom-like spines (Michelsen et al., 2007). Moreover, postweaning social isolation in rats reduces spine density on pyramidal neurons of the mPFC and hippocampus (Silva-Gomez et al., 2003). Studies conducted in the rodent *Octodon degus* show that separation stress during the first postnatal weeks causes deficits in responses to emotional stimuli and motoric hyperactivity, resembling symptoms of attention deficit hyperactivity disorder (ADHD) (Zehle et al., 2007). These behavioral changes coincide with increased numbers of dendritic spines on apical and basal dendrites in the ACd (Zehle et al., 2007). In addition to changes found in ACd, parentally separated 3-week old *Octodon degus* exhibited increased spine density on pyramidal neurons in the CA1 region of the hippocampus, in contrast to granule cells of the dentate gyrus and apical dendrites in the medial nucleus of the amygdala, where a decrease in spine density was observed (Poeggel et al., 2003).

A number of psychiatric disorders e.g. schizophrenia are thought to be related to developmental abnormalties, where accumulation of cellular alterations, such as dendritic spine number and plasticity, acquired at early stages progress with age to manifest in neurobiological illnesses in adulthood or under stressful conditions. This could explain reports that spine density is decreased in cortical pyramidal neurons in late adolescence of schizophrenic subjects (Garey et al., 1998, Glantz and Lewis, 2000, 2001). Similarly, the effects of stress, pre- or postnatal, or early adolescent, on spine plasticity and number in cortical and limbic areas of the brain could contribute to expression of social and emotional behavioral abnormalities later in life.

Age related spine and dendrite changes in limbic regions

In aged Rhesus monkeys cognitive decline is associated with a decrease in synaptic density in dorsolateral PFC, where small flexible spines are affected (Dumitriu et al., 2010, Hara et al., 2011). Studies in rat PFC have reported age-dependent differences in stress-induced plasticity of spines (Bloss et al., 2011). The number of thin immature spines is reduced in middle- and old-aged animals compared to young animals, and there is no effect of stress as typically observed in young animals. Resistance to stress-induced spine changes in aged rats would suggest decreased sensitivity to experience-dependent spine and dendrite remodeling. A recent *in vivo* study reported a critical role of glucocorticoids in maintaining synaptic connections in the mouse barrel cortex (Liston and Gan, 2011). Moreover, the authors found that chronic exposure to high levels of glucocorticoids leads to a loss of spines that were established earlier in development.

The effects of aging on dendritic spine density in rat hippocampus are inconclusive, with some authors reporting no changes in CA1 between young and old animals (Markham et al., 2005, Alcantara-Gonzalez et al., 2010), while others find an age associated increase in CA1 and dentate gyrus cell layers (Calhoun et al., 2008). Recent studies in rat and mouse have reported a reduction in spine density of basal and apical dendrites of CA1 in aged compared to young animals (von Bohlen und Halbach et al., 2006b, Luine et al., 2011), with no change in CA3 pyramidal neurons (Luine et al., 2011). The reason for the differences in these studies could be related to the type of stress, species and even strain of rats tested.

Sex hormones and dendrite organization

Sex steroids, including estrogen, progesterone and testosterone are reported to influence remodeling of neurons in the central nervous system. The importance of sex steroids is

highlighted by the higher incidence of depression in women, which is likely due to abnormal regulation of endocrine feedback and responses (Kessler et al., 1993, Grigoriadis and Robinson, 2007). These sex steroids influence different aspects of neurotransmission (Amin et al., 2005), neurogenesis (Tanapat et al., 1999) and secretion of BDNF (Cavus and Duman, 2003, Scharfman and MacLusky, 2006). Neurons are highly sensitive to gonadal steroid hormones during development, and these hormones continue to influence neuronal connections in adolescence, which contributes to shaping of behavioral responses to sex steroids in adulthood (Sisk and Zehr, 2005). Among the brain regions that are most sensitive to steroid hormones are the medial nucleus of the amygdala (MeA) and CA1 region of dorsal hippocampus, where gonadal hormones directly modulate dendrite architecture (Cooke and Woolley, 2005). The pyramidal neurons in the dorsal CA1 undergo remodeling of dendrite structure during the estrous cycle, with induction of synaptogenesis during phases where levels of estrogen are high. Interestingly, females as opposed to males are resistant to stress induced degeneration of CA3 pyramidal neuron apical dendrites, suggesting a different, sex-related stress response pathway in the hippocampus (McLaughlin et al., 2009).

As chronic stress may differentially influence neuronal morphology in CA1 and CA3 regions of the hippocampus according to hormonal status, a recent report examined the effects of CRS combined with modulation of gonadal hormones (McLaughlin et al., 2010). In CA3 pyramidal neurons 17β-estradiol and cholesterol prevent CRS-induced retraction of apical dendrites, whereas in the CA1 pyramidal cell layer combined treatment increases apical spine density and influences spine shape. Similar changes were observed in ovariectomized and gonad-intact animals. A recent study by the same group addressing the effects of CRS and cyclic estradiol regimen showed increased spine density in CA1 after repeated estradiol administration (Conrad et al., 2011). Such increase in spine density induced by estradiol in dissociated pyramidal neurons is mediated by phosphorylation of CREB and accompanied by an increased cellular calcium response to glutamate and synaptic activity (Murphy and Segal, 1996, Segal and Murphy, 2001). Ovariectomized female rats with estrogen replacement and exposed to immobilization stress showed greater apical dendrite length in PFC neurons projecting to basolateral nucleus of the amygdala than rats without estrogen replacement (Shansky et al., 2010).

Studies in female rhesus monkeys report enhanced immunoreactivity for the spine-associated protein spinophilin in hippocampus and PFC in estrogen treated animals (Hao et al., 2003, Tang et al., 2004). Interestingly, in contrast to aged female rats, aged rhesus female monkeys maintain the capacity for dendrite remodeling and spine induction in response to estrogen. The capacity for generating spines at older ages may have implications for the mood and cognitive benefits of estrogen replacement in postmenopausal women. Clinical trials show that risk of developing depression is two times higher in females compared to males (Kessler et al., 1993), a phenomenon also observed in preclinical studies (Dalla et al., 2008). Women suffering from polycystic ovary syndrome (PCOS), an endocrine disorder, show a strong correlation between androgen levels and development of depression (Rasgon et al., 2002). A gene polymorphism affecting the production of estradiol and therefore its signaling is also associated with increased risk of depression in young women (Kravitz et al., 2006, Mill et al., 2008). The higher risk of mood disorders is associated with estrogen only during the reproductive years, while there is an inverse correlation in postmenopausal women (Almeida et al., 2005, Freeman et al., 2006). In addition, higher serum levels of androgens are associated with premenstrual dysphoria and mood changes (Eriksson et al., 1992). Further research is required to establish a direct connection between estrogen-induction of spine and dendrite remodeling and associated behaviors.

5. Remodeling of spine and dendrite architecture by antidepressants

The reduction in volume of limbic brain regions in depressed patients and the atrophy of neuronal dendrites and spines in models of chronic stress raise a question regarding the influence of antidepressant treatments on dendrite remodeling. There are reports showing that the atrophy of hippocampus is inversely related to the length of antidepressant treatment of depressed patients (Sheline et al., 2003), and antidepressant treatment partially reverses the reduction of hippocampal volume and improves memory function in PTSD patients (Vermetten et al., 2003). Chronic treatment with fluoxetine, a selective serotonin re-uptake inhibitor (SSRI), is reported to improve verbal memory and attention in depressed patients (Vythilingam et al., 2004, Gallassi et al., 2006), which could be related to altered synaptic plasticity and remodeling. Preclinical evidence in support of this hypothesis is discussed in the next section.

Typical Antidepressants

A number of preclinical studies have shown that antidepressant treatment can induce dendrite and spine/synapse remodeling. In rat hippocampus short-term treatment with the SSRI fluoxetine promotes expansion of synapses (Hajszan et al., 2005), and acute treatment with another SSRI fluvoxamine increases spine density in CA1 stratum radiatum and dentate gyrus in juvenile rats (Norrholm and Ouimet, 2000). Chronic fluoxetine treatment also increases dendrite branching of newborn neurons in the adult dentate gyrus granule cell layer (Wang et al., 2008) and increases interneuron dendrite branch dynamics (measured as elongation and retraction) in layers I and II/III of rodent visual cortex (Chen et al., 2011). Chronic administration of fluoxetine or the tricylic antidepressant imipramine is reported to rescue dendrite atrophy and spine loss in hippocampal CA3 and medial PFC layer II/III pyramidal neurons caused by chronic stress (Bessa et al., 2009).

The regulation of dendritic and spine morphology induced by antidepressant treatment may be explained at least in part by the effects of SSRIs on cytoskeleton remodeling, as fluoxetine is reported to modulate microtubule dynamics in rat hippocampus (Bianchi et al., 2009). There has been much less work on norepinephrine selective reuptake inhibitors (NSRI), although two such agents, desipramine and reboxetine, decrease RNA editing and expression of GluR3 in PFC and hippocampus (Du et al., 2004, Barbon et al., 2006), and may thereby influence synaptic function and number. Interestingly, a recent report showed that prenatal exposure to fluoxetine causes alterations in cortical architecture that are correlated with elevated anxiety-like behaviors (Smit-Rigter et al., 2012).

Chronic treatment with the tricyclic antidepressant amitriptyline also rescues dendritic spine loss in hippocampal CA1, CA3 and dentate gyrus cell layers caused by olfactory bulbectomy, another model of depression (Norrholm and Ouimet, 2001). Chronic imipramine administration increases the number of synaptic spines in the CA1 pyramidal cell layer in a rat strain bred for elevated susceptibility to depressive behaviors (Chen et al., 2010), and increases the number of asymmetric axo-spinous synapses but decreases shaft synapses in the CA1 pyramidal layer of hippocampus (Chen et al., 2008a). As asymmetric synapses are considered to be primarily excitatory, it is possible that imipramine administration causes a shift toward a higher number of excitatory synapses. This possibility is supported by a report of increased GluR1 receptor expression in response to imipramine treatment (Du et al., 2004).

Co-administration of imipramine and rolipram, a phosphodiesterase inhibitor with antidepressant actions, significantly increases spine number of hippocampal CA1 pyramidal neurons after acute or short-term treatment (Marchetti et al., 2010). This study found that increased spine number is accompanied by antidepressant behavioral responses in the FST,

as well as increased BDNF, elevated AMPA and NMDA receptor transmission. Interestingly, subchronic treatment increased stubby spines, which are generally considered to be immature (Marchetti et al., 2010). Induction of immature spines is also observed after LTP, and further analysis of the fate of dendritic protrusions could provide information on the type of plasticity caused by impramine + rolipram co-treatment.

Administration of a monoamine oxidase inhibitor (MAOI) moclobemide results in memory improvements (Allain et al., 1992) that may be attributed to regulation of hippocampal neuroplasticity. Chronic administration of another MAOI (−)-deprenyl prevents the dendritic impairments of rat PFC pyramidal neurons caused by social isolation stress (Pascual and Zamora-Leon, 2007). In a very recent study rats treated for 10 days with 9-Methyl-β-carboline, which inhibits MAO-A but also has other effects on monoamine transmission, improved spatial learning in the radial maze and increased dendrite complexity and spine number on dentate gyrus granule cells (Gruss et al., 2012). Chronic tianeptine administration, a clinically effective antidepressant that influences glutamate transmission, reverses the atrophy of dendrites caused by exposure to chronic stress (Kasper and McEwen, 2008). The antidepressant and neuroprotective effects of tianeptine, as well as improved cognition and memory, may involve stimulation of dendrite plasticity, enhancement of GluR1 phosphorylation and normalization of LTP (McEwen et al., 2010). Tianeptine has also been shown to reverse stress-induced attenuation of the MEK/MAPK signaling pathway and promote phosphorylation of the AMPA receptor subunit GluR1 at Ser831 (Qi et al., 2009).

Influence of neonatal SSRI exposure on spine and dendrite remodeling

Neonatal exposure to fluoxetine is reported to reduce dendrite complexity and spine density of layer IV stellate neurons of primary somatosensory cortex (Lee, 2009). In addition, neonatal fluoxetine treatment alters dendrite branching and elongation as well as synaptic excitability of subplate neurons, an important cell population in cortical development (Liao and Lee, 2011). Moreover, neonatal SSRI administration reduces spine density of basal (fluoxetine or fluvoxamine), as well as apical dendrites of CA1 neurons (fluvoxamine) (Zheng et al., 2011). This study also reports that neonatal SSRI exposure increases spine density at basal dendrites later in adulthood (P90) and these changes are accompanied by impaired locomotor activity. Dendrite remodeling resulting from SSRI exposure during the early neonatal period may contribute to depressive-like behaviors observed in adult mice (Ansorge et al., 2004). Fluoxetine exposure during this period also causes growth cone collapse and blocks synaptic transmission in both vertebrate and invertebrate animals (Xu et al., 2010). On the other hand, morphological changes induced by prenatal stress can be rescued by fluoxetine treatment. Early postnatal (between 1–3 weeks) fluoxetine administration rescues deficits in spine density in the CA3 region of the hippocampus in prenatally stressed mice (Ishiwata et al., 2005).

These studies provide important information regarding the influence of stress, either early in life or in adults, on synaptic number and function that could contribute to individual variations in the responses to antidepressant treatments, as well as the underlying causes of depression. While it is difficult to determine the connection between treatment response and synaptic function, studies with rapid acting antidepressant highlight the significance of synaptogenesis in the behavioral actions of these agents in rodent models (see below).

Electroconvulsive shock (ECS) and lithium treatments

Chronic administration of electroconvulsive seizure (ECS), a potent antidepressant therapy used for patients who are resistant to chemical antidepressants, increases axonal sprouting in rat dentate gyrus (Vaidya et al., 1999). In addition, ECS was recently shown to promote

maturation of dendritic spines (increased number of mushroom spines) in newborn granule cells in rat hippocampus without changing the overall spine number (Zhao et al., 2011). ECS also increases the number of spines on mature neurons without promoting maturation. Moreover, repeated ECS increases the number of axo-spinous synapses in the hippocampal CA1 pyramidal cell layer without affecting shaft synapses (Chen et al., 2009). ECS also prevents the reduction in length and number of CA3 pyramidal neuron apical dendrites caused by chronic stress (Hageman et al., 2008).

A number of studies have examined the modulation of dendrites and spines by lithium, typically used for treatment of bipolar disorder but also used as an add therapy for management of depression. Administration of lithium normalizes dendritic spine morphology in a mouse model of fragile X syndrome, and also reverses the behavioral impairments in social interaction and learning (Liu et al., 2011b). A recent study reports that lithium treatment prevents stress-induced hypertrophy of neurons in the basolateral nucleus of the amygdala (Johnson et al., 2009). Chronic administration of lithium is reported to reduce expression of GluR1 at the synaptic membrane of hippocampal neurons (Du et al., 2004, Barbon et al., 2006).

6. Novel rapid acting antidepressants: NMDA antagonists

Recent studies have demonstrated that ketamine, a nonselective NMDA receptor antagonist, produces a rapid (within hours) antidepressant response in depressed patients (Berman et al., 2000, Zarate et al., 2006). Moreover, the antidepressant actions of ketamine are relatively stable (approximately 1 week) and are observed in treatment resistant patients (i.e., failed to respond to two or more typical antidepressants). Ketamine is also effective for the treatment of suicide ideation (DiazGranados et al., 2010b) and bipolar disorder depression (Diazgranados et al., 2010a). These findings represent a major advance for the treatment of depression, demonstrating that ketamine produces a rapid response in hard to treat patients by a mechanism completely different from currently available antidepressants.

NMDA receptors play an important role in the development of axonal and dendritic branching (Lee et al., 2005) and the effects of acute stress on hippocampal synaptic plasticity (LTP and LTD) (Wang et al., 2006), suggesting a possible scenario for the antidepressant action of ketamine through regulation of spine/synapse morphology. Recent studies support this hypothesis, demonstrating that a single dose of ketamine rapidly increases levels of synaptic proteins and the number and function of axo-spinous synapses in rat PFC layer V pyramidal neurons (Li et al., 2010). The increase in spine number is accompanied by an increase in “mushroom” or mature spines, with higher amplitude as well as frequency of neurotransmitter-induced EPSPs (Li et al., 2010). The rapid induction of axo-spinous synapses in the PFC is accompanied by antidepressant behavioral responses in models of depression, including the FST, LH, and novelty suppressed feeding paradigms (Li et al., 2010). In addition, ketamine produces a rapid antidepressant response in the CUS/anhedonia model (Li et al., 2011), compared to the requirement for long-term (3 week) administration of a typical antidepressant. Ketamine also rapidly reverses the CUS-deficit in synaptic proteins and spine number and function in PFC pyramidal neurons (Li et al., 2011). Antagonists selective for the NMDA-NR2B subunit produce similar effects on synaptic proteins and behavior (Li et al., 2010) and a produce a therapeutic response in depressed patients (Preskorn et al., 2008). Together these studies provide evidence that the induction of spines, as well as reversal of the effects of stress, correlate with the rapid antidepressant behavioral actions of ketamine.

Several signaling cascades have been implicated in synapse formation and protein synthesis dependent long-term memory (Holtmaat and Svoboda, 2009, Kessels and Malinow, 2009),

including the mammalian target of rapamycin (mTOR) cascade (Hoeffer and Klann, 2010) (Figure 2). The mTOR pathway is localized to dendrites, as well as cell bodies, and controls protein synthesis in response to neuronal activity, as well as metabolic and endocrine stimuli (Hoeffer and Klann, 2010). Ketamine rapidly activates mTOR signaling in rat PFC, including increased levels of the phosphorylated and activated forms of mTOR, p70S6 kinase, and 4E-BP1 (Li et al., 2010). Moreover, pretreatment with rapamycin, a selective inhibitor of mTOR, completely blocks the induction of synaptic proteins and spine number and function in PFC and inhibits the rapid behavioral actions of ketamine, demonstrating a requirement for mTOR signaling (Li et al., 2010). The antidepressant actions of ketamine on spine number and behavior in the CUS model are also blocked by rapamycin (Li et al., 2011). Recent studies have demonstrated that the induction of spines and behavioral actions of ketamine are blocked in conditional BDNF null mice (Autry et al., 2011) and in BDNF Met knock in mice (Liu et al., 2011a). The study by Autry et al (Autry et al., 2011) did not report a role for mTOR signaling in the actions of ketamine, although this discrepancy can be explained by methodological differences (i.e., mTOR signaling was tested in crude homogenates of hippocampus vs. synaptosome enriched preparations of the PFC, and behavior in the FST was tested 30 min after ketamine, an early time point well before the clinical response and when extrasynaptic glutamate levels are increased, which could complicate the interpretation of the behavioral testing results).

The mechanisms underlying the synaptogenic actions of ketamine are unknown, but could be related to increased glutamate transmission. Ketamine is reported to produce a rapid, transient increase (30 to 60 min) in extracellular glutamate (Moghaddam et al., 1997) that could subsequently lead to induction of axo-spinous synapses and behavioral responses (2 hr). The ability of ketamine to increase glutamate transmission is thought to occur via blockade of NMDA receptors on GABAergic interneurons, which results in disinhibition of glutamate transmission (Moghaddam et al., 1997). Nuclear magnetic resonance studies demonstrate that ketamine increases levels of glutamate cycling in rat mPFC (Chowdhury et al., 2011). In addition, a role for glutamate transmission in the actions of ketamine is supported by studies demonstrating that AMPA receptor blockade inhibits the behavioral actions of ketamine (Maeng et al., 2008, Li et al., 2010). Further support for glutamate transmission in the actions of ketamine is provided by studies demonstrating that blockade of mGluR2/3 presynaptic inhibitory autoreceptors also produces fast antidepressant actions that are dependent on mTOR signaling (Dwyer et al., 2011, Koike et al., 2011).

7. Summary and Future Directions

The evidence presented demonstrates that depression and chronic stress are characterized by atrophy of limbic brain regions and decreased complexity and number of axo-spinous synapses and dendrites in the hippocampus and PFC. Moreover, increasing evidence shows that antidepressants may work at least in part by producing the opposite effects and by reversing the synaptic deficits caused by stress exposure. This is particularly true for the fast acting NMDA receptor antagonists, which cause a rapid induction of axo-spinous synapses and reverses the synaptic deficit caused by CUS. The induction of synaptogenesis could lead to reconnection of limbic circuits that are critical for proper control of emotion (i.e., PFC-amygdala). Additional studies are required to directly test this hypothesis. In addition, there is increasing evidence that the mechanisms underlying the actions of typical antidepressants also include spine remodeling, albeit with the requirement for long-term treatment. Based on evidence that antidepressants increase BDNF it is possible that the regulation of spines and synaptic plasticity are mediated via induction of this as well as other neurotrophic factors. Synaptic studies of antidepressants in BDNF mutant mice, similar to those of ketamine, should be conducted to address this issue. However, typical antidepressants increase BDNF expression, but not release, which may contribute to their slower onset of action compared

to the rapid effects of ketamine. The development of agents that increase glutamate and mTOR signaling, such as the mGlu2/3 receptor antagonists, as well as other pharmacological approaches that rapidly increase spine/synapses and produce antidepressant responses will be required as ketamine has abuse potential and may cause side effects with repeated treatments.

The development of neuroimaging techniques with higher resolution will be needed to study structural anomalies in MDD. Additional postmortem as well as advanced imaging studies will be required to determine if there is a loss of spines and dendrites in depression and whether these effects can be reversed by antidepressant treatments. It is also possible that individual susceptibility to depression or treatment response could be related to genetic vulnerability and interactions with environmental factors, such as early life stress or trauma. Conversely, there is a great deal of interest in genetic and environmental factors (e.g., diet, exercise, enriched environment) that increase resilience to stress and depression. Further longitudinal studies of patients with genetic polymorphisms (e.g., BDNF Met allele) will be required to more completely characterize the complex interactions of factors involved in depression, treatment response, and stress resilience.

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Highlights

- We discuss the role of dendritic remodeling in the pathophysiology of depression.
- We review the evidence that antidepressants increase synaptic plasticity.
- We discuss the effects of ketamine on synaptic remodeling.

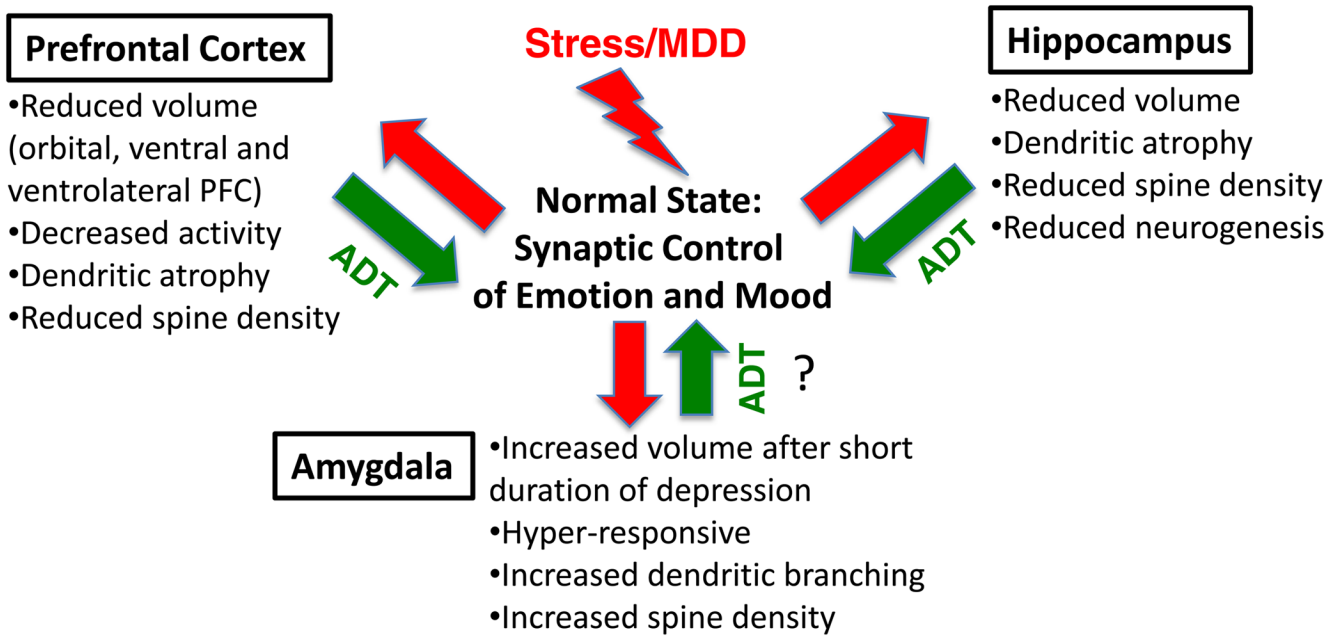

Figure 1. Morphological changes caused by stress

Stress and depression result in opposing effects on spine and dendrite morphology in the PFC, hippocampus and amygdala. In the PFC, as well as hippocampus, chronic stress decreases the number and function of spines, as well as the number and length of dendrite branches of pyramidal neurons. These effects may contribute to the reduced volume of PFC and hippocampus reported in MDD patients. Conversely, chronic stress increases dendrite length and branching in pyramidal neurons in the amygdala. The atrophy of PFC/hippocampus and hypertrophy of amygdala neurons could result in reduction of inhibitory control and increased activity of amygdala, contributing to altered mood, emotion, and anxiety. Antidepressant treatment, particularly new rapid acting NMDA receptor antagonists, can reverse the deficit in synaptic connections in the PFC and thereby reinstate appropriate PFC-amygdala functioning. The effects of antidepressants on stress-induced morphological changes in amygdala have not been determined (indicated by the question mark).

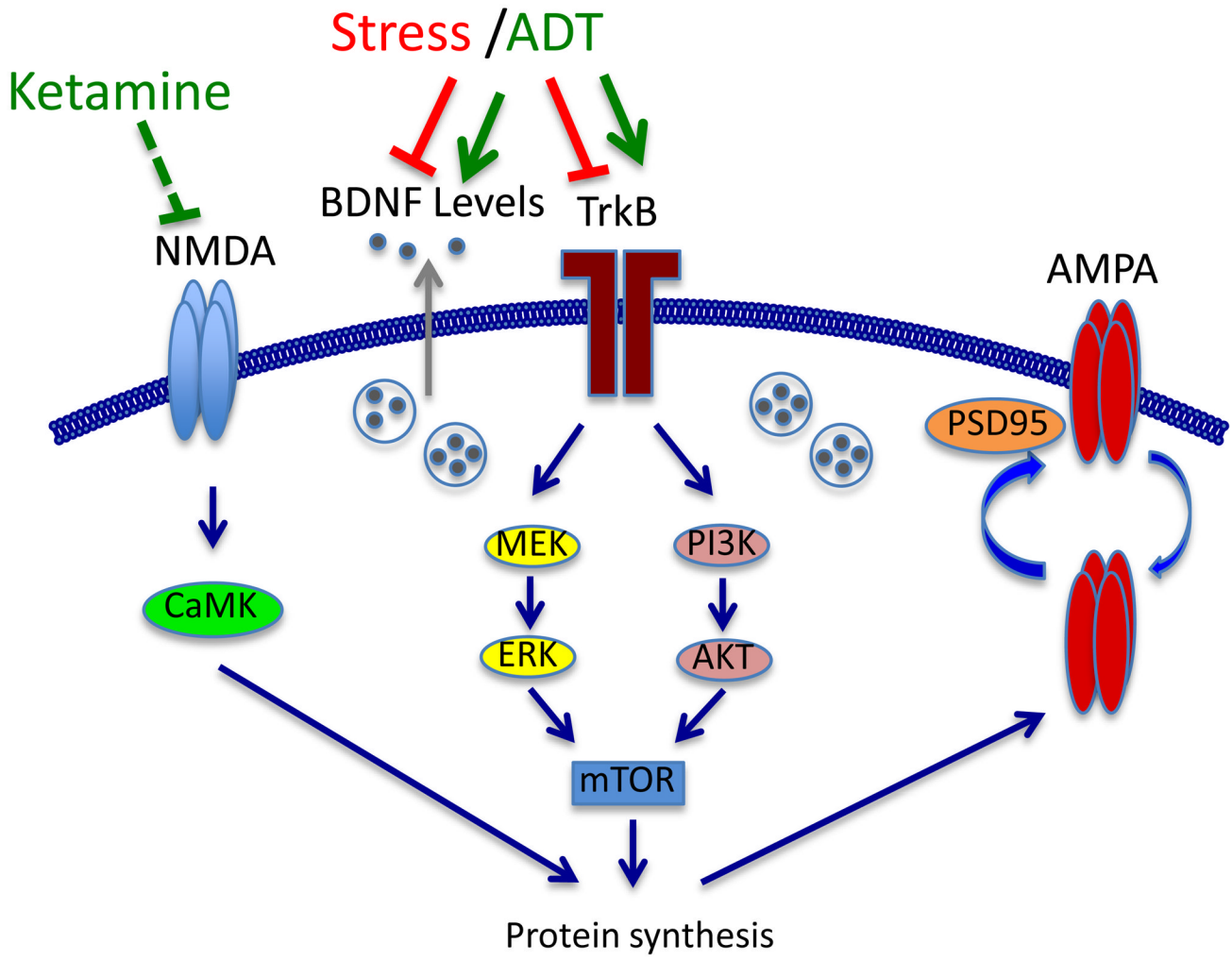

Figure 2. Molecular signaling pathways involved in spine remodeling and neuroplasticity

Shown are the major signaling pathways involved in the regulation of spine remodeling and synaptic plasticity, including NMDA and AMPA glutamate receptor subtypes, neurotrophic factors (i.e., BDNF), and related downstream signaling, particularly the ERK and Akt pathways. Long-term synaptic plasticity and spine formation require protein synthesis, which is regulated in dendrites by activity-dependent activation of the mTOR pathway. Recent studies demonstrate that the rapid synaptogenic and behavioral actions of ketamine are also dependent on mTOR signaling and protein synthesis. Less is known about the mechanisms underlying the atrophy of spines and dendrites in response to stress, but it is possible that inhibition of neurotrophic factor levels, mTOR signaling and synaptic protein synthesis could contribute to the effects of stress.

Abbreviations: BDNF, brain-derived neurotrophic factor; TrkB, tropomysin related kinase (BDNF receptor); NMDA, *N*-methyl-D-aspartate glutamate receptor; AMPA, amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid glutamate receptor; PSD-95; postsynaptic density protein 95; MEK, mitogen activated protein kinase (MAP) kinase kinase; CaMK, calcium-calmodulin-dependent kinase; PI3K, phophotydilinositol-3 kinase; ERK, extracellular-signal-regulated kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin.