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Spine synapse remodeling in the pathophysiology and treatment of depression

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Abstract

Clinical brain imaging and postmortem studies provide evidence of structural and functional abnormalities of key limbic and cortical structures in depressed patients, suggesting that spine synapse connectivity is altered in depression. Characterization of the cellular determinants underlying these changes in patients are limited, but studies in rodent models demonstrate alterations of dendrite complexity and spine density and function that could contribute to the morphological and functional alterations observed in humans. Rodent studies demonstrate region specific effects in chronic stress models of depression, including reductions in dendrite complexity and spine density in the hippocampus and prefrontal cortex (PFC) but increases in the basolateral amygdala and nucleus accumbens. Alterations of spine synapse connectivity in these regions are thought to contribute to the behavioral symptoms of depression, including disruption of cognition, mood, emotion, motivation, and reward. Studies of the mechanisms underlying these effects demonstrate a role for altered brain derived neurotrophic factor (BDNF) signaling that regulates synaptic protein synthesis. In contrast, there is evidence that chronic antidepressant treatment can block or reverse the spine synapse alterations caused by stress. Notably, the new fast acting antidepressant ketamine, which produces rapid therapeutic actions in treatment resistant MDD patients, rapidly increases spine synapse number in the PFC of rodents and reverses the effects of chronic stress. The rapid synaptic and behavioral actions of ketamine occur via increased BDNF regulation of synaptic protein synthesis. Together these studies provide evidence for a neurotophic and synaptogenic hypothesis of depression and treatment response and indicate that spine synapse connectivity in key cortical and limbic brain regions is critical for control of mood and emotion.

Keywords

stress; neurotrophic factor; ketamine; antidepressant; glutamate

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Introduction

Major depressive disorder (MDD) is a devastating illness that affects approximately 17 percent of the population in the United States causing enormous personal and economic consequences [53]. Moreover, the currently available monaminergic agents have significant limitations, including slow onset of action and low response rate [109]. Despite extensive efforts there have been no new therapeutic medications with novel mechanisms, in part due to the heterogeneity and complexity of depression. Therefore, rationale drug design is not possible without a more complete understanding of the underlying pathophysiology of depression.

Nevertheless, there has been significant progress from clinical and preclinical studies that have provided evidence that depression is associated with loss of neurotrophic factor support that leads to atrophy of neurons and reduced connectivity [23, 24]. Clinical brain imaging and postmortem studies demonstrate structural and functional alterations of several limbic and cortical regions in MDD, including the prefrontal cortex (PFC), hippocampus, cingulate cortex, amygdala, and basal ganglia [75, 99]. These studies demonstrate decreased function and atrophy of certain brain regions, including the PFC and hippocampus, but increased function and altered morphology of other regions, including the subcallosal cingulate and amygdala. Altered connectivity of these regions could contribute to the symptoms of depression, in part via reduced function of the PFC (e.g., decreased reaction time and cognitive function), and increased function of the amygdala (loss of control of emotion and mood, and increased fear, anxiety and hypothalamic-pituitary-adrenal axis reactivity). Altered function and connectivity of PFC and the ventral striatum could also underlie reduced motivation and reward in MDD.

The most consistent structural and functional alterations have been observed in the PFC and hippocampus, where reduced volume is inversely correlated with length of illness, time of treatment, and severity of depression [22, 67]. There is limited evidence from postmortem studies demonstrating decreased neuronal cell body size and atrophy of dendritic processes, although there is one report of decreased synapse number in a small cohort of depressed subjects [47]. Additional postmortem studies are needed to confirm and further characterize the synaptic alterations in MDD as well as related illnesses (e.g., psychotic depression) that could also involve disruption of synaptic connections. However, detailed studies of preclinical models of depression have provided extensive evidence demonstrating that chronic stress causes alterations of the density and function of spine synapses in key limbic and cortical brain regions implicated in depression. Here we provide a review of this literature, as well the mechanisms underlying the regulation of spine synapses by stress. In addition, we discuss the opposing effects of antidepressant treatments, notably novel rapid acting agents that increase spine synapses in the PFC and the functional consequences of these changes.

Spine Structure and Function

The small protrusions of the dendritic surface referred to as “spines” are the principal site of most cortical excitatory synapses. The existence of spines greatly increases the surface area

available for synaptic transmission, allowing for a high density of synaptic connections onto individual dendrites and neurons [84]. In addition to providing a physical substrate for synapse formation, the spine functions as a subcellular compartment for postsynaptic responses. Spine heads contain postsynaptic components and are connected to the dendrite via a neck-like structure. The overall shape and volume of spines are important determinants of the extent to which transduced signals are spread within the dendrite, emphasizing a critical relationship between spine morphology and neuronal function [38, 122].

Spines are commonly categorized into morphological subtypes according to size and relative proportions of the spine head and neck. The 3 most commonly categorized types are stubby, thin and mushroom spines [38, 90]. Stubby spines lack a clear distinction between head and neck and are considered an immature type. Thin spines, considered immature with a narrow neck and a relatively small head, are prevalent during development and have a high turnover rate [43]. Large head diameter “mushroom” spines are the most mature and stable, and spine head volume is positively correlated with synapse strength and age. Mushroom spines generally receive synaptic input from large diameter presynaptic terminals, while small thin spines are motile, unstable and form comparatively weak synapses [39, 48, 91, 100]. In addition to these three subtypes there are filopodia, which are long thin spines that lack a distinct head [40, 112]. Filopodia are spontaneously generated spines or spine precursors that are short-lived and thought to provide a substrate for activity-dependent growth and strengthening of spines [37, 65].

Spine synapses are the primary sites for dynamic structural plasticity of excitatory transmission [38, 42]. Spines undergo activity-dependent enlargement and stabilization and persist according to their use, while inactive spines are eliminated [40, 74]. Because different spine types are thought to contribute differently to dendritic excitability, it is important to understand how a particular experimental influence can alter relative proportions of spine types and by extension, influence synaptic function. As illustrated in live imaging studies, spine structure and function are not fixed but are continually changing in a way that is responsive to the current state of the animal and the neuronal environment. Live imaging studies have been particularly interesting in illustrating morphological transitions of spines that occur on a rapid timescale. These studies highlight the reactive and dynamic nature of spine morphology and imply corresponding functional plasticity [40, 87].

Stress Models of Depression

A complete understanding of the underlying disease processes in depression is lacking making it difficult to recapitulate the complete pathophysiology of depression in animal models. Currently used models of depression attempt to produce quantifiable correlates of human symptoms in experimental animals. Examples of measures that can be assessed in rodent behavioral models include motor responses to stress, reward-related responding and social interaction, with the rationale that they reflect levels of helplessness or despair, anhedonia, and social withdrawal, respectively, all relevant to human depression. These measures are most often quantified following chronic stress paradigms. Exposure to stress is a key environmental risk factor associated with the occurrence of depression in humans [51, 52] and stress exposure may interact with genetic risk factors to increase susceptibility to

depression [10, 50]. For these reasons, stress exposure, particularly chronic stress, has been used in animal models to reproduce some core components of major depressive disorder. Chronic restraint stress (CRS), chronic unpredictable stress (CUS) and social defeat stress (SDS) are chronic stress paradigms that have been used in adult rodents to produce depressive-like features that are sensitive to antidepressant treatment. Notably, the neurobiological alterations associated with these behavioral models include alterations of the size or volume of cortical and limbic brain structures implicated in depression as well as the number of spine synapses.

Chronic stress exposure alters the structure of cortical and limbic neurons

Many of the brain areas implicated in depression such as hippocampus, prefrontal cortex (PFC), amygdala and nucleus accumbens (NAC) are highly plastic regions that undergo morphological changes as a result of stress exposure. The hippocampus shows a high degree of functional and structural plasticity in response to many types of stimuli including stress [76]. Along with the PFC and amygdala, the hippocampus is an important part of the neurocircuitry that regulates the hypothalamic-pituitary-adrenal (HPA) axis response to stress [110]. HPA axis dysregulation is a common feature of depression and disruption of hippocampal neuronal morphology plays a role in the dysregulation of HPA axis-controlled glucocorticoid release that results from stress exposure [15, 105].

Hippocampus

A prominent morphological effect of chronic stress in the hippocampus is the atrophy of CA3 pyramidal cells, characterized by decreased length and branching of apical dendrites [68, 117]. Stress-induced dendritic atrophy has also been shown in dentate gyrus granule cells and CA1 pyramidal cells of the hippocampus [6, 106]. Stress-induced hippocampal dendritic atrophy is mimicked by and depends on glucocorticoids [71, 119]. Chronic stress also induces deficits in hippocampal-dependent behaviors such as spatial memory in male rats [66] and alters electrophysiologic measures in association with CA3 dendritic atrophy [88, 104]. Behavioral deficits as well as dendritic atrophy are reversible upon termination of stress exposure, emphasizing the plasticity and possibly adaptive nature of these responses [16, 106]. Chronic corticosterone exposure induces basal dendritic atrophy in CA1 pyramidal cells, although this effect does not normalize with a washout period [35].

Prefrontal cortex

The prefrontal cortex exhibits a high degree of experience-dependent plasticity including vulnerability to stress exposure [77]. The medial PFC (mPFC) is functionally important for the integration of cognitive and emotional information and plays a role in attention and response selection [2]. The efferent and afferent connections of mPFC with limbic, striatal and basal forebrain structures emphasize the potential significance of mPFC to the functioning of a broad cortical-limbic network [2]. Stress-induced atrophy of dendrites has been shown for pyramidal cells in layers II/III and V in mPFC. The duration and intensity of the stress exposures producing these effects range from long-term intensive stress (e.g., 6 hr. restraint/day for 21 days) [18, 95, 97] to short-term mild restraint stress (e.g., 20 min restraint/day for 7 days) [9, 46, 62] and chronic mild/variable stress [60, 93]. A general

feature of this stress effect is that the apical dendrites are more sensitive to stress than the basal dendrites for pyramidal neurons in layers II/II and also layer V. A similar selective sensitivity of apical dendrites is caused by corticosterone treatment [11, 118]. Interestingly, chronic corticosterone treatment causes a shift in the organization of dendrites towards more proximal regions [11, 118]. Stress-induced dendritic changes in PFC are reversible by the removal of stress. A 21-day stress-free recovery period has been shown to reverse the apical dendritic atrophy in layer II/II cells (prelimbic and cingulate), and was also shown to promote proximal apical dendritic extension in layer V cells in the infralimibic PFC [33, 94].

Other brain regions

The effects of stress on dendritic morphology are not similar in all brain regions examined and instead appear to be region and circuit specific. In contrast to hippocampus and PFC, repeated restraint stress causes dendritic hypertrophy in some areas. In one study, the same CRS that induced apical dendritic atrophy in the mPFC, induced apical dendritic hypertrophy in the lateral orbitofrontal cortex (OFC) [61]. The dendrite change in mPFC, but not OFC was accompanied by a corresponding decrease in function. CRS also increases dendritic arborization in the principal neurons of the basoalteral amygdala and this hypertrophy persists following stress termination [114, 115]. These findings have suggested that increased synaptic efficacy in the amygdala could facilitate the development of increased anxiety-like behavior resulting from stress exposure [113]. Furthermore, CRS induces hypertrophy in the BNST, which is a downstream target of the BLA that participates in stress responses [27, 114].

Another study showed divergent effects of CUS on neuronal structure in associative vs. sensorimotor corticostriatal circuits and that these effects were related to behavioral consequences of the CUS. In this study, CUS resulted in apical dendritic atrophy of layer II/III pyramidal cells in mPFC along with evidence for dendritic atrophy in the dorsal medial striatum that receives input from mPFC [20]. The CUS caused hypertrophy of a sensorimotor striatal circuit that was accompanied by a corresponding shift in behavior away from goal-directed (mPFC-dorsomedial striatum-dependent) toward habitual strategies (sensorimotor cortex-dorsolateral striatum-dependent) [20]. Circuit specificity of stress effects has also been demonstrated within the mPFC; a subpopulation of pyramidal cells in the infralimbic region that project to the BLA, does not show the expected dendritic retraction in response to CRS exposure [101].

Chronic stress alters the number and function of spine synapses

Since spines are integral to neuronal function, it is obviously important to assess the effects of chronic stress on these synaptic structures. As discussed below, the density, morphology, and function of spine synapses are altered in chronic stress models of depression.

Hippocampus

The reported effects of chronic stress on dendritic spines in the hippocampus vary. Stress exposure has been shown to result in spine loss in hippocampus CA3 cells [69, 89, 92, 98,

106, 107], although increased or no change in spine density has also been reported [72, 108]. Stress-induced spine loss has been shown in CA1 (and CA3) along with impaired synaptic transmission and depressive behaviors [49, 92]. Decreased spine densities in CA1 neurons has been associated with depression-like behaviors in a light-induced depression model, in the absence of spine changes in CA3 or dendritic changes in CA3 or CA1 [4]. Chronic corticosterone administration, which results in a depressive phenotype, reduces spine density in CA1 and both the spine and behavioral deficits recover with chronic fluoxetine administration [35, 116]. These changes occurred mainly in thin and stubby spines [116]. Given the differential incidence of depression in women it is notable that spine morphologic changes in response to CRS are opposite in male and female rats [103]. Further studies are needed to determine if sex steroid state, notably fluctuations during the menstrual cycle, postpartum, or postmenopausal lead to increased vulnerability to stress and loss of synapses.

Developmental models of stress exposure have been examined to replicate some of the changes in brain circuitry and subsequently in behavior that may be related to risk for pathology in adults. Studies of early-life stress suggest sexually dimorphic outcomes of developmental stress exposure and temporal dependence. CA1 and CA3 spine densities are sensitive to prenatal restraint stress [73]. In addition, CA1 spine density is negatively correlated with spatial memory in a study of chronic stress and estradiol treatment in female rats, suggesting that experimental influences on spines in CA1 were more important to spatial ability than CA3 dendritic arbor regulation [17].

Medial prefrontal cortex: Layer II/III cells

In the PFC, studies of spine density suggest a loss of synaptic efficacy in response to chronic stress. Layer II/III pyramidal neurons in the prelimbic and anterior cingulate regions show reduced spine density following 21 day CRS [95, 96]. CRS-induced reduced spine density was shown to be partially reversed by a 21 day stress-free recovery period [7].

Similar to the effects of chronic stress on dendrites that are preferential for apical vs. basal, stress-induced reductions in spine density are also more pronounced in apical dendrites and are most prominent distally. Limited spine reductions however, have been shown on basal dendrites following chronic stress [78, 96]. Analysis of spine morphology has shown decreased spine volume and surface area along with an overall shift in the spine population from large to small spines in layer II/III cells after CRS [96]. A CRS-induced loss of thin and stubby spines has also been shown [7]. CUS also results in a preferential loss of large spines in layer II/III cells [6, 78, 93]. Vulnerability of mushroom spines to CUS was demonstrated to occur selectively in a subpopulation of prelimbic cells that project to the bed nuclei of the stria terminalis [93]. The association of this effect with decreased Fos expression and enhanced HPA activation suggested that deficits in this afferent pathway from the prelimbic PFC could be important in regulations of the HPA axis after stress.

A shift in spine characteristics from large to small spines, suggests that stress may impair the ability of spines to mature to a stable state. Functionally, a loss of mature stable spines could translate into a loss in synaptic efficacy. A stress-induced reduction in the population of large-diameter mushroom spines has also been demonstrated in a series of studies in layer V

pyramidal cells and this is associated with reduced levels of synaptic proteins and functional deficits as described below [60].

Medial prefrontal cortex: Layer V cells

Liu and Aghajanian have directly investigated the functional correlates of stress-induced dendritic atrophy and spine loss in layer V pyramidal cells in the PFC. Using a combination of whole-cell recording and high-resolution spine imaging they have shown that stress-induced apical dendritic atrophy accompanied by spine loss correlates with decreased physiologic responses to apically targeted excitatory inputs in the same cells [62]. Further studies have shown that stress-induced spine loss and reduced synaptic currents occur in association with reductions in levels of synaptic proteins and increased depression-like behavior in a rodent model [60]. These studies provide compelling support for a role of synaptic changes in depression-related function by demonstrating that rapid-acting antidepressants increased spine diameter/number and reverse stress-induced deficits in synaptic number, function and behavior [60, 63, 111]. The relationship of larger diameter spine populations to enhanced synaptic and behavioral function in these studies emphasizes the relationship of spine morphology to synaptic efficacy and the plastic nature of the changes induced by stress and antidepressants and their functional importance.

Layer V pyramidal cells in the infralimbic region also show apical dendritic retraction and spine loss following CRS, along with impaired D1 receptor facilitated synaptic plasticity [33]. This study found that spine density per layer remained constant despite dendritic remodeling in response to stress exposure, prompting the authors to conclude that spine loss accompanied dendritic retraction after stress and that spine growth co-occurred along with proximal dendritic expansion following a recovery period.

Early life stress models also have shown alterations in dendritic spines in mPFC. Prenatal restraint stress has been shown to exert sexually dimorphic changes in spine densities in mPFC [81–83]. Postnatal stress (maternal separation) has been shown to decrease basal dendritic spine densities in PFC pyramidal neurons in layers II/III and V [8, 34]. Maternal separation stress was also shown to result in basal dendritic atrophy and reduced basal and apical dendritic spine densities in layer II/III [12].

Other brain regions: BLA and NAc

Stress-induced increases in spine density are reliably demonstrated in amygdala. Chronic stress exposure increases spine density in spiny pyramidal neurons of the BLA and given the role of the BLA in anxiety and fear responses, this may contribute along with stress-induced dendritic hypertrophy to affective dysregulation in response to chronic stress [113, 114]. Experiments showed that spine formation in the BLA could be dissociated from dendritic remodeling [79]. An increase in spine density in BLA pyramidal neurons was also seen after chronic corticosterone exposure [35].

The nucleus NAc is another brain region that shows increases in spine densities following chronic stress exposure. NAc medium spiny neurons receive afferents from dopamine neurons of the mesolimbic dopamine pathway that contributes to the regulation of motivation and reward, as well as social interaction. Many of the studies of NAc use social

defeat stress (SDS), a model of depression that produces social avoidance and anhedonia in mice. SDS was shown to result in increased spine density in NAc medium spiny neurons, due to increased numbers of stubby spines with smaller postsynaptic densities [13]. The frequency of mini excitatory postsynaptic currents (EPSCs) was also increased in mice susceptible to chronic SDS suggesting a greater number of functional glutamate synapses. These changes were correlated with social avoidance behavior [13]. These authors also showed that the social avoidance phenotype and the formation of new stubby spines depended on the inhibitor of kappaB kinase (IkK)-nuclear factor kappaB (NFkB) pathway and that constitutively active IkK was sufficient to promote immature spine synapse formation in mice vulnerable to SDS [14].

Mechanisms underlying dendrite and spine deficits caused by chronic stress

In addition to providing fundamental information regarding the regulation spine synapses, characterization of the signaling pathways underlying the loss of spines in response to chronic stress could lead to novel targets for drug development. As discussed above, there is evidence that the effects of stress are mediated in part by elevated levels of adrenal glucocorticoids as many of these effects can be replicated by corticosterone administration. Here we will focus on neurotrophic factor signaling mechanisms involved in regulation of spines in the hippocampus and mPFC. In addition to these mechanisms, there is also evidence for transcriptional pathways that contribute to neuronal atrophy in the PFC [47]. The mechanisms underlying dendrite and spine alterations in other regions (i.e., BLA and OFC) have not been examined in detail and require further study.

Role of brain derived neurotrophic factor (BDNF)

Acute and chronic stress decrease the expression of BDNF in the hippocampus and mPFC raising the possibility that this neurotrophic factor contributes to the dendrite and spine deficits observed in these brain regions [24]. Direct evidence for this hypothesis is provided by studies in BDNF mutant mice. Studies have examined several different lines of mice, and one of the first available was a constitutive deletion mutant line. However, homozygous deletion mutants are lethal, demonstrating the importance of this neurotrophic factor, so heterozygous mutants, $BDNF^{+/-}$, have been examined. The $BDNF^{+/-}$ mice have reduced length and branching of apical dendrites of CA3 pyramidal neurons in the hippocampus, similar to what is observed with stress [70]. Moreover, exposure to stress causes no further loss of dendrites, resulting in occlusion of the stress response, suggesting that the stress response occurs via a reduction in BDNF [70]. Spine density and morphology were not examined in this study.

Another BDNF mutant line that is relevant to clinical studies is a knock-in of a small nucleotide polymorphism (SNP), referred to as BDNF Val66Met that is carried by approximately 25 percent of humans [57]. This is a functional SNP that reduces the processing of pro-BDNF to mature BDNF decreases BDNF transport to terminals, and thereby blocks activity dependent release of BDNF. The BDNF Met allele has been associated with reduced hippocampal volume and executive function in humans [28, 29] and

increased risk for depression in patients exposed to early life stress or trauma [32, 45, 54]. BDNF Met knock-in mice display a reduction in the number and length of branch points of CA3 pyramidal neurons in the hippocampus (spine density was not examined) [57]. In addition, these mice show reduced dendrite length in the layers II/III [120, 121] and V [64] pyramidal neurons in the mPFC, as well as decreased number and function of spines [64]. These dendritic and spine changes area also associated with increased anxiety and depression-like behaviors in rodent models [64, 120].

Role of the mTORC1 signaling pathway

There are several downstream signaling cascades that mediate the actions of BDNF, but one that has been examined with regard to stress and spine density is the mechanistic target of rapamycin complex 1 (mTORC1). The mTORC1 pathway regulates activity dependent protein synthesis and is required for protein synthesis dependent synaptic plasticity [41, 56]. We have found that CUS decreases levels of the signaling components of this pathway in the PFC, including decreased levels of the phosphorylated and activated levels of mTOR and ribosomal p70S6 kinase (S6K) [86]. Moreover, reduced mTORC1 signaling is associated with decreased expression of synaptic proteins and decreased number and function of spine synapses [59, 86].

The phosphorylation and function of mTORC1 signaling is regulated by a number of upstream signaling pathways, notably strong inhibition by the tuberous sclerosis complex (TSC1 and TSC2). The TSC1/2 complex is stabilized by another protein, REDD1 (regulated in DNA damage and repair 1) that is induced by cellular stress and glucocorticoid. We found that chronic stress increases REDD1 expression and that viral expression of REDD1 was sufficient to decrease mTORC1 signaling, decrease spine density in layer V cells in the PFC, and to produce depression like behaviors in rodent models [86]. Moreover, mice with a deletion of REDD1 are resilient to chronic stress, including the deficits in spine density and behavior caused by stress exposure. Finally, the relevance of REDD1 to atrophy of PFC in humans was examined in postmortem tissue from depressed subjects. The results demonstrate that levels of REDD1 are significantly increased in depressed subjects relative to psychiatric controls matched for age, sex, and race [86]. These studies are consistent with the hypothesis that stressful life events lead to increased expression of REDD1 that inhibits mTORC1 signaling and causes loss of spines in the PFC.

Antidepressant effects on spines and synaptic markers

Alterations of dendritic structure, spine number/morphology and synaptic proteins caused by stress and association of these changes with deficits in synaptic function and depression related behavior has focused significant research attention on synaptic mechanisms and synaptogenesis as critical targets of antidepressant treatment. These studies demonstrate differential effects of typical antidepressants that increase synaptic monoamines and new rapid acting agents that influence glutamatergic neurotransmission.

Monoaminergic antidepressants

The monoaminergic antidepressants increase the amount of serotonin and/or norepinephrine in the synapse by blocking the reuptake or breakdown of these neurotransmitters. These agents are modestly effective, producing a therapeutic response in approximately one third of patients after the first agent tested and up to two thirds after multiple drug trials [109]. Notably, there is a therapeutic time lag of several weeks with these agents, which can extend to many months or even years until an effective agent is identified. In preclinical studies, these agents do not appear to have a major impact on spine number when administered to naïve animals but there are reports that monoaminergic drugs are capable of blocking the effects of chronic stress.

Effects of antidepressant agents on dendritic spines have been studied using a CUS model to induce behavioral features of depression [6]. In the CUS model the behavioral deficits were reversible by chronic administration of antidepressant drugs with different primary mechanisms of action (imipramine, fluoxetine, CP 156,526, a type 1 corticotropin releasing hormone receptor antagonist, and SSR 1494515, a type 1b arginine vasopressin receptor antagonist). CUS also produced atrophy of granule cell dendrites and CA3 apical dendritic atrophy in hippocampus along with proximal spine loss. All of the antidepressants tested were effective in reversing these changes. In the PFC, the apical dendritic atrophy in layer II/II pyramidal cells was reversed by the antidepressants tested except for fluoxetine. In the PFC cells, CUS induced spine loss in proximal and distal dendrites was also reversed by the antidepressant treatments. Also in this study, the antidepressants promoted hippocampal neurogenesis, but the neurogenic action was not critical for antidepressant efficacy. Instead, the dendritic and synaptic remodeling were the primary changes associated with behavioral deficits caused by CUS and the improvements resulting from antidepressant treatments. Although fluoxetine alone had no effect, another study found that chronic fluoxetine administration increases spine density in retrosplenial granular cortex [1]. This study also reported that chronic fluoxetine treatment that produced antidepressant behavioral responses in rodent models of depression and anxiety, resulted in up-regulation of N-methyl-D-aspartate (NMDA) receptor subunit NR2A, and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor subunits GluR1 and 2 in forebrain [1]. GluR2 and NR2A were increased in synaptic membranes and postsynaptic densities suggesting synaptic localization of these changes. AMPA receptors are important to synapse maturation and the number and activity of AMPA receptors at the synapse is an important determinant of synaptic strength [19, 102]. The association of the altered subunit levels with increased mushroom spines regionally in the Ampeuro study [1], suggests stabilization of synaptic connections resulted from chronic fluoxetine.

The effect of chronic fluoxetine on synaptic proteins in the CA1 region of hippocampus has also been examined. Chronic fluoxetine was shown to increase expression of phospho-synapsin, PSD-95 and synaptic GluR1 in a rat model of reduced synapse density [85]. PSD-95 is a scaffolding protein that controls activity-dependent AMPA receptor incorporation in spines during experience-dependent synaptic strengthening and is considered to reflect synapse number and/or stabilization [25, 26]. The PSD-95 and associated GluR1 increases could suggest a synaptic maturation effect of chronic fluoxetine.

This study also used a mutant mouse model to implicate involvement of BDNF and signaling at its receptor TrkB in the effect of fluoxetine on PSD-95.

The influence of a norepinephrine reuptake inhibitor, desipramine has also been examined in a learned helplessness model of depression. In this model, rats are exposed to inescapable foot shock and then subsequently are tested for their ability to escape a stressful event. Animals exposed to inescapable stress develop “helpless” behavior and show a dramatic decrease in escape behavior in response to a subsequent foot shock test. Exposure to this paradigm causes loss of synapses, analyzed in this study by electron microscopy, in CA1 and CA3 pyramidal and dentate gyrus granule neurons in the hippocampus [36]. Sub-chronic administration of desipramine (6 days) reversed the synaptic deficits as well as behavioral helplessness in this model.

Novel, rapid acting antidepressants: ketamine and scopolamine

Ketamine—Recent clinical studies have demonstrated that it is possible to achieve a rapid and efficacious antidepressant response in depressed patients. Most notable is the NMDA receptor antagonist ketamine, which produces a rapid antidepressant response even in treatment resistant depressed patients [5, 55, 123]. Ketamine is a nonselective NMDA receptor antagonist that when given at high doses produces sedation and is used as a dissociative anesthetic. At low doses it produces euphoria but also psychotomimetic effects, and has been used to study the neurobiology of schizophrenia [55]. In clinical studies to examine the antidepressant actions of ketamine, a single dose produces a brief dissociative and/or psychotomimetic effect that quickly dissipates within 60 min after administration. This is followed by a dramatic and significant improvement in depression ratings approximately 2 to 4 hrs. later that is sustained for approximately 7 to 10 days [55]. The discover that ketamine produces a rapid and efficacious antidepressant response by blocking a target, NMDA receptors, represents the most significant advance in drug development for depression in over 50 years.

We have examined the mechanisms, including spine synapse alterations that underlie the rapid actions of ketamine. These studies demonstrate that a single, low dose of ketamine increases the number of spine synapses in layer V neurons of the mPFC, and that the increase in spine number is accompanied by increased function measured by increased serotonin-induced ECPCs [59]. The spine changes are also accompanied by antidepressant behavioral responses in rodent models [59]. These synaptic and behavioral actions are observed with low doses of ketamine (3 to 10 mg/kg) that are non-sedating [59]. These studies also examine the mechanisms underlying the actions of ketamine, and demonstrate an up-regulation of the mTORC1 signaling pathway and increased levels of synaptic proteins in the PFC, including GluR1 and PSD95. A requirement for mTORC1 signaling has also been examined using the selective mTORC1 inhibitor rapamycin. Infusion of rapamycin into the lateral ventricle blocks the increase in spine synapses and the antidepressant behavioral actions of ketamine in rodents [59]. The involvement of the mPFC was further examined by direct infusions of rapamycin locally into this region, which completely blocked the behavioral actions of ketamine [59].

In addition to the studies, the influence of ketamine in a CUS model of depression has also been examined [60]. This is a critical test of the ability of ketamine to produce rapid antidepressant responses in rodents, as the actions of typical monoaminergic antidepressant require chronic administration. Three weeks exposure to CUS produced the expected decrease in sucrose preference, a measure of anhedonia, as well as loss of spine synapses in layer V pyramidal neurons in the mPFC. These behavioral and synaptic deficits were rapidly and completely reversed by a single dose of ketamine [60]. Moreover, the ability of ketamine to reverse the CUS induced deficits was blocked by infusions of rapamycin into the lateral ventricles. Together these studies demonstrate that ketamine rapidly reverses the spine synapse and behavioral deficits caused by CUS and that these effects are dependent on activation of the mTORC1 signaling pathway.

Interestingly, further studies have demonstrated a role for BDNF in the synaptic and behavioral actions of ketamine. Initial studies demonstrated that the antidepressant behavioral actions of ketamine were blocked in conditional BDNF deletion mutant mice [3], and confirmed by studies demonstrating that infusion of a function blocking anti-BDNF antibody into the mPFC blocks the behavioral actions of ketamine [58]. In addition, we have reported that the induction of spine synapses as well as antidepressant behavioral responses are blocked in BDNF Met allele knock in mice [64]. Blockade in the BDNF Met mice, which blocks activity dependent release of BDNF, as well as by the function-blocking antibody indicates that BDNF release and activity at extracellular receptors is required.

Scopolamine—Recent clinical studies have demonstrated that the muscarinic receptor antagonist scopolamine also produces rapid antidepressant responses in depressed patients [21, 30, 31]. A single low dose of scopolamine produces significant antidepressant effects at the first time of assessment 3 days later, and there are anecdotal reports of improvement as early as 24 hours after dosing. Because of the rapid actions similar to ketamine, we have also examined the influence of scopolamine on spine synapses and mTORC1 signaling in the mPFC. The results demonstrate that a single low dose of scopolamine increases the number and function of spine synapse in layer V pyramidal neurons and increases mTORC1 signaling in the PFC [111]. We also found that infusion of rapamycin blocked the behavioral effects of scopolamine, demonstrating a role for mTORC1 signaling.

The cellular mechanisms underlying the actions of ketamine and scopolamine are not obvious, but there is evidence that both NMDA and muscarinic receptor antagonists cause a burst of glutamate transmission. Earlier studies have shown that ketamine increases extracellular glutamate in the mPFC [80] and more recent preliminary studies demonstrate that a scopolamine causes a similar increase in levels of extracellular glutamate in this region [111]. This burst of glutamate is then thought to produce an activity dependent increase in spine synapse formation [23]. The cellular mechanisms underlying this paradoxical increase in glutamate by both NMDA and muscarinic receptor is thought to result from disinhibition of GABAergic interneurons that control the firing of glutamate neurons. This is supported by studies demonstrating that ketamine blocks the firing of GABA neurons in vivo [44]. Studies are currently being conducted to selectively delete NMDA and muscarinic receptor subtypes from GABAergic neurons to directly test this hypothesis.

Summary and Future Directions

Chronic stress and depression are associated with alterations of neuronal processes, including spine synapses, in a region dependent manner, resulting in disrupted connectivity of brain circuitry that contributes to depressive symptoms [75, 99]. Conversely, there is evidence that typical monoaminergic agents are capable of reversing the synaptic and behavioral deficits caused by stress, but that this requires chronic administration. Importantly, novel antidepressants such as the NMDA receptor antagonist ketamine cause a fast induction of spine synapses in the PFC and rapidly reverse the synaptic and behavioral deficits caused by chronic stress. Studies are needed to further characterize the molecular and cellular mechanisms that underlie the altered number and function of spine synapses in stress related illnesses. This will contribute to the development of novel fast acting antidepressant agents with fewer side effects, as well as treatment regimens that can sustain and stabilize new spine synapses required for proper connectivity and function of mood and emotion.

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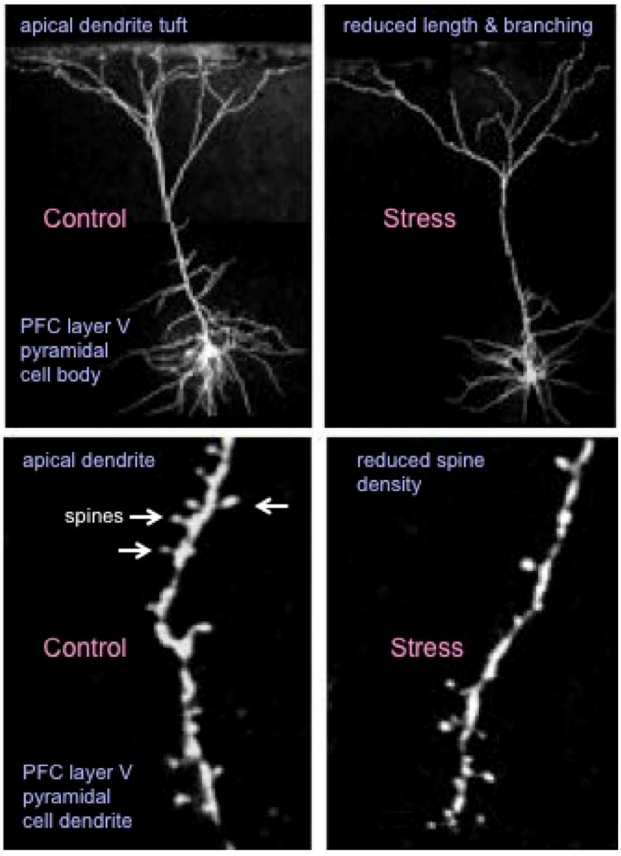

Figure 1.

Chronic stress causes atrophy of layer V pyramidal neurons in the medial PFC. Shown is the influence of repeated restraint stress (30 min per day for 7 d) on layer V pyramidal neurons in the medial PFC. The upper panels demonstrate that effects of stress on the length and branching of apical dendrites, and the lower panels show the effects of stress on the density of spines on apical dendrites of labeled layer V neurons. Neurobiotin labeled neurons were visualized by two-photon laser scanning miscrocopy (see Liu and Aghajanian, 2008).

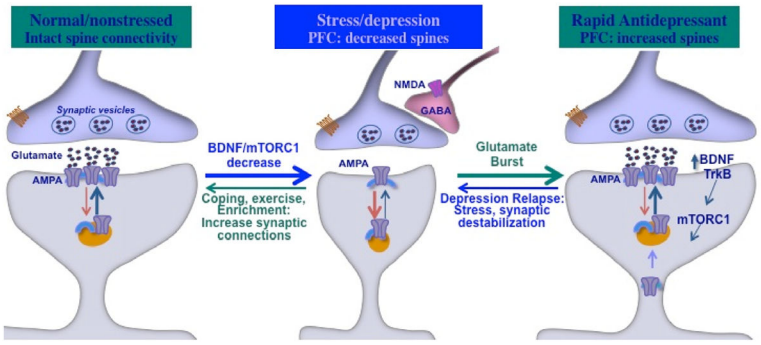

Figure 2.

Schematic of the effects of stress/depression on spine synapses and reversal by rapid acting antidepressants. Under normal/nonstressed conditions spine synapse connections are intact and provide control over mood, emotion, and cognition. Chronic stress or depression leads to decreased levels of BDNF and downstream mTORC1 signaling, which contributes to decreased number and function of spine synapses in layer V pyramidal neurons of the medial PFC. Rapid acting antidepressant such as ketamine rapidly reverse the spine synapse deficits caused by stress via a burst of glutamate, which is thought to result from disinhibition of GABAergic interneurons that control glutamate transmission. This increase in glutamate-AMPA leads to activity dependent release of BDNF-TrkB and stimulation of mTORC1 signaling, resulting in increased synthesis of synaptic proteins required for new spine formation. The antidepressant response to a single dose of ketamine persists for approximately 7 day in humans and rodents before relapse. The new spines induced by ketamine also remain for a similar length of time, and the loss of spines could be related to relapse and reversal of antidepressant responses.