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Cell Atrophy and Loss in Depression: Reversal by Antidepressant Treatment

Mounira Banasr, **Jason M. Dwyer**, and **Ronald S. Duman**
Departments of Psychiatry and Neurobiology Yale University School of Medicine 34 Park Street, New Haven, CT 06508

Abstract

Depression is associated with structural alterations in limbic brain regions that control emotion and mood. Studies of chronic stress in animal models and postmortem tissue from depressed subjects demonstrate that these structural alterations result from atrophy and loss of neurons and glial cells. These findings indicate that depression and stress-related mood disorders can be considered mild neurodegenerative disorders. Importantly, there is evidence that these structural alterations can be blocked or even reversed by elimination of stress and by antidepressant treatments. A major focus of current investigations is to characterize the molecular signaling pathways and factors that underlie these effects of stress, depression, and antidepressant treatment. Recent advances in this research area are discussed and potential novel targets for antidepressant development are highlighted.

Introduction

Depression is a heterogeneous, widespread illness affecting approximately 17 percent of the population, exacting devastating personal and economic consequences [1]. Brain imaging studies demonstrate that depression, and other mood disorders are associated with structural alterations, including decreased volume of brain regions that control emotion and mood and that contribute to stress-related psychiatric illnesses [2]. Studies of postmortem tissue from depressed subjects and animal models further detail alterations at the cellular level, including atrophy of dendrite processes and loss of neurons as well as glial elements [2,3]. While the exact mechanisms underlying these structural alterations have not be determined, recent advances discussed in this review are beginning to elucidate the complex signaling pathways that underlie these cellular alterations and that contribute to disruption of critical brain circuits.

Although cell atrophy and loss would appear to be difficult to repair, there is evidence that these deficits can be reversed or blocked by eliminating stress and treating depression [2,3]. However, currently available antidepressants have significant limitations, including slow onset of action (several weeks to months) and low rates of response or even treatment resistance (30 percent of patients respond to first drug prescribed and up to 65 percent after multiple drug trials) [4*]. The mechanisms underlying the actions of these agents, and

Address correspondence to: Ronald S. Duman, Tel: 203-974-7726, Fax: 203-974-7724, ronald.duman@yale.edu.

evidence for novel fast acting antidepressants that rapidly increase neuronal connections and block the effects of chronic stress are discussed.

Depression and Stress: Neuronal Atrophy and Cell Loss

The cellular alterations associated with stress and depression occur at several different levels and in different neuronal and glial cell populations, and are briefly described.

Neuronal Atrophy

Neuronal atrophy has been documented in rodent chronic stress models and clinical postmortem studies of depressed subjects, most notably in the PFC (prefrontal cortex) and the hippocampus [5]. In postmortem PFC and anterior cingulate cortex of depressed subjects there are reductions of dendritic arborization and spine density, atrophy of neurons, as well as loss of discrete populations of cells [6]. Similarly chronic stress causes loss of spines, the primary points of neurotransmission and connection between neurons, and retraction of apical dendrites of pyramidal neurons of the rat medial PFC [7–10]. These changes affect both the distal and proximal segments of the apical tuft and can be related to reduced synapse-associated proteins such as synapsin I, GluR1 (glutamate receptor 1) and PSD95 (post-synaptic density protein 95 [11**]. Similar effects have been observed in CA3 pyramidal neurons of the hippocampus in rodent models, with less evidence from human studies [12]). Expression of other cytoarchitectural and synaptic genes, identified by genome-wide association studies, are also altered in response to stress and in human postmortem studies [13,14].

Neuronal and Glial Loss

In addition to neuronal atrophy, there is evidence for a reduction in the number of glia and neurons in response to stress and in depressed subjects. Most notable is the loss of non-neuronal cell populations, including astrocytes and oligodendrocytes, cells that play a critical role in the regulation of synaptic function. Postmortem studies report decreased glial density in the PFC and cingulate cortex of depressed subjects [6]. Similar decreases have been reported in stressed animals in both the PFC and hippocampus [15,16]. Toxin-induced loss of glia in the medial PFC is sufficient to cause depressive-like behaviors in rodents [16], demonstrating that glial function is required for normal behavioral responses. In addition to the dysregulation of synaptic function, glial loss could underlie, or contribute to the atrophy of neurons caused by stress and depression. Further studies, such as genetic approaches to selectively ablate subpopulations of astrocytes and oligodendrocytes, are required to test this hypothesis.

Recent studies also report a reduction in the number of GABAergic interneurons in the PFC of depressed patients [17**,18*]. These interneurons provide critical tonic, inhibitory control of the firing of glutamatergic excitatory neurons. Evidence of functional disruption of GABA transmission is provided by magnetic resonance spectroscopy studies, demonstrating decreased GABA levels in depressed patients [19,20]. The vulnerability of GABAergic interneurons could be related to the higher activity levels of these tonically firing neurons, possibly resulting in increased susceptibility to excitoxic cell death, which could also contribute to damage of other neurons.

Decreased Adult Neurogenesis and Gliogenesis

Reductions in cell numbers could also result from decreased birth of new neurons and glia in the adult brain. The hippocampus is one of the few neurogenic zones in the adult brain and stress decreases the birth of new neurons [2,21]. Gliogenesis also occurs throughout the brain and is similarly decreased by exposure to acute of chronic stress [22]. These findings

suggest a role for reduced neurogenesis in depression, but ablation of neurogenesis by irradiation or genetic mutation does not produce depressive behaviors [21,23], indicating that loss of new neurons alone is insufficient to account for the effects of stress. However, a recent study has reported that ablation of neurogenesis increases the susceptibility to stress, so that when animals with reduced neurogenesis are exposed to stress they now display depressive behavior [24]. In addition, antidepressants increase neurogenesis, and new cell birth is necessary for the behavioral actions of these agents in selected rodent models [22]. Antidepressant-induction of cell proliferation has also been reported in postmortem hippocampus of patients treated with antidepressants at the time of death, demonstrating the potential clinical relevance for induction of neurogenesis [25*].

Mechanisms Underlying Cell Atrophy and Loss

Identification of the mechanisms underlying cell atrophy and loss has been an area of key interest, although still not completely defined. There is also considerable overlap and interactions between multiple signaling pathways, that when combined with genetic and environmental factors, lead to increased vulnerability to cell damage and mood disorders. These multiple factors most likely explain individual susceptibility, or why stress can cause depression in certain individuals, while others are resilient.

Glutamate Excitotoxicity

Excessive levels of glutamate, the major excitatory neurotransmitter in the brain, is one potential mechanism that could contribute to neuronal atrophy and loss in response to stress and depression [26]. Stress or glucocorticoids increase the release, as well as decrease the clearance of glutamate, the latter due in part to loss of glia that are responsible for removal of synaptic glutamate [27–30]. The resulting excess glutamate could contribute to cell damage and even death in extreme cases, particularly when combined with other genetic or environmental factors that reduce neuroprotective mechanisms (e.g., neurotrophic factor polymorphisms, see below) or increase neuronal vulnerability (e.g., exposure to hypoxia, ischemia, or hypoglycemia) [12].

Decreased Neurotrophic Factor Expression

Another major factor contributing to the effects of stress and depression is reduction of neurotrophic factor expression and signaling. Stress and depression are associated with decreased expression of several neurotrophic/growth factors in the brain, but most work has focused on BDNF (brain derived neurotrophic factor) [31–33]. Mutant mouse studies demonstrate that heterozygous deletion of BDNF causes atrophy of neurons in hippocampus and PFC, similar to the effects of chronic stress [35*]. A common, functional BDNF polymorphism, Val66Met, occurs in ~30% of humans and blocks the processing and activity-dependent release of BDNF [35*]. The BDNF Met allele is associated with decreased hippocampal volume and cognitive deficits in humans [34]. BDNF Met knock in mice also show atrophy of neurons in the hippocampus and PFC [34,36*]. These studies demonstrate that reduced BDNF expression or release is sufficient to reproduce the atrophy of neurons that is caused by chronic stress. Although BDNF mutation is not sufficient to produce a depressive phenotype, these mice display an increased vulnerability to stress [32,37*]. Similarly, subjects expressing the Met allele and who are exposed to stress or trauma are at risk for higher rates of mood disorders and cognitive deficits [38–40].

Apoptotic Pathways

Disruption of neurotrophic factor expression and signaling could contribute to decreased neuroprotection and increased vulnerability to excitoxicity, resulting in activation of apoptotic pathways [5]. Chronic stress up-regulates the expression of pro-apoptotic

mitochondrial proteins (e.g., Bax) and down-regulates anti-apoptotic factors (i.e., Bcl2, BAG-1) [41–46]. The balance between Bcl2 and Bax is shifted toward cell death in chronic stress conditions while antidepressant treatment has the opposite effect [41,44]. Chronic stress is associated with increased levels of caspase-3 in the cerebral cortex [45], and in the hippocampus with increased TUNEL-positive neurons, an indication of cell death [47]. Enhancement of Bcl2 function, via inhibition of the pro-apoptotic factor Bid (BH3-interacting domain death agonist protein), produces antidepressant-like effects in several behavioral models, similar to known antidepressant treatments [48]. The question remains whether these apoptotic pathways are involved in glial and/or GABAergic cell loss that have been reported.

Antidepressant-induced cell growth and survival

Although stress and depression result in cell atrophy and loss, these effects are reversible upon elimination of stress or with antidepressant treatment. Different classes of antidepressants, including 5-HT and norepinephrine selective reuptake inhibitors, block or reverse some of the effects of stress, including reductions in spine and dendrite number and length, neurogenesis, gliogenesis, and GABAergic cell loss [11**,15,49–51*]. A few of the more prominent signaling pathways underlying these effects are discussed in this section.

Increased Neurotrophic Factor Expression

Studies of antidepressant regulation of neurotrophic factor expression and signaling, combined with evidence of stress-induced cell atrophy and loss, have lead to a neurotrophic hypothesis of depression and treatment response [22,52–54]. The focus has been on BDNF, although there is also evidence that antidepressants increase other factors including VEGF (vascular endothelial growth factor), FGF2 (fibroblast growth factor 2) and IGF-1 (insulin growth factor-1) [32,54,55].

These findings suggest that antidepressant treatment should increase dendrite growth and reverse the atrophy caused by stress, although evidence for such effects is limited [56,57]. In contrast, all major classes of antidepressants increase adult neurogenesis in the hippocampus, as well as gliogenesis (i.e., oligodendrocytes) in the PFC [22,32]. BDNF-TrkB signaling is involved in birth and survival of new neurons in the adult hippocampus [31,58]. Importantly, behavioral studies demonstrate that BDNF signaling is necessary and sufficient for the actions of antidepressants in rodent models of depression [31,33]. Together these studies indicate that BDNF is a key factor in the actions of antidepressant, and that these effects are mediated, in part, by induction of neuronal and glial cell birth and possibly more subtle effects on spine and dendrite complexity. Recent studies demonstrate that VEGF signaling is also necessary and sufficient for the neurogenic and behavioral actions of antidepressants [59,60], indicating that there are complex, overlapping actions of these growth factor systems.

Growth Factor Signaling: MAPK and MKP-1

Growth factor signaling cascades are known to have pleiotrophic effects, including, cell growth, survival, and neuroplasticity, and have been implicated in the effects of stress and antidepressant treatment. BDNF activates TrkB (tropomysin related kinase B), which stimulates several signaling cascades, including the MAPK (mitogen-activated protein kinase) and PI3K (phosphatidylinositol 3-kinase)-Akt pathways. Behavioral studies demonstrate that MAPK is required for the actions of antidepressants [37], and postmortem studies report decreased levels of MAPK signaling proteins in suicide depressed subjects [61,62]. Further evidence of disrupted MAPK signaling is demonstrated by a report that MKP-1 (MAPK phosphatase-1), a protein phosphatase that negatively regulates the MAPK

pathway, is increased in the hippocampus of depressed subjects and by chronic stress in rodents [63**]. Functional studies demonstrate that over expression of MKP-1 in the hippocampus produces depressive behavior in rodent models, and conversely that mice with deletion of MKP-1 are resilient to stress [63**]. Together these studies indicate that decreased MAPK function contributes to the pathophysiology of depression, and that enhanced MAPK signaling (e.g., via blockade of MKP-1) produces an antidepressant response and resilience to stress.

Regulation of Wnt-GSK3 Signaling

Wnt ligands signal through one of a family of frizzled (Fz) receptor subtypes, leading to one of several intracellular pathways, including the phosphorylation and inhibition of GSK3 (glycogen synthase kinase-3) and induction of β-catenin. GSK3 can also be phosphorylated and inactivated by Akt. Evidence for Wnt-GSK3 in the actions of antidepressants has come from several lines of research. First, the discovery that GSK3 is a key target of the mood stabilizer lithium, and subsequent studies that specific inhibitors of GSK3 have antidepressant behavioral actions [64,65]. Second, components of the Wnt-Fz-GSK3 pathway, including certain Wnt and Fz receptor subtypes, as well as β-catenin are up-regulated by different classes of antidepressant [66]. Conversely, there is evidence of decreased expression of Wnt signaling in PFC of depressed subjects [67]. Finally, hippocampal over expression of Wnt2, an upstream regulator of GSK3, or down-regulation of GSK3 induces antidepressant-like effects [66,68].

Wnt signaling plays an important role in the growth and guidance of neurons during development, and Wnt2 over expression stimulates spine formation and dendritic arborization in adult brain [69,70]. Wnt signaling via these pathways could thereby contribute to antidepressant reversal of neuronal atrophy caused by stress, although further studies are required to test this hypothesis.

Novel Rapid-Acting Antidepressant Increases Synapse and Spine Formation

The recent discovery that ketamine, a NMDA (N-Methyl-D-aspartate) receptor antagonist, produces a rapid antidepressant response (~2 hours) in treatment resistant depressed patients offers the promise of addressing the major limitations of current antidepressants (e.g., delayed response and low response rates) [71, 72**, 73**,74*]. Ketamine also produces rapid therapeutic effects for bipolar depression and suicide [75*,76*]. Basic research studies demonstrate that ketamine activates mTOR (mammalian target of rapamycin) signaling and synaptic protein synthesis, resulting in increased synaptogenesis and spine formation [77**]. A single dose of ketamine also rapidly reverses the deficit in spine number and function caused by chronic stress exposure [11**]. These effects of ketamine are dependent on PI3K-Akt and MAPK signaling [77**], as well as BDNF and elongation factor 2 kinase [78**]. The latter study failed to report an effect on mTOR signaling, but this is likely due to the cellular compartment analyzed (i.e., synaptic vs. crude homogenates).

The mTOR signaling pathway is involved in neuronal cell growth and neuroplasticity related to learning and memory [79]. Conversely, disruption of mTOR signaling has been implicated in a variety of neurological and psychiatric disorders [80*]. A recent study reports that levels of mTOR signaling proteins are decreased in PFC of depressed subjects [80*]. Decreased mTOR regulation of translation could contribute to decreased levels of synaptic proteins reported in the same depressed subjects [81,82]. Studies are currently underway to identify the mechanisms underlying the down-regulation of mTOR signaling by stress and in depressed subjects.

Conclusions

Depression and mood disorders are characterized by structural as well as neurochemical alterations in the brain. However, these changes are not permanent, and can be blocked or reversed with behavioral and pharmacological treatments. A major goal is to further define the molecular signaling pathways that underlie these alterations and develop new, improved and safer therapeutic agents. The discovery of the rapid antidepressant actions of ketamine represents a major step toward this goal. However, ketamine is a drug of abuse and can produce neurotoxicity with repeated treatment [83,84]. Characterization of the signaling mechanisms provides new targets for drug development. Some possibilities include positive AMPA receptor potentiating agents that can increase BDNF release, activate mTOR signaling, and increase protein translation and dendrite arborization in cultured cells [85*]. Another possible target is the presynaptic mGlu2/3 receptor, blockade of which increases glutamate-AMPA transmission and downstream signaling. These classes of agents hold promise for rapid and long-lasting antidepressant effects without the side effects of ketamine, although further testing is required to validate these targets.

Highlights

This manuscript highlights recent studies demonstrating cellular and structural changes associated with stress and depression.

A major focus of research efforts has been characterization of the signaling pathways underlying the structural alterations caused by stress and depression.

Evidence that the structural alterations are reversible upon removal of stress or by antidepressant treatment is presented.

Elucidation of the mechanisms underlying the ameliorating effects of antidepressants is discussed.

Recent evidence that fast acting antidepressant agents rapidly reverse the structural deficits caused by chronic stress exposure is presented.

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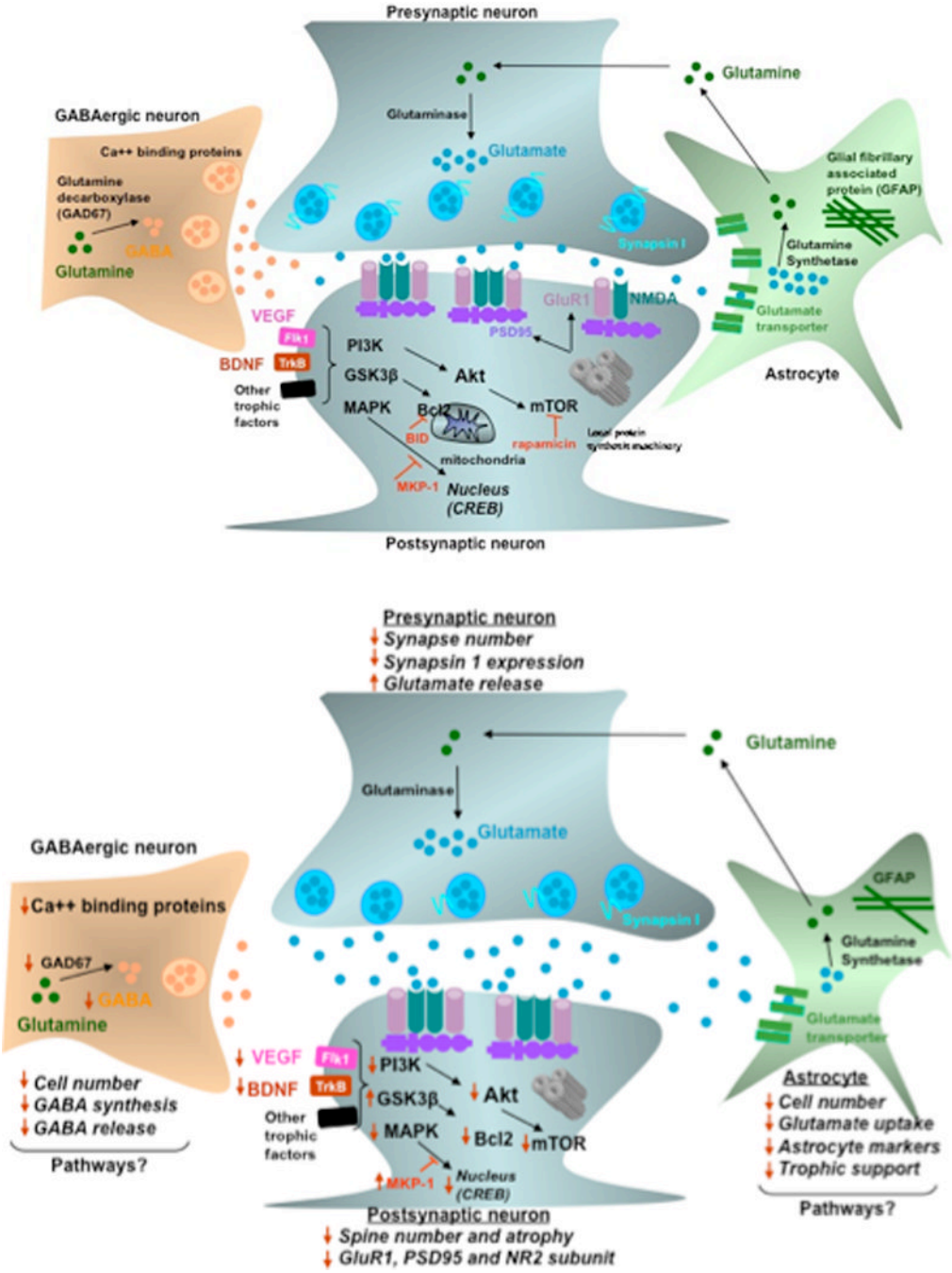

Figure 1. Schematic of a synapse and cellular alterations caused by stress and depression

Shown in the diagram on the top are the major synaptic elements, including pre- and postsynaptic sites, a glial cell (astrocyte), and inhibitory GABAergic input. Glutamate neurotransmission is controlled by signaling pathways that regulate neurotransmitter release at the presynaptic level and ionotropic glutamate receptors and neuroplasticity response pathways at the postsynaptic site. Astrocytes control the reuptake and inactivation of glutamate, as well as cycling of glutamate precursor, glutamine back to the presynaptic element. GABAergic input provides critical tonic inhibition of excitatory neurons. The diagram on the bottom shows the alterations of the cellular components, as well as signaling

pathways, caused by stress and depression in each of these synaptic elements. Arrows indicate the direction of effect up or down. See text for further details.