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Prefrontal Cortex GABAergic Deficits and Circuit Dysfunction in the Pathophysiology and Treatment of Chronic Stress and Depression

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Abstract

Psychiatric diseases, notably major depression, are associated with imbalance of excitatory and inhibitory neurotransmission within the prefrontal cortex (PFC) and related limbic brain circuitry. In many cases these illnesses are precipitated or exacerbated by chronic stress, which also alters excitatory and inhibitory neurotransmitter systems. Notably, exposure to repeated uncontrollable stress causes persistent changes in the synaptic integrity and function of the principal glutamatergic excitatory neurons in the PFC, characterized by neuronal atrophy and loss of synaptic connections. This can lead to dysfunction of the PFC circuitry that is necessary for execution of adaptive behavioral responses. In addition, an emerging literature shows that chronic stress also causes extensive alteration of GABAergic inhibitory circuits in the PFC, leading to the hypothesis that inhibitory neurotransmitter deficits contribute to changes in PFC neuronal excitability and cognitive impairments. Here we review evidence in rodents and human, which point to the mechanisms underlying stress-induced alterations of GABA transmission in the PFC, and its relevance to circuit dysfunction in mood and stress related disorders. These findings suggest that alterations of GABA interneurons and inhibitory neurotransmission play a causal role in the development of stress-related neurobiological illness, and could identify a new line of GABA related therapeutic targets.

Introduction

The prefrontal cortex (PFC) plays a central role in stress adaptation (1, 2), and impaired circuitry and function of PFC subregions are pathological features of many psychiatric illnesses (3, 4). Clinical research has consistently reported that depression and other stress-related illnesses are associated with decreased volume, neuronal atrophy, and altered

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connectivity of PFC (5). These findings in humans are supported by rodent studies demonstrating that chronic stress exposure produces a number of alterations in the PFC, including dendritic atrophy and synapse loss (6–8), as well as loss of neurotrophic factor support. These core features of rodent stress studies have led to the hypothesis that reductions in neurotrophic factor expression result in neuronal and synaptic morphological deficits observed in human subjects (for review see (9)). A related hypothesis suggests that an imbalance in excitatory and inhibitory neurotransmission occurring directly through deficient GABAergic inhibitory signaling in the PFC could account for the outcomes observed in human subjects and rodent models.

In this paper, we review the literature and evidence demonstrating GABA dysfunction in human depression as well as in preclinical rodent stress studies. We then point to recent examples from studies in transgenic mice that shed light on how GABA interneuron subtypes can balance cortical transmission and ultimately shape top down control of depression- and anxiety-like behaviors. Finally, based on recent studies, we propose how intra-cortical GABA inhibition in the PFC can provide important therapeutic targets for the treatment of depression and other psychiatric illness.

GABAergic Neurotransmission in the PFC

The PFC is comprised of a heterogeneous population of neurons, including the glutamatergic principal excitatory neurons and GABAergic inhibitory interneurons. GABAergic interneurons comprise approximately 25% of the neurons within the neocortex (10), and are responsible for inhibitory control via activation of ionotropic $GABA_A$ receptors, which gate chloride entry into neurons (10). GABA transmission is also mediated through metabotropic $GABA_B$ receptors, which are generally thought to be active at higher GABA levels and can act as autoreceptors on presynaptic GABA terminals, as well as provide direct inhibition on principal neurons (11). GABAergic interneurons differ considerably in their morphology, electrophysiological properties, connectivity, and expression of neuropeptides and calcium-binding proteins (10). There are at least 20 different subtypes of cortical GABAergic interneurons that can be differentiated by expression of various molecular markers, such as, parvalbumin (PV), somastostatin (SST), cholecystokinin (CCK), calbindin, calretinin, and vasoactive intestinal peptide (10). Recent advances in genetic manipulation are allowing subtype specific modification of GABAergic interneurons, as well as specific $GABA_A$ receptor subunits that provide insight into the function of GABA mediated inhibition in stress associated disease states. In the following sections, we will discuss how chronic stress and depression cause diverse deficits in GABAergic inhibitory neurotransmission within the PFC, including reduced PFC GABA bioavailability, reduced levels of GABA receptors, and impaired function of specific subtypes of GABA interneurons which potentially contribute to pathological conditions.

PFC GABA Dysfunction in Stress and Depression

Until recently, much of the work on stress, depression, and PFC function has focused on alteration of the principle excitatory glutamatergic neurons. However, accumulating evidence suggests that loss of intra-cortical GABAergic transmission and consequent

imbalances in excitatory and/or inhibitory neurotransmission in the PFC contribute to the etiology of stress-related psychiatric disorders (12). *C*linical studies have reported reduced GABA levels in the frontal cortex of depressed individuals as compared to healthy humans. This includes a preliminary magnetic resonance spectroscopy study reporting that GABA levels are reduced in the occipital cortex of unmedicated depressed individuals (13). Further studies using the same approach demonstrated reduced GABA levels in PFC subregions, which are of greater relevance to depression and other psychiatric illnesses (14), and observed that remission was associated with normalization of GABA levels (15). Similarly, depressed patients that responded to repetitive transcranial magnetic stimulation also demonstrated an increase in GABA levels in the PFC that were absent in non-responders (16). Low plasma GABA levels were also reported to be predictive for the development of other psychiatric illness, such as, posttraumatic stress disorder (PTSD) (17), and maintenance of PTSD with comorbid depression (18).

Although, little is known about the regulation of GABA receptor subunits in psychiatric illness, accumulating evidence suggests that the GABA receptor expression is highly altered in depression. For example, reduced transcripts for $GABA_A$ subunits were observed in Brodmann areas 10 and 11, but not Brodmann 9 in depressed suicide victims (19). Subunit specific hypermethylation of $GABA_A$ promoters in suicide victims previously diagnosed with depression was also observed in Brodmann 10 providing support for transcriptional repression (20). $GABA_A$ subunit upregulation has also been observed most notably within the anterior cingulate region (Brodmann 24) (21, 22), which could represent a compensatory response to the reduced GABAergic tone. Reduced $GABA_A$ receptor binding has also been associated with PTSD (23). Similar studies in the frontal cortex of depressed patients are lacking but reduced $GABA_A$ receptor binding levels were observed in the parahippocampal and lateral temporal regions of depressed individuals (24).

Altered levels of other GABAergic markers have also been reported in depression and other psychiatric disorders. Postmortem brain samples of PFC subregions from unmedicated depressed individuals showed markedly decreased protein and mRNA levels of the GABA synthesizing enzyme glutamic acid decarboxylase (GAD) 67 that was not evident in subjects receiving treatment at the time of death (25). More recently, alterations in levels of specific GABAergic interneuron subtypes have been demonstrated. For example, reductions in the number and size of calbindin-positive neurons were reported in the dlPFC (26), as well as in occipital cortex (27) of depressed subjects. Transcript analyses of postmortem PFC from depressed patients also revealed a reduction in the expression of somastostatin (SST), a neuropeptide that is expressed in a subtype of GABA interneuron that makes up approximately 30% of all cortical GABA interneurons (28). Collectively, the literature summarized indicates that PFC GABAergic transmission is highly dysregulated in stress/depression and related disorders; however, the link between the diminished GABAergic transmission and affective disorders is still unknown.

For the purpose of this focused review, we have concentrated on the PFC and related subregions. However, multiple labs have contributed to the understanding GABAergic regulation in other brain regions in depression and other related disorders (12, 29).

GABA Deficits, PFC and Stress: Insights from Animal Models

Animal models of stress and depression are beginning to elucidate whether and how altered GABA transmission is causally linked to stress-related disorders. The strongest evidence lending support to this notion comes from studies using $GABA_A$ receptor mutant mice (mutant mice heterozygous for the γ2 subunit of the $GABA_A$ receptor, referred to as $\gamma2^{+/-}$) (30, 31). These mice have reduced $GABA_A$ receptor binding, and the behavioral phenotype includes neophobia and behavioral inhibition (31), and anhedonia, which is a core symptom of depression (31). The $\gamma2^{+/-}$ mice also exhibit HPA axis hyperactivity (31), which is an endocrine hallmark of stress-related disorders. Increased anxiety- and depression-related behaviors have also been reported in mice lacking the α2 subunit of $GABA_A$ receptor that is highly expressed in the neocortex (12). Most recent evidence further indicates that $\gamma2^{+/-}$ mutant mice have significantly reduced cell surface expression of N-methyl-D-aspartate (NMDA)- and AMPA- type glutamate receptors along with deficits in density of functional glutamatergic markers in the PFC and hippocampus (32). Interestingly, these deficits in the PFC were normalized following a single dose of ketamine (a rapid-acting antidepressants) (32). These findings in $GABA_A$ mutant lines provide compelling evidence that loss of GABA function plays a casual role in the development of mood and cognitive disorders.

Experiments using chronic stress paradigms in rodents provide further evidence for GABA receptor dysregulation in mood disorders. For example, exposure to maternal separation stress during the first postnatal week decreased the expression of $GABA_A$ receptors in the frontal cortex and other stress-effected brain regions in adulthood (33). Other preclinical studies of chronic stress, such as, chronic cold (34), chronic foot shock (35), and social isolation (36), also report stress-induced decreases in $GABA_A$ receptor expression in cortical brain regions. However, it is important to note that the stress-induced changes in $GABA_A$ receptor expression are highly dependent on stressor modality, intensity, and brain regions analyzed. For example, chronic immobilization stress leads to increased $GABA_A$ receptor expression in the PFC (35). Collectively, the findings indicate that GABAergic system in the PFC is highly sensitive to stress.

Stress also reduces other markers of prefrontal GABA transmission. For instance, social isolation causes a 40% reduction in GABA transporter 1 immunolabeling in the PFC compared to socially housed littermate rats (37). A recent analysis of parvalbumin transcript levels and number of PV-positive cells in PFC following exposure to a chronic unpredictable mild stress paradigm revealed somewhat conflicting results (38). This is intriguing, and one possible explanation could be the sustained hypoactivity of SST interneurons. SST interneurons inhibit PV interneurons, and therefore, sustained SST interneuron loss of function could serve as a primary driver for the hyperactivity of PV interneurons. Further studies are required to test the link between SST and PV interneurons and output of excitatory neurons in the PFC. A similar phenomenon has been described in mouse motor cortex where it has been shown that SST interneurons provide an overall disinhibition signal to pyramidal neurons via inhibition of PV interneurons (39)

It has also been suggested that decreased GABA function could play a causative role in the reduction of excitatory synapses resulting from chronic unpredictable stress CUS (12). This

is supported by evidence that partial (30%) ablation of SST neurons results in compensatory, long-lasting reductions in cortico-cortical excitatory drive (40). Decreased GABA function could contribute to reduction in 5-HT stimulated cortico-cortical drive that is caused by CUS (41). Together, the above evidence indicates that changes in PFC GABAergic transmission increase the vulnerability to stress-related illness.

GABA interneuron subtypes and microcircuit characteristics

The SST and the PV are the two major subtypes of cortical GABAergic interneurons that differ substantially with respect to morphology, electrophysiological properties, firing rate and most importantly targeting of specific cellular domains of pyramidal neurons and other interneurons (Figure 1). Approximately 25% of cortical GABA interneurons express SST and 40% express PV. Subtype specific targetting using CRE recombinase under the control of SST or PV promoters has provided important advances in our knowledge of the functions of interneuron subtypes. The SST and PV subtypes have received the most attention in studies of stress-related disease and are therefore the focus of the current review (Figure 1). However, additional GABA interneuron subtypes may also play an important role in mood disorders.

The SST GABAergic interneurons extend projections that target the dendritic compartment of PFC principal excitatory neurons and are therefore positioned to regulate the effects of incoming signals to principal neurons. Additionally, SST neurons play a role in establishing a balance of excitation and inhibition by directly inhibiting other classes of interneurons, notably PV cells. This has important behavioral implications as putative SST interneuron inhibition of PV cells in the PFC has been demonstrated to govern fear expression (42). Interestingly, investigation of post-mortem human tissue has demonstrated a reduction in SST content in the PFC of individuals with MDD (43–45). The functional consequences of decreased SST have been examined in an elegant study of SST deletion mutant mice. These mice display several depression related phenotypes, including increased basal corticosterone, reduced BDNF transcript levels, and increased anxiety- and depression-like behaviors (46). These findings support the hypothesis that decreased SST expression contributes to the depression related endocrine, neurotrophic, and behavioral symptoms.

Other studies extend this work by testing the influence of chemogenetic inhibition of SST interneurons in the dorsal PFC. The results of these studies show that acute inhibition produces changes in behavior similar to deletion of SST knock-out, an acute increase in depression-like behaviors (47). However, 3 weeks of repeated SST inhibition or ablation SST interneurons in adult mice produced the opposite effects, producing antidepressant-responses (47). One factor to consider, particularly with the acute studies is that analysis of behaviors during this period could be confounded by the acute inhibition of SST neurons and the resulting hyperexcitability of the principle neurons. Nevertheless, these findings demonstrate the complexity of modeling reduced GABAergic signaling in depression, but provide compelling evidence that SST interneurons may play a significant role in pathology of mood disorders.

PV interneurons are a large component of the basket cell population that targets the soma of PFC principal neurons, and exhibit a phasic, fast spiking electrophysiological profile (10). Soma targeting places PV interneurons in a position to gate the output of principal neurons, as opposed to the SST cells that gate input to these neurons. Consistent with this, cell type specific manipulation of PV interneurons has demonstrated their importance in maintaining balance between excitation and inhibition, and relevance to numerous emotional behaviors. Optogenetic studies demonstrate that inhibition of PV interneurons in the dorsal PFC is critical for inhibition of fear expression during extinction (42). In addition, reduced excitatory drive onto PV neurons in the dorsal PFC was observed in mice after exposure to extreme footshock that produces learned helplessness behavior (48); in addition, mice that were identified as resilient could be rendered helpless by chemogenetic inhibition of PV neurons. Based on recent advances and emerging evidence, we have provided a conceptual framework of how SST and PV interneurons gate PFC activity to regulate behavior, and how they interact within the PFC microcircuit prior to, and following, stress (Figure 1), however a clearer and more detailed understanding of the function of these interneuron subtypes will help inform our knowledge of the mechanisms underlying stress associated diseases.

Role of GABA Interneurons in the Actions of Antidepressants

Further support for aberrant regulation of GABAergic tone comes from studies demonstrating normalization of GABA transmission after antidepressant treatment (12). Patients exposed to treatment with SSRIs (49), electroconvulsant therapy (50), and transcranial magnetic stimulation (16) showed normalization of GABA levels. Consistent with human studies, preclinical data obtained from GABA receptor mutant mice ($\gamma 2^{+/-}$) that exhibit anxiety and depressive behaviors show partial normalization following fluoxetine treatment (31). Chronic fluoxetine treatment also increases extracellular GABA levels in brain (51), suggesting that increased GABA contributes to antidepressant behavioral responses. GABA neurotransmission, including synapse formation is controlled by BDNF-TrkB signaling (52) and it is possible that BDNF deficits caused by stress could contribute to deficits in GABA signaling. Conversely, up regulation of BDNF-TrkB signaling in response to antidepressant treatment could promote GABA synaptic activity (53).

Further evidence for GABA interneurons in the treatment of depression come from recent studies of rapid acting antidepressants, particularly ketamine. Clinical studies demonstrate that ketamine (NMDA receptor antagonist), produce rapid (within hours) antidepressant effects in treatment resistant patients (54, 55). This is particularly notable when compared with typical antidepressants that have a significant time lag (weeks to months) and modest efficacy. Interestingly, there is evidence that actions of ketamine include regulation of GABAergic signaling (29). Our previous studies reveal that ketamine rapidly increases synaptic connectivity, and reverses the neuronal atrophy and behavioral deficits caused by chronic stress (56, 57). These effects are activity dependent and are associated with a burst of glutamate in the PFC (58). NMDARs are expressed on interneurons as well as excitatory neurons and because interneurons are more active at resting state are more sensitive to the open channel blocker actions of ketamine. This is supported by evidence that ketamine administration leads to decreased spontaneous firing of GABA interneurons in the PFC and a delayed increase in the firing rate of pyramidal cells (29). Importantly, ketamine-induced

disinhibition would be dependent on the presence of ongoing GABAergic suppression of neocortical activity. The GABA interneurons are divided into different classes with different firing responses (the low threshold spiking SST neurons, fast spiking PV cells, and delayed spiking non PV and non SST interneurons). Out if these, the SST interneurons exhibit high basal firing rates and a > 10 fold higher firing frequency (59), indicating that the spontaneous activity of these GABAergic interneurons mediates the maintenance of a highly suppressed state of cortical synaptic transmission. Together, These findings support a disinhibition hypothesis for the activity dependent actions of ketamine.

Similar effects have been observed for another rapid acting agent, scopolamine, an acetylcholine muscarinic receptor antagonist. Consistent with this hypothesis, our recent study demonstrated that M1-acetylcholine receptor (M1-AchR) expression in the SST interneurons is required for the rapid antidepressant-like effects of scopolamine (60). We found that M1-AChR activation on SST interneurons stimulates the firing of these inhibitory neurons, and that knockdown of M1-AChR on SST neurons blocks the antidepressant behavioral actions of scopolamine. This finding indicates that reduced SST activity within the dendritic field of PFC principal neurons is a necessary component of the rapid antidepressant response.

GABA hypofunction in response to stress and in MDD appears to contradict the ketamine disinhibition mechanism, but there are several key issues to consider. Importantly, the disinhibition hypothesis describes the initial actions (~1 hr) of ketamine, blockade of NMDA receptors on GABA interneurons that triggers a glutamate burst; this initiates, but is distinct from the long-lasting (1–7 d) synaptic (57) and therapeutic actions of ketamine (54, 61). Thus, we propose that ketamine-induced disinhibition causes an adaptive response that restores the excitatory/inhibitory balances (Figure 2). According to this hypothesis, acute, transient suppression of PFC GABAergic interneurons would produce antidepressant behavioral effects. Experiments to test this hypothesis require selective activation and/or inihibition of specific interneuron populations (SST or PV) using a combination of GABA interneuron specific Cre recombinase mice and light or chemically driven manipulation of cell activity.

Conclusion

From early development to adulthood GABA interneurons play crucial role in assembling the microcircuitry and orchestrating the activity of the cerebral cortex. Impairments in the function of the cortical GABAergic transmission exert a strong influence on brain function, including cognitive, mood, learning and behavior. Here, we highlight recent findings that are beginning to delineate how changes in various components of the PFC GABAergic microcircuit are casually linked to stress and depression. Indeed, the studies of ketamine and scopolamine have generated considerable excitement, pointing to a key role of GABAergic transmission in the effects of rapid acting antidepressants, and in the development of next-generation therapeutics (Figure 2).

Despite intensive research, we are left with a number of significant gaps in our understanding of GABA/glutamate balance in the pathophysiology of depression and other

stress related illnesses. One problem that has hindered the complete understanding of the underlying cause of depression is the lack of techniques to selectively manipulate each interneuron subtype. This is now being addressed with advances in optogenetics, chemogenetics, microendoscopy, and imaging technology; these approaches will allow studies to determine the influence of stress on the activity of GABA interneuron subtypes and the effects of activation or inhibition of specific GABA cell populations on neighboring GABA and principle neurons, as well as behavior. Moreover, analysis of sex specific differences in stress-induced effects on GABA interneuron populations are surprisingly incomplete, and could lead to improved treatments for women who experience higher rates of depression compared to men. Progress and new insights in these areas will help us to generate alternative and more efficacious therapeutic strategies and eventually prevention of stress related illnesses such as depression.

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Highlights

- Chronic stress causes atrophy and decreased connectivity of excitatory neurons in PFC.
- Stress causes disruption of GABAergic inhibitory neurons in the PFC.
- GABA subtypes, somatostatin and parvalbumin, are dysregulated by stress.
- Rapid acting antidepressants inhibit GABAergic interneurons.

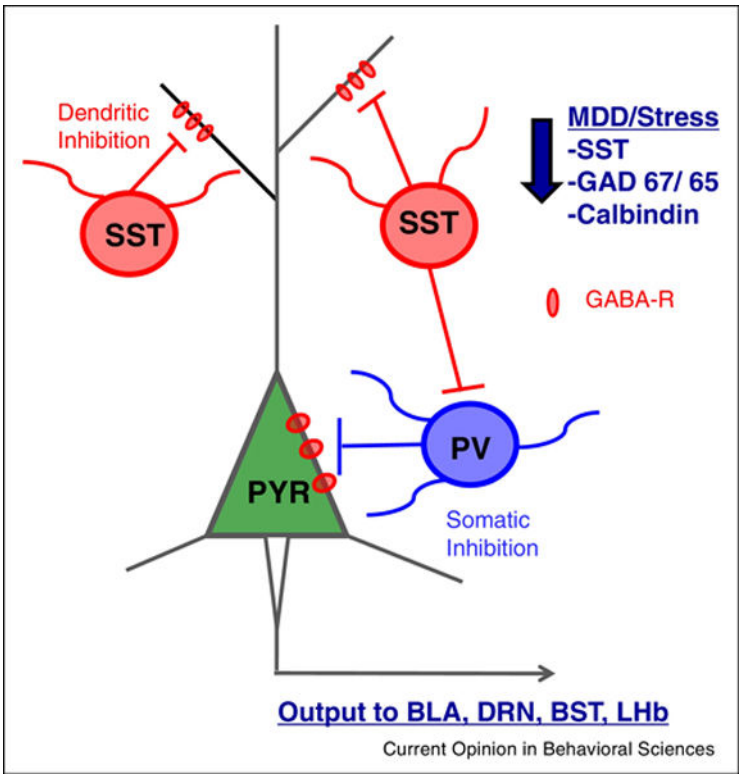

Figure 1. Impact of stress on local GABA interneuron activity and regulation of PFC microcircuitry

The PFC glutamatergic output neuron is under regulatory control of local GABA interneurons, predominantly somatostatin (SST) and parvalbumin (PV). SST provides inhibition of the dendritic compartment of excitatory pyramidal cells as well as to PV subtype GABA interneurons. PV interneurons provide peri-somatic inhibition to the pyramidal cells. The PFC projects to numerous subcortical and brainstem targets, such as the bed nucleus of the stria terminalis (BST), central nucleus of the amygdala (CeA), and dorsal raphe nucleus (DRn) that contribute to regulation of mood and emotion. Studies of MDD subjects and rodent stress models demonstrate reductions in levels of SST, GAD67/65, and calbindin, another marker of SST interneurons.

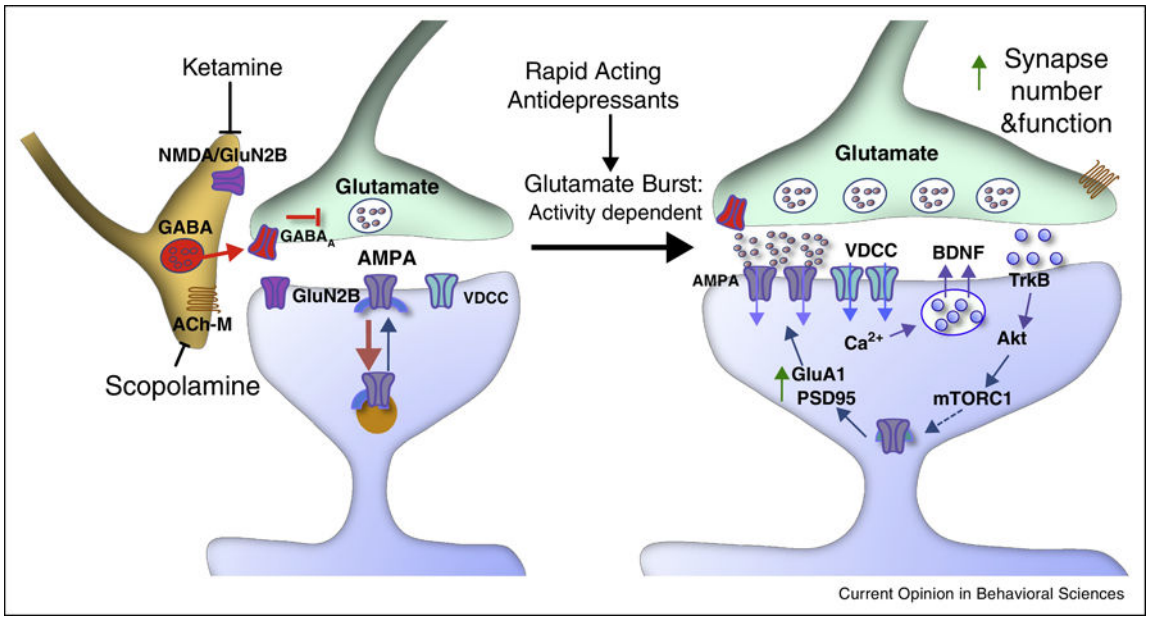

Figure 2. Schematic representation of ketamine- and scopolamine- mediated disinhibition of mPFC pyramidal neurons via inhibition of local GABA interneurons

Ketamine triggers a burst of glutamate that is thought to occur via inhibition of GABA interneurons; the tonic firing of these GABA interneurons is driven by NMDA receptors, and the active, open-channel state allows ketamine to enter and block channel activity. The resulting glutamate burst stimulates AMPA receptors, which causes depolarization and activation of voltage-dependent Ca2+ channels (VDCC), leading to release of BDNF and stimulation of TrkB and Akt, which then activates mTORC1 signaling, leading to the increased synthesis of proteins that are required for synapse maturation and formation (i.e., GluA1 and PSD95). Scopolamine also causes a glutamate burst via blockade of acetylcholine muscarinic M1 (ACh-M1) receptors on GABA interneurons.