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GABAergic control of depression-related brain states

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Abstract

The GABAergic deficit hypothesis of major depressive disorders posits that reduced GABA concentration in brain, impaired function of GABAergic interneurons, altered expression and function of $GABA_A$ receptors, and changes in GABAergic transmission dictated by altered chloride homeostasis can contribute to the etiology of Major Depressive Disorder (MDD). Conversely, the hypothesis posits that the efficacy of currently used antidepressants is determined by their ability to enhance GABAergic neurotransmission. We here provide an update for corresponding evidence from studies of patients and preclinical animal models of depression. In addition, we propose an explanation for the continued lack of genetic evidence that explains the considerable heritability of MDD. Lastly, we discuss how alterations in GABAergic transmission are integral to other hypotheses of MDD that emphasize (i) the role of monoaminergic deficits, (ii) stress-based etiologies, (iii) neurotrophic deficits, and (iv) the neurotoxic and neural circuit-impairing consequences of chronic excesses of glutamate. We propose that altered GABAergic transmission serves as a common denominator of MDD that can account for all these other hypotheses and that plays a causal and common role in diverse mechanistic etiologies of depressive brain states and in the mechanism of action of current antidepressant drug therapies.

Keywords

GABA; BDNF; major depressive disorder; anxiety; antidepressant drug action; excitatory-inhibitory balance; hippocampal neurogenesis

1. Introduction

Major depressive disorder (MDD) is a common and highly heterogeneous psychiatric syndrome and a leading cause of total disability (C. J. Murray & Lopez, 1996; World Health Organization, 2008). The lifetime prevalence of MDD in the US population has been estimated to be between 13 and 17% (Hasin, Goodwin, Stinson, & Grant, 2005; Kessler et

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al., 2003). Depressive disorders are highly comorbid with pathological anxiety, especially generalized anxiety disorder and posttraumatic stress disorder. About 85% of patients with MDD exhibit significant anxiety symptoms, and 58% of patients with a history of depression also suffer from an anxiety disorder (Baldwin, Evans, Hirschfeld, & Kasper, 2002; Gamez, Watson, & Doebbeling, 2007; Gorman, 1996). Currently used antidepressant drug therapies act with a delay of several weeks. Moreover, they are ineffective in that only one third of patients respond to the first agent prescribed (Keller et al., 2000), and the observed therapeutic effect is superior to placebo in approx. 50% of clinical trials only (Khan, Khan, Walens, Kolts, & Giller, 2003). Amongst patients who respond to drug treatment only a fraction shows remission, and recurrence is the rule rather than an exception. Thus, there is an enormous unmet need for better antidepressant therapies.

According to DSMIV the diagnostic criteria for MDD are loosely defined as a cluster of at least five symptoms of which at least one of two core symptoms, depressed mood or loss of interest or pleasure in life activities, is observed in combination with three or four other symptoms during the same two-week-period. These additional symptoms include unintentional weight gain or loss, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, diminished ability to think, concentrate or indecisiveness, and recurrent thoughts of death (American Psychiatric Association, 2000). Most of these symptoms exist on a continuum from normal to pathological, which defies categorical quantification (Angst & Merikangas, 2001). Consequently, two patients can suffer from MDD without sharing any of their diagnostic symptoms. The broad range of symptoms implies that the goal of mapping MDD onto a unique set of abnormal molecules, cells or neural circuits is impossible to attain. Nevertheless, based on a wide range of approaches different subregions of the prefrontal cortex, the subgenual anterior cingulate cortex (sgACC) and the hippocampus have emerged as primary sites of pathology. The amygdala and subcortical reward circuits are also implicated (Drevets, 2001; Russo & Nestler, 2013). Particularly informative on the brain substrate of MDD were insights from brain imaging (E. A. Murray, Wise, & Drevets, 2011), regional brain volume loss (i.e. Bell-McGinty et al., 2002; Hickie et al., 2005; Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009; Sacher et al., 2012; Steffens et al., 2000), circuits underlying cognitive impairments (Fujii, Saito, Yanaka, Kosaka, & Okazawa, 2014), and brain regions and their functional connections that respond to therapeutically effective deep brain stimulation (Holtzheimer & Mayberg, 2011).

Based on family and twin studies MDD shows significant heritability. The nature of this heritability, however, is unexplained as evidence for specific genes that confer risk for MDD continues to be lacking. Therefore, and in contrast to schizophrenia or autism spectrum disorders, current hypotheses on the etiopathology of MDD must rely on empirical information other than human genetic vulnerabilities. The monoamine hypothesis of MDD dates back more than 50 years and posits that depressive disorders are caused by imbalances in serotonergic, noradrenergic and possibly dopaminergic transmitter systems. It is derived from the notion that monoamine oxidase inhibitors, tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs) have in common that they increase the extracellular concentrations of these transmitters (Bunney & Davis, 1965; Coppen, 1967; Matussek, 1969; J. J. Schildkraut, 1995). However, it has become widely accepted that

antidepressant mechanisms do not simply reflect increased monoamine transmitter function and that alterations in these transmitter systems are insufficient to explain the complex nature of affective disorders and antidepressant drug mechanisms. More recently, a number of alternative hypotheses have emerged that focus on the underlying biology rather than pharmacology. We here will provide an update on the GABAergic deficit hypothesis of MDD (Luscher, Shen, & Sahir, 2011). We also discuss the continued lack of concrete evidence for genetic alterations that could explain the heritability of MDD. In addition, we review and emphasize the role of GABAergic deficits in the context of the monoamine deficiency hypothesis, stress-based hypothesis (Holsboer, 2001; Kendler, Karkowski, & Prescott, 1999; Pittenger & Duman, 2008), neurotrophic deficit hypothesis (R. S. Duman & Monteggia, 2006; Krishnan & Nestler, 2008) and glutamatergic hypothesis of MDD (Paul & Skolnick, 2003; Tokita, Yamaji, & Hashimoto, 2012).

2. The GABAergic Deficit Hypothesis of MDD

There is an abundance of evidence that MDD is associated with diverse defects in GABAergic transmission. Given the heterogeneity of MDD it seems likely that none of these individual deficits are representative of MDD. Instead the currently available data suggest that environmental conditions interact with heritable abnormalities to affect different aspects of GABAergic transmission and converge on an impaired balance of neural excitation and inhibition as a common feature that causally contributes to the psychopathology of MDD. In particular, a first line of clinical evidence suggesting reduced GABAergic transmission in depressed patients is based on positron emission tomography (PET) imaging of [^{11}C]-flumazenil binding (Klumpers et al., 2010), These studies revealed reduced expression of $GABA_A$Rs in the limbic parahippocampal temporal gyrus and right lateral superior temporal gyrus, which is consistent with evidence for glucose hypermetabolism in the same brain region of patients (Aihara et al., 2007). There is also evidence for reduced $GABA_A$R expression based on downregulation of subunit transcripts. Comparing the frontopolar cortex of depressed suicide victims with that of non-depressed control subjects that had died from other causes, Merali et al. found evidence for reduced expression of α1,3,4 and δ subunit mRNAs (Merali et al., 2004). However, when brains of depressed and non-depressed suicide victims were compared directly, several $GABA_A$R subunit mRNA levels were increased rather than reduced (Choudary et al., 2005; Klempan et al., 2009; Sequeira et al., 2007; Sequeira et al., 2009). Further experimentation is needed to determine whether differences between transcript studies and PET imaging reflect brain region-specific phenotypes of MDD or whether transcript changes are compensatory for reductions in protein expression. However, the functional expression of $GABA_A$Rs at the cell surface and at synapses is known to be subject to a plethora of posttranslational regulatory mechanisms that ultimately determine receptor function, as illustrated throughout this chapter and summarized comprehensively in previous reviews (Brickley & Mody, 2012; Jacob, Moss, & Jurd, 2008; Luscher, Fuchs, & Kilpatrick, 2011; Tyagarajan & Fritschy, 2014). In particular, $GABA_A$Rs and associated proteins are targets of diverse signaling cascades that, mostly through changes in phosphorylation state, control their trafficking, stability in the plasma membrane and diffusional dynamics at synapses, independently of

changes in transcript levels. Changes in $GABA_AR$ transcript levels therefore must be interpreted with caution.

A second salient feature pointing to GABAergic dysfunction in MDD is based on drastically reduced brain concentrations of GABA in both occipital cortex and ACC (Gabbay et al., 2012; Hasler et al., 2007; Sanacora et al., 2004; Sanacora et al., 1999). This finding is supported by studies of postmortem prefrontal cortex and amygdala showing reduced protein and mRNA encoding glutamic acid decarboxylase (GAD)67, a key enzyme for the synthesis of GABA (Guilloux et al., 2012; Karolewicz et al., 2010). Reduced GAD67 and GABA levels are further consistent with reduced function or densities of specific subtypes of GABAergic interneurons. Specifically, immunostaining of postmortem brain revealed a drastically reduced density of calbindin-positive GABAergic interneurons mainly in the dorsolateral prefrontal cortex (DLPFC) of MDD patients, along with a significant reduction in size of cell bodies (Rajkowska, O'Dwyer, Teleki, Stockmeier, & Miguel-Hidalgo, 2007). Interestingly, calbindin-positive cells were reduced also in occipital cortex (Maciag et al., 2010), again consistent with GABA reductions in this area. In addition, transcript analyses of the postmortem DLPFC and sgACC revealed association of MDD with reduced expression of somatostatin (SST), a neuropeptide marker representative of about 30% of cortical GABAergic interneurons including dendrite-targeting Martinotti cells (Sibille, Morris, Kota, & Lewis, 2011; Tripp, Kota, Lewis, & Sibille, 2011). SST-positive interneurons show variable co-labeling with calbindin (Rossignol, 2011), and it remains to be determined to what extent changes in these two markers are representative of the same neurons. Importantly, SST transcripts and protein were also reduced in the lateral/basolateral/basomedian amygdala of a separate cohort of patients (Guilloux et al., 2012). Furthermore, functional deficits of SST neurons are evidenced by reduced expression of neuropeptide Y (NPY), tachykinin, and cortistatin transcripts, which are co-expressed with SST in the same subpopulation of interneurons (Guilloux et al., 2012). This same study also confirmed earlier evidence that MDD is associated with significantly reduced expression of brain derived neurotrophic factor (BDNF), a key protein in the etiology of MDD and antidepressant drug action [Sections (4) and (6)]. By analyzing two different strains of mice with constitutive or activity-dependent decreases in BDNF Guilloux et al. demonstrated a causal relationship between BDNF functional deficits and reduced expression of markers of SST/NPY-positive interneurons (Guilloux et al. 2012). Abundant evidence from mouse genetics, discussed further below, indicates that BDNF promotes the functional maturation of GABAergic circuits, which is a prerequisite for structural maturation also of dendrites and dendritic spines of glutamatergic neurons.

Importantly, the changes in expression of markers of GABAergic transmission described above are functionally relevant for MDD as indicated by marked reductions in cortical GABAergic inhibition in depressed patients observed by transcranial magnetic stimulation (TMS) (Levinson et al., 2010). The importance of GABAergic deficits for MDD is further suggested by analyses of patients subjected to treatment with SSRIs (Bhagwagar et al., 2004; Kucukibrahimoglu et al., 2009; Sanacora, Mason, Rothman, & Krystal, 2002) or electroconvulsive therapy (Sanacora et al., 2003), which showed that these treatments normalize GABA concentrations in brain and plasma of MDD subjects. Besides GABA, MDD has been shown to involve reduced cerebrospinal fluid concentrations of the

neurosteroid 3alpha-hydroxy-5alpha-pregnan-20-one (allopregnanolone) (Uzunova et al., 1998). Allopregnanolone and other neurosteroids are endogenously produced high affinity ligands of $GABA_A$Rs that dynamically potentiate the function of GABA similar to benzodiazepines. Significantly, chronic treatment with fluoxetine (but not imipramine) increased the allopregnanolone concentrations in rats and normalized its concentration in MDD patents (Uzunov, Cooper, Costa, & Guidotti, 1996; Uzunova et al., 1998). Collectively, it is becoming increasingly evident that antidepressant therapies, including drug therapies designed to normalize monoaminergic transmission, ultimately act to enhance GABAergic transmission.

Alterations in biological markers of GABAergic transmission for the most part are not uniquely found in patients with MDD but also broadly implicated in other psychiatric disorders. While there is a consensus that GABA is reduced in MDD (Gabbay et al., 2011, 2012; Hasler et al., 2007; Sanacora et al., 2004; Sanacora et al., 1999) GABA concentrations appear mostly unchanged or increased in schizophrenia (Kaufman et al., 2009; Ongur, Prescot, McCarthy, Cohen, & Renshaw, 2010; Tayoshi et al., 2010). However, one study found GABA levels trending higher in young patients and lower in older patients with schizophrenia compared to healthy controls (Rowland et al., 2013). By contrast, reduced expression of GAD67 is a well-replicated finding in both MDD and schizophrenia (Curley et al., 2013). However, in schizophrenia GAD67 reductions are selectively found in parvalbumin (PV)-positive interneurons (T. Hashimoto et al., 2003), a subset of reciprocally interconnected soma-targeting GABAergic neurons whose dysfunction in the prefrontal cortex is thought to underlie abnormal gamma-band oscillations and cognitive deficits of schizophrenia (Carlen et al., 2012). PV-neuron-specific dysfunction in schizophrenia is also evident based on reduced expression of PV mRNA (T. Hashimoto et al., 2003). By contrast, PV transcript levels are normal in patients with MDD (Guilloux et al., 2012; Rajkowska et al., 2007; Sibille et al., 2011). However, reduced expression of SST is not exclusively found in MDD but has also been reported for schizophrenia (Guillozet-Bongaarts et al., 2014; Morris, Hashimoto, & Lewis, 2008). Collectively the data suggest that at the cellular and molecular level GABAergic deficits associated with schizophrenia and MDD include both disease-specific and common characteristics. This is consistent with depressive symptoms being a common clinical feature of schizophrenia.

Multiple lines of evidence from preclinical studies confirm that impairments of GABAergic transmission observed in MDD patients can be causal for depression-related phenotypes (Luscher, Shen, et al., 2011; Mohler, 2012; Smith & Rudolph, 2012). In particular, mice that were rendered heterozygous for the γ2 subunit ($\gamma2^{+/-}$ mice) exhibit behavioral, cognitive, neuroendocrine, cellular and pharmacologic alterations expected of an animal model of anxious depression (Crestani et al., 1999; Earnheart et al., 2007; Shen et al., 2010). The phenotypes of these mice include anxiety-like behavior in a number of test paradigms, reduced escape behavior in the Forced Swim and Tail Suspension Tests that may indicate behavioral despair, and reduced sucrose consumption thought to indicate anhedonia. The $\gamma2^{+/-}$ model further includes constitutively elevated serum corticosterone levels, which points to disinhibition of the hypothalamus-pituitary adrenal axis (Shen et al., 2010) and is reminiscent of corresponding neuroendocrine alterations in MDD (Guerry & Hastings, 2011; Kathol, Jaeckle, Lopez, & Meller, 1989). Other than the anhedonia phenotype (which was

not examined), all these phenotypes of the $\gamma2^{+/-}$ model were reproduced in mice in which the same genetic lesion was delimited to glutamatergic neurons of the telencephalon (Earnheart et al., 2007). Thus, the phenotypes of these mice are caused by reduced GABAergic input to glutamatergic neurons, most likely resulting in modest hyperexcitability of these neurons. Moreover, results from the telencephalon-specific γ2-deficient mice indicated that the HPA axis hyperactivity was caused by extra-hypothalamic $GABA_AR$ deficits, most likely due to alterations of neural circuits in the hippocampus and neocortex, which normally delimit HPA axis activity [Section (5)] and where reductions in γ2-containing $GABA_ARs$ are most pronounced (Crestani et al., 1999; Shen et al., 2010). Importantly, the anxiety- and depressive-like behavioral and neuroendocrine abnormalities of $\gamma2^{+/-}$ mice were reversed by chronic but not acute treatment with the norepinephrine transporter-selective reuptake inhibitor desipramine, thereby confirming that this drug acts over time to overcome deficits in GABAergic inhibition (Shen et al., 2010). Notably, in contrast to desipramine, the SSRI fluoxetine was effective in the novelty suppressed feeding test (a conflict test assessing anxiety) only and failed to normalize despair- and anhedonia-like phenotypes as well as the elevated corticosterone serum concentrations of $\gamma2^{+/-}$ mice. The qualitatively lesser responses of $\gamma2^{+/-}$ mice to fluoxetine than desipramine are reminiscent of severe subtypes of anxious depressive disorders including melancholic depression, which tend to show greater responsiveness to TCAs than fluoxetine (Bauer et al., 2002; Clerc, Ruimy, & Verdeau-Palles, 1994; Perry, 1996; Roose, Glassman, Attia, & Woodring, 1994; Swartz & Guadagno, 1998; Young et al., 2004) and are generally less responsive to treatment than depressive disorders without anxiety (Fava et al., 2008). Thus, $\gamma2^{+/-}$ mice represent a model for partially drug-resistant melancholic/anxious depression.

The phenotype of $\gamma2^{+/-}$ mice further includes alterations in hippocampus-dependent cognitive tasks such as enhanced hippocampus-dependent trace fear conditioning and impaired ambiguous cue fear conditioning (Crestani et al., 1999). The latter of these two cognitive phenotypes has recently become recognized as a defect in pattern separation, a task that involves forming distinct memory traces for similar experiences or situations. Moreover, in mice this task is critically dependent on adult hippocampal neurogenesis (reviewed in Aimone, Deng, & Gage, 2011; Clelland et al., 2009). Importantly, defects in pattern separation of emotionally relevant stimuli have emerged as a cognitive phenotype of MDD (Fujii et al., 2014; Leal, Tighe, Jones, & Yassa, 2014). In the context of anxiety disorders defects in pattern separation have been proposed to underlie the commonly observed phenomenon of stimulus generalization (Kheirbek, Klemenhagen, Sahay, & Hen, 2012). In rodents efficient pattern separation is controlled by the continued production and proper functional integration of adult-born granule cell neurons in the hippocampus (Clelland et al., 2009; Sahay et al., 2011). These same neurons are also recognized as a cellular substrate for the behavioral action of antidepressant drugs (Samuels & Hen, 2011). Consistent with a role of impaired pattern separation and hippocampal neurogenesis in the pathology of MDD, $\gamma2^{+/-}$ mice exhibit marked deficits in the maturation and survival of adult-born hippocampal granule cells (Earnheart et al., 2007; Ren et al., 2014). Anxiety- and depression-related behavior and maturational deficits of adult-born hippocampal neurons similar to those of $\gamma2^{+/-}$ mice have also been reported for mice lacking the α2 subunit (Duveau et al., 2011; Vollenweider, Smith, Keist, & Rudolph, 2011). This subunit invariably

co-assembles with γ2 and β subunits to form postsynaptic $GABA_A$Rs. These α2βγ2 receptors are most prominently expressed in limbic neural circuits including neocortex, hippocampus and striatum and they are known to be responsible for the anxiolytic responses of benzodiazepines (Fritschy & Mohler, 1995; Low et al., 2000).

3. GABAergic transmission and heritability of MDD

Based on Meta analyses of high quality family and twin studies the heritability of MDD has been determined to be 37–38%, with significantly higher values in women than men (Kendler, Gatz, Gardner, & Pedersen, 2006). However, to date no genes have been confirmed to carry significant risk specifically for MDD (Flint & Kendler, 2014; Hek et al., 2013; Major Depressive Disorder Working Group of the Psychiatric et al., 2013). Thus, neither the GABAergic deficit hypothesis nor any other proposed etiology of MDD is currently supported by human genetic evidence. The lack of a genetic foundation for MDD is contrasted by corresponding evidence in bipolar disorder and schizophrenia, where genome-wide association (GWAS), twin and adoption studies and evidence for a role of copy number variance have identified an increasing number of risk genes. Although the heritability of bipolar disorder and schizophrenia is much higher than that of MDD (Lichtenstein et al., 2009; P. F. Sullivan, Kendler, & Neale, 2003), there is significant overlap in genetic risk between all three disorders. This is evidenced by familial risk genes for schizophrenia such as DISC1 that confer similar risk also for MDD in the same families (Blackwood et al., 2007), by general familial co-clustering of MDD with bipolar disorder and schizophrenia (Aukes et al., 2012) and by significant correlation of single nucleotide polymorphisms (SNPs) across the genome of subjects with MDD, schizophrenia or bipolar disorder (Cross-Disorder Group of the Psychiatric Genomics et al., 2013).

In addition to phenotypic heterogeneity and considerable environmental contributions, the failure to identify genetic risk factors that are specific for MDD may be due to a very large number of genes and allelic variations that confer very small effects of vulnerability and in only a subset of combinations (Flint & Kendler, 2014). Alternatively, the difficulty of finding risk genes might be due to a large number of rare mutations that have large effects but function independently. These interpretations imply that information on the genetic basis of MDD, even if successfully attained eventually, might be clinically non-actionable. Indeed, therapeutic approaches for highly heterogeneous polygenic syndromes such as MDD would appear most effective if they were targeting cellular mechanisms disrupted in the majority of patients, irrespective of the function of hitherto hypothetical risk genes. Importantly, there is a third and increasingly plausible explanation for the elusiveness of risk genes for MDD. It is based on recent evidence from mice showing that heritability of emotion-related behavioral traits involves experience-dependent epigenetic modifications of DNA. Such changes can be passed on through the male and female germ line over multiple generations (Dias & Ressler, 2014). However, given that they do not involve alterations in the DNA sequence they are not detectable by GWAS. Environmental risk factors implicated in affective disorders that have been shown to program heritable behavioral traits in mice include fearful experiences in adulthood (Dias & Ressler, 2014) as well as early life stress (Bohacek et al., 2014; Franklin et al., 2010). Moreover, the detrimental effects of both chronic and early life stress are likely to involve dysfunction of GABAergic transmission

[Section (5)] (Gunn et al., 2013; Holm et al., 2011; Hu, Zhang, Czeh, Flugge, & Zhang, 2010; Jacobson-Pick, Audet, McQuaid, Kalvapalle, & Anisman, 2012; Martisova et al., 2012; Radley, Gosselink, & Sawchenko, 2009). Genes that encode proteins important for GABAergic transmission that are subject to epigenetic regulation and dysregulated in MDD include BDNF (D'Addario et al., 2013; Karpova, 2014), GAD67 (Dong et al., 2005; Zhang et al., 2010), somatostatin and corticostatin (Jackson et al., 2011; Rubio et al., 2012), as well as genes encoding $GABA_AR$ subunits (Poulter et al., 2008; Zhao et al., 2012). Epigenetic mechanisms are also increasingly implicated in the regulated production and survival of hippocampal granule cells, which are increasingly recognized as a cellular substrate for emotion regulation and certain forms of cognition [Section (2)]. Furthermore, the production and maturation of these neurons is under direct GABAergic control as discussed in the following paragraphs.

4. GABAergic transmission in relation to the monoamine deficiency hypothesis of MDD

Currently used antidepressant drug therapies are universally designed to modulate monoaminergic transmission, by blocking the reuptake or breakdown of serotonin and/or norepinephrine or, less commonly, dopamine. The acute action of these drugs therefore is predicted to increase the occupancy of corresponding receptors and to affect the basal set point of G-protein coupled receptor-signaling pathways. Conversely, the monoaminergic deficit hypothesis of MDD posits that defects in these mechanisms underlie depressive states (Bunney & Davis, 1965; Coppen, 1967; Matussek, 1969; J. Schildkraut, 1965). However, a common denominator of all approved antidepressant medications is that their therapeutic effects develop with a delay of several weeks, indicating that the mechanisms underlying therapeutic effects do not merely reflect altered monoaminergic transmission. Indeed, elevated serotonin concentrations commonly result in internalization of serotonin receptors (Bhattacharyya, Puri, Miledi, & Panicker, 2002; Guthrie, Murray, Franklin, & Hamblin, 2005; Riad et al., 2004; Schlag, Lou, Fennell, & Dunlop, 2004). Moreover, some antidepressants are known to act not only as uptake inhibitors but also as antagonists of monoamine transmitter receptors, indicating that the chronic effects of elevated extracellular monoamine transmitters in many cases involves reduced rather than elevated function of cognate G-protein coupled receptors (de Boer, 1996; Schreiber & Avissar, 2007). Lastly, pharmacological depletion of serotonin or norepinephrine in healthy humans is insufficient to induce depressive episodes (Ruhe, Mason, & Schene, 2007). Collectively, these studies indicate that antidepressants act slowly and indirectly through remote targets to affect the balance of neurotransmitter systems other than serotonin and norepinephrine. This is consistent with clinical and preclinical evidence that antidepressants can normalize the behavioral and neuroendocrine sequelae of defects in GABAergic transmission (Kucukibrahimoglu et al., 2009; Sanacora et al., 2003; Sanacora et al., 2002; Shen et al., 2010; Uzunova et al., 1998). Moreover, fluoxetine can also normalize anxiety and depression-related behavioral abnormalities of mice induced by chronic pharmacological increases in cholinergic transmission (Mineur et al., 2013), which is in keeping with the well-established anticholinergic activity of fluoxetine (Chew et al., 2008).

The detailed mechanisms by which antidepressants affect GABAergic transmission remain poorly understood. However, consistent with evidence from patients mentioned earlier, chronic treatment with fluoxetine increase extracellular GABA levels in brain of rats (Goren, Kucukibrahimoglu, Berkman, & Terzioglu, 2007). Moreover, fluoxetine and other SSRIs but not imipramine stimulate the release of neurosteroids (Pinna, Costa, & Guidotti, 2006, 2009). Neurosteroids act to reduce neural excitability by selective potentiation of neuronal tonic inhibition via δ subunit-containing $GABA_A$Rs (Mihalek et al., 1999; Stell, Brickley, Tang, Farrant, & Mody, 2003; Vicini, Losi, & Homanics, 2002). A third potential GABA-related mechanism of antidepressants might involve strengthening of GABAergic inhibition through a hyperpolarizing shift of the chloride equilibrium potential, E_{Cl}. For example, in the context of corticotropin releasing hormone (CRH) neurons of the VPN, stress is known to impact on GABAergic inhibition by downregulation of potassium-chloride co-transporter 2 (KCC2) [Section (5)], most likely by an NMDAR-mediated mechanism (H. H. Lee, Deeb, Walker, Davies, & Moss, 2011) [Section (7)]. Conversely, Bos et al. (2013) recently showed that activation of 5-HT2A receptors facilitates translocation of KCC2 to the plasma membrane, which results in a hyperpolarizing shift of E_{Cl} and thereby renders inhibitory GABAergic inputs through $GABA_A$Rs more efficient. Although these latter experiments were conducted with spinal cord neurons, it is conceivable that SSRI-mediated augmentation of serotonin has similar effects on GABAergic transmission impaired in MDD. However, ultimately the neural network effects of 5-HT2C ligands will depend also on the relative distribution of these receptors between GABAergic and glutamatergic cells. Indeed, antidepressant-like behavioral effects in rodents have been described for both 5-HT2C-selective agonists (Rosenzweig-Lipson et al., 2007) and antagonists (Dekeyne et al., 2008).

The monoaminergic deficit hypothesis of MDD predicts that genetic ablation of serotonin receptors or transporters that mediate antidepressant drug responses results in depression-related phenotypes in mice. However, evidence to that effect is inconclusive. Knockout of 5-HT1A receptors, which are essential for antidepressant effects of SSRIs in mice (Gross et al., 2002), results in a heightened anxious phenotype combined with an antidepressant phenotype (Heisler et al., 1998; Parks, Robinson, Sibille, Shenk, & Toth, 1998; reviewed in Toth, 2003). Moreover, while adult neurogenesis is essential for many of the behavioral effects of antidepressants (David et al., 2009; Santarelli et al., 2003) [Section (6)], neurogenesis is not affected by knockout of the 5-HT1A receptor gene (Santarelli et al., 2003). Similarly, pharmacologic or genetic depletion of serotonin in mice does not affect basal proliferation of granule cell progenitors, although serotonin is required for potentiation of neurogenesis by exercise (Diaz et al., 2013; Klempin et al., 2013). Moreover, serotonin depletion paradoxically results in dramatically increased survival of adult-born neurons, indicating that it normally promotes apoptosis of granule cell progenitors (Diaz et al., 2013). Immunofluorescent staining for 5-HT1A receptors in the dentate gyrus suggests that these receptors are expressed selectively by radial glia-like astrocytes (RGLs) and hilar GABAergic interneurons but are absent on immature granule cells and barely detectable in mature granule cells (Klempin et al., 2010). Therefore, the 5-HT1A receptor-dependent effects of serotonin and SSRIs on immature neurons must be indirect through 5-HT1A receptors on GABAergic interneurons (Luscher & Fuchs, 2013). Behavioral state-dependent

GABA release by these cells then controls the mitotic activation of RGLs and the differentiation and maturation of granule cell precursors through α4βγ2 and α2βγ2 $GABA_A$Rs, respectively (Duveau et al., 2011; Luscher & Fuchs, 2013; Ren et al., 2014).

Upregulation of BDNF is a key feature of all currently used antidepressant drug therapies and correlated with antidepressant efficacy also among antipsychotics (R. S. Duman & Li, 2012; Nibuya, Morinobu, & Duman, 1995; reviewed in Schmidt & Duman, 2007). Preclinical evidence from mice suggests that BDNF exerts its effects on neural circuits primarily by affecting the efficacy of GABAergic transmission, with secondary effects on glutamatergic transmission. In particular, the principal loss of function phenotype of mice lacking the BDNF receptor TrkB consists of marked and selective defects in GABAergic synapse formation (A. I. Chen et al., 2011; Rico, Xu, & Reichardt, 2002). BDNF is also particularly important for normal interneuron maturation (Hong, McCord, & Greenberg, 2008; Huang et al., 1999; Kohara et al., 2003; Sakata et al., 2009; Waterhouse et al., 2012). Lastly, BDNF and GABAergic transmission are mechanistically intertwined in their support of adult hippocampal neurogenesis, which serves as a cellular substrate for the behavioral effects of antidepressants (David et al., 2009). These interactions are discussed in further detail in Section (6) of this chapter.

BDNF-TrkB signaling promotes the functional expression of $GABA_A$Rs at the cell surface of both mature and immature neurons (Mizoguchi, Kanematsu, Hirata, & Nabekura, 2003; Porcher et al., 2011). Specifically, BDNF/TrkB signaling controls the phosphorylation state of a pair of Tyr residues in the cytoplasmic loop region of the $GABA_A$R γ2 subunit (Vithlani et al., 2013), most likely by Fyn kinase (Jurd, Tretter, Walker, Brandon, & Moss, 2010). Phosphorylation of these residues interferes with clathrin-mediated endocytosis of $GABA_A$Rs, thereby strengthening GABAergic synaptic inhibition (Kittler et al., 2008). Increased cell surface expression of $GABA_A$Rs and enhancement of GABAergic synaptic currents is similarly seen upon treatment of frontal cortex brain slices with BDNF (Vithlani et al., 2013). Predictably, mice carrying phospho-tyrosine-mimicking amino acids substitutions of the γ2 subunit show constitutively elevated cell surface expression of $GABA_A$Rs. Intriguingly, these effects are cell type-specific and most notable in the prefrontal cortex and CA3 region of the hippocampus but absent in the CA1 region (Tretter et al., 2009; Vithlani et al., 2013). Increased cell surface expression of $GABA_A$Rs in the same animals was correlated with increased hippocampal neurogenesis and constitutive antidepressant-like behavior, as well as occluded behavioral responsiveness to BDNF (Vithlani et al., 2013). These phenotypes are consistent with and inverse to those of $\gamma 2^{+/-}$ mice characterized by defects in the survival of adult-born hippocampal neurons, depressive-like behavior and increased behavioral sensitivity to antidepressant drugs (Earnheart et al., 2007; Ren et al., 2014; Shen et al., 2010). Given that BDNF signaling is universally required as a mediator of antidepressant drug responses (Saarelainen et al., 2003; Sairanen, Lucas, Ernfors, Castren, & Castren, 2005) these data suggest that BDNF-mediated enhancement of GABAergic inhibition via γ2-containing $GABA_A$Rs serves as a key mechanism for antidepressant drug treatments.

The accumulation of $GABA_A$Rs at inhibitory synapses is not only regulated by posttranslational modifications of receptor subunits but also by gephyrin, the principal

subsynaptic scaffold protein that exerts effective control over the strength of GABAergic synapses (Essrich, Lorez, Benson, Fritschy, & Luscher, 1998; Kneussel et al., 1999) (reviewed by Tyagarajan & Fritschy, 2014). Gephyrin accumulation at GABAergic synapses is subject to dynamic regulation by phosphorylation, acetylation (Tyagarajan et al., 2013; Tyagarajan, Ghosh, Yevenes, et al., 2011), S-palmitoylation (Dejanovic et al., 2014) and S-nitrosylation (Dejanovic & Schwarz, 2014). Of particular interest is a pair of interdependent Ser phosphorylation sites of gephyrin that function as targets for glycogen synthase kinase (GSK)3β and extracellular signal-regulated kinase (ERK/MAPK)-mediated phosphorylation. The phosphorylation states of these sites control calpain-mediated proteolytic degradation of gephyrin and hence the strength of GABAergic synaptic inhibition (Tyagarajan, Ghosh, Harvey, & Fritschy, 2011; Tyagarajan et al., 2013; Tyagarajan, Ghosh, Yevenes, et al., 2011). Postmortem studies of suicide victims and patients who suffered from depression suggest that the activities of ERK/MAPK and Wnt/GSK3β pathways are altered in MDD (Duric et al., 2010; Dwivedi et al., 2001; Dwivedi et al., 2007; Dwivedi et al., 2010). Moreover, changes in the activity of these two signaling pathways are independently implicated in bidirectional regulation of depression related behavior of rodents by stress and antidepressant drug treatment (C. H. Duman, Schlesinger, Kodama, Russell, & Duman, 2007; Duric et al., 2010; Gourley et al., 2008; Liu et al., 2013; Okamoto et al., 2010) (reviewed in Voleti & Duman, 2012). Importantly, pharmacological inhibition of GSK3β by the mood stabilizing agent lithium in vivo suppresses calpain-mediated degradation of gephyrin, which potentiates GABAergic synaptic transmission (Tyagarajan, Ghosh, Harvey, et al., 2011). The effect of the phosphorylation state of the GSK3β site on calpain-mediated degradation of gephyrin appears to depend on the phosphorylation state of the adjacent ERK site of gephyrin, thereby leading to functional integration of two otherwise independent signaling pathways (Tyagarajan et al., 2013). Collectively, the data suggest that gephyrin and the $GABA_AR$ γ2 subunit serve as key targets that convey the mood stabilizing actions of lithium and antidepressants via enhancement of GABAergic transmission.

5. GABAergic transmission in relation to stress-based etiologies of MDD

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis figures among the most consistently observed neuroendocrine abnormalities of MDD, with excessive stress and early life stress as likely causal factors (Bremne & Vermetten, 2001; Guerry & Hastings, 2011; Stander, Thomsen, & Highfill-McRoy, 2014). In rodents, chronic intermittent exposures to various stressful conditions or chronic administration of corticosterone result in heightened emotion-related behavior and cellular changes expected of animal models of depression. These effects of stress can be prevented or reversed by antidepressant drug treatment (reviewed by Samuels et al., 2011). HPA axis activity is subject to GABAergic inhibitory control by the frontal cortex (Akana, Chu, Soriano, & Dallman, 2001; Diorio, Viau, & Meaney, 1993; Radley et al., 2009) and ventral hippocampus (Cullinan, Herman, & Watson, 1993) at the level of CRH-positive neurons of the paraventricular nucleus (PVN) of the hypothalamus (Diorio et al., 1993; Herman, Cullinan, Morano, Akil, & Watson, 1995; Sapolsky, Krey, & McEwen, 1984). In behaviorally naïve animals these neurons are effectively inhibited by phasic- and tonic-hyperpolarizing currents mediated by γ2- and δ-subunit-containing $GABA_ARs$, respectively (V. Lee, Sarkar, & Maguire, 2014; Verkuyl,

Hemby, & Joels, 2004). Acute stress leads to the release of neurosteroids that potentiate the function of δ-containing $GABA_A$Rs, which limits acute stress-induced HPA axis activation (Sarkar, Wakefield, MacKenzie, Moss, & Maguire, 2011). However, repeated stress leads to downregulation of the chloride transporter KCC2 and hence to a lasting depolarizing shift in the chloride reversal potential of CRH neurons that renders GABAergic inputs ineffective or even depolarizing (Hewitt, Wamsteeker, Kurz, & Bains, 2009). In addition, stress-induced NE release results in β-adrenergic receptor-mediated upregulation of metabotropic glutamate receptors, which in turn results in a lasting potentiation of GABAergic synaptic inputs to CRH neurons and further enhances GABAergic excitatory input to the PVN (Inoue et al., 2013). Chronic stress-induced presynaptic changes that reduce GABA release onto CRH neurons have also been described (Verkuyl et al., 2004). Collectively, chronic stress-induced presynaptic and postsynaptic changes render GABAergic inhibition of CRH neurons ineffective or even excitatory, which explains excessive and constitutive activity of the HPA axis and provides an explanation for the most common neuroendocrine abnormality of MDD.

Early life stress-induced dysfunction leads to pathological changes of the HPA axis and confers considerable risk for MDD and other neuropsychiatric disorders in later life (Bale et al., 2010). Moreover, compared to adulthood the developing brain is far more vulnerable to stress. Recent evidence indicates that stress-induced early life reprogramming of the HPA axis involves stress-induced release of allopregnanolone and corresponding potentiation of tonic GABAergic inhibition mediated by δ subunit-containing $GABA_A$Rs on CRH neurons of the PVN (Gunn et al., 2013). Increased GABAergic inhibition appears to result in a compensatory developmental increase in glutamatergic innervation of these neurons that persists to adulthood. Excessive glutamatergic activation of CRH neurons in adulthood renders these neurons insensitive to stress-induced increases in GABAergic inhibition, which explains the permanent changes in HPA axis activity observed in animals and possibly people exposed to early life stress (Gunn et al., 2013). Importantly, the action of neurosteroids on these receptors expressed by hypothalamic CRH neurons is required also for normal physiological responses of mice to stress (Sarkar et al., 2011). Thus, stress-induced allosteric potentiation of tonically active $GABA_A$Rs serves as a key mechanism underlying both normal and pathological developmental programming of HPA axis function.

The hippocampus and frontal cortex are activated along with the PVN in response to acute emotional stress (H. Y. Li & Sawchenko, 1998) and they represent additional sites of vulnerability to stress (Arnsten, 2009; Calfa, Bussolino, & Molina, 2007; R. S. Duman, Malberg, & Nakagawa, 2001; Maggio & Segal, 2009). In healthy people, stress-induced defects in GABAergic inhibition of the prefrontal cortex include down-regulation of GABA following exposure to psychological stressors (Hasler, van der Veen, Grillon, Drevets, & Shen, 2010). In rats, prefrontal cortical GABA is down-regulated following exposure to immobilization stress (Otero Losada, 1988). Moreover, failure of rats to learn to escape in the learned helplessness task (a stressful test of rodents with predictive validity for antidepressant drug action) is associated with down-regulation of $GABA_A$Rs in the neocortex, hippocampus and striatum (Drugan et al., 1989; H. Tan, Zhong, & Yan, 2004). In the hippocampus of rodents, acute stress results in rapid up-regulation of neurosteroid-sensitive, tonically active δ subunit-containing $GABA_A$Rs (J. Maguire & Mody, 2007;

Serra, Pisu, Mostallino, Sanna, & Biggio, 2008), while chronic stress results in loss or impaired function of PV^+-interneurons (Hu et al., 2010) and down-regulation of GABA (Gronli et al., 2007). A wealth of data from analyses of δ subunit KO mice further supports the conclusion that aberrant steroid synthesis and dysregulation of δ-containing $GABA_A$Rs contribute to stress-, ovarian cycle-, and pregnancy-related mood disorders (J. Maguire, Ferando, Simonsen, & Mody, 2009; J. Maguire & Mody, 2007, 2008; J. L. Maguire, Stell, Rafizadeh, & Mody, 2005) (reviewed in MacKenzie & Maguire, 2014).

Chronic and early life stress has detrimental effects on adult hippocampal neurogenesis (Gould & Tanapat, 1999; Karten, Olariu, & Cameron, 2005; Mirescu, Peters, & Gould, 2004). Importantly, neurogenesis is subject to dynamic control by local GABAergic interneurons and $GABA_A$Rs that control the mitotic activation of stem cells, the pace of neural maturation, and the synaptic integration of neural progenitor cells [Section (6)]. Therefore, it is readily conceivable that excessive stress-induced impairments of GABAergic transmission and excess glutamate release contribute to the lasting detrimental effects of stress on hippocampal function. Notably, hippocampal neurogenesis is essential for hippocampus-mediated inhibition of HPA axis function (Schloesser, Manji, & Martinowich, 2009; Snyder, Soumier, Brewer, Pickel, & Cameron, 2011). Moreover, disinhibition of HPA axis function correlates with depressive-like increases in emotional reactivity of mice with impaired hippocampal neurogenesis (Shen et al., 2010; Snyder et al., 2011). Although several studies have reported normal emotional behavior following ablation of hippocampal neurogenesis in mice (reviewed in Petrik, Lagace, & Eisch, 2012), hippocampal neurogenesis is also essential for hippocampus-dependent pattern separation, a cognitive task that is impaired in MDD (Fujii et al., 2014; Leal et al., 2014).

Compared to the hippocampal formation there is relatively limited information on how chronic stress affects GABA function in the cortex. However, based on data from chronically stressed rats there is a consensus that such treatment results in reduced expression and function of $GABA_A$Rs (Weizman et al., 1989). Recent analyses of the medial prefrontal cortex of chronically stressed rats further revealed dendritic atrophy of Martinotti cells and reduced expression of GAD67 (Gilabert-Juan, Castillo-Gomez, Guirado, Molto, & Nacher, 2013). These changes are reminiscent of molecular and cellular changes observed in postmortem brain of patients with MDD [Section (2)]. Importantly, dysfunction of the prefrontal cortex also leads to disinhibition of the HPA axis (Diorio et al., 1993; R. M. Sullivan & Gratton, 1999). Thus, chronic stress-induced GABAergic dysfunction in the prefrontal cortex and hippocampus may result in HPA hyperactivity even if the HPA axis per se is functioning properly (Shen et al., 2010). The ensuing systemic excessive release of stress hormones is predicted to perpetuate the problem through further impairment of GABAergic mechanisms in hippocampus and cortex. However, this positive feedback loop may be prevented by antidepressants that restore the function of neural circuits in both hippocampus and cortex (Lagace et al., 2010; Snyder et al., 2011; Surget et al., 2011).

6. GABAergic transmission in relation to the neurotrophic deficit hypotheis of MDD

The neurotrophic deficit hypothesis of MDD is principally based on brain imaging studies that have revealed brain volume reductions in limbic regions implicated in depression, including primary areas of pathology such as the hippocampus and prefrontal cortex. In some studies volume reductions of the hippocampus were shown to correlate with duration of untreated illness, suggesting that they may represent long-term consequences rather than predict illness onset (Cobb et al., 2013; MacQueen et al., 2003; Sheline, Sanghavi, Mintun, & Gado, 1999). However, a recent meta analysis of studies investigating first episode depression has found volume losses that are consistent with the neurotrophic deficit hypothesis of MDD (Cole, Costafreda, McGuffin, & Fu, 2011). Similarly in subjects at high familial risk of MDD, volume reductions in areas 24, 25 and 32 of the cortex arise before the onset of illness, suggesting a causal relationship (reviewed in E. A. Murray et al., 2011). Moreover, there is evidence that antidepressant drug treatment can protect from brain volume loss (Sheline, Gado, & Kraemer, 2003). Some studies suggest that brain volume reduction in MDD is due to loss of neurons and/or glia (Drevets, Price, & Furey, 2008; Miguel-Hidalgo & Rajkowska, 2002). However, more recent data suggest that brain volume reduction in MDD is predominantly due to reductions in neuropil rather than cell numbers (Cobb et al., 2013).

Low peripheral BDNF levels and downregulation of BDNF and its receptor TrkB in brain are some of the best-replicated findings in the field of MDD (Banerjee, Ghosh, Ghosh, Bhattacharyya, & Mondal, 2013; Dwivedi et al., 2003; Dwivedi et al., 2009; Guilloux et al., 2012; Y. K. Kim et al., 2007; Shimizu et al., 2003). BDNF deficit-induced gene expression changes in mice are highly correlated with gene expression changes of orthologous genes in postmortem brain of depressed patients (Tripp et al., 2012). Moreover, preclinical studies provide a possible causal link between reduced BDNF/TrkB signaling and loss of brain volume in MDD. While stress decreases the expression of BDNF in limbic structures involved in emotion regulation (Gronli et al., 2006; Roth, Lubin, Funk, & Sweatt, 2009), antidepressant drug treatments invariably result in increased expression and release of hippocampal BDNF (reviewed in R. S. Duman & Monteggia, 2006; Russo-Neustadt & Chen, 2005). Knockdown of BDNF in mice selectively in the dentate gyrus and global reduction of neural activity-induced expression of BDNF results in depression-related behavior (Sakata, Jin, & Jha, 2010; Taliaz, Stall, Dar, & Zangen, 2010). Moreover, the behavioral effects of antidepressants are reduced in BDNF- and TrkB-deficient mice (Sairanen et al., 2005).

Despite overwhelming evidence that BDNF plays a key role in regulating depression-related behavior and antidepressant drug mechanisms in animal models there is no evidence from human GWAS studies for association of BDNF with MDD. However, a role for BDNF in depressive disorders has been proposed based on gene x environment interactions of two allelic versions of the precursor peptide of BDNF, proBDNF. The Met allele of Val66Met proBDNF negatively affects activity-dependent secretion of BDNF (Z. Y. Chen et al., 2004; Egan et al., 2003). Moreover, in a mouse model of this human polymorphism the Met allele

resulted in increased anxiety- and depression-related behavior, increased vulnerability to stress and reduced responsiveness to the antidepressant fluoxetine (Z. Y. Chen et al., 2006; Yu et al., 2012). Consistent with these preclinical findings, an initial analysis of healthy human volunteers for gene x environment interactions revealed that the proBDNF Met allele conferred greater risk for development of an early life stress-associated anxiety or depressive syndrome (Gatt et al., 2009). However, more recent studies found that the Met allele is protective rather than a risk factor in that it reduces risk for suicide attempts or depressive symptoms associated with early childhood trauma or stress (J. Chen, Li, & McGue, 2013; S. J. Kim et al., 2010; Perroud et al., 2008) and delays the onset of symptoms and severity of symptoms in patients with schizophrenia (Suchanek et al., 2013 and references therein). Thus, while BDNF may affect emotional reactivity and risk for psychiatric disorders, the directionality of such effects in humans is not predictable, and the mechanism is not specific for MDD. The ambiguity of interpreting the human genetic data of BDNF may have an explanation in the circuit-specific behavioral functions of BDNF. While BDNF mimics behavioral effects of antidepressants when injected into the dentate gyrus of rodents (Shirayama, Chen, Nakagawa, Russell, & Duman, 2002), its effects in the ventral tegmental area (VTA) are the opposite of those in the hippocampus, with BDNF infused into the VTA promoting behavioral despair (Eisch et al., 2003) and knockdown of its gene in the VTA leading to antidepressant-like effects (Berton et al., 2006).

Functional interactions between BDNF signaling, GABAergic transmission and trophic support of neurons are best illustrated in the context of adult hippocampal neurogenesis, which is increasingly recognized as a cellular substrate for emotion regulation and behavioral antidepressant drug effects. Specifically, while antidepressant drug treatment increases neurogenesis (Malberg, Eisch, Nestler, & Duman, 2000), ablation of neurogenesis by radiation or chemical genetic means abolishes antidepressant-induced behavioral effects (David et al., 2009; Santarelli et al., 2003). Neurogenesis is also essential for antidepressant-mediated protection from detrimental effects of stress (Surget et al., 2011). BDNF deficit-induced defects in the production and maturation of hippocampal granule cells mimic corresponding deficits induced by knockout of $GABA_AR$ subunits (Duveau et al., 2011; Ren et al., 2014; Waterhouse et al., 2012). Moreover, the effects of limiting BDNF on neuronal maturation can be reversed by barbiturates, which is consistent with the earlier notion that BDNF is involved in the maturation of GABAergic input to these neurons (Porcher et al., 2011; Waterhouse et al., 2012) [Section (4)]. Conversely, the fact that hippocampal neurogenesis is critically dependent on normal GABAergic transmission via $GABA_ARs$, suggests that antidepressants (or antidepressant mediated increases in BDNF) act by modulating GABAergic input to these neurons. Neural activity-dependent release of GABA from PV^+ interneurons delimits the mitotic activation of RGLs in the subgranule cell layer of the dentate gyrus (Song et al., 2012). This mechanism is controlled by $\alpha4\beta\gamma2$ subunit-containing $GABA_ARs$ in RGLs and early progenitors (Duveau et al., 2011; Song et al., 2012). The subsequent maturation of dendrites and dendritic spines of granule cell progenitors is critically dependent on $\alpha2\beta\gamma2$ receptors, but independent of δ-containing receptors, which appear to mediate GABAergic inhibition mainly of mature granule cells (Duveau et al., 2011; Ren et al., 2014).

Interestingly, the neuronal survival promoting function of BDNF is critically dependent on NFATc4, a DNA-binding transcription factor whose nuclear translocation and activity is controlled by BDNF through phospholipase C-mediated activation of calcineurin, which enables nuclear translocation of NFATc4 (Groth & Mermelstein, 2003; Quadrato et al., 2012). Dephosphorylation of NFATc4 by calcineurin requires sustained elevation of intracellular Ca^{2+}. In addition to acting downstream of BDNF, NFATc4 may also promote expression of BDNF. Importantly, NFATc4 promotes hippocampal neurogenesis at least in part by enhancing the transcription of $GABA_AR$ α2 and α4 subunit genes (Quadrato et al., 2014). This mechanism is consistent with a role of enhanced GABAergic transmission in neurogenesis-dependent antidepressant drug mechanisms.

Proper maturation and synaptic innervation of developing granule cells is also critically dependent on a cell autonomic gradual change of E_{Cl} (Ge, Pradhan, Ming, & Song, 2007). The chloride concentration of immature neurons is elevated initially and renders GABA depolarizing for these cells. GABA-mediated membrane depolarization then enables a signaling cascade that involves $GABA_AR$-mediated depolarization, depolarization-mediated influx of Ca^{2+} (Borodinsky et al., 2003; Fiszman & Schousboe, 2004; Gascon et al., 2006; Maric et al., 2001; Schmidt-Hieber, Jonas, & Bischofberger, 2004; Tashiro, Sandler, Toni, Zhao, & Gage, 2006), and activation of Ca^{2+}-dependent kinases such as CaMKII and PKC (Shaywitz & Greenberg, 1999). These and other kinases phosphorylate the DNA-binding transcription factor CREB (Fujioka, Fujioka, & Duman, 2004; Gur et al., 2007; Jagasia et al., 2009; Nakagawa et al., 2002) and enable GABA/$GABA_AR$ mediated activation of CREB target genes, including the genes encoding the potassium/chloride co-transporter KCC2 and BDNF (Aguado et al., 2003; Shieh, Hu, Bobb, Timmusk, & Ghosh, 1998; Tao, Finkbeiner, Arnold, Shaywitz, & Greenberg, 1998) (reviewed in Fiumelli & Woodin, 2007). Evidence from cultured cortical neurons indicates that independent of these transcriptional responses, $GABA_AR$-depolarization-mediated Ca^{2+}-influx also promotes the cell surface accumulation of $GABA_ARs$ and secretion of BDNF, thereby further facilitating this signaling mechanism (Porcher et al., 2011). Secreted BDNF in turn acts presynaptically to promote GABA (and glutamate) release and to increase the relative excitability of GABAergic vs. glutamatergic neurons (Jovanovic, Czernik, Fienberg, Greengard, & Sihra, 2000; Wardle & Poo, 2003). The mechanism of BDNF- and depolarizing GABA-dependent maturation of GABAergic circuits appears to be self limiting as BDNF-induced expression of KCC2 drives the change from depolarizing GABA in immature neurons to hyperpolarizing and inhibitory actions in mature granule cells (Aguado et al., 2003; Fiumelli & Woodin, 2007), which terminates GABA-depolarization-mediated Ca^{2+} influx.

There is an expansive body of literature demonstrating trophic actions of GABA in the developing brain. It is well established that in embryonic brain and immature neurons GABAergic excitation provides essential excitatory drive for neurite growth and functional maturation of neurons, preceding glutamatergic synaptic transmission during brain development, and continuing into adulthood in the context of maturation of adult-born neurons (reviewed in Ben-Ari, 2013; Represa & Ben-Ari, 2005). The interplay of neural activity and trophic functions of GABA is pivotal for normal activity-dependent circuit formation but exposes neural circuits to diverse mechanisms of vulnerability by environmental disturbances. Activity-dependent trophic functions of GABA and BDNF also

provide a mechanistic rationale for association of MDD with reduced expression of BDNF even in the absence of a discernable genetic basis for MDD.

7. GABAergic transmission in relation to glutamatergic etilologies of of MDD

The glutamatergic hypothesis locates the primary deficits of MDD in the excitatory component of cognitive-emotional circuits. Brain imaging studies suggest that depression is characterized by an increase in neural activity/excitation in several brain regions believed to be critically involved in the pathology of MDD (Drevets, 2001; Savitz & Drevets, 2009). Elevated glutamate levels measured in blood plasma and post mortem brain tissue suggest altered glutamate transmission in depressed patients (K. Hashimoto, Sawa, & Iyo, 2007; Lan et al., 2009; Mitani et al., 2006) and post mortem brain tissue analysis revealed alterations in glutamate receptor densities (Deschwanden et al., 2011; Feyissa et al., 2010). Mouse models with genetically modified components of the glutamate system show alterations in depressive-like behavior while established animal models of depression have altered glutamatergic neurotransmission (Tokita et al., 2012). Stress (Pittenger & Duman, 2008) and current antidepressant treatments (Kucukibrahimoglu et al., 2009; Maes, Verkerk, Vandoolaeghe, Lin, & Scharpe, 1998) are known to impact the glutamate system and, perhaps most informative, the discovery of antidepressant properties of the NMDA receptor antagonist ketamine has stimulated development of what might become a new generation of fast acting antidepressants (R. S. Duman & Aghajanian, 2012; Krystal, Sanacora, & Duman, 2013).

Consistent with the aforementioned reductions in brain volume, neural cell densities and neuropil in postmortem brain of MDD patients [Section (6)], excess glutamate release is known to lead to atrophy and cell death. The cytotoxic effects of glutamate are thought to involve increased activation of NMDA receptors (Hardingham & Bading, 2010; Papouin et al., 2012) as a consequence of increased neural activity and neurotransmitter release and corresponding synaptic spillover. Given the intricate relationship between GABAergic and glutamatergic transmitter systems and the pivotal need for neural circuits to balance excitation and inhibition it is readily conceivable that excitotoxicity following elevated glutamatergic transmission might be a consequence of the aforementioned reductions in markers of GABAergic inhibitory synaptic transmission [Section (2)].

Excess activation of NMDARs has also been proposed to involve reduced clearance of glutamate caused by loss of astroglia (Rajkowska & Miguel-Hidalgo, 2007). Such a mechanism is supported by reductions in GFAP immunoreactivity (Si, Miguel-Hidalgo, O'Dwyer, Stockmeier, & Rajkowska, 2004) and glia density in postmortem brain of depressed subjects (Rajkowska & Miguel-Hidalgo, 2007) as well as reports of decreased expression of glutamate transporters and glutamine synthase in several brain areas of depressed patients (Miguel-Hidalgo et al., 2010).

The neurotoxic and proapoptotic effects of glutamate have long been thought to involve selective activation of extrasynaptic NMDARs followed by induction of proapoptotic gene expression programs (reviewed in Hardingham & Bading, 2010). More recently, neurotoxic

effects mediated selectively by synaptic NMDARs have also been described (Papouin et al., 2012). As an alternate mechanism, Lee et al. recently showed that elevated glutamate can trigger NMDAR-mediated downregulation of KCC2 in cultured hippocampal neurons, a mechanism that removes the driving force for GABAergic inhibition (H. H. Lee et al., 2011). This type of mechanism is predicted to exacerbate and perpetuate the detrimental effects of excess glutamate by removing GABAergic inhibition and thereby further increasing excitability and glutamate release. Moreover, it could be argued that such an ionic mechanism would be faster than transcription-dependent reprogramming of cells and hence contribute upstream of gene expression-dependent proapoptotic processes.

Additional support for a glutamatergic hypothesis of depression comes from the previously mentioned reversal of chronic stress-related features of animal models of depression by treatment with antidepressants [Section (5)]. Acute and repeated/chronic stressors have different effects that both involve changes in the function of NMDARs. Short time treatment of rats with corticosterone and acute stress result in a delayed and sustained potentiation of the synaptic response and surface expression of NMDARs, which facilitates the working memory function (Yuen et al., 2011). By contrast, repeated stress suppresses glutamate receptor expression and leads to reduced prefrontal cortex NMDA and AMPA receptor expression, and impaired working memory (Yuen et al., 2012). While cortical GABAergic changes under these conditions have not yet been described, the release of stress hormones via HPA axis that triggers cortical changes in NMDAR function is under tight control by GABAergic mechanisms, as already detailed in Section (5). Briefly, activity-dependent changes in the function of CRH neurons in the VPN provide striking examples of interaction between GABAergic and glutamatergic synaptic plasticity mechanisms. In adulthood, excessive stress leads to a depolarization shift of E_{Cl} that renders GABAergic inhibition of CRH neurons ineffective, leading to excessive and prolonged HPA axis activation (Hewitt et al., 2009). This shift in E_{CL} is likely due to NMDAR mediated downregulation of KCC2 (H. H. Lee et al., 2011). Thus, the lasting pathology consists of reduced efficacy of GABAergic inputs, while the cause was an NMDAR dependent change in E_{Cl}. By contrast, in young animals, repeated stress leads to neurosteroid mediated enhancement of GABAergic inhibition and a compensatory yet stable increase in glutamatergic synapse formation that permanently alters the balance between excitatory and inhibitory inputs to CRH neurons and thereby leads to life long hyperexcitability of the HPA axis (Gunn et al., 2013). Thus, the lasting pathology in this case consists of glutamatergic hyperexcitability, and the causal aberration was a developmental and transient change in GABAergic transmission.

A similar scenario can be envisioned for depression-related defects in adult-hippocampal neurogenesis. As mentioned in Section (2) the depressive-like phenotype of $GABA_AR\ \gamma2^{+/-}$ mice includes a marked deficit in dendritic spine maturation of adult-born hippocampal granule cells, indicative of defects in glutamatergic synaptic transmission (Ren et al., 2014) and similar maturational defects were also reported for mice with reduced expression of BDNF (Waterhouse et al., 2012) and mice lacking the $GABA_AR\ \alpha2$ subunit (Duveau et al., 2011). Importantly, the maturational defects of granule cells in $\alpha2$ knockout mice could be reversed by systemic treatment with gabapentin, an antagonist of thrombospondin receptors that acts as a neuroleptic by suppressing the formation of glutamatergic synapses (Duveau et al., 2011). This finding suggests that defects in glutamatergic transmission associated with

depressive states are a consequence of causal GABAergic deficits and an excessive rather than a reduced drive to form new glutamatergic synapses.

Pharmacological antagonism of the NMDA receptor, notably by a single subanesthetic dose of ketamine, has rapid and lasting antidepressant effects in patients and animal models (Berman et al., 2000; Crane, 1959; Garcia et al., 2009; Trullas & Skolnick, 1990) (reviewed in Krystal et al., 2013). More recent studies indicate that GluN2B specific antagonists (i.e. Ro25-6981, CP101,606) have antidepressant effects similar to ketamine although with shorter duration (Maeng et al., 2008; Preskorn et al., 2008). Compared to GluN2A receptors, GluN2B receptors are enriched in the extrasynaptic membrane and implicated in the cytotoxic effects of glutamate. Although the mechanism of action of ketamine remains poorly understood its effects in mice depend on GSK3β (Beurel, Song, & Jope, 2011) and they are augmented by inhibitory phosphorylation of GSK3β (Liu et al., 2013). GSK3β is a key kinase in the Wnt signaling pathway that also serves as a pharmacologically releavant target of the mood stabilizer lithium (Voleti & Duman, 2012). Althought the relevant targets phosphorylated by GSK3β in this context are largely unknown, lithium-mediated inhibition of GSK3β was recently shown to strengthen GABAergic synaptic transmission (Tyagarajan et al., 2013; Tyagarajan, Ghosh, Yevenes, et al., 2011) as detailed already in Section (4). It stands to reason then that the antidepressant mechanisms of ketamine, similar to monoaminergic antidepressants, might involve potentiation of GABAergic transmission.

In keeping with evidence that MDD involves decreased expression of synapse-related genes and reduced density of glutamatergic synapses (Kang et al., 2012), ketamine-induced antidepressant effects involve an mTor-dependent mechanim of synaptogenesis, including rapid induction of spine fomation and increased function of glutamatergic synapses (reviewed in R. S. Duman & Li, 2012; N. Li et al., 2010; N. Li et al., 2011). It follows that in order to maintain the E/I balance and to prevent ketamine-induced neurotoxic release of glutamate, ketamine-induced enhancement of glutamatergic transmission must occur in concert with augmentation of GABAergic transmission. By extension, and given the evidence for GABAergic defects in MDD reviewed in Sectiion (2), it should become abundantly clear that depressive brain states involve not only functional deficits in glutamatergic transmission but also reduced GABAergic activity. GABA sets the tempo of brain development, particularly in the cortex and hippocampus (reviewd in Ben-Ari, 2013; Ge et al., 2007). Its function through $GABA_A$Rs is subject to direct modulation by neurosteroids (reviewed in Comenencia-Ortiz, Moss, & Davies, 2014; Gunn et al., 2014; MacKenzie & Maguire, 2014), and the function of $GABA_A$Rs itself is vulnerable to environmental effects on E_{Cl} (Ben-Ari, Khalilov, Kahle, & Cherubini, 2012). The collective evidence suggests that defects in GABergic transmission are causative rather than a consequence of pathological changes in glutamatergic tansmission.

9. Conclusion

The quest to elucidate the biology underlying MDD is complicated by symptom heterogeneity, the fact that pathological changes are distributed across a multitude of forebrain circuits, and a virtual lack of concrete insights from human GWAS. Nevertheless, there has been remarkable progress in our understanding of the biology of mood disorders

over the last two decades. Here, we have summarized increasing evidence for convergence of the GABAergic deficit hypothesis of MDD with other proposed etiologies of this disorder. We attempted to make the case that alterations in markers of GABAergic transmission associated with MDD are not merely epiphenomena but that they are causally involved in the etiology of the disorder. A GABA-centric view of the biology of MDD has provided novel insights into pathological mechanisms of stress, the detrimental effects of stress on cortical and hippocampal deficits associated with MDD as well as functional changes in the HPA axis. Moreover it is becoming increasingly evident that antidepressant drug effects depend on mechanisms that restore GABAergic inhibition.

A number of aspects of GABAergic transmission in the context of MDD remain unexplained. One major obstacle to the GABAergic hypothesis of MDD is the lack of drug therapies that are based on enhancement of GABA function and show therapeutic efficacy in MDD. In particular, benzodiazepines are largely ineffective as antidepressants, except for the occasional use of alprazolam to augment the efficacy of conventional antidepressant drug therapies (Birkenhager, Moleman, & Nolen, 1995; Petty, Trivedi, Fulton, & Rush, 1995). Possible explanations for this phenomenon include the fact that benzodiazepines induce rapid tolerance and also increase lysosomal degradation of major subtypes of $GABA_A$Rs, rendering these drugs unsuitable for long-term therapies (Jacob et al., 2012; Vinkers et al., 2012), although they are highly effective as anxiolytics. However, it is conceivable that novel subtype-specific agonists of $GABA_A$Rs will alleviate this problem (Rudolph & Mohler, 2014).

Reports on the rapid antidepressant action of ketamine and other NMDAR antagonists has sparked considerable excitement regarding their potential application as next generation antidepressant therapeutics and they point to a key role of altered glutamatergic transmission in the pathology of MDD (Krystal et al., 2013). However, whether altered GABAergic transmission also plays a role in the therapeutic efficacy of NMDAR antagonists is not yet known. Exploring the relationship between GABAergic defects, alterations in glutamatergic transmission and the antidepressant efficacy of NMDAR antagonists will likely provide valuable new insights into the pathophysiology of MDD.

We have reviewed evidence pointing to a key role of reduced GABAergic inhibition in cortex, hippocampus and VPN in the cellular, hormonal and behavioral changes associated with MDD, In addition GABAergic mechanisms are known to exert powerful control over dopaminergic reward circuits in the ventral tegmental area (Brown et al., 2012; K. R. Tan et al., 2012; Tritsch, Ding, & Sabatini, 2012; van Zessen, Phillips, Budygin, & Stuber, 2012) Moreover, preclinical studies suggest that defects in GABAergic transmission may result in reduced reward seeking behavior thought to represent depressive-like traits (Shen et al., 2010). However, the precise location and nature of corresponding changes in GABAergic transmission remains to be explored.

Lastly, the pathobiology of MDD and other psychiatric conditions is closely linked to inflammatory processes, which might also play a causal role in the etiology of MDD (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Walker, Kavelaars, Heijnen, & Dantzer, 2014). For example immunotherapies of viral infections with proinflammatory

cytokines result in side effects including sickness behavior that resemble depressive-like states (Raison et al., 2009). Moreover transcriptome analyses of postmortem brains of MDD patients show significant changes in expression of inflammation-related genes (Shelton et al., 2011). However, whether and how inflammation affects GABAergic and glutamatergic transmission or other mechanisms influencing the excitation/inhibition balance is largely unknown. One speculative indication that GABAergic mechanisms might play a role is based on evidence that inflammatory processes can contribute to epilepsy (Zattoni et al., 2011), pointing to disrupted excitation-inhibition balance of neural circuits. Conversely, epilepsy often emerges as a consequence of genetically determined defects in GABAergic inhibition, and the disease is frequently comorbid with depressive disorder. Progress and new insights in all of these areas should allow us to soon draw a more complete picture on the role of altered GABAergic neurotransmission in the etiology of MDD.

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ABBREVIATIONS

5-HT	5-hydroxytryptamine
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)
BDNF	brain derived neurotrophic factor
CA1	cornus ammonis 1
CA3	cornus ammonis 3
CaMKII	calcium-calmodulin-dependent kinase II
CREB	cAMP-regulated element binding protein
CRH	Corticotropin Releasing Hormone
ERK	extracellular signal-regulated kinase
E_{Cl}	chloride equilibrium potential
DISC1	disrupted in schizophrenia 1
DLPFC	dorsolateral prefrontal cortex
GABA	γ-aminobutyric acid
$GABA_AR$	GABA type A receptor
GAD	glutamic acid decarboxylase
GSK3β	glycogen synthase kinase 3β
GWAS	genome-wide association studies

HPA	hypothalamus-pituitary-adrenal axis
KCC2	potassium-chloride co-transporter 2
MDD	major depressive disorder
NMDA	N-methyl-D-aspartic acid
NPY	neuropeptide Y
PET	positron emission tomography
PKC	protein kinase C
PKA	protein kinase A
PV	parvalbumin
PVN	paraventricular nucleus of the hypothalamus
RGL	radial glia-like astrocytes/stem cell
SERT	serotonin transporter
sgACC	subgenual anterior cingulate cortex
SSRI	selective serotonin reuptake inhibitor
SST	somatostatin
TCA	tricyclic antidepressant
TMS	transcranial magnetic stimulation
TrkB	Tropomyosin related kinase B
VPN	ventral posterior nucleus of the hypothalamus
5-HT	5-hydroxytryptamine

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