



Glutamate-based depression GBD

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ABSTRACT

We describe a new term: glutamate-based depression (GBD). GBD is defined as a chronic depressive illness associated with environmental stress and diseases associated with altered glutamate neurotransmission. We hypothesize that glutamate-induced over-activation of extrasynaptic NMDA receptors in the subgenual cingulate area called Brodmann's 25 plays an important role in the etiology of depression and may be responsible for the high incidence of co-morbid depression associated in diseases with glutamate etiology. While depression is a syndrome with multiple possible etiologies, we propose that a disruption in glutamatergic neurotransmission may underline a substantial proportion of clinically observed depression. The high rates of depressive symptoms associated with various disorders in which altered glutamatergic functions have been identified, may suggest a common pathophysiological mechanism is underlying the diverse clinical presentations.

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Introduction

We hypothesize that GBD results from an impaired ability to efficiently regulate glutamatergic neurotransmission and an increased activation of extra synaptic NMDA receptors in brain regions including the subgenual cingulate area called Brodmann's 25 (BA25) [1]. The excess activation of the extrasynaptic NMDA receptors leads to structural and functional changes in these regions, disrupting neurotransmission in distal regions associated with mood regulation such as the prefrontal cortex. The aberrant activity is secondary to events such as prolonged or extreme stress, or injury that affects glutamate release, clearance and metabolism. This is an extension of the hypothesis proposed by Marsden [2], that stressors induce excessive NMDA receptor activity resulting in the pathology of depression. Under normal conditions, levels of extracellular glutamate are tightly regulated for optimal efficiency and limited excitotoxicity [3]. However, in certain disease states this regulation is disrupted by changes in pre-synaptic release, postsynaptic receptor expression and function, and glial cell mediated glutamate clearance and metabolism, resulting in increased levels of extracellular glutamate and over-activation of the NMDA receptors in regions such as BA25. These events lead to a mal-adaptive survival response at the cellular and behavioral levels causing atrophy of neuropil and immobilizing the person (by dampening neurotransmission) thus increasing the chances

of survival until the injury heals or the organism recovers from illness. Effective treatments of GBD should act by dampening, blocking or normalizing these activated extrasynaptic NMDA receptors. Treatment of GBD and disorders with altered glutamate function would involve a multipronged approach including standard treatments along with the co-administration of an NMDA antagonist.

The link between NMDA receptors, glutamate and depression

Almost all current antidepressants affect the uptake or metabolism of biogenic amines such as serotonin, dopamine and norepinephrine. However, the delayed onset of action (2–6 weeks) of these agents indicates that other processes of neuro-adaptation are also responsible for the mechanism of action. Glutamate is an abundant neurotransmitter that is essential for learning and memory but at high concentrations can produce deleterious effects including neuronal cell death. Ample evidence now indicates that glutamate homeostasis and neurotransmission are disrupted in major depressive disorder [4,5] and drugs that target the NMDA receptor have rapid antidepressant properties in both clinical and preclinical studies. Examples of moderate to fast-acting clinical treatments for depression include NMDA antagonists such as ketamine and CP101606 and deep brain stimulation. Ketamine and deep brain stimulation have been shown to have a near direct effect on dampening BA25. Skolnick [6] provided evidence that all typical antidepressants such as SSRI's and SNRI's work through a common mechanism – the dampening of the NMDA receptor function. Musazzi et al. [7] have also shown that several classes of common antidepressant agents dampen glutamate release following

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acute stress exposure in the rat prefrontal/frontal cortex. Interestingly, tianeptine and agomelatine, two agents with antidepressant properties that do not have direct effects on monoamine uptake or degradation, have been shown to inhibit acute stress-induced increase in glutamate release in the rat amygdala [8] and thus may alleviate the symptoms of depression via normalizing stress-induced disruption of glutamatergic transmission [9,10]. NMDA antagonists are active in multiple animal models of depression including elevated plus-maze, tail suspension test and forced swim test [11–13].

Insertion and removal of NMDA receptors play crucial roles in the regulation of synaptic strength in the CNS. The trafficking of NMDA receptors provides an important way to modulate mood and memory. Regulation of NMDA receptor trafficking has been proposed as important dynamic mechanism for regulation of synaptic function [14]. We propose that a dysregulated balance of synaptic and extrasynaptic activation of NMDA receptors in areas such as BA25 leads to many of the characteristic signs and symptoms of major depressive disorder. Altered astroglia function, as seen in analogous brain regions in rodents following chronic stress exposure [15], is likely to impair extracellular glutamate clearance and may contribute to the chronically dysregulated balance by allowing excess activation of extrasynaptic NMDA receptors in BA25. In addition, a substantial proportion of extrasynaptic NMDA receptors *in vivo* are located adjacent to glia raising the possibility that astrocytic glutamate release may also lead to the chronic activation of these receptors [16]. Evidence is mounting that up regulation or over stimulation of these extrasynaptic NMDA receptors by glutamate in the subgenual cingulate area (BA25) plays a pivotal role in the etiology of GBD. Perturbations in the balance between synaptic and extrasynaptic NMDA receptor activity have been reported to contribute to neuronal dysfunction in a number of diseases of the brain [17]. Increased glutamate levels have been found in the hippocampus and amygdala in preclinical stress models [8,18,19] and in the frontal cortex from patients with bipolar disorder and major depression [20].

The link between BA25 and depression

Converging data implicate the subgenual cingulate region (BA25) in major depression [21]. In addition, glutamate-induced over-activation of NMDA receptors may play an important role in the etiology of MDD [20]. This new glutamate/NMDA hypothesis provides a fresh understanding beyond the limits of the classical serotonin/norepinephrine hypothesis of depression. BA25 is located in the cingulate region as a narrow band in the caudal portion of the subcallosal area adjacent to the paraterminal gyrus. Liotti et al. [22] showed that sadness was accompanied by specific activation of BA25. Neuroimaging has also implicated BA25 in the pathophysiology of depression and this region has been a target for therapeutic neuromodulation. BA25 connects to several structures known to be associated with the pathophysiology of depression, including the medial prefrontal cortex (mPFC), ventromedial striatum (VMStr), mediodorsal nucleus of the thalamus (MD) and dorsal raphe nuclei (DRN). Other antidepressant treatments including chronic serotonin reuptake inhibitors (SSRIs), deep brain stimulation (DBS), and electroconvulsive therapy (ECT) reduce BA25 hyper-activation with time-courses aligned to therapeutic effect [23]. Importantly, the findings that ketamine can produce both a rapid and sustained antidepressant effect in depressed patients [24–26] and can rapidly turn off BA25 [27] supports the hypothesis that ketamine is acting as a pharmacological “switch” whereby the rapid removal of the braking action of BA25 unmasks motivated behavior and improves mood.

Glutamate-induced hyper-activation of BA25 may suppress the normal functioning of brain regions associated with reward

processing and goal-directed behavior leading to a host of symptoms including: anhedonia, psychomotor retardation, and reduced motivational drive. Altered astroglial function, such as that seen following periods of chronic and early life stress in rodents [15], could account for the glutamate-induced hyper-activation of BA25. Astrocytes play a central role in amino acid neurotransmitter metabolism, clearance and recycling of released glutamate and GABA [28,29]. Glutamate is sequestered from the synapse by the astroglial glutamate transporters GLT-1 and GLAST to prevent excitotoxicity due to prolonged activation of the extrasynaptic NMDA receptors. Astrocytes metabolize glutamate into glutamine (Gln) using glutamine synthetase (GS). In addition, the selective loss of glia cells in brain regions analogous to the anterior cingulate is sufficient to induce depressive-like behaviors in rats [30]. Microglia are major producers of tumor necrosis factor- α (TNF) in the brain. TNF- α potentiates glutamate neurotoxicity through the blockade of glutamate transporters [31]. As a result, TNF is cytotoxic and could play a role in the pathology of depression. In light of postmortem studies showing a reduction in the density and numbers of glia cells (whose function is to control glutamate levels) in the subgenual anterior cingulate [32], as well as other frontal cortical regions [33], we propose that the extrasynaptic glutamate levels remain chronically elevated in depressed patients.

Drugs that target the NMDA receptor directly have rapid antidepressant properties in both clinical and preclinical studies. Examples of such drugs include ketamine and CP101606 [25,26,34]. Recently, Li et al. [35] reported that ketamine rapidly activates the mammalian target of rapamycin (mTOR) pathway, leading to increased synaptic signaling proteins and increased number and function of new spine synapses in the prefrontal cortex of rats. We believe that NMDA antagonists act by dampening, blocking or redistributing the extrasynaptic NMDA receptors in BA25, while potentially briefly stimulating synaptic AMPA receptors leading to sustained elevation of synapse-associated proteins and spine number in the prefrontal cortex.

The turning off of BA25 restores normal neurotransmission in brain regions affecting mood and cognition

Some data support that increased glutamate release (and not inhibition) is necessary to produce the fast-acting antidepressant effects of NMDA antagonists such as ketamine. This hypothesis is based on studies showing that the AMPA antagonist NBQX blocks the antidepressant activity of the NMDA antagonists in the rodent forced swim test (FST) [36]. There is also a strong relationship between the doses that appear to stimulate glutamate cycling and those that have antidepressant-like effects. The NBQX mechanism has been called into question by Dybala et al. [37] who tested the NMDA antagonist CGP37849 in mouse FST (using the same protocol used by Maeng et al. [36]), and showed that NBQX did not block the antidepressant effect of CGP37849. We need better tools, e.g., NMDA antagonists that do not cause hyperactivity in rodents, to strengthen the AMPA activation hypothesis.

Further evidence of the role of BA25 was provided by Pizzagalli et al. [38] who reported that melancholia was associated with reduced activity in BA25, manifested by increased inhibitory delta activity (1.5–6.0 Hz) and decreased glucose metabolism, which themselves were inversely correlated. Following antidepressant treatment, depressed subjects with the largest reductions in depression severity showed the lowest post-treatment subgenual PFC delta activity. Schatzberg et al. [39] have reported that these regions play a role in the pathology of patients with psychotic major depression. They demonstrated impaired performance on both the color-word portion of the Stroop Color-Word Test and the Paragraph Recall Test (verbal memory) in these patients. Mayberg

et al. [21] have demonstrated consistent involvement of BA25 in acute sadness and antidepressant treatments. They applied chronic deep brain stimulation to BA25 and showed remission of depression in patients with treatment-resistant depression. BA25 is linked by glutamate pathways to regions of the brain known involved in behaviors that are altered in depressed patients. Segal et al. [40] placed microdialysis probes into the brain of a baboon in the regions with glutamatergic connections to BA25 that included the medial prefrontal cortex. They showed that local high frequency electrical stimulation of BA25 resulted in the release of dopamine and serotonin in regions distal to BA25 but known to be involved in the pathology of depression. Salvatore et al. [41] found that increased activity in the BA25 in response to faces showing negative emotional expressions was positively correlated with rapid antidepressant response to ketamine. It is interesting that the same brain region has been implicated as a putative biomarker, of treatment response to ketamine, during a cognitively demanding task [42]. Harrison et al. [43] reported that healthy volunteers, that received typhoid vaccine showed increased circulating interleukin-6 and significant mood reduction within three hours of injection. This was accompanied by enhanced activity in BA25. They suggested that the central neurobiological circuits supporting adaptive motivational reorientation during sickness might be “hijacked” during clinical depression. The difference in the rapidity of the effect of ketamine versus DBS can be explained by direct (for ketamine) versus indirect (for DBS) effects. Ketamine acts directly at the NMDA receptor rapidly normalizing the extrasynaptic versus synaptic ratio. In contrast, DBS acts indirectly resulting in a longer time for the NMDA receptor ratios to compensate. This has been discussed previously as increasing point to point glutamatergic drive and increased ratio of AMPA/NMDA receptor activation [44].

The hypothesis

We define glutamate-based depression (GBD) as a chronic depressive illness associated with environmental stress and diseases associated with altered glutamate neurotransmission. Changes in the balance between synaptic and extrasynaptic NMDA receptor activity have been proposed to contribute to neuronal dysfunction in neurodegenerative diseases [1,17]. We hypothesize that glutamate-induced over-activation of extrasynaptic NMDA receptors in BA25 plays an important role in the etiology of depression and may be responsible for the high incidence of co-morbid depression associated in diseases with glutamate etiology. Effective treatments of depression reset the ratio of synaptic and extrasynaptic NMDA receptors to their normal pre-disease state in BA25, resulting in the restitution of normal neurotransmitter release in regions involved in mood and cognition.

Risk factors for depression

Inflammation

Major depression is accompanied by activation of the inflammatory response including increased production of pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6 and interferon (IFN gamma). These cytokines may play a crucial role in the immune and acute phase response in depression. Müller and Schwarz [45] reported that an elevation of proinflammatory cytokines, leads to an enhanced production of quinolinic acid, a strong agonist of the NMDA receptor. Quinolinic acid activates receptors containing NR1 + NR2A and NR1 + NR2B subtypes of the NMDA receptor. Activated macrophages are also known to release large amounts of glutamate which may contribute to the exacerbation of the inflammatory response [46]. The inflammatory cytokines, IL-1

and TNF- α dose-dependently inhibit human astrocyte glutamate uptake [47]. TNF- α also modulates glutamate transport in the CNS and is a critical determinant of outcome from viral encephalomyelitis [48]. TNF- α potentiates glutamate-induced spinal cord motoneuron cell death [49]. These data link two important pathogenic mechanisms, excitotoxicity and neuroinflammation. The relationship between depression and elevation of certain inflammatory molecules may be linked to glutamate via the NMDA receptor and activated astrocytes and microglia. Finally, Wolkowitz et al. [50] reported shortening of leukocyte telomeres (a proposed biomarker of cell aging) in patients with chronic depression. In this study, IL-6 concentrations were inversely correlated with telomere length in depressed subjects. They hypothesize that telomere shortening could explain the higher deaths and co-morbidity in chronically depressed patients.

Interferon-induced depression

In humans, exposure to the cytokine, interferon leads to depression. Glutamatergic neurotransmission functions can be affected by IFN- α . Brain inflammation is associated with increased pro-inflammatory and cytotoxic cytokines, such as IL-1, TNF- α and IFN- α [51]. This may be accompanied by high extracellular glutamate concentrations, followed by an increased risk for excitotoxic cell death. Glutamate uptake by astrocytes has been postulated to play an important neuroprotective role during brain inflammation. Hu et al. [47] showed that the pro-inflammatory cytokines IL-1, TNF- α and IFN- γ inhibit glutamate uptake by astrocytes. In addition, TNF- α potentiates glutamate neurotoxicity in primary human neuronal cell cultures. Since IFN- α induces TNF- α and IL-1, one might postulate that glutamate concentrations increase during administration of IFN- α via blockade of glutamate re-uptake, and that this mechanism may enhance symptoms of depression.

Coronary artery disease

Depression is a factor in cardiovascular disease. Major depression occurs in almost 20% of patients with coronary artery disease (CAD). Glassman et al. [52] reported that depression is often persistent, impairs health status more than heart disease itself, and substantially increases morbidity and mortality in these patients. In addition, they also reported that these individuals have an exaggerated inflammatory response to psychological stress compared to those who do not suffer from depression. There are significantly larger percentages of cardiac events occurring in depressed patients versus non-depressed patients with CAD [53]. Thus far, attempts to treat the depression to improve heart disease outcomes have been unsuccessful. This could be due to modest treatment response and small sample size. Until better treatments for depression become available, large prospective trials may be needed, to establish both the potential cardiovascular benefit and safety of current depression treatments [54].

Depression observed following acute coronary syndrome (ACS) is common and associated with an increased risk of mortality. Medically healthy individuals who suffer from depression are at significantly increased risk of developing heart attacks and strokes later in life. In addition, acute cardiovascular events can precipitate depression in some patients. An estimated 600,000 people become depressed soon after a heart attack [55]. Depression used to be thought of as an understandable and inevitable reaction to the severe circumstances accompanying a heart attack or CABG surgery. As a result, it is not always treated. There is a clear need to develop more efficacious treatments for depression in patients with coronary artery disease [56].

Inflammation and immune activation are important in the pathogenesis of CAD. Induction of inflammatory cytokines can have a

downstream deleterious effect on the brain. Wirleitner et al. [57] demonstrated enhanced degradation of tryptophan in CAD patients along with an increase in the kynurenine to tryptophan ratio. They attributed this to the induction of indoleamine (2,3)-dioxygenase (IDO) an enzyme that degrades tryptophan to kynurenine. Kynurenine is metabolized to 3-hydroxy-kynurenine (3-OH-KYN) and quinolinic acid (QUIN). Both of these metabolites have toxic effects on brain function. 3-OH-KYN is able to produce oxidative stress by increasing the production of reactive oxygen species (ROS). QUIN over-stimulates hippocampus NMDA receptors, which leads to apoptosis and hippocampus atrophy. Overproduction of reactive oxygen species and hippocampus atrophy caused by NMDA overstimulation has been associated with depression [58].

An additional link between coronary artery disease, NMDA and major depression may be via synapse-associated protein 97 (SAP97). This protein is found in abundance in the heart and the brain, where it is believed to play a role in cardiac contractions and memory creation [59]. In the brain, SAP97 is known as a “scaffolding” protein that serves to tether proteins inside the cell critical to nerve signaling and keeping them close to NMDA receptors at the cell surface. SAP97 mediates the clustering of NMDA receptors and interacts with the NMDA receptor both *in vitro* and *in vivo*. A similar scaffolding mechanism is at work in the heart, where it affects basic functions, including the heartbeat. These data support a shared pathophysiology with both diseases that could explain the high incidence of morbidity in depressed patients with coronary artery disease.

Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory disorder primarily affecting the joints, leading to their progressive destruction. Co-morbid depression is an independent risk factor for mortality in patients with rheumatoid arthritis (RA). The prevalence of co-morbid depression in patients with RA ranges between 13% and 20% [60–62]. Depression has been demonstrated to be an independent risk factor for mortality (non-suicide) in patients with RA [63]. This study involved 1290 patients with RA, showed that the cohort with persistent or recurrent depression over an initial four-year period had higher mortality rates than those without depression, when followed over the subsequent 18 years. Rates and patterns of suicide in patients with RA have also been studied. Timonen et al. [64] showed that 50% of their cohort of 19 patients with RA who had committed suicide were women, a much higher female percentage compared with the general population (18% in their study). About 90% of these women had suffered from co-morbid depression. Treharne et al. [65] found that 11% of hospital outpatients with RA had suicidal ideation at one time. Glutamate is the key neurotransmitter in communication between the periphery and spinal dorsal horn. Painful pressure to inflamed joints leads to enhanced glutamate release and strong depolarization, which activates both NMDA and AMPA receptors [65]. NMDA receptors play an essential role in central sensitization. Parada-Turskaa [66] has shown that glutamate receptor antagonists inhibit the proliferation of synovial fibroblasts *in vitro*. Matrix metalloproteinase 2 and 9 (MMP-2, MMP-9) are elevated in the synovial fluid of patients with rheumatoid arthritis [67] and contribute to cartilage degradation in rheumatoid arthritis. Flood et al. [68] reported that activation of NMDA receptors on human synoviocytes could contribute joint destruction by increasing IL-6 expression in these cells. It is of interest that Domenici et al. [69] reported that MMP-9 and other inflammatory cytokines were significantly elevated in the plasma of depressed patients. Based on these findings, they suggest that glutamate receptor antagonists may have a disease-modifying effect on rheumatoid synovial proliferation. As with CAD, these data suggest that RA and MDD share a common pathophysiological mechanism involving glutamate signaling.

Chronic pain

Chronic pain and depression have long been linked, and patients with chronic pain suffer a high incidence of major depressive disorders. Disabling chronic pain is present in more than 40% of patients with depression versus 10% of those without depression [70]. The prevalence of depression in individuals with chronic pain conditions is 11.3%, versus 5.3% in those without [71]. Glutamate plays a significant role in pain processing. Glutamate and glutamate receptors are located in areas of the brain, spinal cord and periphery that are involved in pain sensation and transmission. NMDA receptors have an important role in persistent inflammatory pain by reinforcing glutamate sensory transmission. Windup pain is caused by the induction of glutamate NMDA receptors in the dorsal horn [72]. A vicious cycle occurs of increased glutamate release, release of substance P, and increased sensitization of the NMDA receptors. In particular, there is over expression of the NR2B NMDA receptor subtype associated with windup pain [73]. NMDA receptors have an important role in persistent inflammatory pain by reinforcing glutamate sensory transmission. Drugs targeting NMDA NR2B subunits in the forebrain could serve as a medicine for controlling persistent pain and depression in humans. Finally, there is also a growing literature about the use of ketamine to treat pain. To date, there have been nine positive reports published using ketamine to control complex regional pain syndrome [74]. Intravenous ketamine also showed efficacy in burn patients, with a reduction in secondary hyperalgesia when compared with opioid analgesia alone. In addition, combination therapy of ketamine and morphine resulted in the abolishment of windup pain [75]. Hocking and Cousins [76] published a comprehensive review of the efficacy of ketamine in multiple pain indications. All of these authors cautioned about concluding the efficacy of ketamine in treating pain because of potential side-effects and under reporting of failed trials. They suggest performing large well controlled pain trials to firmly establish ketamine's efficacy in treating pain. A number of companies are developing ketamine for various pain indications.

Diabetes

There is a 24% lifetime prevalence of depression in individuals with diabetes mellitus [77]. This is a prevalence rate three times higher than the general population. An aberrant glutamate system has been identified as a part of the pathogenesis of diabetes. Significantly elevated levels of plasma glutamate have been reported in patients with non-insulin dependent diabetes [78]. Li and Puro [79] showed that the loss of function of glutamate transporter in glial cells is one of the earliest changes reported in diabetes. This change precedes the decrease in activity of glutamine synthetase, which is the rate-limiting enzyme for the conversion of glutamate to glutamine in these cells. They proposed a mechanism by which these cells play a role in the progression of diabetic retinopathy. Dysfunction of the glutamate transporter and the resultant elevation of glutamate levels and activation of the NMDA receptor may create a positive feedback loop that further increases oxidative stress and thereby promotes progression of diabetic complications. In addition, chronic low-grade inflammation and activation of the innate immune system are closely involved in the pathogenesis of type-2 diabetes [80]. Riluzole (a drug that blocks glutamatergic neurotransmission) attenuated the VEGF – induced cell proliferation in a concentration – dependent manner in a rat model of retinopathy [81] again establishing a link between glutamate, depression and diabetes. Disruption of glutamate homeostasis along with low-grade inflammation could contribute to the high prevalence of co-morbid depression in this patient population.

Stroke

Stroke is the third most common cause of death among human diseases and claims 175,000 lives in the US each year [82]. The link between elevated glutamate, the NMDA receptor, and the etiology of stroke is firmly established [83]. In human, massive and persistent release of glutamate into the intracellular space occurs following stroke [84]. Although the location of the infarct can vary from patient to patient, the amount of glutamate released could affect distal regions such as BA25. High levels of glutamate have also been measured in plasma and cerebrospinal fluid (CSF) in patients with acute ischemic stroke [85]. When the glutamate concentrations cannot be decreased or controlled, the neuron can die. Depression is the most commonly reported post-stroke psychiatric condition with more than 50% of patients depressed at 1 year. In one review of the literature, Gordon and Hibbard [86] found prevalence of depression varying from 25% to 79%. Prolonged ischemia leads to decreased ATP levels in astrocytes leading to glutamate efflux due to a reversal of ionic gradients that drive transporter function (reversed uptake) [87]. Although astrocytes modulate synaptic transmission via the vesicular release of glutamate, under ischemic conditions, dysregulation of this process may lead to enhanced glutamate release [88]. In addition, following a stroke, astrocytic swelling due to glutamate uptake or excessive K^+ spatial buffering can result in depolarization of these cells, leading to release of glutamate via transporter reversal [88]. Together, these processes lead to increased extracellular glutamate concentration and excitotoxic-mediated cell death.

Alzheimer's disease

Involvement of glutamatergic neuronal excitotoxicity in Alzheimer's disease (AD) is well established. Memantine is the first NMDA antagonist to be approved for the treatment of moderate to severe patients with AD. More than 20% of AD patients have major depression [89]. Major depression was associated with substantially greater impairment, worse non-mood behavioral disturbance (such as aggression), and more frequent serious wandering, even after adjusting for severity of dementia or co-morbid health problems. Maragos et al. [90] provided data to support the hypothesis that glutamate dysfunction is involved in the pathophysiology of Alzheimer's disease and can account for many of the neurochemical and behavioral deficits observed in this disease.

Parkinson's disease

Parkinson's disease (PD) is a debilitating neurodegenerative movement disorder that is the result of a degeneration of dopaminergic neurons in the substantia nigra pars compacta. The resulting loss of striatal dopaminergic tone is believed to underlie a series of changes in the circuitry of the basal ganglia that ultimately lead to severe motor disturbances due to excessive basal ganglia outflow. Depression is common in PD and is associated with reduced cognitive performance and quality of life. In a prospective study over 11 years, Hughes et al. [91] reported that depression and dementia, but not motor symptoms, were associated with increased mortality in PD. Major depression and panic disorder are significantly more common in PD than in controls. Over 20% of patients with PD have major depression. Glutamate plays a central role in the disruption of normal basal ganglia function, and it has been hypothesized that agents acting to restore normal glutamatergic function may provide therapeutic interventions that bypass the severe motor side effects associated with current dopamine replacement strategies. Increased glutamatergic transmission in the basal ganglia is implicated in the pathophysiology of PD. Marino et al. [92] reported that the analysis of the effects of glutamate

receptor ligands in the basal ganglia circuit suggests that drugs that target the NMDA receptor would have anti-Parkinson actions. In particular, NMDA receptor antagonists that selectively target the NR2B subunit were cited. The first observation of the effects of DBS came from early successful thalamic DBS to treat Parkinson's tremor [93]. Mayberg et al. [21] selected BA25 for DBS based on neuroimaging findings implicating hyperactivity of BA25 in treatment-resistant depression and association of decreases in activity with clinical improvement. Data support that separate brain regions i.e., neural circuits are involved in mood and disease symptoms. This is supported by the work of Follett et al. [94] who compared pallidal versus subthalamic deep-brain stimulation in PD patients. In this study, patients undergoing subthalamic stimulation were slightly more depressed ($p = 0.02$) at 24 months even though they had significantly improved motor function. These data support that different regions are associated with mood and PD movement symptoms.

Huntington's disease

Huntington's disease (HD) is a neurodegenerative genetic disorder that affects muscle coordination and leads to cognitive decline and dementia. HD patients have a high incidence of depression, anxiety, and apathy with prevalence of 33–76% [95]. Arzberger et al. [96] reported a significant difference in the distribution of NMDA receptors and glia-bound glutamate transporter (GLT1) mRNAs in postmortem brains of HD patients. Okamoto [97] reported a difference in the relationship between NMDA synaptic and extrasynaptic activity, in mice possessing the mutant Huntingtin protein (mtHtt). They demonstrated that low-dose memantine blocked extrasynaptic (but not synaptic) NMDARs and ameliorated neuropathological and behavioral manifestations in mutant mice. The same extrasynaptic activity could also be playing a mechanistic role in the high incidence of depression in HD patients. In Huntington's patients, the pathology is heterogeneous with pronounced changes in the primary motor cortex accounting for motor dysfunction and cell loss in the cingulate cortex accounting for changes in mood [98].

Fibromyalgia syndrome

Fibromyalgia syndrome (FMS) is characterized by widespread pain, hypersensitivity to palpation at specific body locations (tender points) [99]. The frequency of lifetime diagnoses of major depression and anxiety disorders in patients with FMS ranges from 26% to 71%, a rate much higher than the general population [100,101]. A growing body of evidence supports the involvement of peripheral and central sensitization disturbances of pain-related processes underlying fibromyalgia. This involves increased glutamate transmission through interaction with the NMDA receptor. Studies supporting the involvement of glutamate in fibromyalgia demonstrated increased levels of glutamate in the cerebrospinal fluid of affected patients [102]. Smith et al. [103] reported that a subgroup of FMS patients had a complete resolution of their symptoms by removing both monosodium glutamate (MSG) and aspartame from their diets. Several research groups have reported that NMDA antagonists improve the symptoms of FMS patients supporting excessive glutamate activity is responsible for producing FMS symptoms [104–106].

Conclusions

We provide a hypothesis and explanation for the high rates of co-morbid depression in diseases linked to disruption in glutamate homeostasis which we define as glutamate-based depression or

GBD. The high rates of depressive symptoms associated with various disorders in which altered glutamatergic functions have been identified, may suggest a common pathophysiological mechanism is underlying the diverse clinical presentations. GBD provides an underlining biological mechanism for the high incidence of depression in these diseases and provides a possible way forward for managing the pathophysiology of these diseases along with their co-morbidities. There is mounting evidence that many antidepressant drugs work through this common mechanism of dampening NMDA glutamate receptors. Such information, along with additional supporting evidence, has led to the hypothesis that excessive stimulation of extrasynaptic NMDA receptor is directly involved in the pathophysiology of major depression. Recent clinical studies with the NMDA antagonist, ketamine, showed rapid (within 2 hours) antidepressant effects in treatment-resistant depressed patients [24–26]. In addition, the antidepressant effect lasted for days. Ketamine is approved for human use, and is commonly used in pediatric emergencies, in ECT rooms, in palliative care, and in the military when conventional anesthesiology apparatus is not available. Although ketamine has been generally well tolerated in depression studies, the potential of substance abuse and the need for medical monitoring may limit its use. Safer glutamate blockers along with treatment of low-grade inflammation could provide these patients with relief from their debilitating diseases.

Conflict of interest

Dr. Sanacora is a consultant for AstraZeneca and has participated as Principal Investigator in a number of clinical trials.

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