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Review article

Glutamate theory in developing novel pharmacotherapies for obsessive compulsive disorder: Focusing on N-methyl-D-aspartate signaling

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ABSTRACT

Obsessive compulsive disorder (OCD) is a prevalent and debilitating illness that often follows a chronic course. Up to 40% of OCD patients received little or no benefit from currently available pharmacotherapy or exposure-based behavior psychotherapy. Thus, there is an urgent need to develop new strategies for the treatment of OCD. Although the neurobiology and etiology of OCD are not completely understood, growing clinical and preclinical evidence appears to support the abnormalities of glutamatergic neurotransmission, including N-methyl-D-aspartate subtype receptor (NMDAR) function, in the pathophysiology and treatment of OCD. This review summarizes the findings from neuro imaging, candidate genes, animal models, and treatment studies in the context of glutamatergic dysregulation, with particular emphasis on the synaptic NMDAR function. The converging evidence indicates the potential of glutamate-modulating agents in the development of novel treatment for OCD.

1. Introduction

Obsessive compulsive disorder (OCD) is characterized by intrusive thoughts or images (obsessions) that increase anxiety and by ritualistic behaviors (compulsions) that can temporarily relieve such anxiety. OCD is a debilitating psychiatric disorder estimated to affect 2%–3% of the world population [1]. Unfortunately, only 40%–60% of patients with OCD responded to currently available pharmacotherapy and exposure-based psychotherapy, and a great proportion of treatment responders remained markedly ill [2]. There is an urgent need to develop novel strategies for OCD patients who are inadequately responsive to currently available therapies.

Although clinical experience and research of OCD have mostly focused on the serotoninergic and dopaminergic systems (see refs [3–5]), convergent lines of evidence support

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an important role of the glutamatergic system in the pathophysiology and treatment of OCD (see refs [6,7]]. In this review, we will focus on recent finding on the N-methyl-D-aspartate (NMDA) subtype receptor (NMDAR) function in OCD.

2. Clinical studies with glutamate-modulating agents on the treatment of OCD

Preliminary case reports and small open trials showed that resistant OC symptoms might benefit from adjunctive nonselective glutamate antagonists such as riluzole [8–10], topiramate [11], and lamotrigine [12,13]. In three case reports and one small open-label trial, memantine, a weak uncompetitive NMDAR antagonist, proved to be efficacious as add-on treatment to resistant OCD [14–17]. Extracellular glycine is an obligatory coagonist with glutamate on the activation of NMDAR [18]. Greenberg and colleagues [19] conducted the first randomized trial using glycine as adjunctive treatment for refractory OCD. There seemed to be a trend favoring glycine treatment.

Following a new paradigm using D-cycloserine (DCS), a partial agonist acting on NMDA glycine site, as "cognitive enhancer" [20] to facilitate exposure therapy for anxiety disorders [21,22], two trials on OCD found advantage of adjunctive DCS over placebo [23,24], but another one did not [25]. But the administration of DCS is intermittent, immediately before each exposure session.

3. Genetic, neuroimaging, and animal studies on OCD

Genetic association studies of OCD have identified two susceptibility genes, which are vital for glutamatergic neurotransmission: a glutamate transporter gene, *SLC1A1* [26–29] and the N-methyl-D-aspartate receptor [NMDAR) subunit 2B gene, *GRIN2B* [30]. Functional neuroimaging studies for OCD demonstrated metabolic disturbance in the frontal-subcortical circuit (FSC) [31], where glutamatergic neurotransmission play the role as the principal input [32]. Two recent transgenic animal models demonstrated phenotypical compulsive behavior: SAPAP3 knockout mouse which demonstrated striatum-specific alternation of NMDAR subunit composition [33] and G72/G30, a presumed D-amino acid oxidase (DAAO) activator [34], transgene mouse[35]; while DAAO is the main degrading enzyme of D-serine, an allosteric coactivator of NMDARs. Both of them were associated with NMDA functional alternation.

It is suggested that OCD is a prefrontal cortex hyperglutamatergic condition [36]. Glutamate levels estimated by magnetic resonant spectroscopy are significantly elevated in the caudate of treatment-naive pediatric OCD patients [37], but significantly reduced in anterior cingulated cortex (ACC) in drug-naïve pediatric OCD patients [38]. Cerebral spinal fluid (CSF) glutamate levels are greatly elevated in OCD patients than in normal controls [39]. NMDAR antagonists such as (2R)-amino-5-phosphonovaleric acid, ketamine, and phencyclidine caused pathologically increased glutamate efflux in the hippocampus, prefrontal cortex, and possibly the striatum [40–42], which was reversible with the use of either NMDAR agonists such as glycine or nonspecific glutamate inhibitors such as lamotrigine, in both animal and human preclinical studies [43,44].

A NMDAR antagonist MK-801 exacerbated the repetitive climbing and leaping behavior in a transgenic D1CT-7 mouse model of comorbid Tourette syndrome (TS) and OCD [45]. Therefore, potentiation of NMDA function may correct the OCD-like behaviors. However, memantine, amantadine, and MK-801, but not α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonist and riluzole, significantly inhibited murine marble-burying behavior, a potential animal model for OCD [46], suggesting both agonist and partial antagonist of NMDA receptors can improve the symptoms of OCD.

4. Focusing on modulation of NMDAR functioning

Taken together, insufficient clinical data is available to explain why both nonspecific glutamate inhibitors (or a weak uncompetitive NMDAR antagonist) and NMDA agonist/partial agonist as add-on treatment may benefit patients with OCD. A nonspecific glutamate inhibitors (or a weak uncompetitive NMDAR antagonist) and NMDA agonists may share a common mechanism of reducing glutamatergic neurotransmission in frontal regions and provide therapeutic efficacy for the patients with OCD [19,45]. We postulate that enhancing NMDA neurotransmission in FSC may be beneficial for OCD. Glycine transporter-1 (GlyT-1) regulates and maintains subsaturating concentrations of glycine at the glycine site of NMDARs [47,48]. Blockade of glycine uptake by glial GlyT-1 could increase the availability of synaptic glycine near NMDARs [47,48] and potentiate NMDA excitatory postsynaptic potential (EPSCs) [48].

N-methylglycine (sarcosine) is a potent endogenous antagonist of GlyT-1 [47,49]. In an open-label [50], flexible-dosing study to investigate the potential efficacy and safety of sarcosine therapy in patients with OCD, we found that (a) sarcosine treatment for 10 weeks significantly reduced the Yale-Brown obsessive compulsive scores in patients with OCD, especially those who were drug naïve, (b) five of the eight final responders met criteria of response within 2 to 4 weeks of sarcosine treatment, which is quicker than the onset of therapeutic response with serotonin reuptake inhibitors, and (c) the therapeutic effect occurs with doses lower than the dose for the patients with schizophrenia at 2 g/day [51–53]. The study is limited in its open-label design, a relatively small sample, and concurrent treatment with psychotropic medications in the add-on group. Despite these limitations, the low dropout rate, significant improvement in Yale-Brown Obsessive Compulsive scale (Y-BOCS) scores, particularly the naïve group, and overall favorable tolerability suggest that sarcosine may be of clinical benefit to the patients with OCD. The efficacy of sarcosine adds to the literature implicating the NMDA neurotransmission in the pathophysiology of OCD, while GlyT-1 may be a novel therapeutic target for OCD treatment.

As yet, we do not know how GlyT-1 inhibitors or glycine exert their therapeutic effects in OCD. What we have known from clinical samples and animal studies were: The

polymorphism of NR2B subunit gene *GRIN2B* has been involved with OCD [30], and the *SAPAP3* gene-deleted mouse has the striatum NR2A/NR2B ratio decreased, the field EPSCs significantly reduced, and exhibited OCD-related phenotype [33].

In preclinical studies, distinct NMDA modulating agents may have pharmacologically, regionally and temporally differential effects in the FSC relevant to OCD, given that:

(1) The developmental and physiological properties of NMDARs: NMDARs are composed of different subunits (NR1, NR2A–D, and, in some cases, NR3A or NR3B) and differentially expressed both regionally in the brain [54–56] and temporally during development [57]. Alternative composition of the NMDAR channel results in functional diversity of the channel [55,56,58].
(2) Differences in neuronal NMDAR properties are largely attributed to the NR2 subunits. NMDARs containing the NR2A subunit have the highest affinity for competitive antagonists [59], while NMDARs containing the NR2B subunit have greater affinity for agonists such as glycine and D-serine [54,56,59,60]. It is the presence of the NR2A subunit that allows increased glycine concentrations to potentiate the NMDAR response [61].
(3) From an anatomical perspective, synaptic processing of excitatory input is different in the ventromedial and dorsolateral striatum; either glycine or D-serine increased the peak current of NMDAR mediated excitatory postsynaptic currents selectively in dorsolateral striatum [59]. Interestingly, electrophysiological experiments demonstrated that glycine or another GlyT-1 inhibitor CP-802,079 exerted an inverted-"U" dose-response profile for the synaptically evoked NMDA currents in prefrontal cortex slices [48], while ketamine has a dose-associated biphasic influence on the outflow of glutamate in the prefrontal cortex [40].

Given the molecular, anatomical and physiology complexities of NMDA function, the “direct” and “indirect” pathways unbalanced hypothesis [38,62] may partially explain the clinical and preclinical reports that both NMDA agonists and some uncompetitive NMDA antagonists are efficacious for OCD.

5. The relationship between serotonergic and NMDA signaling

The cortico-raphe glutamatergic and raphe-cortical serotonergic projections may form an excitatory-inhibitory loop by which excitatory input signals are converted into inhibitory output projecting back to cerebral cortex [64,65]. It is possible that the therapeutic effect of SRIs or sarcosine for OCD may converge on diminishing ventromedial basal ganglia activity relative to that in the dorsolateral system, or reducing glutamatergic hyperactivities in the frontal cortex. Either SRIs or NMDA agents alone may reach a therapeutic ceiling and combination treatment can bring less improvement in the drug-exposed group than the drug-naïve group. This can be understood provided that chronic administration of SRIs leads to altered levels of mRNA encoding NMDAR subunits and region-specific change of NMDAR function in CNS [65,66]. Besides, the effects of SRIs were different on lateral PFC versus ventral frontal paralimbic serotonin regulation [67], while serotonin may exert dual actions by stimulating 5-hydroxytryptophan (5-HT) 2A receptors on γ-aminobutyric acid (GABA)ergic interneurons and 5-HT1A receptors on glutamatergic neurons in the prefrontal cortex [63,64], thus indirectly inhibiting the primary glutamatergic output to the ventral striatum.

6. Conclusion and future perspectives

In recent years, converging lines of evidence implicate glutamatergic neurotransmission in the pathophysiology and treatment of OCD. Glutamatergic signaling through NMDAR had showed controversial effects in clinical and preclinical studies. This may attribute to that the distinct NMDA modulating agents may have pharmacologically, regionally, and temporally differential effects in the frontal-striatal circuitry relevant to OCD. The use of animal models for screening NMDAR modulating agents, and combining genetic and neuroimaging studies in clinical patients may expand our understanding of the neurobiology as well as novel treatments for OCD.

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