Glutamate-Modulating Drugs as Novel Pharmacotherapeutic Agents in the Treatment of Obsessive-Compulsive Disorder

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Summary: Obsessive-compulsive disorder (OCD) is a common psychiatric disorder that produces significant morbidity. The introduction of serotonin reuptake inhibitors in the 1980s represented an important advance in the treatment of OCD. However, few patients show complete remission of their symptoms, and some patients show minimal improvement with existing treatments. We review current treatment strategies and initial data supporting the efficacy of glutamate modulating agents as a novel class of pharmaceuticals for the treatment of OCD. Functional neuroimaging studies repeatedly reported metabolic hyperactivity in the cortico-striato-thalamo-cortical circuitry in patients with OCD. Recent magnetic resonance spectroscopy studies provide evidence of elevated glutamate levels in several brain regions in patients suffering from OCD. These findings raised the possibility that agents that reduce glutamate hyperactivity or its consequences in the CNS might be efficacious as novel therapeutic interventions. Indeed, initial evidence from our group suggests that the antiglutamatergic agent riluzole (Rilutek), which was developed for the treatment of amyotrophic lateral sclerosis, is effective in treatment-resistant OCD. Case reports suggest that other agents that modulate glutamatergic activity may likewise be effective. This new application of glutamate modulating agents holds promise for the treatment of this disabling and often inadequately treated disease. **Key Words:** ALS, obsessive-compulsive disorder, magnetic resonance spectroscopy, glutamate, riluzole, treatment-resistant.

INTRODUCTION

Obsessive-compulsive disorder (OCD) was once thought to be extremely rare, but recent epidemiological studies have shown it to be the fourth most common psychiatric disorder (after substance abuse, specific phobias, and major depression), affecting 2.5–3.0% of the population.[1,2] Patients with OCD experience the persistent intrusion of thoughts that they generally perceive as foreign and irrational but which cannot be dismissed. The anxiety associated with these unwanted and disturbing thoughts can be extremely intense; it is often described as a feeling that something is incomplete or wrong, or that terrible consequences will ensue if specific actions are not taken. Many patients engage in repetitive, compulsive behaviors that aim to discharge the anxieties associated with these obsessional thoughts.[3,4] Severely affected patients can spend many hours each day in their obsessional thinking and resultant compulsive behaviors, leading to marked disability.

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While OCD patients exhibit a wide variety of obsessions and compulsions, symptoms tend to fall into specific clusters. Common patterns include obsessions of contamination, with accompanying cleaning compulsions; obsessions with symmetry or order, with accompanying ordering behaviors; obsessions of saving, with accompanying hoarding; somatic obsessions; aggressive obsessions with checking compulsions; and sexual and religious obsessions. There is mounting evidence that these symptom constellations may be somewhat independent of one another[5] and may best be conceptualized as different overlapping dimensions of the disorder, perhaps with distinct genetic associations.[6,7] For example, patients with predominant hoarding symptoms are notoriously difficult to treat with both established pharmacologic agents and psychotherapeutic strategies,[8] and thus represent a population for whom novel therapeutic strategies are particularly needed.

Recent efforts have highlighted the development of novel pharmacotherapies for treatment resistant and treatment refractory symptoms in OCD patients.[9,10] The label "treatment resistant" is generally used to describe symptoms that have failed to respond to at least two

adequate trials of serotonin reuptake inhibitors (SRIs), whereas "treatment refractory" refers to a greater degree of treatment failure. Three general strategies have been essayed to enhance treatment efficacy: monotherapy with different primary pharmacological agents; augmentation with a drug of a different class; and more invasive therapies, including ablative psychosurgery, deep brain stimulation, electroconvulsive therapy, and repetitive transcranial magnetic stimulation.

Several lines of evidence suggest that abnormalities of glutamate neurotransmission in the cortico-striato-thalamo-cortical (CSTC) circuitry may contribute to OCD, as we review below. This has led us, and others, to speculate that glutamate-modulating medications may prove efficacious for treatment-resistant OCD symptoms.[11,12] Preliminary studies support the promise of this approach. In this article, we briefly review the current state of the art in the treatment of OCD. We then review the preclinical and clinical evidence implicating glutamatergic dysfunction in the pathophysiology of OCD, and preliminary clinical evidence for the efficacy of glutamate-modifying agents as augmentation therapy in treatment-resistant OCD. Finally, we suggest some future directions for this line of research, and promising avenues for the further development of novel therapeutic strategies based on modulation of glutamatergic neurotransmission.

TREATMENT OF OCD: ESTABLISHED THERAPIES

In the last two decades, efficacious pharmacological and psychotherapeutic treatments for OCD have been developed and extensively validated.[3,13,14] Clomipramine, the tricyclic antidepressant that is the most specific inhibitor of serotonin reuptake, was shown to be efficacious in the treatment of obsessive-compulsive symptoms in uncontrolled trials the 1960s[15,16] and was well established in controlled trials by 1990.[3,17] Beginning with the demonstration that fluvoxamine can reduce symptoms in a substantial fraction of patients[18,19] and is superior to tricyclic antidepressants other than clomipramine,[20] numerous studies have shown that selective serotonin reuptake inhibitors (SSRIs) are effective pharmacotherapy for many patients. Because of their more benign side effect profile, SSRIs are now considered first-line pharmacotherapy for OCD in most contexts, although clomipramine continues also to be widely used.

Clinical trials and accumulated clinical experience show that the management of SRIs in OCD differs from that in depression, in several regards. First, higher doses are often required before clinical improvement is seen than is the case in depression. Second, improvement is gradual; an adequate medication trial is considered to be at least 10–12 weeks in duration.[3,21] For these reasons, several careful trials of SSRIs and/or clomipramine must be completed with little or no improvement before a patient's OCD can clearly be considered resistant to SRI pharmacotherapy.

Behavioral and cognitive-behavioral therapies are also established first-line therapy for OCD, and their efficacy has been validated in more than 30 studies. The behavioral strategy with the best proven efficacy is exposure and response prevention (ERP), in which anxiety and obsession-inducing stimuli are systematically presented in a controlled environment and patients are prevented from engaging in their usual compulsions.[22,23] Because ERP is problematic in some patients (especially those who are reluctant to engage in the anxiety-provoking exercise associated with exposure to the feared stimuli or those with pure mental obsessions or compulsions that render response prevention exercises difficult), more purely cognitive therapies have also been established and show efficacy in some studies.[24]. When properly delivered, behavioral and cognitive-behavioral therapy are efficacious and can be appropriate first-line treatments.[25]

Although first-line treatment for OCD could reasonably include either cognitive behavioral therapy (CBT) or medication management, the combination of the two treatments are regarded as most effective by many clinicians.[3] Large, controlled studies examining the efficacy of the CBT, pharmacotherapy and the combination of CBT with pharmacotherapy in OCD are lacking,[26] although a few open-label studies suggest that CBT may be efficacious in some patients whose symptoms fail treatment with SRIs alone.[27–29]

TREATMENT-RESISTANT SYMPTOMS IN OCD

Despite the proven efficacy of both SRIs and behavioral and cognitive-behavioral therapies, a substantial percentage of patients receive little benefit from these standard approaches. Although definitions of "acceptable treatment response" vary between studies, making comparisons somewhat difficult, only 40–60% of patients achieve such a response in most studies when treated with an adequate trial of an SRI with or without CBT.[30] The large fraction of patients without substantial response to standard treatment experiences significant morbidity.[31]

In addition, treatment response to an SRI in OCD research studies is not generally defined as treatment to remission of symptoms. Response is typically operationalized as a decline in symptoms, as measured by a 30–35% reduction in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)[32,33] or a decline in symptoms below a threshold of 16 (i.e., the boundary between mild and moderate OCD symptoms). This means that "treatment responsive" patients may continue to have levels of

symptoms in the mild-moderate range and spend hours daily preoccupied with their obsessions and compulsions. There is a clear need for novel therapeutic avenues to target both partially responsive and treatment-resistant populations.

A number of therapeutic strategies have been attempted in the treatment-resistant population.[9,10,30] As noted above, they can be conceptualized as falling into three categories: alternative monotherapies, adjunctive pharmacotherapies, and invasive procedures. While evidence exists for efficacy of several different modes of treatment in the treatment-resistant OCD population, there is currently no clear consensus as to how best to treat patients once SRIs and CBT have proven inadequate.

Alternative monotherapies

Early studies with tricyclic antidepressants, which act on both serotonin and norepinephrine, suggested that blockade of serotonin reuptake was required for antiobsessional effect.[34] Clomipramine, the tricyclic with the most SRI action, is the one that has been proven to have antiobsessional activity, in multiple studies. The importance of the serotonin system in the standard treatment of OCD is reinforced by the efficacy of the SRIs in approximately half of patients, as summarized above.

Nevertheless, some investigators have hypothesized that a dual-acting agent might be more effective in treatment-resistant patients. This hypothesis is supported by the fact that clomipramine, which retains some norepinephrine reuptake inhibitory (NRI) effect relative to the SSRIs and whose metabolite desmethylclomipramine has significant NRI activity, appears to be more effective than the more selective agents in meta analyses, though not in head-to-head comparisons.[17] For example, in a meta-analysis of studies including over 1000 adolescents with OCD performed by Geller et al.,[35] clomipramine was shown to have greater efficacy compared with fluoxetine, fluvoxamine, paroxetine, and sertraline. SSRIs remain more widely prescribed as first-line pharmacotherapy despite such results because of their more benign side-effect profile. The possible contribution of NRI properties to the efficacy of clomipramine has motivated several trials of the serotonin-norepinephrine dual-acting reuptake inhibitor venlafaxine, both in treatment-naive patients and in patients refractory to treatment with SRIs alone. An open-label trial of venlafaxine, both in treatment-naive and treatment-resistant OCD, suggested superior efficacy to SSRIs,[36] and a head-to-head comparison suggested comparable efficacy to clomipramine.[37] However, a more recent head-to-head crossover comparison with paroxetine actually showed venlafaxine to be less effective than the SSRI.[38] At present, it seems clear that venlafaxine is an effective agent in the treatment of OCD, but the evidence that it provides benefit in the treatment of symptoms refractory to SRI treatment is equivocal.[39]

Another strategy based on the efficacy of the SRIs is to use other agents that target the serotonin system. A single study suggests that mirtazapine, a 5HT2A agonist, can accelerate the effect of paroxetine on OCD symptoms,[40] although the long-term benefit is unclear.[41] Mirtazapine has also been shown to be efficacious as monotherapy.[42] As is the case with venlafaxine, the limited evidence suggests that mirtazapine is an effective agent in OCD, but its benefit in treatment-resistant cases is unclear.

Finally, a few studies suggest that higher effective doses of SRIs, such as can be achieved through intravenous infusion, can be efficacious treatment when standard oral dosing of SRIs has failed. Both intravenous clomipramine[43,44] and intravenous citalopram[45] have been shown to lead to a substantial improvement in symptoms in some treatment-resistant patients.

Augmentation therapy

A number of different agents have been used as augmentation strategies for standard SRI therapy in treatment-refractory OCD, with some success. In particular, agents with modes of action beyond the serotonin system have shown the capacity to significantly improve symptoms in patients with limited response to SRI therapy alone.[46]

Obsessive-compulsive disorder is highly comorbid with Tourette's syndrome in the pediatric population,[47] and potentially overlapping pathological changes in the basal ganglia are implicated in the two disorders.[48,49] The clear efficacy of both typical and atypical antipsychotic agents in Tourette's syndrome[50,51] therefore motivates trials of dopamine antagonists as augmentation therapy in OCD. Indeed, augmentation with typical[52] or atypical antipsychotics[53–61] improves symptoms in a substantial fraction of patients whose symptoms are refractory to SRI treatment alone. Early studies suggested that the benefit of antipsychotic medications was most pronounced in patients with OCD and comorbid tics,[52] but more recent studies[53] show benefit in treatment-resistant patients with and without tics. The evidence for efficacy of augmentation with atypical antipsychotic agents in SRI-resistant OCD continues to grow.[62]

A smaller number of studies have examined the utility of augmentation therapy with opioid agents. Morphine given once weekly has shown efficacy in treatment-resistant obsessive-compulsive disorder in a single double-blind study,[63] and administration of the opioid agonist tramadol hydrochloride has also been shown to diminish OCD symptoms.[64,65] The mechanism of this interesting effect is unknown, but opioids may inhibit glutamate release in cortex via disinhibition of serotonergic neurons.

A number of other augmentation agents have been tried in treatment-resistant OCD, generally in small case series, and with more equivocal results. Medications that have been tried either as monotherapy or as augmentation agents include clonazepam, inositol, clonidine, monoamine oxidase inhibitors, and antiandrogens.[66]

Finally, a small, open label study examining the efficacy of augmentation with the antiglutamatergic agent riluzole in SRI-resistant OCD patients has demonstrated significant efficacy.[11] Agents manipulating glutamate neurotransmission are particularly exciting candidates for the pharmacotherapy of treatment-resistant OCD because they represent a new perspective on its pathophysiology, distinct from the focus on the monoaminergic modulatory systems that has characterized most pharmacological treatment strategies for the past two decades. We return to a more full discussion of these agents below.

Invasive treatment options

SRI-resistant obsessive-compulsive disorder is one of the few diagnoses in modern psychiatry for which invasive neurosurgical procedures are part of the established treatment armamentarium. This underscores the clinical challenges posed by treatment-resistant OCD and the exquisite suffering of severely affected patients.

Neurosurgical approaches to treatment-refractory OCD have recently been reviewed.[9,67] Briefly, several different neurosurgical lesion approaches, using a variety of techniques (including standard craniotomy, implantation of radioactive seeds for local ablation, and gamma knife coagulative lesions) have shown some efficacy in open trials of limited numbers of patients with treatment-resistant OCD. The efficacy of neurosurgical ablative techniques for the treatment of severe OCD is further emphasized by a few case reports of reduced obsessive-compulsive symptoms after neurosurgical removal of epileptic foci.[68,69]

All ablative neurosurgical techniques target the CSTC circuits that are believed to be hyperactive in OCD. Several specific procedures have been described. Anterior cingulotomy involves a lesion targeting the anterior cingulated cortex and cingulum. Anterior capsulotomy targets the subcaudate white matter, interrupting frontothalamic fibers. Limbic leucotomy combines these two, lesioning both cingulum and subcaudate white matter. Because of the technical and ethical issues involved, existing studies describe small numbers of patients and are not blinded or well controlled. There is some evidence that patients' improvement correlates with the extent of the lesion interrupting the CSTC circuitry: patients undergoing limbic leucotomy after unsuccessful cingulotomy showed a higher response rate in one study than those in whom limbic leucotomy was the first ablative procedure.[70]

Because of the invasive and irreversible nature of neurosurgical lesion techniques, and because of the problematic history of psychosurgery,[71] ethical considerations require extensive safeguards before any such techniques can be brought to bear on a given treatment-resistant patient. The development of deep brain stimulation (DBS) techniques that can reversibly manipulate the activity of specific brain circuitry has therefore garnered increasing recent interest as a possible treatment modality for OCD and other intractable neuropsychiatric conditions.[72–75] The efficacy of such an approach was first suggested by case reports of the amelioration of obsessive-compulsive symptoms with DBS in Parkinson's disease; several small case series have since demonstrated that amelioration of symptoms is possible in at least some cases of severe, treatment-resistant OCD.[75] Furthermore, prospective, blinded studies with larger number of patients are needed before such techniques can be brought to bear on the large treatment-resistant OCD population.

Finally, the use of electroconvulsive therapy, transcranial magnetic stimulation (S),[76] and vagal nerve stimulation have been explored as less invasive methods of treatment than neurosurgical intervention. None of these therapies have demonstrated marked efficacy in the limited studies done to date.[77]

Limitations of available augmentation strategies

Despite the availability of these several treatment options, treatment-resistant OCD symptoms remain a pressing clinical problem. Using conservative figures of a 2% prevalence of OCD and a 20% frequency of treatment resistance suggests that over a million patients in the U.S. may fall into this category, although only a fraction of this number come to psychiatric attention. Whereas the addition of atypical neuroleptics holds promise for increasing the number of patients who will respond to standard pharmacotherapies, other approaches do not as of yet have any clear evidence base behind them. The neurosurgical approaches briefly described above hold promise, but much more research is needed before they can be applied more broadly; and expense, ethical considerations, and the limited supply of qualified surgical personnel are likely to limit the applicability of such approaches for the foreseeable future.

There is thus an urgent need for conceptually novel pharmacological strategies. Recent advances in our understanding of the pathophysiology of OCD provide opportunities for the development of such strategies. In the remainder of this review, we discuss the evidence for dysfunction of glutamatergic neurotransmission, and our early experiences with glutamate modulating agents in the treatment of SRI treatment-resistant OCD.

GLUTAMATE DYSREGULATION IN OCD

Convergent lines of evidence support the notion that dysregulation of glutamate neurotransmission contributes to the pathophysiology of OCD. This perspective is independent of the monoaminergic hypotheses that underlie established treatments.

There is reason to hope, therefore, that patients whose symptoms are relatively untouched by pharmacological therapies aimed at the monoaminergic systems may find relief in novel therapies aimed at normalizing glutamatergic neurotransmission.

Preclinical evidence suggesting increased glutamate activity worsens OCD-like behaviors

A few rodent models of OCD and OCD-spectrum disorders have been developed. In some cases, involvement of molecules or brain regions hypothesized to be involved in OCD, or response to SRI medication, lends a degree of face validity. Phenotypically, current models are largely characterized by observable repetitive behaviors.

In one such model, transgenic mice express a neuropotentiating subunit of the cholera toxin in dopamine D1 receptor-expressing limbic cortical cells. This is presumed to increase their firing rate in a way that may resemble the hyperactive limbic cortical areas seen in functional imaging of OCD patients; indeed, these transgenic mice are described as engaging in perseverative behaviors that mimic some aspects of OCD and Tourette's syndrome.[78,79] MK-801, a noncompetitive use-dependent antagonist of the NMDA glutamate receptor that may indirectly increase presynaptic glutamate release,[80] has been shown to worsen these perseverative behaviors, and to induce an additional category of "limbic seizure-like" stereotypies.[81] Interestingly, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline (NBQX), an antagonist of AMPA-type glutamate receptors, does not affect baseline OCD-like behaviors in these mice or their exacerbation by MK-801, but does reduce the "seizure-like" stereotypies. Although numerous caveats must attend any interpretation of results from a limited animal model of OCD, the exacerbation of OCD-like behaviors by glutamatergic agents in this study supports an important role for increased glutamatergic tone in the pathogenesis of obsessive-compulsive disorder, and possibly in its treatment.

There are several limitations to this and other rodent models of OCD that warrant mention. OCD is a difficult disorder to model in experimental animals because the diagnosis often depends on verbal report of obsessions, which are an entirely internal phenomenon, and expression of burdensome compulsions. It is potentially problematic to interpret behaviors as compulsions merely because they are repetitive and without apparent adaptive value; repetition does not necessarily imply the distinct internal experience that defines a compulsion. Repetitive behaviors are also seen in autism, Tourette's syndrome, some forms of mental retardation, catatonic schizophrenia, and other disorders; it is not necessarily true that all such repetitive behaviors share an etiologic mechanism with the compulsions seen in OCD, nor is it clear which of them, if any, are best modeled by observed repetitive behaviors in existing animal models.

Magnetic resonance spectroscopy (MRS) measurements of glutamate dysfunction in OCD

MRS allows measurement of the concentration of certain small molecules in the brain and other tissues. It has come to be widely used in neurology as a tool to assess the health and cellular composition of different regions of the normal or diseased brain. The more recent development of methods to measure amino acid neurotransmitters in the brain has allowed levels of glutamatergic compounds and GABA to be investigated in neuropsychiatric disorders.[82] Recent MRS findings implicate dysregulation of glutamate neurotransmission in CSTC circuits in OCD (Table 1).

Before summarizing these findings, however, a methodological caveat is in order. MRS distinguishes small molecules by their chemical shift in a magnetic field. Measurement of the concentration of any given molecule therefore requires that its MR chemical shift be clearly distinguishable from that of similar molecules with neighboring peaks in the spectrum. Under standard magnetic field strengths such resolution is difficult with glutamate and GABA, although specific identification of glutamate and GABA peaks can be achieved in some brain regions with special coils and magnetic pulse sequences.[83–85] More commonly, an aggregate measure termed "Glx" is reported; Glx measurements reflect levels of glutamate, glutamine, homocaronsine, and GABA.[86] Abnormal Glx measurements in OCD, or any other neuropsychiatric disorder, can therefore be interpreted to reflect perturbations in amino acid neurotransmitter levels in general but cannot necessarily be interpreted to specifically reflect abnormal levels of glutamate.

Even accepting that increased Glx signal indicates increased tissue glutamate in MRS studies, the physiological implication of such an alteration is unclear. Increased glutamate could represent either increased glutamatergic neurotransmission or an increased metabolic pool of glutamate. Indeed, increased glutamate could indicate intraneuronal accumulation of glutamate, and therefore correspond to reduced glutamatergic synaptic activity. Despite these caveats, however, the ability of MRS to probe the levels of small molecules and neurotransmitters in the intact brain is an exciting methodological advance and has produced new insights into possible glutamatergic dysregulation in OCD.

TABLE 1. *MRS Studies of OCD*

Structure	Metabolite	Change	Comments	Ref.
Right striatum anterior cingulate	N-acetylaspartate (NAA)	↓	12 OCD subjects and 6 controls	91
Left striatum	NAA Glutamate, GABA	↓ No change	13 OCD subjects and 13 controls.	92
Lenticular nuclei (putamen/globus pallidus)	NAA, creatinine: choline	No change	12 OCD subjects, 12 controls	93
Caudate	Glx	↑	Case study. Glx increased in pediatric OCD patient, normalized with SSRI treatment	88
Bilateral medial thalamus	NAA	↓	11 treatment naive pediatric OCD patients and 11 matched controls	94
Caudate	Glx	↑	Increased Glx in pediatric OCD; normalized with SSRI treatment	89
Occipital cortex	Glx	No change		
Medial thalamus	Choline	↑	Increased choline in medial but not lateral thalamus bilaterally	95
Caudate	Glx	↑	Case study. Normalization of caudate Glx with SSRI treatment persists after medication discontinuation.	96
Anterior cingulate	Glx	↓	Reduced anterior cingulate Glx in both OCD and major depressive disorder	90

NAA is marker of neuronal viability; reduced NAA is thought to indicate neuronal loss.

Rosenberg and colleagues[87] have reported abnormal Glx measurements in several brain regions in OCD. Glx is increased in the striatum of patients with OCD, consistent with the known metabolic hyperactivity of the CSTC circuitry. Interestingly, this elevation in Glx has been shown to normalize in OCD subjects who respond to treatment with SRI medications.[88,89] In contrast, the same group recently found decreased Glx levels in the anterior cingulated in subjects with OCD.[90] As these authors point out, the combined finding of reduced anterior cingulate Glx concentrations and increased caudate Glx parallels prior studies demonstrating an inverse relationship between anterior cingulate and basal ganglia volume in patients with OCD. The specific glutamatergic dysfunction in OCD remains to be elucidated and may vary between brain regions.

Elevated CSF glutamate in OCD

The most direct evidence for excessive glutamatergic activity in OCD derives from a recent study examining CSF from patients with OCD. Chakrabarty et al.[97] examined the CSF of 21 drug-naive OCD patients and 18 control subjects, and found CSF glutamate levels to be significantly elevated in those subjects with OCD. This study requires replication with a larger number of patients, but it supports the MRS data in suggesting glutamatergic dysfunction as an important component of the pathophysiology of OCD.

Increased cortical excitability in OCD

Either increased glutamatergic tone or reduced GABA activity in the cortex may alter the excitatory-inhibitory balance in the cortex. This balance can be probed with transcranial magnetic stimulation (S), by measuring the motor response to a threshold cortical stimulation and other parameters. Using this methodology, Greenberg and colleagues[98] recently demonstrated increased cortical excitability in OCD. Future S studies are warranted to follow up on this preliminary finding.

Genetics

The genetics of OCD, as is the case in many psychiatric disorders, are complex, and the disorder is presumably polygenic. Although OCD is believed to have a significant genetic component,[99] genetic loading, no clearly replicated genetic loci have been convincingly demonstrated to be causally involved in its pathogenesis. Nevertheless, several genes involved in glutamatergic neurotransmission have been implicated in single association studies. These include a preliminary association with the NMDA glutamate receptor subunit GRIN2B[100] and a negative association with a particular allele of the

GRIK2 kainate receptor gene.[101] Such associations are very preliminary; but if these or similar genetic associations with components of the glutamate neurotransmission and regulatory systems are substantiated, they would bolster the evidence that dysregulated glutamate is an important aspect of the etiology of OCD.

PRELIMINARY CLINICAL STUDIES OF GLUTAMATE-MODULATING AGENTS IN OBSESSIVE-COMPULSIVE DISORDER.

Pharmaceutical agents that directly attenuate glutamatergic outflow have only recently become available. Riluzole (Rilutek; Aventis Pharmaceuticals, Bridgewater, NJ) is an antiglutamatergic agent that is approved by the Food and Drug Administration for neuroprotection in amyotrophic lateral sclerosis (ALS).[102] Among its proposed mechanisms of action are inhibition of sodium currents in glutamatergic (and other) axon terminals, reducing neurotransmitter release[103]; reduction of P/Q-type calcium currents in the axon terminals, with a similar effect on transmitter release[104]; extension of the open time of certain potassium channels[105]; and increased astrocytic uptake of glutamate.[106] Although it has significant effects on glutamatergic function, riluzole is not a purely an antiglutamatergic agent. *In vitro* studies suggest that it also modulates release of acetylcholine and dopamine,[107] potentiates receptors for GABA and glycine,[108,109] and enhances expression of BDNF.[110,111]

Preliminary studies suggest efficacy of riluzole therapy several neuropsychiatric disorders in which excessive glutamatergic activity has been implicated. Case reports and open label studies suggest efficacy in the treatment of major depression,[11,12,112,113] bipolar depression,[114,115] anxiety,[12] and OCD.[12] Ongoing studies examining the effect on schizophrenia have also begun at our center (Zimolo, Z., Yale University, personal communication).

We have used riluzole in treatment-resistant obsessive-compulsive disorder in an open-label study.[11,12] Thirteen patients with a DSM-IV diagnosis of OCD who had shown little improvement with at least 8 weeks of adequate dose SRI therapy were treated with the addition of riluzole to their existing medication regimen. Most patients had failed several SRI trials, augmentation strategies with dopamine antagonists, and CBT. Over the course of treatment, mean Y-BOCS scores in this treatment-resistant cohort fell from 30.7 (SEM 6.6), in the severe range, to 17.7 (SEM 8.6), representing a 42% reduction in OCD symptoms for the entire cohort (responders and nonresponders). Seven of the thirteen patients (59%) demonstrated a 35% or greater reduction in baseline Y-BOCS score at the end of study, and 5 of 13 (39%) were judged to be treatment responders with the added criteria of achieving a final Y-BOCS score of less than 16. Although limited by the open-label design, the small number of Figure 1 subjects, and the lack of a control group, this preliminary study lends supports the hypothesis that glutamatergic dysfunction contributes to the pathophysiology of OCD and that glutamate-modulating agents may prove to be efficacious in treatment-resistant OCD.

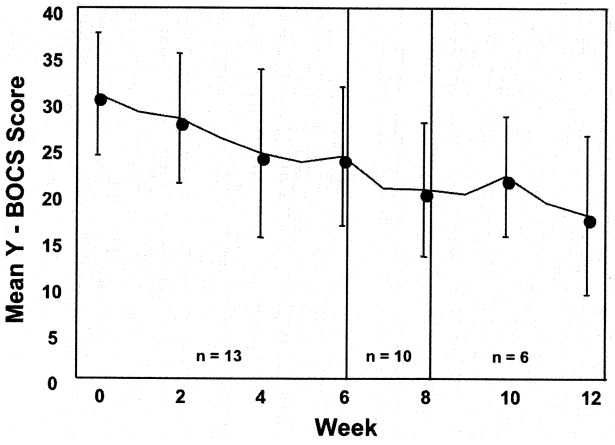

FIG. 1. Y-BOCS scores in a cohort of 13 patients with treatment-resistant OCD symptoms with the addition of riluzole (100 mg daily) to their existing medication regimen. Y-BOCS scores declined significantly across 12 weeks of treatment ($P < 0.001$). Reprinted from *Biological Psychiatry,* 58, Coric et al., Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial, 424–428, Copyright 2005 with permission from the Society of Biological Psychiatry.[12]

These promising early results with riluzole encourage trials of other glutamate-modulating agents in OCD. The anticonvulsant lamotrigine is thought to act by inhibiting axonal voltage-gated sodium channels and thereby reducing the release of excitatory neurotransmitters, a mechanism that overlaps with that of riluzole However, in a small case series of eight patients in which lamotrigine was added to SRI therapy in treatment-resistant patients, only a single patient reported significant improvement, and symptom improvements as measured by the Y-BOCS were marginal.[116] It may be that lamotrigine does not adequately dampen glutamatergic outflow despite is theoretical effects on glutamate release.

The amino acid N-acetylcysteine (NAC) is widely used for its antioxidant properties and as an antidote for acetaminophen toxicity; however, recent preclinical studies suggest that NAC also modulates CNS glutamate. NAC is converted to cystine, a substrate for the glutamate/cystine antiporter located on glial cells. The uptake of cystine by glia causes glial release of glutamate into the extrasynaptic space, where it appears to stimulate inhibitory metabotropic glutamate receptors on glutamatergic nerve terminals and thereby reduces the synaptic release of glutamate.[117] Systemic administration of NAC has been shown to reverse the susceptibility to reinstitution of compulsive cocaine use in a rodent model by

restoring re-establishing normal extracellular glutamate concentrations in the nucleus accumbens.[118]

In addition to attenuating synaptic glutamate release, NAC may enhance clearance of glutamate by glial cells at the synapse. Elevated levels of glutamate deplete glutathione within glial cells, impair cystine transport, and thereby increase the vulnerability of glia to oxidative stress.[119] Preclinical studies demonstrate that NAC protects glial cells against glutamate toxicity, repletes levels of glutathione, and attenuates toxic levels of glutamate.[120–123]

We hypothesize that NAC, through its inhibition of presynaptic glutamate release and protection of glial function, may be beneficial in disorders of glutamatergic dysregulation. If effective in OCD or other disorders, NAC would be an attractive treatment option, because of its benign safety profile and low cost. We have therefore begun to treat a small number of OCD patients with NAC, and find evidence for benefit in compulsive behaviors in two preliminary case reports.[123,124] As noted above, NAC also reduces the tendency toward relapse in a rat model of cocaine abuse, suggesting that it may have more general efficacy against compulsive behaviors and maladaptive habits.[118] This agent merits further investigation.

It is important to note that not all agents that modulate glutamate show evidence of benefit in treatment-resistant OCD. The antiepileptic agent topiramate blocks postsynaptic AMPA-type glutamate receptors, among other actions, and has been reported to induce obsessive-compulsive symptoms in a case report.[125] We found the NMDA blocking agent memantine to be without effect on obsessive-compulsive symptoms, in a small number of patients (Pittenger, C., and V. Coric, unpublished observations). The lack of efficacy of agents that block postsynaptic AMPA and NMDA receptors is consistent with mouse model data, in which neither NMDA antagonists nor AMPA antagonists alleviated OCD-like symptoms in transgenic mice (as discussed above).[81] Cannabinoids are reported by some patients to moderate obsessive symptoms and may reduce cortico-striatal glutamatergic tone through an indirect mechanism.[126] However, we found the synthetic cannabinoid agent dronabinol to be without effect in a patient with treatment-resistant OCD. Additionally, dronabinol presented tolerability problems in several patients and a quickly reversible exacerbation of OCD symptoms in another patient (Coric, V., unpublished observations).

Whereas current preclinical and clinical studies are insufficient to provide irrefutable evidence for glutamatergic hyperactivity in obsessive-compulsive disorder, they do, in aggregate, suggest that agents that target the glutamate system may have therapeutic potential in the treatment of obsessive-compulsive symptoms. Indeed, current pharmacological treatments for OCD may work, in part, through indirect attenuation of glutamatergic activity. For instance, SRI medications may increase activity of modulatory serotonergic afferents to glutamatergic corticostriatal projections. Additionally, augmentation with dopamine antagonists may alter the balance between the direct and indirect pathways through the basal ganglia, reducing glutamatergic outflow from the thalamus to the cortex.

WHAT'S WRONG WITH GLUTAMATE IN OCD?

These preclinical data and clinical observations support the hypothesis that glutamatergic dysfunction in specific brain regions plays a role in the pathophysiology of OCD, and that certain agents that modulate glutamate may provide benefit in patients with SRI-resistant OCD. However, available data do not clarify the precise abnormality in glutamate neurotransmission. Abnormalities in glutamate neurotransmission may include increased or decreased presynaptic release of glutamate, impaired clearance of synaptic glutamate by glial cells, or abnormalities in postsynaptic glutamate receptor expression or function. Sufficiently increased glutamate is excitotoxic and has been hypothesized to result in neurobehavioral symptoms.

If glutamate is indeed elevated in the striatum of OCD patients, what is the significance of this elevation? Specifically, is the elevated glutamate a reflection of the primary underlying biological defect that leads to obsessive-compulsive symptomatology? Or is it an epiphenomenon of elevated cortical neural activity or some other neurophysiological abnormality that is more closely related to the underlying pathophysiology of the disorder? Answering these questions may not be essential to the development of novel therapeutics; pharmacological normalization of glutamate activity could be beneficial to OCD patients even if regulation of glutamate is not the primary abnormality leading to the disorder. But a clearer understanding of the causal role of glutamate abnormalities in the development of OCD would better guide the development of the next generation of therapeutics.

It is well established that the striatum, globus pallidus, orbitofrontal cortex, and other components of the CSTC circuitry are hypermetabolic in OCD.[127] Because cortico-striatal projections are predominantly glutamatergic, excess striatal glutamate in OCD may simply be a by-product of increased firing of coritco-striatal projection neurons. If this is the case, then increased Glx measurement in MRS studies[87] and increased glutamate in the CSF of OCD patients[97] may simply be a surrogate marker for excessive firing of these projection neurons; and the observed normalization of Glx levels by MRS with treatment[87] may similarly be equivalent to the normalization of hyperactive brain regions when OCD symptoms are treated.[127]

Few data exist to evaluate this possibility. It is notable that Glx has been reported to be decreased, not increased, in the anterior cingulate in OCD,[90] despite the fact that the anterior cingulate is often found to be hypermetabolic in the disorder. This may indicate that glutamate is differentially disrupted within the circuitry implicated in OCD, and therefore be inconsistent with Glx simply serving as a surrogate marker for activity of excitatory cortical neurons. However, the caveats to the interpretation of Glx apply. Furthermore, it could be argued that glutamate levels in the anterior cingulate reflect the activity of afferent projection neurons rather than the anterior cingulate neurons themselves; reduced Glx in the anterior cingulate might then reflect a circuit-level attempt at compensation for hyperactivity in this region, and be quite consistent with the interpretation of elevated glutamate simply reflecting increased excitatory tone.

An alternative interpretation of the data implicating dysregulated glutamate in OCD is that alterations in glutamate neurotransmission are in fact an important part of the pathophysiology of the disorder. Reports of increased cortical excitability in motor cortex, which is not known to be hypermetabolic in OCD, may suggest a general dysregulation of glutamate, not one confined just to the CSTC circuitry.[98] Such a pathogenic role for alterations in glutamate has been proposed in major depressive disorder (MDD)[82]; indeed, the high degree of comorbidity between the two disorders is one argument in favor of a similar role in OCD. Until the details of glutamatergic dysregulation in OCD are better resolved, this is likely to remain an open question.

Where is the glutamate excess?

Available data do not distinguish between synaptic and extrasynaptic glutamate excess. This is a potentially critical distinction: increased tissue glutamate may represent excess extrasynaptic glutamate, which can actually contribute to and reflect reduced synaptic glutamate.[82] Increased total tissue glutamate may therefore correspond either to increased or decreased synaptic glutamatergic tone.

Current data and neuroimaging techniques do not allow definitive resolution of this question. The fact that glutamate excess appears to correlate with increased neuronal activity (in CSF glutamate levels and, at least in some structures, by MRS measurements of Glx) would seem to suggest that synaptic glutamate is increased in hyperglutamatergic regions in OCD. Likewise, the efficacy of riluzole, which acts primarily by reducing synaptic glutamate release, suggests synaptic glutamatergic excess in the pathological state. However, riluzole may also potentiate glial uptake of glutamate,[105] which would be expected to have a greater impact on extrasynaptic glutamate levels.

FUTURE DIRECTIONS

The suggestion that glutamate dysregulation may contribute to the pathophysiolgy of OCD is relatively new, and many questions remain.

A number of questions remain as to how and where glutamate is perturbed in OCD. Future studies must resolve some of these questions. One difficulty with existing studies is the reliance of MRS measurements of glutamate on Glx, which, as described above, is a complex measurement that reflects concentrations of glutamate, glutamine, GABA, and other small molecules. Better specificity is possible at higher field strengths and with complex pulse sequences,[85] but to date specific measurements of glutamate and GABA have been possible only in the occipital cortex. Improvements in this technology to better and more specifically measure glutamate levels in the striatum and other structures are an essential step toward clarifying the role of glutamate in OCD and other neuropsychiatric disorders.

The increased interest in deep brain stimulation in treatment-resistant OCD may create an opportunity to measure tissue glutamate levels in OCD patients in a more direct way. When depth electrodes are placed in the human brain for therapeutic reasons, as is frequently done in epilepsy, it is possible to sample local CSF and examine the concentration of its various components.[128] Although optimal localization of depth electrodes for treatment of OCD by DBS has yet to be firmly established, it is clear that many electrodes will be targeted to areas known to be hypermetabolic, and hyperglutamatergic.[73] In the near future, therefore, it might be possible to directly measure extracellular glutamate levels in relevant brain areas in OCD, thereby bypassing some of the interpretative difficulties that attend less direct measurement techniques.

Validating the efficacy of antiglutamatergic agents

More rigorous clinical trials examining the efficacy and tolerability of glutamate-modulating agents are needed. A double-blind, placebo controlled trial of riluzole in OCD is in progress; if the results of this more rigorous trial replicate the promising findings of the initial open-label trial,[12] glutamate-modulating agents will be confirmed to be a promising novel avenue for the substantial fraction of OCD patients whose symptoms are resistant to currently available therapies.

If and when riluzole or other glutamatergic agents are established for augmentation in cases resistant to SRI treatment alone, it may be appropriate to study them as monotherapy. Although SRIs are generally well tolerated, they are not without side effects. An expanded armamentarium of primary pharmacological treatment options for OCD might be of benefit to many patients.

Recent investigations suggest that OCD represents several overlapping symptom dimensions.[6] It may that

patients with different categories of symptoms will preferentially respond to primary therapies that target different classes of molecular targets. If further research clarifies such correlations, pharmacological treatment for many patients could be markedly improved. In this context, it is noteworthy that OCD patients with prominent hoarding symptoms are often resistant to SRI pharmacotherapy,[8] and that two of the responders in our open-label study of riluzole were hoarders.[12] It would be premature to propose that antiglutamatergic agents may be of particular use for hoarders; but this type of symptom-therapy association may be possible with a broader armamentarium of effective pharmacological agents.

Other antiglutamatergic agents

Finally, other agents with antiglutamatergic properties may prove equally or more efficacious in the treatment of OCD. The choice of such agents will best be informed by increasing understanding of the specific way in which glutamate neurotransmission is perturbed in OCD. Agents with more specific effects on subtypes of glutamate receptors, such as NMDA modulating agents and AMPAkines, may prove to be interesting potential treatment avenues for some neuropsychiatric disorders. However, excessive blockade of these postsynaptic receptors may precipitate new psychiatric symptoms (e.g., NMDA blockade by PCP producing psychotomimetic effects; our recent observation of the combination of riluzole, memantine, and bupropion producing visual hallucinations in a susceptible patient.[129]

An exciting new possibility is raised by a recent study revealing unexpected glutamate modulating properties of β-lactam antibiotics. Rothstein and colleagues[130] tested over 1000 drugs in an *in vitro* assay and found that multiple β-lactam compounds specifically upregulated the glial glutamate uptake transporter; tested β-lactams proved to have neuroprotective effects in a mouse model of ALS, demonstrating the physiological activity and potential clinical relevance of the compounds. Because of the extensive tolerability data on such compounds, they represent an exciting and unexpected group of potential antiglutamatergic agents for use in OCD and other neuropsychiatric disorders.

CONCLUSION

Obsessive-compulsive disorder is a prevalent neuropsychiatric disorder that creates a great deal of morbidity. Although existing treatments help many patients, a substantial minority is treatment resistant, and many patients who are classified as treatment responders remain markedly symptomatic. Novel therapeutic strategies are therefore urgently needed.

We have reviewed the evidence that glutamate neurotransmission is disrupted in obsessive-compulsive disorder. Although gaps in this evidence remain, there are significant data to suggest such a disruption; and our initial clinical observations with riluzole and certain other glutamate-modulating agents suggest that pharmacological strategies that target the glutamate system hold promise for the treatment of the refractory obsessive-compulsive population (as well as for other depressive and anxiety symptoms).

Existing pharmacological strategies for the treatment of OCD focus on manipulation of monoaminergic neuromodulatory systems: SRIs are well established to reduce symptoms in a majority of patients; and atypical antipsychotics appear to be efficacious augmentation agents in some patients. Agents targeting glutamate neurotransmission represent a qualitatively new strategy for alleviating symptoms of OCD. Patients who are refractory to treatments based on monoaminergic systems may respond to treatments aimed at a different set of molecular targets.

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