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New Horizons in OCD Research and the Potential Importance of Glutamate: Can We Develop Treatments That Work Better and Faster?

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First-line treatments for obsessive compulsive disorder (OCD) – cognitive behavior therapy, drug therapy with selective serotonin reuptake inhibitors (SSRIs), or both – are quite effective for many patients. However, approximately one third of patients do not experience a significant reduction in symptoms from these treatments, or from established second-line interventions. Even in patients who do respond, symptom reduction usually occurs only over the course of two to three months, and response is often not complete. The development of treatments that work better and faster is a major goal of ongoing research.

Glutamate in OCD

Existing medications for OCD target two neurotransmitters (brain chemicals): serotonin and dopamine. However, there has been substantial interest over the last eight years in the potential involvement of another neurotransmitter, glutamate, in OCD. Glutamate is the most abundant excitatory neurotransmitter in the brain; it is critical to the communication of nerve cells with one another in practically every circuit in the nervous system. An abnormally high level of glutamate can lead to neuron damage, and glutamate-modulating therapies (medications aimed at affecting or normalizing the actions of glutamate in the brain) have been explored in medical conditions such as "Lou Gehrig's Disease" (ALS) and in stroke.

Evidence from several sources suggests that abnormal levels of glutamate may contribute to OCD. Investigators at the Ruhr University in Germany examined the cerebrospinal fluid (CSF) of patients with OCD who were not on any medication. They found that individuals with OCD had higher levels of glutamate in the CSF than psychiatrically healthy controls. Since the CSF bathes the brain, this suggests that the brain is exposed to high levels of glutamate in patients with OCD. A similar increase of glutamate in the brain has been seen using another technique, magnetic resonance spectroscopy (MRS), by investigators at Wayne State University, and elsewhere.

The presence of abnormally high levels of glutamate in the brains of individuals with OCD does not prove that it contributes to the disease – problems with glutamate could be a consequence of the illness, rather than a cause. However, recent genetic findings lend support to the idea that glutamate imbalance may be an important causal factor in at least some cases of OCD. Two independent groups, from the University of Toronto and the University of Chicago, published evidence in 2006 that a protein that carries glutamate in the brain is linked to OCD in some cases; more recent studies from groups at the Massachusetts General Hospital and Johns Hopkins University have found the same thing. Although it is not yet clear whether these genetic linkages correspond to a functional problem with this protein, problems with these glutamate transporters can increase the amount of glutamate found outside neurons, which might explain the increased glutamate seen in the brain, and possibly lead to OCD symptoms.

Recent findings in mice further support the idea that changes in glutamate in the brain can produce behaviors that resemble OCD. Researchers at Duke University have described a mouse that is anxious and grooms itself compulsively. They genetically altered the mouse, so that it is missing the SAPAP3 gene. The SAPAP3 gene is a critical piece in structure of the glutamate receptor. The anxiety and compulsive grooming behavior of these mice decreased when they were given an OCD medication – a selective serotonin reuptake inhibitor (SSRI). A few doses of an SSRI did not decrease compulsive symptoms; the medication has to be given over a long period of time to have an affect – the same pattern seen with patients taking SSRIs to treat their OCD.

Although it remains unclear whether this gene (SAPAP3) is involved in OCD, the one genetic study performed to date in humans with OCD, from researchers at Duke and Johns Hopkins, showed preliminary evidence of a relationship to grooming disorders such as Trichotillomania but no links to OCD. Regardless, further work in this and related animal models will increase our understanding of how changes in the brain glutamate, and how neurons respond to it, can lead to compulsive behavior patterns.

Glutamate-targeting Medications

Is it possible then that medications that affect glutamate in the brain will benefit patients whose OCD does not respond to existing therapies? This hope has guided research in our clinic over the past several years, and early results, from our group and elsewhere, are promising – although the evidence for such drugs is not yet conclusive.

Fortunately, a number of medications that affect glutamate levels are already FDA approved for other medical conditions and are therefore readily available for research and clinical use. One such medication is riluzole (Rilutek®), which has been marketed since 1996 for Lou Gehrig's disease (ALS). Riluzole affects glutamate levels in several ways. In an initial open-label study in 2005 and a case series in 2008, we found that approximately half of the severely ill, treatment-refractory patients who have not responded to other treatments improved significantly when riluzole was added to their SSRI. Researchers at the National Institute of Mental Health have found similar results using riluzole in children with OCD. Controlled, double-blind studies (the best way to test the effectiveness of a medication) for riluzole in adult and pediatric OCD have already begun.

A second drug that is already available and affects how neurons respond to glutamate is memantine (Namenda®). Several case reports and two recent open-label case series suggest that the addition of memantine to standard medication therapy can benefit both children and adults with OCD. As in the case of riluzole, these studies are uncontrolled and need to be replicated in larger, placebo-controlled studies.

There is also some limited evidence suggesting that a third medication - N-acetylcysteine or NAC - also has benefit in the treatment of OCD. NAC is available without a prescription. It is an antioxidant and is used in cases of acetaminophen (Tylenol®) overdose to protect the liver from damage. However, animal studies by researchers at the Medical University of South Carolina have found that NAC can affect levels of brain glutamate as well. We worked with a patient with OCD who improved significantly after we added NAC to her existing medications. Unpublished clinical experience, from our group and elsewhere, further suggests that the agent may be of benefit in at least some patients with OCD. Well-controlled studies have shown benefit from NAC in a variety of other disorders of compulsive and impulsive behaviors including pathological gambling, Trichotillomania, and drug craving. Because it is inexpensive, has no significant side effects, and is available over-the-counter, this drug is a potentially attractive therapeutic option, though the evidence for benefit in OCD remains extremely thin.

Glutamate in Depression and the Possibility of a Rapidly-acting Anti-obsessional Drug

Abnormal glutamate levels may also play an important role in major depressive disorder. All of the medications discussed above (riluzole, memantine, and N-acetylcysteine) have been investigated in depression by researchers at Yale, the National Institutes of Health, and elsewhere. Indeed, an important question for future research is how the glutamate problems in these two disorders, which often occur together, differ from one another.

Glutamate is a neurotransmitter – a chemical that communicates from one nerve cell to another. A neuron can respond to glutamate when it binds to a specific kind of protein, a receptor (a receiver of a brain chemical message, like your cell phone receiving a phone call). So alterations in glutamate affect nerve cells by changing the activation of these receptors, and targeting the receptors with medications can change how the neurons respond to glutamate. There are several receptors for glutamate; a particularly important one is called the NMDA receptor. Drugs that affect these NMDA receptors have recently been found to produce a remarkably rapid antidepressant response. This contrasts starkly with the delayed response typically seen with SSRIs in both depression and OCD. This observation was first made by researchers at Yale, who reported in 1998 that depressed patients receiving a single dose of the NMDA-targeting drug ketamine became rapidly better, and stayed better for up to a week. Ketamine can produce a short "high," lasting 1 or 2 hours. However, the improvements of mood were greatest at 24 hours and lasted in some subjects for as long as seven days, making it clear that they were not just

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a result of this high. This striking and unexpected effect was reproduced in a double-blind study at the National Institutes of Health in 2006.

Memantine also affects NMDA receptors, but its effect is much weaker than that of ketamine. Unfortunately, a controlled study of memantine in depression from the National Institute of Mental Health did not show benefit. Newer medications that act on this NMDA receptor are under development.

Ketamine is by no means the answer for major depression. The antidepressant effects of ketamine usually wear off by a week or two. Furthermore, ketamine's addictive and abuse potential and the fact that it needs to be administered intravenously limit its long-term use. Potentially unpleasant psychological symptoms, such as anxiety, sadness, disorientation, flashbacks, and hallucinations can sometimes emerge during ketamine administration and also limit its potential for widespread use. However, a limited trial of ketamine may be useful to help a patient break out of a particularly severe or treatment-refractory depression. In addition, the rapid antidepressant effect of ketamine opens a window into an entirely new way of thinking about how to treat depression. A better understanding of how this drug works in the brain could lead to the development of new drugs that do not have ketamine's drawbacks, but do have its advantages - in particular, a more rapid effect than any standard antidepressants.

These observations raise exciting new possibilities for the field of OCD research. If glutamate contributes to both depression and OCD, and if ketamine can produce a rapid antidepressant effect, would this medication, or similar drugs that affect glutamate or the NMDA glutamate receptor, also be effective treatments for OCD? Depression frequently occurs along with OCD – could drugs that affect the NMDA receptor, like ketamine, be of benefit to both? Most excitingly, the antidepressant effects of ketamine are remarkably rapid – much more so than traditional medication or psychotherapy. It has long been possible to rapidly treat severe depression using ECT; but ECT is not effective in the treatment of OCD, and no rapid treatments have been available. Perhaps this unfortunate limitation will change.

In sum, increasing evidence indicates that abnormal levels of the neurotransmitter glutamate contribute to OCD and may be a fruitful target for new therapies. Ketamine's unexpected, rapid antidepressant effect suggests that similar anti-obsessional effects are a real possibility, since the disorders frequently occur together and problems with glutamate appear to be associated with both. No investigations of ketamine in OCD have been published to date, but developing new clinical treatments like this based on our advancing understanding of OCD at the molecular, cellular, and systems level has the potential to usher in a new era of therapeutics that work better and faster than those we have today.

Research Digest

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"Natural" treatments for various diseases, disorders, and ailments have been a topic of interest for centuries. Even though almost all of the attempts in the past to cure or treat disorders with vitamins, herbs, minerals, and other nutritional or dietary supplements have been unsuccessful, people continue to hope that through research and study we will be able to find "natural" cures and treatments for a number of disorders, including OCD, that will be safer, more tolerable, cheaper, and possibly more effective than current treatment options.

Since there is so much public interest in nutritional and dietary therapies in general, it is not surprising that both the OC Foundation and the Obsessive Compulsive Information Center receive hundreds of calls each year from individuals who want to know if there are any dietary, nutritional or other "natural" treatment approaches that have been shown to help OCD.

In the Fall 2007 OCD Newsletter Research Digest, we reviewed a pilot study of exercise added to ongoing serotonin reuptake inhibitors and/or cognitive-behavior therapy, both treatments of proven benefit in OCD. Before exercise started, the average Y-BOCS score was 22.9. After 12 weeks of exercise it had decreased 7.7 points to an average of 15.2, a worthwhile gain. Mood