Neuroscience 165 (2010) 408–417

REVIEW

THE GLUTAMATE-BASED GENETIC IMMUNE HYPOTHESIS IN OBSESSIVE-COMPULSIVE DISORDER. AN INTEGRATIVE APPROACH FROM GENES TO SYMPTOMS

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Abstract—Recent advances in multiple areas of research have contributed to the identification of several pathophysiological factors underlying obsessive-compulsive disorder (OCD). In particular, the glutamate transporter gene SLC1A1 has been associated with the diagnosis of OCD. Immunological and infectious studies have reported alterations of the immune system and the presence of immune complexes directed against the Borna disease virus in OCD patients. In addition, neuroimaging of OCD patients has demonstrated abnormalities in the anterior cingulate cortex, orbitofrontal cortex, thalamus, and the basal ganglia. Neuropsychological assessments have found several cognitive disruptions that have been identified in OCD, especially impairments in cognitive flexibility. Here, we attempt to bridge the gap between these remarkable findings through several previously unpredicted pathophysiological mechanisms. We propose an integrative hypothesis that indicates how genetic and environmental factors may contribute to the structural and functional alterations of cortico-subcortical circuits, leading to the characteristic cognitive disruptions underlying OCD symptoms.

Key words: anterior cingulate cortex, Borna disease virus, glutamate, obsessive-compulsive disorder, orbitofrontal cortex, thalamus.

Contents

Obsessive-compulsive disorder (OCD) is a disabling and chronic anxiety disorder with a lifetime prevalence of 3% in the general population. It is clinically defined by the presence of obsessions and compulsions. Obsessions are unwelcome, intrusive, and recurrent thoughts, impulses, or images. Compulsions are behaviors or mental acts performed in a repetitive or ritualistic way (Stein, 2002). Cognitive and behavioral therapy and several pharmacological agents, especially serotonin reuptake inhibitors (SRIs) and antipsychotics, improve OCD symptoms and the quality of life in about 70% of patients (Rasmussen et al., 1993; Stein, 2002; Pallanti and Quercioli, 2006). However, up to 40–60% of OCD patients do not have a satisfactory outcome and still have significant disability and morbidity after treatment (Pallanti and Quercioli, 2006). The high rate of non-responders to psychotherapy treatment or psychotropic drugs has recently led to the development of neuro-

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Abbreviations: ACC, anterior cingulate cortex; BDV, Borna disease virus; EAAC-1, excitatory amino acid carrier-1; EAAT-3, excitatory amino acid transporter-3; GABHS, Group A beta-hemolytic streptococcus; mGlu1R, metabotropic glutamatergic receptor 1; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PANDAS, pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection; SLC1A1, solute carrier family 1, member 1; SRI, serotonin reuptake inhibitor.

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doi:10.1016/j.neuroscience.2009.10.043

surgical treatments such as deep brain stimulation. Although neurosurgical treatments allow for considerable improvements in symptoms for some treatment-refractory patients, full remission of OCD symptoms after surgery has rarely been obtained (Greenberg et al., 2006).

Therefore, resolving the factors contributing to OCD's pathophysiology presents a major challenge for refining current therapeutic strategies or developing new therapeutics. During these last few decades, multiple efforts in several research areas have contributed to our understanding of OCD pathophysiology (Stein, 2002; Aouizerate et al., 2004). Genetic investigations into OCD have highlighted associations with gene polymorphisms, and infectious disease studies have identified a pathogenic agent and immunopathological reactions in OCD patients. Furthermore, neuroimaging studies have reported structural and functional alterations in several brain regions in OCD patients. Finally, neuropsychological studies have demonstrated impairments in several cognitive processes that contribute to OCD symptomatology. However, these findings have been considered independently. Here, an attempt has been made to bridge the gap between these different research areas on the basis of what is currently known about OCD. The construction of a coherent and integrative model is not expected to provide a cure, but to address numerous questions concerning possible relationships between genetic, infectious, immunological, cerebral, and cognitive alterations. Therefore, this approach should lead to new and exciting hypotheses to be tested in the future.

GENETIC ALTERATIONS AND THEIR CONSEQUENCES ON THE GLUTAMATERGIC SYSTEM IN OCD

Genetic factors in OCD

Family and twin studies have contributed to elucidating the participation of genetic and environmental factors in OCD. The familial aggregation described in OCD patients suggests that a genetic factor may take part in this familial transmission. Furthermore, twin studies have consistently reported greater concordance rates in monozygotic twins than in dizygotic twins, thereby supporting the importance of a genetic component in OCD pathophysiology (Aouizerate et al., 2004; Pauls, 2008). Moreover, several genes have been proposed as possible candidates for OCD. On the basis of the efficacy of SRIs and antipsychotics in OCD, research groups have primarily focused on serotoninergic and dopaminergic systems. However, among the serotonin- or dopamine-related candidate genes studied, "none have achieved genome-wide significance and with the exception of the glutamate transporter gene, none have been reliably replicated" (see for review, Pauls, 2008).

The glutamate transporter gene SLC1A1 in OCD

The glutamate transporter gene SLC1A1 (solute carrier family 1, member 1) has recently been proposed as a potential candidate gene for OCD. Three independent research groups have reported a significant association between SLC1A1 variability and the diagnosis of OCD (Arnold et al., 2006; Dickel et al., 2006; Stewart et al., 2007). Although two of these studies were ascertained through child probands (Dickel et al., 2006; Stewart et al., 2007), the largest study by Arnold et al. was conducted in adults with OCD (Arnold et al., 2006). Secondary analyses reported by the authors suggested the importance of the age of onset with regard to the relationship between SLC1A1 variability and OCD. This finding was in accordance with the idea that the genetic factors contributing to early-onset OCD may differ from late-onset OCD (Eichstedt and Arnold, 2001; Arnold et al., 2006). Furthermore, a recent family-based association study showed a significant association with one single nucleotide polymorphism that may be a part of a regulator for SLC1A1, and therefore, may influence the function of SLC1A1 coding for the glutamate transporter EAAC-1 (excitatory amino acid carrier-1) (Shugart et al., 2009).

Functional properties of the glutamate transporter EAAC-1

EAAC-1, also called EAAT-3 (excitatory amino acid transporter-3), is localized in the brain as well as several non-nervous tissues such as the heart, intestine, and kidney (see for review: Danbolt, 2001). In the brain, EAAC-1 is predominately found in the cortex, thalamus, basal ganglia, hippocampus, and cerebellum. In particular, it localizes to the somas and dendrites of small and large pyramidal neurons of the cortex (Rothstein et al., 1994; He et al., 2000; Danbolt, 2001). In general, glutamate transporters contribute to the regulation of glutamatergic neurotransmission by maintaining low extracellular glutamate levels, thereby influencing the kinetics of glutamate receptor activation (Fig. 1) (Bergles and Jahr, 1997; Diamond and Jahr, 1997).

Alterations of the glutamatergic system in OCD

There are several lines of evidence in the literature supporting the existence of glutamatergic hyperactivity associated with OCD, which may represent the consequence of functional alterations of the glutamate transporter EAAC-1 (see for review: Carlsson, 2000). For example, the level of glutamate measured in the cerebrospinal fluid of OCD patients is elevated in comparison with healthy subjects (Chakrabarty et al., 2005). Pharmacological studies showed that antiglutamatergic agents, such as riluzole or memantine, may be helpful for decreasing the severity of OCD symptoms (Coric et al., 2005; Grant et al., 2007). Furthermore, the established relationship between the metabolic rate of neurons and glutamatergic transmission (Sibson et al., 1998; Shen et al., 1999) suggests the existence of glutamatergic hyperactivity in OCD, which was indicated by the glucose metabolic rate changes reported in positron emission tomography studies (Baxter et al., 1988; Swedo et al., 1989a; Aouizerate et al., 2004). In a study using transcranial magnetic stimulation in OCD patients, Greenberg et al. (2000) reported decreased intracortical inhibition, thereby indicating increased cortical