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Review article

A review of the role of serotonin system genes in obsessive-compulsive disorder

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ABSTRACT

Obsessive-compulsive disorder (OCD) is a debilitating neuropsychiatric disorder that causes the patient to experience intrusive thoughts and/or to carry out repetitive, ritualized behaviors that are time consuming and impairing. OCD is familial and heritable. The genetic factors responsible for pathogenesis, however, remain largely unknown despite the numerous candidate gene studies conducted. Based on efficacy of serotonin reuptake inhibitors (SRIs) in treating OCD, serotonin system genes have been a dominant focus in OCD candidate gene studies. We review the most commonly studied candidate serotonin system gene variants (specifically in *SLC6A4*, *HTR2A*, *HTR1B*, and *HTR2C*) and their association with OCD. Although findings to date are mixed, serotonin transporter polymorphism *5-HTTLPR* and *HTR2A* polymorphism rs6311 (or rs6313) are most consistently associated with OCD. Mixed findings may be the result of genetic complexity and phenotypic heterogeneity that future studies should account for. Homogenous patient subgroups reflecting OCD symptom dimensions, OCD subtypes, and sex should be used for gene discovery.

1. Overview of obsessive-compulsive disorder (OCD)

OCD is a neuropsychiatric disorder characterized by recurring, intrusive thoughts and/or repetitive and often ritualized behaviors that are carried out in response to obsessions or set rules and usually intended to reduce distress (American Psychiatric Association [APA], 2013). The worldwide prevalence of OCD is 2–3% and the World Health Organization lists the disorder as one of the top ten most debilitating illnesses (Murray and Lopez, 1996; Angst et al., 2004; Kessler et al., 2005; Murphy et al., 2013). OCD is a phenotypically heterogeneous disorder with multiple symptom dimensions that sometimes overlap (Bloch et al., 2008a). These symptom dimensions are captured in a widely-used clinical measure, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), which provides a checklist of OCD symptoms and yields a severity score for obsessive, compulsive, and total symptoms (Goodman et al., 1989a; Goodman et al., 1989b). OCD patients often present with comorbid disorders including a lifetime tic disorder in up to 30% of OCD patients, anxiety disorders, and major depressive disorder. Tic disorders are particularly common in males with early-onset OCD (onset typically in childhood or early adolescence), and children sometimes present with a combination of OCD, tic disorder, and attention-deficit/hyperactivity disorder (ADHD) (APA, 2013).

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The etiology of OCD remains elusive. A number of lines of evidence point to a prominent role for genetic risk factors in OCD. First, OCD is familial. Relatives of individuals with OCD are at higher risk of having the disorder than relatives of healthy individuals, with an 8.2% aggregate risk in first-degree relatives of subjects with OCD versus 2% in control relatives (Hettema et al., 2001; Pauls et al., 2014). Second, twin studies demonstrate that the familiality in OCD is largely due to genetic factors; i.e., the disorder is heritable (Pauls et al., 2014). Genetic factors may play a particularly relevant role in childhood or early-onset OCD. OCD is more common in first-degree relatives of probands with early-onset OCD, compared to first-degree relatives of probands with late-onset OCD (onset typically in late adolescence or early adulthood) (Do Rosario-Campos et al., 2005; Hanna et al., 2005; Taylor, 2011; Pauls et al., 2014). Symptom heritability is also higher in children with OCD (45–65%) versus adults with OCD (27–47%) (Van Grootheest et al., 2005). Intense research has endeavored to identify the specific risk variants associated with OCD, with much focus on the neurotransmitter, serotonin (5-hydroxytryptamine, or 5-HT) (Pauls et al., 2014).

2. OCD and the serotonin system

OCD is most commonly treated with drugs that act on the serotonin system, serotonin reuptake inhibitors (SRIs), which include selective serotonin reuptake inhibitors (SSRIs), combined serotonin-norepinephrine reuptake inhibitors (SNRIs), and clomipramine (a tricyclic compound) (Murphy et al., 2004; Millan et al., 2015). The discovery of SRI efficacy in treating OCD symptoms was the original catalyst for decades of investigation into the role of serotonin, including serotonin system genetics, in the pathobiology of OCD. Several neuroimaging studies have examined the serotonin transporter protein (SERT) and serotonin 2A (5-HT_{2A}) receptor binding or availability in OCD with mixed results: some studies showing increased (Pogarell et al., 2003; Adams et al., 2005), decreased (Stengler-Wenzke et al., 2004; Hesse et al., 2005; Hasselbalch et al., 2007; Reimold et al., 2007; Zitterl et al., 2007; Perani et al., 2008; Matsumoto et al., 2010), or similar binding or availability within specific brain regions of interest (Simpson et al., 2003; Van der Wee et al., 2004; Simpson et al., 2011). A number of studies also reported neuroimaging differences related to age of OCD onset (Pogarell et al., 2003; Simpson et al., 2011) or symptom severity (Hesse et al., 2005; Reimold et al., 2007; Zitterl et al., 2007; Perani et al., 2008; Hesse et al., 2011).

Serotonin is a major monoamine neurotransmitter in the central nervous system. The serotonin system originates in the midbrain raphe nuclei and projects to several cortical and sub-cortical brain regions. Serotonin is essential to a wide range of functions, including mood, behavior, eating patterns, cognition, sleep, reproduction, and motor functions (Vanhoutte, 1990; Murphy et al., 2004; Murphy et al., 2008; Murphy and Lesch, 2008). The serotonin system has also been implicated in the pathogenesis of various psychiatric traits, disorders, and medical conditions. These include OCD, depression, anxiety, neuroticism, autism, ADHD, bipolar disorder, Tourette syndrome (TS), sudden infant death syndrome (SIDS), irritable bowel syndrome, and pulmonary hypertension (Murphy et al., 2004; Nonnis Marzano et al., 2008).

Serotonin is released from the presynaptic neuron into the synapse where it can activate an array of downstream receptors in both the pre and postsynaptic neuronal cell membranes. SERT is located in the presynaptic membrane and facilitates the reuptake of serotonin back into the presynaptic cell to be recycled after its use. As such, SERT plays a critical role in serotonin-based neuronal signalling (Stahl, 1998; Vanhoutte, 1990; Heils et al., 1996; Murphy et al., 2004, 2008; Murphy and Lesch, 2008; Nichols and Nichols, 2008) (Fig. 1). At least 14 serotonin receptor subtypes have been identified (Nichols and Nichols, 2008; Palacios, 2016). Among the most commonly studied in OCD are the 5-HT_{2A} receptor, the serotonin 1B (5-HT_{1B}) receptor (or 5-HT1Dβ receptor in earlier literature), and the serotonin 2C (5-HT_{2C}) receptor. The 5-HT_{2A} receptor activates phosphoinositide hydrolysis to accommodate developmental and cell migration processes in response to serotonin (Dickel et al., 2007; Nichols and Nichols, 2008). The 5-HT_{1B} receptor modulates serotonin release from neuronal axon terminals of serotonergic neurons in the raphe nuclei and also plays a role in the function of non-serotonergic neurons, such as γ-aminobutyric acid (GABA)-ergic and glutamatergic neurons (Dickel et al., 2007; Nichols and Nichols, 2008). Both the 5-HT_{2A} receptor and the 5-HT_{2C} receptor influence dopaminergic neurotransmission (Lappalainen et al., 1995; Nichols and Nichols, 2008).

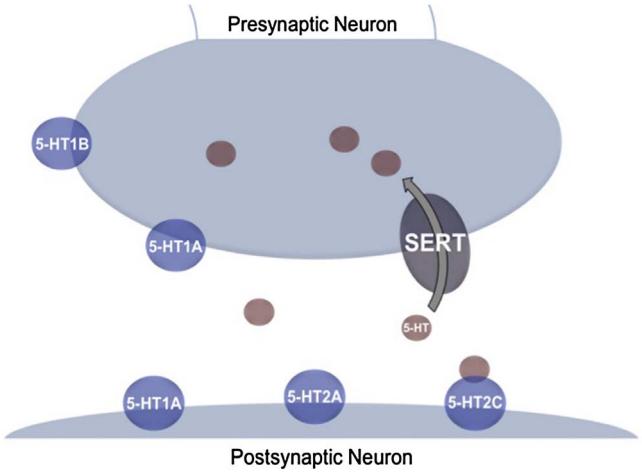

Fig. 1. Serotonin Signaling: Diagram of a synapse between two neurons communicating via the neurotransmitter, serotonin, referred to here as 5-HT. 5-HT is released into the synaptic space where it can activate downstream receptors in the pre and postsynaptic membranes, such as the serotonin 2A receptor, the serotonin 1B receptor, the serotonin 2C receptor, and the serotonin 1A receptor (proteins respectively referred to here as 5-HT2A, 5-HT1B, 5-HT2C, and 5-HT1A). The serotonin transporter protein (SERT), located in the presynaptic membrane, is responsible for the reuptake of 5-HT back into the presynaptic neuron.

2.1. Pharmacological mechanisms of SRIs

The exact mechanisms of action of SRIs are still largely unknown, with hypotheses largely derived from studies conducted in rodents (Blier and de Montigny, 1998; Stahl, 1998; Murphy et al., 2008). SRIs directly block the reuptake of serotonin via negative allosteric modulation of SERT, resulting in an immediate accumulation of serotonin in the synapse (Blier et al., 1990; Billett et al., 1997; Stahl, 1998; Murphy et al., 2008). Chronic SRI treatment increases extracellular serotonin, which produces several downstream effects. These effects include desensitization of serotonin receptor subtypes, such as the serotonin 1A (5-HT_{1A}) receptor and the 5-HT_{2A} receptor, and ultimately enhanced serotonin neurotransmission (Blier et al., 1990; Blier and de Montigny, 1998; Stahl, 1998). Overall, SRIs trigger a number of complex downstream actions that vary by SRI type, brain region, and neurodevelopmental stage. Acute effects are believed to mediate side effects that accompany SRI usage while effects of chronic treatment mediate the therapeutic effects of SRIs, as well as developed tolerance to side effects. SRIs take longer to yield a therapeutic response in patients with OCD rather than depression, suggesting that there are different mechanisms driving OCD pathogenesis and that SRIs may take longer to affect these mechanisms (Blier et al., 1990; Blier and de Montigny, 1998; Stahl, 1998).

3. Candidate gene studies of serotonin system genes in OCD

To date, over 100 association studies of OCD have been published. Candidate gene studies have focused mainly on genes from