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The Pathogenesis and Treatment of Obsessive-Compulsive Disorder

Yixin Hu[1, *]

[1]College of Life Sciences, Wuhan University, Wuhan, China

*Corresponding author: huyixin@whu.edu.cn

Abstract:

Obsessive-compulsive disorder (OCD) is a common, chronic, severe psychiatric disorder in which people have persistent and unwanted thoughts and rigid behaviors. The main treatments for OCD include cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) but the results are not significant and very few people achieve complete remission. The cortico-striato-thalamo-cortical (CSTC) circuit is widely considered to be the neuroanatomical substrate of OCD. Based on genetic research, this circuit is operation is significantly influenced by genes that regulate the glutamatergic, dopaminergic, and serotonergic systems as well as their interactions. However, the inability to pinpoint the precise pathophysiology behind this intricate and varied condition has impeded attempts to create novel treatments or improve those that already exist. This review focuses on the pathogenesis and contributing factors associated with research aimed at elucidating the pathophysiology of OCD and advancing therapeutic interventions. By studying the neurobiological basis of OCD, including neural circuits, neurotransmitter system and genetic factors, people can understand the pathogenesis of OCD deeply, and provide a scientific basis for formulating more effective therapeutic strategies.

Keywords: Obsessive-compulsive disorder; cognitive behavioral therapy; pathogenesis and treatment.

1. Introduction

Obsessive-compulsive disorder (OCD) is a common, chronic, and oftentimes disabling disorder characterized by unwanted and distressing thoughts (obsessions) and repetitive behaviors that the individual feels driven to perform (compulsions) [1]. It is a clinically heterogeneous disorder with a wide range of symptomatic expression [1]. OCD impacts between 2%–3% of Americans and is linked to significant functional impairment as well as an elevated risk of premature death [1,2].Individuals with OCD are at increased risk of suicidal thoughts and behaviors [3]. Empirical evidence from family and twin research conclusively indicates that a greater risk of having OCD is influenced by both hereditary and environmental variables [4]. In support of this, candidate gene and genome-wide association studies have iden-

tified specific genetic variations within the serotonergic, dopaminergic, and glutamatergic systems that are associated with the manifestation of OCD. Wang et al. screened out rare de novo mutations (DNMs) that were only present in patients and found that 24 single-point deletion mutations and 1 large deletion mutation severely affected the structure of proteins that regulate chromatin modification [5]. In addition, they found that the genes involved in these mutations are concentrated in a biological subnetwork with „chromatin regulation“ that is closely related to many neurotransmitter-related genes [5]. This finding confirms that aberrant regulation of chromatin structure caused by ultra-rare mutations may be an important factor in the pathological process of OCD.

Furthermore, imaging studies, along with neuropsychological and treatment research, have implicated frontal-subcortical circuits in the disorder‘s pathophysiology [6]. Among these, the cortico-striato-thalamo-cortical (CSTC) circuit has emerged as the prevailing model for understanding the neural mechanisms underlying OCD [6]. However, cognitive-behavioral therapy combined with exposure/response prevention (ERP) [7] and serotonin reuptake inhibitor drugs (SRIs) remain the only proven first-line therapies for OCD [8]. Currently, approved first-line therapies including cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) only partially alleviate symptoms, and between 30 and 40 percent of patients develop drug resistance [9]. Thus, trying to understand the neurobiology of OCD is beneficial to develop new treatments or enhance extant interventions.

This review will concentrate on the most recent advancements in pathogenesis, moderating variables, and sophisticated neural circuit discoveries, which contribute to a deeper comprehension of the biological mechanisms underlying OCD from a genetic to a circuit-level perspective and offer guidance for future research endeavors in this field.

2. Pathogenesis of OCD

2.1 The Abnormality of Cortico-Striato-Thalamo-Cortical (CSTC) Circuit is Closely Related to the Pathological Mechanism of Obsessive-Compulsive Disorder (OCD)

Neuroimaging findings from humans with OCD support a CSTC circuit model focused on a network of brain regions, which is widely considered to be the prevailing model [6][10]. In individuals with OCD, the CSTC circuits show irregular activity both when at rest and during situations that trigger symptoms [11-13]. However, these circuits normalize in patients who respond to first-line treatment interventions [14]. Additionally, neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), and transcranial direct current stimulation (tDCS) have been reported to have a relevant positive effect by modulating underlying disruptions in the CSTC neural circuit and may operate remotely for patients who are not responding to treatment [15]. Therefore, further knowledge about CSTC networks is necessary to comprehend how brain abnormalities might result in obsessions and compulsions.

The CSTC pathway is a multi-synaptic neuronal circuit that entails a direct and indirect pathway [10]. In the normally functioning CSTC circuit, the striatum becomes excitable due to glutamatergic impulses originating from the frontal cortex, notably the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) [6]. In the direct pathway, this activation enhances inhibitory GABA signals to the globus pallidus interna (GPi) and substantia nigra (SNr), which in turn reduces their inhibitory output to the thalamus, resulting in increased excitatory signals from the thalamus back to the frontal cortex[6]. This creates a positive-feedback loop. Conversely, in the indirect pathway, the striatum inhibits the globus pallidus externa (GPe), allowing it to exert less inhibition on the subthalamic nucleus (STN) [6]. Consequently, the STN can stimulate the GPi and SNr, inhibiting the thalamus. It is believed that OCD symptoms are caused by an excess of tone in the direct loop relative to the indirect loop, which is the result of an imbalance of activity between the two loops [6].

2.2 An Imbalance between Excitatory and Inhibitory Neurotransmission Leads To Compulsive Behavior

Biria et al. measured the levels of glutamate and γ-amino butyric acid (GABA) in the anterior cingulate cortex (ACC) and supplementary motor area (SMA) of healthy volunteers and patients with OCD [14]. In the SMA, glutamate levels were linked to the clinical measures and aspects of compulsive behaviors, while the glutamate to GABA ratio was linked to the index of habitual control. In the ACC, the same relationship was observed in OCD patients, with glutamate levels being elevated and GABA levels being lowered [14]. The results suggest that the potential imbalance between excitatory and inhibitory neurotransmission may contribute to compulsive behavior. The Common Association found in all subjects suggests that obsessive-compulsive is a common phenomenon associated with frontal lobe regions. This may help to develop new neuro-regulatory therapies for OCD, by rebalancing the neurotransmitter levels in these brain circuits.

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2.3 Dopamine Regulates Repetitive Behavior

The prefrontal cortex (PFC) plays a key role in emotion, reward learning and behavioural flexibility [15]. Dopamine regulates working memory in the prefrontal cortex (PFC) and is critical for OCD. Hebbian learning rules and reward learning indicate that a decrease in dopamine reuptake influences synaptic plasticity, which in turn influences the strength of synaptic connections between neurons and results in learnt and obsessive obsessions. Yin et al. establish a biophysical model of the role of dopamine (DA) in PFC, to explain how high dopamine concentrations induce sustained neuronal activity and trap the network in a deep, stable attractor state, which can lead to defects in working memory and tends to be obsessive and compulsive [16].

Consequently, various mechanisms suggest that elevated dopamine levels play a significant role in the maintenance and development of OCD.

Moreover, they explain how dopamine antagonists operate in OCD, indicating that dopaminergic medications could be beneficial for treatment, even if the underlying issue stems from glutamate hypermetabolism rather than dopamine dysregulation [16]. The hypothesis highlights how crucial behavior therapy and early intervention are for OCD. It might provide OCD sufferers a fresh perspective on dopaminergic drugs and psychotherapy.

Lu et al. established a mouse model of obsessive-compulsive disorder using chronic optogenetic activation of the ventromedial prefrontal cortex-Ventral tegmental area pathway and observed a significant increase in self-grooming time in mice [17]. Inhibition of Pars compacta and Ventral tegmental area projections from the midbrain to the Ventral tegmental area (VMS) by optogenetic means significantly reduced the time of self-grooming in mice, inhibition of VTA-VMS projection terminals showed no significant effect, indicating that SNc-derived dopamine can regulate obsessive-compulsive symptoms [17].Further studies identified and confirmed the dopaminergic projections of SNC to the lateral orbitofrontal cortex (lOFC), and activation of this projection terminal also reduced self-grooming time in ocd-like mice. These results suggest that SNC dopaminergic neurons may regulate repetitive behaviors through SNc-lofc-vms environment [17]. The results suggest that dopaminergic neurons in the substantia nigra of the midbrain can dual regulate repetitive behaviors by projecting to the striatum (SNc-VMS) and cortex (SNc-lOFC-VMS), respectively [17]. It is also found that there are differences between the two VMS microcircuits. snc-VMS regulates the PV-SOM-MSN micro loop in VMS, while snc-lofc-VMS regulates the PV-MSN microloop [17]. Different populations of PV neurons (PV1 and PV2) are involved in the regulation of different long-range projections, and there is a causal relationship between the activity of these two microcircuits and repetitive behaviors [17]. The study further showed that SNc-VMS and SNc-lOFC-VMS regulate repetitive behaviors through D1R on PV1 neurons in VMS and D2R on the terminals of SNC dopamine neurons in LOFC, this finding was validated in a Sapap3 knockout mouse model[17]. It can be concluded that the precise loop basis of dopamine regulation of repetitive behavior and the differential regulatory mechanism of different DR subtypes on repetitive behavior. The results of this study may provide new targets for the diagnosis and treatment of repetitive stereotyped behaviors, which are common symptoms of OCD.

3. OCD is Inherited

3.1 Whole-genome Sequencing (WGS) Reveals the Genetic Mechanism of OCD

Lin et al. discovered de novo mutations related to chromatin modification in OCD through WGS [5]. Wang et al. initially conducted WGS of 53 parent-offspring families with OCD to investigate all rare de novo variants and insertions/deletions [5]. They found that genes involved in chromatin modification were significantly enriched in co-expression modules during human brain development [5]. Four genes, namely SETD5, KDM3B, ASXL3, and FBL, presented strong evidence of clustering and had functional convergence in transcriptional epigenetic regulation, suggesting an important risk mechanism for OCD [5]. These results indicate that chromatin modification involving SETD5, KDM3B, ASXL3, and FBL may be an upstream regulator of neurotransmitter system expression, which governs essential neural cognitive functions. Any disruption of this cascade could result in abnormal obsessive phenotypes.

This finding confirms that aberrant regulation of chromatin structure caused by super-rare mutations may be an important factor in the pathological process of OCD. The study analyzed extremely rare OCD mutations at a genome-wide level to investigate the cause of OCD, the discovery that environmental factors interact with genetic factors to cause Epigenetics disorder has important implications for the study of the genetic mechanism of OCD.

3.2 Single Nucleotide Polymorphism (SNP) is used to Identify the OCD Related Genes

Noh et al. focused on which SNPs were significantly more prevalent in patients with OCD. This analysis identified

four genes with a high degree of association with OCD among 608 genes [18]. These four genes all play crucial roles in synapses. NRXN1 encodes a synaptic/cell adhesion protein that affects cell location or interaction and thereby influences synaptic function; HTR2A encodes a G protein-coupled serotonin receptor that is widely expressed in the central nervous system; the protein encoded by REEP3 affects the endoplasmic reticulum within neurons and may subsequently affect the functions of these neurons; CTTNBP2 regulates synapse formation [18].

The four genes identified in this study strongly support the genetic factors behind OCD. Furthermore, all four genes are involved in the neural pathways associated with OCD, affecting serotonin and glutamate signaling and synaptic connections from multiple angles. Therefore, they are likely potential drug target sites. Further isolation and characterization of these genes will lead to an understanding of the biology underlying OCD and, in turn, the development of effective treatment options.

4. Treatments of OCD

4.1 CBT

Psychological treatment for OCD consists primarily of CBT incorporating in-vivo ERP [19]. During ERP, patients learn that obsessive routines are not required to stop feared outcomes by interacting with stimuli that cause symptoms while resisting the urge to follow them [20]. The neurobiological mechanisms can be delved into by examining the therapeutic approaches rooted in psychology and cognitive-behavioral therapy. For instance, understanding the neurobiological basis of OCD can be achieved through studying the neural correlates of ERP responses [21]. The treatment effect of ERP is not very good, so it is crucial to improve the treatment effect. One promising method to enhance the therapeutic effects of ERP treatment involves targeting the N-methyl-D-aspartic acid (NMDA) receptors in the amygdala, along with the NMDA partial agonist d-cycloserine (DCS), which is a crucial factor involved in fear extinction [22].

4.2 SSRI

Modifications in serotonergic transmission, namely the augmentation of serotonin-induced postsynaptic signaling, have been linked to ameliorations in obsessive-compulsive disorder symptoms [23]. In physiological neurotransmission, vesicular monoamine transporters carry serotonin into the easily releasable synaptic pool after it has been reabsorbed from the synaptic cleft back into the presynaptic neuron by membrane transporter proteins [24]. Because these membrane transporters are selectively blocked by selective serotonin reuptake inhibitors (SSRIs), serotonin builds up in the synaptic cleft [21]. Research indicates that the most effective strategy for treating OCD symptoms involves the long-term administration of SSRIs [21]. This treatment modality not only alleviates symptoms but also addresses the underlying neurobiological factors contributing to the disorder. Moreover, studies suggest that when SSRIs are combined with CBT or ERP focused specifically on OCD, the outcomes can be even more favorable [21]. This integrative approach allows for both pharmacological and psychological interventions to work in tandem, maximizing the effectiveness of the treatment and providing patients with a more comprehensive strategy for managing their symptoms [21]. By utilizing both SSRIs and therapeutic techniques, patients can experience significant improvements in their quality of life and a reduction in the severity of their OCD symptoms.

4.3 TMS

Based on the findings of a crucial trial, the FDA has approved deep TMS (dTMS), a type of repetitive transcranial magnetic stimulation (TMS), for the treatment of OCD [25]. Out of the 99 participants in this double-blind randomized controlled trial (RCT), 38 percent responded to the device whereas only 11 percent received a sham therapy [25]. The H-shaped coil used in this device was intended to penetrate deeper structures, ranging from 3 to 5 cm, as opposed to the standard figure-8 coils‘ approximate 2 cm electromagnetic stimulation depth [26]. Medial PFC (mPFC) and ACC, two brain regions assumed to be overactive in OCD, were the targets of dTMS [25].

5. Conclusion

Through the in-depth study of the CSTC (cortex-striatum-thalamus-cortex) circuit, the key role of CSTC in the pathophysiology of OCD was clarified, and the importance of the interaction between genetics and environmental factors in disease susceptibility was emphasized. In addition, genome-wide analysis and SNP analysis provide evidence for specific genetic variants, revealing the relationship between OCD and neurotransmitter systems, specifically serotonin systems. Taken together, these studies not only enrich our understanding of the biology of OCD, but also provide new targets and strategies for clinical treatment.

On the therapeutic front, CBT particularly through ERP remains the cornerstone of psychological treatment, with enhanced outcomes observed when combined with pharmacological interventions like SSRIs. The recent FDA clearance of DTMs offers an innovative option for patients

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who do not respond adequately to traditional treatments.

By analyzing the results of this paper, it can be seen that understanding the complex pathological mechanism of OCD lays the foundation for the development of personalized treatment plans and interventions, and also points out the path for future research directions. The insights from this study suggest that future research on OCD should continue to deepen its neurophysiological aspects to help identify potential biomarkers and effective treatments.

However, the limitation of this article is that it mainly focuses on known biological factors and treatments, and fails to deeply explore the interaction between OCD and other psychiatric disorders, as well as psychosocial factors (such as traumatic experiences, stress, etc.) that may affect OCD symptoms. In addition, the heterogeneity of existing research methods may affect the generalizability of the results, and future studies should strengthen the systematic consideration of these influencing factors.

Looking forward to future research, it will be important to further explore the neurobiological basis, genetic predisposition, and environmental impact of OCD as technology advances, especially in the fields of genomics and neuroimaging. In addition, the development of new interventions and integrated treatment strategies will provide more effective solutions for patients with OCD. With the deepening of the understanding of the pathological mechanism of OCD, individualized and precise medical methods will play an increasingly important role in promoting the clinical management of OCD and improving the quality of life of patients.

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