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Review

WNT/β-catenin pathway and circadian rhythms in obsessive-compulsive disorder

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From the Contents

Abstract

The neuropsychiatric disease named obsessive-compulsive disorder is composed by obsessions and/or compulsions. Obsessive-compulsive disorder etiologies are undefined. However, numerous mechanisms in several localizations are implicated. Some studies showed that both glutamate, inflammatory factors and oxidative stress could have main functions in obsessive-compulsive disorder. Glycogen synthase kinase-3β, the major negative controller of the WNT/β-catenin pathway is upregulated in obsessive-compulsive disorder. In obsessive-compulsive disorder, some studies presented the actions of the different circadian clock genes. WNT/β-catenin pathway and circadian clock genes appear to be intricate. Thus, this review focuses on the interaction between circadian clock genes and the WNT/β-catenin pathway in obsessive-compulsive disorder.

Key Words: circadian rhythms; glutamatergic pathway; inflammation; obsessive-compulsive disorder; oxidative stress; WNT/β-catenin pathway

Introduction

The neuropsychiatric disease named obsessive-compulsive disorder (OCD) affects around one to 2% of people during their life (Pellegrini et al., 2020). OCD is composed by distinctive compulsions or/and obsessions and involves significant disorders for people and their surroundings. OCD etiologies are undefined. However, numerous mechanisms in several localizations are implicated, as the brain's limbic system, orbitofrontal cortex, basal ganglia, neurotransmitters and thalamus (Noh et al., 2017). Moreover, associations between biochemical and neuro-anatomical mechanisms remain unclear (Bloch et al., 2014). OCD patients show anxiety and obsessions due to an highly response to threatening the different stimulation processes (Apergis-Schoute et al., 2017; Rouhani et al., 2019) and deficits in extinction of fear (Dougherty et al., 2018). Currently, oxidative stress (OS) (Alici et al., 2016), inflammation (Attwells et al., 2017) and glutamatergic pathway (Grassi and Pallanti, 2018) can play major functions in OCD etiologies. Few investigations showed the interaction between circadian rhythms (CRs) and OCD (Paterson et al., 2013). Recently, WNT/β-catenin pathway is known to be dysregulated in OCD (Thompson and Dulawa, 2019) and the association between WNT/β-catenin pathway and CRs become to be better understanding. Thus, this review focuses on the interaction between circadian clock genes and the WNT/β-catenin pathway in OCD.

Search Strategy and Selection Criteria

Studies cited in this narrative review published from 1980 to 2020 were searched on the PubMed database using the following keywords: obsessive-compulsive disorder, oxidative stress, inflammation, WNT/β-catenin pathway, glutamate, circadian clock genes, circadian rhythms.

Pathophysiology of Obsessive-Compulsive Disorder

Obsessive-compulsive disorder and Oxidative stress

OS mechanism is an the interaction between generation and destruction of reactive oxygen species (ROS) and reactive nitrogen species (Duracková, 2010). The production of ROS is involved by cell affections numerous lipids oxidation or nitration, proteins and DNA. The NADPH oxidase enzyme implicates ROS through the oxidation of intracellular NDAPH to $NADP^+$. The deregulation of the mitochondria is correlated with the excess of production of ROS and the decrease in the production of ATP showing the increase of the OS mechanism (Vallée et al., 2021c). The factors of inflammation, including leukocytes, are generated from the affect localizations to enhance the re-uptake of O_2 releasing and accumulating the ROS. NADPH oxidase, stimulated by inflammatory factors, can leads to OS (Vallée and Lecarpentier, 2018). Superoxide dismutase (SOD), a major antioxidant, is produced by the stimulation of OS. Moreover, its activation is associated with the increase in cell damages through the production of H_2O_2 (Behl et al., 2010). Glutathione peroxidases are enzymes catalyzing hydroperoxide reduction at the level of glutathione (Behl et al., 2010).

Free radicals lead to the diminution in efficacy of synapses (Cobley, 2018) through the affections of synaptic potentials (Pellmar, 1987). Free radicals can alter the membrane lipids through peroxidation of lipids, causing the depletion in ATP, and damages in neurons and DNA (Phaniendra et al., 2015). Central nervous system (CNS) is mainly associated to free-radical-induced alterations, with their high-function-oxygenation of organs and their low in catalase activities (Pellmar et al., 1989). The CNS presents high rate of polyunsaturated fatty acids and iron but fewer levels of glutathione and SOD (Behl et al., 2010). Numerous findings showed that ROS-neuronal alteration has a main function in the development of neuropsychiatric disorders through the stimulation of the activity of SOD (Oswald et al., 2018). Comorbidities in OCD present the possible enhancement of the basal ganglia process (Parolari et al., 2021). Depression symptom is associated with stimulated of activity of monoamine oxidase and increased rates of antioxidant. Currently, SOD rates are elevated in patients with OCD face to non-OCD patients (Behl et al., 2010). Increased rate of production of ROS metabolites, affecting the activity of catalase, or augmentation of the generation of hydroxyl ions leading to the reduction of activation of catalase (Pigeolet et al., 1990). Several investigations have presented an association between OCD and OS through the enhancement of ROS and defense by antioxidants (Behl et al., 2010). Moreover, free-radicals affect cellular structure and MMP compounds by altering genetic structure, OS, dysregulation in mitochondria and impaired metabolism (Alici et al., 2016).

Inflammation

Some findings have highlighted the major function involved through inflammation in the etiology of psychiatric diseases (Khandaker et al., 2017). In OCD initiation, the association of immune system process and inflammatory factors has been shown recently (Grassi and Pallanti 2018). Some findings have shown that both inflammation and immune mechanism can lead to children OCD through increased $CD16^+$ monocytes in comparison to non-OCD participants (Rodríguez et al., 2017).

However, evidence of inflammatory factors and autoimmune system in process of OCD could be not restrained to children and acute OCD forms but may be also observed in adults (Mataix-Cols et al., 2018). Inflammatory role of factors in OCD was reinforced through the increased level of anti-basal ganglia antibodies compared to control subjects (Gnanavel et al., 2017). Significantly higher rates of cytokines and inflammation markers were shown in OCD patients, including TNF-α and interleukins, compared to non-OCD patients (Rao et al., 2015). In OCD patients, by the use of PET imagery, observed inflammatory factors in the cortico-striatal-thalamo-cortical circuit leads for the activation of microglial cell (Attwells et al., 2017).

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Microglial deregulation
Microglia are little cells of the macrophage stages from progenitors of hematopoiesis observed in brain. These cells can be observed in brain due to their macrophage markers expression (Wolf et al., 2017). Microglia can be quiescent in physiological circumstances and can be stimulated under immune conditions. Microglia can operate on neurogenesis control (Diaz-Aparicio et al., 2020), and neuronal and homeostasis regulation (Li and Barres, 2018). Under pathological circumstances, the over-stimulation of microglia implicates brain infiltration by macrophages (Li and Barres, 2018). In OCD, microglia present a specific action on these mechanisms (Greer and Capecchi, 2002). Nevertheless, these processes remain unknown.

Glutamate
In OCD, the dysregulation of glutamate pathway could be the main target in pharmacological studies. In OCD, glutamate is the major neurotransmitter of the cortico-striatal-thalamo-cortical circuit (Batistuzzo et al., 2021). Glutamate neurons are involved in the brain function compared to serotonin and dopamine, utilized by a fewer neuronal cells. Some OCD findings have presented a glutamatergic deregulation (Marinova et al., 2017; Grassi and Pallanti, 2018).

Glutamate pathway has a main function for plasticity of neurons, learning and memory (Javitt et al., 2011). SLC1A1 (solute carrier, family 1, member 1) gene can be considered as the major candidate gene for OCD patients (Huang et al., 2021). SLC1A1 participates in the neuronal excitatory EEAT3 (Na^+-dependent amino acid transporter 3). In astrocytes, EAAT1 and EAAT2 are the major glutamate transporters while EAAT3 is major in neurons. In astrocytes, glutamate is transformed into glutamine to be release. Neurons reuptake glutamine to re-converted it into glutamate (Daikhin and Yudkoff, 2000). EAAT3 role is to modulate glutamate pathway controlling pre-synaptic N-methyl-D-asparate and metabotropic glutamate receptors activity (Delgado-Acevedo et al., 2019). The activity of EAAT3 is deregulated by the stimulation of glycogen synthase kinase (GSK)-3β activity (Abousaab and Lang, 2016).

Higher rates of glutamate in OCD patients were observed in cerebrospinal fluid (Chakrabarty et al., 2005; Ting and Feng, 2008). Furthermore, some findings focused on magnetic resonance spectroscopy showed stimulated glutamatergic pathway and associated brain components, such as central nodes of the cortico-striatal-thalamo-cortical circuit in OCD (Grassi and Pallanti, 2018). Moreover, genetic pathways have also shown an association between glutamatergic genes and OCD symptoms (Xu et al., 2019).

The Canonical WNT/β-Catenin Pathway

The WNT/β-catenin pathway is implicated in several signals and molecular signaling, including cell proliferation, embryogenesis, cell migration and cell polarity, apoptosis, and organogenesis (Loh et al., 2016). However, the WNT/β-catenin pathway can be deregulated during numerous pathological states, including chronic inflammation, neurological diseases, metabolic diseases, tissue fibrotic and cancer processes (Oren and Smith, 2017).

The WNT/β-catenin pathway belongs to the family of secreted lipid-modified glycoproteins (Al-Harthi, 2012). WNT ligands are generated by neurons and immune sytem cells of the CNS (Wang et al., 2021).

GSK-3β is one of the major negative modulators of the WNT/β-catenin pathway (Vallée et al., 2021a, b, c). GSK-3β is a negative controller of the WNT/β-catenin pathway. GSK-3β is implicated in modulation of numerous pathological pathways, including cell membrane signaling, cell polarity, and inflammatory process (Duda et al., 2020). GSK-3β interacts by downregulating cytoplasmic β-catenin and stabilizes it leading to its migration into the nucleus. Inflammatory process is an age-associated mechanism correlated with stimulation of GSK-3β and the diminution of WNT/β-catenin pathway (Orellana et al., 2015).

Mutant mice of OCD present higher rates of GSK-3β. GSK-3β activity may be a therapeutic perseverative behaviors (Thompson and Dulawa, 2019). Alterations of GSK-3β activity is involved in the initiation of several disorders, as neuropsychiatric diseases (Giese, 2009).

Obsessive-Compulsive Disorder and WNT Pathway

In OCD, few findings have shown the implication of the WNT/β-catenin pathway. Brain-derived neurotrophic factor (BDNF) is a well-known factor associated with psychiatric disorders (Motamedi et al., 2017). BDNF is mainly generated in the CNS and participates in neuron viability (Colucci-D'Amato et al., 2020). A study has presented that BDNF over-activation involves the growth of neurons in association with the WNT/β-catenin pathway through the diminution of GSK-3β (Yang et al., 2015). BDNF activation enhances the stimulation of the PI3/Akt signaling. Akt signaling is a major negative regulator of the activity of the GSK-3β (Tayyab et al., 2018). Furthermore, findings show that the downregulation of BDNF may be correlated to OCD (Hall et al., 2003) or with a sub-phenotype (Timpano et al., 2011). Recent investigations have shown that different types of BDNF genes are correlated with OCD (Wendland et al., 2007).

The sequential bind of beta-catenin with a alpha-catenin is responsible for this action in the case of CDH2/N-cadherin (Shapiro et al., 2007). N-cadherin is essential for cerebral mechanisms, such as long-term potentiation and synaptic adhesion and to control glutamatergic receptors (Kawauchi et al., 2010).

Loss of the integrity of this target domain enhances the loss of function of adhesion (Oyama et al., 1994). N845 is observed in the 'interaction region 2' by which N-cadherin binds with β-catenin (Huber et al., 1999). A hydrogen bind is composed in association with a β-catenin domain. In OCD, in N-cadherin, N845S mutation is required to control cadherin–β-catenin binding (Moya et al., 2013). Cadherins binds to the WNT/β-catenin pathway in many mechanisms (Chen et al., 2021). Cadherins are associated with the actin cytoskeleton by their interactions with β-catenin, acting to the adherens junction (Diaz et al., 2021). The cellular mechanisms that N-cadherin can functionally interact with LRP5/6 implicate AXIN recruitment, forming a complex AXIN–LRP5 leading to AXIN-linking domains in the cytosol with LRP5 (Marie and Haÿ, 2013). In OCD, the decrease of both BDNF and N-cadherin is correlated with the decrease of the WNT/β-catenin pathway.

WNT/β-catenin pathway and oxidative stress
The production of ROS is correlated with the diminution of the WNT/β-catenin pathway through the separation of β-catenin to TCF/LEF to Forkhead box class O (FoxO) (Almeida et al., 2009). This mechanism implicates the cytosolic accumulation of β-catenin in association with FoxO, acting as a cofactor, and then stimulating FoxO nuclear activity (Rao et al., 2021). FoxO activates the expression of apoptotic genes (Nasrollahzadeh et al., 2021). FoxO3a interrupts the cell-cycle by the diminution of the expression of cyclin D1 (Yang et al., 2021). The stimulation of FoxO induces of apoptosis (Nasrollahzadeh et al., 2021). Nevertheless, the stimulation of the WNT/β-catenin pathway can diminish FoxO3a in the cytoplasm to counteract mitochondrial membrane permeability loss, release of cytochrome c, Bad phosphorylation, and the stimulation of caspases activities (Shang et al., 2010).

Interplay between inflammation and the WNT/β-catenin pathway
The activation of WNT/β-catenin signaling decreases inflammatory markers and enhances neuroprotective actions through several interplays between astrocytes and microglia-macrophages (Halleskog et al., 2011; L'episcopo et al., 2011).

Numerous findings have observed an opposing interplay between the WNT/β-catenin and nuclear factor kappa B (NF-κB) pathways (Ma and Hottiger, 2016). The NF-κB transcription factor family comprises 5 compounds in the cytoplasm under non-stimulated circumstances: NF-κB 1 (p50/p105), NF-κB 2 (p52/p100), RelA (p65), RelB and c-Rel (Mitchell et al., 2016). B-catenin complexes with both the compounds RelA and p50 to diminish NF-κB signaling (Deng et al., 2002). Furthermore, by binding to the PI3K, β-catenin decreases the NF-κB signaling pathway (Jiang et al., 2021). Downregulating role of β-catenin focused on the NF-κB pathway was observed in several cells (Ma and Hottiger, 2016). Moreover, the activation of GSK-3β inhibits β-catenin to stimulate the NF-κB signaling (Liu et al., 2020). Upregulation of β-catenin expression is correlated with increased PI3K/Akt pathway leading to a decrease in inflammatory response (Jiang et al., 2021). NF-κB pathway stimulation inhibits the complex β-catenin/TCF/LEF by increasing LZTS2 in cancer cells (Cho et al., 2008). The inhibitor DKK1 is targeting by the NF-κB pathway to enhance an opposing interplay for inhibiting the β-catenin expression in cytoplasm (Fliniaux et al., 2008). GSK-3β control the modulation of β-catenin expression through a direct interaction with the NF-κB pathway (Beurel et al., 2010).

Interplay between WNT/β-catenin pathway and glutamate
The modulation of the expression of β-catenin is associated with the stimulation or the inhibition of both EAAT2 and GS in astrocytes by stimulated TCF/LEF complex formation (Lutgen et al., 2016). In prefrontal cortex, the decrease of expression of β-catenin induces decreased activity of both EAAT2 and GS (Lutgen et al., 2016). The decrease of β-catenin in astrocytes was correlated with decrease of the expression of both EAAT2 and GS (Lecarpentier et al., 2020). Deregulation of the WNT/β-catenin signaling involves a glutamatergic excitotoxicity leading to the stimulation of both OS and inflammation (Lecarpentier et al., 2020).

Circadian rhythms in obsessive-compulsive disorder
CRs are autonomic 24-hour cycles form gene expression to behaviour which occur in the environmental inputs and dysregulation of the expressions of lifetime rhythms could be implicated in pathologies (Roenneberg and Merrow, 2016). Recent studies have observed that CRs can play a main action in psychiatric disorders (Taylor and Hasler, 2018). Several immune and cerebral axis are modulated by CRs. The dysregulation of CRS could be mainly associated with impairment of these lifetime processes (McClung, 2013). Nevertheless, in OCD few studies have observed the function of CRs (Nota et al., 2015; Cox and Olatunji, 2019). Patients who present OCD symptoms can show dysregulation of sleep phase occurring some disorders (Schubert and Coles, 2013). Production of both cortisol and melatonin is damaged in OCD patients (Kluge et al., 2007) and total sleep time is decreased (Cox and Olatunji, 2016; Coles et al., 2020; Vitale et al., 2020).

Circadian clock genes
Numerous mechanisms are modulated by the circadian "clock" (circadian locomotors output cycles kaput). The circadian clock is shown to be in the hypothalamic suprachiasmatic nucleus. CRs are endogenous and entrainable free-running steps which last around 24 hours. Several markers could modulate CRs. These gene markers are called brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1 (Bmal1), cryptochrome (Cry),

circadian locomotor output cycles kaput (Clock) and period (Per) (Gekakis et al., 1998; **Figure 1**). They are modulated by opposed self-feedback-regulations controlled (Reppert and Weaver, 2002). Clock and Bmal1 dimerize and involve to the transcription of Per and Cry (Ko and Takahashi, 2006). The dimer formed by Per/Cry decreases its stimulation by a negative loop. It translocates back to the nucleus to decrease the Clock/Bmal1 heterodimer to decrease its proper activation (Ko and Takahashi, 2006). The dimer Clock/Bmal1 stimulates the transcription of retinoic acid-related orphan nuclear receptors and Rev-Erbs. By a positive loop, retinoic acid-related orphan nuclear receptors activate the stimulation of Bmal1, while by a negative loop, Rev-Erbs decrease their proper activation (Ko and Takahashi, 2006).

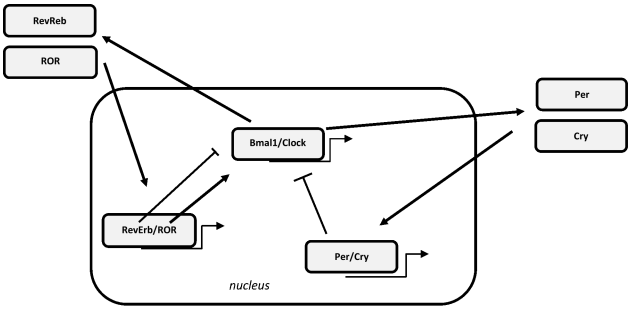

Figure 1 | **Interplay between the cross-regulation of the different circadian clock genes.**
Bmal1: Brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1; Clock: circadian locomotor output cycles kaput; Cry: cryptochrome; Per: period.

Interplay between oxidative stress and circadian rhythms
The dysregulation of Per involves OS in concordance with circadian oscillations (Beaver et al., 2012). The inhibition of Per enhances OS injuries (Krishnan et al., 2009). In neurons, Per deletion causes oxidative injuries (Krishnan et al., 2008). High rates of cortex oxidative damages are correlated to Bmal1 depletion (Musiek, 2015). At cerebral level, Bmal1 modulates in a direct manner the expression of several redox defense genes (Musiek, 2015).

Interplay between inflammation and circadian rhythms
Cytokines and chemokines are produces in a CR manner (Segal et al., 2018). Cytokine expression can be observed at different blood levels along the day stages. The dimer Bmal1/Clock can modulate the observed levels. Stimulation of Clock gene is associated with stimulation of NF-κB signaling (Spengler et al., 2012). The decrease of Clock gene by Bmal1 is also associated with the diminution of the activity of NF-κB. Moreover, Cry diminishes the protein kinase A to decrease the expression of inflammatory makers (Narasimamurthy et al., 2012).

Interplay between glutamate and CRs
Very little findings had focused on this possible association. However, light-modulation in CNS functions are controlled through the glutamate expression (Biello et al., 2018). The receptors N-methyl-D-asparate possess behavioral shifts controlled by light (Colwell et al., 1990). In astrocytes, glutamatergic pathway is a major modulator of the control of CR action in the CNS (Brancaccio et al., 2019). Glutamate controls the rhythmicity of the dimer Per/Cry (Brancaccio et al., 2017).

Interplay between WNT/β-catenin pathway and CRs
Retinoic acid-related orphan nuclear receptors modulate the β-catenin expression (Chen, 2004). CRs genes could modulate the cell cycle stages through the modulation of the WNT/β-catenin pathway (Soták et al., 2014). Bmal1 decrease is correlated with the decrease of the WNT/β-catenin pathway (Guo et al., 2012). WNT-related genes rates are augmented compared to the levels of Bmal1 in CRs knockdown mice (Janich et al., 2011). The cellular progression cycle is controlled by Bmal1 which stimulates the WNT/β-catenin pathway (Lin et al., 2013). Bmal1 enhances the transcription of β-catenin, decreases the degradation of β-catenin and then, downregulates the GSK-3β activity (Sahar and Sassone-Corsi, 2009). The depletion of Per2 stimulates β-catenin expression (Yang et al., 2009). In CNS normal states, CR genes act in particular circles to maintain the molecular and cellular clock-works. CR genes permit the modulation of the other peripheral clocks genes (Reppert and Weaver, 2002). Per1 and Per2 keep cell CRs and control target genes activities, such as c-Myc (Sancar et al., 2004).

In parallel, peroxisome proliferator-activated receptor gamma (PPARγ) binds the clock genes (Chen and Yang, 2014). PPARs are implicated in several cellular mechanisms, including, proteins metabolism, lipids metabolism, cell differentiation, adipocyte differentiation, insulin sensitivity and inflammatory process (Hernandez-Quiles et al., 2021). PPARγ ligands, including thiazolidinediones, can diminish inflammation (Wang et al., 2016). PPARγ interacts with clock genes and presents diurnal modulations (Wang et al., 2008). Diurnal rhythms dysregulation were involved by the decrease of PPARγ expression (Yang et al., 2012). PPARγ controls CRs signals in a direct manner (Yang et al., 2012). PPARγ agonists could activate Bmal1, the heterodimer Clock/Bmal1 (Wang et al., 2010) and Rev-Erbs (Fontaine et al., 2003). Decrease of Nocturin is associated with the decrease of PPARγ oscillations. In normal conditions, Nocturin acts on PPARγ to activate its transcriptional activity (Green et al., 2007) (**Figure 2**). Decreased PPARγ expression alters the CR role of 15-Deoxy-D 12,14-prostaglandin J2 (Yang et al., 2012). A negative loop is well-known between PPARγ and the WNT/β-catenin pathway (Vallée et al., 2021). The PI3K/Akt signaling, which is modulated in a positive manner by β-catenin, acts by the phosphorylation of GSK-3β to inhibit PPARγ (Grimes and Jope, 2001). PPARγ agonists diminish β-catenin levels through stimulating GSK-3β activity (Jeon et al., 2016). Furthermore, PPARγ agonists activate DKK1 to inhibit the WNT/β-catenin pathway (Gustafson et al., 2010). PPARγ agonists activate GSK-3β to directly inhibit β-catenin cytosolic levels (Jeon et al., 2016). Moreover, β-catenin decreases in a direct manner the NFκB pathway (Beurel et al., 2010).

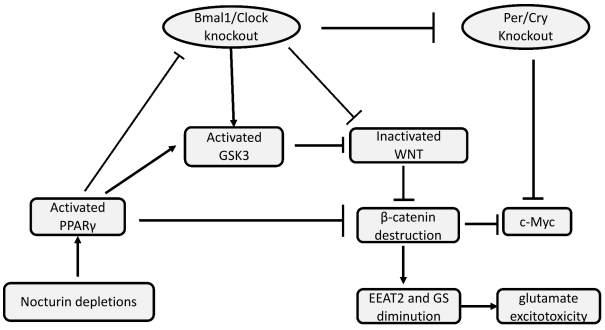

Figure 2 | **Interactions between the different molecular pathways involved and circadian clock genes in obsessive-compulsive disorder.**
Bmal1: Brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1; Clock: circadian locomotor output cycles kaput; Cry: cryptochrome; EEAT2: glutamate transporter; GSK: glycogen synthase kinase; Per: period; PPARγ: peroxisome proliferator-activated receptor gamma.

Conclusion

Few findings have studied the interaction between CRs and OCD. In OCD, very few studies have still studying the WNT/β-catenin pathway. However, in OCD patients, the over-activity of the GSK-3β, one of the major negative controller of the WNT/β-catenin pathway, which is consistent with a decrease of the WNT/β-catenin pathway in this disorder. The dysregulation of this signaling coupled with a deregulation in CRs could be a novel mechanism to better understand the pathophysiology of OCD characterized by OS, inflammation and dysregulated glutamate. Further clinical and animal studies are needed to better understanding the links between circadian clock genes and their expression with OCD.

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