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REVIEW ARTICLE

Possible actions of cannabidiol in obsessive-compulsive disorder by targeting the WNT/β-catenin pathway

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Abstract

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder characterized by recurrent and distinctive obsessions and/or compulsions. The etiologies remain unclear. Recent findings have shown that oxidative stress, inflammation, and glutamatergic pathways play key roles in the causes of OCD. However, first-line therapies include cognitive-behavioral therapy but only 40% of the patients respond to this first-line therapy. Research for new treatment is mandatory. This review focuses on the potential effects of cannabidiol (CBD), as a potential therapeutic strategy, on OCD and some of the presumed mechanisms by which CBD provides its benefit properties. CBD medication downregulates GSK-3β, the main inhibitor of the WNT/β-catenin pathway. The activation of the WNT/β-catenin could be associated with the control of oxidative stress, inflammation, and glutamatergic pathway and circadian rhythms dysregulation in OCD. Future prospective clinical trials could focus on CBD and its different and multiple interactions in OCD.

Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder which affects around 1–2% of the population in their lifetime [1]. OCD is formed by recurrent and distinctive obsessions and/or compulsions and leads to significant problems for patients and their families. The etiologies of OCD remain unclear, but there are several functional disorders in many structures as the brain's orbitofrontal cortex, limbic system, basal ganglia and thalamus and neurotransmitters [2] Nevertheless, the links between neuro-anatomical and biochemical model have not been well understood definitively [3]. In the recent years, oxidative stress and free radicals [4], inflammation [5] and glutamatergic pathway [6] have been shown to play key roles in the causes of OCD.

First-line therapies include cognitive-behavioral therapy [7]. Augmentation strategies with antipsychotics could provide some benefits in at least 30% of patients in the case of treatment resistance. Only 40–60% of the patients respond to first-line therapy and research for new treatment beyond current guidelines is mandatory [8]. Patients with OCD show anxiety and obsessions due to an excessive responsiveness to threatening stimuli [9, 10] and deficits in extinction of fear [11].

Cannabidiol (CBD) is a non-psychotomimetic phytocannabinoid derived from Cannabis sativa plant which possesses many therapeutic properties across a range of neuropsychiatric disorders [12, 13]. Since few years, CBD presents an increased interest as potential anxiolytic therapy [14–16]. CBD downregulates GSK-3-β activity, an inhibitor of WNT/β-catenin pathway [17]. Moreover, CBD was reported to suppress pro-inflammatory signaling and neuroinflammation [18, 19]. A recent meta-analysis has shown that CBD could be an interesting drug in the treatment of several psychiatric disorders, such as schizophrenia, cannabis-related disorders, attention deficit hyperactivity disorder, comorbidities in autism spectrum disorder, anxiety disorders, insomnia, bipolar disorder, post-traumatic stress disorder, and Tourette syndrome [20, 21]. Moreover, the use of CBD drug is associated with few side

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effects, including decrease in appetite loss, irritability and decrease in caving [22], but several studies have shown that CBD administration present no significant complications [23–26]. Until today, very few studies have been published reporting effects of CBD on OCD [20, 27–29]. Only one placebo-controlled investigation of cannabis use in OCD was performed. The results of this study shown that smoked cannabis, whether containing primarily THC or CBD, could present impact on OCD symptoms [30]. Thus, this review focuses on the potential effects of CBD, as a potential therapeutic strategy, on OCD by acting on the WNT/β-catenin pathway and some of the presumed mechanisms by which CBD provides its benefit properties.

Pathophysiology of obsessive-compulsive disorder

Obsessive-compulsive disorder and oxidative stress

Oxidative stress process presents an imbalance between elimination and production of reactive metabolites and free radicals (ROS and RNS) [31]. ROS production is due to cell damages by nitration and oxidation of several lipids, proteins and DNA. The NADPH oxidase (NOX) enzyme involves ROS by intracellular oxidation of NDAPH to NADP+. Intracellular and extracellular environmental conditions are modulated by ROS production [32]. A mitochondrial dysfunction associated with excessive ROS production and a diminution in ATP production characterize the oxidative stress process [33]. Inflammation markers, such as leukocytes, are recruited from the damage sites and then participate to the increase uptake of oxygen for release of ROS and thus, its accumulation. NOX, activated by the inflammation process, also enhances the oxidative stress [33, 34]. The main antioxidants are superoxide dismutase (SOD), glutathione peroxides, and catalase. SOD is synthesized in response to oxidative stress and acts as an antioxidant but its elevation in intracellular increases cell damage by generation of H_2O_2 [35]. Glutathione is one of the first-line defense against oxidative stress. Glutathione peroxidases are selenoenzymes which catalyze the reduction in hydroperoxide at the expense of glutathione [35]. The heme-containing enzyme Catalase has a major role in the removal of hydrogen peroxide [36]. They protect biomembranes against oxidative attack, lipid peroxidation by H202 and slow down H2O2-dependent free-radical attack on lipids [37].

Free radicals (ROS and RNS) induce a decrease in synaptic efficacy [38] by affecting excitatory and inhibitory synaptic potentials [39]. Free radicals deteriorate membrane lipids by lipid peroxidation, cause ATP depletion, DNA damage and neurons [40]. Nervous systems are especially prone to free-radical-induced damage, due to their highly-oxygenated organ function [41] and their low in catalase activities [42]. The brain presents a large amount of iron and polyunsaturated fatty acids and moderate amount of SOD and glutathione peroxides [35]. Several studies have shown that free-radical-mediated neuronal dysregulation plays a key role in the pathophysiology of psychiatric diseases by augmented SOD activity levels, such as schizophrenia [43]. Comorbidity observed in OCD raises this possibility of basal ganglia involvement [44]. Major depression presents increased monoamine oxidase activity and elevated antioxidant levels [45]. Recent studies have shown that SOD levels were higher in OCD patients in comparison to control group [35]. Higher production of reactive oxygen metabolites, as superoxide anion affecting catalase activity [46], or the increase in production of hydroxyl ions reducing catalase activity [47]. Numerous studies have shown a link between OCD and oxidative stress by involvement of free-radicals and antioxidant defense [35, 45]. Moreover, free-radicals damage the cell structure and extracellular matrix compounds by disrupting genetic structure, oxidative stress, mitochondrial dysfunction and impaired metabolism [4].

Obsessive-compulsive disorder and inflammation

Numerous evidence has shown an important role of the immune system (i.e., inflammation) in the etiology of psychiatric disorders [48]. The link between immune system and inflammation in OCD pathophysiology is recent and had emerged in the early nineties [6]. Indeed, the pediatric autoimmune neuropsychiatric disorder associated with group A β-hemolytic streptococcus (GABHS) (PANDAS) and thus the recalled pediatric acute neuropsychiatric syndrome (PANS) have shown that numerous agents rather than streptococcus could be implicated in these acute-onset forms of OCD [49]. The hypothesis for PANS and PANDAS was a link between gangliosides in basal ganglia neurons with the GABHS and/or other agent [49]. Other studies have presented evidence of inflammatory and immune system increase in pediatric OCD by higher monocytes and CD16+ monocytes compared to healthy control subjects [50].

Nevertheless, the importance of inflammation in OCD seems not limited to subsets of pediatric and acute-onset forms of OCD but could be of interest in adults [51]. The role of inflammation in OCD has been strengthened by the higher rate of anti-basal ganglia antibodies in patients with primary OCD versus control subjects [52]. Moreover, significantly increased levels of cytokines and inflammatory agents have been observed in OCD patients, such as IL-2/4/6/10 and TNF-α in comparison to controls [53]. In a study using positron emission tomography (PET) imagery, inflammation presence in the

cortico-striatal-thalamo-cortical circuit induces microglial cell activation in OCD patients [5].

Obsessive-compulsive disorder and microglial dysregulation

Microglia are the brain's resident immune cells. Microglia are small cells of the macrophage lineage from hematopoietic progenitors present in the brain. They can be identified in brain tissue by their expression of a numerous macrophage markers [54]. Microglia have been presumed to be quiescent under physiological conditions and activated upon immune stimulation. They act in the regulation of neurogenesis [55], neuronal function and homeostasis under physiological conditions and in the absence of inflammation [56]. The dysregulated activation of microglia leads to the infiltration of brain by macrophages under pathological conditions [56]. A specific role for microglia in OCD have been suggested in mouse models [57]. However, this mechanism remains unclear.

Obsessive-compulsive disorder and glutamatergic pathway

Glutamatergic dysfunction is becoming the principal focus in pharmacological research in the OCD field. Glutamate is an amino-acid responsible for the brain's primary excitatory neurotransmission. Glutamate is considered as the main neurotransmitter within the cortico-striatal-thalamic circuit involved in OCD [58]. Glutamatergic neurons are embedded in every brain circuit in comparison to dopamine and serotonin which are used by a small minority of neural cells in the brain. Numerous evidences have shown a glutamatergic dysfunction in OCD [6, 59].

Glutamate is the main excitatory neurotransmitter in brain and is present in more than 50% of synapses. This signaling plays a major role for neuronal plasticity, memory and learning [60]. Rapid neurotoxicity enhanced by neuronal excitotoxin has been observed with abnormal glutamate levels [61]. In neurons, glutamate is stored in synaptic vesicles from which it is released. Glutamate release increases glutamate concentration in the synaptic cleft to bind ionotropic glutamate receptors. The main consistent candidate gene in OCD is SLC1A1 (solute carrier, family 1, and member 1) gene [62]. SLC1A1 encodes for the neuronal excitatory Na+-dependent amino-acid transporter 3 (EAAT3). EAAT1 and EAAT2 are the main astrocyte glutamate transporters whereas EAAT3 is the major neuronal glutamate transporter. Glutamate is converted into glutamine in astrocytes and thus release it. Then, glutamine is take up by neurons to be re-converted into glutamate [63]. The role of the EAAT3 is to control glutamate spillover which affects presynaptic N-methyl-D-asparate (NMDA) and metabotropic glutamate receptors activity [64, 65]. EAAT3 activity is dysregulated by the overexpression of GSK-3β [66].

Augmented glutamate levels in adult unmedicated patients with OCD has been shown in cerebrospinal fluid (CSF) [67, 68]. Moreover, studies based on magnetic resonance spectroscopy (MRS) have observed increased glutamate and related components in brain areas, including central nodes of the cortico-striatal-thalamo-cortical circuit in OCD patients [6, 69]. In addition, genetic studies have involved a correlation of glutamatergic genes with OCD [70].

The endocannabinoid system and obsessive-compulsive disorder

Increased activity in the cortico-striato-thalamo-cortical circuit has been associated with OCD [71, 72]. The endocannabinoid system (ECS) is localized throughout the central and peripheral nervous systems. The ECS could be associated with the maintenance of homeostasis to control energy balance, neurogenesis, immune system, sleep/awake cycle, stress reactivity, pain, reward process [20], glutamate and serotonin [73], and dopamine pathways [74]. In the CNS, the ECS can participate in the prevention of the initiation of excessive neuronal stimulation [75] by controlling downstream targets, including the goal of "relax, sleep, forget and protect" [76]. The ECS is consists of two receptors (CB1R and CB2R), endogenous ligands ("endocannabinoids"), and synthetic/metabolic enzymes [77].

CB1R and CB2R are bound by endocannabinoids to involve cellular pathways to induce gene transcription, synaptic function, and cell migration [20]. Endocannabinoids can also activate several non-cannabinoid receptors, such as the transient receptor potential vanilloid 1 (TRPV1) receptor, PPARs, and the orphan G protein-coupled 55 receptor (GPCR55) [78, 79]. CB1R is the main receptor of the ECS in the CNS. High levels of CB1R have been found in the basal ganglia, hippocampus, cerebellum, amygdala, and in prefrontal cortex. These brain regions are involved in OCD, suggesting a role of ECS in the neural circuitry of OCD [80]. The use of cannabis-related medicines shows its greater interest in several diseases, through the ECS, in brain development [81, 82], the stress regulation [80], the neuromodulation of brain system [83], and also the pathophysiology of OCD [84]. The ECS presents several targets involved in psychiatric conditions [30]. The ECS can regulate neurophysiological mechanisms such as sleep [85], memory [86], and affective state [80]. The ECS could affect symptoms of OCD, as a disabling condition marked by recurrent anxiety-producing thoughts, repetitive behaviors [20], and control of neural circuitry [80].

Cannabidiol

Cannabinoids refer to a heterogeneous group of compounds classed into three major groups: endogenous, synthetic, and phytocannabinoids [13, 87]. CBD is a non-psychotomimetic phytocannabinoid derived from *Cannabis sativa plant*. The Cannabis sativa plant produces 66 components, such as delta9-tetrahydrocannabinol (THC), responsible for psychological effects, and CBD, the major non-psychotomimetic component in the plant [88]. In contrast to THC, CBD does not interact with blood pressure or body temperature and does not lead to psychomotor psychological function [89]. CBD attenuates brain damages and neurodegeneration. Humans can tolerate high dose of CBD [89]. Furthermore, CBD can interact with synaptic plasticity and induces neurogenesis. The mechanisms of the CBD effects remain clear but seem to have multiple pharmacological targets. Traditional medicines used Cannabis sativa for centuries. CBD, one of the main component of Cannabis sativa, has recently highlighted its interest for many neuropsychiatric disorders [90]. CBD presents numerous possible medication properties including anxiolytic, antidepressant, neuroprotective, anti-inflammatory and immunomodulatory [13]. Cannabinoids could be considered as a new class of drugs because of their possible actions on neuropsychiatric disorders [91]. CBD has a potential medication role in neuropsychiatric disorders such as schizophrenia, epilepsy, addiction, and neonatal hypoxic-ischemic encephalopathy [92].

Cannabidiol in obsessive-compulsive disorder

Few studies have suggested that CBD could be a novel therapeutic for OCD [30, 78, 93–95]. All the mechanisms of CBD actions in OCD remain unknown [96]. Nevertheless, the anti-OCD properties of CBD could be attributed to the indirect control of CB1 receptor-mediated neurotransmission and the increase of anandamide levels [97]. CBD presents little direct activity with CB1R [98], and some studies have shown a negative allosteric control role of CBD on CB1R [98, 99]. The actions of CBD should act on the ECS by the CB1R with indirect pathways. CBD could stimulate CB1R by the inhibition of FAAH to increase the levels of N-arachidonoylethanolamine (AEA) [98]. AEA is targeting by COX-2 which is associated with the WNT/β-catenin pathway [97]. Moreover, CBD can facilitate adenosine signaling to induce anxiolytic effects [99]. Other studies have shown that CBD can stimulate the WNT/β-catenin and PI3K/Akt pathways and produces medication effects in schizophrenia [100–102]. Several trials have investigated the anti-psychiatric properties of CBD [103–108]. CBD could control the mechanism underlying the serotonin release and then control OCD symptoms [95]. CBD could reduce anxiety and psychotic symptoms [90] and this, with few adverse effects [109].

Activation of the canonical WNT/β-catenin pathway by Cannabidiol: a potential therapeutic strategy

WNT/β-catenin pathway

WNT name is derived from Wingless drosophila melanogaster and its mouse homolog Int. WNT/β-catenin pathway is implicated in numerous signaling and regulating pathways, including embryogenesis, cell proliferation, migration and polarity, apoptosis, and organogenesis [110]. However, during numerous pathological states, the WNT/β-catenin pathway can be dysregulated, such as inflammatory, metabolic and neurological disorders, tissue fibrosis, and cancers [111].

The WNT pathway is one of the member of the secreted lipid-modified glycoproteins family [112]. WNT ligands are produced by neurons and immune cells in the central nervous system [113]. Control of the WNT/β-catenin pathway implicates, embryonic development, cell fate, epithelial–mesenchymal transition, metabolism. WNT pathway dysregulation contributes to several neurodegenerative diseases including PD [114–117]. The WNT pathway has a main stage which is the β-catenin/T-cell factor/lymphoid enhancer factor (TCF/LEF). Accumulation of β-catenin in the cytoplasm is modulated by the destruction complex composed by AXIN, glycogen synthase kinase-3 (GSK-3β) and tumor suppressor adenomatous polyposis coli (APC). In absence of WNT ligands, this destruction complex leads to hyper-phosphorylation of the cytoplasmic β-catenin and involves its proteasomal degradation. In contrast, in their presence, the WNT ligands complex to Frizzled (FZL) and LDL receptor-related protein 5/6 (LRP 5/6) to stop the action of the destruction complex and to prevent the proteasomal β-catenin degradation. β-catenin translocates to the nucleus to bind to TCF/LEF. This phenomenon stimulates the WNT target genes [118–120].

GSK-3β is one of the main inhibitors of the WNT/β-catenin pathway [121–126]. GSK-3β, an intracellular serine-threonine kinase, is a major controller and inhibitor of the WNT pathway [127]. It is implicated in the regulation of numerous pathophysiological pathways, including cell membrane signaling, cell polarity, and inflammation [128–130]. GSK-3β directly inhibits cytoplasmic β-catenin and stabilizes it leading to its nuclear migration. Inflammation is an age-related phenomenon associated with stimulation of GSK-3β activity and the diminution of the WNT/β-catenin signaling [131] (Fig. 1).

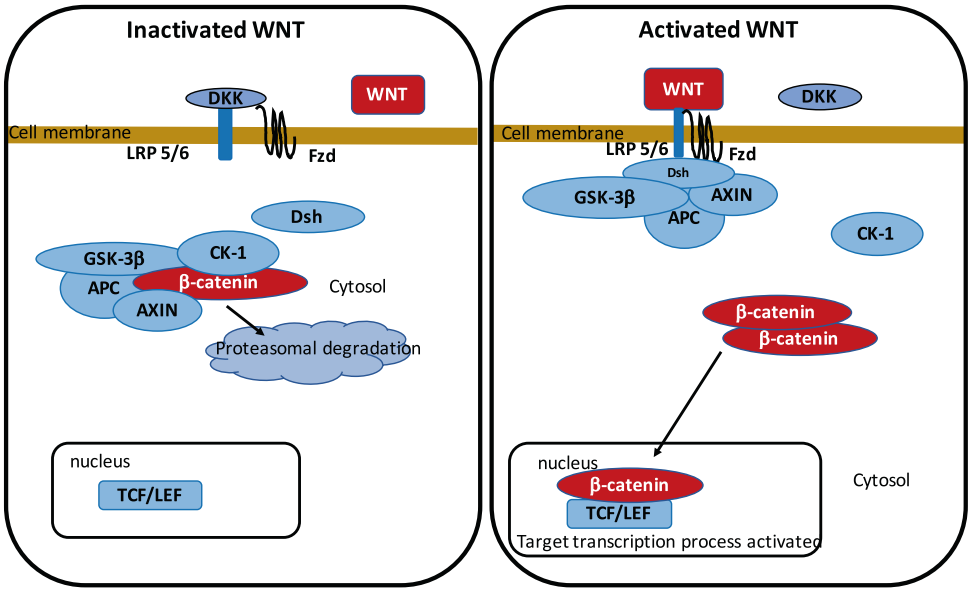

Fig. 1 Activated and deactivated WNT pathway. Inactivated WNT leads to the activation of the beta-catenin complex destruction and then, the non-activation of transcription gene targets. Activated WNT leads to the inactivation of the beta-catenin destruction complex resulting in its cytosolic accumulation and then its nuclear translocation to stimulate transcription gene targets.

WNT/β-catenin pathway: a potential target in OCD

Very few studies have focused on the interest of the WNT/β-catenin pathway in OCD. Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family which includes nerve growth factor, neurotrophin-3, and neutorophin-4. BDNF is a well investigated factor associated with mental illness [132, 133]. BDNF is broadly expressed in the CNS and supports the survival of neurons during development [134] The secretion of BDNF is activity dependent, and it is shown to be secreted by both presynaptic and postsynaptic terminals at different stimulation intensities [135]. Currently, a recent study have shown that BDNF overactivation can lead to the growth of neurons by the interplay of the canonical WNT pathway through the downregulation of GSK-β [136]. BDNF activation is associated with the bind to Tropomyosin receptor kinase B (TrK B) leading to PI3/Akt pathway stimulation. Protein kinase B (Akt) pathway is one the key inhibitor of the GSK-3β [137]. Moreover, data suggest that the downregulation of BDNF could be associated with OCD [138] or with a hoarding sub-phenotype [139]. Recent investigations found that multiple haplotypes in the BDNF gene were associated with OCD diagnosis [138, 140, 141].

In parallel, single-nucleotide polymorphisms within the canine neuronal cadherin gene (CDH2) presented a main risk for canine compulsive disorder (CCD) [142]. Cadherins constitute a superfamily of adhesion molecules featuring an N-terminal tandem series of ectodomains, followed by a single anchoring transmembrane domain and a C-terminal cytoplasmic region (B150 amino acids) which binds cadherins to the underlying cytoskeleton. In the case of CDH2/N-cadherin, this is via sequential binding of beta-catenin to alpha-catenin and then through intermediates to actin [143, 144]. N-cadherin is required for critical brain mechanisms, such as long-term potentiation, pre- to post-synaptic adhesion, dendritic spine elongation, thereby controlling glutamate receptor trafficking, and neuronal migration [145–147].

The CDH2 N845S variant lies in the highly conserved cytoplasmic domain of β-catenin. Loss of integrity of this domain leads to loss of adhesive function [148]. N845 is localized in the "interaction region 2" of the extended region through which N-cadherin binds with β-catenin [149]. A hydrogen bond is formed with a domain of β-catenin. Phosphorylation of Y654 by Src and other cytoplasmic kinases reduces the association of cadherins with β-catenin, leading to the dissociation of the cadherin-β-catenin complex. Thus, the N845S mutation in N-cadherin appears well placed to modulate cadherin–β-catenin interactions in OCD [150]. Cadherins were shown to interact with this WNT pathway in several ways [151–153]. Cadherins are linked to the actin cytoskeleton through their binding to β-catenin, which participate to the adherens junction [154]. The molecular processes by which N-cadherin can functionally bind to LRP5/6 involve the intracellular recruitment of AXIN, leading to the formation of an AXIN–LRP5 complex involving AXIN-binding sites in the cytoplasmic tail of LRP5 [155]. The downregulation observed of both BDNF and N-cadherin in OCD participate in the potential decrease in WNT pathway (Fig. 2).

Cannabidiol and WNT/β-catenin pathway

A recent study has observed that mutant murine models of OCD presented increased GSK-3β activity and thus its

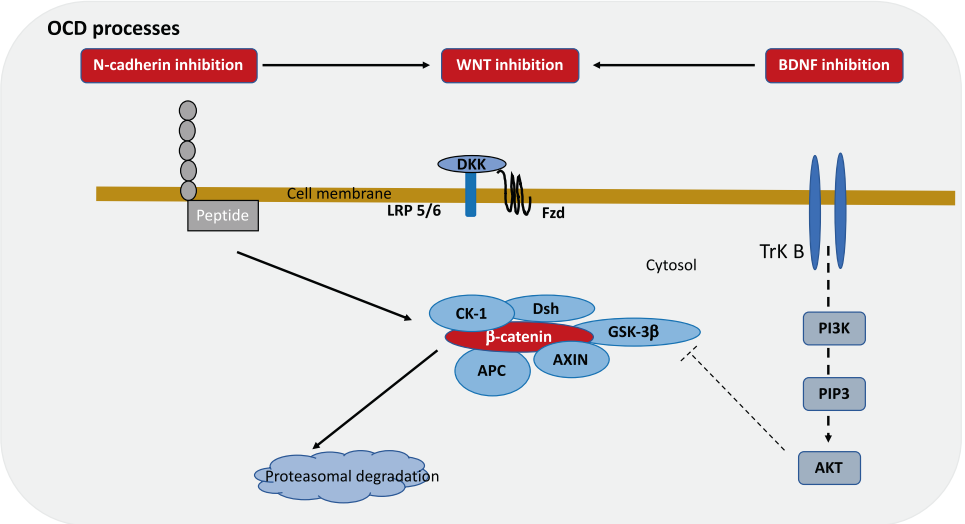

Fig. 2 WNT pathway inhibition in OCD. In OCD, the downregulation of the BDNF is associated with a nonbinding with Tropomyosin receptor kinase B (TrK B) leading to the non-activation of the PI3K/Akt pathway and then to the non-inhibition of the GSK-3β. The disruption of the N-cadherin by a competitor peptide leads to its inhibit its bind to AXIN and LRP5/6 enhancing the inhibition of the WNT pathway.

inhibition could be a treatment of perseverative behaviors [156].

Dysfunction of GSK-3β is involved in the pathogenesis of several diseases, including neuropsychiatric disorders [157]. GSK-3β is a regulator of several pathways such as inflammation, neuronal polarity, or either cell membrane signaling [129]. GSK-3β is known to be the main inhibitor of the WNT/β-catenin signaling [125, 158–160]. GSK-3β downregulates the canonical WNT/β-catenin pathway by inhibiting β-catenin cytosolic stabilization and its translocation in the nucleus [161]. Moreover, several studies have shown a link between neuroinflammation and the increase of the GSK-3β activity and in parallel the decrease of the WNT/β-catenin pathway and the Akt pathway [121].

CBD downregulates the expression of GSK-3β through the promotion of the PI3K/Akt signaling [162, 163]. PI3K/Akt signaling regulates GSK-3β activity [164]. Cannabinoids control the PI3K/Akt/GSK-3β axis [165, 166]. Genes encoding for the PI3K/Akt pathway are increased in CBD-GMSCs (mesenchymal stem cells derived from gingiva treated by CBD) [162].

WNT/β-catenin pathway and oxidative stress

FoxO (Forkhead box class O) transcription factors are main intracellular controllers of numerous metabolic signaling such as glucose production, and the cellular response to oxidative stress [167]. ROS is associated with the inhibition of the WNT pathway by diverting β-catenin from TCF/LEF to FoxO [168]. This leads to the accumulation and binding of β-catenin to FoxO as a cofactor, and in increasing FoxO transcriptional activity in the nucleus [169, 170]. FoxO stimulates apoptotic genes [171–173]. FoxO3a stops the cell-cycle by stimulating of the production of the cyclin-dependent kinase inhibitor p27 kip1 and the inhibition of cyclin D1 expression [174, 175]. The activation of FoxO induces apoptosis [176]. However, the activation of the WNT pathway can downregulate FoxO3a in the cytosol to prevent the loss of mitochondrial membrane permeability, cytochrome c release, Bad phosphorylation, and activation of caspases which activates ROS production and oxidative stress [177].

WNT/β-catenin pathway and inflammation

The stimulation of the WNT pathway cascade restrains inflammation and leads to the neuroprotection via interactions between microglia/macrophages and astrocytes [178, 179].

Several studies have shown a negative crosstalk between WNT/β-catenin pathway and NF-κB signaling pathway, one of the main marker of inflammation [180]. The NF-κB transcription factor family belongs of five members in the cytosol under non-activated conditions: NF-κB 1 (p50/p105), NF-κB 2 (p52/p100), RelA (p65), RelB, and c-Rel [181]. B-catenin can complex with RelA and p50 to diminish the activity of the NF-κB signaling [182]. Moreover, by interacting with the PI3K, β-catenin inhibits the functional activity of NF-κB [183]. This inhibitory function of β-catenin on NF-κB pathway activity has been observed in numerous cell types, such as fibroblasts, epithelial cells, hepatocytes, and osteoblasts [180]. In parallel, the over-activation of GSK-3β leads to an inhibition of the β-catenin and then an activation of the NF-κB pathway [184]. The potential protective action of β-catenin was due to the activation of PI3K/Akt pathway and thus the reduction of TLR4-driven inflammatory response in hepatocytes [185]. NF-κB activation leads to the diminution of the complex β-catenin/TCF/LEF by the upregulation of LZTS2 in cancer cells [186]. DKK, a WNT inhibitor, was a target gene of the

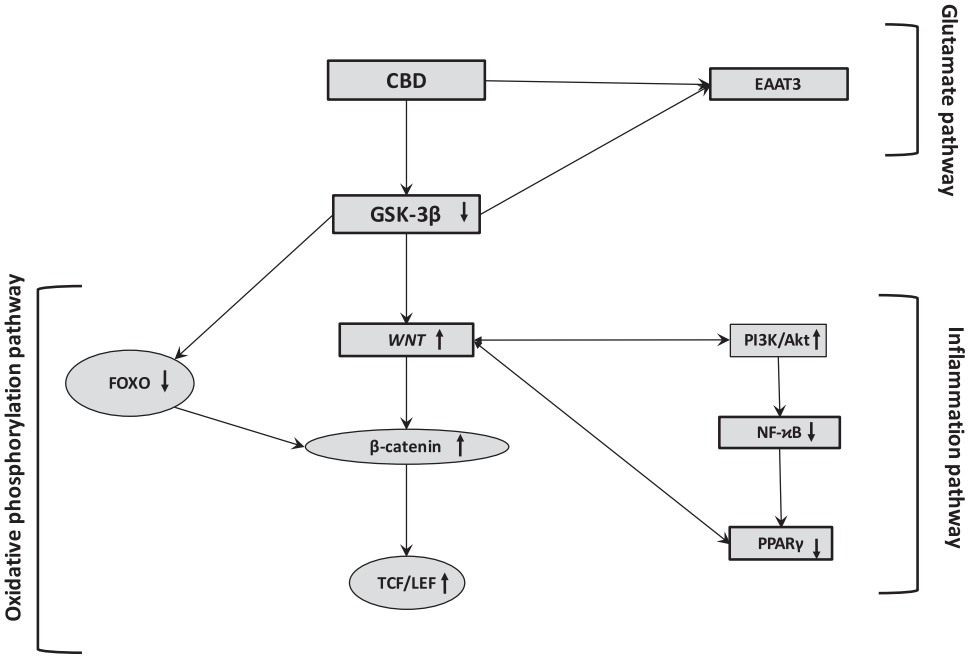

Fig. 3 Cannabidiol interactions with oxidative stress, inflammation, and glutamatergic pathways. CBD directly inhibits GSK3b to increase the activity of the WNT leading to decrease inflammatory process (byt inactivating the PPARg), to diminish the oxidative stress (by decreasing FOXO) and then to modulate the glutamatergic pathway (by modulating the EEAT3).

NF-κB pathway leading to a negative feedback to diminish the β-catenin signaling [187]. Activated B-catenin inhibits the NF-κB-mediated transcription of pro-inflammatory genes. This effect is controlled by the GSK-3β. GSK-3β is a direct inhibitor of the β-catenin levels and an activator of the NF-κB pathway [188, 189].

WNT/β-catenin pathway and glutamatergic pathway

B-catenin activates EAAT2 an GS at the transcriptional level in progenitor-derived astrocytes through the activation of TCF/LEF [190]. The knockdown of β-catenin leads to the diminution of EAAT2 and GS expression in prefrontal cortex [191]. In astrocytes, the inhibition of β-catenin is associated with diminution of both EAAT2 and GS expression [192]. The dysregulation of the WNT/β-catenin pathway induces a glutamate excitotoxicity resulting in the increase of both inflammation and exudative stress [192].

Cannabidiol and oxidative stress

Energy and glucose metabolisms involved during oxidative stress are mainly controlled by the intracellular FOXO transcription factors (FOXO1, 3a, 4) [167]. The interaction between β-catenin and FOXO transcription factors promotes cell quiescence and cell-cycle arrest. B-catenin blocks its transcriptional complex with TCF/LEF through the interaction with FOXO-induced ROS [168]. β-catenin does not translocate to the nucleus and thus accumulates in the cytosol to inactivate the WNT/β-catenin pathway (Fig. 3) [169, 170].

CBD can reduce the redox balance through the modification of both the level and activity of oxidants and antioxidants [193]. CBD stops the free-radical chain reactions through the capture of free radicals and then by reducing their activities [194]. CBD downregulates the oxidative conditions through the prevention of the formation of superoxide radicals, generated by xanthine oxidase (XO), and NADPH oxidase (NOX1 and NOX4) [195, 196]. Moreover, CBD can enhance the diminution in NO levels in the liver of doxorubicin-treated mice [197]. CBD diminishes reactive oxygen species (ROS) production through the chelation of transition metal ions implicated in the Fenton reaction to form extremely reactive hydroxyl radicals [198]. CBD acts on the classic antioxidant butylated hydroxytoluene (BHT) to prevent the dihydrorodamine oxidation in the Fenton reaction [199].

The antioxidant activity of CBD is characterized by the activation of redox-sensitive transcription factor which referred to the nuclear reythroid 2-related factor (Nrf2) [200] responsible for the transcription of cytoprotective genes [201]. Superoxide dismutase (SOD) and enzymatic activities of Cu, Zn, and Mn-SOD, which are responsible for the metabolism of superoxide radicals, are increased by CBD [202]. Glutathione peroxidase and reductase are increased by CBD to decrease the malonaldehyde (MDA) levels [203]. Enzymatic activities are altered during oxidative modifications of proteins. CBD, by targeting glutathione and cytochrome P450, car inhibit their biological activity to decrease oxidative stress [197, 204]. Moreover,

through the diminution of ROS levels, CBD can prevent and protect nonenzymatic antioxidants [202], including vitamins A, E, and C [205].

Cannabidiol and inflammation

Cannabinoids present anti-inflammatory action by endogenous receptors, such as cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) [206]. Cannabinoids interact with PI3K/Akt pathway through [207, 208]. N-Oleoyl glycine (OLGly), a lipoamino acid, increases adipogenic genes including PPARγ, a marker of inflammation, and the mRNA expression of CB1 receptor. The inhibition of CB1 receptor by its antagonist SR141716 downregulates the actions of OLGly on the expression of PPARγ. Moreover, OLGly activates the Akt pathway and inhibits FoxO activity [209]. CBD can bind PPARγ [102, 210]. PPARγ is a main factor of inflammation by interacting with NFκB. This bind occurs between the ligand-binding domain of PPARγ and the Rel homology domain region of the p65 subunit of NFκB. Proteasomal degradation of p65 is caused by Lys48-linked polyubiquitin of the ligand-binding domain of PPARγ [211]. Thus, PPARγ can modulate inflammation through the ubiquitination proteasomal degradation of p65 leading to the control of cyclooxygenase (COX-2), TNF-α, IL-1β, and IL-6 [102]. PPARs are ligand-activated transcription factors which bind PPRE (PPAR-response elements). PPARs are implicated in numerous pathophysiological mechanisms, such as cell differentiation, proteins metabolism, lipids metabolism, carcinogenesis [212, 213], adipocyte differentiation, insulin sensitivity, and inflammation [214, 215]. PPARγ ligands, such as thiazolidinediones (TZDs), are able to decrease the inflammatory activity [216]. A negative crosstalk has been well described between PPARγ and the WNT pathway [33, 158, 217, 218]. The PI3K/Akt pathway, which is positively induced by β-catenin [160, 217, 219–221], acts through the phosphorylation of GSK-3β to negatively control the PPARγ expression [222]. PPARγ agonizts decrease β-catenin expression by over-activating GSK-3β [223]. Moreover, PPARγ agonizts stimulate Dickkopf-1 (DKK1) activity to diminish the canonical WNT/β-catenin pathway and then downregulate the differentiation of fibroblasts [224]. Moreover, PPARγ agonizts stimulate GSK-3β to diminish β-catenin expression [223]. In parallel, β-catenin directly inhibits NF-κB activity (Fig. 3) [188, 189].

Cannabidiol and glutamatergic pathway

Few studies have investigated the interaction between the endogenous cannabinoid system and the glutamatergic pathway in the brain [225]. CBD diminishes the glutamate release in neural signaling implicated in compulsive behavior [226]. Many studies highlighted that the actions of CBD on dopamine and GABA levels was correlated with its strong antioxidant properties through the modulation of nitric oxide synthase expression and the inhibition of ROS-generating NADPH oxidases [227]. However, it has been highlighted that endogenous cannabinoids can bind to the cannabinoid CB1 receptor and dampen presynaptic glutamate release [228]. Moreover, the inhibition of GSK-3β can decrease EAAT3 activity [66]. Nevertheless, the relation between CBD and the glutamatergic pathway remains unclear. CBD can block the actions of CB1R/CB2 combined receptor agonist [229] and can act as CB1R antagonist [230] (Fig. 3).

Circadian rhythms in OCD: new insights

Circadian rhythms

Circadian rhythms (CRs) are important biological mechanisms found in all universal processes. Their main characteristic resides in an innate oscillation which is found associated with a period longer than 1 day. All the living organisms studied present this kind of oscillations. Many cellular functions have shown temporal variations which were induced by these circadian pathways, including gene expression, metabolic pathways, but also molecular and cellular pathways. Different integration strata make it possible to observe CRs, such as the behavior of endocrine, physiological or neuronal cells. Although the coordination of CRs are shaped by structures derived from specific pacemakers, so-called primary circadian oscillations are controlled at the cellular level. These oscillations are determined by many clock genes [231]. The modulation of the circadian clock is based on a temporal tracking system at the intracellular level that allows organisms to modulate their direction and thus adapt their behavior and physiological functioning during their lifespan [232]. It has been recognized that many animal species possessing this circadian clock are formed by specific sets of transcription factors that make up its molecular architecture. These factors are used in both positive and negative feedback which themselves are autonomously controlled by the cell [233].

Endogenous oscillations generate a repetition period close to 24 h in order to maintain constant ambient conditions for the organism. These oscillators, at the molecular level, are based on the products of clock regulating genes hierarchized in transcriptional feedback loops. Thus, the observed circadian oscillations result from post-transcriptional modifications of proteins [234]. These complex loops are regulated by activators of transcription of

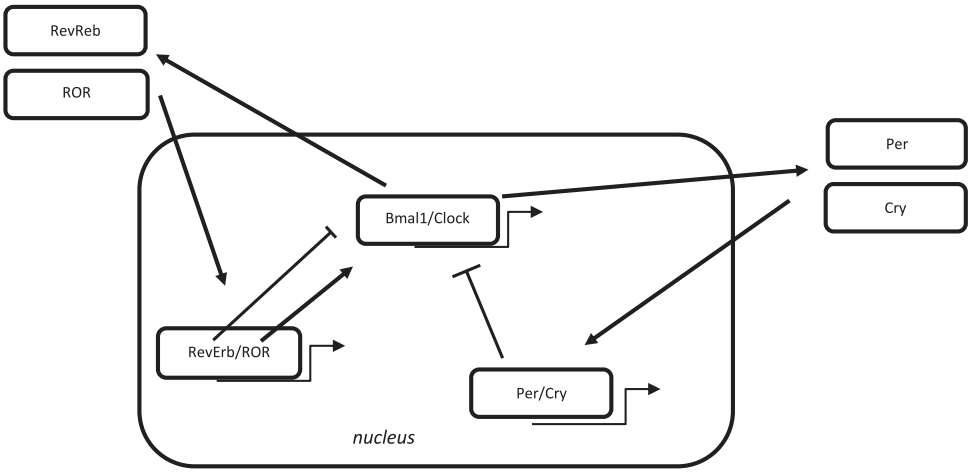

Fig. 4 Circadian clock genes mechanism. The clock consists of a stimulatory loop, with the Bmal1/Clock heterodimer stimulating the transcription of Per and Cry genes, and an inhibitory feedback loop with the Per/Cry heterodimer translocating to the nucleus and repressing the transcription of the Clock and Bmal1 genes. An additional loop involves the RORs and Rev-Erbs factors with a positive feedback by ROR and a negative feedback by Rev-Erbs.

the clock gene which in turn are regulated by clock genes having a negative feedback inhibiting their expression by disrupting the activity of their activators [235]. Many input channels concern environmental information interacting with the different components of the oscillators. The oscillators are synchronized with the 24 h solar day. The input channels generate a time of day for transposition by the oscillators to the output channels. These output pathways thus control the expression of circadian clock genes to generate what is called rhythmicity. In parallel, the output pathways are planned to be rhythmic and then modulated by the transcription factors of the clock gene. These compounds, in turn, downregulate the circadian clock genes in specific ways corresponding to each time of day [236]. The body's internal clock allows this process to synchronize with its environmental time. To be synchronous with the environment, the input channels remain vital to maintain the synchronous rhythmicity of the oscillators. Input channels can reset oscillator activity to maintain the 24 h period and remain compliant with the environment [236]. The signals coming from the environment are detected by the input channels in order to adapt the control mechanisms of the activity of the oscillators in order to maintain a perfect synchronization with the time of day. This phenomenon can be easily observed in many physical mechanisms such as nutrition, social interactions or even the adaptation of body temperature [237, 238]. In addition, the clock allows the implementation of a strategy called gating to restrict responses to environmental signals at certain times of the day.

Diurnal organisms are not sensitive to light pulses during the day. Even so, during the night, a pulse of light can move the clock forward or backward to synchronize diurnal mammals with the environment [233]. Environmental signals can interact with molecular oscillators in some cells of multicellular organisms. Whereas in single-celled organisms, each cell is controlled by oscillators in response to light [239]. However, in multicellular organisms, only a part of the cells has sensory capacities leading to clock oscillators. The oscillators are located in mechanisms composed of a main pacemaker associated with peripheral oscillators [240]. Faced with these so-called bewitching inputs, the organism has certain nervous systems which have environmental locating capacities such as central oscillators or cardiac pacemakers rather than towards individual cells. In humans, the sensory clock inputs are located in the brain, where signals from the primary pacemaker lead to oscillators in certain body tissues.

Nonvisual retinal ganglion cells receive and perceive light, and transmit this information to the primary pacemaker (located in the hypothalamus) through neural connections. The central stimulator synchronizes the oscillators with other tissues through the circadian input pathways of the nervous system to peripheral cellular systems. In addition, to maintain the drive of these peripheral oscillators by the environment, this central system guarantees that the cellular oscillations within the tissues are always in rhythmic phase between cellular and individual phases [241]. The sleep–wake mechanism is modulated by both CRs and homeostasis. Sleep pressure was stimulated during the waking phase and then decreased during the sleep phase. This model is thus controlled by the light-dark cycle [242]. Thanks to a feedback curve, this model can also control CRs and thus act on them. For many studies, this model can be defined as an interface between environmental information (social, mood, and cognition) and CRs [243].

Circadian clock

Numerous physiological processes are modulated by the circadian "clock" (circadian locomotors output cycles kaput) (Fig. 4). The circadian clock is located in the hypothalamic suprachiasmatic nucleus (SCN). CRs are endogenous and entrainable free-running periods that last

~24 h. Several transcription factors can modulate CRs. These factors are called Per1 (Period 1), Per2 (Period 2), Per3 (Period 3), Bmal1 (brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1), Cry 1 and Cry 2 (Cryptochrome 1 and 2), and Clock (circadian locomotor output cycles kaput) [244–246]. They are controlled by negative and positive self-loop-regulation mediated by CRs [233, 247]. Clock and Bmal1 heterodimerize and involve to the transcription of Per1, Per2, Cry1, and Cry2 [248]. The Per/Cry heterodimer downregulates its stimulate by a negative feedback. It translocates back to the nucleus to inhibit the Clock/Bmal1 complex and then inactivate its proper transcription [248]. The Clock/Bmal1 heterodimer stimulates the transcription of retinoic acid-related orphan nuclear receptors, Rev-Erbs and retinoid-related orphan receptors (RORs). By a positive feedback, RORs stimulates the transcription of Bmal1, while by a negative feedback, Rev-Erbs inhibits their transcription [248].

Circadian rhythms and OCD

CRs are 24 h autonomous cycles form gene expression to behavior occurring environmental inputs and the dysregulation of these rhythm expressions can lead in diseases [249]. Recent findings have shown that CRs may have a major role in psychiatric diseases [243, 250]. Monoaminergic neurotransmitters, immune system, and hypothalamic–pituitary–adrenal axis are impacted by the dysregulation of CRs [251]. However, small evidence has highlighted the role of CRs in OCD [252, 253]. OCD patients report delayed sleep phase disorder [254]. In OCD, secretion of cortisol and melatonin is altered [255] and total sleep time is decreased [256].

Recent studies have shown a possible relationship between circadian rhythms and chronotype with OCD [253, 257, 258]. The abnormalities in CRs in OCD could be highlighted by diurnal variations [253], such as the likelihood of experiencing obsessions peaks in the afternoon [259]. This pattern is corroborated by other findings showing anxiety-related symptoms peak mid-day in a sample of adults with panic attacks [260]. These symptoms are clearly distinct from findings suggesting that anxiety declines across the day in healthy adults [261, 262]. OCD symptoms in the afternoon could show a deviation from the normative diurnal rhythm of anxiety. Nevertheless, few studies have investigated this increased theorizing on a role of CRs in OCD [252, 253, 263], and no recent studies have investigated mid-sleep, the preferred method for measuring chronotype [264] or physiological indicators of circadian rhythms, such as dim light melatonin onset or core body temperature in OCD. An association between fewer hours of light exposure and increased OCD prevalence has been previously observed [265].

Circadian rhythms and oxidative stress

The deregulation of Per leads to of OS associated with circadian oscillations [266]. The deletion of Per enhances oxidative injuries and shortens lifespan [267, 268]. Per deletion causes oxidative injuries in neurons [267]. High levels of cortex oxidative damages are associated with Bmal1 depletion [269]. Bmal1 directly controls the transcription of numerous redox defense genes in the brain [269].

Circadian rhythms and inflammation

Chemokines and cytokines are secreted in circadian rhythm manner [270]. There levels can be detected at different blood levels according the day phases. Bmal1 and Clock control these expressions. Activation of Clock leads to the activation of NF-κB pathway [271]. The diminution of clock by Bmal1 also decreases the expression of NF-κB. In parallel, Cry decreases protein kinase A to reduce inflammatory factors [272].

Circadian rhythms and glutamatergic pathway

Few studies have focused on this interaction. Nevertheless, light-driven in nervous system responses are controlled by the excitatory neurotransmitter glutamate [273]. NMDA receptors have light-induced behavioral shifts [274]. In astrocytes, glutamate is one the main mediator of the control of circadian function in the nervous system [275]. Glutamate drives circadian rhythmicity of Cry and Per [276].

Circadian rhythms and WNT/β-catenin pathway

RORs can control the WNT/β-catenin pathway [277]. CR genes can control the cell-cycle progression by targeting the WNT pathway [278, 279]. Bmal1 knockdown is associated with the diminution of the WNT/β-catenin pathway [280]. In wild-type mice, WNT-related genes levels are elevated and higher than the levels shown in Bmal1 knockdown mice [281, 282]. Progression of cell-cycle are modulated by Bmal1 which stimulates the WNT/β-catenin pathway [283]. Bmal1 enhances the transcription of β-catenin, decreases the degradation of β-catenin and then, downregulates the GSK-3β activity [284]. In the intestinal mucosa of ApcMin/+ mice, the degradation of Per2 increases β-catenin levels [285]. In physiological conditions, CR genes act in accurate feedback loops and keep the molecular clockworks in the SCN. CR gens permit the control of peripheral clocks [233, 247]. Per1 and Per2 maintain cell CRs and control cell-related gene activity, including c-Myc, a target of the WNT pathway [286, 287].

In parallel, PPARγ binds the clock genes [288]. PPARγ directly binds with the clock genes and shows diurnal variations [289, 290]. Dysregulation diurnal rhythms are involved by a decrease of PPARγ expression [291]. CRs metabolism is controlled by PPARγ [291]. PPARγ agonizts can activate Bmal1, the heterodimer Clock/Bmal1 [290, 292], and Rev-Erb [293]. Decrease of Nocturin leads to the diminution of the oscillations of PPARγ. In physiological conditions, Nocturin acts on PPARγ to enhance its transcriptional activity [294]. Diminution of PPARγ expression damages the circadian function of 15-Deoxy-D 12,14-prostaglandin J2 (15-PGJ2) [291]. By binding with PPARγ, the WNT/β-catenin pathway presents another way to interact on the CRs [114].

Novel role of CBD in Circadian rhythms

Few studies have shown the role of CBD on CRs [295]. However, pharmacological insights have presented that some elements of the endocannabinoid family can control the sleep phase [296]. CBD has been shown to upregulated Cry and Per1 [297]. Here, we can hypothesize that CBD can act on CRs by modulating the activity of the WNT/β-catenin pathway and then on oxidative stress, inflammation and glutamatergic pathway in OCD.

Conclusion

Currently, few studies have studied CBD as possible alternative therapeutic way to treat OCD patients. However, CBD may appear to be interesting against OCD because of its potential inhibitory effect on oxidative stress, inflammation, and glutamatergic pathway and this with few adverse effects. No study has still studying the expression of the WNT/β-catenin pathway in OCD. Nevertheless, the over-activity of the GSK-3β, the main inhibitor of the WNT pathway, in OCD patients is consistent with a downregulation of the WNT pathway in this disease. By stimulating the WNT/β-catenin pathway, through the diminution of GSK-3β, CBD could be an innovative therapeutic way in OCD. New insights on CBD could be its use by acting on CRs which modulate the different mechanisms involved in OCD. Future prospective studies could focus on CBD and its different and multiple interactions in OCD.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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