

Review

# Effects of cannabidiol interactions with Wnt/ $\beta$ -catenin pathway and PPAR $\gamma$ on oxidative stress and neuroinflammation in Alzheimer's disease

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## Abstract

Alzheimer's disease (AD) is a neurodegenerative disease, in which the primary etiology remains unknown. AD presents amyloid beta ( $A\beta$ ) protein aggregation and neurofibrillary plaque deposits. AD shows oxidative stress and chronic inflammation. In AD, canonical Wntless-Int (Wnt)/ $\beta$ -catenin pathway is downregulated, whereas peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) is increased. Downregulation of Wnt/ $\beta$ -catenin, through activation of glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) by  $A\beta$ , and inactivation of phosphatidylinositol 3-kinase/Akt signaling involve oxidative stress in AD. Cannabidiol (CBD) is a non-psychotomimetic phytocannabinoid from *Cannabis sativa* plant. In PC12 cells,  $A\beta$ -induced tau protein hyperphosphorylation is inhibited by CBD. This inhibition is associated with a downregulation of p-GSK-3 $\beta$ , an inhibitor of Wnt pathway. CBD may also increase Wnt/ $\beta$ -catenin by stimulation of PPAR $\gamma$ , inhibition of  $A\beta$  and ubiquitination of amyloid precursor protein. CBD attenuates oxidative stress and diminishes mitochondrial dysfunction and reactive oxygen species generation. CBD suppresses, through activation of PPAR $\gamma$ , pro-inflammatory signaling and may be a potential new candidate for AD therapy.

**Key words:** cannabidiol, Wnt/ $\beta$ -catenin pathway, PPAR $\gamma$ , Alzheimer's disease, PI3K/Akt pathway, oxidative stress, neuroinflammation, GSK-3 $\beta$

## Introduction

Alzheimer's disease (AD) is a neurodegenerative disease (ND), in which the primary etiology remains unknown. AD is marked by two main postmortem pathological phenomena: amyloid beta ( $A\beta$ ) protein aggregation forming plaque deposits and tau protein hyperphosphorylation resulting in neurofibrillary tangles (NFTs). Diminution of cognitive function, diminution of memory, and

other neurobehavioral manifestations are common symptoms in AD [1]. Other behavioral and cognitive symptoms include social withdrawal, poor facial recognition ability, increased motor agitation, and likelihood of wandering [2,3]. Oxidative stress and chronic inflammation are considered as likely underlying causes of AD [4,5]. Increased oxidative stress may be an early indication of AD risk [6,7].

In AD, canonical Wingless-Int (Wnt)/ $\beta$ -catenin is downregulated, whereas peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) is increased [8]. Conversely, other NDs, like Amyotrophic lateral sclerosis, have canonical Wnt/ $\beta$ -catenin pathway upregulated, while PPAR $\gamma$  is decreased [9]. Subsequently, NDs have recently been classified into these two categories, per the regulation of Wnt/ $\beta$ -catenin and PPAR $\gamma$  [10].

In AD, A $\beta$  protein accumulation decreases Wnt/ $\beta$ -catenin pathway [11]. Downregulation of  $\beta$ -catenin reduces the expression of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway [12,13]. Inactivation of Wnt/ $\beta$ -catenin/PI3K/Akt pathway involves oxidative stress in mitochondria [14]. Thus, stimulating Wnt/ $\beta$ -catenin signaling could represent an interesting therapeutic target for AD [15,16].

PPAR $\gamma$  is upregulated in AD due to the neuroinflammation [17]. PPAR $\gamma$  agonists are utilized in AD and show beneficial effects [18,19]. The anti-inflammatory effect induced by PPAR $\gamma$  agonists may explain their positive effect in AD.

Cannabinoids belong to a heterogeneous group of compounds: endogenous, synthetic and phytocannabinoids [20,21]. Cannabidiol (CBD) is a non-psychotomimetic phytocannabinoid from *Cannabis sativa* plant. CBD can attenuate brain damage associated with neurodegeneration [22].

CBD reduces activation of GSK3- $\beta$ , an inhibitor of Wnt pathway [23]. In AD PC12 cells, A $\beta$ -induced tau protein hyperphosphorylation is inhibited by CBD. This effect involves increasing Wnt/ $\beta$ -catenin pathway and results in attenuation of oxidative stress [24,25].

Activation of PPAR $\gamma$  induces anti-inflammatory effects in AD [26]. CBD increases neuronal survival by reducing apoptosis and decreasing amyloid precursor protein (APP) level through activation of PPAR $\gamma$  receptors [27]. CBD can suppress pro-inflammatory pathway and neuroinflammation [28,29].

In this review, the links between CBD and the interplay canonical Wnt/ $\beta$ -catenin-PPAR $\gamma$  in AD are discussed.

## AD: Oxidative Stress and Neuroinflammation

The pathological events of AD include senile plaques, due to the extracellular accumulation of A $\beta$  protein [30], and NFTs, caused by the aggregation of hyperphosphorylated tau [31].

A $\beta$  is mediated by the sequential cleavage of the APP, mediated by the  $\beta$ -secretase (BACE-1) and  $\gamma$ -secretase complex [32]. NFTs are composed of the aggregated hyperphosphorylated microtubule-associated protein (MAP) tau. Tau is a microtubule-stabilizing protein. Tau preserves neuronal cell structure and axonal transport. In AD, tau is disproportionately phosphorylated by several kinases, such as the glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), cyclin-dependent protein kinase-5 (CDK5), calmodulin-dependent protein kinase II (CAMKII), dual specificity tyrosine-phosphorylation-regulated kinase 1A, and mitogen-activated protein kinases (MAPKs) are the best known [32–35].

Several pathways such as genetic factors, chronic inflammation induced-cytokine release, oxidative stress, and neurotoxicity elements have been proposed as likely underlying causes [4,5]. A $\beta$  and NFTs generate chronic inflammatory response and oxidative damage, which enhance the progressive neurodegeneration. Increased oxidative stress may be an early indication of AD risk [6,7]. No effective therapies can counteract A $\beta$  or hyperphosphorylated-tau formation, thus new therapeutic drugs are needed.

Mitochondrial damage in AD leads to excessive produce of reactive oxygen species (ROS) and lowered ATP production [36,37]. Mitochondrial defects damage the cell by increasing production and

releasing ROS which cause cell damage and death by ATP depletion through decreased oxidative phosphorylation [38]. Oxidative stress and mitochondrial dysfunction involve dementia with cell death [39–41].

A $\beta$ -induced oxidative stress alters cellular signaling pathways [42]. Incubation of the A $\beta$  peptide induces a neurotoxic effect characterized by oxidative stress, apoptosis and damage to membrane and cytosolic proteins, mitochondrial DNA, and lipids [43].

Cell damage and worsening of cell signaling with accumulation of ROS in the cell can induce oxidative stress [42]. ROS provide essential molecular services. Neutrophils generate superoxide via NADPH oxidase, a membrane-associated enzyme, to sequester or eliminate pathogens [44]. Superoxide forms from oxidative phosphorylation present mitochondrial respiratory chain, especially in the sites of NADH dehydrogenase (complex I) [45]. A $\beta$  causes a deficiency of both complex I (NADH dehydrogenase) and complex IV (cytochrome c oxidase). Complex I is one of the major ROS generation sites in mitochondria under normal physiological conditions, and changes in complex I function could be responsible for an increase in ROS production [46]. Mitochondrial-derived ROS and A $\beta$  toxicity are strongly inhibited in resistant cells relative to sensitive cells. Through the repression of mitochondrial respiration, A $\beta$ -resistant cells produce less ROS and show higher resistance to mitochondrial depolarization [14].

Amyloid oligomers induce lipid peroxidation and oxidative damage in proteins and biomolecules [47]. Alterations in the membrane, by A $\beta$  accumulation, induce a massive influx of Ca<sup>2+</sup>, which alters the homeostasis of Ca<sup>2+</sup> causing mitochondrial dysfunction, synapse loss, and neuronal death. Low levels of glutathione (GSH), in response to increased Ca<sup>2+</sup> release, result in ROS accumulation [48]. Brain's detoxification of ROS needs GSH redox cycling [49]. ROS activity affects DNA transcription by leading to DNA and related protein oxidation [50,51].

Tau induces mitochondrial dysfunction, severe ATP dysfunction, ROS and nitrogen species generation [52], which could also disturb the integrity of biological membranes and induce synaptic failure [53].

Higher levels of ROS enhance pro-inflammatory-induced transcription of genes and release cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- $\alpha$ ), leading to the neuroinflammation process [41]. A $\beta$ -related inflammatory component of the pathology is considered to be a major target to regulate AD [54,55]. A $\beta$  accumulation involves a chronic inflammatory state, causing damage and neuronal death [54,56].

## Inactivation of Wnt/ $\beta$ -Catenin and Activation of PPAR $\gamma$ in AD

### Canonical Wnt/ $\beta$ -catenin pathway

The Wnt pathway activity is observed in neural development for embryogenesis and in the mediation of neuronal homeostasis in adulthood [57–59]. The Wnt pathway is composed by a family of secreted lipid-modified glycoproteins, being strongly conserved across different species [60]. The canonical Wnt/ $\beta$ -catenin pathway plays a major role in metabolism, embryonic development, cell fate, and epithelial-mesenchymal transition. The canonical Wnt activity shows high level of  $\beta$ -catenin in the nucleus and/or cytosol, which can be observed by immunohistochemically staining and western blot analysis. Its dysregulation is implicated in several diseases, particularly in NDs [10]. Wnt family genes comprises 19 ligands which are departed in canonical Wnts and non-canonical Wnts. Canonical

Wnt ligands (Wnt1, Wnt2, Wnt3, Wnt8a, Wnt8b, Wnt10a, and Wnt10b) are activators of the Wnt signaling. Wnt signaling activates the intracellular Wnt signaling (such as the  $\beta$ -catenin nuclear translocation), and secreted by neurons and immune cells in the central nervous system (CNS) [61]. Wnt ligands are composed by ~350–400 amino acids that contain an N-terminal signal peptide for secretion since they are lipid-modified secreted proteins [62].

$\beta$ -Catenin/T-cell/lymphoid enhancer (TCF/LEF) transcription is the main effector of the canonical Wnt pathway. The destruction complex is composed by Axin, tumor suppressor adenomatous polyposis coli (APC), and GSK-3 $\beta$ . It applies a strong control on the  $\beta$ -catenin pathway. In the absence of Wnt ligands ('off state'), the destruction complex phosphorylates  $\beta$ -catenin for its degradation in the proteasome. In the presence of Wnt ligands ('on state'), the Wnt receptor dimerizes with Frizzled (Fz) and LDL receptor-related protein 5/6 (LRP5/6). Wnt receptor is associated with Dishevelled (Dsh). This triggers the dysregulation of the destruction complex and hampers the degradation of  $\beta$ -catenin in the proteasome. Then,  $\beta$ -Catenin translocates to the nucleus and dimerizes with TCF/LEF leading to the activation of  $\beta$ -catenin target genes such as PDK1, MCT-1, c-Myc, cyclin D1, Cox-2, and Axin2 [63–67].

Neuroinflammation is a process age-related and associated with augmentation of GSK-3 $\beta$  activity and decreased Akt and Wnt/ $\beta$ -catenin pathways in the hippocampus of older rats [68]. GSK-3 $\beta$  and Dickkopf-1 (DKK1) are two inhibitors of the Wnt signaling [69–72]. DKK1 binds to LRP5/6 co-receptors for inhibition of Wnt signaling [73]. The  $\beta$ -catenin/TCF complex can regulate DKK1 transcription by a negative feedback loop [74]. GSK-3 $\beta$  is a neuron-specific intracellular serine-threonine kinase implicated in the control of many patho-physiological signalings (cell membrane signaling, neuronal polarity, and inflammation) [74–76]. GSK-3 $\beta$  inhibits  $\beta$ -catenin cytosolic stabilization and its translocation in the nucleus [77].

### Inactivation of Wnt pathway in AD

Many studies show a downregulation of the Wnt/ $\beta$ -catenin signaling in the development of AD [8,67,77–80]. There is a decreased level of  $\beta$ -catenin and an increased activity of both GSK-3 $\beta$  and DKK1. A $\beta$  induces dysfunction of Wnt pathway in AD [11,81,82]. A $\beta$  favors DKK1, a secreted glycoprotein. In AD, DKK1 binds to LRP5/6, blocks the interaction of Wnt/Fzd and inhibits the interaction with Wnt ligands [83]. Increased DKK1 is observed in Alzheimer's brain of humans and transgenic mice [8,24,84]. GSK-3 $\beta$  expression and activity are augmented in the hippocampus of AD patients [59,85]. In AD, GSK-3 $\beta$  phosphorylates MAP tau leading to NFTs [86–88]. In AD, increased GSK-3 $\beta$  decreases  $\beta$ -catenin level and increases tau phosphorylation and NFT formation [89]. Activation of GSK-3 $\beta$  favors the APP cleavage [90]. Cellular damages induced by A $\beta$  are reversed by inhibition of GSK-3 $\beta$  [91]. GSK-3 $\beta$  has a critical role in AD, through the phosphorylation of tau and the promotion of A $\beta$  production.

### Inactivated Wnt/ $\beta$ -catenin pathway leads to oxidative stress in AD

**Figure 1** summarizes the role of Wnt/ $\beta$ -catenin pathway in oxidative stress in AD. Oxidative damage and mitochondrial stress are important pathological events in the appearance of early AD [92]. In affected neurons, A $\beta$  peptide accumulation promotes mitochondrial dysfunction, oxidative stress, and synaptic deteriorations [93].

### Lowered ATP production by inactivation of Wnt pathway

Cerebral hypometabolism is correlated temporally with severity and has strong predictive interest for onset of dementia [94]. Decreases in transport of glucose and enzyme phosphorylation rate in AD brain could be due to a decreased ATP demand caused by synaptic dysfunction [14].

Glut-1 and Glut-3 play a major role in the insulin-sensitive homeostasis of glucose transport in the human brain [95]. Glut-3 is the main neuronal transporter of glucose [96]. Glut-1 and Glut-3 expressions are diminished in AD brain and are correlated with cerebral hypometabolism [97]. After entry into the cell, glucose is phosphorylated to glucose-6-phosphate by the enzyme hexokinase (HK). Amyloidogenic AD transgenic mouse models and postmortem human AD brain tissues show decreased levels of HK [98].

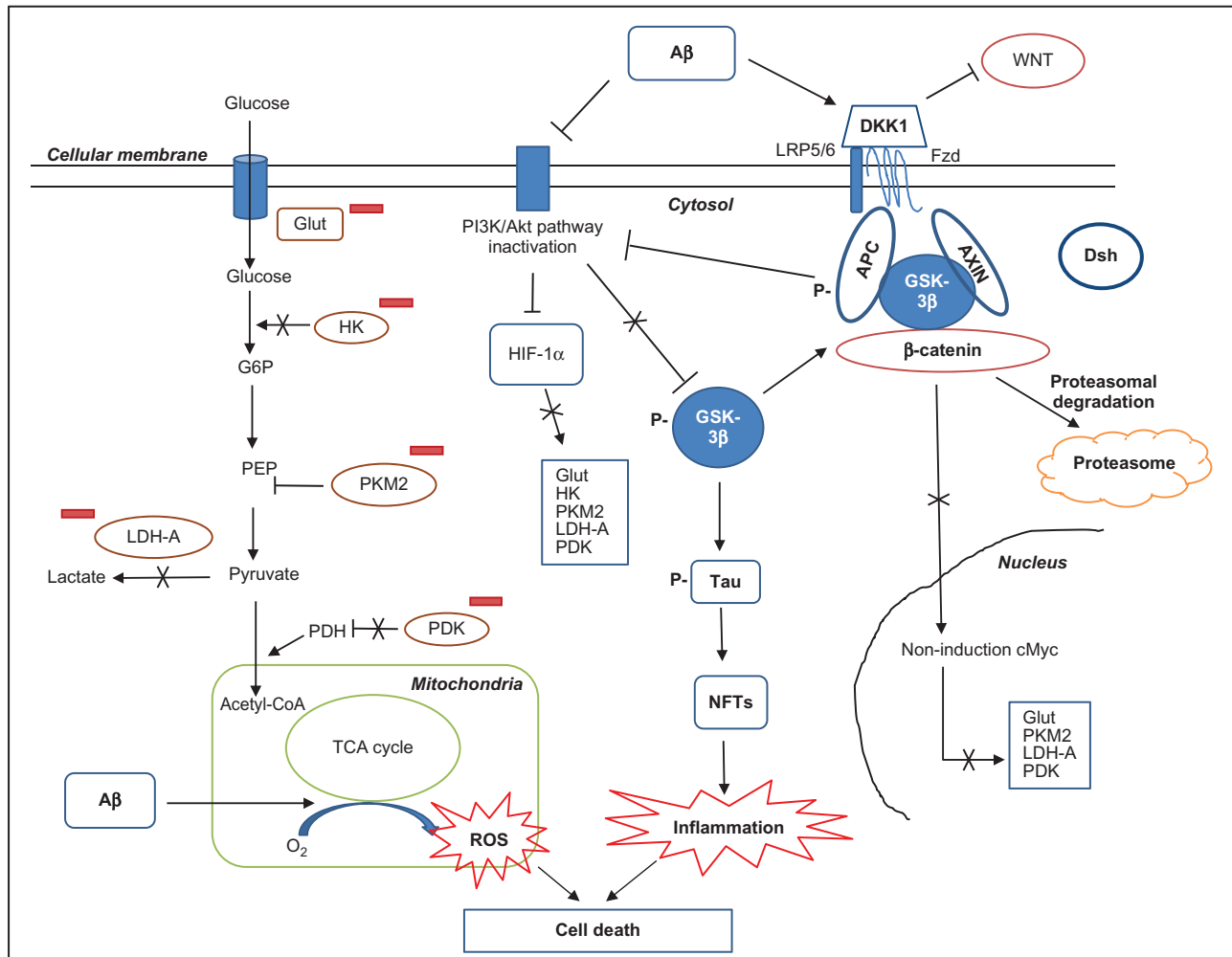
The final stage in glycolysis is the transformation of phosphoenolpyruvate (PEP) and ADP into pyruvate by the enzyme pyruvate kinase (PK). PK has four isoforms: PKM1, PKM2, PKL, and PKR. PKM2 shows low affinity with PEP [99]. Under high glucose concentration, PKM2 is acetylated, which diminishes its activity and targets it toward lysosome-dependent degradation [100]. Under high glucose concentration, peptidyl-prolyl isomerase (Pin1) action stimulates PKM2 translocation to the nucleus [14]. Nuclear PKM2 binds  $\beta$ -catenin and then activates c-Myc-mediated expression of glycolytic enzymes such as Glut, lactate dehydrogenase A (LDH-A), pyruvate dehydrogenase kinase 1 (PDK1), and PKM2 [101]. PDK1 phosphorylates the pyruvate dehydrogenase complex (PDH), which is decreased and stops in the mitochondria the conversion of pyruvate into acetyl-CoA [102]. Activation of PI3K/Akt pathway is correlated with increasing rate of glucose metabolism [103]. Activation of PI3K/Akt pathway stimulates hypoxia-inducible factor 1-alpha (HIF-1 $\alpha$ ) activity [104]. HIF-1 $\alpha$  activation induces expression of Glut, LDH-A, PDK1, and PKM2 [103,105].

Accumulation of A $\beta$  protein in the AD brain decreases levels of PI3K and Akt activity [106]. A $\beta$  protein accumulation decreases Wnt and results in degradation of  $\beta$ -catenin [8,11]. Downregulation of  $\beta$ -catenin reduces the expression of PI3K/Akt signaling [12,13]. A $\beta$  protein accumulation decreases the level of PI3K/Akt pathway signaling and results in inactivation of HIF-1 $\alpha$ . Inactivation of HIF-1 $\alpha$  involves PKM2 non-translocation to the nucleus. PKM2 inhibits PEP cascade and the formation of pyruvate. PKM2 does not bind with  $\beta$ -catenin and does not induce c-Myc-mediated expression of glycolytic enzymes (Glut, LDH-A, and PDK1). Hypometabolism of glucose and deficits in energy are observed in AD [107].

### ROS accumulation and Wnt pathway

Pin1 dysregulation is observed in AD [108]. PKM2 is decreased by acute increases in intracellular concentrations of ROS by C358 oxidation, which enhances glucose flux and facilitates the production of the reducing molecule NADPH [105].

Upregulation of LDH-A leads to pyruvate being diverted towards the formation of lactate [109]. LDH-A activation produces NAD<sup>+</sup> which sustains the NADH/NAD<sup>+</sup> redox balance and allows continued glycolysis and biosynthetic reactions [110]. Production of ROS and oxidative stress resulting from apoptotic signaling is reduced by the transition from mitochondrial respiration to lactate production [111]. Recent studies have shown that nerve cells resistant to A $\beta$  toxicity show a metabolic reprogramming and an activation of aerobic glycolysis through the stabilization of HIF-1 $\alpha$  and upregulation of PDK1 and LDH-A [112,113]. Overexpression of PDK1 and LDH-A represses oxidative stress and confers resistance to A $\beta$  toxicity [113,114].



**Figure 1. Schema of interactions between  $A\beta$  and energetic cellular metabolism in AD** In AD,  $A\beta$  protein induces activation of DKK1, a Wnt pathway inhibitor. In absence of Wnt ligands, cytosolic  $\beta$ -catenin is phosphorylated by GSK-3 $\beta$ . APC and Axin interact with GSK-3 $\beta$  and  $\beta$ -catenin to stimulate the destruction in the proteasome.  $\beta$ -Catenin does not translocate to the nucleus and does not bind with TCF/LEF co-transcription factor. Wnt target genes, such as c-Myc, are not activated.  $A\beta$  protein accumulation decreases level of PI3K/Akt pathway and results in inactivation of HIF-1 $\alpha$ . Downregulation of  $\beta$ -catenin reduces the expression of PI3K/Akt signaling. HIF-1 $\alpha$  inactivation does not stimulate GLUT, HK, PKM2, LDH-A, and PDK1. Inactivation of HIF-1 $\alpha$  involves PKM2 non-translocation to the nucleus. PKM2 inhibits PEP cascade and the formation of pyruvate. PKM2 does not bind with  $\beta$ -catenin and does not induce c-Myc-mediated expression of glycolytic enzymes (GLUT, LDH-A, and PDK1). Inhibition of GLUT and HK involves glucose hypometabolism with decreased in glucose transport and phosphorylation rates. PDK1 does not inhibit PDH, which stimulates pyruvate entrance into mitochondria.  $A\beta$  toxicity is associated with mitochondrial-derived ROS. GSK-3 $\beta$  phosphorylation activates tau hyperphosphorylation, which induces neurofibrillary tangles and neuroinflammation. Acetyl-coA, acetyl-coenzyme A; APC, adenomatous polyposis coli; APP, amyloid precursor protein; Dsh, Disheveled; Fzd, Frizzled; GK, glucokinase; GLUT, glucose transporter; GSK-3 $\beta$ , glycogen synthase kinase-3 beta; HK, hexokinase; LDH, lactate dehydrogenase; LRP5/6, low-density lipoprotein receptor-related protein 5/6; PI3K/Akt, phosphatidylinositol 3-kinase/protein kinase B; PDH, pyruvate dehydrogenase complex; PDK1, pyruvate dehydrogenase kinase; PFK-1, phosphofructokinase-1; PK, pyruvate kinase; RTK, receptor tyrosine kinase; ROS, reactive oxygen species; TCF/LEF, T-cell factor/lymphoid enhancer factor; TCA, tricarboxylic acid.

$A\beta$  toxicity, through inactivation of Wnt/ $\beta$ -catenin pathway, is associated with mitochondrial-derived ROS [14]. Forkhead box class O (FoxO) transcription factors are major intracellular regulators of several metabolic pathways including production of glucose and the oxidative stress cellular response [115]. ROS inhibit Wnt/ $\beta$ -catenin pathway by hijacking  $\beta$ -catenin from TCF/LEF to FoxO [116]. This involves accumulation and binding of  $\beta$ -catenin to FoxO as a cofactor, and the activation of nuclear FoxO transcriptional activity [117,118]. FoxO activates the expression of apoptotic genes [119–121]. FoxO3a arrests cell cycle through the activation of the CDK inhibitor p27kip1 production and the repression of cyclin D1 expression [122,123]. FoxO activation results in induction of apoptosis [124]. Inhibition of FoxO protects against  $A\beta$  exposure [125].

Activation of the Wnt signaling can counter apoptosis through post-translational phosphorylation and sequestration of FoxO3a in the cytosol to inhibit the loss of mitochondrial membrane permeability, cytochrome c release, Bad phosphorylation, and activation of caspases [126].

#### Inactivated Wnt/ $\beta$ -catenin pathway leads to neuroinflammation in AD

Neuroinflammation is characterized by release of pro-inflammatory cytokines, blood–brain barrier breakdown and leukocyte infiltration in the brain [127]. Neuroinflammation contributes to neuronal degeneration [128]. Nuclear factor-kappa B (NF- $\kappa$ B) and pro-inflammatory

mediators including cytokines, and prostaglandins lead to chronic inflammation in the CNS [129–132]. In normal condition, Wnt pathway plays a role in inflammation-induced immune response [133]. A crosstalk exists between Wnt and NF- $\kappa$ B [134–139]. Wnt co-receptor LRP5 contains an anti-inflammatory macrophage phenotype and can decrease monocyte differentiation into macrophage [140].  $\beta$ -Catenin diminishes transcription of pro-inflammatory genes by inhibition of NF- $\kappa$ B. This action is regulated by GSK-3 $\beta$ . GSK-3 $\beta$  is a negative regulator of the  $\beta$ -catenin level and a positive regulator of the NF- $\kappa$ B signaling [141,142].

$\beta$ -Catenin acts as a transcriptional activator by controlling the expression of anti-inflammatory genes.  $\beta$ -Catenin is considered as a target gene of PPAR $\gamma$  [135,143]. PPAR $\gamma$  agonists may exert an anti-inflammatory action by inhibiting the NF- $\kappa$ B-mediated transcription of downstream genes [144]. PPAR $\gamma$  stimulation decreases GSK-3 $\beta$  activity [145]. Many studies have suggested a crosstalk between PPAR $\gamma$  and GSK-3 $\beta$  [135,146–149]. In AD, diminution of  $\beta$ -catenin is correlated with the augmentation of NF- $\kappa$ B activity and neuroinflammation [150].

### Peroxisome proliferator-activated receptor $\gamma$

PPAR $\gamma$  is a ligand-activated transcriptional factor from the nuclear hormone receptor super family. PPAR $\gamma$  has been shown in several cell types, including adipose tissues, muscles, brain, and immune cells. A few endogenous ligands of PPAR $\gamma$  are identified, and these include fatty acids, phytanic acid, oxidized metabolites of linoleic acid, such as 9-hydroxy and 13-hydroxy octadecadienoic acids (9-HODE and 13-HODE), polyunsaturated fatty acids (e.g. arachidonic acid), and eicosanoids [151–155]. Anandamide, an endogenous cannabinoid receptor ligand, interacts with PPAR $\gamma$  for differentiation of mouse 3T3-L1 fibroblasts into adipocytes [156]. The major endogenous ligand of PPAR $\gamma$  is 15-deoxy- $\Delta$ 12,14-prostaglandin J2 (15d-PGJ2) [151]. PPAR $\gamma$  ligands induce PPAR $\gamma$  heterodimer with retinoid X receptor (RXR), a nuclear receptor. The PPAR $\gamma$ -RXR complex changes PPAR $\gamma$  receptors, followed by its dissociation from corepressor molecules. The complex then binds with many coactivators or response elements, as PPAR response elements (PPREs). Therefore, PPAR $\gamma$  stimulates the expression of many genes and mediates glucose homeostasis, insulin sensitivity, lipid metabolism, immune responses, cell fate, and inflammation [149,150]. PPAR $\gamma$  is strongly expressed in adipose tissue but scarcely expressed in heart, skeletal muscle, and liver [157–159]. PPAR $\gamma$  is lowly expressed in CNS and presents in many cell types such as neurons, astrocytes, oligodendrocytes, and microglia [160–162]. In neurons, PPAR $\gamma$  immunoreactivity appears mainly as a nuclear labeling although sometimes cytosolic staining is observed in some cortical neurons [163]. PPAR $\gamma$  agonist thiazolidinedione (TZD) ameliorates insulin sensitivity in peripheral tissues [164] and ameliorates glucose tolerance and insulin sensitivity in Type 2 diabetic patients [165]. TZDs interact with the promoters of glucose transporter (Glut2) and glucokinase (GK) in pancreatic  $\beta$ -cells and liver. Abnormalities of PPAR $\gamma$  have been shown in many pathological states like cancers, diabetes, obesity, and atherosclerosis. Some TZDs have served for Type 2 diabetes treatment. PPAR $\gamma$  also plays a major role in the regulation of cardiovascular rhythms through the control of blood pressure circadian variations and heart rate through Bmal1 [166,167].

### PPAR $\gamma$ and neuroinflammation in AD

PPAR $\gamma$  levels are elevated in AD and play a role in the modulation of neuroinflammation [17]. PPAR $\gamma$  plays a role in regulating

induced inflammatory responses, by inhibiting inflammatory cytokine production such as TNF, interleukin-1 $\beta$  (IL-1 $\beta$ ), and IL-6, the production of nitric oxide and the expression of matrix metalloproteinase 9 and macrophage scavenger receptor 1 in many cell types, such as monocytes, macrophages, and epithelial cells [168,169].

Moreover, decreased level of Wnt signaling by GSK-3 $\beta$  activates NF- $\kappa$ B signaling and neuroinflammation [141,142]. Inhibition of Wnt/ $\beta$ -catenin pathway involves upregulation of PPAR $\gamma$  in many diseases such as AD or arrhythmogenic right ventricular cardiomyopathy (ARVC) [8,170,171].  $\gamma$ -Catenin shares structural similarities with  $\beta$ -catenin [172], and it translocates to the nucleus, and competes with and inhibits  $\beta$ -catenin [173]. This phenomenon enhances adipogenesis and summarizes the phenotype of human ARVC [170,171].

PPAR $\gamma$  can induce anti-inflammatory effect and this leads to the hypothesis that PPAR $\gamma$  might be beneficial in CNS diseases presenting inflammatory processes, especially in AD [8]. Anti-inflammatory effects of PPAR $\gamma$  may be explained by the fact that PPAR $\gamma$  can inhibit several pathways by interacting directly with NF- $\kappa$ B, AP-1, STAT1, and NFAT [26,174]. PPAR $\gamma$  agonists diminish microglia A $\beta$  activation and prevent hippocampal and cortical neurons from death [175–177]. PPAR $\gamma$  regulates inflammation of microglia due to A $\beta$  [161]. High doses of PPAR $\gamma$  agonists diminish A $\beta$  plaques [178]. Rosiglitazone, a PPAR $\gamma$  agonist, decreases A $\beta$ -42 in ADS transgenic mice brain [19]. PPAR $\gamma$  activation increases APP ubiquitination and diminishes A $\beta$  production [179]. Troglitazone, a PPAR $\gamma$  agonist, has an anti-inflammatory effect on neurons independently of its PPAR $\gamma$  activity [180].

Nonsteroidal anti-inflammatory drugs (NSAIDs) act directly on the generation of A $\beta$  [181]. Ibuprofen inhibits GSK-3 $\beta$ , reverses the decrease in Wnt signaling due to A $\beta$  and stabilizes  $\beta$ -catenin [182]. NSAIDs activate PPAR $\gamma$  and inhibit inflammatory processes in AD [183].

## CBD and AD

### Cannabidiol

Cannabinoids are a heterogeneous group of compounds classified into three main groups: endogenous, synthetic, and phytocannabinoids [20,21]. CBD is a non-psychotomimetic phytocannabinoid from *Cannabis sativa* plant. The *Cannabis sativa* plant produces more than 66 compounds, including especially delta9-tetrahydrocannabinol (THC), responsible for psychological effects, and CBD, the main non-psychotomimetic component in this plant [184]. CBD does not change blood pressure or temperature of body and does not induce psychomotor psychological function like THC [22]. CBD can attenuate brain damage associated with neurodegeneration. Animals and humans can tolerate high dose of CBD [22]. Moreover, CBD alters synaptic plasticity and stimulates neurogenesis. CBD effects are still not clear but seem involving several pharmacological targets. CBD shows a large spectrum of potential therapeutics properties such as anxiolytic, antidepressant, neuroprotective, anti-inflammatory, and immunomodulatory effects [185]. Cannabinoids may be considered as a new class of drugs because of their potential effects on neurodegenerative and neuropsychiatric disorders [20,186]. CBD has an interesting therapeutic action in neuropsychiatric disorders such as schizophrenia, epilepsy, addiction, and neonatal hypoxic-ischemic encephalopathy [187]. CBD can activate Wnt/ $\beta$ -catenin and PI3K/Akt pathways and produce therapeutic effects in schizophrenia [188–190].

### CBD's effects in AD models

CBD may be a potential promising candidate for AD therapy [191]. CBD promises potential for the multimodal treatment of AD

through its neuroprotective, anti-inflammatory, and antioxidant properties [192–196]. CBD may counter many pathological AD symptoms. Indeed, many *in vitro* studies have shown that CBD treatment attenuates A $\beta$ -induced neurotoxicity [24], tau protein-induced hyperphosphorylation [23], cell death and promotes hippocampal and adult neurogenesis [29,197]. CBD administration may reverse A $\beta$ -induced memory impairments in rodents [198] and may reduce A $\beta$  formation [27].

In neuroblastoma cells overexpressing APP (SHSY5YAPP+), CBD administration also reduces A $\beta$  production by the promotion of its ubiquitination [27]. *In vivo* CBD treatment can reverse the cognitive deficits in a double transgenic AD mouse model (APP/PS1) [199]. CBD treatment during long-term can prevent the initiation of social recognition deficit in APP  $\times$  PS1 mice [200]. CBD can be used as a long-term preventative AD treatment option and may be especially relevant for social withdrawal and facial recognition [200]. CBD reduces p38 MAPK phosphorylation and prevents nuclear NF- $\kappa$ B translocation and the transcription of pro-inflammatory genes [23].

Mesenchymal stem cells derived from gingival (GMSCs) have a high ability to differentiate into neural cells through their neural crest embryonal origin [201,202]. GMSCs are an attractive perspective for the treatment of AD [203]. CBD can generate the GMSC transcriptional profile of the genes correlated with AD. CBD treatment downregulates the expression of genes which encode kinases (GSK-3 $\beta$ , CMK, and MAPK) responsible for aberrant tau phosphorylation. CBD prevents tau hyperphosphorylation and subsequent NFT formation, by the reduction of the transcription level of these kinases.  $\beta$ -Secretase (BACE1) and  $\gamma$ -secretase, the genes coding for A $\beta$  production, are also downregulated under CBD treatment [203]. Vanilloid receptor 1 (TRPV1) stimulation by CBD in GMSCs can activate PI3K/Akt signaling, which in turn inhibits GSK-3 $\beta$  by phosphorylating Ser9, thereby decreasing tau phosphorylation and A $\beta$  production [203].

### CBD: an anti-oxidative role via stimulation of Wnt pathway in AD

A $\beta$  toxicity decreases PI3K/Akt pathway [14]. PI3K/Akt signaling is involved in GSK-3 $\beta$  activity regulation [204]. Cannabinoids can modulate the PI3K/Akt/GSK-3 $\beta$  axis [205,206]. Genes coding for the PI3K/Akt signaling are upregulated in GMSCs treated with CBD [203]. CBD inhibits the expression of GSK-3 $\beta$  by promoting PI3K/Akt signaling [203,207].

Cannabinoids exert anti-inflammatory function through endogenous receptors, such as cannabinoid receptor 1 (CB1) and CB2 [208]. Cannabinoids activate the PI3K/Akt pathway by binding with CB1 receptor on neurons and glial cells, and in a less manner with CB2 receptor in the body's immune system [209,210]. THC is blocked by administration of rimonabant [211]. THC is a one-sided agonist of the CB1 receptor [212], while rimonabant is considered as an inverse agonist of CB1 receptor [213]. N-Oleoyl glycine (OLGly), a lipoamino acid, increases adipogenic genes such as PPAR $\gamma$ , and CB1 receptor mRNA expression. The decrease of CB1 receptor by SR141716 inhibits the actions of OLGly on PPAR $\gamma$  expression. OLGly increases Akt signaling pathway and decreases FoxO activity [214].

Nevertheless, several studies have demonstrated that CBD can prevent the negative actions of THC [215]. CBD also appears not to be rimonabant-like in its action [216]. The effects of CBD can be inverted by CB1 receptor inverse agonists and CBD may exert 'indirect agonism' at CB1 receptor [216]. However, several studies

have demonstrated that CBD shows small binding affinity with the CB1 receptor [212,217]. CBD could not proceed by the CB1 receptor but possesses several other targets that can play a role in NDs or psychiatric disorders [218].

In AD, PI3K/Akt is downregulated via the inactivated Wnt/ $\beta$ -catenin pathway [106]. In PC12 cells, CBD induces neuroprotective effects on A $\beta$ -induced toxicity [24]. CBD inhibits A $\beta$ -induced tau protein hyperphosphorylation in PC12 cells. This action is correlated with the activity reduction of p-GSK-3 $\beta$ , the phosphorylated active form of GSK-3 $\beta$ , and results in increasing Wnt/ $\beta$ -catenin pathway [23]. Activation of this pathway can protect against A $\beta$  neurotoxicity in AD [8,67,84,219–222].

CBD attenuates oxidative and nitrate stress, improves mitochondrial function and enhances mitochondrial biogenesis [223]. CBD attenuates oxidative stress through the attenuation of mitochondrial dysregulation and ROS generation or by the decrease of the expression of several ROS generating NADPH oxidase isoforms [25,224,225]. In a concentration-dependent manner, CBD stimulates cell survival, whereas diminishes ROS, nitrite production, lipid peroxidation, and inducible nitric oxide synthase (iNOS) protein expression [192].

However, inhibition of p-GSK-3 $\beta$  by CBD may be due to the antioxidant effects of CBD [24]. However, other antioxidants like vitamin C failed to relieve Wnt pathway in A $\beta$ -stimulated PC12 cells [23,226]. Nevertheless, other antioxidants, which have a phenolic ring structure, such as vitamin E, can target the Wnt pathway [227]. It has been shown that CBD, which has a similar chemical structure as vitamin E, can decrease tau hyperphosphorylation not only with its antioxidant action but also through Wnt pathway increase [23]. However, DKK1 negatively modulates the canonical Wnt pathway. But, no data have been shown about the relationship between antioxidants and DKK1 [23].

### CBD: an anti-inflammatory role via stimulation of PPAR $\gamma$ in AD

*In vivo* studies reported that CBD reduces A $\beta$ -induced neuroinflammation in rats and mice [29,228]. Inflammation driven by the cytokines (TNF- $\alpha$  and IL-1 $\beta$ ) is attenuated by CBD [198,228]. CBD modulates *in vitro* function of microglial cells and elicits benefic effects in mice [229]. CBD can diminish lipopolysaccharide (LPS)-induced pro-inflammatory signaling in cultured microglial cells, such as NF- $\kappa$ B and STAT1 activation, while enhancing STAT3-related anti-inflammatory signaling [28]. Microglial cultures stimulated with the bacterial endotoxin LPS and treated with CBD show lower levels of cytokines like TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 [28]. PPAR $\gamma$  modulates the expression of pro-inflammatory mediators such as NO, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, iNOS, and COX-2 [230,231]. PPAR $\gamma$  activation represses NF- $\kappa$ B-mediated inflammatory signaling [232]. PPAR $\gamma$  is a molecular target for CBD and can be generated in mediating transcriptional effects in BV-2 microglial cells [233]. CBD also blocks reactive gliosis by reducing glial stimulation and production of pro-inflammatory mediators [228]. This effect is linked to its possible action as a potent inhibitor of NF- $\kappa$ B stimulation induced by A $\beta$  challenge [23].

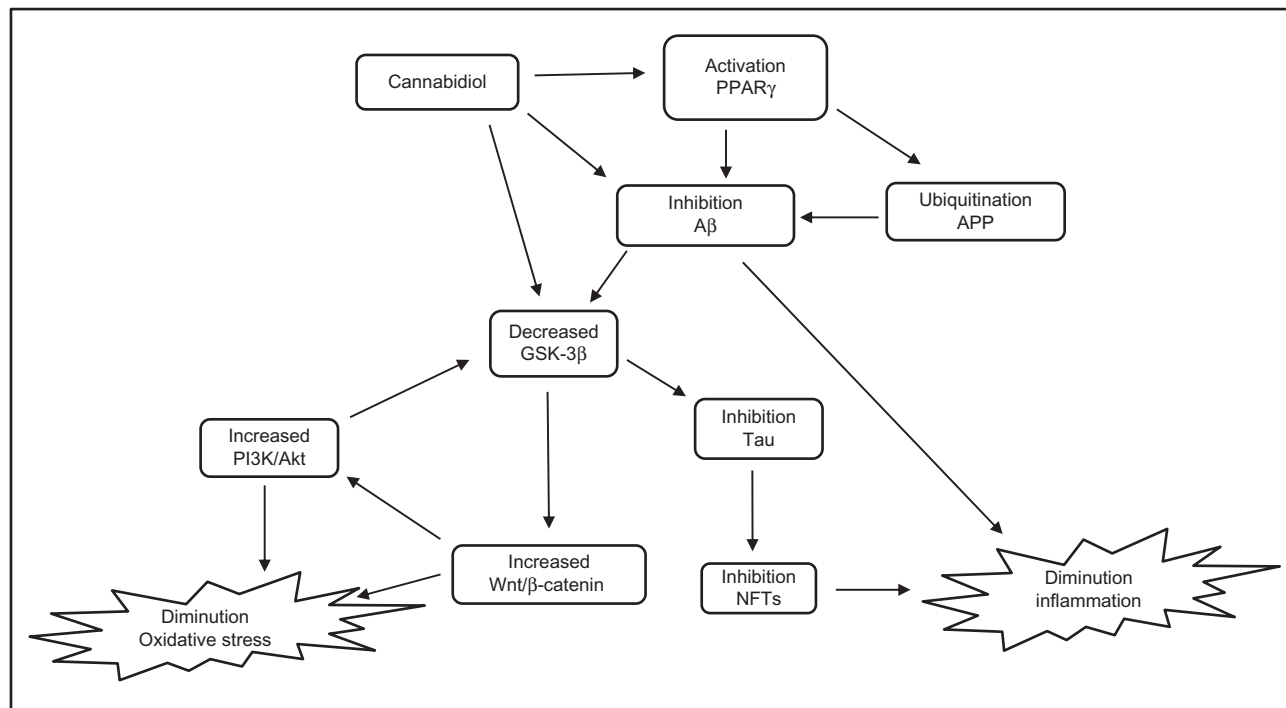
CBD has antioxidant properties and neuroprotective effects by increasing cell viability and decreasing oxidative parameters. In PC12 cells stimulated by A $\beta$ , pretreatment of CBD reduces ROS accumulation, lipid peroxidation, caspase-3 level, and DNA fragmentation [24].

CBD acts like a PPAR $\gamma$  agonist through receptor-dependent mechanisms [23,234,235]. PPAR $\gamma$  receptors are attractive drug

targets for inflammatory-associated neuropsychiatric disorders such as AD [235–237]. PPAR $\gamma$  receptors are involved in cellular proliferation, in apoptosis and in reduction of damage induced by ROS. Activation of PPAR $\gamma$  receptors inhibits transcription of pro-inflammatory genes and prevents the NF- $\kappa$ B pathway [235,236].

CBD prevents A $\beta$ -induced neuronal death by reducing oxidative stress and ROS accumulation. PPAR $\gamma$  seems to induce the same effects as nuclear-erythroid-2-related factor 2 (Nrf-2) [187]. Nrf-2 and PPAR $\gamma$  regulate each other [186]. There are binding sites for Nrf-2 (antioxidant response elements) in the PPAR $\gamma$  promoter and

PPREs in the Nrf-2 promoter [237]. Genes associated with oxidative stress are controlled by Nrf-2 [233]. CBD activates PPAR $\gamma$  and this effect is associated with impairment of the NF- $\kappa$ B pathway [238]. CBD also upregulates genes encoding negative regulators of NF- $\kappa$ B transcriptional activity through Nrf2 activation [233]. CBD, through activation of PPAR $\gamma$ , also decreases cell and neuronal death and promotes hippocampal neurogenesis in murine genetic model of AD [236]. Likewise, CBD increases neuronal survival by reducing apoptosis and decreasing APP level through activation of PPAR $\gamma$  receptors [27]. Traditional PPAR $\gamma$  agonists, such as TZD, diminish



**Figure 2. Interactions between CBD and the interplay canonical Wnt/ $\beta$ -catenin and PPAR $\gamma$  in AD** CBD inhibits A $\beta$ , thus A $\beta$  does not activate GSK-3 $\beta$ . CBD decreases GSK-3 $\beta$  activity, which leads to the increase of Wnt/ $\beta$ -catenin pathway and PI3K/Akt pathway and in diminution of oxidative stress in AD. CBD acts through PPAR gamma activation. CBD stimulates ubiquitination of APP and inhibition of A $\beta$ . Inhibition of A $\beta$  and GSK-3 $\beta$  inhibits tau protein and NFTs, which leads to the diminution of neuroinflammation in AD. AD, Alzheimer's disease; APP, amyloid precursor protein; CBD, Cannabidiol; GSK-3 $\beta$ , glycogen synthase kinase-3beta; PPAR $\gamma$ , peroxisome proliferator-activated receptor gamma; PI3K-Akt, phosphatidylinositol 3-kinase-protein kinase B; NFTs, neurofibrillary tangles.

**Table 1. Interactions of CBD with Wnt/ $\beta$ -catenin pathway and PPAR $\gamma$  in AD**

CBD effects in AD	References
CBD attenuates A $\beta$ -induced neurotoxicity	[24,203]
CBD reduces A $\beta$ formation and production	[27,198]
CBD attenuates tau protein-induced phosphorylation	[23,203]
CBD induces ubiquitination of APP protein	[27,201]
CBD attenuates neuroinflammation	[23,28,29,228,233–236,240]
CBD upregulates PPAR $\gamma$ activity	[23,29,228,234,244]
CBD increases survival and reduces apoptosis through PPAR $\gamma$ activation	[27]
Upregulation of PPAR $\gamma$ attenuates neuroinflammation	[8,26,161,174,180,183]
Upregulation of PPAR $\gamma$ decreases A $\beta$ formation	[8,19,175–179]
CBD increases cell survival, decreases ROS, nitrite production, lipid peroxidation, and iNOS protein expression	[192]
CBD attenuates oxidative stress	[25,224,225,244]
CBD attenuates cytokines activity (TNF $\alpha$ , IL-1 $\beta$ )	[198,228,241–243]
CBD attenuates NF- $\kappa$ B transcriptional activity	[23,28,233,237]
CBD inhibits expression of GSK-3 $\beta$ by promoting PI3K/Akt signaling	[23,24,203–207]
CBD increases Wnt/ $\beta$ -catenin pathway	[23,24,227]
Activation of Wnt/ $\beta$ -catenin pathway protects against A $\beta$ neurotoxicity and oxidative stress	[8,67,84,126,219–222]

the overproduction of NO, IL-6, and TNF- $\alpha$  as well as the augmented expression of the inducible enzymes iNOS and COX-2 induced in LPS-stimulated astrocytic and microglial cultures [238–240]. Through activation of PPAR $\gamma$ , CBD provokes a diminution of NO, TNF- $\alpha$  and IL-1 $\beta$  release with a diminution of glial fibrillary acidic protein, S100 calcium-binding protein B (S100B) and iNOS expression. The diminution of S100B induced by CBD and mediated by PPAR $\gamma$  is a major stage in the interruption of self-perpetuation of the reactive gliosis cycle in stopping self-perpetuation of the reactive gliosis cycle. The over-release of this astroglial-derived neurotrophin actively stimulates the pro-inflammatory cytokine loop generated by A $\beta$  activation. This abundantly stimulates amyloidogenicity through the promotion of the cleavage of APP to A $\beta$ , and generates tau hyperphosphorylation by dysregulation the Wnt pathway [241–243]. PPAR $\gamma$  activation results in an inhibition of APP expression [175]. PPAR $\gamma$  upregulation promotes APP ubiquitination. CBD ubiquitination activity is controlled by PPAR $\gamma$  [27]. CBD induces the ubiquitination of APP protein, and this effect generates a diminution of APP full length protein level in SHSY5YAPP+ cells [27]. Figure 2 illustrates the anti-oxidative and anti-inflammatory roles of CBD in AD.

## Conclusion and Perspectives

Table 1 summarizes the interactions of CBD with Wnt/ $\beta$ -catenin pathway and PPAR $\gamma$  in AD. The primary etiology of AD remains unknown; however, oxidative stress and chronic inflammation have been suggested as possible underlying causes of AD. AD is an ND in which canonical Wnt/ $\beta$ -catenin is downregulated while PPAR $\gamma$  is upregulated. A $\beta$  protein accumulation decreases Wnt/ $\beta$ -catenin, while PPAR $\gamma$  is upregulated due to the neuroinflammation. Downregulation of Wnt/ $\beta$ -catenin pathway decreases PI3K/Akt pathway and glucose metabolism. This effect exacerbates oxidative stress in mitochondria and generates cell death. CBD inhibits GSK-3 $\beta$  and DKK1, two inhibitors of Wnt pathway. CBD administration increases Wnt/ $\beta$ -catenin pathway and diminishes oxidative stress in mitochondria. CBD induces the ubiquitination of APP protein through activation of PPAR $\gamma$ , decreases cell death and promotes hippocampal neurogenesis. PPAR $\gamma$  activation by CBD decreases neuroinflammation in AD. CBD may be a promising candidate for AD therapy by inhibiting oxidative stress and neuroinflammation through the interaction with Wnt/ $\beta$ -catenin and PPAR $\gamma$ .

## References

- Pandi-Perumal SR, BaHammam AS, Brown GM, Spence DW, Bharti VK, Kaur C, Hardeland R, *et al.* Melatonin antioxidative defense: therapeutic implications for aging and neurodegenerative processes. *Neurotox Res* 2013, 23: 267–300.
- Chung JA, Cummings JL. Neurobehavioral and neuropsychiatric symptoms in Alzheimer's disease: characteristics and treatment. *Neurol Clin* 2000, 18: 829–846.
- Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982, 139: 1136–1139.
- Ehrnhoefer DE, Wong BK, Hayden MR. Convergent pathogenic pathways in Alzheimer's and Huntington's diseases: shared targets for drug development. *Nat Rev Drug Discov* 2011, 10: 853–867.
- Jucker M, Walker LC. Pathogenic protein seeding in Alzheimer disease and other neurodegenerative disorders. *Ann Neurol* 2011, 70: 532–540.
- Dalle-Donne I, Rossi R, Colombo R, Giustarini D, Milzani A. Biomarkers of oxidative damage in human disease. *Clin Chem* 2006, 52: 601–623.

- Pratico D, Clark CM, Liun F, Rokach J, Lee VY, Trojanowski JQ. Increase of brain oxidative stress in mild cognitive impairment: a possible predictor of Alzheimer disease. *Arch Neurol* 2002, 59: 972–976.
- Vallée A, Lecarpentier Y. Alzheimer disease: crosstalk between the canonical Wnt/ $\beta$ -catenin pathway and PPARs alpha and gamma. *Front Neurosci* 2016, 10: 459.
- Lecarpentier Y, Vallée A. Opposite interplay between PPAR gamma and canonical Wnt/ $\beta$ -catenin pathway in Amyotrophic lateral sclerosis. *Front Neurol* 2016, 7: 100.
- Lecarpentier Y, Claes V, Duthoit G, Hébert JL. Circadian rhythms, Wnt/ $\beta$ -catenin pathway and PPAR alpha/gamma profiles in diseases with primary or secondary cardiac dysfunction. *Front Physiol* 2014, 5: 429.
- Wan W, Xia S, Kalionis B, Liu L, Li Y. The role of Wnt signaling in the development of Alzheimer's disease: a potential therapeutic target? *Biomed Res Int* 2014, 2014: 301575.
- Park K, Lee R, Kang S, Han S, Park K, Yang K, Song YS, *et al.* Neuronal differentiation of embryonic midbrain cells by upregulation of peroxisome proliferator-activated receptor gamma via the JNK-dependent pathway. *Exp Cell Res* 2004, 297: 424–433.
- Yue X, Lan F, Yang W, Yang Y, Han L, Zhang A, Liu J, *et al.* Interruption of beta-catenin suppresses the EGFR pathway by blocking multiple oncogenic targets in human glioma cells. *Brain Res* 2010, 1366: 27–37.
- Harris RA, Tindale L, Cumming RC. Age-dependent metabolic dysregulation in cancer and Alzheimer's disease. *Biogerontology* 2014, 15: 559–577.
- Zhang X, Yin WK, Shi XD, Li Y. Curcumin activates Wnt/ $\beta$ -catenin signaling pathway through inhibiting the activity of GSK-3 $\beta$  in APPs we transfected SY5Y cells. *Eur J Pharm Sci* 2011, 42: 540–546.
- Inestrosa NC, Ríos JA, Cisternas P, Tapia-Rojas C, Rivera DS, Braidy N, Zolezzi JM, *et al.* Age progression of neuropathological markers in the brain of the chilean rodent octodon degus, a natural model of Alzheimer's disease. *Brain Pathol* 2015, 25: 679–691.
- de la Monte SM, Wands JR. Molecular indices of oxidative stress and mitochondrial dysfunction occur early and often progress with severity of Alzheimer's disease. *J Alzheimers Dis* 2006, 9: 167–181.
- Risner ME, Saunders AM, Altman JF, Ormandy GC, Craft S, Foley IM, Zvartau-Hind ME, *et al.* Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *Pharmacogenomics J* 2006, 6: 246–254.
- Escribano L, Simón AM, Gimeno E, Cuadrado-Tejedor M, López de Maturana R, García-Osta A, Ricobaraza A, *et al.* Rosiglitazone rescues memory impairment in Alzheimer's transgenic mice: mechanisms involving a reduced amyloid and tau pathology. *Neuropsychopharmacology* 2010, 35: 1593–1604.
- Campos AC, Moreira FA, Gomes FV, Del Bel EA, Guimaraes FS. Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. *Philos Trans R Soc Lond B Biol Sci* 2012, 367: 3364–3378.
- Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses* 2006, 66: 234–246.
- Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. Safety and side effects of cannabidiol: a *Cannabis sativa* constituent. *Curr Drug Saf* 2011, 6: 237–249.
- Esposito G, De Filippis D, Carnuccio R, Izzo AA, Iuvone T. The marijuana component cannabidiol inhibits  $\beta$ -amyloid-induced tau protein hyperphosphorylation through Wnt/ $\beta$ -catenin pathway rescue in PC12 cells. *J Mol Med* 2006, 84: 253–258.
- Iuvone T, Esposito G, Esposito R, Santamaria R, Di Rosa M, Izzo AA. Neuroprotective effect of cannabidiol, a non-psychoactive component from *Cannabis sativa*, on beta-amyloid-induced toxicity in PC12 cells. *J Neurochem* 2004, 89: 134–141.
- Rajesh M, Mukhopadshay P, Batkai S, Patel V, Saito K, Matsumoto S, Kashiwaya Y, *et al.* Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. *J Am Coll Cardiol* 2010, 56: 2115–2125.



26. Daynes RA, Jones DC. Emerging roles of PPARs in inflammation and immunity. *Nat Rev Immunol* 2002, 2: 748–759.
27. Scuderi C, Steardo L, Esposito G. Cannabidiol promotes amyloid precursor protein ubiquitination and reduction of beta amyloid expression in SHSY5YAPP+ cells through PPAR gamma involvement. *Phytother Res* 2014, 28: 1007–1013.
28. Kozela E, Pietr M, Juknat A, Rimmerman N, Levy R, Vogel Z. Cannabinoids  $\Delta^9$ -tetrahydrocannabinol and cannabidiol differentially inhibit the lipopolysaccharide-activated NF-kappaB and interferon-beta/STAT proinflammatory pathways in BV-2 microglial cells. *J Biol Chem* 2010, 285: 1616–1626.
29. Esposito G, Scuderi C, Valenza M, Togna GI, Latina V, De Filippis D, Cipriano M, et al. Cannabidiol reduces A $\beta$ -induced neuroinflammation and promotes hippocampal neurogenesis through PPAR gamma involvement. *PLoS One* 2011, 6: e28668.
30. Gouras GK, Almeida CG, Takahashi RH. Intraneuronal A accumulation and origin of plaques in Alzheimer's disease. *Neurobiol Aging* 2005, 26: 1235–1244.
31. Selkoe DJ. Alzheimer's disease results from the cerebral accumulation and cytotoxicity of amyloid  $\beta$ -protein. *J Alzheimers Dis* 2001, 3: 75–80.
32. Chow VW, Mattson MP, Wong PC, Gleichmann M. An overview of APP processing enzymes and products. *Neuromol Med* 2010, 12: 1–12.
33. Dolan PJ, Johnson GVW. The role of tau kinases in Alzheimer's disease. *Curr Opin Drug Discov Dev* 2010, 13: 595–603.
34. Ferrer I, Barrachina M, Puig B, Martinez de Lagran M, Marti E, Avila J, Dierssen M. Constitutive Dyrk1A is abnormally expressed in Alzheimer disease, Down syndrome, Pick disease, and related transgenic models. *Neurobiol Dis* 2005, 20: 392–400.
35. Yoshimura Y, Ichinose T, Yamauchi T. Phosphorylation of tau protein to sites found in Alzheimer's disease brain is catalyzed by Ca<sup>2+</sup>/calmodulin-dependent protein kinase II as demonstrated tandem mass spectrometry. *Neurosci Lett* 2003, 353: 185–188.
36. Castellani R, Hirai K, Aliev G, Drew KL, Nunomura A, Takeda A, Cash AD, et al. Role of mitochondrial dysfunction in Alzheimer's disease. *J Neurosci Res* 2002, 70: 357–360.
37. Gibson GE, Sheu KFR, Blass JP. Abnormalities of mitochondrial enzymes in Alzheimer's disease. *J Neural Transm* 1998, 105: 855–870.
38. Luque-Contreras D, Carvajal K, Toral-Rios D, Franco-Bocanegra D, Campos-Pena V. Oxidative stress and metabolic syndrome: cause or consequence of Alzheimer's disease? *Oxid Med Cell Longev* 2014, 497802.
39. Benilova I, Karran E, De Strooper B. The toxic A $\beta$  oligomer and Alzheimer's disease: an emperor in need of clothes. *Nat Neurosci* 2012, 15: 349–357.
40. Sochocka M, Koutsouraki ES, Gasiorowski K, Leszek J. Vascular oxidative stress and mitochondrial failure in the pathobiology of Alzheimer's disease: a new approach to therapy. *CNS Neurol Disord Drug Targets* 2013, 12: 870–881.
41. Islam T. Oxidative stress and mitochondrial dysfunction-linked neurodegenerative disorders. *Neurol Res* 2017, 39: 73–82.
42. Zuo L, Hemmelgarn BT, Chuang CC, Best TM. The role of oxidative stress-induced epigenetic alterations in amyloid-beta production in Alzheimer's disease. *Oxid Med Cell Longev* 2015, 2015: 604658.
43. Reddy PH, Beal MF. Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. *Trends Mol Med* 2008, 14: 45–53.
44. Remijns Q, Vanden Berghe T, Wirawan E, Asselbergh B, Parthoens E, De Rycke R, Noppen S, et al. Neutrophil extracellular trap cell death requires both autophagy and superoxide generation. *Cell Res* 2011, 21: 290–304.
45. Adam-Vizi V. Production of reactive oxygen species in brain mitochondria: contribution by electron transport chain and non-electron transport chain sources. *Antioxid Redox Signal* 2005, 7: 1140–1149.
46. Bobba A, Amadoro G, Valenti D, Corsetti V, Lassendro R, Atlante A. Mitochondrial respiratory chain Complex I and IV are impaired by beta-amyloid via direct interaction and through Complex I-dependent ROS production, respectively. *Mitochondrion* 2013, 13: 298–311.
47. Butterfield DA, Drake J, Pocernich C, Castegna A. Evidence of oxidative damage in Alzheimer's disease brain: central role of amyloid beta-peptide. *Trends Mol Med* 2001, 7: 548–554.
48. Ferreira E, Oliveira CR, Pereira CM. The release of calcium from the endoplasmic reticulum induced by amyloid-beta and prion peptides activates the mitochondrial apoptotic pathway. *Neurobiol Dis* 2008, 30: 331–342.
49. Walton JR. Evidence for participation of aluminum in neurofibrillary tangle formation and growth in Alzheimer's disease. *J Alzheimers Dis* 2010, 22: 65–72.
50. Ghosh R, Mitchell DL. Effect of oxidative DNA damage in promoter elements on transcription factor binding. *Nucleic Acids Res* 1999, 27: 3213–3218.
51. Parsian AJ, Funk MC, Yao TY, Hunt CR. The effect of DNA damage on the formation of protein/DNA complexes. *Mutat Res* 2002, 501: 105–113.
52. Patterson KR, Remmers C, Fu Y, Brooker S, Kanaan NM, Vana L, Ward S, et al. Characterization of prefibrillar tau oligomers *in vitro* and in Alzheimer disease. *J Biol Chem* 2011, 286: 23063–23076.
53. Rapoport SI. Coupled reduction in brain oxidative phosphorylation and synaptic function can be quantified and staged in the course of Alzheimer disease. *Neurotox Res* 2003, 5: 385–397.
54. Andreasson KI, Bachstetter AD, Colonna M, Ginhoux F, Holmes C, Lamb B, Landreth G, et al. Targeting innate immunity for neurodegenerative disorders of the central nervous system. *J Neurochem* 2016, 138: 653–693.
55. Zolezzi JM, Inestrosa NC. Wnt/TLTR dialog in neuroinflammation, relevance in Alzheimer's disease. *Front Immunol* 2017, 8: 187.
56. Zolezzi JM, Inestrosa NC. Peroxisome proliferator-activated receptors and Alzheimer's disease: hitting the blood-brain barrier. *Mol Neurobiol* 2013, 48: 438–451.
57. Harrison-Uy SJ, Pleasure SJ. Wnt signaling and forebrain development. *Cold Spring Harb Perspect Biol* 2012, 4: a008094.
58. Salinas PC. Wnt signaling in the vertebrate central nervous system: from axon guidance to synaptic function. *Cold Spring Harb Perspect Biol* 2012, 4: pii: a008003.
59. Oliva CA, Vargas JY, Inestrosa NC. Wnts in adult brain: from synaptic plasticity to cognitive deficiencies. *Front Cell Neurosci* 2013, 7: 224.
60. Al-Harathi L. Wnt/ $\beta$ -catenin and its diverse physiological cell signaling pathways in neurodegenerative and neuropsychiatric disorders. *J Neuroimmune Pharmacol* 2012, 7: 725–730.
61. Marchetti B, Pluchino S. Wnt your brain be inflamed? Yes, it Wnt! *Trends Mol Med* 2013, 19: 144–156.
62. MacDonald BT, Tamal K, He X. Wnt/beta-catenin signaling: components, mechanisms, and diseases. *Dev Cell* 2009, 17: 9–26.
63. Pate KT, Stringari C, Sprowl-Tanio S, Wang K, TeSlaa T, Hoverter NP, McQuade MM, et al. Wnt signaling directs a metabolic program of glycolysis and angiogenesis in colon cancer. *EMBO J* 2014, 33: 1454–1473.
64. He TC, Sparks AB, Rago C, Hermeking H, Zawel L, da Costa LT, Morin PJ, et al. Identification of c-MYC as a target of the APC pathway. *Science* 1998, 281: 1509–1512.
65. Shtutman M, Zhurinsky J, Simcha I, Albanese C, D'Amico M, Pestell R, Ben-Ze'ev A. The cyclin D1 gene is a target of the beta-catenin/LEF-1 pathway. *Proc Natl Acad Sci USA* 1999, 96: 5522–5527.
66. Angers S, Moon RT. Proximal events in Wnt signal transduction. *Nat Rev Mol Cell Biol* 2009, 10: 468–477.
67. Orellana AMM, Vasconcelos AR, Leite JA, de Sá Lima L, Andreotti DZ, Munhoz CD, Kawamoto EM, et al. Age-related neuroinflammation and changes in AKT- GSK-3 $\beta$  and WNT/  $\beta$ -CATENIN signaling in rat hippocampus. *Aging (Albany NY)* 2015, 7: 1094–1111.
68. Sharma C, Pradeep A, Wong L, Rana A, Rana B. Peroxisome proliferator-activated receptor gamma activation can regulate beta-catenin levels via a proteasome-mediated and adenomatous polyposis coli-independent pathway. *J Biol Chem* 2004, 279: 35583–35594.
69. Rosi MC, Luccarini I, Grossi C, Fiorentini A, Spillantini MG, Prisco A, Scali C, et al. Increased Dickkopf-1 expression in transgenic mouse

- models of neurodegenerative disease. *J Neurochem* 2010, 112: 1539–1551.
70. Clevers H, Nusse R. Wnt/ $\beta$ -catenin signaling and disease. *Cell* 2012, 149: 1192–1205.
  71. Inestrosa NC, Montecinos-Oliva C, Fuenzalida M. Wnt signaling: role in Alzheimer disease and schizophrenia. *J Neuroimmune Pharmacol* 2012, 7: 788–807.
  72. Kawano Y. Secreted antagonists of the Wnt signalling pathway. *J Cell Sci* 2003, 116: 2627–2634.
  73. Niida A, Hiroko T, Kasai M, Furukawa Y, Nakamura Y, Suzuki Y, Sugano S, *et al.* DKK1, a negative regulator of Wnt signaling, is a target of the  $\beta$ -catenin/TCF pathway. *Oncogene* 2004, 23: 8520–8526.
  74. Wu D, Pan W. GSK3: a multifaceted kinase in Wnt signaling. *Trends Biochem Sci* 2010, 35: 161–168.
  75. Hur EM, Zhou FQ. GSK3 signalling in neural development. *Nat Rev Neurosci* 2010, 11: 539–551.
  76. Ambacher KK, Pitzul KB, Karajgikar M, Hamilton A, Ferguson SS, Cregan SP. The JNK- and AKT/GSK3 $\beta$ -signaling pathways converge to regulate Puma induction and neuronal apoptosis induced by trophic factor deprivation. *PLoS One* 2012, 7: e46885.
  77. Libro R, Bramanti P, Mazzon E. The role of the Wnt canonical signaling in neurodegenerative diseases. *Life Sci* 2016, 158: 78–88.
  78. Alvarez AR, Godoy JA, Mullendorff K, Olivares GH, Bronfman M, Inestrosa NC. Wnt-3a overcomes beta-amyloid toxicity in rat hippocampal neurons. *Exp Cell Res* 2004, 297: 186–196.
  79. Takada I, Kouzmenko AP, Kato S. Wnt and PPAR gamma signaling in osteoblastogenesis and adipogenesis. *Nat Rev Rheumatol* 2009, 5: 442–447.
  80. Lu D, Carson DA. Repression of  $\beta$ -catenin signaling by PPAR gamma ligands. *Eur J Pharmacol* 2010, 636: 198–202.
  81. Thies W. Stopping a thief and killer: Alzheimer's disease crisis demands greater commitment to research. *Alzheimers Dement* 2011, 7: 175–176.
  82. Silva-Alvarez C, Arrázola MS, Godoy JA, Ordenes D, Inestrosa NC. Canonical Wnt signaling protects hippocampal neurons from A $\beta$  oligomers: role of non-canonical Wnt-5a/Ca<sup>2+</sup> in mitochondrial dynamics. *Front Cell Neurosci* 2013, 7: 97.
  83. Mao B, Wu W, Li Y, Hoppe D, Stanek P, Glinka A, Niehrs C. LDL-receptor-related protein 6 is a receptor for Dickkopf proteins. *Nature* 2001, 411: 321–325.
  84. Caricasole A, Copani A, Caraci F, Aronica E, Rozemuller AJ, Caruso A, Storto M, *et al.* Induction of Dickkopf-1, a negative modulator of the Wnt pathway, is associated with neuronal degeneration in Alzheimer's brain. *J Neurosci* 2004, 24: 6021–6027.
  85. Hooper C, Killick R, Lovestone S. The GSK3 hypothesis of Alzheimer's disease. *J Neurochem* 2008, 104: 1433–1439.
  86. Buée L, Troquier L, Burnouf S, Belarbi K, Van der Jeugd A, Ahmed T, Fernandez-Gomez F, *et al.* From tau phosphorylation to tau aggregation: what about neuronal death? *Biochem Soc Trans* 2010, 38: 967–972.
  87. Mendoza J, Sekiya M, Taniguchi T, Iijima KM, Wang R, Ando K. Global analysis of phosphorylation of tau by the checkpoint kinases Chk1 and Chk2 *in vitro*. *J Proteome Res* 2013, 12: 2654–2665.
  88. Rosso SB, Inestrosa NC. WNT signaling in neuronal maturation and synaptogenesis. *Front Cell Neurosci* 2013, 7: 103.
  89. Oliva CA, Vargas JY, Inestrosa NC. Wnt signaling: role in LTP, neural networks and memory. *Ageing Res Rev* 2013, 12: 786–800.
  90. Inestrosa NC, Varela-Nallar L. Wnt signaling in the nervous system and in Alzheimer's disease. *J Mol Cell Biol* 2014, 6: 64–74.
  91. Li XH, Du LL, Cheng XS, Jiang X, Zhang Y, Lv BL, Liu R, *et al.* Glycation exacerbates the neuronal toxicity of beta-amyloid. *Cell Death Dis* 2013, 4: e673.
  92. Alev G, Priyadarshini M, Reddy VP, Grieg NH, Kaminsky Y, Cacabelos R, AZshraf GM, *et al.* Oxidative stress-mediated mitochondrial and vascular lesions as markers in the pathogenesis of Alzheimer disease. *Curr Med Chem* 2014, 21: 2208–2217.
  93. Tillement L, Lecanu L, Papadopoulos V. Further evidence on mitochondrial targeting of b-amyloid and specificity of b-amyloid-induced mitochondrial toxicity in neurons. *Neurodegener Dis* 2011, 8: 331–344.
  94. Mosconi L, Pupi A, De Leon MJ. Brain glucose hypo- metabolism and oxidative stress in preclinical Alzheimer's disease. *Ann N Y Acad Sci* 2008, 1147: 180–195.
  95. McEwen BS, Reagan LP. Glucose transporter expression in the central nervous system: relationship to synaptic function. *Eur J Pharmacol* 2004, 490: 13–24.
  96. Schubert D. Glucose metabolism and Alzheimer's disease. *Ageing Res Rev* 2005, 4: 240–257.
  97. Liu Y, Liu F, Iqbal K, Grundke-Iqbal I, Gong CX. Decreased glucose transporters correlate to abnormal hyperphosphorylation of tau in Alzheimer disease. *FEBS Lett* 2008, 582: 359–364.
  98. Cuadrado-Tejedor M, Vilarino M, Cabodevilla F, Del Rio J, Frechilla D, Perez-Mediavilla A. Enhanced expression of the voltage-dependent anion channel 1 (VDAC1) in Alzheimer's disease transgenic mice: an insight into the pathogenic effects of amyloid- $\beta$ . *J Alzheimers Dis* 2011, 23: 195–206.
  99. Lv L, Li D, Zhao D, Lin R, Chu Y, Zhang Z, Liu Y, *et al.* Acetylation targets the M2 isoform of pyruvate kinase for degradation through chaperone-mediated autophagy and promotes tumor growth. *Mol Cell* 2011, 42: 719–730.
  100. Yang W, Zheng Y, Xia Y, Chen X, Guo F, Lyssiotis CA, Aldape K, *et al.* ERK1/2-dependent phosphorylation and nuclear translocation of PKM2 promotes the Warburg effect. *Nat Cell Biol* 2012, 4: 1295–1304.
  101. Roche TE, Baker JC, Yan X, Hiroshima Y, Gong X, Peng T, Dong J, *et al.* Distinct regulatory properties of pyruvate dehydrogenase kinase and phosphatase isoforms. *Prog Nucleic Acid Res Mol Biol* 2001, 70: 33–75.
  102. Hunt TK, Aslam RS, Beckert S, Wagner S, Ghani QP, Hussain MZ, Roy S, *et al.* Aerobically derived lactate stimulates revascularization and tissue repair via redox mechanisms. *Antioxid Redox Signal* 2007, 9: 1115–1124.
  103. Sun Q, Chen X, Ma J, Peng H, Wang F, Zha X, Wang Y, *et al.* Mammalian target of rapamycin up-regulation of pyruvate kinase isoenzyme type M2 is critical for aerobic glycolysis and tumor growth. *Proc Natl Acad Sci USA* 2011, 108: 4129–4134.
  104. Semenza GL. HIF-1: upstream and downstream of cancer metabolism. *Curr Opin Genet Dev* 2010, 20: 51–56.
  105. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? *Free Radic Biol Med* 2010, 49: 1603–1616.
  106. Li H, Kang T, Qi B, Kong L, Jiao Y, Cao Y, Zhang J, *et al.* Neuroprotective effects of ginseng protein on PI3K/Akt signaling pathway in the hippocampus of D-galactose/A $\beta$ 1 $\beta$  inducing rats model of Alzheimer's disease. *J Ethnopharmacol* 2016, 179: 162–169.
  107. Szablewski L. Glucose Transporters in Brain: In Health and in Alzheimer's Disease. *J Alzheimers Dis* 2017, 55: 1307–1320.
  108. Anastasiou D, Pouligiannis G, Asara JM, Boxer MB, Jiang JK, Shen M, Bellinger G, *et al.* Inhibition of pyruvate kinase M2 by reactive oxygen species contributes to cellular antioxidant responses. *Science* 2011, 334: 1278–1283.
  109. Lee TH, Pastorino L, Lu KP. Peptidyl-prolyl cis-trans isomerase Pin1 in ageing, cancer and Alzheimer disease. *Expert Rev Mol Med* 2011, 13: e21.
  110. Chiarugi A, Dolle C, Felici R, Ziegler M. The NAD metabolome—a key determinant of cancer cell biology. *Nat Rev Cancer* 2012, 12: 741–752.
  111. Le A, Cooper CR, Gouw AM, Dinavahi R, Maitra A, Deck LM, Royer RE, *et al.* Inhibition of lactate dehydrogenase A induces oxidative stress and inhibits tumor progression. *Proc Natl Acad Sci USA* 2010, 107: 2037–2042.
  112. Soucek T, Cumming R, Dargusch R, Maher P, Schubert D. The regulation of glucose metabolism by HIF-1 mediates a neuroprotective response to amyloid beta peptide. *Neuron* 2003, 39: 43–56.
  113. Newington JT, Pitts A, Chien A, Arseneault R, Schibert D, Cummiog RC. Amyloid beta resistance in nerve cell lines is mediated by the warburg effect. *PLoS One* 2011, 6: e19191.
  114. Newington JT, Rappon T, Albers S, Wong DY, Rylett RJ, Cumming RC. Overexpression of pyruvate dehydrogenase kinase 1 and lactate

- dehydrogenase A in nerve cells confers resistance to amyloid beta and other toxins by decreasing mitochondrial respiration and ROS production. *J Biol Chem* 2012, 287: 37245–37258.
115. Barthel A, Schmoll D, Unterman TG. FoxO proteins in insulin action and metabolism. *Trends Endocrinol Metab* 2005, 16: 183–189.
  116. Almeida M, Ambrogini E, Han L, Manolagas SC, Jilka RL. Increased lipid oxidation causes oxidative stress, increased peroxisome proliferator-activated receptor-gamma expression, and diminished pro-osteogenic Wnt signaling in the skeleton. *J Biol Chem* 2009, 284: 27438–27448.
  117. Essers MA, de Vries-Smits LM, Barker N, Polderman PE, Burgering BM, Korswagen HC. Functional interaction between beta-catenin and FOXO in oxidative stress signaling. *Science* 2005, 308: 1181–1184.
  118. Hoogeboom D, Essers MAG, Polderman PE, Voets E, Smits LMM, Burgering BMT. Interaction of FOXO with beta-catenin inhibits beta-catenin/T cell factor activity. *J Biol Chem* 2008, 283: 9224–9230.
  119. Brunet A, Bonni A, Zigmond MJ, Lin MZ, Juo P, Hu LS, Anderson MJ, et al. Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. *Cell* 1999, 96: 857–868.
  120. Reif K, Burgering BM, Cantrell DA. Phosphatidylinositol 3-kinase links the interleukin-2 receptor to protein kinase B and p70 S6 kinase. *J Biol Chem* 1997, 272: 14426–14433.
  121. Stahl M, Dijkers PF, Kops GJ, Lens SM, Coffey PJ, Burgering BM, Medema RH. The forkhead transcription factor FoxO regulates transcription of p27Kip1 and Bim in response to IL-2. *J Immunol* 2002, 168: 5024–5031.
  122. Schmidt M, Fernandez de Mattos S, van der Horst A, Klompmaaker R, Kops GJ, Lam EW, Burgering BM, et al. Cell cycle inhibition by FoxO forkhead transcription factors involves downregulation of cyclin D. *Mol Cell Biol* 2002, 22: 7842–7852.
  123. Fernández de Mattos S, Essafi A, Soeiro I, Pietersen AM, Birkenkamp KU, Edwards CS, Martino A, et al. FoxO3a and BCR-ABL regulate cyclin D2 transcription through a STAT5/BCL6-dependent mechanism. *Mol Cell Biol* 2004, 24: 10058–10071.
  124. Monolopoulos KN, Klitz LO, Korsten P, Bornstein SR, Barthel A. Linking Alzheimer's disease to insulin resistance: the FoxO response to oxidative stress. *Mol Psychiatry* 2010, 15: 1046–1052.
  125. Shang YC, Chong ZZ, Hou J, Maiese K. The forkhead transcription factor FoxO3a controls microglial inflammatory activation and eventual apoptotic injury through caspase 3. *Curr Neurovasc Res* 2009, 6: 20–31.
  126. Shang YC, Chong ZZ, Hou J, Maiese K. Wnt, FoxO3a, and NF-kappaB oversee microglial integrity and activation during oxidant stress. *Cell Signal* 2010, 22: 1317–1329.
  127. Erickson MA, Dohi K, Banks WA. Neuroinflammation: a common pathway in CNS diseases as mediated at the blood-brain barrier. *Neuroimmunomodulation* 2012, 19: 121–130.
  128. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. *Cell* 2010, 140: 918–934.
  129. Kawai T, Akira S. TLR signaling. *Cell Death Differ* 2006, 13: 816–825.
  130. Lehnardt L. Innate immunity and neuroinflammation in the CNS: the role of microglia in Toll-like receptor-mediated neuronal injury. *Glia* 2010, 58: 253–263.
  131. Xiang W, Chao ZY, Feng DY. Role of Toll-like receptor/MYD88 signaling in neurodegenerative diseases. *Rev Neurosci* 2015, 26: 407–414.
  132. Kawai T, Akira S. Signaling to NF-kappaB by Toll-like receptors. *Trends Mol Med* 2007, 13: 460–469.
  133. Silva-García O, Valdez-Alarcón JJ, Baizabal-Aguirre VM. The Wnt/ $\beta$ -catenin signaling pathway controls the inflammatory response in infections caused by pathogenic bacteria. *Mediators Inflamm* 2014, 2014: 310183.
  134. Du Q, Geller DA. Cross-regulation between Wnt and NF- $\kappa$ B signaling pathways. *For Immunopathol Dis Ther* 2010, 1: 155–181.
  135. Ajmone-Cat MA, D'Urso MC, Di Blasio G, Brignone MS, De Simone R, Minghetti L. Glycogen synthase kinase 3 is part of the molecular machinery regulating the adaptive response to LPS stimulation in microglial cells. *Brain Behav Immun* 2015, 55:225–235.
  136. Deng J, Miller SA, Wang HY, Xia W, Wen Y, Zhou BP, Li Y, et al. Beta-catenin interacts with and inhibits NF-kappa B in human colon and breast cancer. *Cancer Cell* 2002, 2: 323–334.
  137. Deng J, Xia W, Miller SA, Wen Y, Wang HY, Hung MC. Crossregulation of NF-kappaB by the APC/GSK-3beta/beta-catenin pathway. *Mol Carcinog* 2004, 39: 139–146.
  138. Umar S, Sarkar S, Wang Y, Singh P. Functional cross-talk between beta-catenin and NFkappaB signaling pathways in colonic crypts of mice in response to progastrin. *J Biol Chem* 2009, 284: 22274–22284.
  139. Zhang Y, Hu W. NF $\kappa$ B signaling regulates embryonic and adult neurogenesis. *Front Biol (Beijing)* 2012, 7(4).
  140. Borrell-Pages M, Romero JC, Crespo J, Juan-Babot O, Badimon L. LRP5 associates with specific subsets of macrophages: molecular and functional effects. *J Mol Cell Cardiol* 2016, 90: 146–156.
  141. Beurel E, Michalek SM, Jope RS. Innate and adaptive immune responses regulated by glycogen synthase kinase-3 (GSK3). *Trends Immunol* 2010, 31: 24–31.
  142. Hoeflich KP, Luo J, Rubie EA, Tsao MS, Jin O, Woodgett JR. Requirement for glycogen synthase kinase-3beta in cell survival and NF-kappaB activation. *Nature* 2000, 406: 86–90.
  143. Jansson EA, Are A, Greicius G, Kuo IC, Kelly D, Arulampalam V, Pettersson S. The Wnt/beta-catenin signaling pathway targets PPAR gamma activity in colon cancer cells. *Proc Natl Acad Sci USA* 2005, 102: 1460–1465.
  144. Cabrero A, Laguna JC, Vázquez M. Peroxisome proliferator-activated receptors and the control of inflammation. *Curr Drug Targets Inflamm Allergy* 2002, 1: 243–248.
  145. Inestrosa NC, Godoy JA, Quintanilla RA, Koenig CS, Bronfman M. Peroxisome proliferator-activated receptor gamma is expressed in hippocampal neurons and its activation prevents beta-amyloid neurodegeneration: role of Wnt signaling. *Exp Cell Res* 2005, 304: 91–104.
  146. Farshbaf MJ, Ghaedi K, Shirani M, Nasr-Esfahani MH. Peroxisome proliferator activated receptor gamma (PPAR $\gamma$ ) as a therapeutic target for improvement of cognitive performance in Fragile-X. *Med Hypotheses* 2014, 82: 291–294.
  147. Liu JJ, Dai XJ, Xu Y, Liu PQ, Zhang Y, Liu XD, Fang ZG, et al. Inhibition of lymphoma cell proliferation by peroxisomal proliferator-activated receptor- $\gamma$  ligands via Wnt signaling pathway. *Cell Biochem Biophys* 2012, 62: 19–27.
  148. Yi R, Chen B, Zhao J, Zhan X, Zhang L, Liu X, Dong Q. Krüppel-like factor 8 ameliorates Alzheimer's disease by activating  $\beta$ -catenin. *J Mol Neurosci* 2014, 52: 231–241.
  149. Elbrecht A, Chen Y, Cullinan CA, Hayes N, Leibowitz M, Moller DE, Berger J. Molecular cloning, expression and characterization of human peroxisome proliferator activated receptors gamma 1 and gamma 2. *Biochem Biophys Res Commun* 1996, 224: 431–437.
  150. Fajas L, Auboeuf D, Raspe E, Schoonjans K, Lefebvre AM, Saladin R, Najib J, et al. The organization, promoter analysis, and expression of the human PPARgamma gene. *J Biol Chem* 1997, 272: 18779–18789.
  151. Behl T, Kaur I, Goel H, Kotwani A. Implications of endogenous PPAR-gamma ligand, 15-Deoxy-Delta-12,14-prostaglandin J2, in diabetic retinopathy. *Life Sci* 2016, 153: 93–99.
  152. Grygiel-Gorniak B. Peroxisome proliferator-activated receptors and their ligands: nutritional and clinical implications—a review. *Nutr J* 2014, 13: 17.
  153. Shappell SB, Gupta RA, Manning S, Whitehead R, Boeglin WE, Schneider C, Case T, et al. 15S-Hydroxyeicosatetraenoic acid activates peroxisome proliferator-activated receptor gamma and inhibits proliferation in PC3 prostate carcinoma cells. *Cancer Res* 2001, 61: 497–503.
  154. Guan Y, Breyer MD. Peroxisome proliferator-activated receptors (PPARs): novel therapeutic targets in renal disease. *Kidney Int* 2001, 60: 14–30.
  155. Schild RL, Schaiff WT, Carlson MG, Cronbach EJ, Nelson DM, Sadovsky Y. The activity of PPAR gamma in primary human

- trophoblasts is enhanced by oxidized lipids. *J Clin Endocrinol Metab* 2002, 87: 1105–1110.
156. Bouaboula M, Hilairet S, Marchand J, Fajas L, Le Fur G, Casellas P. Anandamide induced PPAR gamma transcriptional activation and 3T3-L1 preadipocyte differentiation. *Eur J Pharmacol* 2002, 517: 174–181.
  157. Bright JJ, Kanakasabai S, Chearwae W. PPAR regulation of inflammatory signaling in CNS diseases. *PPAR Res* 2008, 2008: 658520.
  158. Burkart EM, Sambandam N, Han X. Nuclear receptors PPAR beta/delta and PPAR alpha direct distinct metabolic regulatory programs in the mouse heart. *J Clin Invest* 2007, 117: 3930–3939.
  159. Canevari L, Abramov AY, Duchen MR. Toxicity of amyloid beta peptide: tales of calcium, mitochondria, and oxidative stress. *Neurochem Res* 2004, 29: 637–650.
  160. Braissant O, Fufelle F, Scotto C. Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-alpha, -beta, and -gamma in the adult rat. *Endocrinology* 1996, 137: 354–366.
  161. Chen YC, Wu JS, Tsai HD. Peroxisome proliferator-activated receptor gamma (PPAR-gamma) and neurodegenerative disorders. *Mol Neurobiol* 2012, 46: 114–124.
  162. Chiang MC, Chen CM, Lee MR. Modulation of energy deficiency in Huntington's disease via activation of the peroxisome proliferator-activated receptor gamma. *Hum Mol Genet* 2010, 19: 4043–4058.
  163. Chiang MC, Cheng YC, Nicol CJ. Rosiglitazone activation of PPARgamma-dependent signaling is neuroprotective in mutant huntingtin expressing cells. *Exp Cell Res* 2015, 338: 183–193.
  164. Rangwala SM, Lazar MA. Peroxisome proliferator-activated receptor gamma in diabetes and metabolism. *Trends Pharmacol Sci* 2004, 25: 331–336.
  165. Picard F, Auwerx J. PPAR(gamma) and glucose homeostasis. *Annu Rev Nutr* 2002, 22: 167–197.
  166. Wang N, Yang G, Jia Z, Zhang H, Aoyagi T, Soodvilai S, Symons JD, et al. Vascular PPARgamma controls circadian variation in blood pressure and heart rate through Bmal1. *Cell Metab* 2008, 8: 482–491.
  167. Lecarpentier Y, Claes V, Hebert JL. PPARs, cardiovascular metabolism, and function: near- or far-from-equilibrium pathways. *PPAR Res* 2010, 2010, doi:10.1155/2010/783273.
  168. Delerive P, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors in inflammation control. *J Endocrinol* 2001, 169: 453–459.
  169. Willson TM, Brown PJ, Sternbach DD, Henke BR. The PPARs: from orphan receptors to drug discovery. *J Med Chem* 2000, 43: 527–550.
  170. Garcia-Gras E, Lombardi R, Giocondo MJ, Willerson JT, Schneider MD, Khoury DS, Marian AJ. Suppression of canonical Wnt/ $\beta$ -catenin signaling by nuclear plakoglobin recapitulates phenotype of arrhythmogenic right ventricular cardiomyopathy. *J Clin Invest* 2006, 116: 2012–2021.
  171. Djouadi F, Lecarpentier Y, Hébert JL, Charron P, Bastin J, Coirault C. A potential link between peroxisome proliferator-activated receptor signaling and the pathogenesis of arrhythmogenic right ventricular cardiomyopathy. *Cardiovasc Res* 2009, 84: 83–90.
  172. Moon RT, Bowerman B, Boutros M, Perrimon N. The promise and perils of Wnt signaling through  $\beta$ -catenin. *Science* 2002, 296: 1644–1646.
  173. Zhurinsky J, Shtutman M, Ben-Ze'ev A. Differential mechanisms of LEF/TCF family-dependent transcriptional activation by  $\beta$ -catenin and plakoglobin. *Mol Cell Biol* 2000, 20: 4238–4252.
  174. Pascual G, Fong AL, Ogawa S, Gamliel A, Li AC, Perissi V, Rose DW, et al. A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma. *Nature* 2005, 437: 759–763.
  175. Combs CK, Johnson DE, Karlo JC, Cannady SB, Landreth GE. Inflammatory mechanisms in Alzheimer's disease: inhibition of  $\beta$ -amyloid-stimulated proinflammatory responses and neurotoxicity by PPARgamma agonists. *J Neurosci* 2000, 20: 558–567.
  176. Kim EJ, Kwon KJ, Park JY, Lee SH, Moon CH, Baik EJ. Effects of peroxisome proliferator-activated receptor agonists on LPS-induced neuronal death in mixed cortical neurons: associated with iNOS and COX-2. *Brain Res* 2002, 941: 1–10.
  177. Luna-Medina R, Cortes-Canteli M, Alonso M, Santos A, Martinez A, Perez-Castillo A. Regulation of inflammatory response in neural cells *in vitro* by thiazolidinones derivatives through peroxisome proliferator-activated receptor gamma activation. *J Biol Chem* 2005, 280: 21453–21462.
  178. Heneka MT, Sastre M, Dumitrescu-Ozimek L, Dewachter I, Walter J, Klockgether T, Van Leuven F. Focal glial activation coincides with increased BACE1 activation and precedes amyloid plaque deposition in APP[V717I] transgenic mice. *J Neuroinflammation* 2005, 2: 22.
  179. D'Abbramo C, Massone S, Zingg JM, Pizzuti A, Marambaud P, Dalla Piccola B, Azzi A, et al. Role of peroxisome proliferator-activated receptor gamma in amyloid precursor protein processing and amyloid  $\beta$ -mediated cell death. *Biochem J* 2005, 391: 693–698.
  180. Nishijima C, Kimoto K, Arakawa Y. Survival activity of troglitazone in rat motoneurons. *J Neurochem* 2001, 76: 383–390.
  181. Weggen S, Eriksen JL, Das P, Sagi SA, Wang R, Pietrzik CU, Findlay KA, et al. A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. *Nature* 2001, 414: 212–216.
  182. Farias GG, Godoy JA, Vazquez MC, Adani R, Meshulam H, Avila J, Amitai G, et al. The anti-inflammatory and cholinesterase inhibitor bifunctional compound IBU-PO protects from  $\beta$ -amyloid neurotoxicity by acting on Wnt signaling components. *Neurobiol Dis* 2005, 18: 176–183.
  183. Landreth G, Jiang Q, Mandrekar S, Heneka M. PPAR gamma agonists as therapeutics for the treatment of Alzheimer's disease. *Neurotherapeutics* 2008, 5: 481–489.
  184. Pertwee RG. Endocannabinoids and their pharmacological actions. *Handb Exp Pharmacol* 2015, 231: 1–37.
  185. Alline C, Campos MV, Fogaça AB, Sonogo FS. Cannabidiol, neuroprotection and neuropsychiatric disorders. *Pharmacol Res* 2016, 112: 119–127.
  186. Fernandez-Ruiz J, Sagredo O, Pazos MR, Garcia C, Pertwee R, Mechoulam R, Martinez-Orgado J. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? *Br J Clin Pharmacol* 2013, 75: 323–333.
  187. Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, Katz R, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* 2014, 55: 791–802.
  188. Renard J, Norris C, Rushlow W, Laviolette SR. Neuronal and molecular effects of Cannabidiol on the mesolimbic dopamine system: implications for novel schizophrenia treatments. *Neurosci Biobehav Rev* 2017, 75: 157–165.
  189. Emamian ES. AKT/GSK3 signaling pathway and schizophrenia. *Front Mol Neurosci* 2012, 15: 33.
  190. Liu Y, Pham X, Zhang L, Chen PL, Burzynski G, McGaughey DM, He S, et al. Functional variants in DPYSL2 sequence increase risk of schizophrenia and suggest a link to mTOR signaling. *G3 (Bethesda)* 2015, 5: 61–72.
  191. Karl T, Cheng D, Garner B, Arnold JC. The therapeutic potential of the endocannabinoid system for Alzheimer's disease. *Expert Opin Ther Targets* 2012, 16: 407–420.
  192. Booz GW. Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress. *Free Radic Biol Med* 2011, 51: 1054–1061.
  193. Iuvone T, Esposito G, De Filippis D, Scuderi C, Steardo L. Cannabidiol: a promising drug for neurodegenerative disorders? *CNS Neurosci Ther* 2009, 15: 65–75.
  194. Krishnan S, Cairns R, Howard R. Cannabinoids for the treatment of dementia. *Cochrane Database Syst Rev* 2009, 15: CD0077204.
  195. Scuderi C, Esposito G, Blasio A, Valenza M, Arietti P, Steardo L Jr, Carnuccio R, et al. Palmitoylethanolamide counteracts reactive astrogliosis induced by  $\beta$ -amyloid peptide. *J Cell Mol Med* 2011, 15: 2664–2674.
  196. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Rev Bras Psiquiatr* 2008, 30: 271–280.
  197. Wolf SA, Bick-Sander A, Fabel K, Leal-Galicia P, Tauber S, Ramirez-Rodriguez G, Muller A, et al. Cannabinoid receptor CB1 mediates

- baseline and activity-induced survival of new neurons in adult hippocampal neurogenesis. *Cell Commun Signal* 2010, 8: 12.
198. Martin-Moreno AM, Reigada D, Ramirez BG, Mechoulam R, Innamorato N, Cuadrado A, de Ceballos ML. Cannabidiol and other cannabinoids reduce microglial activation *in vitro* and *in vivo*: Relevance to Alzheimer's disease. *Mol Pharmacol* 2011, 79: 964–973.
  199. Cheng D, Low JK, Logge W, Garner B, Karl T. Chronic cannabidiol treatment improves social and object recognition in double transgenic APPswe/PS1DE9 mice. *Psychopharmacology (Berl)* 2014, 231: 3009–3017.
  200. Cheng D, Spiro AS, Jenner AM, Garner B, Karl T. Long-term cannabidiol treatment prevents the development of social recognition memory deficits in Alzheimer's disease transgenic mice. *J Alzheimer Dis* 2014, 42: 1383–1396.
  201. Santamaria S, Sanchez N, Sanz M, Garcia-Sanz JA. Comparison of periodontal ligament and gingiva-derived mesenchymal stem cells for regenerative therapies. *Clin Oral Invest* 2016, doi:10.1007/s00784-016-1867-3.
  202. Tomar GB, Srivastava RK, Gupta N, Barhanpurkar AP, Pote ST, Jhaveri HM, Mishra GC, et al. Human gingiva-derived mesenchymal stem cells are superior to bone marrow-derived mesenchymal stem cells for cell therapy in regenerative medicine. *Biochem Biophys Res Commun* 2010, 393: 377–383.
  203. Libro R, Diomedea F, Scionti D, Piattelli A, Grassi G, Pollastro F, Bramanti P, et al. Cannabidiol modulates the expression of Alzheimer's disease-related genes in mesenchymal stem cells. *Int J Mol Sci* 2017, 18: 26.
  204. Hernandez F, Gomez de Barreda E, Fuster-Matanzo A, Lucas JJ, Avila J. GSK3: a possible link between amyloid peptide and tau protein. *Exp Neurol* 2010, 223: 322–325.
  205. Trazzi S, Steger M, Mitrugno VM, Bartesaghi R, Ciani E. CB1 cannabinoid receptors increase neuronal precursor proliferation through AKT/glycogen synthase kinase-3 $\beta$ -catenin signaling. *J Biol Chem* 2010, 285: 10098–10109.
  206. Ozaita A, Puighermanal E, Maldonado R. Regulation of PI3K/Akt/GSK-3 pathway by cannabinoids in the brain. *J Neurochem* 2007, 102: 1105–1114.
  207. Giacoppo S, Pollastro F, Grassi G, Bramanti P, Mazzon E. Target regulation of PI3K/Akt/mTOR pathway by cannabidiol in treatment of experimental multiple sclerosis. *Fitoterapia* 2017, 116: 77–84.
  208. Pertwee RG. The pharmacology of cannabidiol receptors and their ligands: an overview. *Int J Obes* 2006, 30: S13–S18.
  209. Gomez Del Pulgar T, De Ceballos ML, Guzman M, Velasco G. Cannabinoids protect astrocytes from ceramide-induced apoptosis through the phosphatidylinositol 3-kinase/protein kinase B pathway. *J Biol Chem* 2002, 277: 36527–36533.
  210. Molina-Holgado E, Vela JM, Arevalo-Martin A, Almazan G, Molina-Holgado F, Borrell J, et al. Cannabinoids promote oligodendrocyte progenitor survival: involvement of Cannabinoid receptors and phosphatidylinositol-3 kinase/Akt signaling. *J Neurosci* 2002, 22: 9742–9753.
  211. Justinova Z, Munzar P, Panlilio LV, Yasar S, Redhi GH, Tanda G, Goldberg SR. Blockade of THC-seeking behavior and relapse in monkeys by the cannabinoid CB1-receptor antagonist rimonabant. *Neuropsychopharmacology* 2008, 33: 2870–2877. doi:10.1038/npp.2008.21.
  212. Pertwee RG. The diverse CB<sub>1</sub> and CB<sub>2</sub> receptor pharmacology of three plant cannabinoids:  $\Delta^9$ -tetrahydrocannabinol, cannabidiol and  $\Delta^9$ -tetrahydrocannabivarin. *Br J Pharmacol* 2008, 153: 199–215.
  213. Ward SJ, Raffa RB. Rimonabant redux and strategies to improve the future outlook of CB1 receptor neutral-antagonist/inverse-agonist therapies. *Obesity* 2011, 19: 1325–1334.
  214. Wang S, Xu Q, Shu G, Wang L, Gao P, Xi Q, Zhang Y, et al. N-Oleoyl glycine, a lipoamino acid, stimulates adipogenesis associated with activation of CB1 receptor and Akt signaling pathway in 3T3-L1 adipocyte. *Biochem Biophys Res Commun* 2015, 466: 438–443.
  215. Niesink RJM, van Laar MW. Does cannabidiol protect against adverse psychological effects of THC? *Front Psychiatry* 2013, 4: 130.
  216. McPartland JM, Duncan M, Di Marzo V, Pertwee RG. Are cannabidiol and  $\Delta^9$ -tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. *Br J Pharmacol* 2015, 172: 737–753.
  217. Jones NA, Hill AJ, Smith I, Bevan SA, Williams CM, Whalley BJ, Stephens GJ. Cannabidiol displays antiepileptiform and antiseizure properties *in vitro* and *in vivo*. *J Pharmacol Exp Ther* 2010, 332: 569–577.
  218. Zlebnik NE, Cheer JF. Beyond the CB1 receptor: is Cannabidiol the answer for disorders of motivation? *Annu Rev Neurosci* 2016, 39: 1–17.
  219. Maguschak KA, Ressler KJ. The dynamic role of beta-catenin in synaptic plasticity. *Neuropharmacology* 2012, 62: 78–88.
  220. Purro SA, Dickins EM, Salinas PC. The secreted Wnt antagonist Dickkopf-1 is required for amyloid beta-mediated synaptic loss. *J Neurosci* 2012, 32: 3492–3498.
  221. Shruster A, Eldar-Finkelman H, Melamed E, Offen D. Wnt signaling pathway overcomes the disruption of neuronal differentiation of neural progenitor cells induced by oligomeric amyloid beta-peptide. *J Neurochem* 2011, 116: 522–529.
  222. Vargas JY, Fuenzalida M, Inestrosa NC. *In vivo* activation of Wnt signaling pathway enhances cognitive function of adult mice and reverses cognitive deficits in an Alzheimer's disease model. *J Neurosci* 2014, 34: 2191–2202.
  223. Hao E, Mukhopadhyay P, Cao Z, Erdélyi K, Holovac E, Liaudet L, Lee WS, et al. Cannabidiol protects against Doxorubicin-induced cardiomyopathy by modulating mitochondrial function and biogenesis. *Mol Med* 2015, 21: 38–45.
  224. Pan H, Mukhopadhyay P, Rajesh M, Patel V, Mukhopadhyay B, Gao B, et al. Cannabidiol attenuates cisplatin-induced nephrotoxicity by decreasing oxidative/nitrosative stress, inflammation, and cell death. *J Pharmacol Exp Ther* 2009, 328: 708–714.
  225. Rajesh M, Mukhopadhyay P, Batkai S, Hasko G, Liaudet L, Drel VR, Obrosova IG, et al. Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption. *Am J Physiol Heart Circ Physiol* 2007, 293: H610–H619.
  226. Szabo B, Schlicker E. Effects of cannabinoids on neurotransmission. *Handb Exp Pharmacol* 2005, 168: 327–365.
  227. Quintanilla RA, Muñoz FJ, Metcalfe MJ, Hirschfeld M, Olivares G, Godoy JA, Inestrosa NC. Trolox and 17 $\beta$ -estradiol protect against amyloid  $\beta$ -peptide neurotoxicity by a mechanism that involves modulation of the Wnt signalling pathway. *J Biol Chem* 2005, 280: 11615–11625.
  228. Esposito G, Scuderi C, Savani C, Steardo L Jr, De Filippis D, Cottone P, Iuvone T, et al. Cannabidiol *in vivo* blunts beta-amyloid induced neuroinflammation by suppressing IL-1 $\beta$  and iNOS expression. *Br J Pharmacol* 2007, 151: 1272–1279.
  229. Martín-Moreno AM, Reigada D, Ramírez BG, Mechoulam R, Innamorato N, Cuadrado A, et al. Cannabidiol and other cannabinoids reduce microglial activation *in vitro* and *in vivo*: relevance to Alzheimer's disease. *Mol Pharmacol* 2011, 79: 964–973.
  230. Cabral GA, Griffin-Thomas L. Emerging role of the cannabinoid receptor CB2 in immune regulation: therapeutic prospects for neuroinflammation. *Expert Rev Mol Med* 2009, 11: e3.
  231. Scuderi C, Filippis DD, Iuvone T, Blasio A, Steardo A, Esposito G. Cannabidiol in medicine: a review of its therapeutic potential in CNS disorders. *Phytother Res* 2009, 23: 597–602.
  232. Necela BM, Su W, Thompson EA. Toll-like receptor 4 mediates cross-talk between peroxisome proliferator-activated receptor  $\alpha$  and nuclear factor- $\kappa$ B in macrophages. *Immunology* 2008, 125: 344–358.
  233. Juknat A, Pietr M, Kozela E, Rimmerman N, Levy R, Coppola G, Geschwind D, et al. Differential transcriptional profiles mediated by exposure to the cannabinoids cannabidiol and delta9-tetrahydrocannabinol in BV-2 microglial cells. *Br J Pharmacol* 2012, 165: 2512–2528.
  234. O'Sullivan SE. Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors. *Br J Pharmacol* 2007, 152: 576–582.

235. Rodrigues LC, Gobira PH, de Oliveira AC, Pelicao R, Teixeira AL, Moreira FA, Campos AC. Neuroinflammation as a possible link between cannabinoids and addiction. *Acta Neuropsychiatr* 2014, 26: 334–346.
236. Stabel PF, Smith WR, Bruchis J, Rabb CH. Peroxisome proliferator-activated receptors: key regulators of neuroinflammation after traumatic brain injury. *PPAR Res* 2008, 2008: 538141.
237. Cho HY, Gladwell W, Wang X, Chorley B, Bell D, Reddy SP, Kleeberger SR. Nrf2-regulated PPAR[gamma] expression is critical to protection against acute lung injury in mice. *Am J Respir Crit Care Med* 2010, 182: 170–182.
238. Mecha M, Feliu A, Inigo PM, Mestre L, Carrillo-Salinas FJ, Guaza C. Cannabidiol provides long-lasting protection against the deleterious effects of inflammation in a viral model of multiple sclerosis: a role for A2A receptors. *Neurobiol Dis* 2013, 59: 141–150.
239. Napimoga MH, Benatti BB, Lima FO, Alves PM, Campos AC, Pena-Dos-Santos DR, Severino FP, *et al.* Cannabidiol decreases bone resorption by inhibiting RANK/RANKL expression and pro-inflammatory cytokines during experimental periodontitis in rats. *Int Immunopharmacol* 2009, 9: 216–222.
240. Ben-Shabat LO, Katzavian G, Gallily R. New cannabidiol derivatives: synthesis, binding to cannabinoid receptor, and evaluation of their anti-inflammatory activity. *J Med Chem* 2006, 49: 1113–1117.
241. Bianchi R, Giambanco I, Donato R. S100B/RAGE-dependent activation of microglia via NF-kappaB and AP-1 co-regulation of COX-2 expression by S100B, IL-1beta and TNF-alpha. *Neurobiol Aging* 2010, 31: 665–677.
242. Esposito G, Scuderi C, Lu J, Savani C, De Filippis D, Iuvone T, Steardo LJr, *et al.* S100B induces tau protein hyperphosphorylation via Dickkopf-1 up-regulation and disrupts the Wnt pathway in human neural stem cells. *J Cell Mol Med* 2008, 12: 914–927.
243. Mori T, Koyama N, Arendash GW, Horikoshi-Sakuraba Y, Tan J, Town T. Overexpression of human S100B exacerbates cerebral amyloidosis and gliosis in the Tg2576 mouse model of Alzheimer's disease. *Glia* 2010, 58: 300–314.
244. Sonogo AB, Sepulveda-Diaz JE, Michel PP, Del-Bel EA, Guimarães FS, Raisman-Vozari R. Cannabidiol reduces LPS-induced activation and oxidative stress in primary microglial culture via PPARgamma receptor. *Soc Neurosci Annu Meet* 2015, 58, (Poster Abstract 4.10/R11, Book 2).