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Amyotrophic Lateral Sclerosis: Role of the Canonical Wnt/Beta-Catenin Pathway and PPAR Gamma

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Abstract

Amyotrophic lateral sclerosis (ALS) is one of the most common adult-onset debilitating neurodegenerative diseases (NDs) which is characterized by a chronic progressive degeneration of upper and lower motor neurons, resulting in muscular atrophy, paralysis and ultimately death. It has been established that in ALS, the canonical Wnt/beta-catenin pathway is upregulated. Peroxisome proliferator-activated receptor gamma (PPAR gamma) generally varies in opposite way compared with the Wnt/beta-catenin signaling. Several studies carried out on ALS transgenic mice have shown the beneficial effects induced after treatment by PPAR agonists partly due to anti-inflammatory effects induced by PPAR gamma. The coupling between the Wnt/beta-catenin signaling and PPAR gamma has led to divide NDs into two classes: NDs in which the Wnt/beta-catenin pathway is upregulated whereas PPAR gamma is downregulated (ALS, Parkinson's disease, Huntington's disease and Friedreich's ataxia); and NDs in which the Wnt-beta-catenin pathway is downregulated while PPAR gamma is upregulated (Alzheimer's disease, bipolar disorder and schizophrenia).

Keywords: Wnt/beta-catenin, PPAR gamma, amyotrophic lateral sclerosis, riluzole, ALS

1. Introduction

Neurodegenerative diseases (NDs) are frequent and often present a pejorative prognosis. Two major systems play a key role in the pathophysiology of NDs, i.e., the canonical Wnt/beta-catenin pathway and PPAR gamma. Several studies have demonstrated the opposite interaction between the canonical Wnt/beta-catenin pathway and the PPAR gamma [1–7]. It has recently been shown that certain NDs can be divided into two classes [8]: on one hand, NDs

in which the Wnt/beta-catenin pathway is upregulated whereas PPAR gamma is downregulated. Among these NDs, we find amyotrophic lateral sclerosis (ALS), Parkinson's disease, Huntington's disease and Friedreich's ataxia. PPAR agonists exert protective effects in ALS neurons of transgenic mice and may represent therapeutic targets in human ALS. On the other hand, NDs in which the Wnt-beta-catenin pathway is downregulated while PPAR gamma is upregulated. Among these NDs, we find Alzheimer's disease, bipolar disorder and schizophrenia. This list is not exhaustive.

2. Amyotrophic lateral sclerosis (ALS)

ALS is one of the most common adult-onset debilitating NDs with the prevalence of about 5 per 100,000 individuals. The pathophysiology of ALS in humans is particularly complex, due to the numerous interconnected pathological processes and, today, has not been fully elucidated. However, it remains to determine those really responsible for the disease from those simply involved in its development. ALS has been first described by J.M. Charcot in 1869. ALS is a fatal neurodegenerative disorder and is characterized by chronic progressive degeneration of upper and lower motor neurons, resulting in muscular atrophy, paralysis and ultimately death. And, 82% of ALS are sporadic. The most frequent mutations in inherited or familial ALS (FALS) are found in the gene for Cu, Zn superoxide dismutase (SOD1). Among numerous abnormalities, this FALS presents glutamate toxicity, axonal transport defects, aberrant neurotrophic factors, mitochondrial dysfunction [9]. Numerous *in vivo* studies have used transgenic mice expressing FALS mutants of human SOD1 [10]. This transgenic model develops a progressive motor neuron pathology which is reminiscent of the human ALS phenotype [11]. The human sporadic ALS differs little clinically from SOD1-related FALS. Both forms of ALS induce degeneration of motor neurons which leads to paralysis and death within 3–5 years from the appearance of the first symptoms. Today, no pharmacological therapeutic can really stop the progression of the disease. Although riluzole is approved for ALS patients, the benefits of this drug are marginal [12–15].

3. Canonical Wnt/beta-catenin pathway

Wnt signaling plays a key role in carcinogenesis, embryonic development, cell fate, cell migration and NDs [16, 17]. A hallmark of the canonical Wnt pathway activation by Wnt ligands is the increase in the cytoplasmic beta-catenin protein level, the subsequent nuclear translocation and further activation of beta-catenin specific gene transcription [4, 18–20]. In the absence of Wnt ligands, beta-catenin is recruited into a destruction complex that contains adenomatous polyposis coli (APC) and Axin, which facilitate the phosphorylation of beta-catenin by glycogen synthase kinase-3beta (GSK-3beta). GSK-3beta phosphorylates the N-terminal domain of beta-catenin, thereby targeting it for ubiquitination and proteasomal degradation. In the presence of a Wnt ligand, the binding of Wnt to Frizzled (Fzd) leads to activation of the phosphoprotein Dishevelled (Dsh). Dsh recruits Axin and the destruction

complex to the plasma membrane, where Axin directly binds to the cytoplasmic tail of the low-density lipoprotein-receptor-related proteins (LRP5-6). The activation of Dsh also leads to the inhibition of GSK-3 β by phosphorylation, which further reduces the phosphorylation and degradation of beta-catenin. The beta-catenin degradation complex is inactivated with recruitment of Axin to the plasma membrane, thus stabilizing the non-phosphorylated beta-catenin which translocates to the nucleus. Beta-catenin binds to T cell/lymphoid-enhancing binding (Tcf/Lef) transcription factors. The resulting complex becomes active by displacing Groucho, leading to activation of numerous target genes including c-myc, cyclin D1, TFF-1, Axin-2, CD44, Cox2, MMP-7, PPAR beta/delta, [21–23]. Upregulation of the canonical Wnt/beta-catenin pathway is observed in metabolic diseases such as type 2 diabetes, hypertension, in cancers (colon, lung, breast, leukemias) and certain NDs. Downregulation is observed in osteoporosis, cardiac hypoxia, cardiac hypertrophy, arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) and certain NDs [8].

4. PPAR gamma

Peroxisome proliferator-activated receptor gamma (PPAR gamma) is a ligand-activated transcriptional factor that belongs to the nuclear hormone receptor superfamily. PPAR gamma regulates the expression or activity of a large number of genes in a variety of signaling pathways, including regulation of insulin sensitivity, glucose homeostasis, lipid metabolism, immune responses, inflammation, redox balance, cardiovascular integrity and cell fate [24, 25]. PPAR gamma is expressed in various cell types, such as adipose tissues, immune cells and brain cells including microglia and astrocytes which contribute to anti-inflammatory response in the central nervous system. During the past decade, the role of PPAR gamma in neurodegeneration has been established. The administration of PPAR gamma ligands has been shown to be beneficial in many NDs such as ALS, Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease and stroke [26]. PPAR gamma has been shown to have anti-inflammatory and neuroprotective effects [27, 28]. Astrocytic GLT1/EAAT2 gene is a target of PPAR gamma, leading to neuroprotection by increasing the glutamate uptake [29]. PPAR gamma is a direct transcriptional modulator of the pyruvate carboxylase gene [30]. Given the fact that ALS patients suffer from massive weight loss, this provides a possible explanation for the potential protective effects of pioglitazone through increased lipogenesis.

5. PPAR gamma activation induces repression of the beta-catenin pathway

The thiazolidinedione PPAR gamma agonists (TZDs), troglitazone, rosiglitazone and pioglitazone, and a non-thiazolidinedione PPAR gamma activator, GW1929, inhibit the beta-catenin-induced transcription in a PPAR gamma-dependent fashion [1–3, 5]. Troglitazone-mediated activation of PPAR gamma is associated with an inhibition of beta-catenin at a post-transcriptional level. The functional interaction between beta-catenin and PPAR gamma involves the Tcf/Lef factor-binding domain of beta-catenin and a catenin-binding domain within PPAR

gamma [5]. Treatment with PPAR gamma agonists decreases mRNA and protein levels of beta-catenin in 3T3L1 adipocytes [1]. TZDs induce a reduction in the levels of cytoplasmic beta-catenin in hepatocytes [3]. PPAR gamma suppresses Wnt/beta-catenin pathway during adipogenesis [2].

6. Deactivation of the Wnt/beta-catenin pathway induces activation of PPAR gamma

Inhibition of Wnt/beta-catenin pathway leads to an increase in transcription of PPAR gamma. Activation of the Wnt/beta-catenin signaling leads to osteogenesis, but not to adipogenesis. The canonical Wnt/beta-catenin-PPAR gamma system regulates the molecular switching of osteoblastogenesis versus adipogenesis [6]. Wnt signaling maintains preadipocytes in an undifferentiated state through inhibition of both adipogenic transcription factors C/EBP alpha and PPAR gamma. Deactivation of Wnt/beta-catenin pathway and activation of PPAR gamma are observed in ARVD [4, 31]. Taken together, these studies suggest that the canonical Wnt/beta-catenin signaling downregulates PPAR gamma expression, inhibition of Wnt/beta-catenin signaling upregulates PPAR gamma expression and PPAR gamma agonists inhibit the canonical Wnt/beta-catenin pathway.

7. ALS and Wnt/beta-catenin pathway

The canonical Wnt/beta-catenin signaling is involved in numerous NDs, particularly in ALS. Several studies have shown that this pathway is upregulated in motor neurons of ALS model mice [32–35]. In the spinal cord of SOD1(G93A) ALS transgenic mice, expression of Wnt2, Wnt7a and GSK-3beta has been determined [32]. Both Wnt2, Wnt7a mRNA and protein in the spinal cord of ALS mice have been found to be upregulated when compared with wild type. The immune-reactivity of Wnt2 and Wnt7a is strong in ALS adult transgenic mice, whereas it is weak in wild-type mice. Neurodegeneration upregulates the expression of Wnt2 and Wnt7a in the spinal cord of ALS mice, which in turn activates Wnt signaling and inhibits GSK-3beta activity in ALS adult transgenic mice. Expression of Wnt3a, beta-catenin and Cyclin D1, three key molecules of the Wnt/beta-catenin signaling, have been determined in the adult spinal cord of SOD1(G93A) ALS transgenic mice at different stages [33]. It has been found that mRNA and protein of Wnt3a and Cyclin D1 in the spinal cord of the ALS mice are upregulated compared with wild-type mice. Moreover, beta-catenin translocates from the cell membrane to the nucleus and subsequently activated transcription of the target gene Cyclin D1. Wnt3a, beta-catenin and Cyclin D1 are also expressed in both neurons and astrocytes. For the authors, these findings suggest that neurodegeneration activates the Wnt/beta-catenin pathway, in the spinal cord of adult ALS transgenic mice. Changes in Wnt5a and Fzd2 expression in the spinal cord of SOD1(G93A) transgenic mice (ALS), SOD1(G93A) transfected NSC-34 cells and primary cultures of astrocytes from SOD1(G93A) transgenic mice have been observed [35]. Expression of Wnt1 and Fzd1 has been found to be increased in the spinal cords of SOD1G93A

ALS transgenic mice [34]. In the *in vitro* model of ALS (G93A mutated forms of human Cu/Zn superoxide dismutase-1; SOD1), a cytosolic aggregation of beta-catenin has been observed. This suggests that Wnt/beta-catenin pathway could play critical role in the neurodegeneration of motor neurons in ALS [36]. Beta-catenin is activated in a subset of myofibers in extraocular muscles and limb muscles in ALS subjects [37].

8. ALS and riluzole

Today, no really efficient treatment exists for ALS [38, 39]. However, riluzole has been approved for the treatment of ALS in most countries and is tested in people based on results supporting a role of glutamate toxicity in ALS. Riluzole has numerous pharmacodynamics properties, i.e., presynaptic inhibition of the glutamate release, inhibition of G-protein-dependent processes, modulation of N-methyl-D-aspartate ionotropic receptor and blockade of the voltage-gated sodium channel, etc. [39]. Two trials [12, 13] have demonstrated the weak efficacy of riluzole in ALS with prolongation of median survival by 2 to 3 months and safety of riluzole. Thus, riluzole appears to slow the progression of ALS, and may improve survival in patients with disease of bulbar onset [12]. Riluzole is well tolerated and lengthens survival of patients with ALS [13]. Two other studies have led to almost the same conclusions [14, 15]. The FDA-approved drug, riluzole, 100 mg daily is reasonably safe and probably prolongs median survival by about 2 to 3 months in patients with ALS.

Importantly, riluzole has been found to be an enhancer of the Wnt/beta-catenin signaling in melanoma [40]. For the authors, treating melanoma cells with riluzole *in vitro* enhances the ability of WNT3A to regulate gene expression, promote pigmentation and decrease cell proliferation. Like WNT3A, riluzole decreases metastases in a mouse melanoma model. Moreover, riluzole enhances Wnt/beta-catenin signaling in the primary screen both in HT22 neuronal cells and in adult hippocampal progenitor cells [40]. As the Wnt/beta-catenin pathway is upregulated, at least in genetic ALS mice [32–35], this can partly explain poor results in trials testing riluzole in ALS as shown previously [12–15]. Lithium, an activator of the Wnt/beta-catenin signaling, has also been evaluated as a treatment for ALS [41]. Surprisingly, in ALS patients treated with lithium, the disease progression has been shown to be markedly attenuated. In the genetic ALS G93A mouse model, there is a marked neuroprotection induced by lithium, which delayed disease onset and duration and augmented the life span. The use of the enhancer Wnt/beta-catenin lithium can be discussed in ALS in which the Wnt/beta-catenin pathway has been shown to be upregulated in several animal studies [32–35]. GSK-3beta-inhibitor lithium chloride enhances activation of the canonical Wnt signaling [42–44]. Lithium activates downstream components of the Wnt signaling pathway *in vivo*, leading to an increase of the beta-catenin protein. This pathway is implicated in the pathophysiology and treatment of bipolar disorder [45, 46]. Riluzole reduces symptoms of obsessive-compulsive disorder, unipolar and bipolar depression and generalized anxiety disorder [47]. This is not surprising due to the fact that the Wnt/beta-catenin pathway is downregulated in bipolar syndrome [8] and that like lithium, riluzole is an enhancer of Wnt/beta-catenin signaling.

9. ALS and PPAR gamma

In ALS, expression of PPAR gamma (mARN and protein) has not been precisely investigated in neurons. However, the upregulation of Wnt/beta-catenin signaling observed in ALS suggests that PPAR gamma might be downregulated due to the fact that these two systems generally operate in the opposite way [1–3, 5]. Neuroinflammation is a common pathological feature in NDs, particularly in ALS. PPAR gamma may be a key regulator of neuroinflammation. PPAR gamma inhibits NF-kappaB-mediated inflammatory signaling at multiple sites [48]. PPAR gamma might be a relevant regulator of neuroinflammation and possibly a new target for the development of therapeutic strategies for ALS. A potentially therapeutic pathway in ALS may be the activation by PPAR gamma agonists due to their ability to block neuropathological damages caused by inflammation [49]. The neuroprotective effect of pioglitazone has been demonstrated in G93A SOD1 transgenic mouse model of ALS and shows a significant increase in their survival. Pioglitazone protects motor neurons against p38-mediated neuronal death and NF-kappaB-mediated glial inflammation via a PPAR gamma-independent mechanism [50]. In ALS, PPAR gamma controls natural protective mechanisms against lipid peroxidation [51]. PPAR gamma-driven transcription selectively increases in the spinal cord of hSOD1G93A mice. This is correlated with the upregulation of lipid detoxification enzymes such as the lipoprotein lipase and glutathione S-transferase alpha-2, implied in scavenging lipid peroxidation by-products. Anticipation of protective reactions by pharmacological PPAR gamma modulation of the transcriptional activity attenuates neurodegeneration induced by lipid peroxidation. PPAR gamma activation is neuroprotective in a *Drosophila* model of ALS [52]. This *Drosophila* model of ALS based on TDP-43 recapitulates several aspects of ALS pathophysiology. Pioglitazone rescues TDP-43-dependent locomotor dysfunction in motor neurons and glia. PPAR gamma activation in neurons and glia is partially neuroprotective and restores metabolic alterations in ALS. Superoxide dismutase (SOD1)-G93A transgenic mice benefit from oral treatment with the PPAR gamma agonist pioglitazone [53]. Pioglitazone-treated transgenic mice reveal improved muscle strength and body weight, exhibit a delayed disease onset and survive significantly longer than non-treated SOD1-G93A mice. Pioglitazone-induced neuroprotection of motor neurons of the spinal cord is complete at day 90. There is also preservation of the median fiber diameter of the quadriceps muscle, indicating a morphological and functional protection of motor neurons induced by pioglitazone. However, in a phase II double-blind controlled clinical trial, the PPAR gamma agonist pioglitazone in combination with riluzole does not increase survival in ALS patients [54].

PPAR gamma coactivator-1alpha (PGC-1alpha) is a transcriptional coactivator that works together with the transcription factor PPAR gamma in the regulation of mitochondrial biogenesis. PGC-1alpha plays a role in several neurodegenerative pathologies [26]. PGC-1alpha protects neurons and alters disease progression in a PGC-1alpha transgenic mice crossed with SOD1 mutant G93A DL mice [55]. In these mice, the progression of the disease has been shown to be significantly slower. There is also a markedly improved performance on the rotarod test associated with an improved motor activity with a decreased loss of motor neurons and less degeneration of neuromuscular junctions. By using a double transgenic mouse model where PGC-1alpha is over-expressed in a SOD1 transgenic mouse (TgSOD1-G93A/

PGC-1alpha), it has been found that motor function and survival are improved [56]. This is accompanied by a reduction of motor neuron loss, a restoration of mitochondrial electron transport chain activities and an inhibition of stress signaling in the spinal cord. Thus, in the double-transgenic mice, there are improved motor performance, slowed ALS progression, decreased weight loss, and reduced motor neuronal death. Survival and disease improvement are greater in higher-expressing PGC-1alpha mice. Therefore, PPAR gamma is a possible target for ALS as it functions as a transcription factor that interacts with PGC-1alpha. Elevated PGC-1alpha activity sustains mitochondrial biogenesis and muscle function without extending survival in a mouse model of inherited ALS [57]. Increasing PGC-1alpha activity in muscles represents an attractive therapy for maintaining muscle function during the progression of ALS.

10. Conclusions

PPAR agonists represent promising therapeutics for NDs such as multiple sclerosis, ALS and Alzheimer's disease (AD). Their activation affects many pathological mechanisms. PPAR activation can weaken or reprogram the immune response, stimulate metabolism, improve mitochondrial function, promote axon growth and induce progenitor cells to differentiate into myelinating oligodendrocytes [58]. The mechanisms of action of PPAR agonists are various and may be useful at many stages of diseases. Type, timing and dose of PPAR agonists may vary depending on injury severity, progression of disease or cellular targets such as neurons, microglia, oligodendrocytes, and may explain a number of conflicting results in several studies. PPAR gamma may be useful due to its anti-inflammatory properties. Moreover, PPAR gamma agonists induce beta-catenin inhibition [3, 5], which represents a rationale to use it when the Wnt/beta-catenin pathway is upregulated such as in Parkinson's disease, multiple sclerosis, ALS, Huntington's disease and Friedreich's ataxia [8]. However, in AD, PPAR gamma levels (mRNA and protein) have been found to be elevated in brain tissues [59, 60]. Although PPAR gamma expression is high in AD, PPAR gamma agonists have been used in AD humans and various AD animal models and have been shown to induce beneficial effects, partly due to their anti-inflammatory effects [61–67]. Even if the PPAR gamma agonist pioglitazone, in combination with riluzole, does not increase survival in ALS patients [54], PPAR gamma represents a useful therapeutic target in several animal models. Inhibition of the Wnt/beta-catenin pathway might also represent a therapeutic approach in ALS animal model.

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