Review

Rapamycin, Autophagy, and Alzheimer’s Disease

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Abstract: Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by cognitive impairment and multiple pathological lesions. At the molecular level, AD is characterized by overt amyloid β (Aβ) production and tau hyper-phosphorylation. Hence, pharmacological agents that can attenuate Aβ accumulation and tau hyper-phosphorylation have potential promise for treatment of AD. Rapamycin, an inhibitor of mammalian target of rapamycin (mTOR), is believed to be one of such pharmacological agents. It is neuroprotective in neurodegenerative diseases and its primary action is thought to be via enhancement of autophagy, a biological process that not only facilitates the clearance of mutant proteins but also significantly reduces the build-up of toxic protein aggregates such as Aβ. Since rapamycin enhancement of autophagy has been associated with abrogation of AD pathological processes such as clearance of Aβ and neurofibrillary tangles (NFTs) as well as reduction of tau hyper-phosphorylation and improvement of cognition, rapamycin is emerging as a potential therapeutic compound for AD.

Keywords: Alzheimer’s disease; autophagy; mTOR; neuroinflammation, rapamycin, oxidative stress, synaptic impairment

1. Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disease of aging [1, 2]. Patients with AD suffer from progressive functional impairment, the loss of independence, emotional distress, and behavioral symptoms [3]. AD is pathologically characterized by the presence of cerebral atrophy, extracellular amyloid plaques, and intra-neuronal neurofibrillary tangles (NFTs) [4, 5]. Beta-amyloid peptide (Aβ) generation and deposition is recognized as a major contributor in the triggering of AD. NFTs, the insoluble twisted fibers found intracellularly in the AD brain, are also recognized as another important pathological manifestation of the disease.

Rapamycin, a drug approved by the U.S. Food and Drug Administration for preventing the immune system from attacking transplanted organs, may fight AD [6]. In this review, we focus on the roles of rapamycin in rescuing the pathology of amyloid plaques and NFTs, which are the two main factors in AD that can impair synaptic structure and function as well as neural plasticity and cognition. We also present evidence that rapamycin exerts its neuroprotective effects through autophagy enhancement. In addition, whether rapamycin could be an effective therapeutic compound for preventing or reversing AD pathology is also discussed.

2. Rapamycin

Rapamycin (Fig. 1), first isolated from a strain of Streptomyces hygroscopicus indigenous to Easter Island, is a member of a family of macrolide immunosuppressants used to prevent rejections following organ transplantation via the inhibition of T and B cell proliferation [7-9]. Rapamycin inhibits the mammalian target of rapamycin (mTOR) pathway via direct binding of mTOR Complex 1 (mTORC1) that is a nutrient-sensitive kinase [10, 11]. Therefore, rapamycin is involved in many cellular functions, such as cell growth, proliferation, protein synthesis, and autophagy. Studies have shown that rapamycin can extend the lifespan of organisms and slow the progression of aging [12, 13]. For example, rapamycin was shown to extend lifespan and retard aging in yeast [14] and mouse [15], respectively. Moreover, as rapamycin has anti-proliferative effects [16, 17], it may benefit patients with cancer [18, 19], adipogenesis [20, 21], diabetes [22, 23], tuberous sclerosis [24, 25], cardiovascular diseases [26-29], and neurological disorders [30, 31]. In the brain, the most
striking effect of rapamycin is its neuroprotective effects, making it a potential therapeutic pharmacological compound to curb neurodegenerative disorders [32] such as Alzheimer's disease [6, 12, 33, 34], Parkinson’s disease [35, 36], and Huntington's disease [37, 38]. The underlying neuroprotective mechanisms of rapamycin are thought to be related to its effects on autophagy enhancement [39-41].

3. Autophagy

Autophagy is a lysosome-mediated, self-digesting degradation mechanism that involves the removal of damaged organelles and misfolded or nonfunctional proteins [42, 43]. Autophagy is essential for cell growth, survival, differentiation, development as well as protein homeostasis, and maintains a balance between the synthesis, degradation, and subsequent recycling of cellular products [44, 45]. Autophagy plays an important role in a variety of pathologies such as cancer [46, 47] and neurodegeneration [6]. Numerous studies have shown that the process of autophagy is negatively regulated by the activation of mTOR because mTORC1 and Atg1/ULK complexes can coordinately regulate autophagy in response to pathophysiological stress [48-51].

4. Rapamycin and neuroprotection in Alzheimer’s disease

Increasing evidence indicates that rapamycin is an effective inhibitor of the neurodegeneration that occurs in AD. Evidence includes: 1) rapamycin inhibition of mTOR improves AD-linked cognitive deficits [12, 52]; 2) rapamycin enhancement of autophagy reduces Aβ accumulation [6, 34]; and 3) rapamycin enhancement of autophagy attenuates tau hyper-phosphorylation [53, 54]. Fig. 2 summarizes the potential protective mechanisms of rapamycin in AD.

4.1. Rapamycin ameliorates the cognitive deficits in AD

The clinical manifestations of patients with AD usually include insidiously progressive memory loss, language disorders, and cognitive dysfunction in both visuospatial skills and executive functions. The cognitive deficits may be associated with slowly progressive behavioral changes. At later stages of AD, the patients develop memory and mobility loss, exhibits unusual behavior, and have problems with communication and continence. As studies have revealed in mouse models of AD that rapamycin attenuates the accumulation of Aβ and hyper-phosphorylated tau, decreases neuroinflammation, improves synaptic plasticity, and helps to ameliorate the loss of cognitive function [33, 52, 55], it is possible that in humans rapamycin may have similar effects.

4.1.1. Effects of rapamycin on aging and AD

It is well accepted that aging is the greatest risk factor for AD. It has been demonstrated that, in mice, the chronic inhibition of mTOR by rapamycin not only enhances learning and memory but also modulates their behavior throughout their lifespan [56]. For example, the performance of 18-month-old mice on a task measuring their spatial learning and memory is significantly improved when treated with rapamycin, an effect that has been determined to be mediated by IL-1β and NMDA signaling [57]. Thus, rapamycin could be an effective cognition-improving agent in aging and AD.

4.1.2. Effects of rapamycin on oxidative stress and neuroinflammation

Oxidative stress and neuroinflammation have been reported to promote cognitive impairment in AD as they can facilitate Aβ generation and NFTs formation [58, 59] that in turn contribute to the progressive cognitive deficits of AD [52, 60, 61]. Many studies have demonstrated that rapamycin improves learning and memory through the inhibition of Aβ and tau accumulation by interfering with several signaling cascades [34, 62, 63] that involve interactions between oxidative stress and neuroinflammation [58, 64]. Therefore, rapamycin is thought to exert its neuroprotective actions via its antioxidant and anti-inflammatory capabilities [35, 65-67], which may also be associated with its ability to ameliorate cognition impairment.

4.1.3. Effects of rapamycin on synaptic impairment

Synaptic impairment is the basis of memory loss in AD, and synaptic loss is an early feature of AD [68, 69]. Extensive data have demonstrated that the memory impairment observed in AD is closely associated with decreased hippocampal synaptic plasticity. As there is also a positive correlation between the extent of synaptic loss and the severity of dementia [68, 70], rapamycin, via inhibiting dysregulation of the mTOR pathway that leads to loss of synaptic plasticity in AD [71], can exhibit favorable effects on neuronal survival and plasticity, and
facilitate memory improvement. Studies have indicated that rapamycin not only directly renovates long-term synaptic plasticity in the hippocampus [72], but also improves synaptic function by limiting Aβ accumulation and tau hyper-phosphorylation that otherwise can impair synaptic structure, function and plasticity, as well as memory [73].

5. Rapamycin reduces the level of Aβ and enhances Aβ clearance

Under normal physiological conditions, Aβ that is generated and aggregated can be degraded by the autophagy-lysosome system [74-76]. However, when function of the autophagy-lysosome system is impaired, Aβ could be accumulated and there could also be a failure in removing it [77, 78]. In this sense, rapamycin protects against neurodegeneration because it can enhance autophagy that then facilitates the clearance of Aβ aggregates [79, 80].

Specifically, it has been shown that rapamycin decreases Aβ-related pathologies [12, 34, 81], induces neuronal survival and plasticity, and hence can rescue cognitive deficit. With respect to the underlying mechanisms, it has been reported that in PC12 cells rapamycin activates the autophagy pathway, upregulates Aβ42-induced Beclin-1 expression that promotes cell survival [82]. When Beclin-1 is down-regulated by the autophagy inhibitor 3-methyladenine, cell death is promoted [82]. Such results suggest that activation of Beclin-1-dependent autophagy can prevent neuronal cell death and that inhibition of Beclin-1-dependent autophagy can promote cell death [82]. As autophagy plays an important role in Aβ generation by modulating metabolism of amyloid precursor protein (APP) and controlling the expression of β- and γ-secretases [83-87], rapamycin enhancement of autophagy can thus modulate APP metabolism, lower β- and γ-secretase expression, and result in decrease in Aβ levels. Additionally, similar to rapamycin’s effect on cognition improvement, it is likely that rapamycin lowers Aβ levels also through its antioxidant and anti-inflammatory properties, which have been characterized by rapamycin’s impact on several redox signaling pathways, such as PI3K/Akt [63, 88, 89], mTOR [88-90], CaMKIIβ/AMPK [91], and insulin/IGF-1 signaling [92, 93].

6. Rapamycin restrains tau hyperphosphorylation

Increasing evidence indicates that the activation of mTOR signaling is involved in tau phosphorylation and degradation [94, 95]. Hence, suppressing mTOR signaling with rapamycin can enhance autophagy that further ameliorates the tau pathology and improves cognitive deficits [81]. The PI3K/Akt/mTOR signaling pathway regulates tau phosphorylation at many sites by controlling the GSK-3-dependent phosphorylation of tau [96-98], and excessive activation of mTOR can also induce the occurrence of tau-phosphorylated proteins in the hippocampal tissue of rats with type 2 diabetes and AD [99]. It should be noted that tau protein expression is also associated with levels of mTOR and its downstream targets, such as the eukaryotic initiation factor 4E binding protein 1 (4EBP1), eukaryotic elongation factor 2 (eEF2), and eEF2 kinase [100]. Interestingly, similar to rapamycin, phosphatidic acid can also activate the mTOR pathway, thereby modulating tau phosphorylation and oxidative stress [101]. Additionally, it is also known that rapamycin suppresses the translation of both tau and collapsing response mediator protein 2 (CRMP2), which play important roles in axon formation from neurites through their interactions with microtubules [102, 103]. These results demonstrate that rapamycin can exert a variety of effects on tau via different mechanisms.

While enhancement of autophagy by rapamycin promotes the clearance of the hyper-phosphorylated tau [6], rapamycin may also attenuate the process of tau hyper-phosphorylation. For example, it has been reported that rapamycin could decrease tau phosphorylation at Serine-214 via the regulation of cAMP-dependent kinase, leading to less build-up of...
hyper-phosphorylated tau [62]. Therefore, by controlling the autophagy pathway, rapamycin can regulate both tau phosphorylation and the build-up of hyper-phosphorylated tau.

7. Discussions and perspectives

It is well established that mTOR plays a central role in the maintenance of protein homeostasis [42, 43], which deteriorates during aging and in age-related neurodegeneration. Therefore, not surprisingly, mTOR could be involved in lifespan regulation and in age-related pathogenesis [13, 16, 57, 104, 105]. By restraining the activity of mTOR signaling, inhibiting mTOR protein biosynthesis, and enhancing autophagy, rapamycin can thus protect against Aβ toxicity and tau pathology, promote neuronal survival and plasticity, thereby leading to learning rescue and memory enhancement. Therefore, rapamycin targeting of mTOR could be a potential approach for treating AD.

Although rapamycin exhibits beneficial effects in AD as described above, several studies have also shown that rapamycin could cause detrimental effects. For example, it was reported that rapamycin could exacerbate the neurotoxicity of Aβ peptides [106], and could also accelerate Aβ generation by decreasing the activation of a disintegrin and metalloproteinase domain-10 (ADAM-10), which is an important target of α-secretase [107]. However, the discrepancy between these beneficial and deleterious effects of rapamycin remains unknown at this point.

Finally, whether the results obtained in mice and tissue cultures can also be observed in humans remains unknown. As an immunosuppressant, rapamycin treatment of AD patients over a prolonged period might be harmful to the immune system, a potential adverse effect that needs to be investigated. Moreover, further clinical studies also remain to be conducted to determine whether rapamycin could indeed be a successful therapeutic compound for the treatment of AD.

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