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Resveratrol as a possible multitarget drug for Alzheimer's Disease

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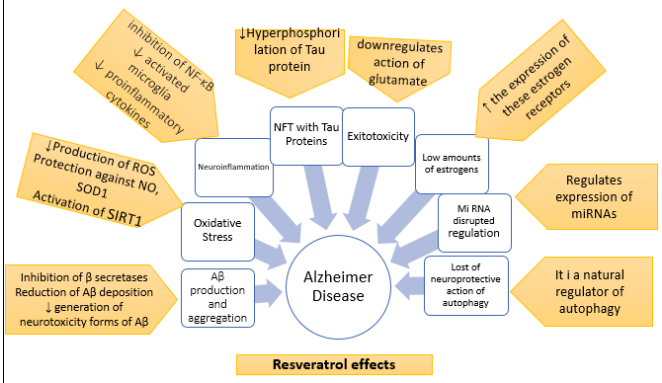
Graphical Abstract



Abstract.

Alzheimer's Disease is considered a multifactorial and really complex disorder. Pathological mechanisms are not completely identified and actual drugs have poor effects on disease's progression. Consequently, multi-target therapeutic turns attractive in the way to find new drug options. As a result of their antioxidant and anti-inflammatory benefits add to their regulation effects in signal transduction, apoptosis pathways, and cellular differentiation, polyphenols have an enormous value as chemoprotectors in SNC diseases. Resveratrol has multiple anti-AD effects including anti-inflammatory and anti-oxidant actions in neurodegeneration disorders, reduction of Aβ production and deposition, reduction of hyper phosphorylation of tau protein, regulation of mi RNA a gene translation, modulation of estrogen-dependent receptors, regulation of cell autophagy and neurotransmissor toxicity. Despite the pharmacokinetic challenges, resveratrol is a potential drug for a multi-target therapy model.

Introduction

Alzheimer´s Disease(AD) is a central nervous system pathology, characterized by a process of neurodegeneration, mostly present in advanced ages [1]. Nowadays, available drugs for AD improve cognition but their capabilities are limited in moderate AD and they have poor effects on disease´s progression [2]. Alzheimer´s Disease is considered a multifactorial and complex disorder. Pathological mechanisms of AD are not completely identified, and some of the known ones generate a complicated network of pathological interactions. Consequently, multi-target therapy models turn attractive in the way to find new drug options [3].

The anti-oxidative benefits of polyphenols, compounds derived from vegetables and fruits, have been shown multiple times. They have been related to potential therapy of several cardiac pathologies, obesity, and neurodegenerative disorders. As a result of their antioxidant and anti-inflammatory benefits added to their regulation action in signal transduction, apoptosis pathways and cellular differentiation, polyphenols have an enormous value as chemoprotectors in SNC diseases [4]. In the lasts years Resveratrol has been more deeply analyzed for the anti-AD possible effects, particularly the potential as an anti-inflammatory drug in the SNC and anti-amyloid genic agent [5].

Resveratrol's chemistry

Resveratrol is a polyphenol, it could be isolated for plants including grapes, berries and peanuts. Naturally, it acts as phytoalexina which provide plants of resistance to infections [6]. The anabolize action on resveratrol occurs by the catalytic activity of stilbene synthase (STS), which can have inducted by many physical forms of stress like UV irradiation or pathogenic insult. It is synthesized by three condensation reactions involving Coumaryl-coenzyme A and malonyl-CoA, and the posterior generation of resveratrol by the STS removing of terminal carboxyl group [4].

Effects of resveratrol in oxidative stress and SIRT 1

Oxidative stress is known as a cause of neurodegeneration, brain is one of the most vulnerable organs to cytotoxic effects of reactive oxygen species (ROS), these process can be accelerated due to a low quantity of antioxidant. Oxidative damage on the mitochondria produce significant amounts of ROS. Eventually, this reactive species damage structure compounds as proteins, lipids and nucleic acids. ROS incremented levels are also associated with the induction of Aβ production and aggregation. Resveratrol has protected murine cortical neurons of the toxic effect of mutant super oxide dismutase (SOD1), it also attenuated nitric oxide (NO) toxicity in hippocampal cultured cells and inhibited their production, additionally, it has suppressed activity of nitric oxide synthase. In microglial cells stimulated with LPS resveratrol has shown to inhibit PGE2 and levels of expression of mPGES-1 and COX-1[7].

An important neuroprotective mechanism of resveratrol is their activation function of SIRT1. SIRT 1 and SIRT 2 are emerging biomarkers in neurodegeneration. Sirtuins are enzymes associated with a major lifespan and longevity, at a neuronal level SIRT 1 acts by deacetyling an important amount of transcription factors including PPARα, where the activation is NAD+ dependent [8]. Increased activity of SIRT with resveratrol prevents Aβ-induced microglial activation and its dead, in consequence, improves cognitive function. Furthermore, the overexpression of SIRT1 plays an important role in neuronal protection because it regulates reactive oxygen species (ROS), nitric oxide (NO), proinflammatory cytokine production, and Aβ expression in AD patients [4].

Deposits of amyloid-beta(Aβ)

One of the principal theories of pathogenesis is the amyloid aggregation. Amyloid-beta protein (Aβ) is produced by the neurons, but, in AD the lost equilibrium between production and cleavage by the Amyloid precursor protein leads into a pathological accumulation. Then, cells suffer changes like disruption of intracellular electrolytic homeostasis and the cACh neurotransmission, induction of apoptotic pathways and the formation of neurofibrillary tangles (NFTs) causing the progressive loss of cognitive capacity [9]. Another important characteristic of Amylod beta protein is the ability of generate ionic complexes with Fe, Cu an Zn. These agents confer to Aβ a major capacity to produce brain damage. In murine models and cell lines resveratrol has shown benefits about this pathological mechanism, it inhibits β secretases, reduces aggregation of Aβ by regulation of multiple pathways associated to inflammation and oxidative stress, and prevents the generation of neurotoxicity forms of Aβ [4]. A rodent model demonstrated the reduction of Aβ oligomerization with resveratrol add to a better cognitive function. In clinical studies, a group pf AD patients treated with resveratrol reduce their CSF Aβ40 and plasma Aβ40 levels according of expectations of disease progression [1].

Neuroinflammation

In AD there is over-activation of microglia, more importantly, this pathological condition induces the amyloid deposit. Increased activated microglia leads into an inflammatory ambiance, a higher number of cytokines within other proinflammatory mediators and rises the reactive nitrogen species that could generate forms of Aβ with an increased toxic action. In a study with 119 patients with mild-moderate AD, resveratrol attenuates levels of pro-inflammatory mediators in plasma, their anti-inflammatory

benefits could protect against the induction of neuroinflammation by Aβ add to inhibition of NF-κB pathway in microglia and astrocytes. Resveratrol minimized, indeed, the number of activated microglia in a murine model [4]. The pharmanutricetic have shown to decrease the secretion of proinflammatory cytokines and increase the amount of anti-inflammatory cytokines; at the same time, it down regulates the expression of leukocyte chemoattractant agents and adhesion proteins. Resveratrol apparently acts on the transcription factors AP-1 and NF-κB in addition of the gene COX2 expression [10].

Tau protein

Hyperphosphorylation of Tau, a highly soluble protein associated to microtubule function, is considered another pathologic mechanism of Alzheimer´s disease. this protein gives stability to the microtubules and maintains cytoleskeletic structure in cells. The phosphorylation of this protein by multiple kinases causes the formation of neurofibrillary tangle aggregates (NFTs) [4]. Resveratrol tended to decrease hyperphosphorylation of tau in NFTs in bran sections of mice [11].

MiRNA and gene translation

Several studies have shown a relation between microRNA (miRNA) and the pathogenesis of AD, especially in the role of miRNA in gene translation expression. A wide list Micro RNA´s present in extracellular fluid and CSF have probable implications in AD [12,13]. Despite the limited studies about the effects of resveratrol in micro RNA´s at the SNC, there is evidence that it changed the up or down regulation in ischemic reperfused (IR) myocardium samples in more than the half percent of expressed miRNAs [14]. On the other hand, the resveratrol decrement cleavages of DNA and acts as a mediator of apoptosis trough deacetylation of p53 [4].

Other targets of resveratrol

One of the less studied targets in Alzheimer is the role of estrogens in this condition, during the last ten years, substantial information suggests that brain estrogen has an important impact on cognitive improvement, because of their tissue-maintain work. Concerning this, it has been shown that 17β-estradiol promote neurogenesis in the hippocampus and activate new neurons in response to spatial memory recovery [15]. Low inherent levels of estradiol are associated with a major prevalence of AD and an increment in the incidence in older women. In a study performed in a mouse model, Resveratrol treated subjects get higher levels of ERα and ChAT, estrogen-dependent receptors associated to cognition and spatial memory. This could be interpreted as the compound can modulate pathological development of AD by controlling the expression of these estrogen receptors [16].

Alternatively, resveratrol downregulates action of glutamate resulting in a minor toxicity of this neurotransmissor and prevent cellular loss caused by synaptic density [4]. In addition, it acts as a natural regulator of autophagy, some studies demonstrate that in presence of an autophagy function disruption, like in AD, Aβ deposition and tissue damage are increased, resulting in a major Alzheimer´s disease incidence [1].

Pharmacokinetics and possible solutions

Unfortunately, in contrast of all the benefits resveratrol could offer to AD therapy, this chemical compound has poor solubility and lack of permeability across the brain blood barrier, consequently it has a poor bioavailability. In fact, it is also very photosensitive, thus, is difficult to use a s a pharmacological solution [17]. Recently, many option of delivery systems for resveratrol has been created; techniques like nanoemulsion, use of polymeric nanoparticles and micellar system still in research and they could be a solution about the problematic pharmacokinetics of this compound [18]. The association with other components and discovery of analogs of resveratrol also suggest a possible option of drugs [19].

Conclusions

Despite the vast amount of information available about the etiopathogenesis of Alzheimer's Disease, its exact nosogenic mechanism remains not completely known. The actual treatments are insufficient against the complex physiopathology development in brain. Thus, it is necessary to find better options for regulate the progression of this illness. In summary, resveratrol has an important action in almost every target and AD biomarker reported until these days, under those circumstances, it must be considering as a potential multi target therapy in Alzheimer's Disease; even if resveratrol pharmacokinetic conditions are unfavorable for been considered as a real possibility as a drug option. to amplify the researching of delivery systems for make resveratrol and its properties accessible for the clinical population.

References

1. Chen Y. G. (2018). Research Progress in the Pathogenesis of Alzheimer's Disease. *Chinese medical journal*, *131*(13), 1618–1624. doi:10.4103/0366-6999.235112
2. Blesa, R., Toriyama, K., Ueda, K., Knox, S., & Grossberg, G. (2018). Strategies for Continued Successful Treatment in Patients with Alzheimer's Disease: An Overview of Switching Between Pharmacological Agents. *Current Alzheimer Research*, *15*(10), 964-974.
3. Braidy, Nady & Jugder, Bat-Erdene & Poljak, Anne & Jayasena, Tharusha & Mansour, Hussein & Nabavi, Seyed & Sachdev, Perminder & Grant, Ross. (2016). Resveratrol as a Potential Therapeutic Candidate for the Treatment and Management of Alzheimer's Disease. Current topics in medicinal chemistry. 16. 10.2174/1568026616666160204121431
4. Erdogan Orhan, I., & Sezer Senol, F. (2016). Designing multi-targeted therapeutics for the treatment of Alzheimer's disease. *Current topics in medicinal chemistry*, *16*(17), 1889-1896
5. Van Bulck, M., Sierra-Magro, A., Alarcon-Gil, J., Perez-Castillo, A., & Morales-Garcia, J. A. (2019). Novel Approaches for the Treatment of Alzheimer's and Parkinson's Disease. *International journal of molecular sciences*, *20*(3), 719.
6. Berman, A. Y., Motechin, R. A., Wiesenfeld, M. Y., & Holz, M. K. (). The therapeutic potential of resveratrol: a review of clinical trials. *NPJ precision oncology*, *1*, 35. doi:10.1038/s41698-017-0038-6
7. Wang, H., Jiang, T., Li, W., Gao, N., & Zhang, T. (2018). Resveratrol attenuates oxidative damage through activating mitophagy in an in vitro model of Alzheimer's disease. *Toxicology letters*, *282*, 100-108.
8. Donmez, G., & Outeiro, T. F. (2013). SIRT1 and SIRT2: emerging targets in neurodegeneration. *EMBO molecular medicine*, *5*(3), 344–352. doi:10.1002/emmm.201302451
9. Sawda, C., Moussa, C., & Turner, R. S. (2017). Resveratrol for Alzheimer's disease. *Annals of the New York Academy of Sciences*, *1403*(1), 142–149. doi:10.1111/nyas.13431
10. Martin, E., & Delarasse, C. (2018). Complex role of chemokine mediators in animal models of Alzheimer's disease. *Biomedical journal*, *41*(1), 34-40
11. Yu, K. C., Kwan, P., Cheung, S., Ho, A., & Baum, L. (2018). Effects of Resveratrol and Morin on Insoluble Tau in Tau Transgenic Mice. *Translational neuroscience*, *9*, 54–60. doi:10.1515/tnsci-2018-0010
12. Femminella, G. D., Ferrara, N., & Rengo, G. (2015). The emerging role of microRNAs in Alzheimer's disease. *Frontiers in physiology*, *6*, 40. doi:10.3389/fphys.2015.00040
13. Pogue, A. I., & Lukiw, W. J. (2018). Up-regulated pro-inflammatory microRNAs (miRNAs) in Alzheimer's disease (AD) and age-related macular degeneration (AMD). *Cellular and molecular neurobiology*, *38*(5), 1021-1031.
14. Mukhopadhyay, P., Pacher, P., & Das, D. K. (2011). MicroRNA signatures of resveratrol in the ischemic heart. *Annals of the New York Academy of Sciences*, *1215*, 109–116. doi:10.1111/j.1749-6632.2010. 05866.x
15. Li, R., Cui, J., & Shen, Y. (2014). Brain sex matters: estrogen in cognition and Alzheimer's disease. *Molecular and cellular endocrinology*, *389*(1-2), 13-21.
16. Grissom, E. M., & Daniel, J. M. (2016). Evidence for Ligand-Independent Activation of Hippocampal Estrogen Receptor-α by IGF-1 in Hippocampus of Ovariectomized Rats. *Endocrinology*, *157*(8), 3149–3156. doi:10.1210/en.2016-1197
17. Ruivo, J., Francisco, C., Oliveira, R., & Figueiras, A. (2015). The main potentialities of resveratrol for drug delivery systems. *Brazilian Journal of Pharmaceutical Sciences*, *51*(3), 499-513
18. Ruivo, J., Francisco, C., Oliveira, R., & Figueiras, A. (2015). The main potentialities of resveratrol for drug delivery systems. *Brazilian Journal of Pharmaceutical Sciences*, *51*(3), 499-513.
19. Lange, K. W., & Li, S. (2018). Resveratrol, pterostilbene, and dementia. *BioFactors*, *44*(1), 83-90