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Review Article

Multi-Target Drugs to Control the Progression of Age-Related Neurodegenerative Disorders

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ABSTRACT

Alzheimer's disease (AD), the most common cause of dementia, is predominantly sporadic, accounting for 60–80 percent of all cases, with symptoms often appearing between 30 and 50 years of age. Cases of age-associated disorders, including dementia, have dramatically increased globally. The two conditions most frequently linked to AD are glaucoma and age-related macular degeneration (AMD) the leading causes of permanent blindness in developed nations. The primary causes of AD are extracellular amyloid β (Aβ) build-up and the deposition of hyperphosphorylated tau (p-tau), which results in neuroinflammation and iron dyshomeostasis in the brain. AD and AMD may share the same pathogenesis since AMD is characterized by the build-up of Aβ and iron in drusen and p-tau in retinal ganglion cells (RGC), which are mostly linked to glaucoma. This review focuses on common pathological pathways between AD and AMD to establish the use of multi-target drugs as a treatment approach in the future.

1. INTRODUCTION

Drug repurposing is a recently emerged cost- and time-saving strategy that could be used in the development of therapeutic opportunities for rare diseases. Gaps in research on Neurodegenerative diseases are high due to their high complexity and novel leads in their prevention, diagnosis, and treatment are required.[1] A dramatic increase in the number of cases of age-associated diseases, including dementia has been recorded worldwide, Alzheimer's disease (AD) being the frequent cause of dementia is mainly sporadic, and accounts for 60–80% of all cases, while genetic mutations cause a rare where the symptoms develop earlier, typically between 30 and 50 years of age. Though AD occurs in late life, its prevalence of occurring doubles every 5 years after the age of 65.[2] There is a marked increase in the occurrence of AD in women when compared to men and the underlying biological mechanisms for the increased incidence in women are still being investigated.

AD is most commonly associated with Age-related macular degradation (AMD) and glaucoma. Age-related macular degeneration (AMD) and glaucoma, the degenerative conditions of the retina the main causes of irreversible blindness in developed countries. Extracellular accumulation of amyloid β (Aβ) and deposition of hyper-phosphorylated tau (p-tau) are the main factors of AD that cause Neuroinflammation and brain iron dyshomeostasis. AMD is characterized by the accumulation of Aβ and iron in drusen, and p-tau accumulation in retinal ganglion cells (RGC), mainly implicated in glaucoma suggesting an overlapping pathology between AD and AMD.

Insights on common therapeutic options for diseases that share common pathological mechanisms could shed light on drug-repurposing approaches.

2. LINK BETWEEN AMD AND AD

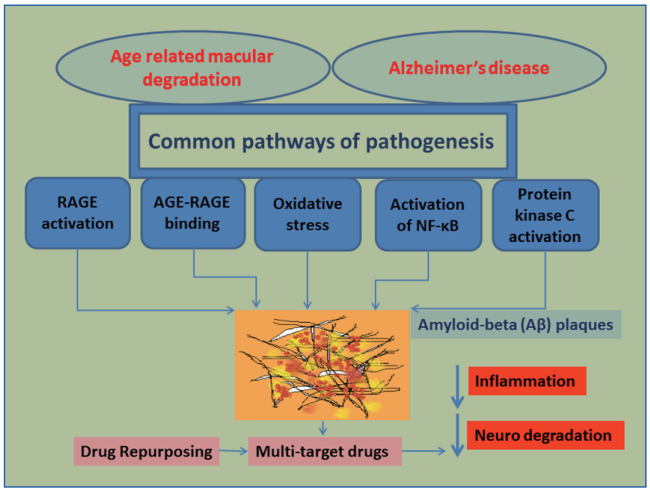
Advanced glycation end products (AGEs) are implicated in the induction of neurodegeneration by interacting with the receptors of AGE (RAGE) and are reported to play an important role in the pathogenesis of Alzheimer's disease (AD) and age-related macular degradation.[3] The link between AGE-RAGE signalling and AD pathology has not been studied extensively and exploited. Brain samples of AD reveal that AGE-RAGE regulates Amyloid Precursor Protein (APP) processing and tau phosphorylation in primary cortical neurons. An increase in tau phosphorylation is mediated by increased expression of cathepsin B and asparagine endopeptidase (AEP) induced by AGE-RAGE binding.[4]

Immunohistochemical localization of AGEs in the human brain suggests its contribution to neuronal dysfunction leading to the progression of various neurodegenerative diseases, including Alzheimer's disease.[5] Glycation of tau protein enhances the formation of paired helical filaments and also enhances its aggregation of amyloid β protein (Aβ). AGEs cause extensive protein crosslinking, oxidative stress, and neuronal cell death. RAGE expression in brains with non-demented and AD cases indicates RAGE expression paralleled the severity of AD. Apart from AGEs, Aβ serve as a ligand for RAGE. AGE inhibitors, RAGE-antagonists, and RAGE signaling inhibitors such as membrane-permeable antioxidants may be promising therapeutic strategies to slow down the progression of AD.[6]

AGE-RAGE plays multiple pathological roles including glial inflammatory amplification, alteration of neuronal properties and functions, increase in oxidative stress, amyloidosis, and vascular dysfunction. Interestingly, flavonoids have been researched for their anti-amyloidogenic properties along with their antioxidative, and anti-inflammatory properties and might offer protection from AD by interfering with the production and aggregation of Aβ peptides and/or decreasing the aggregation of tau. Flavonoids have also been reported to promote the clearance of Aβ peptides and inhibit tau phosphorylation by the mTOR/autophagy signaling pathway. Also, flavonoids represent anti-Alzheimer agents, due to their potency in inhibiting cholinesterase, enhancement of cognitive performance slows down the advancement of the disease pathogenesis.[7]

AGE-RAGE binding mediates activation of NF-κB, greatly associated with aging and a major risk factor of AD, reactive oxygen species (ROS) being the main inducer of NF-κB.[8] Activation of NF-κB transcribes several different proteins, including endothelin-1, ICAM (intercellular adhesion molecule-1), E-selectin, and VEGF (vascular endothelial growth factor), which are mainly responsible for neovascularization. Figure 1 schematically represents the factors involved in age related macular degradation and Alzheimer's disease.

Figure 1. Schematic representation of factors involved in age related macular degradation and Alzheimer's disease



3. PATHOLOGICAL SIMILARITIES BETWEEN AD AND AMD

AD is characterized by the formation of amyloid-beta plaques that accumulate in the brain tissues, interrupting signalling between the neurons similar to the Aβ deposits underneath the retina along with protein-lipid materials called drusen, in the progression of AMD.[9] Both the neurodegenerative diseases, AMD and AD, associated with increased age, share similar risk factors as well as histopathological features including the deposition of Aβ in ocular drusen and senile plaques. Other risk factors such as oxidative stress, inflammation, and complement activation are thought to be implicated in both diseases. Understanding the common pathways of pathogenesis could provide new insights into treating both diseases. Further research linking the diseases is needed for an effective treatment strategy.[10]

Flavonoids have shown beneficial effects by interaction with the neuronal signalling pathways. Several flavonoid-binding sites on neurons have been identified that can be exploited in research on neurodegenerative diseases. Flavonoids have the potency to interact with protein kinase and lipid kinase signaling cascades, such as the PI3K/Akt, tyrosine kinase, protein kinase C, and the nuclear factor-κB pathway.[11]

Though the potential of flavonoids in promoting memory, and cognitive function is well established and is mediated by their antioxidant capacity, low bioavailability due to limited absorption in the brain has been a major limitation. Increasing bioavailability could improve memory, protect neurons and induce neurogenesis.

4. MAIN TARGETS IN AD AND AMD

RAGE activation, AGE-RAGE binding, oxidative stress-induced activation of NF-κB that activates proinflammatory cytokines, and accumulation of Aβ are the main factors involved in the pathogenesis of AD and AMD.[12]

Aldose reductase inhibitors could act as multi-target drugs since they could inhibit the multiple factors that are involved in causing diabetic retinopathy; AGE-RAGE binding, NF-κB, protein kinase C, and the proinflammatory cytokines. Therefore, repurposing flavonoids that inhibit aldose reductase in the treatment of AD and AMD would be a heuristic approach.[13]

5. ANTI-INFLAMMATORIES TO TREAT AMD AND AD

Inflammation is a key factor in the etiology and progression of neurodegenerative disorders, and it is aided by innate immunity and autoimmune components. Anti-inflammatory agents such as corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressive agents (e.g., methotrexate and rapamycin), and biologics (e.g., infliximab, daclizumab, and complement inhibitors) may provide an adjunct or alternative mechanism to suppress the inflammatory processes driving AMD progression. Both neovascular and non-neovascular AMD must be evaluated in efficacy and safety studies on the long-term use of these medicines.

Because of the inflammatory involvement in AMD, the traditional treatment that focuses primarily on decreasing angiogenesis may not be appropriate. Anti-inflammatory drugs may be effective as preventative or adjuvant treatments in conjunction with anti-VEGF therapy since inflammation develops early in AMD pathogenesis. Patients with AMD who do not respond to traditional anti-VEGF medication may benefit from anti-inflammatory therapy.[14]

Inflammation has also been linked to the development of Alzheimer's disease, marked by gradual cognitive impairment, the major worldwide health problem. Although various molecular mechanisms in the pathogenesis of Alzheimer's disease are well understood, innovative therapeutic agents with the potential to change disease activity are still missing.

6. NEURODEGENERATIVE DISEASES THAT SHARE SIMILAR PATHOLOGICAL PATHWAYS

A strong relationship exists between the major pathways of neurodegeneration increasing the pressing need for biomarker identification.

Aging is the major risk factor for neurodegenerative diseases since an impairment of self-repair occurs. Aging is associated with functional impairments such as dementia and motor neuron disability in neurodegenerative diseases such as AD and (Parkinson's disease) PD. At the cellular level, aging is associated with accumulating oxidative stress, declining mitochondrial function, impaired DNA repair, and decreased tissue regeneration take part in the development of AD and PD. However, the increase of free radicals in the brain is not caused by the elevation of oxidative stress. Studies show that the activities of superoxide dismutase (SOD), catalase, glutathione peroxidase, and glutathione reductase were reduced in affected brain regions in AD and PD. As mitochondrial efficiency declines with age, several observations have led researchers to speculate that mitochondrial dysfunction may contribute to the formation of misfolded protein aggregates and subsequently lead to AD and PD.[15]

7. MULTI-TARGET DRUGS AND INTERVENTIONS

The expression of pro-inflammatory cytokines results in neuronal cell death, and neuroinflammation is the primary mechanism underlying the progression of many neurodegenerative illnesses, including Parkinson's, Alzheimer's, and multiple sclerosis. Few natural substances have been thoroughly investigated for therapeutic usage, despite the fact that their neuroprotective potential has been evaluated for their capacity to control the inflammatory responses associated with neurodegenerative disorders, such as flavonoids.[16] In order to prevent brain injury, quercetin, genistein, and epigallocatechin-3-gallate have been shown to down-regulate inflammatory markers and inhibit the expression of pro-inflammatory cytokines (IL-6, TNF-, IL-1, and COX-2). Microglial cells are principally responsible for this anti-inflammatory function, which is mediated via their effects on the NF-B signalling pathway and a number of other variables that reduce inflammation and prevent neuronal degeneration.[17]

It has been observed that the flavonol taxifolin, which has potent anti-oxidative and anti-glycation properties, can break down amyloid-β *in vitro*.[18] When taken orally, taxifolin increased cerebral blood flow, reduced inflammation, glutamate levels, oxidative tissue damage, and amyloid-β buildup in the brain, and prevented cognitive impairment.[19] Further taxifolin restored decreased cerebral blood flow and cerebrovascular reactivity by disassembling amyloid-β and proved to have therapeutic potential in attenuating cerebral amyloid angiopathy (CAA).[20]

Several in vitro and in vivo studies have shown that flavonoids can act within processes and pathways relevant to AD, such as Aβ and tau pathology that increase inflammation, and oxidative stress.[21] Though flavonoids are therapeutically proven to be effective

for neurodegenerative diseases, lack of mechanistic data on metabolism and bioavailability of flavonoids in vivo have limited their use.

8. CONCLUDING REMARKS

AD and AMD share similar pathways involved in neurodegeneration. The pathophysiology of both diseases is similar with similar targets. The involvement of multiple factors including RAGE activation, AGE-RAGE binding and oxidative stress-induced activation of NF-κB suggests the application of multi-target drugs for the treatment of neurodegenerative diseases.

Repurposing compounds with anti-inflammatory, anti-glycation, and anti-oxidant properties to treat neurodegenerative disorders could be a heuristic approach to cause a positive difference along with a reduction in time to identify novel drugs and hence could hold promising benefits.

AUTHOR CONTRIBUTION

All the authors contributed equally to the manuscript.

CONFLICTS OF INTEREST

The Authors declare that there is no conflict of interest.

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