Review

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Role of erythropoietin in the treatment of Alzheimer's disease: the story so far

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Abstract

This review aims to explore the potential of erythropoietin, a glycopeptide hormone, as a treatment option for Alzheimer's disease, which is the commonest cause of dementia. Despite years of focus and research, therapeutic options for Alzheimer's disease are not yet completely satisfactory. And as people age, they are likely to develop Alzheimer's Disease, further pressuring the healthcare system. So, it is definite to develop treatment options that meet superior outcomes with minimal negative effects. A comprehensive review of the literature was conducted in PubMed and Google Scholar using a combination of keywords, including Alzheimer's disease, dementia, erythropoietin, and neuroprotection. Search results were assessed for relevance before using the data for this study. The beneficial implications of erythropoietin as a therapeutic option have been explored, along with the side effects and mechanisms of erythropoietin in Alzheimer's disease. Overall, the authors' review indicates that erythropoietin presents a promising avenue for mitigating the progression of Alzheimer's disease, with minimal associated side effects.

Keywords: Alzheimer's disease, dementia, erythropoietin, neurodegenerative diseases, neuroprotection

Introduction

Alzheimer's disease (AD) is an irreversible, progressive, degenerative neurological disorder characterized by cognitive decline, memory loss, and behavioural problems resulting in impairment of daily activities. The condition is driven by the accumulation of beta-amyloid protein in the brain resulting in irreversible neuronal death and brain damage[1]. AD is the most common type of dementia accounting for 50–70% of cases[2,] and affects more than 50 million people globally[3]. The WHO estimates that between 5 and 8% of people over 60 have dementia, with Alzheimer's disease being the most prevalent kind[4]. As of now, it is estimated that 6.5 million Americans aged 65 and older are living with AD, by the year 2060, this number is projected to reach 13.8 million[5].

HIGHLIGHTS

- Oxidative stress damages DNA and other cellular components, exacerbates inflammatory response, and aggravates neuronal degeneration and so dementia.
- Erythropoietin (EPO) receptors are also expressed in neural cells, and EPO has shown neuroprotective effects by reducing oxidative stress damage, Aβ accumulation and limiting tau phosphorylation.
- EPO has a pro-coagulant activity, and to overcome this, nasal EPO/neuroEPO is developed.
- So far only one clinical trial was conducted in humans, which concluded improved clinical outcomes with negligible adverse outcomes.
- Our study suggested that EPO presents a promising avenue for mitigating the progression of Alzheimer's disease, with minimal associated side effects.

Since there is currently no cure for AD, available therapies focus on symptom relief and delaying the onset of the illness. Acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists are the two most used pharmacological treatments for AD[6,7]. Also, these medications are accompanied with a number of negative effects and have a limited efficacy[8]. And attempts are continuously made for a new therapeutic approach for AD. Despite significant efforts over the past 35 years, the cognitive decline associated with AD has remained frustratingly resistant to prospective disease-modifying therapies with billions of dollars invested so far. However, recently, erythropoietin (EPO), a hormone that controls red blood cell synthesis, has been demonstrated to have neuroprotective and neurotrophic effects in various neurological conditions like stroke, traumatic brain injury, multiple sclerosis[9,10].

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EPO exhibits a range of mechanisms that contribute to neuroprotection, including promoting angiogenesis, reducing inflammation, and enhancing spasticity. With this new development, EPO has been studied as a potential treatment drug for AD.

This review will assess the findings of preclinical and clinical studies, evaluate efficacy and safety of EPO in AD patients. This review will also consolidate potential mechanisms of action of EPO in AD, adverse effects of EPO as well as prospective future research avenues.

Methods and results

Databases, PubMed, Web of Science and Google Scholar, were selected for a thorough search of all original research without time restrictions by a selected set of key terms, "Erythropoietin," "Alzheimer's Disease," "Neuroprotection," and "Dementia." We used our inclusion and exclusion criteria to reduce the number of publications because we generated a large number of papers. Articles written in the English language up until 18 September 2022, the last day of our data search, are included in the inclusion criteria. Additionally, we considered animal studies, adults, and kids of all ages as well as teenagers aged 0–18. Letter to editors and articles in a non-English language was put under the exclusion criteria.

We discovered 12 542 articles. Following the application of exclusion and inclusion criteria, 5083 articles could be eliminated. Because of duplicates or issues with their titles and abstracts, we chose not to use 5313 of the remaining 7459 papers. After reviewing the remaining 2146 papers, we eliminated 2128 more because of the study design, methodology, relevance to the research question, quality of data, publication type, adherence to ethical guidelines, ability to access the article.

We used various quality assessment tools to determine the eligibility of the papers we chose. The Newcastle–Ottawa instrument Scale for non-randomized clinical trials served as a quality assessment instrument. For qualitative research, we employed the Critical Appraisal Skills Programme (CASP) Checklist. If not possible to classify an article, we choose to evaluate its quality using the Scale for the Assessment of Narrative Review Articles (SANRA) scale. The extracted data is tabulated in the Tables 1–3 for the convenience of the reader.

Animal studies

Table 1.

Clinical studies of EPO in Alzheimer

A comprehensive search on the clinical use of EPO in AD yielded only one human clinical trial, published in 2020 and one case report, published in 2018.

Table 2.

Following studies were not conducted in AD patients but studied the effect of EPO on domains related to AD

Table 3.

Discussion

Alzheimer's disease

Despite studies on AD dating back long, several areas related to cause, pathogenesis of the disease are still in grey areas. There are various recognized risk factors that contribute to the development and progression of the disease. Age is the strongest risk factor for AD, and the risk of AD exponentially rises with age, and it is more prevalent in people over 65[29]. This is attributed to the buildup of cellular damage over time, which results in a breakdown of cellular functions and, ultimately, AD pathology[30]. Genetics is also a well-recognized risk factor for AD. The apolipoprotein E (APOE) 4 allele is the most well-known genetic risk factor for AD. Individuals carrying one or two copies of the APOE 4 allele have a heightened risk of developing AD[30]. This allele is implicated in AD pathogenesis through mechanisms such as increased amyloid-beta deposition, inflammation, and impaired clearance of amyloid-beta from the brain[31,32]. Cardiovascular disease (CVD) is one of the most important modifiable risk factors for AD[33] with other lifestyle factors like physical inactivity, poor diet, and smoking also contributing to the progression of AD[34]. Recent research has also emphasized the significance of the gut microbiome in the development of AD, even though the processes behind this association are still poorly understood[35]. Along with environmental factors[35] and social factors[36], Traumatic brain injury (TBI) has also been tagged to the risk factors for AD[37]. A single severe TBI is known to increase AD risk by up to fourfold[38].

The pathophysiology of AD involves multiple overlapping mechanisms - accumulation of Aβ peptides, neurofibrillary tangles, oxidative stress, inflammation, all leading to synaptic dysfunction. Accumulation of Aβ peptides is the pathological hallmark of AD, and these peptides derive from amyloid precursor protein (APP) through secretase action, forming Aβ plaques. These plaques induce inflammation and oxidative stress, creating a toxic environment for neurons[39] and also stimulating microglial and astrocytic cells. These cells release pro-inflammatory cytokines and chemokines, further aggravating the inflammation[40]. Oxidative stress intensifies this inflammation and neuronal degeneration by damaging DNA and other cellular components[41]. Another characteristic of AD is the development of neurofibrillary tangles, which are caused by the aggregation of hyperphosphorylated tau protein leading to cytoskeleton disruption and neuronal dysfunction[42]. All these pathological changes contribute to synaptic dysfunction, which is an early finding during the progression of the disease[43].

Therapy options

Both cognitive and non-cognitive symptoms are part of the clinical characteristics of AD with cognitive symptoms being the hallmark of AD. Cognitive symptoms include memory loss, language problems, and deteriorated judgment and spatial reasoning[44]. These cognitive symptoms deteriorate progressively, resulting in significant impairment of cognition and diminished independence over time[45]. Changes in mood, conduct, and personality, as well as disturbed sleep patterns and agitation, can all be non-cognitive signs of AD[46]. Further progression of the disease may result in physical symptoms such as weight loss, appetite loss, movement and balance issues[47,48]. For the management of symptoms and enhancement of quality of life, early AD diagnosis and therapy are essential.

As mentioned in the introduction part of this paper, current pharmacological therapies are not curative and focus on relieving symptoms and providing comfort for patients. AChEIs and NMDA receptor antagonists are the current pharmacological

Table 1

Animal studies.

S No.	Primary author	Animals	EPO treatment regime	Comment
1	Li *et al.*[11]	Aβ42-injected mice	Intraperitoneal administration of EPO	Study discovered that intraperitoneal EPO administration effectively stopped tau hyperphosphorylation and attenuated A-induced memory impairments.
2	Chang *et al.*[12]	10 male APPswe/PSEN1dE9 (APP/PS1) transgenic mice	BBB-penetrable analogue of EPO (fused EPO to a chimeric monoclonal antibody targeting the transferrin receptor)	The fusion protein offered therapeutic benefits compared to the control mice group. The study did not report any side effects that are usually seen in high doses of EPO uses.
3	Rodríguez Cruz *et al.*[13]	APPSwe (Tg2576) mice, a transgenic model of AD	Intranasal EPO	In a transgenic mouse model of AD, this study showed the neuroprotective activity of intranasal EPO, free of erythropoietic side effects.
4	Cevik *et al.*[14]	24 Sprague-Dawley adult rats, divided into 4 groups	Recombinant human erythropoietin (rhEPO) administered intraperitoneally	The study suggested rhEPO may be beneficial for treating AD
5	Arabpoor *et al.*[15]	A rate model of AD (bilateral intracerebroventricularly streptozotocin injected mice)	EPO administered through intraperitoneal route	The histological findings demonstrated that EPO greatly enhances neuronal growth in the dentate gyrus of the hippocampus.
6	Khairallah *et al.*[16]	45 adult male mice were divided equally into 3 groups	EPO given Intraperitoneally	This study established that EPO has great neuroprotective and neurotrophic properties by increasing gene expression of brain derived neurotrophic factor (BDNF).
7	Dara *et al.*[17]	7 Albino male Wistar rat groups	Intravenous EPO-loaded Solid Lipid Nanoparticle (EPO-SLN)	The results of this study suggested that EPO-SLN may be able to prevent the impairment of spatial recognition memory caused by Aβ deposition. This study also showed that when coupled to lipid nanoparticles, the positive benefits of EPO could be increased at lower dosages.
8	Choi *et al.*[18]	Female transgenic PS 19 mouse strain	JM4-a 19'mer cyclic peptide derived from the first loop of human erythropoietin, administered subcutaneously.	Initiated prior to the onset of the disease, JM4 therapy reduced neurological deficiency, increased lifespan, and rescued memory impairment in mice.
9	Moosavi *et al.*[19]	4 groups of In-house breeding adult male Wistar rats weighing 250 – 350 g (each group has n = 8)	Carbamylated Erythropoietin-Fc (CEPO-Fc), administered intraperitoneally	Study results indicate that CEPO-Fc may be able to reverse the learning and memory deficits caused by Intracerebroventricularly streptozotocin administered mice, a metabolic model of sporadic AD
10.	Esmaeili Tazangi *et al.*[20]	Male Sprague-Dawley rats weighing 200–250 g were used in this study	Intraperitoneal EPO	EPO therapy improved memory impairments brought on by Aβ which is likely mediated through increasing the release probability of neurotransmitter vesicles
11.	Hooshmandi *et al.*[21]	Adult male Wistar rats weighing 250-350 g were used	Carbamylated erythropoietin-Fc (CEPO-Fc) was injected peritoneally	An EPO derivative called CEPO-Fc protects the hippocampus from Aβ-induced memory loss.

AD, Alzheimer's disease; EPO, erythropoietin.

options for AD[6,7]. Non-pharmacological approaches that improve cognitive functions in AD patients include lifestyle changes such as healthy diet, regular physical activity and social changes such as social engagement, joining peer groups[49].

Monoclonal antibodies like Aducanumab, which slows the progression of disease by targeting Aβ are also approved for the treatment of AD[50]. However, the potential negative effects and long-term efficacy of these monoclonal antibodies are still being investigated. Additionally, medications like levetiracetam, an antiepileptic drug, and cromolyn, an anti-allergic medication, are showing potential to reduce amyloid-beta accumulation and improve cognitive function[51,52]. Targeting tau therapies[53],

Table 2

Clinical studies of EPO in AD.

S No.	Primary author	Patients	Administration of the drug	Comparison	Side effects	Comment
1	Pérez *et al.*[22]	69 (Clinical Trial	Dose of 0.5 or 1.0 mg 3 times a week for 48 weeks was administered by nasal route for a period of 48 weeks	Placebo	No serious adverse events related to NeuroEPO were reported.	NeuroEPO improves clinical outcomes in patients with AD with a good security profile. Therefore, it could be useful in the treatment of AD.
2	Kumaga *et al.*[23]	1 (case report)	EPO preparation once per 2 weeks, for a total of six doses1			Erythropoietin preparation drastically improved activities of daily living.

AD, Alzheimer's disease; EPO, erythropoietin.

Table 3

Other relevant studies.

S No.	Primary author	Type of study	Patients	EPO	Comment
1	Pickett *et al.*[24]	Clinical trial	20 patients with End stage renal disorder (ERSD).	rHuEPO	Patients on anaemic dialysis have shown improved brain and cognitive function after receiving rHuEPO treatment.
2.	Ehrenreich *et al.*[25]	Clinical trial	8 patients with Multiple Sclerosis (5 patients received 48 000 IU and 3 patients received 8000 IU)	rHuEPO	low-dose EPO (8000 IU) did not significantly improve cognitive function in MS patients' condition compared to High -dose (48 000). This failure may be explained by the insufficient concentration of EPO that was achieved in the central nervous system.
3	Miskowiak *et al.*[26]	Clinical trial	12 healthy volunteer patients	rHuEPO	One week after delivery, EPO increased memory-relevant hippocampus response, consistent with greater hippocampal plasticity, and good memory.
4.	Miskowiak *et al.*[27]	Clinical trial	12 healthy volunteer patients	rHuEPO	This follow-up study supports the theory that the hippocampal effect observed after one week may be mediated by neuroplasticity mechanisms rather than spillover effects of neurotransmitter release as EPO had no effect on memory-related hippocampal response on day 3.
5	Hung *et al.*[28]	Retrospective study	43 906 adults with ESRD on haemodialysis were analyzed retrospectively.	rHuEPO	Regardless of whether EPO is used alone or in conjunction with iron, findings imply that the use of EPO drugs in HD patients is linked to a decreased risk of Vascular dementia and Unspecified Dementia, but not AD.

AD, Alzheimer's disease; EPO, erythropoietin; HD, Hemodialysis; MS, Mutiple sclerosis.

Deep brain stimulation (DBS)[54], and EPO[55] are some of the new options, currently being researched.

Erythropoietin

Human EPO, a 165-amino acid protein with a molecular weight of ~30 kDa, is a highly glycosylated hormone with the primary function being the regulation of erythropoiesis. While the primary source of EPO is the kidney, it is also expressed in the liver, brain and uterus[56,57]. By binding to EPO-receptor (EPOR) on the surface of erythroid progenitor cells, EPO activates JAK2 (Janus kinase 2) and subsequently phosphorylates EPOR[58]. As a result, several signalling pathways, such as the Ras/MAPK (mitogen-activated protein kinase), PI3K (phosphatidylinositol 3-kinase)/AKT (protein kinase B), and STAT (signal transducer and activator of transcription) pathways, become activated downstream. These pathways in turn promote the growth, differentiation, and survival of erythroid progenitor cells[58].

EPO is primarily used to treat anaemia. So, patients with chronic kidney disease, cancer chemotherapy, and HIV infection are greatly benefited from the use of EPO[59]. However, overusing it has negative consequences. One of its most important side effects is an increased risk of thrombosis (blood clots), due to EPO's pro-coagulant activity[60]. Aydin *et al*. study revealed that high dose EPO (33 000 IU per day for a total of 100 000 IU) significantly enhanced the incidence of thrombotic events[61]. According to Cariou *et al*.[62], patients receiving high doses of EPO (40 000 IU daily for a total of 200 000 IU) experienced thrombotic problems more frequently than patients in the control group (EPO $=12.4\%$, Control $=5.8\%$, $P=0.01$). EPO use has also been linked to a higher risk of hypertension, seizures, and cardiovascular events[63].

EPO use is also associated with decreased overall survival in cancer patients taking chemotherapy[64]. However, prolonged EPO use in cancer patients resulted in the creation of neutralizing antibodies that lessen the hormone's efficacy and resulted in pure red cell aplasia (PRCA)[65]. One more constraint for the use of EPO is its low blood-brain barrier (BBB) penetration capacity[66] and so requires higher concentrations thereby more prone to adverse effects. So, recent research has concentrated on creating EPO derivatives with little side effects and efficient neural penetration. This led to the development of NeuroEPO and has had fruitful outcomes thus far[67].

EPO in AD

EPO receptors are also expressed in neural cells and EPO has shown neuroprotective effects[68]. Several pathways are proposed for the role of EPO in improving Alzheimer's disease—reducing Aβ accumulation, limiting tau phosphorylation[69], and neuronal regeneration[70]. Also, it has been shown that EPO enhances synaptic plasticity (the ability of neurons to establish and repair connections with other neurons) by increasing neurotransmitter release and the growth of new synapses. This synaptic plasticity is required for learning and memory functions, which is diminished in AD[11].

In addition, EPO decreased the inflammation by preventing the activation of microglia cells[71,72], and enhances angiogenesis in the brain tissue[73]. This is supported by the observation that EPO usage improved cerebral glucose metabolism in the brain[74]. All these mechanisms promote cognitive improvement in patients suffering from AD. Very recently, Shim *et al.*[75] conducted an in-vivo protein assay for the hippocampus and cortex tissue in AD mice model and indicated that Dopamine, serotonin, and adrenaline are among the neurotransmitters that are modulated by EPO medication. The serotonin receptor's activity was significantly restored by EPO therapy and proposed that the EPO administration might be therapeutic for AD by activating the serotonergic pathway. A schematic presentation of possibles mechanism by which EPO exerts it effects is presented in Figure 1.

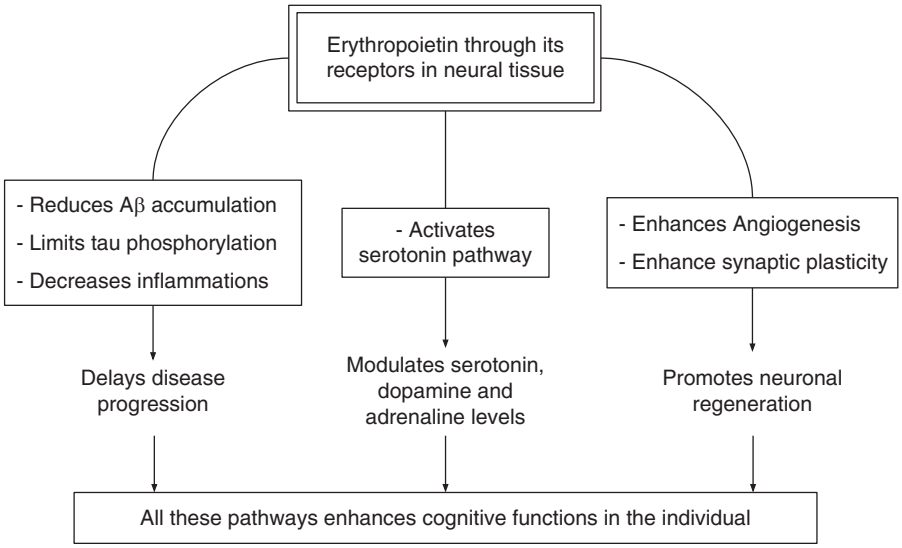

Figure 1. Schematic presentation of possibles mechanism by which erythropoietin exerts it effects.

Limitations

This idea to use EPO in AD has originally emerged from the finding that ESRD who were on EPO have shown improved brain function[76] by targeting multiple pathways. Preclinical studies demonstrated substantial advantage of EPO in AD model animals; but translating to humans is challenging, with only one trial conducted. Even while this experiment showed better results with little adverse effects, there is still uncertainty about wider safety. Related research demonstrated improved cognition, better results, and neuroprotection, suggesting not only a delaying the progression but also a possible therapeutic method. Validation is necessary, although. To evaluate EPO's long-term effects on participants and ascertain the sustainability of neuroprotective benefits after treatment cessation, more research is necessary.

Conclusion and future prospects

The serious public health problem of Alzheimer's disease needs to be addressed immediately. Considering the enormous interest in this therapeutic strategy, the scarcity of strong data and evidences have remained a rather disappointing element. Investigations are currently ongoing to determine the precise pathways through which EPO exerts its neuroprotective benefits, yet with the information available so far, EPO as a promising avenue for mitigating the progression of Alzheimer's disease and might even be curative, pending future research. With its neuroprotective and neurotrophic effects, it is a viable contender for the therapy of this chronic disease. However, to completely comprehend the potential advantages of EPO in treating Alzheimer's disease and to establish the ideal dosage and treatment plans, more clinical trials involving a large number of subjects are required. Also, further research must be done for the long-term effectiveness, route of administration, type of EPO, safety of the drug with studies so far suggesting the use of low-dose EPO/neuroEPO to reduce adverse effects.

The future healthcare must take into consideration the secular trends and device efficient treatment strategies for better delivery of the drug and minimizing the side effects. Molecular Trojan Horse Technology might be the solution, pending further research. Also, with its neuroprotective effects EPO can be studied as a curative option in other neurodegenerative diseases.

Ethical approval

Ethics approval was not required for this review.

Consent

Informed consent was not required for this review.

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Author contribution

P.K.R. suggested the concept first. P.K.R., S.B., S.V. further developed the idea, searched the databases, went through the articles and screened them. R.R.G., M.M., S.S. contributing by extracting and compiling the data. C.R.G. and S.R.G. contributed by structuring the article, checking the references, verifying the data. All the authors contributed to the writing and approved the final manuscript.

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None of the authors have conflicts of interest to disclose.

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Guarantor

All the authors are the Guarantor for this work.

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None.

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