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MINIREVIEWS

Linking multiple pathogenic pathways in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a chronic neurodegenerative disorder presenting as progressive cognitive decline with dementia that does not, to this day, benefit from any disease-modifying drug. Multiple etiologic pathways have been explored and demonstrate promising solutions. For example, iron ion chelators, such as deferoxamine, are a potential therapeutic solution around which future studies are being directed. Another promising domain is related to thrombin inhibitors. In this minireview, a common pathophysiological pathway is suggested for the pathogenesis of AD to prove that all these mechanisms converge onto the same cascade of neuroinflammatory events. This common pathway is initiated by the presence of vascular risk factors that induce brain tissue hypoxia, which leads to endothelial cell activation. However, the ensuing hypoxia stimulates the production and release of reactive oxygen species and pro-inflammatory proteins. Furthermore, the endothelial activation may become excessive and dysfunctional in predisposed individuals, leading to thrombin activation and iron ion decompartmentalization. The oxidative stress that results from these modifications in the neurovascular unit will eventually lead to neuronal and glial cell death, ultimately leading to the development of AD. Hence, future research in this field should focus on conducting trials with combinations of potentially efficient treatments, such as the combination of intranasal deferoxamine and direct thrombin inhibitors.

Key words: Alzheimer's disease; Etiologies; Iron; Oxidative stress; Thrombin; Vascular risk factors

Core tip: Patients with Alzheimer's disease (AD) have not benefited from any disease-modifying drug until now. Multiple etiologic pathways have been explored and suggest promising solutions in the

future. The iron chelator deferoxamine is one potential therapeutic solution around which future studies are being directed. Another potential therapeutic solution is related to thrombin inhibitors. In this minireview, a common pathophysiological pathway is suggested for the pathogenesis of AD that is initiated by the presence of vascular risk factors inducing brain tissue hypoxia and endothelial cell activation. In predisposed individuals, this can lead to thrombin activation and iron decompartmentalization. The resulting oxidative stress will eventually lead to neuronal and glial cell death.

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INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disorder presenting as progressive cognitive decline with dementia[1-3]. In spite of considerable research, proven disease-modifying drugs are still lacking[1-3]. Currently, all phase 3 drug trials have failed to produce the desired results[1-3]. An increasing amount of literature now supports the vascular-neuronal axis hypothesis in the pathogenesis of AD owing to common risk factors for both AD and cardiovascular conditions[4]. However, it has also become widely established that disturbance in cerebral iron homeostasis also participates to the genesis of AD[5]. In this review, we will attempt to link these multiple physiopathological pathways to prove that these mechanisms converge onto the same cascade of neuroinflammatory events.

VASCULAR RISK FACTORS AND AD

Diagnostic criteria categorize dementias into vascular dementias or AD dementias even though mixed forms are frequently encountered[6]. In fact, as presented in a recent review by Hooijmans *et al*[7], there is an increasing amount of literature supporting the fact that cardiovascular risk factors (*i.e.*, diabetes, hypertension, dyslipidemias) are predisposing factors for vascular and AD dementias, and because the clinical manifestations and pathological findings are also common, the two conditions should not be seen as separate. Accordingly, there seems to be a direct increase in the risk for dementia, including AD, in the presence of these cardiovascular risk factors[8-13]. Hypertension and atherosclerotic disease both bring about vascular changes, causing alterations in the blood brain barrier and cerebral ischemia. Ultimately, this will initiate the pathological process of AD[7]. Indeed, there is *in vitro* and pathology evidence concerning chronic localized brain ischemia as playing a crucial role in the genesis and progression of AD. The ensuing hypoxia stimulates the production and release of reactive oxygen species and pro-inflammatory proteins[14]. There also appears to be data concerning vascular risk factors and cardiovascular diseases as potentially being able to quicken Aβ 40-42 production, aggregation, and precipitation[6]. On another level, there is also evidence that endothelial dysfunction, due to cerebrovascular risk factors that include diabetes and hypoxia, precedes cognitive decline in AD and might contribute to its pathogenesis through the activation of thrombin[15].

The hypoxia inducible factor 1 (HIF-1) is a sensor for hypoxia, and its levels are increased in the cerebral circulation in both mouse and human models of AD[14]. However, an increasing amount of literature is in favor of an elevation in pro-inflammatory substances in the endothelium of the cerebral microcirculation in oxygen-deficient conditions[14]. Together, those results suggest a relationship between hypoxia and inflammation in the brain. Another phenomenon that occurs in response to hypoxia is the secretion of a strong inducer of angiogenesis known as vascular endothelial growth factor (VEGF). In AD, however, the vascular response to VEGF is deficient, resulting in an increased production of pro-inflammatory and neurotoxic substances[14].

In conclusion, recent studies are in favor of targeting vascular risk factors *via* lifestyle adjustments (physical exercise, dietary modification and abstinence of smoking) and medications (namely, cholesterol-lowering drugs) to preserve cognitive functions in the aging population and to reduce the progression toward AD. This seems to occur through the reduction of chronic focal ischemia and hypoxia in the brain, which are both harbingers of cerebral inflammation and oxidative stress[7,16].

THE EFFECT OF THROMBIN ACTIVATION IN AD

Thrombin has been demonstrated to be a key regulator of the pro-inflammatory reaction of cerebral endothelial cells in response to ischemic changes[13]. Moreover, prothrombin and thrombin are widely expressed in neurons and particularly in neurofibrillary tangles and senile plaques. This hypothesizes that thrombin could have a role in tau degradation and that a deficiency in this process could cause tau protein accumulation[17,18]. In an animal model on rats, direct intra-cerebral injection of thrombin caused in neuronal death and subsequent cognitive impairment[19]. Likewise, it was shown that thrombin can directly exert neurotoxic effects[20]. Thus, introduction of heparin, an indirect thrombin inhibitor, in the arsenal of AD medications hoped it could enhance the brain's micro-vasculature *via* its antithrombotic properties[21]. Accordingly, rats of advanced age displayed a partial but significant improvement of behavioral problems after heparin injection[22]. Moreover, an animal experiment demonstrate protective actions of heparin after injection of amyloid peptide into the amygdala[23]. Furthermore, due to the potential side effects of long-term treatment with heparin, it has been suggested that a more specific treatment that directly inhibits thrombin would be more appropriate in terms of safety and efficacy. Indeed, direct thrombin inhibitors, such as dabigatran, would be a better choice because of their high selectivity in the inhibition of thrombin activity, thus ensuring a better side effect profile than an indirect inhibitor, such as heparin[15,24]. Dabigatran is a competitive reversible non-peptide antagonist of thrombin. Thrombin has many functions: Fibrinogen transformation into fibrin, fibrin strengthening and cross-linking, stimulation of additional thrombin production, platelet activation, and stimulation of protein C, which increases pro-thrombotic activity. Dabigatran inhibits most of these steps[25].

THE EFFECT OF VASCULAR RISK FACTORS ON ERYTHROCYTE LYSIS AND IRON DEPOSITION

Iron is crucial for the metabolic demands and functions of numerous cells, but when dysregulated, iron can become potentially harmful for these same cells. Iron circulates with the action of its transporter transferrin, which binds iron released in the blood from two sources: Enterocytes (following absorption) and the reticulo-endoplasmic cells. The iron-transferrin complex binds to the transferrin-receptor-1 so that it can be internalized within cells. Iron then enters mitochondria, where it takes part in heme synthesis. Superfluous iron is stowed and detoxified in ferritin[26].

In the central nervous system, iron, a key component for many proteins essential for brain metabolism, is predominantly concentrated in the motor system, and more specific, within glial cells[27,28]. Evidence supports the fact that iron deposition might exert a neurotoxic effect. For example, intracerebral hemorrhage causes extraversion of red blood cells (RBCs) into the parenchyma followed by hemolysis and decompartmentalization of iron, which later promotes long-term neurological deficits and brain atrophy[29-31]. In humans, iron deposition in the endothelium and vascular media is strongly associated with the progression of atherosclerotic lesions[32]. Indeed, atherosclerotic plaques with subsequent neovascularization and intra-plaque hemorrhage may constitute an important source of iron deposition in blood vessels and the brain parenchyma, but in a more localized fashion than what is observed after an intracerebral hemorrhage. Furthermore, in atherosclerotic plaques, cholesterol crystals coincide with glycophorin A (distinctive protein of red cell membranes), implying cholesterol from erythrocyte membranes could participate in the deposition of lipids and expansion of the lipid core following intra-plaque bleeding[33]. Moreover, some data support the fact that hypercholesterolemia might enhance the crossing of iron into the brain parenchyma *via* an augmentation of endothelial permeability to iron[34]. Hence, the potential efficacy of cholesterol-lowering agents (*i.e.*, statins) in slowing the progression towards AD might be related to their indirect neuroprotective actions of preventing iron-induced neurotoxicity[34-36].

During an intra-plaque hemorrhage, red cells penetrate the oxidative environment of atherosclerotic lesions containing cytotoxic products of lipid peroxidation that can trigger the lysis of RBCs[37]. Hemoglobin released outside RBCs is oxidized and will release high-valence iron compounds with potent oxidative and inflammatory activities[38]. These activities can increase vascular endothelial activation and subsequent thrombin release. However, the known *in vitro* effect of iron ions on thrombin activity is in favor of the inhibition of its clot-forming effect[39].

EFFECT OF IRON DEPOSITION ON AD

In 1991, the first study evaluating the effect of deferoxamine (DFO) in patients suffering from AD was published[40]. DFO was evaluated because of its aluminum chelating properties and because of the evidence linking this metal ion to AD[40]. The study concluded that DFO may slow the progression of AD[40]. However, since then, additional evidence has linked the other metal ion chelated by DFO, iron, with the pathogenesis of AD. In patients with AD, iron accumulation in the cerebral cortex and hippocampus co-localizes with neurofibrillary tangles and senile plaques[41]. In their review, Peters *et al*[42] hypothesized that amyloid production is actually amplified to compensate for excessive iron levels and "patch" the subsequent vascular damage. High neuronal levels of iron stimulate amyloid protein precursor translation, and along with concomitant abnormal secretase activity, increase extracellular Aβ-42 deposition and tau protein phosphorylation. Peters *et al*[42] concluded the finding that increased iron deposition increases amyloid production emphasizes the importance of iron management in the treatment of AD.

The ability of iron to interact with oxygen is crucial for cell functioning, but it is also a source of free radicals according to Fenton's reaction: $Fe^{+n} + H_2O \rightarrow Fe^{+(n-1)} + OH^{-}$ (hydroxyl radicals).

Reactive oxygen species that are formed through this reaction subsequently damage intracellular structures *via* lipid peroxidation, or induction of DNA mutations[43]. In a 2015 review on vascular dysfunction in AD, Di Marco *et al*[14] fact found that high levels of lipid peroxidation and DNA oxidation were a frequent observation in AD. Furthermore, they posited that the blood-brain barrier is a central player in oxidative-stress-related tissue injury, in that it is both a source and a target of reactive oxygen species and pro-inflammatory substances. This hypothesis was based on the observation that Aβ plaques contain redox-active

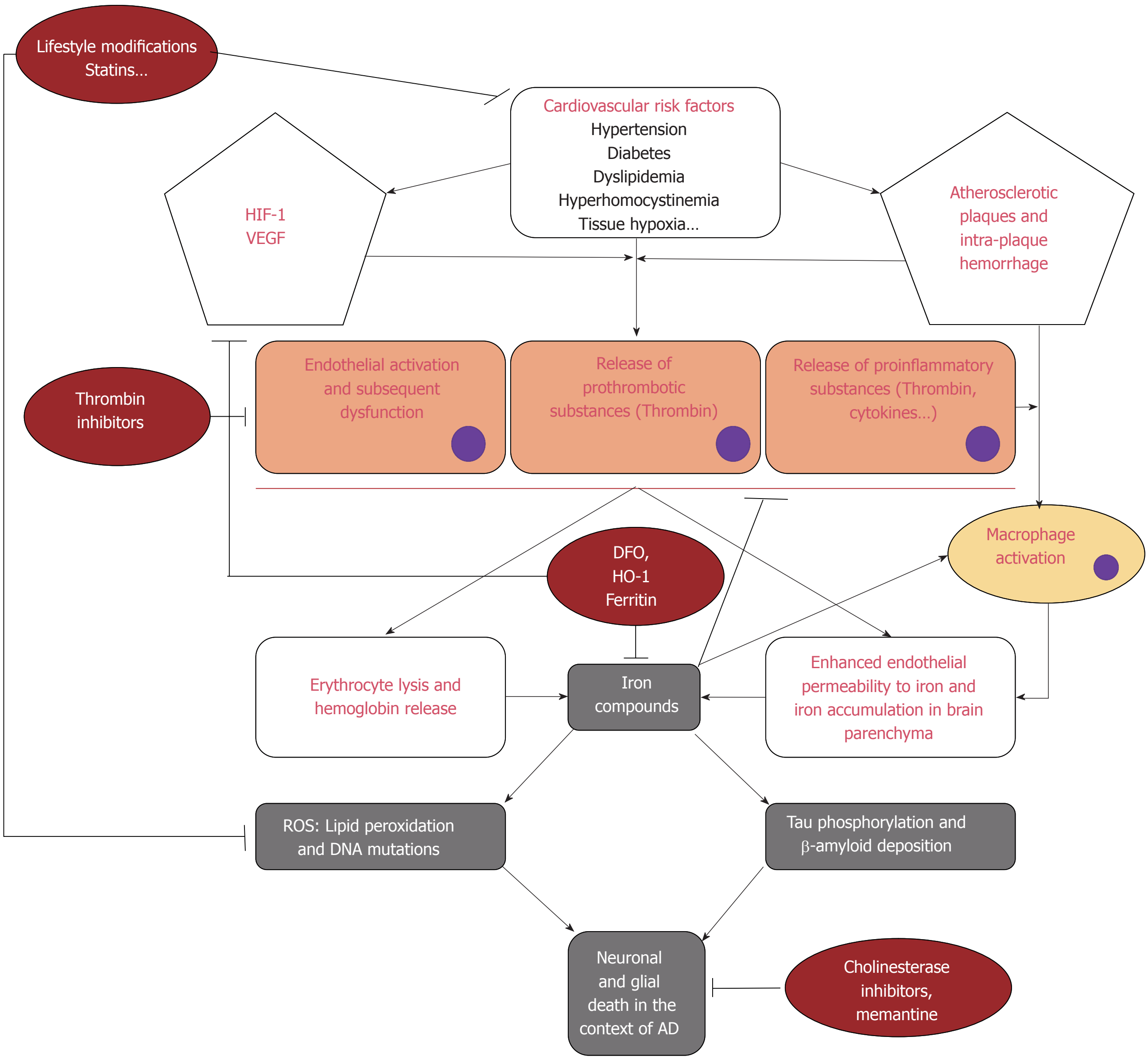

Figure 1 The physiopathological pathways linking endothelial dysfunction and thrombin activation to the neurotoxic effects of iron ions through enhancement of the oxidative stress that leads to neuronal and glial cell death. Dark red ovals: Therapeutic agents; Light orange boxes: Pathophysiological mechanisms taking place in the vascular endothelium; Gray boxes: Pathological events observed in AD; Light yellow oval: Macrophages. AD: Alzheimer's disease; DFO: Deferoxamine; HO-1: Heme oxygenase-1; ROS: Reactive oxygen species.

metals and that Aβ deposits preferentially locate in perivascular spaces[14].

β-amyloid in itself is a substrate for hydroxyl radicals[44]. Studies utilizing magnetic resonance imaging have found a positive correlation between aging and iron deposition in the brain that renders the brain more vulnerable to iron-mediated oxidative stress[45,46]. Accordingly, iron can attach to phosphorylated tau-proteins and lead to its aggregation, which causes the creation of neurofibrillary tangles[47]. Furthermore, it has been found that intranasal DFO inhibits tau phosphorylation in the brain of transgenic mice with AD[48]. It has also been demonstrated that the potential progression of senile plaques through the affinity of iron ions to β-amyloid and its precursor (*i.e.*, amyloid protein precursor) might be prevented in transgenic mice *via* administration of intranasal DFO[49].

DISCUSSION

AD has been considered to be caused by a multitude of neuropathogenic pathways that all eventually lead to neuronal death and cognitive impairment. However, in this review, we have demonstrated in a theoretical manner that these multiple pathophysiological pathways (namely the endothelial vascular activation through thrombin activation and the neurotoxic effect of redox species through iron ion decompartmentalization) are actually interlinked (for a schematic representation of these pathophysiological pathways see Figure 1). As a matter of fact, AD might be considered a disease of the neurovascular unit that seems to be triggered by vascular risk factors that affect the endothelium of small vessels and capillaries inside the brain. Vascular risk factors may induce atherosclerotic changes at the bifurcation of vessels, which would lead to tissue hypoxia in the brain parenchyma irrigated by the corresponding vessel. The endothelial cells lining the arterioles and capillaries in the hypoxic brain region are normally highly sensitive to hypoxic changes in the surrounding brain parenchyma and usually secrete substances that include VEGF and HIF-1 to promote neovascularization. When resources for neutralizing the oxidative stress provoked by hypoxia, such as in the elderly brain, are out-weighted by the amount and duration of oxidation, these normal responses become deleterious. A deficient vascular response to tissue hypoxia may promote intra-plaque hemorrhages. Deficient neovascularization and intra-plaque hemorrhages may be the cause of erythrocyte lysis, iron ion deposition in the brain parenchyma due to increased endothelial permeability and thrombin secretion and activation. Erythrocyte lysis liberates more iron ions that will further increase the oxidative stress. Moreover, thrombin activation may increase tissue hypoxia through increased clot formation and vasoconstriction that will also lead to increased oxidative stress. After exposure to oxidative stress compounds, many neuronal and glial cell modifications will ensue, such as lipid peroxidation, DNA mutations, cytoskeleton breakdown, *etc.* In addition, iron ions may also be responsible for the deposition of β-amyloid plaques and neurofibrillary tangles because it is implicated in enhancing amyloid protein metabolism and tau protein phosphorylation and aggregation. Accordingly, current research in AD therapeutics is focusing on one of the multiple branches of these interlinked pathophysiological pathways. However, a lack of a more global perspective may explain why no disease-modifying treatment has been discovered until now. For example, treatment with DFO may be an interesting solution for iron ion decompartmentalization but this treatment does not take into consideration the positive role that iron may play in the hypoxic tissue by reducing thrombin activation and subsequent clot formation, thus avoiding further hypoxia. Moreover, it becomes more obvious when looking at these interlinked pathways that no one molecule with a single mechanism of action can easily attenuate all the deleterious effects initiated by hypoxia secondary to vascular risk factors. Accordingly, we suggest that future research in this field should focus on testing combinations of potentially efficient treatments, such as the combination of intranasal DFO and direct thrombin inhibitors.

CONCLUSION

In this minireview, a common physiopathological pathway has been suggested for the pathogenesis of AD. This pathway is initiated by the presence of vascular risk factors that induce brain tissue hypoxia and subsequent endothelial cell activation. The endothelial activation may become dysfunctional in predisposed individuals, leading to thrombin activation and iron ion decompartmentalization. The oxidative stress that results from these modifications in the neurovascular unit will eventually lead to neuronal and glial cell death.

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