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Indoleamine 2,3-Dioxygenase: The Key to Pathogenesis and Treatment of Alzheimer's and Related Neurodegenerative Diseases

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

Several neurodegenerative brain diseases (primarily Huntington's, Parkinson's, and ALS) have distinctive differences but they share similar, incurable pathologies with Alzheimer's disease. These pathologies have mechanisms in common that involve oxidant stress. More than 20 years ago, research identified indoleamine 2,3-dioxygenase (IDO) as a significant site of oxygen toxicity resulting in convulsions. More recently, (IDO1), the rate-limiting enzyme of the kynurenine pathway in brain and some other tissues was identified as an eclectic, immunoregulatory agent including maternal T-cell tolerance. IDO1 is currently known to be a complex biomolecule with the catalytic activity of an enzyme and a coenzyme-like heme iron component that responds to changes in oxidant stress and equips it to function in a highly-regulated manner. Thus, IDO1 is known to perform non-enzyme functions that include reprogramming the expression profiles of immune cells with roles in autoimmune diseases, chronic inflammation, pregnancy, and cancer. I propose that

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brain IDO1, functioning as a highly-regulated enzyme of the kynurenine pathway, and as a sensor of and responder to oxidant stress, is deeply involved in the mechanisms leading to neurodegenerative brain diseases, and Alzheimer's serves as a representative, basic, mechanistic example. Following this connection offers new hope for elucidating the mechanisms of neurodegenerative brain diseases and for discovering treatments and cures.

Keywords: Neurodegenerative diseases; Alzheimer's; ALS; indoleamine 2,3-dioxygenase; IDO1; kynurenine pathway; Reactive Oxidant Species (ROS), Oxidant Stress (OS).

1. INTRODUCTION

Alzheimer's disease, described more fully in Section 2, is a neurocognitive disease with major and specific, incurable pathologies producing dysfunctions in complex tasks involving cognition, attention, learning and memory, language, and perceptual-motor dysfunctions. Alzheimer's was characterized by Alois Alzheimer and named by Emil Kraepelin. It is a chronic deterioration of neuronal integrity that involves mood fluctuations, changes in thinking and language as initial symptoms and it progresses to a gradual onset of memory loss and deterioration of social and behavioral functioning" [1]. In 2022, about 44 million people worldwide suffered from Alzheimer's [2]. Yang et al. [3] provided "a detailed history of Alzheimer's disease including the first patient, Auguste Deter age 52, whose autopsied brain cerebral cortex was noted to be "generally thinned and the region controlling memory, language, judgement, and thinking was severely impaired. Senile plaques were formed in neurons, and tangles were found in nerve fibers... Currently, this case would be diagnosed as early-onset Alzheimer's dementia."

In Sections 3-5 the focus is on the production of reactive oxygen species (ROS) and on the antioxidant defenses relative to their involvement in the causation and development of the neurodegenerative pathologies with a focus on Alzheimer's disease. Clues are to be found for the causation mechanism of Alzheimer's in studies of the toxicity of oxygen where oxygen at high pressure was known to cause convulsion (the Paul Bert effect) [4]. Subsequent research provided specific evidence that free radical toxicity for enzymes of the kynurenine pathway mediated these oxygen-induced convulsions in rats [5,6]. The kynurenine pathway (see Section 3) functions to metabolize tryptophan to nicotine adenine dinucleotide (NAD) and produces neurotoxic intermediates, including quinolinic acid (quinolinate), in the brain that have been implicated in Alzheimer's.

The kynurenine pathway (Fig. 1), and its relevant role, are described in the article *Kynurenine Pathway Metabolites in Humans: Disease and Healthy States* [7]. It describes the pathway's relationship to various brain disorders. The role of kynurenine pathway intermediates and oxidant stress mechanisms in Alzheimer's have been specifically described [8]. Also, oxidant-stress mechanisms have been proposed to be involved in Huntington's [9]; and in Parkinson's [10] and have been implicated in the degeneration of dopaminergic neurons that involves oxidative damage to proteins, lipids, and DNA. Mutations in genes associated with Huntington's also affect mitochondrial function and increase susceptibility to oxidative stress.

Tryptophan (metabolized by the kynurenine pathway (Fig. 1) is an essential amino acid with significant biological functions. In mammals, approximately 90% of dietary tryptophan is metabolized via the kynurenine pathway to NAD which is a cofactor in cell respiration and energy production as adenosine triphosphate (ATP). The kynurenine pathway also is recognized to have metabolites "with neuroactive and redox properties" [11], including quinolinic acid (see Section 4). The first (and regulatory) step is the oxidative cleavage of tryptophan.

2. ALZHEIMER'S DISEASE

The Alzheimer's Association Report of 2023 [12] describes in detail the public health impact of Alzheimer's including prevalence and incidence, mortality and morbidity. The report was updated in 2024 and was titled 2024 Alzheimer's Disease Facts and Figures, Special Report Mapping a Better Future for Dementia Care Navigation [13]. It has the categories: Overview; Prevalence; Mortality and Morbidity; Caregiving; Workforce; Use and Costs of Health Care; Long-Term Care and Hospice; Special Report – Mapping a Better Future for Dementia Care Navigation; and Appendices. The 2023 [12] report is especially useful for providing information about the disease

and its incidence. It states: “An estimated 6.7 million Americans age (sic) 65 and older are living with Alzheimer’s dementia today... Alzheimer’s remains the fifth-leading cause of death among Americans 65 and older.” A simplified overview of the disease states: “The accumulation of the protein fragment beta-amyloid into clumps (called beta-amyloid plaques) outside neurons and the accumulation of an abnormal form of the protein tau (called tau tangles) *inside* [emphasis in the original] neurons are two of several brain changes associated with Alzheimer’s. These changes are followed by damage to and destruction of neurons, called neurodegeneration, which along with beta-amyloid and tau accumulation is a key feature of Alzheimer’s disease.” The report [12] addresses treatment and states that the FDA has approved seven drugs for the treatment of Alzheimer’s and five are aimed at improving symptoms but do not “affect the underlying brain changes that cause symptoms, nor do they alter the course of the disease. With the exception of memantine, they improve symptoms by increasing the amount of chemicals called neurotransmitters in the brain.” Memantine (Namzaric®) protects the brain from excessive concentrations of glutamate. Glutamate and aspartate are major excitatory neurotransmitters in the brain and function at synapses in nerve impulse transmission. Chronic excitotoxicity has been hypothesized to have a role in neurodegenerative diseases including Alzheimer’s [14]. The status is changing and Two FDA-approved drugs (aducanumab and lecanemab) affect underlying biology of the disease by removing beta-amyloid from the brain. Lecanemab reduced markers of amyloid in early Alzheimer’s disease and there was moderately less decline in cognition and function at 18 months but this was associated with adverse events and longer trials are needed [15].

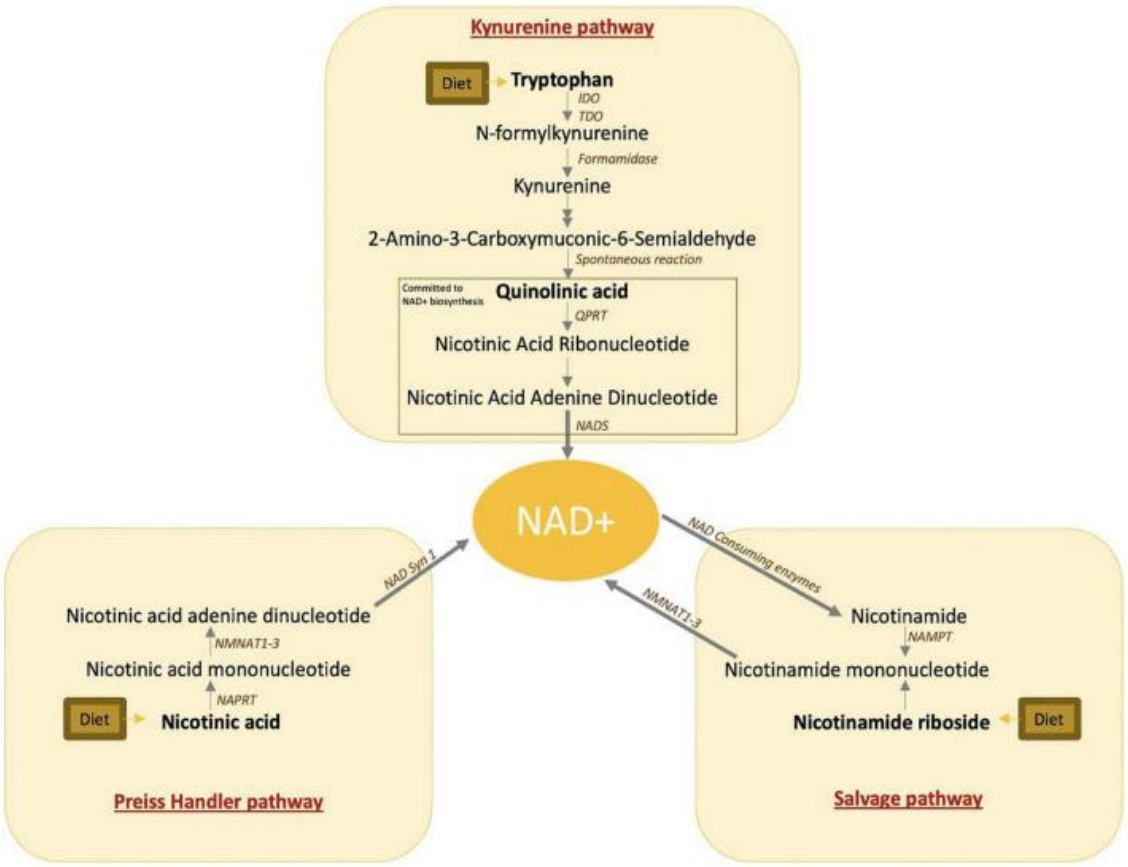

Fig. 1. The kynurenine pathway and connections to NAD pathways. Used with permission from [25]. IDO is indoleamine-pyrrole 2,3-dioxygenase; TDO is tryptophan 2,3-dioxygenase; QPRT is quinolinate phosphoribosyltransferase; NAD is nicotinamide adenine dinucleotide; NADS is nicotinamide adenine dinucleotide synthetase 1; NMNAT is nicotinamide mononucleotide adenylyl transferase; NAPRT is nicotinate phosphoribosyltransferase; and NAMPT is nicotinamide phosphoribosyltransferase

Oxidative stress is a significant feature of the disease pathology of Alzheimer's and it results in amyloid β formation that produces plaques in the brain. There also is impaired mitochondrial function, and oxidative damage to lipids and proteins in the brain. In this perspective review, we focus primarily on the oxidant mechanisms.

Quinolinic acid is the product of the kynurenine pathway (Fig. 1) that is converted into NAD and it is a toxin with multiple targets in the human body, including the brain [16]. Guillemin briefly reviewed the history of quinolinic acid including for the brain [17] and he stated that it was reported to be a toxin by Henderson as early as 1949. Guillemin [17] also described that in the early 1960s Lapin documented that injection of quinolinic acid into the brain induced convulsions. In 1981, Stone and Perkins showed that quinolinic acid selectively activated the N-methyl-D-aspartate receptor; and Schwarez showed that this led to axonal degeneration. Currently, it is generally recognized that quinolinic acid is a gliotoxic, proinflammatory agent.

3. THE ROLE OF THE BRAIN KYNURENINE PATHWAY

The kynurenine pathway was recently the subject (in 2023) of a systematic review of Alzheimer's [18]. Twenty-two studies with a total of 1,356 participants were reviewed. There was a shift toward the kynurenine pathway in both the brain and in the periphery and a change toward increased kynurenic acid production in the brain but decreased production in the peripheral blood. The authors concluded "changes in the kynurenine pathway are suggested to be a core component of AD" [18].

Neuroactive metabolites of the kynurenine pathway are closely linked to the pathogenesis of neurodegenerative diseases including Alzheimer's. The title of a paper, authored by Savitz et al. and published in 2019, is informative about its role: *The kynurenine pathway: a finger in every pie* [19]. The kynurenine pathway has a critical role in many processes involved in diseases including Alzheimer's: (a) in generating energy via formation of nicotinamide adenine dinucleotide (NAD) whose requirement increases during the immune response; (b) pathway intermediates are neuroactive, modulate neuroplasticity, exert neurotoxic effects via receptor signaling and glutamatergic neurotransmission; thus, its role in Alzheimer's [19].

The kynurenine pathway (a central pathway of tryptophan metabolism) generates metabolites and oxidant radicals that are increased with disturbed tryptophan metabolism in Alzheimer's disease. There is a resultant deficiency of tryptophan-derived neurotransmitters and raised concentrations of quinolinic acid that are associated with neuroinflammation, depression, and neurodegeneration [20]. Increased synthesis of quinolinic acid (an N-methyl-D-aspartate receptor agonist) and increased concentrations of inflammatory cytokines occurs in Alzheimer's (and other neurodegenerative conditions including Parkinson's and amyotrophic lateral sclerosis). Increased oxidative stress results from increased indole-dioxygenase activity and increased kynurenine may add to inflammatory responses including the production of cytokines [20]. Increased quinolinic acid occurs at the expense of kynurenine and the neuroprotective picolinic acid [20].

Hested et al. [20] provided an overview of tryptophan metabolism and described consequences when its biological pathways are not appropriately regulated that is focused on depressive and neurodegenerative diseases. The authors concluded that pharmacological interventions focused on ameliorating the effects of oxidative stress were warranted, and I agree; this is imperative.

L-kynurenine has been studied as a potential neuroprotective molecule. It is prone to oxidation and it has been studied as a potential oxidant radical scavenger with the conclusion that "L-KYN increased the GHS content and the activity of glutathione reductase and glutathione peroxidase, and also prevented the oxidative damage induced by the ex vivo exposure to pro-oxidants. Altogether, these findings strongly suggest that L-KYN can be considered as a potential endogenous antioxidant" [21].

Consideration of its interactive functions and metabolites reveals the central role of oxygen radicals in Alzheimer's and some other neurodegenerative diseases. Several pathway metabolites can modulate activity of glutamate receptors and generate free radicals. Imbalances in absolute and relative concentrations of kynurenine pathway components have been strongly associated with neurodegenerative disorders including... Huntington's, Alzheimer's, Parkinson's. [22]. The kynurenine pathway is implicated in neurological disorders via neuroactive metabolites that function as pro-

oxidant and anti-oxidant regulators [22,23]. Significantly, the metabolism of tryptophan is altered by ageing and neurodegenerative diseases and leads to decreased biosynthesis of nicotinamide and decreased activity of nicotinamide requiring coenzymes. These metabolic processes are required for aerobic bioenergetic mechanisms and for protein synthesis.

As recently as 2014 [24], it was logically deduced that "endogenous tryptophan and its metabolites can interact [with] and/or produce reactive oxygen species... of great importance [because] oxidative stress, alterations in KP [kynurenine pathway] metabolites [cause] energetic deficit, cell death, and inflammatory events." It is noteworthy, however, that this same paper stated "no one has established any direct link between alterations in KP and these metabolites" [24]. With the accumulated evidence, we submit that it is appropriate to state that the evidence now is sufficient to justify the hypothesis that oxidant stress mechanisms are significantly involved in the pathogenesis of Alzheimer's disease. Pursuing this prospect offers hope for prevention and treatment. It has been a long process to reach this point. Hested et al. [20] wrote: "Emerging evidence suggests that neuroinflammation is involved in both depressive and neurodegenerative diseases. The kynurenine pathway, generating metabolites which may play a role in pathogenesis, is one of several competing pathways of tryptophan metabolism." They describe evidence that 'disturbed' tryptophan metabolism resulted in increased production of quinolinic acid which may result in deficiencies in tryptophan and its derived neurotransmitters. Quinolinic acid, a receptor antagonist of N-methyl-D-aspartate, is elevated in brain in Alzheimer's disease. Oxidative stress, inflammatory responses, increased indole-dioxygenase activity and increased kynurenine formation is proposed to increase the production of cytokines. Increased quinolinic acid logically would result in decreased concentrations of kynurenine and the neuroprotective picolinic acid.

Parkinson's disease shares some mechanisms, including a link to the kynurenine pathway and oxidative stress and ROS) with Alzheimer's. Parkinson's is characterized by striatal dopaminergic neuronal loss with localized neuroinflammation in the midbrain region and there is activation of microglia involving inflammatory mediators with the kynurenine pathway a site of major regulatory and immune responses leading to the neuroinflammatory and neurotoxic cascade seen in Parkinson's [26]

Zadori et al. [27] provided a patient review titled: *Inhibitors of the kynurenine pathway as neurotherapeutics: a patient review (2012-2015).* They stated: "The proven pathological alterations in the kynurenine pathway of tryptophan metabolism, either in preclinical models of neurological and psychiatric disorders or in human samples themselves, elicited numerous attempts to restore the altered balance via pharmaceutical manipulations of the pathway." They offered the relevant expert opinion: "Although the clinical and preclinical data are reassuring, there is a lack of applicable drugs in daily clinical practice. However, the recent determination of enzyme structures considerably promoted the development of potent inhibitors, most of them having been designed as a structural analog of the natural enzyme substrate. Especially, the inhibition of indolamine 2,3-dioxygenase in central nervous system tumors, the inhibition of kynurenine aminotransferase in cognitive dysfunction, and the inhibition of kynurenine 3-monooxygenase in neurodegenerative disorders, such as Huntington's disease, each show great promise" [27].

Zadori et al. in the article "*Alzheimer's disease: recent concepts on the relation of mitochondrial disturbances, excitotoxicity, neuroinflammation, and kynurenines* [28] (a review published in 2018 that cites 318 papers) stated in part: "The pathomechanism of Alzheimer's disease (AD) certainly involves mitochondrial disturbances, glutamate excitotoxicity, and neuroinflammation... Several abnormalities have been described regarding the activation of certain steps of the kynurenine (KYN) pathway of tryptophan metabolism in AD... activation of indolamine 2,3-dioxygenase, the first and rate-limiting step of the pathway, is well-demonstrated. 3-hydroxy-L-KYN and its metabolite, 3-hydroxy-anthranalic acid have prooxidant, antioxidant, and potent immunomodulatory features, giving relevance to their alterations in AD. Another metabolite, quinolinic acid, has been demonstrated to be neurotoxic, promoting glutamate excitotoxicity, reactive oxygen species production, lipid peroxidation, and microglial neuroinflammation, and its abundant presence in AD pathologies has been demonstrated. Finally, the neuroprotective metabolite, kynurenic acid, has been associated with antagonistic effects at glutamate receptors,

free radical scavenging, and immunomodulation, giving rise to potential therapeutic implications."

4. THE NEUROTOXIN QUINOLINIC ACID

Guillemin wrote an informative minireview of quinolinic acid in 2012 [29] and provided a brief history. This history included that Henderson described quinolinic acid in 1949 and Lapin about 20 years later reported that injection of quinolinic acid into the brain ventricles of mice caused convulsions [29], and Stone and Perkins found that quinolinic acid could selectively activate the N-methyl-D-aspartate receptor. Schwarcz [30] found that injection of quinolinic acid caused axonal neurodegeneration. Evidence has accumulated that quinolinic acid is "involved in the neuropathogenesis of several major neurological diseases." [29].

There is empirical evidence for elevated neuronal quinolinic acid concentrations in patients with Alzheimer's disease [20], and quinolinic acid is associated with neuroinflammation. Logic strongly support that an excessive concentration of quinolinic acid correlates with the progression of Alzheimer's disease and likely with significant pathologies of other neurodegenerative brain diseases.

Quinolinic acid is naturally present in human brain and cerebrospinal fluid in nanomolar concentrations and implicated in the pathogenesis of several human neurological diseases including "Alzheimer's, Huntington's, and Parkinson's diseases" [16]. More specifically, tryptophan metabolism via the kynurenine pathway produces neurotoxic intermediates in Huntington's and oxidative stress via 3-hydroxykynurenine and 3-hydroxyanthranilic acid damages neuronal tissues and is proposed to contribute to neurodegeneration via subsequent amyloid-β accumulation, glial activation, and up-regulation of the kynurenine pathway [31]. Quinolinic acid has been described as an "endogenous neurotoxin with multiple targets" [11]. It is an agonist of the N-methyl-D-aspartate (NMDA) receptor and it is a highly potent excitotoxin [11,32]. Quinolinic acid is readily taken up by the brain and in neurons its degrading enzyme is readily saturated. Thus, extracellular quinolinic acid can accumulate and stimulate NMDA receptors. However, the toxicity of quinolinic acid in the brain "cannot be fully explained by its activation of NMDA receptors" [11]. Specifically for Alzheimer's disease, postmortem brains of Alzheimer's patients have elevated quinolinic acid concentrations and quinolinic acid can chemically associate with tau proteins [30].

In 2022, A systematic review of quinolinic acid in human urine and its relationship to disease concluded: "Quinolinic acid has been implicated in the pathophysiology of multiple conditions. Its urinary accumulation appears to be a feature of acute physiological stress and several chronic diseases" [25]. Fifty-seven articles met the inclusion criteria and "in critically ill patients, elevated quinolinic acid in urine predicted a spectrum of adverse outcomes including hospital mortality" [25].

L-tryptophan (Fig. 1), one of the eight essential amino acids in humans, functions in physiological events mediated by neurotransmitters. Tryptophan has the lowest reserves and is prone to deficiency [20]. Approximately 1% is used for protein synthesis. Via the kynurenine pathway, it is metabolized to produce several physiologically active enzymes, substrates and metabolites which produce various physiological and pathological effects. A significant pathway converts tryptophan into serotonin (90% in the small intestines and about 10% in the central nervous system) via two enzymes. Thus, the pathway is involved in physiological and pathologic outcomes that include endocrine, hematologic, gastrointestinal, immunological, inflammatory, bioenergetic, and neurologic [1]. Imbalances in the kynurenine pathway are associated with cellular "redox potential, immunoregulatory mechanisms, inflammatory pathways, cell survival channels, and cellular communication in close association with several neurodegenerative changes... The kynurenine pathway is intricately linked to Alzheimer's pathogenesis owing to the influence of kynurenine metabolites upon excitotoxic neurotransmission, oxidative stress, uptake of neurotransmitters, and modulation of neuroinflammation, amyloid aggregation, microtubule disruption, and their ability to induce a state of dysbiosis." [1].

5. OXIDANT STRESS AND FREE RADICALS IN ALZHEIMER'S AND OTHER NEURODEGENERATIVE DISEASES

Oxidative stress is generally defined as a state of imbalance of oxidants and antioxidants that results in a pathologic increase of the concentrations of oxidants. However, the

'balance' of pro-oxidants and antioxidants cannot be adequately defined by assessing a single pair of entities. Helmut Sies, a pioneering authority on oxidant stress, wrote [33]: "Oxidative stress' as a concept ... was formulated in 1985; at the beginning of 2015, approx. 138,000 PubMed entries show for this term." Sies identified the importance of focusing on what he called "molecular switches governing oxidative stress." Sies also pointed out the 'Pitfall' of of the indiscriminate use of oxidative stress without a clear relation to redox chemistry. He stated: "The major role in antioxidant defense is fulfilled by antioxidant enzymes, not by small-molecule antioxidant compounds."

Dean Jones in the article *Redefining Oxidative Stress* [33] concluded: "oxidative stress may be better defined as a disruption of redox signaling and control. Adoption of such a definition could redirect research to identify key perturbations of redox signaling and control and lead to new treatments for oxidative stress-related disease processes."

Singh, et al., in 2019 [34] concluded: "Various neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), among others, can be the result of biochemical alteration (due to oxidative stress) in bimolecular components" (see Fig. 2). Singh et al. [34] also stated: "There is a need to understand the processes and role of oxidative stress in neurodegenerative disease." These authors defined and described the role and importance of sensors and biomarkers, mitochondria, pro-oxidants, heavy metals, ferroptosis (a 'new' term iron-dependent oxidative stress induced cell apoptosis with neuronal damage), senescence vs. apoptosis, and modulation of neurodegenerative diseases for Alzheimer's, Parkinson's, Amyotrophic lateral sclerosis, and Huntington's diseases. Singe, et al. [34] concluded: "Increased oxidative stress has been viewed as one of the potential etiologies in various neurodegenerative diseases… The onset of oxidative stress produces ROS… causing lipid peroxidation, protein misfolding and aggregation, DNA damage, and mutations. Owing to the high consumption of oxygen and enrichment in PUFA, the brain is the most vulnerable part of the body."

The 2017 review by Liw et al. [35] suggests that there is growing consensus that antioxidant therapeutics are helpful in neurodegenerative diseases. They state: "Novel antioxidant compounds have been developed that show potential in mediating disease phenotypes. For example, Fer-1, as a potent antioxidant, can effectively prevent neuronal cell death in HD and PD, via the inhibition of lipid peroxidation and the attenuation of glutamate toxicity..." They note that more than one kind of ROS is involved and conclude that a single antioxidant supplement is likely to be insufficient and "may even result in a disturbance of redox balance in the body." Elevated ROS have been found to be associated with AD, PD, HD, ALS, and SCA (see Fig. 2).

Ageing is related to increased risk in development of Alzheimer's and Sas et al. [36] in the review titled: *Mitochondria, Oxidative Stress and the kynurenine System, with a Focus on Ageing and Neuroprotection* provided evidence for a modulating role of the kynurenine pathway in the ageing process. This review, published in 2018 will be cited extensively because of its significance for our conclusions about the prominent role of ROS in Alzheimer's, and to avoid paraphrasing by retaining the original language of the authors. They stated [36]: "During ageing, a decrease in mitochondrial dynamics was reported, potentially compromising the function of mitochondria... and mitochondria are supposed to play a prominent role in cell death during senescence... The role of reactive oxygen species (ROS) in the ageing process is widely acknowledged... In the case of extensive DNA damage, PARP-1 becomes overactivated and rapidly depleted the intracellular NAD^+ and ATP pools... Alterations in the kynurenine system have been linked with the ageing process and several age-related disorders. The kynurenine pathway degrades tryptophan (TRP) to several metabolites, among others kynurenine (KYN), kynurenic acid (KYNA) and quinolinic acid (QUIN). The end-product of the route is NAD^+. The first metabolic reaction is mediated by TRP-2,3-dioxygenase (TDO) or indolamine-2,3-dioxygenase (IDO), the latter being induced by inflammation, and it is thought to have a significant role in several disorders and in ageing. Research is currently focusing on the KNY pathway, since several intermediates possess neuro- and immunoactive properties, and hence are capable of modulating the activity of certain brain cells and inflammatory responses... The broad actions of the KYN-intermediates in brain excitation/inhibition and their role in regulating immune responses may provide the possibility of modifying the pathological processes in an array of age-associated diseases in the future."

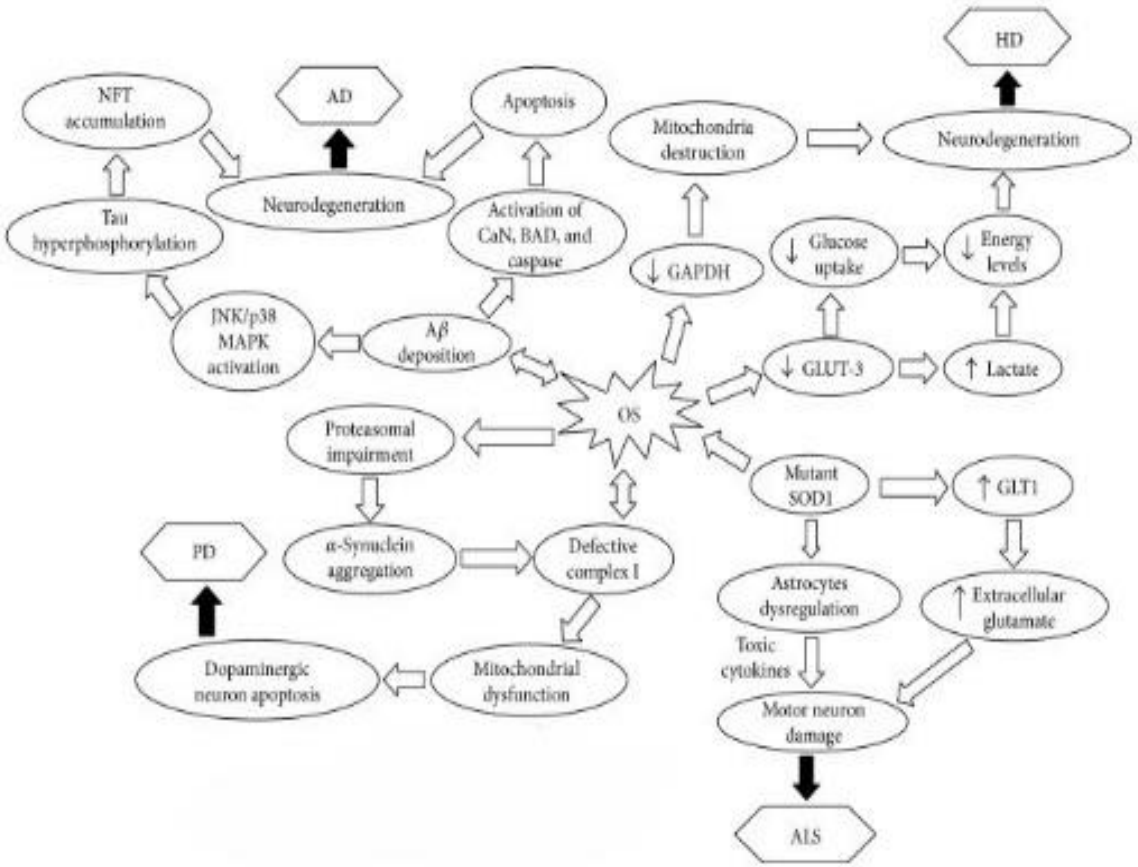

Fig. 2. The roles of oxidant stress (OS) in the development of Alzheimer's and other neurodegenerative diseases. Definitions for abbreviations are: AD (Alzheimer's disease); HD (Huntington's disease); PD (Parkinson's disease); ALS (amyotrophic lateral sclerosis); and SCA (spinocerebellar ataxia). A*β*: amyloid beta; BAD: Bcl-2-associated death promoter; CaN: calcineurin; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; NFT: neurofibrillary tangle; OS: oxidative stress; SOD superoxide dismutase. Used by permission from Citation with modification [35]

Fig. 2 provides a picture of the central role of oxidative stress for Alzheimer's disease and for several neurodegenerative diseases to provide perspective. A useful source of information is the paper: *A multitude of Signaling Pathways Associated with Alzheimer's Disease and their Roles in AD Pathogenesis and Therapy* [37].

5.1 Apoptosis

Alzheimer's disease is characterized by accumulation of hyperphosphorylated tau and amyloid-β (Aβ) proteins resulting in synaptic destruction and apoptosis. Aβ and tau deposition are the triggers of apoptotic pathways leading to neuronal death. During apoptosis various proteins (including the Bcl-2 family and caspases including initiator, effector and inflammatory caspases) act to cause cell disintegration [38]. The apoptotic elements interact with other factors (specific signaling molecules involved in the cell cycle) and this leads to cell disintegration [38]. A cell surface receptor (TREM2), primarily expressed on microglia, has a critical role in the pathogenesis and progression of Alzheimer's [39]. TREM2 inhibits tau hyperphosphorylation and neuronal apoptosis which indicates that upregulation of TREM2 could provide a target to protect against tau pathology [39].

5.2 Amyloid Precursor Protein and A/3 Deposition

A/3 is a cleavage product of an amyloid precursor protein (APP) [40]. It is a transmembrane protein whose cleavage produces fragments (including Aβ peptides) which aggregate to form amyloid plaques which

are the hallmark pathology of Alzheimer's disease, and a potential site for developing a therapy for this consequence of oxidant stress and free radical damage [40,41].

5.3 NFT Accumulation

Neurofibrillary tangles (NFTs) are a fundamental neuropathological hallmark of Alzheimer's disease [42]. The precise molecular mechanism associating the loss of cytoskeletal elements to the creation of NFTs is unknown, signal transduction pathways involving protein phosphorylation are probably involved [42]. The paper *Alzheimer's disease clinical variants show distinct regional patterns of neurofibrillary tangle accumulation* by Catherine Petersen et al. [43] showed that regional burdens of neurofibrillary tangles correlate with clinical presentation and region-specific cognitive scores, and stated: "Overall, our results suggest domain-specific functional consequences of regional neurofibrillary tangle accumulation."

5.4 Tau Hyperphosphorylation

Abnormal hyperphosphorylation of tau (a microtubule-associated protein) occurs in Alzheimer's and has a vital role in molecular pathogenesis of the disease that is traceable to oxygen stress damage. Development of drugs that would prevent this are a focus of therapeutic strategies. A 'cocktail' (multi drug) treatment strategy targeting Aβ, tau, acetylcholinesterase, inflammation, oxidative stress, and cognitive symptoms has been proposed [44]. The review article by Neha Basheer in *Nature* in 2023 [45] is titled: *Does modulation of tau hyperphosphorylation represent a reasonable therapeutic strategy for Alzheimer's disease? From preclinical studies to the clinical trials.* They state: " Tau protein hyperphosphorylation was the first pathological post-translational modification of tau protein described in Alzheimer's disease… Amongst the few PKIs (protein kinase inhibitors) and PP2A (protein phosphatase 2 A activators) that progressed to clinical trials, most failed on the efficacy front." They concluded: "…the intimate connection tau hyperphosphorylation has to tau pathology genesis and progression is apparent in numerous preclinical studies. The translation to clinical practice has so far eluded grasp…"

5.5 Activation of CAN

Calcineurin (CaN) is a calcium-dependent phosphatase enzyme involved in neuronal signaling [46], and in this review the broad scope of its functioning was described. Calcineurin is the most abundant Ca^{2+}/CaM binding protein in the brain. It functions as a protein phosphatase with "well-established roles in the cardiovascular, nervous, and immune systems. Dysregulation of calcium homeostasis can result in increased activity of calcineurin contribute to neuronal dysfunction and even to degeneration that link to tau hyperphosphorylation, loss of synaptic functions and also to activation of apoptosis and/or GBAD. Technically, it is a unique calcium ion and calmodulin-dependent serine/threonine phosphatase that activates substrates in cell processes including apoptosis" [47].

5.6 Activation of BAD

The BAD pathway (Bcl-2-associated death promotor) contributes to neuronal cell death when dysregulation results triggering this pathway with apoptosis during progression of the disease. The Bcl-2 family has both proapoptotic proteins and antiapoptotic proteins; they have a role in mitochondrial integrity and therefore are important regulators of the mitochondria-dependent intrinsic apoptotic pathway in other pathologies as well [48]. The review article: *The role of Bcl-2 proteins in modulating neuronal Ca2+ signaling in health and in Alzheimer's disease* by Manon Callens et al., in 2021 [49] describes the role of Bcl-2 acting in mitochondria to control the initiation of apoptosis . They stated stated: "… it has become clear that this family of proteins is also involved in controlling intracellular Ca^{2+} signaling… including [in] neurons… this dysregulation contributes to the onset, development, and progression of neurodegeneration in the context of Alzheimer's disease (AD)" [emphasis in the original].

5.7 Activation of Caspase

Caspases are a family of protease enzymes involved in apoptosis (programmed cell death). Oxidative stress is a significant mechanism leading to involvement of caspase. The recent (2023) article: *Caspases in Alzheimer's Disease: Mechanisms of Activation, Role, and Potential Treatment* [50] is informative. Although the article reaffirms that the exact pathological mechanism remains unknown, it states: "...the most popular theories associate AD with abnormalities in the Tau and β-amyloid (Aβ) proteins, which lead to their deposition and

neuronal death" [50]. The role of the caspase-8/RIPK3 axis in Alzheimer's disease pathogenesis was described by Sushanth Kumar et al. in a research paper in 2023 [51]. They concluded: "The molecular mediators of cell death and inflammation in Alzheimer's disease (AD) have yet to be fully elucidated. Capsase-8 is a critical regulator of several death and inflammatory pathways; however, its role in AD pathogenesis has not yet been examined in detail." They concluded that "therapeutic targeting caspase-8 may represent a novel strategy to limit αβ amyloidosis and neuroinflammation in AD."

5.8 Activation of JNK and p38 MAPK

JNK (c-jun N-terminal kinase) and p38 MARK (mitogen-activated protein kinase) are activated by inflammatory stimuli and sustained activation can elevate neuronal damage. These pathways are involved in the oxidant stress response leading to neuronal apoptosis and synaptic dysfunction with hyperphosphorylation of tau protein. Kheiri et al. [52] reported evidence that a myriad of environmental and genetic factors and aging contribute to Alzheimer's disease. We agree with these authors who stated: "Neuroinflammation is and has been the focus of interest, as a common gateway for initiation of many of the underlying pathologies of AD. Amyloid beta (Aβ) toxicity, increasing RAGE expression, tau hyperphosphorylation, induction of apoptosis, and deregulated autophagy are among other mechanisms, partly entangled and being explained by activation of mitogen-activated protein kinase (MAPK) and MAPK signaling. p38 MAPK is the most essential regulator of Aβ induced toxicity from this family" [52].

6. THE ROLES OF QUINOLINIC ACID, IRON, AND ROS IN DEGENERATIVE BRAIN DISEASES WITH A FOCUS ON THE PATHOLOGY OF ALZHEIMER'S

The rate-limiting (and first) step of the kynurenine pathway is catalyzed in the brain by the enzyme indoleamine 2,3-dioxygenase (IDO), which is low in concentration but inducible, and which reacts with either oxygen or superoxide and with tryptophan or other indoleamines (see Fig. 1). Tryptophan 2,3-dioxygenase (TDO), present mainly in liver and kidney, reacts with oxygen and is specific for tryptophan. Quinolinic acid, which does not pass the 'blood brain barrier', is produced within the brain and it is an excitotoxin and convulsant. Dang et al., in 2000 (in research done in my laboratory) [53] proposed that hyperbaric oxygen induced convulsions by an increased flux through the kynurenine pathway in the brain to produce toxic concentrations of quinolinic acid. This was confirmed by in vitro assessments of the effects of hyperoxia on the brain IDO-catalyzed step but not seen in the TDO-catalyzed step as measured by the quinolinic acid produced. TDO activity was appreciable even at 30 microM oxygen and rose steeply to a maximum at 40 microM. Conversely, IDO had almost no detectable activity at or below 100 microM oxygen and maximum activity was not reached until about 1150 microM (rat blood plasma, with air breathing, has about 215 microM oxygen).

In this context, it is most relevant that indoleamine 2,3-dioxygenase (IDO), the rate-limiting enzyme of the kynurenine pathway (which converts tryptophan to kynurenine) contains heme iron in the active site. It is a mononuclear iron center coordinated by histidine and other residues. It is responsible for catalyzing the oxidation of tryptophan to N-formylkynurenine (Fig. 1). It is essential for the enzymatic conversion of tryptophan to the neurotoxic quinolinic acid. Dennis Flint et al. [54]. in collaborative research done in my laboratory reported that the iron-sulfur containing enzyme dihydroxy-acid dehydratase (which contains another form of iron, the Fe-S cluster) was inactivated by hyperbaric oxygen (ROS) by destruction of the Fe-S cluster, but the enzyme [55] remains in the cell in a form that can be reactivated. This enzyme was determined to be the most sensitive enzyme in *E. coli* to inactivation by hyperbaric oxygen (involving ROS), [55,56]. Thus, I propose that the iron site (although different than that of the Fe-S cluster) is a candidate for 'reversable' ROS damage in Alzheimer's and also should be explored as a therapeutics site.

7. THE KEY ROLE OF IDO1 IN NEURODEGENERATION

The extensive, previously described, evidence for the central role of IDO1 in immunosuppression, and for some cancers, is the empirical basis for the proposal that there is a key role for oxidant stress-mediated regulation of IDO1 and the kynurenine pathway for Alzheimer's and related neurodegenerative diseases. There is a complex role of IDO1 in regulation of oxidant stress, formation of toxic intermediates and cell signaling.

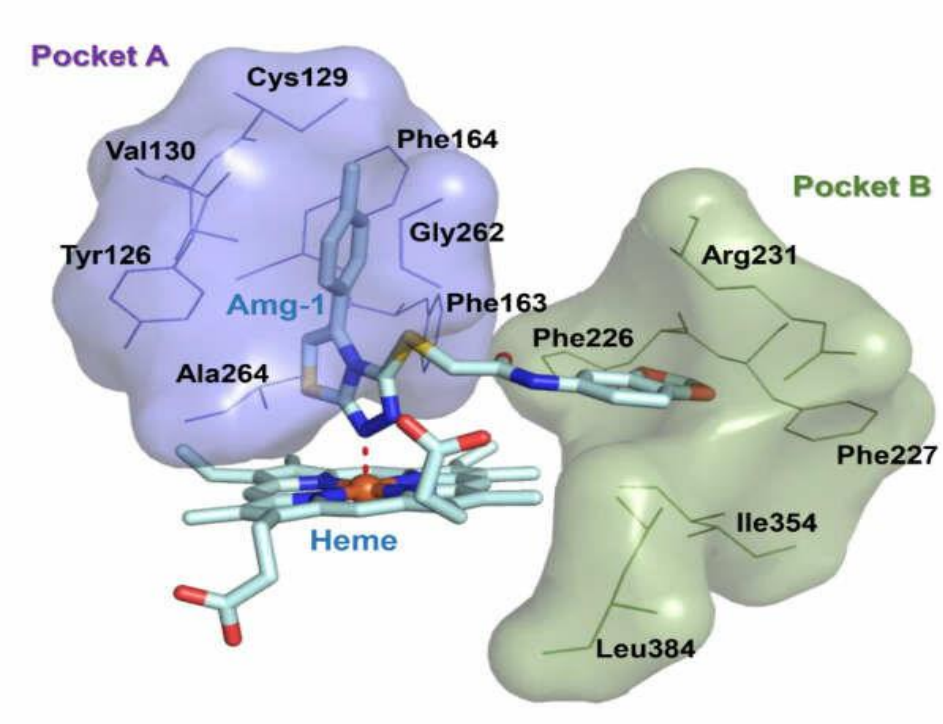

Fig. 3. Crystal structure map of IDO1. The relationships of the heme group and the amino acids of pocket A (purple) and pocket B (green) are depicted. Creative Commons Attribution 4.0 International, no changes made, published in [57]

As documented throughout this Perspective Review, the search for inhibitors of IDO1 (as potential therapeutics) has established that IDO1 is an important intervention site in various diseases including cancer, infection, and suppression of autoimmunity. Inhibition of IDO1 "may lead to clinical benefits in different therapeutic settings" [58]. The structure of IDO1 and binding pockets relative to various IDO1 inhibitors are depicted in detail [57], and the authors state: "L-Trp binding induces a positive potential at the heme iron, with increases the reductive potential and hinders O_2 binding." This should be explored in the search toward understanding Alzheimer's and related neurodegenerative diseases.

The consumption of L-tryptophan is known to block proliferation of T-cells and promote the differentiation of T-cells into regulatory T-cells. Metabolites of the of KYN activate signaling pathways that enhance immune tolerance. The toxicity of accumulated kynurenine pathway metabolites also causes T-cell apoptosis which occurs in many types of cancer [59]. We describe this in some detail because we propose that a different outcome is involved with ROS in neurodegeneration in Alzheimer's and other diseases (Fig. 2). Logically, we propose ROS specifically attacks the heme group as the sensitive site in IDOI. There is a large catalytic domain holding the heme group and a comparatively small non-catalytic domain holding the heme group and the interactions and relevance to functioning have been described [60]. Fig. 4, taken in modified form from the paper *Positive allosteric modulation of indoleamine 2,3-dioxygenase 1 restrains neuroinflammation* [61] shows relationships of the heme group and catalytic activity. This should be the focus of research to elucidate oxidant stress regulatory mechanisms and for future searches for therapy.

Indoleamine 2,3-dioxygenase 1 (IDO1): an up-to-date overview of an eclectic immunoregulatory enzyme published in FEBS in 2022 by Pallotta et al. [62] melts a snowball of information that creates a river of support for a fresh approach to understanding Alzheimer's that also applies to other neurodegenerative diseases. Pallotta et al. [62] surmised: "When discovered more than 50 years ago, IDO1 was thought to be an effector molecule capable of mediating a survival strategy based on the deprivation... of the essential amino acid tryptophan. Since 1998, when tryptophan

catabolism was discovered to be crucially involved in the maintenance of maternal T-cell tolerance, IDO1 has become the focus of several laboratories around the world... IDO1 is now considered as an authentic immune regulator not only in pregnancy but also in autoimmune diseases, chronic inflammation, and tumor immunity... and a bulk of new information – including structural, biological, and functional evidence – on IDO1 has come to light...IDO1 has a peculiar conformational plasticity and, in addition to complex and highly regulated catalytic activity, is capable of performing a nonenzymatic function that reprograms the expression profile of immune cells toward a highly immunoregulatory phenotype." Pallotta [62], also stated that "IDO1 should be considered a moonlighting protein... that is capable of mediating distinct functions in response to distinct cellular needs, and as such should be taken into account as drug targets for a more effective immunotherapy."

Nelp et al. [63] published results showing that cells expressing the hemeprotein IDO1 are "able to profoundly alter their surrounding environment to suppress the immune response... IDO1 is dynamically bound to its heme cofactor in what is likely a critical step in the regulation of the enzyme." We propose that oxidant stress is connected to the reversible regulation of the heme cofactor and this has a specific role in neurodegeneration. This is amplified by the work of Freewan et al. [64] who reported that hydrogen peroxide activates the peroxidase function of IDO and induces protein oxidation and inhibits IDO enzyme activity. They state: "This study identifies IDO as a heme peroxidase that, in the absence of substrates, self-activated dioxygenase activity via compound I-initiated protein oxidation. L-Trp protects against dioxygenase activity...and peroxidase-mediated dioxygenase inactivation, NO consumption, or protein nitration may modulate the biological actions of IDO expressed in inflammatory tissues where the levels of H_2O_2 and NO are elevated and L-Trp is low" [64].

Mondanelli, et al. [65] stated in the paper *Positive allosteric modulation of indoleamine 2,3-dioxygenase 1 restrains neuroinflammation*: "L-tryptophan... is the precursor of a wide array of immunomodulatory metabolites produced by the kynurenine and serotonin pathways. In the associated serotonin pathway, the metabolite N-acetylserotonin has been shown to possess antioxidant, anti-inflammatory, and neuroprotective properties in an animal model of multiple sclerosis as cited in [65].

The paper *Indolamine 2,3-dioxygenase is a signaling protein in long-term tolerance by dendritic cells* [66] provides additional connection of this enzyme to brain pathology. The authors state: " Regulation of tryptophan metabolism by indolamine 2,3-dioxygenase (IDO) in dendritic cells is a highly versatile modulator of immunity... IDO has a tonic, nonenzymatic function that contributes to TGF-β-driven tolerance in noninflammatory contexts." The paper by Wanjun Chen [59] and titled: *IDO: more than an enzyme,* is informative. The author states: "Indoleamine 2,3-dioxygenase (IDO) acts as an intracellular signal transducer, in response to transforming growth factor-β (TGF-β)."

Therefore, much evidence, to which we have referred, links indoleamine 2,3-dioxygenase to immune tolerance. This function is relevant to neurodegeneration and Mellor et al. [67] stated: "... if inflammation with IDO involvement is not resolved, a chronic immune activation at such sites causes progressive tissue damage over time. They link the kynurenine pathway to neuronal signaling and neurotoxicity, pain sensitivity, and 'mood and depression' and they state: "Elevated IDO activity manifests in many settings of high clinical significance, driving substantial interest in manipulating IDO and the Kyn pathway for clinical benefit."

With relevance to development of therapy for neurodegenerative diseases, the paper *Antioxidants Inhibit Indoleamine 2,3-dioxygenase in IFN-y-Activated Human Macrophages: Posttranslational Regulation by Pyrrolidine Dithiocarbamate* by Shane Thomas et al. [68] provides support for the thesis that the antioxidant 2-ME inhibit IDO protein expression and enzyme activity, and to pyrrolidine dithiocarbamate (a known antioxidant) which works post-translationally.

8. CONCLUSIONS

Based on empirical evidence it is factual to say that more is currently known about the progression of Alzheimer's, and the other neurodegenerative diseases discussed in this Perspective Review, than about their initiating causes. The latter is surely multifactorial and accumulating complex ageing changes are contributory. The evidence is strong that mechanisms leading to ROS and oxidant stress are involved in initiation of sequential dysregulation that includes many cell-signaling

molecules that contribute to the pathologies of neurofibrillary tangles, apoptosis, and neurodegeneration. Because ROS strongly appear to be fundamental initiators of essential dysregulations in Alzheimer's disease and other neurodegenerative diseases (including Huntington's disease, amyotrophic lateral sclerosis, Parkinson's disease) prevention and treatment must involve 'normalizing' the effects of ROS. The new proposal is made that dysregulation of IDO1, that involves oxidant stress and heme iron as a cofactor, of the kynurenine pathway is a fundamental cause of the pathology of neurodegenerative diseases and the evidence is more abundant for Alzheimer's but also strong for Parkinson's and ALS with variations in the effects initiated by ROS. The role of oxidant stress as an initiator of neuronal damage and regulation and dysregulation by cell-signaling processes involving IDO1 and leading to neurodegeneration should be a major focus of research for understanding causation and progression mechanisms of Alzheimer's and other neurodegenerative diseases and for guiding the design of future therapies.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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