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Getting Away from Alzheimer's: Nitric Oxide Mediates Neuroprotection Against Neurotoxicity

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive memory loss and behavioral changes. There are currently no known treatments or medications for AD. Nitric oxide (NO) has long been regarded as a component of the neurotoxic insult brought on by Alzheimer's disease neuroinflammation.

However, this perception is being altered by focusing on early developments, prior to the onset of cognitive symptoms. This has brought to light NO's compensatory, neuroprotective function, which increases neuronal excitability to safeguard synapses. Modulation of voltage-gated potassium channel activity (Kv7 and Kv2) is one potential mechanism by which NO can increase excitability. An important next step for the field is to determine the ionic mechanisms and signaling pathways that mediate this protection. A potential therapeutic option for preventing synapse loss early in disease could be found by harnessing the protective function of NO and related signaling pathways.

Introduction

Alzheimer's disease is a type of neurodegenerative disorder in which memory loss, cognitive decline, and ultimately death are all accompanied by a disease-specific loss of synapses and neurons [1].The most prevalent form of dementia is Alzheimer's disease (AD), which affects 36 million people worldwide and is predicted to triple by 2050 [2].The global economic cost of Alzheimer's disease (AD) was estimated to be $604 billion in 2010 , making it the leading cause of disability and the most common reason for elderly people to require care. There is currently no known cure for AD, and the medications that are available are only effective in mild to moderate cases and only treat symptoms rather than the disease's underlying cause .AD will soon become an epidemic of epidemic proportions as the world's population ages ; in this way, there is a steadily expanding need for suitable treatment choices or a fix.

The exact cause of the majority of AD cases, also known as sporadic or late-onset AD, is currently unknown ; However, significant risk factors include advanced age and the transmission of the allele of the apolipoprotein E gene [5]. Numerous genetic mutations have been identified in familial or early-onset AD, a rare and inherited form of AD. The presenilin-1 or presenilin-2 genes (PSEN1, PSEN2) are the most prevalent mutations in familial Alzheimer's disease . Additionally, duplications and mutations in the amyloid precursor protein (APP) have been linked to the condition. Patients with sporadic AD typically present with symptoms between the ages of 65 and 80, whereas familial patients typically present with symptoms as early as the mid-20s [6].

Multifactorial Disease and Clinic Drug Failure

AD is a multifactorial, complex disorder that has made pathogenesis difficult to study. Through the lens of postmortem tissue, snapshots of AD have been studied, resulting in a complex and sometimes unintelligible mass of data. Engaging in longitudinal studies must be the key to comprehending the disease. The discovery of biomarker-based agents that can precisely track the progression of a disease has been fundamental to this. Arising information from long haul studies propose that sickness pathogenesis begins a very long time before mental deterioration [7-9].Before the accumulation of A and phosphorylated tau, AD brains have been shown to experience oxidative and nitrosative stress, which are respectively caused by elevated levels of reactive oxygen and nitrogen species .The formation of A and phosphorylated tau can both exacerbate and elicit the production of reactive oxygen and nitrogen species. Additionally, it has been shown that activation of microglia, inflammation, and disruptions in neuronal calcium signaling all contribute to AD pathogenesis [10]. Synaptic loss and neuronal death are the collective effects of these pathogenic mechanisms, particularly for cholinergic neurons in memory and language-related brain regions .In the end, the disease spreads throughout the brain, resulting in cognitive decline and death.

In Alzheimer's Disease, Nitric Oxide : Mechanisms and Effects

Nitric oxide (NO) is a potent signaling molecule with far-reaching cellular consequences that can be both protective and maladaptive because it is a gasotransmitter that can freely diffuse across membranes. A coordinated effect on brain function is made possible by NO's multiple physiological effects as a vasodilator, inflammatory mediator, and neuromodulator. The neuronal, inducible, and endothelial NO synthases (nNOS , iNOS , and eNOS , respectively) are encoded by three distinct genes, NOS1, NOS2, and NOS3.While iNOS expression is induced in inflammatory cells and is not dependent on Ca2+/calmodulin, both nNOS and eNOS are constitutively expressed and require Ca2+/calmodulin for activation. In the Alzheimer's disease brain, each of these cell types—neurons, endothelial cells, and inflammatory cells-is altered. The breakdown of the blood-brain barrier, deficits in the cerebro vasculature , increased inflammatory signaling, and changes in neuronal signaling are all important features of AD [11] .There is a seemingly contradictory message regarding the role of NO in AD and whether it is neuroprotective or neurotoxic, as

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each of the three NOS isoforms has been hypothesized to play a role in either AD progression or prevention.

The extent to which the molecule of nitric oxide is either neuroprotective or neurotoxic is a point of contention regarding the role of NO in the pathogenesis of AD .Through its induction of the cGMP pathway, several studies have demonstrated that NO possesses neuroprotective properties .Through inhibition of NMDA receptors at glutamatergic synapses, this causes vasodilation and subsequent increases in cerebral blood supply to neurons, thereby reducing the risk of oxidative stress .Both intracellular and extracellular sources of pathogenic NO to neurons have been suggested by the properties that permit retrograde messenger activity and increased NO synthesis caused by overactivation of neuronal NMDA receptors and microglial activation .Presenilin-1 nitrotyrosine increased A1-42 production in aging rat hippocampal neurons in a manner similar to that of PSEN1 mutations associated with familial AD .This finding indicates a specific mechanism by which nitrosative stress might cause one of AD's hallmarks . In addition, prolonged NO exposure can induce the formation of cytoplasmic tau oligomers in SH-SY5Y cells, providing evidence of a potential mechanism underlying tau neuropathogenesis in AD , despite the fact that AD is associated with the presence of S-nitrosylated proteins and tau. Overexpression of AD markers in cell lines has been used in experiments to try to figure out the mechanism, but these experiments only have a limited capacity to accurately model AD. Findings from clinically relevant samples must now be replicated. This opportunity is provided by sporadic Alzheimer's patients induced pluripotent stem cells.

Potassium Channels and Nitric Oxide

Enhancement of Synaptic Plasticity and Neuronal Excitability One of the major issues with studying postmortem tissue is that the cells necessary for research-vulnerable neurons-have been destroyed by the disease. As a result, it can be challenging to evaluate the differences between cases and controls. Identifying early changes in neurons that may result in degeneration or survival is an important aspect of AD research. After that, if these pathways are changed, they might be targets for interventions.

Early changes in neurons that could be targeted have been identified in recent studies using AD mouse models. Three genes involved in familial AD are mutated in the 3x Tg-AD mouse model : APP ; PSEN1 and MAPT, the protein encoding amyloid precursor ; a component of the -secretase complex called presenilin-1also tau Thus, these mice show moderate neuropathology, including plaques and tangles, notwithstanding hippocampal synaptic brokenness. Prior to memory loss, the brain's loss of synapses is an early sign of Alzheimer's disease. As a result, synapse density is a better predictor of cognitive impairments than plaques or tangles . NO functions to maintain both LTP and long-term depression, as well as to increase the likelihood of neurotransmitter release, according to a study on pre-symptomatic AD mice . Synaptic plasticity can be enhanced by altering NO signaling pathways in this manner. In a system that is pathologically dampened, these findings suggest that NO raises the excitability of presynaptic neurons to encourage neurotransmitter release. Presynaptic neurons increased excitability is still not fully understood to be mediated by NO. Presynaptic ion channel activity modulation, on the other hand, is most likely the mechanism. As important regulators of neuronal excitability, M-channels (Kv7 channels) are a potential candidate for this role. channels are outward potassium channels that are voltage-gated and remain open at the neurons' resting membrane potential. Therefore, M-current inhibition increases action potential firing while M-current increases neuronal excitability. NO is a potent neuromodulator that can increase excitability in sensory neurons by inhibiting the M-current . NO-interceded changes in sensitivity have been recognized in the mouse hippocampus, balancing outward potassium flows .Potentiation of Kv2 currents and suppression of Kv3 currents were two of these effects, both of which contributed to the promotion of sustained action potential firing . Indeed, M-channel modulators are being touted as potential therapeutic options for AD and other disorders of neuronal excitability .As a result, drug targets that work include those that alter neuronal excitability and potassium channel activity.

Conclusion

The hypothesis that NO and proinflammatory factors are responsible for the progression of AD has also been challenged by other recent studies. Some intriguing outcomes have been obtained by manipulating the effect of inducible NO in mice to levels comparable to those found in humans. Based on these findings, degeneration of specific brain regions may be the result of local immune suppression rather than immune activation .More thought needs to be given to the timing of interventions and the creation of models that are clinically representative. As a field, we need to establish universality in the selection of samples and in longitudinal studies that cover a time period that corresponds to disease processes (for example, 20 years). A commitment to funding such projects over the long term is essential to this.

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