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Short Communication

A Hypothesis about a Possible a Molecular Mechanism in Alzheimer's Disease

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Abstract

It has been asserted that nucleic acid triple helices might play a role in the molecular pathophysiology of Alzheimer's disease. Could changes in polyamine levels drive this? Could this partially explain why the Mediterranean diet is associated with a reduced risk of Alzheimer's disease?

Introduction

Polyamines have diverse physiological effects including, it is thought, diverse effects on the brain [1]. Polyamines may play roles in: protein synthesis, stabilization and compaction of DNA, the modulation protein kinases, influencing epigenetic regulation, influencing acetyl cholinesterase activity, affecting various ionic channels –including modulating N-Methyl-D-Aspartate receptors (NMDAR), and might modify the conformation and aggregation of proteins - including the aggregation of amyloid-beta (Aβ) peptide [1, 2, 3,4, 5, 6]. This is of particular interest in Alzheimer's disease, where it is believed that there are changes in polyamine concentrations [5]. Considering these diverse physiological effects, a central question is what is the net effect of the altered polyamines levels found in brains affected by Alzheimer's disease? In a mouse model, it appears that inhibition of polyamine system reverses the memory impairment induced by Aβ [7]. Another question is could other molecular mechanisms of polyamines also be involved?

A Hypothesis

DNA is a highly dynamic molecule. While nearly everyone is familiar with the B-helix from high school biology, DNA can actually form many different conformations [8-10]. These structures are believed to have biological relevance [8 -10]. One class of conformations is the nucleic acid triple helix [8 -10]. The third strand binds in the major groove of the double helix through Hoogsteen or reverse Hoogsteen bonding [8 -10]. The third strand targets a polypurine track on the double helix. In H-DNA, the DNA folds back, resulting in intramolecular triple helix formation along with an unpaired stretch of DNA [9, 10]. Alternatively an RNA oligonucleotide can bind in the major groove of the DNA [8 -10]. It has been asserted that nucleic acid triple helices have biological functions *in vivo* [8 -10]. There is speculation about multiple mechanisms by which nucleic acid triple helices might influence gene expression [8-12]. It has been speculated that the polypurine tracks in genes differentially expressed in Alzheimer's might be targets for triplex formation [13, 14].

The question is what influences triplex formation? One of the ways might be polyamine levels [8, 15, 16]. Nucleic acid triple helices are stabilized by positively charged polyamines which reduce repulsion between the negatively charged phosphates along the backbones of the three nucleic acid strands. There is evidence that polyamines may help stabilize nucleic acid triple helices. Furthermore, there is evidence that polyamines may be elevated in the brains individuals with Alzheimer's [17]. This raises the question is gene expression in the brains of patients with Alzheimer's altered via nucleic acid triplexes that are stabilized by elevated polyamine levels?

What might help control polyamine levels? Cancer researchers believe that polyphenols might help to curb polyamine levels [18, 19].The traditional Mediterranean Diet contains polyphenol-rich components such as fruits, vegetables, olive oil, and legumes [19, 20]. Could this partially explain why the polyphenol-rich Mediterranean Diet has been associated with a reduced risk of Alzheimer's disease [21, 22]?

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