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Open Peer Commentary: **Metabolic and Hormonal Contributors to Neuronal Necrosis in Alzheimer's Dementia**

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Running Title: Processes In Alzheimer's Dementia

Abstract

Research into the causes of neurotoxicity in Alzheimer's Dementia (AD) has focused on neurofibrillary tangles and beta amyloid (Aβ) plaques. This paper proposes the heterodox theory that these hallmarks of AD are the visible effects, not direct causes of neuronal necrosis. Rather AD results from a combination of age-induced, disproportional decline in physiological support for aerobic metabolism, and dysregulation of the sleep cycle processes. The hypothesis is that the decimation of neurons in AD results from a combination of neurotoxicity and increased apoptosis caused by:

1. direct damage from toxic waste products of anaerobic glycolysis due to a progressive decline in the capacity of neurons to perform oxidative phosphorylation (OXPHOS) and an increased reliance on anaerobic glycolysis to meet metabolic needs
2. impaired cellular repair and effluent release due to dysregulation of non-rapid eye movement (NREM) sleep allowing damage to cell membranes and synaptic junctions to accumulate inducing a chronic inflammatory response
3. indirect damage from products produced by inflammatory reaction to toxic metabolites

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4. neuronal apoptosis from the AβPP-mediated pathway due to the age-induced decline of growth hormone (GH), GH-releasing hormone (GHRH) and insulin-like growth factor (IGF)

Keywords: Alzheimer's Dementia|anaerobic neurotoxicity|inflammation|neuronal apoptosis|Non-REM Sleep

Introduction

Chronic inflammation has been implicated as a risk factor for AD and a potential initiator of pathogenic processes. [1] [2] [3] The inflammatory process and its consequences in AD have been studied extensively. However, absent trauma, the pre-symptomatic initiator of inflammatory process in the neocortex has not been conclusively determined. It is possible that damage to neuronal cell membranes and synapses could initiate an inflammatory response years before the onset of symptoms.

Disturbance or reduction of non-rapid eye-movement (NREM) sleep is a highly-correlated with β-amyloid (Aβ) deposition and risk factor for development of AD. [4] [5] The consensus hypothesis is that (Aβ) deposition causes NREM sleep disturbance. Instead we argue that inflammation caused by damaging episodes of anaerobic glycolysis in the neocortex impairs NREM processes and memory consolidation. This in-turn reduces flushing of waste products and cellular repair by neocortical neurons during NREM cycles in a syndromic cycle. [6]

Research in neural plasticity has determined that the adult human brain is capable a rewiring and adapting in response to injury, stress, or new stimuli. Such rewiring includes the formation of new axonal and synaptic connections (neurogenesis) and pruning (neuro-apoptosis) of unused pathways or connections to remove stressed or diseased neurons.[7] Research in the structure and function of amyloid precursor protein (AβPP) has uncovered evidence that it may be involved in both neurogenesis, and neuro-apoptosis pathways.[8][9]

Circulatory and Metabolic Response to Synaptic Energy Demand

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The brain has the highest energy and oxygen requirements of any organ in the human body. The frontal lobes of neocortex have arguably the highest requirements of the brain's regions [10] [11]. The consequence is that when resting human brains transition to high levels of neocortical synaptic activity glycolysis disproportionally increases [12] [13]. In adolescence and young adulthood after a short delay, the neocortical circulatory network reacts to increase capacity to deliver oxygen and nutrients to meet the energy requirements of a burst of synaptic activity and remove lactate through vascular and perivascular drainage. Normal aerobic metabolism (OXPHOS) then resumes and normal neuronal functions are restored with little or no neuronal damage [11].

By the seventh decade of life, or earlier in some cases, the adult neocortex retains most of the energy and nutrient requirements of its younger self, but the physiological support is usually disproportionally diminished. Neuronal mitochondrial function may measurably decline [14] [15]. Overall cardiovascular and aerobic capacities are generally lower. Arterial sclerosis may decrease the responsiveness of the neocortical vascular network and provoke an inflammatory response. Background inflammation may produce reactive oxygen species (ROS) and deplete antioxidant reserves. All of these factors to various degrees may result in an increased frequency and duration of anaerobic glycolysis, and provide less energy to regenerate oxidized antioxidants. The brief episodic reliance on glycolysis typical of young adulthood may progressively expand to include anaerobic glycolysis to damaging effect.

Anaerobic Glycolysis in Neocortical Inflammation

Cycling between OXPHOS and anaerobic glycolysis during periods of high synaptic activity may damage neurons and astrocytes of the hippocampus and frontal cortex internally and externally. While relying on anaerobic glycolysis, neurons would not have sufficient energy to take up and convert lactate from astrocytes. Astrocytes would be confronted by an extracellular environment containing lactate expelled from neurons in addition to their own resulting in a high concentration of lactate before vascular dilation facilitates removal [16]. There is experimental evidence that high concentrations of lactate, and resulting low pH surrounding neurons unable to use it leads to neuronal necrosis [15] [17] [18]. Hypothetically, episodic exposure to the low pH over a period of years or decades leads to cumulative damage, and

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chronic inflammatory responses in the neocortex and a self-reinforcing cycle of neuronal damage, inflammation and decreased capacity for OXPHOS.

In neurons, proton leakage from mitochondria and calcium channel reversal during periods of anaerobic metabolism may cause internal damage [19]. Episodes of anaerobic metabolism would incur an oxygen and energy debt resulting in an unusually high metabolic demand to recover. Hypothetically, the switch back to aerobic respiration may temporarily overwhelm antioxidant response resulting in a short-term concentration of ROS in the cerebrospinal fluid and oxidative damage to cell membranes [20]. Neurons recovering from the oxygen and energy debt would be less capable of supporting synaptic activity while recovering. Oxidative damage to cell membranes could prolong the duration of recovery and reduced aerobic capacity into the sleep cycle causing reduced participation in sleep cycle processes.

Anaerobic glycolysis is unlikely to provide more than the minimum energy required to allow the affected neurons to survive until aerobic metabolism resumes. It is possible that this could result in a reduction or cessation of synaptic activity and protein synthesis for ion transport [11]. When aerobic metabolism resumes neurons may up-regulate ion-transport and resume protein synthesis in order to support synaptic activity. Initially, the energy output may not sufficiently energize cell membranes resulting in dysregulation of ion transport helper proteins. When the cell membrane is sufficiently energized the influx of metal ions may be exceed the capacity of the protein storage complexes before ion transport is down-regulated, forcing neurons to excrete surplus metal ions. In the absence of a robust antioxidant response, the presence of ROS, metal ions and AβPP in the extracellular medium provide the constituents of amyloid beta (Aβ) and the energy potential to catalyze conformal changes to convert AβPP into Aβ [21].

Aβ May Not Be Neurotoxic

However, episodic production of Aβ and the presence of Aβ plaques does not correlate well with clinical assessments of cognitive decline. [22] One explanation is that AD is prevented if neurons are allowed to repair the damage and clear Aβ from the extracellular medium during the sleep cycle. NREM sleep relieves the hippocampus and neocortical neurons and synaptic astrocytes of the much of the energy

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burden of supporting the synaptic storm of consciousness. The reduction of synaptic activity in NREM sleep allows these neurons to devote energy to essential maintenance and repair functions coincident with flushing Aβ from the cerebrospinal fluid. [8]

The cellular processes that can create Aβ are present throughout life but the accumulation of amyloid beta (Aβ) is particularly associated with reduced NREM sleep [7] [15]. NREM provides the neocortical equivalent of skeletal muscle relaxation that allows neurons and astrocytes to regenerate depleted antioxidants, re-energize cell membrane and clear cellular waste products. [23] In theory, Aβ need not be inherently toxic to contribute to neuronal decimation. Aβ could be indirectly responsible for neuronal toxicity by impeding uptake of oxygen during periods of high synaptic activity, physically impeding removal of waste products or by inducing an inflammatory response to facilitate its removal.

AβPP as a Waste Product

Research has focused on the conversion of AβPP into Aβ as the primary cause of AD. However, numerous drug trials focused on reducing the production of AβPP, conversion of AβPP into Aβ or elimination of Aβ plaques have failed [24] [25]. One possible explanation is that this is not the causal mechanism, and that accumulated AβPP is a waste product resulting from failed neurogenesis. In AD neurogenesis fails with increasing frequency resulting in more AβPP in proximity to neurons and coincident conversion into Aβ plaques.

Neurogenesis could fail due to one or more of the following: insufficient growth factors, insufficient energy due to compromised metabolism, the presence of toxic metabolites or inflammatory ROS, or insufficient time due to fragmented or missing REM and/or NREM cycles.

Conclusion

This theory suggests that neuronal decimation is due to a combination of toxicity, inflammation, apoptosis, and reduced repair and regeneration. Hypothetically, the decreased capacity for OXPHOS, increasing anaerobic and oxidative damage, and reduced time and energy available during NREM sleep for recovery, repair and to clear waste products create conditions for the development of AD. It is possible that any of these mechanisms could manifest independently to initiate neurodegenerative

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processes indicative of AD. It is also possible that the speed of neurodegeneration and resistance to treatment could be proportional to the number of causal mechanisms at work as each could become syndromic in isolation or when acting in concert with the others.

Neuronal necrosis through apoptosis is a normal function that facilitates neural plasticity. However, the process could become a syndromic driver of AD if AβPP is both mediator of neurogenesis, and neuro-apoptosis. [7] [9] It is possible that AβPP plays a role in memory consolidation during sleep. If GH and IGF mediate synaptic construction for the formation of permanent memories, then declining levels of these hormones would tend to impair memory formation. [26] If so, then incomplete memory consolidation could lead to up-regulated production of AβPP. It is possible that the function of AβPP is determined by a pathway initiated by GH or IGF, and lack of the growth factors during sleep could switch the function of AβPP to neuro-apoptosis. Up-regulated production of AβPP would lead to an accelerating cycle of over-production of AβPP, apoptosis, and accumulations of Aβ. A rigorous clinical study of GHRH focused on neurochemical changes found that supplementation of GHRH had favorable effects on cognition in adults with mild cognitive impairment. [27]

Theory suggests that measuring the changes in the scope and intensity of the processes sited here will have better correlation with rate of cognitive decline as measured by clinical assessment than imaging measurements of Aβ and AβPP. On a more hopeful note, it suggests that therapies targeting these processes may slow or even reverse cognitive decline, and if treated preemptively delay AD from developing for decades beyond what is common today. Most important to persons at risk for early onset AD, preventive treatment to preserve youthful memory synapse formation through supplementation of GHRH, dietary antioxidants and anti-inflammatories with exercise and sleep therapy would pose little or no risk to health yet could provide significant protection against the development of AD.

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