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IS BRAIN AMYLOID PRODUCTION A CAUSE OR A RESULT OF DEMENTIA OF THE ALZHEIMER TYPE?

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Abstract

The amyloid cascade hypothesis has guided much of research into Alzheimer disease (AD) over the last 25 years. We argue that the hypothesis of beta amyloid (A β) as the primary cause of dementia may not be fully correct. Rather, we propose that decline in brain metabolic activity, which is tightly linked to synaptic activity, actually underlies both the cognitive decline and the deposition of A β . A β may further exacerbate metabolic decline and result in a downward spiral of cognitive function, leading to dementia. This novel interpretation can tie the disparate risk factors for dementia to a unifying hypothesis and present a roadmap for interventions to decrease the prevalence of dementia in the elderly population.

Keywords

Amyloid beta Protein; Apolipoprotein E; Metabolism; Dementia; Olfactory Pathways; Mitochondria; Etiology; Pathology; Therapeutics

INTRODUCTION

CURRENT HYPOTHESIS

The amyloid cascade hypothesis has guided much of research into Alzheimer disease (AD) over the last 20 years [1,2]. The amyloid cascade hypothesis posits some primary abnormality of processing of the amyloid precursor protein (A β PP) that causes an overproduction of the 4 kD A β fragment. This fragment spontaneously aggregates in a β -

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pleated sheet structure. The 4kD fragment is toxic to neurons and synapses either as an early soluble monomeric, dimeric or oligomeric form, or as an aggregated deposition, the senile or neuritic plaque. Toxic effects of A β are proposed to cause the dementia. The diagnostic requirement for both dementia and A β senile or neuritic plaques [3] for a diagnosis of AD, emphasizes the assumed causation of dementia by A β . Hence, major scientific effort has focused on inhibiting formation or facilitating clearance of A β from the brain.

We argue that, although these data are not incorrect *per se*, the hypothesis of A β directly causing dementia may not be fully correct. For example, multiple myeloma is often detected when a patient presents with kidney dysfunction [4], and although a kidney biopsy finds IgG forming β -pleated amyloid, and these deposits may directly cause renal dysfunction, the ultimate etiology of the renal dysfunction is a neoplastic process. We propose a causative event further upstream precedes A β deposition. This causative event may be a decline in central nervous system metabolic activity. A β is deposited as a secondary consequence of metabolic decline.

PROBLEMS WITH THE AMYLOID CASCADE HYPOTHESIS FOR DEMENTIA

Three major observations raise difficulties with the amyloid cascade hypothesis. The first observation is functional: A β is normally present in the brain and must serve some function other than causing dementia. Of note is that soluble A β concentration is higher in younger individuals than older in the absence of dementia [5]. One possible role for A β is modifying neuroplasticity [6,7,8,9]. The second observation is that individuals with fully penetrant mutations of either A β PP or one of the processing enzymes (gamma secretases), do not show dementia until 20–40 years of age [10]. The third observation is that 20–30% of cognitively intact individuals carry significant numbers of pre- or postmortem detected amyloid plaques [11,12]. Importantly, for this third observation, immunotherapy can remove A β deposition but does not significantly affect the progress of dementia [13,14] suggesting that A β alone may not be sufficient to cause dementia in AD.

These problems, among others, have led to questioning the accuracy of A β as the primary cause of AD [15,16]. The major problem with this skepticism was that, until recently, no alternative hypothesis could explain the cognitive decline, A β deposition, and numerous other changes characteristic of AD, such as abnormal tau accumulation or evidence of excessive reactive oxygen species.

AN ALTERNATIVE HYPOTHESIS

We propose an alternative hypothesis based on findings in the last few years which are discussed below. We hypothesize that a decline in brain metabolic activity regardless of etiology, is the underlying cause of cognitive decline and dementia. Decreased metabolic activity increases beta secretase (BACE) which, in turn, increases A β deposition as a secondary response.

BRAIN METABOLIC ACTIVITY AND COGNITIVE FUNCTION

Decreased brain metabolic activity measured either by PET or fMRI, has been shown to be associated with dementia [17,18]. The assumption of most brain metabolism studies in dementia is that cell death, plaques and neurofibrillary tangles cause the metabolic decline. However, brain metabolic decline is also correlated with cognitive decline in aged rodents [19,20,21] which do not produce A β that aggregates to form senile plaques. Thus, it is possible that declines in brain metabolic activity lead to or are in response to cognitive impairment.

Synaptic activity and brain metabolism are strongly correlated. Estimates suggest a close to one-to-one correlation between synaptic activity and glucose utilization. [22,23]. Glucose utilization is required for transmitter release and uptake, post-synaptic activity, axon depolarization and repolarization, and other processes associated with synaptic transmission. Importantly, severity of dementia correlated better with synaptic loss [24,25] and mitochondrial abnormalities [26] than did A β deposition. The observation of a tight coupling between brain metabolic and synaptic function and their correlation with dementia emphasizes the importance of evaluating the role of metabolism in the formation of AD lesions.

METABOLIC ACTIVITY REGULATES BACE ACTIVITY

Key elements in our hypothesis are the data indicating that synaptic activity and brain metabolic activity modulate BACE, the initiating enzyme in A β formation in rodent species. Expression of BACE and proteins derived from A β PP increase in response to decreased metabolic activity [27,28,29]. A recent study reported that chronically induced cerebral hypoperfusion in rats resulted in increased BACE and A β and poorer learning in a Morris water maze [30]. Synaptic control of BACE and A β PP products is especially well shown by unilateral closure of the external nares. Unilateral closure, blocking stimuli from reaching olfactory receptors in the olfactory epithelium, suppresses synaptic and metabolic activity both in the olfactory bulb (OB) and in downstream cortical sites [27,31]. The mitochondrial enzymes cytochrome oxidase and succinic dehydrogenase (indicators of brain metabolic activity) decline. Importantly, BACE is upregulated in the axon terminals of the olfactory receptor neurons as metabolism declines [27]. Upregulation of BACE results in ipsilateral increased production of c-terminal fragments of A β PP and the 4kD A β rodent homologue. Moreover, in mice lacking BACE, closure also suppresses cytochrome oxidase and succinic dehydrogenase showing that the metabolic deficits are a primary response to synaptic activity decline and not increased BACE and A β [27]. Hence, synaptic activity could dynamically control the expression of BACE and c-terminal fragments of A β PP by modulating metabolic activity.

THE ROLE OF BACE IN NORMAL COGNITIVE FUNCTION

What then is the role of BACE and A β in normal function of the brain? Data are limited, but we hypothesize that A β is integral to modulation of neuroplasticity. In preparations that maintain reasonably normal synaptic connectivity (e.g., brain slices), A β can either facilitate or inhibit long term potentiation and synaptic activity by a concentration-dependent mechanism [6,7,8,32]. Therefore, the olfactory bulb (OB) presents a model for understanding how the BACE/A β system might function to modify plasticity. The olfactory receptor neurons in the olfactory epithelium are replaced throughout life leading to a great deal of neuroplasticity [33]. New neurons grow an axon and form synapses in the OB [33,34]. Hence, evidence of synaptic plasticity is extremely high in the OB as is the expression of BACE [35]. Following unilateral naris closure, OB BACE significantly increases in the presynaptic terminals of the olfactory nerve ipsilateral to the closure. Moreover, changes can be reversed within days by simply opening the naris [27]. The products of BACE could modulate synaptogenesis in the OB when olfactory input is transiently lost following injury, disease, or during normal regeneration of olfactory receptor neurons. In addition, our unpublished studies of BACE localization in human and monkey tissues show that BACE is conspicuously absent in layer IV, where thalamic axons terminate and where plasticity may be disruptive to function. We suggest that BACE is part of a dynamic system to regulate axonal growth and synaptic plasticity.

DELAYED DEMENTIA ONSET IN AUTOSOMAL DOMINANT DEMENTIA

The second problem, adult onset of autosomal dominant dementia in individuals with A β PP or gamma secretase mutations, can also be explained by a relationship between metabolic and BACE activity. At about 30 years of age, brain metabolic activity [36,37,38,39] and mitochondrial function [40] appear to decline in normal individuals. We hypothesize that this normal age-associated metabolic decline results in upregulation of BACE and over- or aberrant production of A β in those with the abnormal genotype. This leads to decline of synaptic activity and further metabolic decline. Onset during childhood does not occur because metabolic activity may be high enough to suppress BACE, BACE may not be functional during the maturational period of the brain, or other fundamental developmental processes (e.g. synaptogenesis) mask or neutralize A β production. After maturation, when brain metabolic activity declines [36,37,39], BACE increases enough to support A β deposition in those with a predisposing genotype. Hence, the development of dementia in the autosomal dominant forms of AD may occur as a consequence of maturation of synaptic connectivity in the brain and decreasing metabolic activity. Age-related decrease of metabolic activity would start the defective processing of A β and the downward course of cognitive decline.

THE ROLE OF A β AND COGNITIVE DECLINE

The apparent lack of efficacy of A β removal on stopping cognitive decline is the final problem to address. Although published studies showed that deposits of A β were substantially reduced, no slowing of the dementing process occurred [13,14]. Furthermore, 20–30% of elderly individuals with normal cognitive function have substantial amounts of A β plaques [11] or show brain amyloid binding in life [12]. We propose that these discordances represented the indirect relationship between A β and cognitive decline. A β deposition may not be the primary cause of dementia but rather a response to some other process that occurs. We propose that brain metabolic decline might be the principal cause of dementia. Deposition of A β may be a response to that decline.

A METABOLIC SCENARIO FOR ALZHEIMER TYPE DEMENTIA

We propose the following scenario for cognitive dysfunction and A β deposition (Figure 1). Due to multiple, etiologically diverse and independent factors, metabolic activity in the adult brain declines. This may lead to mild cognitive decline and simultaneous BACE activation. Regardless of why metabolic/synaptic activity decreases, BACE expression and, hence, A β (and the rodent homologue that doesn't aggregate) increase. At a slightly later stage, A β and other products from A β PP further adversely affect mitochondria and energy metabolism [41,42,43]. Compromised mitochondria may further suppress synaptic and metabolic activity and increase reactive oxygen species and injure mitochondria [15,44]. In sum, we would have a self-reinforcing system; any initial event suppressing metabolic/synaptic activity could amplify itself, leading to more BACE and A β [35]. A small perturbation could result in effects that would potentiate over time leading to the co-occurrence of dementia and A β .

RISK FACTORS FOR DEMENTIA

Factors that cause the initial metabolic decline could include maturational changes, cerebral vascular aging, chronic diseases (e.g., diabetes), injury or sedentary lifestyle selection. Since none of these conditions acts in isolation, we would expect synergistic effects on metabolism/synaptic activity and cognitive function decline, progressing to dementia.

Maturation changes would be characterized by declines of metabolic activity that occur with normal maturation [36,38,39,40], which could underlie the onset of autosomal dominant forms of AD. Chronic diseases, such as Type I and type II diabetes would also be a logical etiology for cognitive compromise if they chronically decrease CNS metabolic activity [45,46,47]. Of note are studies that propose a decrease of brain glucose utilization in long-term diabetics [48], decreased brain metabolic activity during mild hyperglycemia [49] and cognitive compromise in Type I diabetics [50]. Moreover, the increased risk for cognitive decline in type II diabetes is not associated with a greater density of A β deposition than non-diabetics but with evidence for more small strokes [51].

Acute injuries, such as stroke, can result in both local and remote changes. Local effects occur in response to vascular insufficiency and from resulting neuronal death. Brain-wide effects (diaschisis), represent decreased brain activity remote from the infarct [52]. Decreased metabolic activity could start a progressive decline leading to further decline. Even the role of apolipoprotein E, apart from its role in transport of A β , fits this schema, since the ϵ 4 isoform of apoE is less effective than either the ϵ 2 or ϵ 3 isoforms in facilitating neuronal process regeneration [33,53]. If neurite regeneration and synaptogenesis are slowed, then recovery from insults (e.g., strokes) would be impeded and synaptic activity/metabolic activity may not recover. Delayed regeneration/restoration of function would leave neurons deafferented and dysfunctional for longer periods and would further exacerbate decreased metabolic/synaptic activity.

Finally, lifestyle factors would fit into this scenario. Educational achievement and cognitive/social engagement seem to decrease the risk for dementia [54,55]. Physical exercise, which has been shown to increase brain activity, and diet can be protective against onset/progression of dementia [56,57,58]. Even estradiol replacement in the perimenopausal period appears to decrease the risk of developing dementia later in life [59], and estradiol replacement increases synaptic activity [60]. Hence, lifestyle choices influence the production of BACE and A β .

CONCLUSION

We propose that the underlying cause of dementia is decreased brain synaptic/metabolic activity independent of the etiology. Decreased activity leads to cognitive decline and also, indirectly to A β deposition. A β may cause further declines in synaptic/metabolic activity, but critically, at least in the earliest stages of the disease, it is the synaptic loss and metabolic decline that cause the dementia. A β production is a secondary phenomenon that may, as in multiple myeloma, result in further clinical decline. The obvious interventional approach, if this hypothesis is correct, is to identify and address factors that cause decreased metabolic/synaptic activity, neuronal death and dysfunction. A proximate goal would be to find and emphasize ways to increase brain metabolic activity. These interventions would, ideally, occur prior to the onset of dementia. Maintenance rather than intervention may be the optimal direction of future behavioral and pharmacological interventions but study of these would require a significant investment in long term studies.

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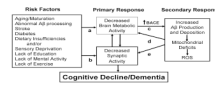
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1. .

This figure summarizes our hypothesis about the causes of cognitive decline leading to Alzheimer Disease. The first column (Risk Factors) includes conditions implicated in cognitive decline. The first five are “physical” factors. The latter four could be considered life-style factors although we propose substantial overlap of the two categories. The second column (Primary Response) represents the response of the CNS to the Risk Factors that decrease either metabolic (a) OR synaptic activity (b). Although presented as separate factors, metabolic and synaptic activity are closely tied. Critically, decreased synaptic activity leads to cognitive decline. BACE (c) is substantially regulated by metabolic activity; decreased metabolic activity increases BACE leading to increased production of A β . The final column (Secondary Factors) indicates that A β , either as soluble or fibrillary amyloid, may disrupt metabolic activity by suppressing mitochondrial activity or producing ROS (d) which further disrupts metabolic activity. Alternatively, A β can also disrupt synaptic function (e) that could feed back on metabolic activity. The key to the progressive nature of AD is that we propose that the Primary and Secondary factors are a self-reinforcing cycle that can exacerbate effects of the numerous Risk Factors on metabolism and synaptic activity.