The Pathogenesis of Alzheimer Disease: An Alternative to the Amyloid Hypothesis

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Abstract. This paper attempts to put together in the form of a flow sheet (Fig. 1) the several known alterations, both chemical and structural, of brain tissue in Alzheimer disease, which ultimately result in dementia. While most investigators in the field believe strongly that amyloid deposition is at the core of the disease, this writer finds that a more coherent and thus more satisfying schema can be based on the centrality of cytoskeletal abnormality. Not only do all four identified genes interact one way or another with the cytoskeleton, but abnormality of the latter leads to alterations of the Golgi apparatus with effects on protein processing, and on axoplasmic flow such that one can expect loss of synapses and subsequent loss of neurons with consequent disconnection and loss of neurotransmitters. Dementia is the result.

Key Words: Alzheimer; Axoplasmic flow; Cytoskeleton; Golgi; Synapses; Transmitters.

INTRODUCTION

A textbook of cell biology could well be written utilizing Alzheimer disease as the paradigm around which nearly the whole of cell metabolism could be described. Interestingly, there has been very little written applying the principles of cell biology to Alzheimer disease despite the recognition that several important cellular structures are obviously involved. The actual and hypothetical effects of amyloid on the brain tissue have so dominated thinking in the field as to make many neglect other mechanisms which might well be of even greater causal significance. The following brief dissertation will attempt to assemble the several disparate parts and findings of the Alzheimer complex with reference to the overall flow diagram in Figure 1.

FORMULATION

At the genetic level (keeping in mind that this area other than ApoE has to do with a minority of patients), it has been reported that presenilin 1 (chromosome 14) is markedly diminished in cells with neurofibrillary tangles (1). It is said that presenilin 2 (chromosome 1) is genetically homologous to presenilin 1 (2), and it aggregates with the cytoskeleton fraction (personal communication, R. Tanzi). Amyloid precursor protein (chromosome 21) (APP) contains an epitope which is found again in the paired helical filaments of the tangle (3). ApoE (chromosome 19) binds to amyloid at approximately physiologic concentrations (4), but also affects microtubular metabolism by its relation to tau and MAP2c (5).

In all AD cases destabilization of the cytoskeleton is clear in the observed deficiency of formed microtubules (6) within the neurons, and in the formation of paired helical filaments (7), which are made of hyperphosphorylated tau (8). Normal tau is essential to the stability of tubules (9). Destabilization of the microtubular system in the perikaryon causes breaking of the Golgi apparatus into small fragments (10). This dispersion of the Golgi would be expected to have an effect on processing and targeting of proteins (11), and thus on the processing of APP. Abnormal post-translational processing of APP might well lead to abnormal amounts of β-protein, leading to its deposition in the extracellular space. Amyloid can be deposited through several more-or-less independent mechanisms: constitutive amyloid with ApoE4, degraded Golgi processing, and dystrophic axons.

Loss of the microtubule system must have a major effect on axoplasmic flow, which is dependent on the tubules as a track (12) along which kinesin acts as the motor (13). Diminished axoplasmic flow would lead to a diminished supply of substrate to the distant terminals, especially in the axon but also in dendrites, causing dystrophic changes in affected neurites (14). Study of human brain biopsies (6) and examination of aged canine (15) and primate specimens (16) have all shown that dystrophic neurites precede deposition of amyloid in the formation of neuritic plaques (17).

Given poor flow and resultant dystrophic neurites, synaptic loss would be predictable, and is well known to occur (18, 19). Loss of synapses has multiple effects. One that is not often mentioned is that with reduced terminal arbor, there would be lessened retrieval of trophic factors from the target area for retrograde transmission by the deficient flow system back to the neuronal perikaryon. This would lead to death of the neurons, probably by the apoptotic program. Degenerating synapses would also activate microglia in the neuropil between plaques. These activated microglia release lytic cytokines and complement which add to the synaptic destruction (20). Finally, loss of synapses results in topographic disconnections (21), leading to the syndrome which is characteristic of dementia. Loss of neuronal perikarya, and loss of the transmitting apparatus lead to a deficiency of neurotransmitters first recognized in the cholinergic system (22), but subsequently in several others (23, 24).
Finally, the disconnection of topographic functional areas and the loss of neurotransmitters lead to the dementia which we recognize as Alzheimer disease.

It is to be noted in this schema that amyloid plays a relatively small and peripheral role in the pathogenesis of AD. In this regard one can point out that mutations of the APP gene are associated with fewer than one-tenth of one percent of Alzheimer patients. Why amyloid is present in all the other cases of AD, but not in other diseases, is unknown. Fibrillar amyloid does not arrive in the brain before other changes in humans (14), primates (15), or even in the Athena transgenic mouse, where at two months there is a deficiency of GAP 43, at four months a deficiency in synapse number; and at six months, finally, amyloid is found (E. Masliah, personal communication). Evidence of amyloid toxicity has not been satisfactorily revealed in vivo despite frequent in vitro demonstrations. Diffuse plaques containing only nonfilamentous amyloid have no effect on the number of synapses in their area (25), while neuritic plaques with dense amyloid cores display only local alterations without diffusion into adjacent tissue. Only 5 to 10% of cortical volume is occupied by plaques. Certainly no one would suggest that damaging 10% of the cortex is harmless, let alone that amyloid is good for the brain, but it does not seem to play a central role, and other mechanisms of damage seem more important.

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