LETTER TO THE EDITOR

About the Neuronal and Non-neuronal Origin of Amyloid-β Plaques and the Source of Amyloid Deposits in Congophilic Angiopathy


This paper is an interesting review of current thinking about the pathogenesis of neuritic (senile) plaques and congophilic angiopathy in Alzheimer disease (AD). However, certain aspects of plaque formation need a broader discussion.

In the introduction, the authors stated, “two major types of senile plaques have been identified: classic and diffuse senile plaques, which are both abundant in AD brains.” Actually, the classical plaques (with a central core or amyloid star) are only a minority of the plaques. Primitive plaques (without the central core of amyloid) and diffuse plaques are the most abundant types of plaques in AD (1). Furthermore, in contrast to the statement of the authors that “it is suggested that diffuse senile plaques gradually transform into fibril-containing classic senile plaques,” there is no evidence for such transformation. Our studies of plaque development in Down syndrome (2) and in aged dogs have shown that diffuse and neuritic (senile) plaques have separate cellular origins. This important issue in plaque pathogenesis has not been discussed by the authors.

Furthermore, the authors discuss the cellular involvement in the generation of senile plaques, based only on immunohistochemical staining of brain sections for APP. The authors state that “neurons of normal and AD brains, but not microglia cells or astrocytes, expressed APP.” They discard microglia as a source of amyloid β (Aβ), stating that “it is possible that they have a secondary function, for example, in processing Aβ into fibrils. Alternatively, their expression of Fc and complement receptors and of a marker indicative of an enhanced lysosomal activity suggest that they function as phagocytes and remove Aβ. In summary, it is likely that neurons are the major candidates for the production of APP and Aβ in senile plaques, whereas microglia cells and astrocytes may have an accessory function in senile plaque formation.” However, our studies and others showed that microglia can be the source of Aβ. Electron microscopic studies of the relationship between amyloid deposits and microglia cells clearly showed that amyloid formation in classical and primitive plaques is a cell membrane-associated phenomenon similar to Kupffer cells in systemic amyloidosis. The first amyloid fibrils appear in the area of altered endoplasmic reticulum membrane and deep infoldings of cytoplasm membranes (3). Previously, microglia have been found to produce APP mRNA (4) and APP protein. We also found APP in transformed murine microglia cell lines, generated and kindly donated by Dr M. Righi (Milan, Italy). The cellular levels of APP were between 50% and 80% of those in neuroblastoma human cells SY5Y or rat cells PC12 (Fig. 1). Microglia, in contrast to neuroblastoma cells, produce only a trace amount of immature APP 695. Untransformed microglia isolated from brains of dogs were also found to produce APP, mainly isoforms that contain the KPI domain. These primary cultures of microglia also produce Aβ. The secretion of Aβ in LPS-stimulated microglia measured by ELISA was 25 pg/10⁵ cells/24 hours (5). This secretion is about 4 times lower than Aβ production in smooth muscle cells that are moderately involved in amyloidogenesis, but more than 3 times higher than in fibroblasts (5).

In discussing the role of Aβ-associated proteins in congophilic angiopathy, the authors stated that “early Aβ deposits in CA have been identified close to the basement membrane.” Actually, extensive electron microscopic studies (6) have shown that the first amyloid fibers appear in the central portion of the basal lamina between the smooth muscle cells. Therefore, polymerization of the Aβ into fibrils in the vessel walls is clearly an extracellular event; in contrast, as indicated above, in microglia and
perivascular cells, it is a cell membrane-associated process.

REFERENCES


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RESPONSE

Amyloid Formation in Senile Plaques and Congophilic Angiopathy

Response to “About the Neuronal and Non-neuronal Origin of Amyloid Plaques and the Source of Amyloid Deposits in Congophilic Angiopathy.” (H. M. Wisniewski and J. Frackowiak)

We appreciate the time Drs Wisniewski and Frackowiak invested to comment on our review that summarizes the arguments for a different pathogenesis of senile plaques and congophilic angiopathy in Alzheimer disease, which appeared in the July issue of this volume.

The first issue raised by the authors is a matter of terminology important to the classification of the ββ-containing lesions of Alzheimer disease. The terminology we used may have been somewhat confusing. Diffuse and classic senile plaques were mentioned as examples of two clearly morphologically distinct types of ββ deposition in the Alzheimer disease brain. In addition to these two types, primitive senile plaques form a considerable population in the Alzheimer disease brain. Together with classic senile plaques, they belong to the subtype of neuritic senile plaques. Probably, it is more appropriate to make a classification of senile plaques into “diffuse,” “neuritic,” and “amyloid” plaques to avoid potential confusion, as recently suggested by Dickson (1).

The second point made by Wisniewski and Frackowiak concerns the cellular involvement in the pathogenesis of senile plaques and the role of microglial cells in particular. The authors refer to their own studies in which they described a clear and intimate association between microglial cells and the amyloid fibrils of classic senile plaques. There is no doubt that activated microglial cells cluster around classic senile plaques; this has been confirmed by many other authors (2). However, since their conclusions are exclusively based on static morphological observations and are limited to classic senile plaques, it is rather speculative to conclude, as the authors do, that these cells produce the amyloid—it can also be interpreted from this data that the cells are simply attracted to the amyloid. Several other studies have shown, however, that there is no increase in the number of microglial cells associated with diffuse senile plaques as observed in neuritic senile plaques (2, 3). Therefore, it is less likely that microglial cells are the principal cellular source of ββ (4). Moreover, it has been shown that cultured microglial cells may remove amyloid fibrils. The authors also refer to the pathological situation of systemic amyloidosis to support their view that microglial cells produce the amyloid “similarly as in Kupffer cells in systemic amyloidosis.” Contrary to their suggestion, it is still a matter of debate whether the production and processing of the amyloid are accomplished by the same cell type, e.g. macrophages or macrophage-like cells. For example, it is well-known that in light chain amyloidosis of the liver, plasmacytoma cells elsewhere in the body are the source of the amyloidogenic protein, and furthermore, it still remains obscure whether Kupffer cells play a role in processing the protein into fibrils.

Third, the authors proposed contradictory mechanisms of amyloid fibril formation in senile plaques on the one hand and in the vessel wall on the other; formation of amyloid fibrils in the former lesion is an intracellular process, whereas in the latter lesion it is an extracellular process. They concluded that in microglial cells “the first amyloid fibrils appear in the area of altered endoplasmic reticulum membrane and deep infoldings of cytoplasm membrane,” thus suggesting that amyloid formation is an intracellular process. If at all true, this would indeed be in contrast with the situation in the vessel wall, where amyloid fibril formation is “clearly an extracellular event.” However, the issue of intracellular formation of amyloid fibrils is a very disputed one since it is also