John Hardy

The Amyloid Hypothesis: history and alternatives

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Summary

In this centenary review, I outline two emerging hypotheses for us to consider if anti-amyloid approaches fail to have significant clinical impact.

The amyloid hypothesis of Alzheimer's disease, which was first explicitly proposed on the basis of genetic data by my colleagues and me in 1991 and 1992 (Hardy and Allsop 1991; Hardy and Higgins 1992) and, contemporaneously, by Selkoe (1991) and was implicit in the earlier work of Glenner and Murphy (1989) and Masters and Beyreuther (1987), has become the dominant philosophy driving research into the disorder.

While there has been much debate about whether the amyloid hypothesis is close to correct, until recently no coherent alternatives had been put forward that explain the genetic data. In this brief review to mark the 100th year of Alzheimer's lecture, I thought it would be more interesting, rather than merely outlining the amyloid hypothesis again (see Hardy and Selkoe 2002), to discuss two recent suggestions that offer coherent alternatives. I regard this as a valuable exercise at this time because several amyloid-based therapies are now in clinical trials, and if they are positive, we will feel the amyloid hypothesis is correct: if they are not, clearly, we should rethink our approaches to the disease.

The strength of the amyloid hypothesis is that it is consistent with the genetic findings: the autosomal dominant mutations in APP and in the presenilins all alter APP processing such that more Aβ42 is produced. Down's syndrome individuals, except those who are not trisomic for APP, develop Alzheimer pathology and those individuals who have a duplication of the APP locus also develop disease (Hardy 2006a). In addition, individuals with tau mutations develop tangle pathology and cell loss but not amyloid pathology, suggesting that tangle pathology is downstream of amyloid pathology. Mouse transgenic work has been completely consistent with the simple view outlined in Fig. 1.

The major weakness of the amyloid hypothesis, from a basic science perspective, has been the continued failure to identify the biochemical pathway that links amyloid to tangle formation. Transgenic experiments suggest there is a relatively direct link, and limited experiments in cultured neurons from mice in which the MAPT locus is deleted suggest that tau is needed for amyloid toxicity (Rapoport et al. 2002). However, work in this area has progressed slowly, and while we might have expected that there would be a rather direct link between amyloid and tau, none has yet been found.

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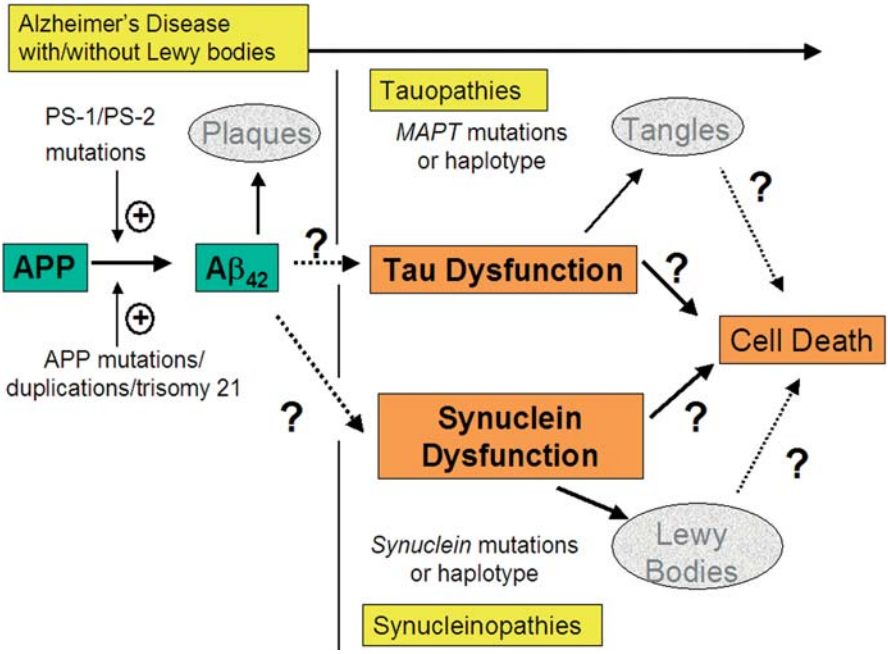

Fig. 1. The outline of the relationship between Aβ, Tau and α-Synuclein according to the amyloid hypothesis

Two emerging hypotheses have been suggested as alternatives to the amyloid hypothesis, which I will call the *presenilin inhibition hypothesis* and the *physiologic Aβ hypothesis*, which I outline below.

Presenilin inhibition hypothesis

This hypothesis has been suggested, in slightly different forms, by Shen (Beglopoulos and Shen 2006) and by Sambamurti (Sambamurti et al. 2006). These authors note that all the pathogenic presenilin mutations are, to some extent at least, a loss of its function as γ-secretase. The evidence that this is so is quite compelling. Presenilin knockdown increases Aβ42 production (Refolo et al. 1999); the mutation homologous to the *sel-12* Notch loss of function mutation is an Alzheimer-causing mutation that increases Aβ42 production (Lewis et al. 2000). γ-Secretase has many substrates besides APP (Sambamurti et al. 2006); however, APP is the predominant substrate, and it is possible that APP is a competitive inhibitor for the metabolism of presenilin's other substrates. Perhaps the problem in Alzheimer's disease reflects a more general inhibition of γ-secretase: in APP mutation cases, including those involving APP duplications, perhaps the problem is competitive inhibition of γ-secretase and there is a more direct relationship between presenilin inhibition and tangle formation and cell death (Beglopoulos and Shen 2006).

This hypothesis is almost as consistent with the genetic data as the amyloid hypothesis. The Swedish mutation can be accommodated because that causes increased flux through the pathway, as can the effects of APP duplications (Rovelet-Lecrux et al. 2006), but it is difficult immediately to accommodate the London mutations. From a therapeutic perspective, the hypothesis would predict that β-secretase inhibition may do more harm than good since this may lead to an increase in substrate levels for γ-secretase. From a basic science perspective, the hypothesis suggests that the connection between APP and tangles may relate to other presenilin substrates and signaling pathways rather than to APP.

Physiological Aβ hypothesis

An implicit assumption of the amyloid hypothesis has been that Aβ is just an accident of APP metabolism and that amyloid deposition is a pathological process, not a physiological process. In fact, this view has, in many ways, been eroding for some time. First, it was assumed that Aβ would not be a normal product of APP metabolism, and it was seen as a surprise when this was found not to be the case. And then it was seen as surprising that Aβ had a depressant effect on neurons, although this depressant effect has been noted without any discussion of the possible function of synaptic depression. Perhaps, indeed, these effects are physiological.

The pathology of Alzheimer's disease, by definition, includes amyloid plaques and neurofibrillary tangles. However, amyloid deposition also occurs as pronounced amyloid angiopathy. The relationship between the angiopathy and the neuritic plaques has not been clear and has been disputed for many years. However, recent data have shown that most, if not all, neuritic plaques are centered on angiopathic blood vessels (Kumar-Singh et al. 2005). Cullen and colleagues (2006) and Falangola and colleagues (2005) have presented data, in concurrence with earlier suggestions, that amyloid plaques are the sites of microhemorrhages (Miyikama et al. 1982; Hardy et al. 1986). Previously, Weller and colleagues (1998) have suggested that Aβ drains from the brain's extracellular fluid compartment via the perivascular space.

Together, these finding can be used to suggest a novel view of the relationships between Aβ, amyloid angiopathy, neuritic plaques and neuronal damage with the following components:

1. the initiating events in Alzheimer's disease are usually microhemorrhages;
2. one result of these events, either direct or indirect, is to alter the structure of γ-secretase from the Aβ40 to the Aβ42 producing conformation;
3. Aβ42 acts as a quick sealant for the blood vessel;
4. Aβ42 also acts as an immediate synaptic depressant to reduce metabolic demand during recovery;
5. tangles and neuronal damage and death are consequences of the hemorrhages and oxygen deprivation rather than a direct result of the amyloid deposition.

Under this scheme, the switch between Aβ40 and Aβ42 is physiological, not pathological, whose purpose (from an evolutionary perspective) is to act as a rapid protectant from cerebral hemorrhages.

This hypothesis is not immediately compatible with genetic data on the APP and presenilin mutations. Clearly, the people with these mutations would have a predisposition to form amyloid angiopathy and plaques but, unless they caused vascular damage and subtle hypoxia, it is not clear why they would lead to tangle formation and neuronal death. However, it is compatible with a surprising diversity of previously disparate and unexplained findings:

1. the presence of high concentrations of APP in platelets where, one presumes, it is part of the sealing cascade;
2. the fact that ApoE2 is associated with cerebral hemorrhages (Woo et al. 2005). The E4 allele is associated with amyloid deposition and Alzheimer's disease, whereas the E2 allele is associated with a paucity of deposition and, therefore, with hemorrhages;
3. the fact that so many presenilin mutations and so many pharmacologic agents can shift the metabolism of APP from Aβ40 to Aβ42 suggests that both ɣ-secretase conformations are stable;
4. the side effect of Aβ immunization of meningioencephalitis, which only occurred in cases with Alzheimer's disease (Nicoll et al. 2003). Presumably this side effect could relate to the reopening of vascular damage: a pulling off of the scab.

Of course, this hypothesis is also consistent with the epidemiologic evidence suggesting a relationship between vascular disease and Alzheimer's disease (Launer 2005), although in many ways it resembles a more sophisticated retake of the old designation of Alzheimer's disease as a hardening of the arteries.

This hypothesis would suggest that strategies designed to improve vascular health would be the most profitable route to Alzheimer therapy and that treatments based solely on Aβ would be likely to have side effects related to cerebral hemorrhages

Conclusion

Aβ-modulating therapies are now in progress; if they work, well and good. If, over the next period, these therapeutic strategies are not successful, we will have to rethink our approach. These two hypotheses offer a start in this direction.