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Commentary

## Truncating the amyloid cascade hypothesis: the role of C-terminal A $\beta$ peptides in Alzheimer's disease

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The long-term goal of studies of Alzheimer's disease (AD) is the development of ways to prevent or treat the disease. In order to accomplish this goal, much work has been devoted to understanding the etiology and pathobiology of the disorder. Not surprisingly, intense research efforts have focused on neurofibrillary tangles (NFT) and amyloid deposits, the two histopathologic hallmarks of Alzheimer's disease [1]. Morphological studies, using histological, immunochemical, and electron microscopic methods, have provided a wealth of information about the gross neuroanatomical effects of AD, the types of molecules which compose or may be associated with tangles and amyloid deposits, and the ultrastructural features of NFT and amyloid fibrils. Biochemical and biophysical studies have provided substantial information about the primary and higher order structure of the proteins found in NFT and amyloid deposits. Geneticists have made tremendous progress in identifying genes which cause AD or act as risk factors. This, in turn, has enabled development of transgenic mouse models which allow study of key etiologic factors controlling development of AD and provide the means to assess the efficacy of potential therapies. A clear result of these research efforts has been the realization that AD is an exceedingly complex disorder with a multifactorial etiology.

The complexity of AD has made development of unifying hypotheses of disease pathobiology difficult. In addition, the increasing importance of AD to the public health, coupled with the competitive (and unfortunately often acrimonious) environment in the AD field, has sometimes resulted in the promulgation of embryonic ideas and hypotheses which later are found to be without merit. In formulating any hypothesis, each element of the supporting data must be the result of a rigorous and critical experimen-

tal process. Second, the integration of these elements into the hypothesis should produce a consistent whole, one based on the most straightforward interpretation of all relevant data extant. Third, clear means for testing the hypothesis should be an integral part of the proposition. In the accompanying paper, Andrew Larner hypothesizes that amino-terminally truncated amyloid  $\beta$ -protein peptides (NTTA $\beta$ ) contribute to the pathogenesis of Alzheimer's disease. This hypothesis, although not novel [7,13,14], is intriguing and may have merit. However, a number of the key elements of the hypothesis may be questioned. In addition, it is unclear how an unambiguous test of the hypothesis can be made.

Teleologically, the presence of NTTA $\beta$  in amyloid deposits argues they do have a role in AD. The issue, however, is the significance of this role. In the case of full-length forms of A $\beta$ , their importance is indisputable. An ever-increasing body of genetic and biochemical data has demonstrated that increased production of A $\beta$ , or an increase in the ratio of A $\beta$ (1–42) to A $\beta$ (1–40) is linked to the development of AD (for reviews, see [8,16]). The longer form of A $\beta$ , A $\beta$ (1–42), has a greater propensity to form fibrils than does A $\beta$ (1–40), and fibrils are clearly neurotoxic. Finally, neuritic plaques and vascular amyloid deposits contain an abundance of these two forms of A $\beta$ . The most obvious hypothesis evolving from these data are that full-length forms of A $\beta$  are the key players in AD pathogenesis. What role is left for NTTA $\beta$ , and if a role does exist, of what importance could it have relative to that of the full-length A $\beta$  molecules?

Larner argues that diffuse amyloid deposits, which contain abundant amounts of NTTA $\beta$  (especially p3, i.e., A $\beta$ (17–42)) are the progenitors of neuritic plaques. This is an old idea which is controversial and has remained so due to the difficulty of monitoring temporal changes in plaque morphology. Larner further suggests that there is a causal relationship between the presence of p3 in diffuse plaques and the maturation of diffuse plaques into neuritic plaques.

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Even if one assumes that this maturation process does, indeed, occur, three sets of facts argue against a causal link between p3 and senile plaque genesis. First, cerebellar diffuse plaques, which are rich in NTTA $\beta$ , do not evolve into neuritic plaques, nor do diffuse plaques in the caudate and putamen [5,9]. Second, little fibrillar A $\beta$  exists in diffuse amyloid deposits [17]. Although the dearth of fibrillar deposits is at odds with the hypothesis, the author argues strongly that p3 could be important *in vivo* because *in vitro* it forms fibrils that are neurotoxic. There is simply no evidence of NTTA $\beta$ -induced neuronal loss, or any neuronal loss, for that matter, in diffuse amyloid deposits *in vivo* [9]. Third, little or no p3 is found in senile plaques. If, as the author argues, p3 has an increased propensity toward aggregation and fibril formation, it should remain within the developing plaque and subsequently be detectable.

Larner proposes that increased synthesis of NTTA $\beta$  could trigger a cascade of events leading to plaque formation, much in the same way that  $\beta$ -amyloid precursor protein (APP) and presenilin mutations lead to increased A $\beta$  production and deposition. No mutations in any species have been described which selectively increase the levels of secretion of NTTA $\beta$ . In fact, in the Swedish form of familial AD, the ratio of p3/full-length A $\beta$  actually decreases, both in fibroblasts from pre-symptomatic and symptomatic patients and in human embryonic kidney 293 (HEK293) cells transfected with cDNA encoding the Swedish APP protein [3,4]. A decreased ratio of p3/full-length A $\beta$  has also been observed in HEK293 cells transfected with cDNA encoding the Flemish mutant APP [7]. It should be noted, however, that in this latter study, a *relative* increase in the percentage of secreted A $\beta$ (5–40) was observed. Subsequent studies have also revealed an increase in the relative levels of secretion of A $\beta$ (11–40) in HEK293 cells transfected with cDNA encoding the Dutch mutant form of APP [18]. If, in the future, these effects are recapitulated *in vivo*, and if increased levels of these particular NTTA $\beta$  molecules are shown to have significant pathologic consequences, the hypothesis would certainly be on firmer ground.

Another important piece of the Larner hypothesis is that NTTA $\beta$  induce changes in cytoskeletal proteins, leading to development of neuritic dystrophy. This is a tantalizing idea, in no small part due to the fact that connecting amyloid deposition with cytoskeletal pathology could mollify the more fanatical “ $\beta$ Aptists” and “ $\tau$ auists” among us. As mentioned by Larner, evidence does exist from studies of cultured neurons that A $\beta$  fibrils can induce tau phosphorylation and a consequent inability to bind microtubules [2]. In fact, recent studies have shown that injection of fibrillar A $\beta$  into the brains of aged non-human primates results in tau phosphorylation, neuronal loss, and microglial proliferation [6,12]. In one study, rhesus monkeys were affected more than marmosets, while rats showed no significant effects [6]. This type of species-specific effect may explain why transgenic mice expressing elevated levels of human APP, while developing abundant amyloid deposits, do not pro-

duce NFT. The observations above are consistent with the Larner hypothesis, but because tangle formation does not occur in the experimental animals examined, one cannot assess whether A $\beta$  or NTTA $\beta$  have the potential to induce the *full* spectrum of AD neuropathology.

If the hypothesis is true, what are the clinical implications? Larner argues that the most important implication is that strategies designed to proteolyze full-length forms of A $\beta$  could be counterproductive because they might generate NTTA $\beta$ . This leads the author to suggest, in essence, that amyloid deposits should then be ignored and that treatments be provided to inhibit generation of reactive oxygen species (ROS) and to control intracellular Ca<sup>++</sup> concentrations. However, if proteolysis strategies result in the digestion of A $\beta$  into non-fibrillogenic peptides, this suggestion would be moot. In addition, logic suggests that blocking early steps in the amyloid cascade offers greater hope of achieving therapeutic benefits than attempting to ameliorate the serious consequences of progression down the pathway. It must also be pointed out that the involvement of ROS in the pathogenesis of AD is still hypothetical, as is Ca<sup>++</sup>-mediated cytotoxicity. However, even if these hypotheses are true, how would the relevant therapeutic strategies be executed? How would drugs be targeted to the brain and how would their activities be restricted to those redox or ion transport processes associated with susceptible neurons? Trials with vitamin E have certainly been encouraging [15], but the efficacy of this therapeutic approach is limited.

It is difficult to conceive of an unambiguous test of the hypothesis. For example, if formation of NTTA $\beta$  were blocked in an experiment animal and AD-like pathology were observed, this would not rule out involvement of NTTA $\beta$  in AD. Conversely, development of AD-like pathology in an animal in which *only* NTTA $\beta$  were expressed would not prove that NTTA $\beta$  were necessary to induce the pathology in humans, only sufficient. Nevertheless, with these caveats in mind, a number of experiments could be informative. An obvious experiment would be micro-injecting synthetic NTTA $\beta$  into the brains of non-human primates. Would these animals demonstrate tau phosphorylation, plaque formation, or neuronal loss? Transgenic animals could also be created using APP constructs encoding truncated versions of A $\beta$ . Although gross cytoskeletal anomalies would not be expected to occur in these animals, one should observe amyloid deposition if these peptides are indeed the A $\beta$  species initially deposited in AD. In fact, development of double transgenics, expressing truncated as well as full-length A $\beta$  species, could potentially recapitulate the seeding and plaque transformation processes occurring in humans. One might also ask, in these animals or in the available transgenic mouse models of AD, whether p3 or other NTTA $\beta$  species are the earliest A $\beta$  peptides found in the amyloid deposits. In fact, in the PDAPP transgenic mouse model, the earliest detected A $\beta$  species starts at Asp<sup>1</sup> [11]. Only later do NTTA $\beta$  beginning at pyroglutamate<sup>3</sup> appear, and then in substantially lower levels than those of

Asp<sup>1</sup> or D-Asp<sup>1</sup>. p3 species also appear late and are by far the least abundant of the peptides studied, although this latter observation must be interpreted carefully because questions exist about the avidity and specificity of the p3-specific antibodies used. Unfortunately, however, even if NTTA $\beta$  were deposited early and abundantly during the course of disease in these animals, one is still left with the difficult problem of relevance. As discussed earlier, species-specific differences in APP metabolism, amyloid deposition, and cytoskeletal pathology would make extrapolation to humans of the effects of NTTA $\beta$  in these systems problematic.

A more relevant model would be that of Down's syndrome, where characterization of temporal changes in the distribution of A $\beta$  species in the diffuse and neuritic amyloid deposits could facilitate evaluation of the Larner hypothesis. In Down's syndrome, early and extensive amyloid deposition occurs [10]. Recent studies by Lemere (personal communication) suggest that, in temporal and frontal cortex of young Down's syndrome patients (12–29 years old), the NH<sub>2</sub>-termini of the earliest A $\beta$  species deposited are Asp<sup>1</sup> and pyroglutamate<sup>3</sup>. The level of p3 deposition in these patients is currently unknown. Unfortunately, these data, although provocative, neither prove nor disprove the hypothesis. In the final analysis, this type of result is typical of the complexity of AD and illustrative of both the frustration and the challenge of building and testing hypotheses of AD pathogenesis.

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