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Neurobiology of Aging 23 (2002) 1097–1099

NEUROBIOLOGY OF AGING

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Commentary

Amyloid-β: a (life) preserver for the brain

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Received 5 March 2002; accepted 6 March 2002

For nearly two decades, the amyloid-β hypothesis [22] has dominated the field of Alzheimer's disease (AD) and during that time, massive efforts have focused on the role of amyloid-β in the pathogenesis of the disease. Given such focus, it is truly unfortunate that it is still unclear whether amyloid-β is either necessary or sufficient for the frank development of AD or whether amyloid-β causes the associated neurodegeneration or behavioral and cognitive deficits that accompany the disease. Therefore, it is perhaps long overdue that we in the field consider other views of amyloid-β, views which involve more complex relationships and that are more meaningful than merely classifying amyloid-β, and its isoforms, as either irrelevant (something to be dismissed) or all encompassing (the origin of AD). In this regard, a number of research groups have begun to question the supremacy of the amyloid-β hypothesis and, with this, the pendulum may now have swung completely in the opposite direction, with many now considering amyloid-β to be a protective consequence to an underlying disease mechanism. Notably, the same is true of the other major proteinaceous lesions of the disease, i.e. neurofibrillary tangles, which many also consider protective [16,25]. Viewing the known lesions of AD as a compensatory response places them in an environment that is both adaptive and protective, and it is clear that without some compensatory change to insults, the brain, arguably the most vital organ in the body, would certainly not survive long and certainly not for the protracted time as seen in AD.

In questioning the "Church of the Holy Amyloid" [9], researchers have started a dialogue that is challenging the dogma surrounding the proposed toxicity of amyloid-β. In the accompanying issue, Robinson and Bishop outline an alternative to the amyloid-β hypothesis, which supports our previous assertion that amyloid-β is protective [9,17,19,24,25]. The authors maintain that amyloid-β is produced normally to bind neurotoxic solutes, such as metal ions, and that subsequent precipitation into plaques is an efficient means of presentation to phagocytic cells. Further, they elucidate some of the predictions of the amyloid-β hypothesis that are inconsistent with the experimental data and much of the cited evidence provides equal support for alternative roles for amyloid-β. The viewpoints that they present are consistent with the neuroprotective properties that we, and others, have previously described [5,9,15–19,24,25].

In support of brain protection by amyloid-β, it is notable that amyloid-β has many physiological roles. These pleiotrophic effects of amyloid-β are numerous, some of which include redox-active metal sequestration [1,2,10,20,23], superoxide dismutase-like activity [6,7], and as an acute phase reactant protein (reviewed in [3]). Further, amyloid-β is upregulated by many forms of stress, including injury and head trauma, and as such may be a response to oxidative challenges in these conditions [9]. Indeed, amyloid-β burden has been shown to be inversely correlated with oxidative stress markers [15,16] suggesting that amyloid-β may have antioxidant effects [6]. Such metal sequestering properties of amyloid-β also explain the in situ finding that soluble amyloid-β levels are inversely correlated with synaptic loss [13]. Finally, it is important to note that amyloid-β is neurotrophic at low (nM) concentrations [28].

There is increasing evidence that amyloid-β, and its isoforms, may function as a trap or sink, as Robinson and Bishop note. This would likely serve an analogous function in the brain similar to that of albumin in the systemic circulation, which can bind metals, drugs, metabolites and proteins [11]. Accumulating evidence suggests that amyloid-β also binds cholesterol, which may play a role in the pathogenesis of AD [14]. Notably, serum cholesterol increases with advancing age and diet-induced hypercholesterolemia enhances amyloid-β accumulation accompanied by microgliosis in vivo [26,27]. Ultimately, the processes of sequestration, oxidative stress, and the resulting inflammation, accumulate over time to result in the neurodegeneration seen in AD and other disorders. Concurrently, multiple compensatory mechanisms become activated and are aimed

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PII: S0197-4580(02)00038-6

Fig. 1. Amyloid-β (Aβ) life preservers afford protection to neurons adrift in a cauldron of oxidative stress.

at arresting neurodegeneration [17,25]. One of the major players in this opera is amyloid-β (Fig. 1).

In ending, the therapeutic relevance of amyloid-β is important to discuss since it is widely assumed that the removal of amyloid-β plaques would be a beneficial treatment for AD and restore cognition [21]. However, such a proposed return to cognition may have other barriers, namely, those of concomitant cytokine stress, oxidative stress, inflammation, autoimmunity and imbalances in amyloid-β concentration at necessary sites of action. Cytokine stress would most likely accompany deposit clearance by microglia activation, through the complement cascade, or through the acute-phase response. In this regard, products of inflammatory reactions such as complement proteins, adhesion molecules and other cytokines are neurotoxic [9]. As the recent suspension of phase II clinical trials in France of the amyloid-β vaccine has shown, inflammation is, in fact, a real problem. This event also calls into question the validity of the amyloid-β vaccine and ties into our understanding of the function of amyloid-β. Finally, soluble amyloid-β components are necessary to maintain substrate pools for future protection or other actions. The potential imbalance in amyloid-β concentration between the cerebrospinal fluid and that of the neuropil [4,8,12] may lead to unforeseen consequences, which could feed forward dementia rather than reversing it [17,24,25]. Since sensitivity of the neuronal environment to insults increases with advancing age, it is very likely that the most important parameter in the development of AD involves mechanisms, e.g. oxidative stress, strongly associated with aging [9]. In this regard, individuals predisposed to AD represent an already declining system and amyloid-β serves as a life preserver to neurons that are surrounded by a sea of oxidative stress(Fig. 1).

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