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Invited Review

Oxidative stress and amyloidosis

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Summary. From recent findings concerning free radical injury in several types of amyloidosis, it appears that free radical injury is involved either amyloid formation or in post-fibrillar modification. As we show in this review, among the more than 20 different types of amyloidosis, only a few types of amyloidosis present direct evidence of free radical involvement in amyloid formation. However, if we search further for other types of amyloidosis, other important information on free radical injury may be forthcoming. Free radical injury is probably central for the toxic properties of amyloid deposits.

Key words: Advance glycation end-product, Alzheimer disease, Familial amyloidotic polyneuropathy, Immunohistochemistry, Radical scavenger

Introduction

Oxygen toxicity has a major impact on most biomolecules, such as nucleic acids, protein, lipids, carbohydrates, and other low molecular weight compounds (McCord, 1980). Thus, the organism's ability to protect itself from oxidative stress is one of the prerequisites for aerobic life. Although intracellular levels of oxidative protective enzymes, such as superoxide dismutase, glutathione peroxidase, catalase, and other heme-containing peroxidases are high, the levels in the extracellular compartments are comparatively low (Hirota et al., 1989). Therefore, free radical injury, has been suggested to be involved in the pathogenesis of various diseases, or to have acted as a propagation factor, and several therapeutic trials to reduce oxidative injury have been performed (Ando et al., 1989a, 1990; Hirota et al., 1990; Steinberg, 1993; The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group, 1994).

It has been suggested that in both systemic and in localised amyloidosis, free-radical injury may be involved in the amyloid formation process, and several in vitro and in vivo studies have implicated free radical activity in several types of amyloidosis, such as Alzheimer disease, familial amyloidotic polyneuropathy (FAP), and ß2 microglobulin amyloidosis.

In the following, a survey of the studies implicating free-radical injury in amyloid diseases is presented. Advances in immunohistochemistry techniques, and the development of new antibodies have increased the possibility of detecting injury caused by oxidative stress.

Alzheimer disease

One of the histopathological hallmarks of Alzheimer's disease is the senile plaques that are found in the neocortex and hippocampus (Alzheimer, 1907). The main constituent of the core of these plaques is a 40-43 peptide sequence called ß-amyloid (Aß), which is capable of destabilising calcium homeostasis and exhibits neurotoxic properties (Yankner et al., 1990; Mattson et al, 1992).

In a number of studies, the cytotoxicity of Aß(1-40) and its active fragment Aß(25-35) could be suppressed by catalase and antioxidants, i. e., vitamin E and melatonin (Behl et al., 1994; Lockhart et al., 1994; Pappolla et al., 1997). Treatment of both cultured hippocampal neurones and synaptosomes with Aß(25-35) produces substantially increased concentrations of the lipid peroxidation product: 4-hydroxy-2-nonenal (HNE) (Keller et al., 1997; Mark et al., 1997). Furthermore, neurotoxic effects of both Aß(25-35) and HNE could be prevented with glutathione ethyl ester, whereas the antioxidant, propyl gallate, was effective only against Aß(25-35) neurotoxicity (Mark et al., 1997). Aß-resistant subclones of PC12 cells do not, unlike the parent cells, accumulate peroxides upon Aß(25-35) treatment, due to an over expression of antioxidant

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enzymes (Sagara et al., 1996). Taken together, these data suggest that the neurotoxic effects of Aß are mediated via hydrogen peroxide and HNE.

Proteases from polymorphonuclear leukocytes and macrophages are present in amyloid fibrils from all types of systemic amyloidosis (Skinner et al., 1986; Stone et al., 1993), so release of free radicals from these cells may be involved in amyloid formation. Since hydroxyl radicals readily induce lipid peroxidation (Capeillere-Blandin et al., 1991), products of this reaction should be present in amyloid deposits if free radicals are involved in the process. Several reports of accumulation of aldehydic lipid peroxidation products during oxidative stress conditions have been published (Benedetti et al., 1980; Hurst et al., 1987; Younes et al., 1987; Granger, 1988; Siems et al., 1989). HNE is a lipid peroxidation product that exhibits several toxic properties: cell and enzyme stimulation, enzyme inactivation and modifications (Benedetti et al., 1980; Hurst et al., 1987; Younes et al., 1987; Granger, 1988; Siems et al., 1989). By using a purified polyclonal antibody to HNE (Toyokuni et al., 1994; Uchida et al., 1995), this toxic metabolite can be detected immunohistochemically in tissues.

Ando et al. (1998) reported the detection of HNE immunoreactivity in amyloid deposits of the brain of Alzheimer disease patients by comparing Alzheimer vs. non-Alzheimer disease patients. Positive HNE immunoreactivity was found in amyloid deposits in all Alzheimer specimens examined. HNE immunoreactivity was noted in 89% of the vessels in perivascular areas, where amyloid deposits were found by Congo red staining. On the other hand, in non-Alzheimer disease specimen, only 20% of the vessels showed HNE-immunoreactivity. Furthermore, Congo red-negative vessels of Alzheimer specimens showed no HNE immunoreactivity. Twenty-one per cent of senile plaques, that were positive for amyloid by Congo red staining, reacted with HNE antibody. Since the senile plaques change form in the course of the illness (Yamaguchi et al., 1989), the degree of HNE immunoreactivity may depend on the stage of the senile plaque. It should be noted that perivascular amyloid is localised outside the blood-brain barrier (BBB) whereas senile plaques are formed within the BBB (Wisniewski and Weigel, 1993). This difference in location may affect the stability and metabolism of HNE, which is a labile molecule. HNE immunoreactivity in a few perivascular areas without amyloid deposits was noted in non-Alzheimer disease patients, especially in aged patients, suggesting that HNE adducts are generated by free radical activity in atherosclerotic vessels (Hoff and O'Neil, 1991). An increase in HNE immunoreactive neurones in APOE4 homozygote Alzheimer disease patients has also been reported (Basso et al., 1994). However, they did not investigate the association of HNE with amyloid deposits, such as senile plaque and perivascular amyloid deposition.

$ß_2$-microglobulin amyloidosis and oxidative stress

In $ß_2$-microglobulin amyloidosis, free-radical injury has been implicated in amyloid formation (Capeillere-Blandin et al., 1991). In vitro studies showed that $ß_2$-microglobulin may be modified by the action of hydroxyl radicals (Capeillere-Blandin et al., 1991). Basso et al. (1994) demonstrated that urinary thiobarbituric acid-reactive substances (TBARS) reflect the presence of renal tubular damage, which may be the cause or the consequence of lipid peroxidation (Basso et al., 1994). The presence of advance glycation end-product (AGE) in amyloid deposits in $ß_2$-microglobulin amyloidosis also suggests the involvement of free-radical injury in amyloid formation in this type of amyloidosis. We will discuss AGE and amyloidosis in this paper later on.

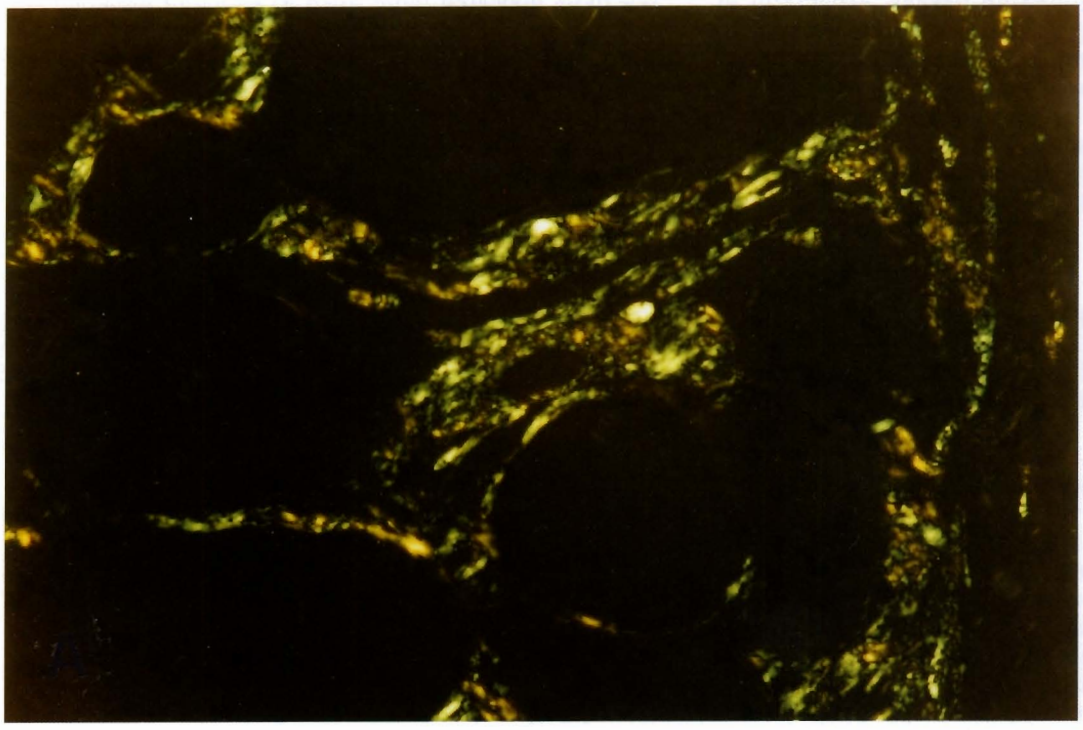
Familial amyloidotic polyneuropathy (FAP)

FAP is a collective term for a heterogeneous category of hereditary amyloid diseases characterized by a progressive peripheral polyneuropathy (Andrade, 1952; Andersson, 1976; Ando et al., 1993; Benson and Uemichi, 1996). There is invariably accumulation of amyloid fibrils in the peripheral nerves and other organs (Andersson, 1976; Ando et al, 1993; Benson and Uemichi, 1996). FAP, both Type I and II, is caused by variant forms of transthyretin (TTR) (Tawara et al., 1983; Dwulet and Benson, 1986). Type I FAP is the more common (Araki, 1984; Ando et al, 1993; Benson and Uemichi, 1996), and is caused by the replacement of valine by methionine in TTR in position 30 (TTR Met30) (Tawara et al., 1983; Benson and Uemichi, 1996). Although all carriers have similar levels of TTR Met 30 in their plasma and cerebro-spinal fluid, the age at onset of symptomatic disease varies between 20 and 70 years (Araki, 1984; Ando et al., 1993; Benson and Uemichi, 1996). Furthermore, the expression of the trait in Sweden is below 5% and asymptomatic homozygote individuals have been identified (Holmgren et al., 1988, 1994). Lately, discordant expression of the trait in identical twins, where one is sick and the other absolutely healthy, has been reported (Holmgren et al., 1997). Therefore, additional unknown factor(s) and/or protein(s) besides the genetic trait are necessary for amyloid formation (Ando et al., 1989b). There is a possibility that post-translational modification of TTR in the circulation or post-fibrillar modification of amyloid by free radical injury may play an important role.

HNE adduct in amyloid has been detected immunohistochemically by Ando et al (1997) using an affinity purified HNE-antibody (Fig. 1). By comparing immunoreactive areas with those in the corresponding consecutive section stained by Congo red, it was evident that amyloid deposits reacted with HNE antibodies in specimens from FAP patients. Likewise, reactivity to the anti-HNE antibody in areas with amyloid deposits was found in biopsy specimens from patients with primary or

secondary amyloidosis. It is noteworthy that HNE immunoreactivity was present in amyloid-positive vessels only; no reactivity was found in vessels negative for amyloid. HNE deposits are indicative of lipid peroxidation and to further substantiate the findings, the concentration of TBARS, another indicator of lipid peroxidation (Toyokuni et al., 1994), was measured together with determination of protein carbonyl levels, a useful marker of protein modifications by free radical injury (Levine et al., 1990).

TBARS levels were significantly higher in the amyloid-rich tissues of FAP patients than in those of



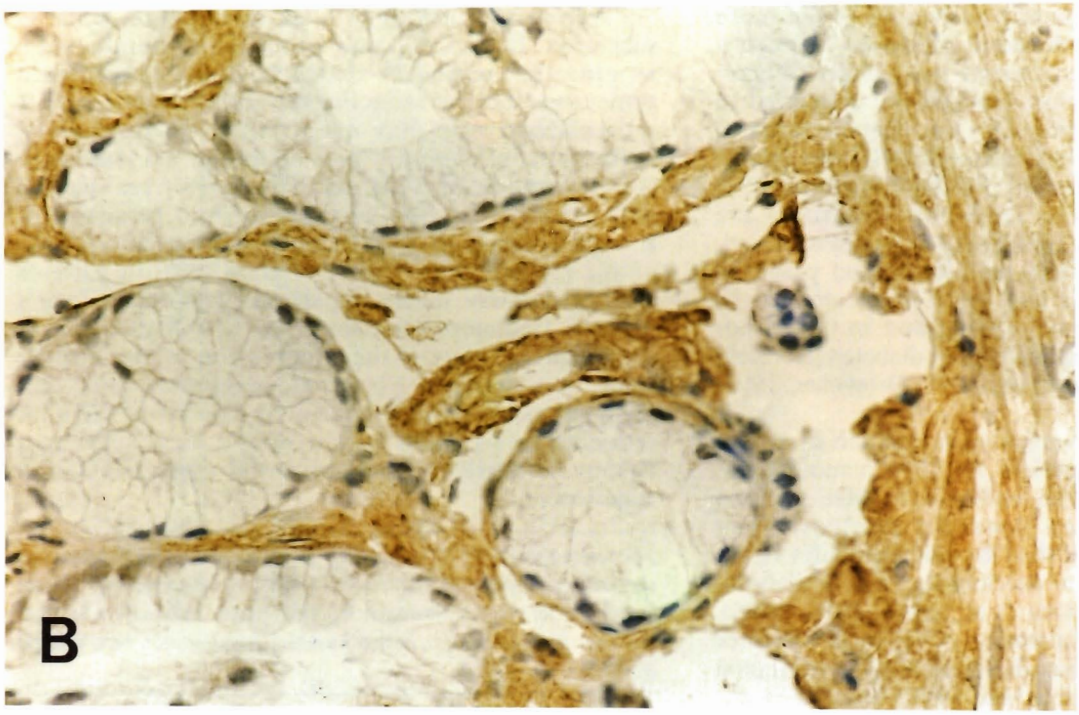


Fig. 1. Submucosa of the colon of a patient with familial amyloidotic polyneuropathy stained by alkaline Congo red **(A)** as examined in polarised light. Amyloid deposits are greenish birefringent. Consecutive section of the same area stained by the avidin-biotin complex method **(B)** using HNE antibodies. The immunoreactive areas are dark brown. x 400

control subjects. Carbony protein groups, calculated per mg protein in amyloid-rich tissues from FAP patients, revealed significantly increased concentrations compared with those from control subjects. The investigation provided firm evidence of the presence of oxidative stress in amyloid deposits.

The toxic properties of HNE can explain the injury amyloid caused in surrounding tissues, especially in neural tissues as in FAP. Nerve tissues are susceptible to oxidative stress, and even in patients with only minor amyloid deposits in peripheral nerves, pronounced clinical symptoms may be present, predominantly from the autonomic nervous system (Ando et al., 1992). This can be attributed to oxidative stress and HNE toxicity, to which the mainly unmyelinated postganglionic autonomic nerve fibres may be more susceptible than myelinated fibres.

Whether oxidative stress is involved in amyloid formation, or if the amyloid fibrils trigger an oxidative stress reaction is not known. However, the protein modulating properties of free radicals present in amyloid deposits increase the likelihood that they are involved in the fibril formation.

Advanced glycation end-products in FAP

Advanced glycation end-products (AGE) are a group of post-translational modified proteins that accumulate in tissues as a function of time and sugar concentration in an oxidative-dependent manner (FuMin-Xin et al., 1996; Meng et al., 1996). They are produced by the so-called Maillard reaction in which reversible Schiff's bases are formed by a condensation reaction between the proteins' amino groups and reducing sugars. These Schiff bases are subsequently converted to the more stable covalently bound Amadori products. Through a series of chemical rearrangements such as dehydration and fragmentation, Amadori products are converted to AGE (Miyata et al., 1995). Of the different types of AGEs, N^{ϵ}-(carboxymethyl) lysine (CML) and pentosidine have been characterised (FuMin-Xin et al., 1996; Ikeda et al., 1996). The AGE modifications are associated with crosslink formation, matrix dysfunction, reduced protein solubility, and increased protease resistance, and AGE has now been implicated in the pathophysiology of normal ageing and in the pathogenesis of long-term complications of diabetes (Horiuchi and Araki, 1994; Makino et al., 1995; Brownlee, 1995; Kimura et al., 1995).

Miyata et al. recently reported that acidic $ß_2$-microglobulin purified from amyloid fibrils of hemodialysis-treated patients reacted with antibodies to AGE and also with an antibody to an Amadori product. They concluded that AGE-modified $ß_2$-microglobulin is the predominant constituent of amyloid deposits in dialysis-related amyloidosis (Miyata et al., 1993, 1995, 1996). Furthermore, accumulation of AGE in Alzheimer disease patients' tissues has also been noted (Harrington and Colaco, 1994; Vitek et al., 1994; Kimura et al., 1995).

The involvement of AGE in systemic amyloidosis, such as FAP, primary amyloidosis, and secondary amyloidosis has been investigated (Ando et al., 1996). AGE antibodies reacted with amyloid deposits of FAP patients though not uniformly, as a few deposits were non-reactive to the antibody. Furthermore, immunoreactivity appeared more often to surround the amyloid deposits instead of being a part of them. Reactivity was even found in a few structures in which no amyloid deposits were present, although these AGE-positive structures were situated in areas close to amyloid deposits. No inflammatory cells, such as polymorphonuclear leukocytes or macrophages, were detected in or around the amyloid deposits. In samples from patients with AA and AL amyloidosis, no reactivity to the anti-AGE antibodies was detected, either in structures corresponding to amyloid deposits or in other parts of the samples.

There is evidence of a connection between free radicals and AGE in amyloidosis. In amyloid fibrils from hemodialysed-amyloidosis patients, inflammatory cells such as macrophages infiltrate into and around the amyloid deposits and these cells have the capacity to induce free radical formation. Furthermore, the presence of HNE in amyloid deposits may induce AGE formation, since lipid peroxidation is an important source of AGEs (Ikeda et al., 1996). CML is readily formed during lipid peroxidation reactions (Ikeda et al., 1996), and GA-adduct may also very well be formed by this type of reaction.

Therapy by free radical scavengers

Administration of radical scavengers, such as vitamins E and C, and thiol compounds such as glutathione and N-acetyl-cysteine may play a protective role by reducing the toxic effects of free radicals and they may even reduce amyloid fibril formation in systemic and localised amyloidosis. Administration of SOD, or SOD derivatives may be also effective by reducing the amyloid formation if a large amount of human SOD is available (Ando et al., 1989a, 1990; Hirota et al., 1990). In patients with moderately severe impairment from Alzheimer's disease, treatment with selgiline, MAO inhibitor, or α-tocopherol slowed the progression of the disease (Sano et al., 1997). Since catecholamines generates hydrogen peroxide, MAO inhibitor may be effective for reducing free-radical injury. Free-radical scavenger therapy for amyloidosis awaits further basic and clinical experience.

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