ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol. Exp. 2003, 63: 131-145

Alzheimer's β-amyloid peptide as a source of neurotoxic free radicals: the role of structural effects

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Review

Abstract. This mini review gives a brief overview over the oxidation mechanism of methionine (Met), relevant for processes which may lead to the oxidation of amyloid β-peptide (βAP), involved in the pathogenesis of Alzheimer's disease. The Cu^{II}-catalysed oxidation of C-terminal Met^{35} in βAP depends on the secondary structure of the peptide. That seems to be the key to the known propensities of this peptide to form reactive oxygen species and free radicals. The pro-oxidant character of βAP is not associated with its β-sheet insoluble form. On the contrary, the α-helically organised structure is responsible for βAP redox-related cytotoxicity.

Key words: ageing, Alzheimer's disease, β-amyloid, copper, free radicals, histidine, hydroxyl radical, methionine, methionine sulphoxide, one-electron oxidation, oxidative stress, peptides, reactive oxygen species, sulphide radical cation, thiyl radicals, transient metals

INTRODUCTION

This mini-review will not attempt a complete summary of the current knowledge on the free radicals related pathogenesis of Alzheimer disease (AD). For more comprehensive treatment, the reader is directed to several recent reviews, (Atwood et al. 1999, Brown et al. 2002, Bush 2000, Butterfield 1996, 1997, Butterfield et al. 2001, Butterfield and Lauderback 2002, Cuajungco et al. 2000, Gibson 2002, Grant 1997, Huang et al. 2000, Kontush 2001a, Lynch et al. 2000, Mattson 1997a, Miranda et al. 2000, Robinson and Bishop 2002, Rottkamp et al. 2000, Sayre et al. 1997, Schöneich 2001, 2002, Smith et al. 1996, 2000, 2002, Tabner et al. 2002, Varadarajan et al. 2000a), chapters of fundamental books (Cadenas and Packer 1999, Cutler et al. 1995, Davies 1992, Grant 1997, Halliwell and Gutteridge 1999, Mattson 1997a, Pal You 1993, Sies 1991, Simic et al. 1988, Smith and Perry 1998, Stadtman 1998b, 1998a, von Sonntag 1987, Winyard et al. 2000), frequently updated AD-related web pages: (www.alzheimers.org, www.alzheimers.org.uk, www.alzhforum.org), and current publications listed in the MEDLINE data base provided by National Library of Medicine (USA) under electronic address: www.nlm.nih.gov, covering different aspects of oxidative stress hypothesis of AD.

Rather, we will address some recently developed mechanistic concepts, that might have an impact on the current understanding of molecular basis of free radicals related cytotoxicity of amyloid β-peptide.

ALZHEIMER'S DISEASE (AD). SENILE PLAQUES OF β -AMYLOID PEPTIDE βAP

Alzheimer's disease (AD) is one of the main causes of elderly dementia (Barcikowska 1999, Blain and Jeandel 1998, Gabryelewicz 1999, Henderson and Finch 1989, McDowell 2001, Rowan 1993, Tanzi et al. 1994). The aetiology of AD is complex and involves the formation of intracellular fibrils of polymerised protein τ, extracellular amyloid deposits and, in general, the degradation of neurones (Beyreuther et al. 1991, Selkoe 1996). β-Amyloid protein (βAP), a relatively small 4-4.5 kDa polypeptide (Näslund et al. 2000), represents a major component of the amyloid deposits. The presence of increased level of βAP deposits in the brain region particularly susceptible to neurodegenerative degradation accompanies all inherited forms of Alzheimer's disease. Thus, the presence of β-amyloid plaques in the brain has become recognised as the major hallmark of this type of senile dementia.

The majority of gathered research data indicates, that βAP is toxic *in vitro* for neurones and cloned cell lines (Mattson 1997b, Pike et al. 1991, Yankner et al. 1990) leading to the widespread conviction of a special role of βAP in pathogenesis of AD (Butterfield et al. 2001, Selkoe 1996). However, the coexisting to the 'amyloid hypothesis' (Hardy and Selkoe 2002, Taylor et al. 2002), the 'bioflocculant hypothesis' of AD wins growing number of supporters (Robinson and Bishop 2002). This 'bioflocculant hypothesis' presumes that βAP is normally produced to bind neurotoxic solutes (such as metal ions), while the precipitation of βAP plaques represents an efficient means of a physiological response to injury presenting these toxins to phagocytes. There are also examples that βAP may serve as an antioxidant (Kontush et al. 2001a, 2001b, Kontush 2001a, 2001b).

In summary, the issue of elucidation of the cause and the effect relationship between the AD pathology and symptoms seems still not to be unequivocally resolved. Moreover, an assumption of some positive aspects of βAP presence in cells does not completely exclude a toxic action of its certain structures (Kontush 2001a).

POSTULATED CAUSES OF βAP NEUROTOXICITY

Several mechanisms by which βAP and its aggregates may cause neurotoxicity have been proposed: (i) the interaction with cell surface receptors, e.g., RAGE (Yan et al. 1996) or the substance P receptor NK-1 (Shimohigashi et al. 1993); (ii) membrane disruption (Buchet and Pikuła 2000, Koppaka and Axelsen 2000, McLaurin and Chakrabartty 1996) and/or the formation of ion channels (Durell et al. 1994, Dworakowska and Dołowy 2000) directly connected with; (iii) the disruption of cell ion homeostasis (Gibson 2002, Hensley et al. 1995a, Mattson 1997b); and (iv) the formation of free radicals and/or reactive oxygen species (*ROS*) eventually leading to lipid and protein oxidation (Butterfield 1996, 1997, Butterfield and Lauderback 2002, Heinecke 2002, Koppaka and Axelsen 2000, Yan et al. 1996).

SEQUENCES AND CONFORMATIONS OF βAP CONGENERS PRESENTED IN THE PATTERN OF THE DISEASE

The βAP1-42[1] is the major βAP sequence identified in plaques, whereas its shorter fragment βAP1-40 circulates in cerebrospinal fluid (Haass et al. 1992, Seubert et al. 1992). Other βAP congeners such as βAP25-35 and βAP31-35, have been found to generate free radicals/ROS and/or to be neurotoxic *in vitro* (Butterfield 1997, Butterfield et al. 1994, Hensley et al. 1995a, 1995b), but are less important *in vivo*. The 2D-NMR/MD structural assessment of βAP1-40 and βAP1-42 in micelles (Sticht et al. 1995) shows that native βAP between 1-14 and 37-40(42) residues possess disordered structure, two α-helical sections 15-24 and 28-36 separated by a kink or hinge of residues 25-27 (Coles et al. 1998, Shao et al. 1999, Sticht et al. 1995). Moreover, the two-electron oxidation of Met^{35}, which results in the methionine sulphoxide formation, disturbs the C-terminal α-helix of βAP1-40 (Watson et al. 1998). Similar structural assessment performed for N-terminal βAP1-28 congener in diluted aqueous solution (< 300 μM, pH 5.6), has shown the complete lack of the α-helix presence (Lee et al. 1995). However, the α-helix is presented in βAP1-28 dissolved in organic solvents (Sorimachi and Craik 1994, Talafous et al. 1994, Zagorski and Barrow 1992). Importantly, an introduction of Cu^{2+} and Zn^{2+} cations to the negatively charged lipid environment induces in βAP1-28 and βAP1-42 conformational changes from the β-sheet to the α-helix, accompanied by oligomerisation of the peptide and upraising its penetration into the membranes (Curtain et al. 2001). The metal-free βAP1-40 exhibits only a limited solubility in aqueous solution and undergoes a concentration-dependent cooperative random coil ↔ β-structure transition for $C_{pep} > 10$ μM (Seelig et al. 1995, Terzi et al. 1995). The equilibrium is shifted further toward β-structured aggregates in the presence of acidic lipid. However, β-structured aggregates exhibit only a modest surface activity and are not able to penetrate into the membrane interior (Terzi et al. 1997). The other study on the βAP16-22 fibrils shows that the β-sheets are likely antiparallelly organised (Balbach et al. 2000). The βAP1-40 and βAP25-35 β-structured aggregates at high lipid-to-protein ratios (> 40) undergo concentration-dependent conformational changes adopting the helix conformations (Terzi et al. 1997). Recent MD simulations (Straub et al. 2002) performed for βAP(10-35)-congener show probable transition pathway connecting its collapsed (random) coil, α-helical, folded β-sheet, and extended conformation. Significant energy barriers separate all conformations with distinct minima on the transition pathway. Coincidentally, the barriers or the transition state regions of the pathways are the minima on the solvation energy surface, where more open transition state structure exposes polar residues to the solvent. All transition pathways include early formation of a turn in the $V^{24}GSN^{27}$ region. The same turn region has been found to with relatively well-conserved structures in the collapsed coil and α-helical conformation. These results suggest that the turn may in fact act as a potential nucleus in the formation of a collapsed coil and α-helical compact structures in solution. Studies on the aggregation behaviour of synthetic βAP1-40 and βAP1-42 in solution using dynamic light scattering have shown fibrils coexisting with oligomeric βAP species (Thunecke et al. 1998). The pronounced difference has been observed in the aggregation of βAP1-40 and βAP1-42 sequences in acetonitrile-water mixtures. Contrary to previous gel chromatography observation (Huang et al. 1997) cofactors such as Zn^{2+} have been found to induce deaggregation of βAP instead of its aggregation (Thunecke et al. 1998).

THE FREE RADICALS HYPOTHESIS OF β-PEPTIDE NEUROTOXITY. TRANSIENT METALS COMPLEXATION. NEIGHBOURING GROUP ASSISTED OXIDATION OF MET^{35} TRIGGERS OFF THE FENTON-LIKE PROCESS

The free radicals hypothesis of β-peptide toxicity seems to be well established, since the Alzheimer's brain is characterised by widespread oxidative stress and high level of redox-active transient metals such as Cu and Fe (Flitter et al. 1983, Atwood et al. 2000, Bush 2000, Butterfield et al. 1994, 1996, Christen 2000, Harris et al. 1995, Hensley et al. 1994, 1995a, 1995b, Lynch et al. 2000, Markesbery 1997, Riley 1994, Rottkamp et al. 2000, 2001, Sayre et al. 1997, 2000, Selkoe 1996,

[1]The βAP1-42 in the one-letter code presents as follow: $DAEFRH^{6}DSGY^{10}EVH^{13}H^{14}QKLVFFAEDV^{24}G^{25}SN^{27}KG A^{30}I^{31}IGLM^{35}VGGV^{39}V^{40}IA^{42}$

Smith et al. 1991, 1992, 1997, 1998, 2000, 2002, Smith and Perry 1998, Varadarajan et al. 2000a, 2001). The metal chelation has even been proposed as a potential therapy for AD (Cherny et al. 2000, 2001, Cuajungco et al. 2000). The deleterious action of βAP-derived free radicals and ROS on neuronal cells has been documented by monitoring various markers of oxidative stress (Stadtman and Berlett 1997). Evidence has been provided that the action of βAP-derived free radicals and ROS on neurones results in the formation of protein associated carbonyls and lipid peroxidation products (e.g., 4-hydroxynonenal) (Butterfield 1997, Butterfield et al. 1994, 2001, Hensley et al. 1995a, Mattson et al. 1997) and in increased level of intracellular Ca^{2+}, potentially triggering apoptosis (Mark et al. 1995, Mattson et al. 1997, Yuan and Yankner 2000).

However, no comprehensive mechanism of βA-dependent formation of free radicals and *ROS* has been characterised, as yet. The proofs of "spontaneous" autooxidation and fragmentation of βAP1-40 and its shorter congener βAP25-35 in aqueous buffer, paralleled by the formation of spin trapping detected free radicals, have been shown (Butterfield et al. 1994, 1996, Hensley et al. 1994, 1995b). Indeed, the βA-dependent formation of free radicals and *ROS* has been identified as an important pathway of AD pathology, since to some extent neurotoxicity of βAP seems to be correlated with its ability to both spontaneous reduction of complexed Cu^{II} (concentration of Cu in amyloid plaques reaches 400 μM (Huang et al. 1999a)) and formation of free radicals (Huang et al. 1999b, Varadarajan et al. 2001).

It has been shown recently (Schöneich and Williams 2002), that in the presence of ascorbic acid (*ca.* 720 μM) Cu^{II} complexed by βAP1-16, βAP1-28 and βAP1-40, is anaerobically reduced to Cu^{I} (in reactions (1) and (2), where AH^{-}, $A^{\bullet-}$ and A represents ascorbate, ascorbyl radical anion and dehydroascorbate, respectively),

$$Cu^{II} + AH^{-} \rightleftharpoons Cu^{I} + A^{\bullet-} + H^{+} \quad (1)$$

$$Cu^{II} + A^{\bullet-} \rightleftharpoons Cu^{I} + A \quad (2)$$

In the presence of oxygen or H_2O_2, Cu^{I} may subsequently catalyse free radical oxidation of the peptide in the Fenton like process (Stadtman 1990, Urbański and Beręsewicz 2000). Similar reactions have been observed for other proteins (Schöneich 2000, Stadtman 1990) e.g. hGH (Zhao et al. 1997a) or PrP^{Sc} prion protein of Creutzfeldt-Jakob disease (CJD) (Bush 2000, Wong et al. 1999).

Oxidation products of βAP (i.e. 2-oxo-His-derivatives identified by the ESI-TOF MS/MS method) confirm that the major target of Fenton process generated $^{\bullet}OH$-radicals are His^{13} and His^{14} residues, while the next in line residues are His^{6} and Tyr^{10} (Schöneich and Williams 2002).

It has been proven that His^{13}, His^{14}, His^{6} and Tyr^{10} residues contribute in the complexation of Cu in βAP. This conclusion is in line with the earlier EPR (Curtain et al. 2001) and Raman spectroscopy results (Huang et al. 1999b, Miura et al. 2000). The higher His^{13} and His^{14} oxidation susceptibility over His^{6}, has been explained by low electron density on His^{6} residue. This phenomenon is rationalised by the bridging with the second Cu^{II}-βAP complex. Similar interaction has been observed for His^{61} bridging Cu^{II} and Zn^{II} in bovine SOD (Kurahashi et al. 2001). Moreover, the complexation of Tyr^{10} with Cu through the phenoxyl oxygen decreases the electron density in the aromatic ring which results in a decrease of the oxidation rate constant, thus making Tyr^{10} residue a bad competitor against the His residues (Schöneich and Williams 2002).

A strong tendency of native βAP to reduce complexed Cu^{II} has been recently discovered (Huang et al. 1999b, Varadarajan et al. 2001). It is worth to note, that neither C-terminally truncated sequence βAP1-28, nor N-terminally truncated sequence βAP25-35 are able to reduce Cu^{II}. Therefore, it has been postulated that N-terminally bonded Cu^{II} has to be reduced by electrons originating from the C-terminal Met residue (Huang et al. 1999b, Rauk et al. 2000a, Varadarajan et al. 2001). Thereby, an involvement of Met^{35} in copper reduction of βAP1-42 is an important, although not completely understood, phenomenon. The βAP1-28 fragment, which lacks Met^{35} is not capable of reducing Cu^{II} despite the presence of all three metal binding His residues in the sequence. Addition of exogenous Met to βAP1-28 greatly enhances Cu^{II} reduction by βAP1-28 (Curtain et al. 2001). Moreover, βAP1-42 in which Met^{35} is substituted by norleucine (CH_2 for S) or by already oxidised Met sulphoxide is neither oxidative nor neurotoxic (Varadarajan et al. 2001). Yet, both peptides form fibrils (Varadarajan et al. 2000b, 2001). However, fibrils are thought by some researches to be a necessary step in the mechanisms underlying pathology of AD (Lorenzo and Yankner 1994). On the other hand, the fibrillar state of

βAP seems not to be as critical to the oxidative stress and neurotoxic properties of βAP as initially thought, as in the presence of certain proteins βAP is even more toxic than βAP alone, yet no fibrils are formed (Aksenov et al. 1996, Oda et al. 1995).

The postulated direct oxidation of Met^{35} by Cu^{II} appears thermodynamically quite unfavourable. Such conclusion is based on the reduction potentials of the Cu^{I}/Cu^{II} and Met/Met radical cation couples: The unusually positive peak potential of copper in βAP $E^{0}_{Cu^{I/II}\beta AP} \approx 0.5 - 0.55$ V (vs. $Ag/AgCl_2$ electrode) has been reported (Huang et al. 1999b) Whereas, the anodic potentials (vs. $Ag/AgCl_2$ electrode) of zwitterionic (pH 8.2) and fully protonated (pH 2.1) Met are *ca.* 1.26 V and *ca.* 1.5 V, respectively (Sanaullah et al. 1994). Thus, at normal conditions, the potential equal *ca.* 0.7-1.0 V will shift the equilibrium (3) to the left hand side.

$$MetS + Cu^{II} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} MetS^{\bullet+} + Cu^{I} \qquad (3)$$

Thus, the reduction of Cu^{II} would not be expected. On the other hand, both products of reaction (3), can be efficiently removed from the equilibrium and thus shifting it to the right hand side. In a recent review, Schöneich quotes an example of analogous case taking place in the oxidation of p-xylene through Ce^{IV} (Schöneich 2002). Thermodynamically unfavourable electron transfer is accelerated by the subsequent strongly exoenergetic reaction of deprotonation, leading to the formation of 4-methylbenzyl radical (Baciocchi et al. 1980). The radical cation $MetS^{\bullet+}$ may also undergo fast deprotonation in reactions (4a) and (4b) (Hiller et al. 1981), with estimated $pK_a(MetS^{\bullet+}) \approx -6$ (comparable to that of $ArCH_3^{\bullet+}$ in p-xylene) for deprotonation in the γ position (reaction (4a)) and $pK_a(MetS^{\bullet+}) \approx -2$ for deprotonation in the ε position (reaction (4b)) (Rauk et al. 2000a).

$$MetS^{\bullet+} + B \rightarrow Met(-^{\bullet}CHSCH_3) + BH^{+} \qquad (4a)$$

$$MetS^{\bullet+} + B \rightarrow Met(-CH_2SCH_2^{\bullet}) + BH^{+} \qquad (4b)$$

Thus, per analogy to the p-xylene/Ce^{IV} system, the one-electron oxidation of Met^{35} in βAP through Cu^{II} should not be considered impossible. However, if the process is accelerated by reactions (4a) and (4b), than practically it should not depend on the structure of the peptide.

The O_2-dependent formation of H_2O_2 during the incubation of βAP1-42 (Huang et al. 1999b) suggests that Cu^{I} is removed from the equilibrium (3), probably through the formation of Cu^{II}/superoxide complexes (reaction (5)) (Fox and Karlin 1995, Zuberbühler 1993). It, can lead subsequently, to the formation of superoxide radical anion, which undergoes spontaneous or SOD-catalysed dismutation producing H_2O_2 (Halliwell and Gutteridge 1999).

$$Cu^{I} + O_2 \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} Cu^{II}\ldots O_2^{\bullet-} \qquad (5)$$

There are other processes that can affect the equilibrium (3) supporting the formation of $MetS^{\bullet+}$. In general, the redox processes of organic sulphides are affected by neighbouring groups, which can kinetically and thermodynamically stabilise radical cations such $MetS^{\bullet+}$ as radical cation-nucleophile complexes (Asmus 1979, Bobrowski et al. 1997, Pogocki and Schöneich 2002a, Steffen et al. 1991). This is displayed in the general reaction (6) where X represents the heteroatoms S, Se, Te, O, N, P, Cl, Br, and I (L = organic ligands, m = 0-2; n = 0,1).

$$R_2S^{+\bullet} + (L_mX)^{n-} \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} [R_2S\text{-}XL_m]^{(1-n)+} \qquad (6)$$

The stabilisation of sulphur-centred radical cation can occur through the overlap of the double occupied *p* orbital of the heteroatom and the single occupied *p* orbital of sulphur, leading to the formation of the three-electron bond of the $2\sigma/1\sigma^*$-type (Asmus 1979, Asmus 1990, Clark 1988). This cause in the Met case may lowering the one-electron redox potential of $MetS^{\bullet+}$ (Glass et al. 1977, 1988, Schwarz and Dodson 1984) thus enhance k_3 and lower k_{-3}.

For Met^{35} in βAP the peptide bonds are only nucleophiles presented in the nearest vicinity. Recent experiments in our laboratory (Bobrowski et al. 2003, Schöneich et al. 2000, 2003) have shown that such interactions play, in fact, an important role in redox reactions of Met-containing peptides. We have characterised in detail the reaction of Met sulphide radical cations, $MetS^{\bullet+}$, in the model peptides including GGGMGGG and N-Ac-GGGMGGG by means of pulse radiolysis

with time-resolved UV spectroscopy and conductometry. $MetS^{\bullet+}$ derives significant kinetic and thermodynamic stabilisation through fast ($t_{1/2} < 0.3$ μs) intramolecular bond formation with electron ion pairs from either the carbonyl oxygen or amide nitrogen of the peptide bond (Schöneich et al. 2003).

STRUCTURE DEPENDENT FREE RADICAL FORMATION PROPENSITY OF βAP. THE LACK OF THE α-HELICAL COMPONENT OF THE PEPTIDE ABOLISH INTERACTION BETWEEN THE ILE^{31} AMIDE OXYGEN AND THE MET^{35} SULPHUR

We have hypothesised, based on the results obtained for model peptides (see above), that one-electron oxidation of Met^{35} in βAP may be facilitated through the SO-bond formation. Such assumption seems to be reasonable, as in the *ca.* 3.6 Å average S-O distance between Met^{35} and Ile^{31}-C=O in the energy optimised structures (Coles et al. 1998) is close to the sum of the van der Waals radii of the atoms (Bondi 1964). We have obtained additional support for the hypothesis applying quantum mechanical calculations (Pogocki et al. 2003). The SCC-DFTB calculations for radicals derived from model Met-containing peptides show that the secondary structure of the peptide may facilitate the formation of particular SO-bonded radicals. The fully regular 3.6-α-helical conformation of the peptide facilitates formation of the 1,6-; 1,15- and the 1,13-type SO-bonds[2]. On the other hand, formation of the 1,16- and the 1,6-type SO-bond might be expected (Pogocki et al. 2003) in the βAP conformation observed experimentally (Coles et al. 1998).

Due to the fact that direct experimental detection of the (S-O)-bonded structures in βAP is difficult because of the low solubility of these peptides, we have obtained some mechanistic details through molecular modelling. The LD modelling has shown that due to the specific structural properties βAP26-40 (representative part for native βAP1-42) manifests higher tendency to form (S-O) intramolecular bonds in comparison either to the truncated congener βAP26-36, or to the peptide of reverse sequence βAP40-26 (Pogocki and Schöneich 2002b). Calculations performed for the peptide βAP26-40(Ile^{31}Pro), (Ile^{31} residue has been mutated by helix braking Pro residue) (Reiersen and Rees 2001), have shown that the peptide βAP1-40(Ile^{31}Pro) should be significantly less toxic than native βAP. This conclusion can be rationalised by the fact that Ile^{31}Pro mutation significantly reduces the "frequency of the contacts" between sulphide radical cation centre and the carbonyl oxygens of neighbouring peptide bonds (Pogocki and Schöneich 2002b). This idea has been recently supported by the experiment, which unambiguously confirmed that the mutation Ile^{31}Pro in βAP1-42 abolishes oxidative stress and alters neurotoxicity of the peptide *in vitro* (Kański et al. 2002). Although the absolute structure of βAP1-42(Ile^{31}Pro) is unknown, the CD spectroscopy experiment presented in (Kański et al. 2002) has shown significant difference in the ellipticity between the Ile^{31}Pro mutant and native βAP1-42, indicating changes in secondary structure. Importantly, Ile^{31}Pro substitution completely abolishes the α-helical component of the peptide likely abolishing any structure-dependent interaction between the amide oxygen C-terminal to the residue in position 31 and the Met^{35} sulphur. Hence, any one-electron oxidation of Met^{35} in the Ile^{31}Pro variant should be more difficult compared to native βAP1-42.

On the other hand, the presence of the α-helical structure in the peptide can be additionally stabilised by relatively strong "nonbonded" interactions between Met sulphur and oxygen, similar to that observed in some biomolecules (Burling and Goldstein 1992, Garcia et al. 2000, Nagao et al. 1998). It could eventually promote βAP toxicity!

A BRIEF REVIEW OF REACTION OF MET SULPHIDE RADICAL CATION

The broad spectrum of the Met sulphide radical cation has been recently reviewed (Schöneich 2002). It should be once again emphasise, that one-electron oxidation of Met to $MetS^{\bullet+}$ may unleash the sequence of radical events that can occur with participation of βAP (Butterfield 1997, Schöneich 2002). For example, sulphide radical cation $MetS^{\bullet+}$ or its complex with a nucleophile ultimately undergoes deprotonation in practically irreversible reactions (4a) and (4b) (Rauk et al. 2000a), which in aerobic conditions may lead to the formation of peroxyl radicals (reaction (7)).

[2]Here, any transient sulphur-oxygen association might be of the 1,(6+3*n*)-type with amide bonds C-terminal of Met and the 1,(7+3*n*)-type with amide bonds N-terminal of Met (*n* = 0, 1, 2,...).

$$R'\text{-}S\text{-}^{\bullet}CH\text{-}R + O_2 \rightarrow R'\text{-}S\text{-}CH(\text{-}OO^{\bullet})\text{-}R \qquad (7)$$

Peroxyl radicals are classic initiators of lipids peroxidation (Halliwell and Gutteridge 1999), the phenomenon associated with βAP oxidation (Butterfield 1997, Butterfield and Lauderback 2002, Mattson et al. 1997). *In vivo* $MetS^{\bullet+}$ may also oxidise the endogenic antioxidants such as ascorbate and thiols (Bonifacic et al. 1985) leading to the formation of thiyl radicals ($RS^{\bullet}$), which themselves may participate in the chain reactions of oxidation of lipids, amino acids, free sugars and the sugar moieties of nucleic acids (Akhlaq et al. 1987, Carter et al. 2000, Chatgilialoglu et al. 2000, Ferreri et al. 1999, Nauser and Schöneich 2003, Pogocki and Schöneich 2000, 2001, Pryor et al. 1973, Rauk et al. 1998, Robins and Ewing 1999, Schöneich et al. 1989, 1990, 1992, 1995, Schöneich 1995, Schöneich and Asmus 1990, Schwinn et al. 1998, Smoluk et al. 1988, Stubbe and van der Donk 1998, von Sonntag 1990, Wardman 1995, Wardman 1998, Zhao et al. 1997b, Zhao 1998). Obviously, the efficiency of these reactions depends on the concentration of reduced glutathione GSH in the cell compartments, high in the cytosol but low in membranes. Importantly, the average concentration of GSH in the cells taken from the brains of healthy rats amounts to *ca.* 2 mM (Halliwell and Gutteridge 1999). Moreover, an increased level of homocysteine (the physiological precursor of GSH) is observed in the AD blood (Clarke et al. 1998), however its role in oxidative stress remains unclear (Diaz-Arrastia 1998, Mosharov et al. 2000, White et al. 2001, Zappacosta et al. 2003).

The Met sulphide radical cation may also undergo very fast reaction (8) ($k_8 \approx 5\times10^9$ $M^{-1}s^{-1}$) (Miller et al. 1996, Miller et al. 1998) with superoxide radical anion, originated from a Cu^{II}-superoxo complex formed in reaction (5). Reaction (8) leads to the Met sulphoxide (MetO), which has been detected in βAP sequences isolated from AD senile plaques (Näslund et al. 1994).

$$MetS^{\bullet+} + O_2^{\bullet-} \xrightarrow{\text{Met}} 2MetO \qquad (8)$$

Until now there is no direct evidence for free superoxide in the process (Huang et al. 1999b), however, such a mechanism should depend on the distance between the Cu^{II}-superoxo complex ($Cu^{II}..O_2^{\bullet-}$) and radical cation $MetS^{\bullet+}$. Reaction (8) requires none or negligible activation energy, and collisions between the $Cu^{II}..O_2^{\bullet-}$ centre and $MetS^{\bullet+}$ on the nanosecond time scale (i.e. time scale much shorter than the average lifetime of $MetS^{\bullet+}$ or its complexes with nucleophiles (Hiller et al. 1981, Schöneich et al. 2000)). The last process is controlled by the peptide dynamics. Our studies with Met-containing model peptides have shown that even very short-lived reactive intermediates at the Met sulphur can interact with remote functional groups based on a highly flexible and dynamic peptide structure (Pogocki et al. 2001). MetO discovered in senile plaques may obviously be formed *via* reaction of Met^{35} with H_2O_2 formed during the incubation of βAP (Huang et al. 1999a) (*in vivo*, H_2O_2 may also result from other sources such as an inflammatory response of glial cells (Halliwell and Gutteridge 1999) to βAP deposition (Butterfield et al. 2001, Ferencik et al. 2001), or presence of aluminosilicates in plaques (Christen 2000, Evans and Harrington 1998, Evans et al. 1989, 1992, Savory et al. 1996, Yokel 2000)).

The another possibility of $MetS^{\bullet+}$ damaging role has been discussed: $MetS^{\bullet+}$ may abstract H-atoms at the C_α-H bond of Gly located in the fibrillar antiparallel β-sheets (Rauk et al. 2000b). This reaction has been proposed based on the relatively low C_α-H bond dissociation energy (*ca.* 361 kJ mol^{-1}) of Gly in antiparallel β-sheets (Rauk et al. 2000a) compared to Gly residues in other secondary structure elements such as parallel β-sheets or α-helix (Rauk et al. 2000b). Though theoretically feasible, there is as yet no experimental conformation of this hypothesis.

CONCLUDING REMARKS. GENERAL ASPECT OF PROPOSED MECHANISM

The oxidation of Met^{35} in βAP by redox-active cations of transient metal seems to be important for pathogenesis of AD. Alzheimer's disease brain contains significant levels of redox-active transition metals such as copper and iron (Lovell et al. 1998) and is characterised by extensive oxidative stress, potentially originating within neurofibrillary tangles and senile plaques (Sayre et al. 2000). The detailed mechanism of βAP neurotoxicity and free radical formation are unknown, however a series of recent investigations suggest that βAP reduces βAP-bound Cu^{II} dependent on the presence of either Met^{35} or free Met, followed by the generation of H_2O_2. It is reasonable to assume that

metal-catalysed oxidation occurs *in vivo,* considering, the high affinity of βAP to Cu^{II} (Huang et al. 1999b). Based on the sulphide oxidation mechanism, available in the organic-radicals chemistry literature, the one-electron oxidation of Met^{35} in βAP by βAP-bound Cu^{II} seems to be possible, in particular, in highly organised α-helical conformation of the βAP C-terminal region containing Met^{35}, where neighbouring group effects may play an important role.

The applicability of emerged mechanism might go beyond the AD pathogenesis. It has been suggested that Met residues may be an essential part of the mechanism of the antioxidant activity exhibited by normal prion protein (PrP^{C})(Wong et al. 1999). Considering, that the direct precursors of βAP (APP protein) and PrP prion protein share the same physiological function of copper carriers (Brown et al. 1998, 1999, Brown 2002, Simons et al. 2002, Viles et al. 1999, White et al. 1999a, 1999b). One may hypothesise, that prion protein may be capable of spontaneously reducing the N-terminally bonded Cu^{II} (Aronoff-Spencer et al. 2000, Burns et al. 2002, Stockel et al. 1998, Viles et al. 1999) by mechanism analogous to proposed for βAP, as in hPrP three of nine Met residues (namely 205, 206 and 213) are located in the α-helical segments (Zahn et al. 2000). More detailed analysis of the hPrP structure, uncovers for Met^{206} vs. Asp^{202}-C=O, and Met^{213} vs. Val^{209}-C=O, the S-O-distance lower then the sum of the van der Waals radii of the two atoms (Bondi 1964). It suggests possibility of the 1,16-type S-O-bonds formation, which might accelerate oxidation of Met by Cu^{II}.

ACKNOWLEDGEMENT

The support by The Research Training Network "Sulphur Radical Chemistry of Biological Significance: The Protective and Damaging Roles of Thiol and Thioether Radicals" (SULFRAD) of the European Commission is gratefully acknowledged.

ABBREVIATIONS

AD	-	**A**lzheimer's **d**isease
APP	-	**a**myloid **p**recursor **p**rotein
βAP	-	**beta a**myloid **p**eptide
CD	-	**c**ircular **d**ichroism
CJD	-	**C**reutzfeldt-**J**akob **d**isease
2D-NMR	-	**two d**imensional **n**uclear **m**agnetic **r**esonance
EPR	-	**e**lectron **p**aramagnetic **r**esonance = **ESR** – **e**lectron **s**pin **r**esonance
ESI-TOF MS	-	**e**lectro**s**pray **i**onisation **t**ime-**o**f-**f**light **m**ass **s**pectrometry
FALS	-	**f**amilial **a**myotrophic **l**ateral **s**clerosis
FR	-	**f**ree **r**adicals
hGH	-	**h**uman **g**rowth **h**ormone
hPrP	-	**h**uman **pr**ion **p**rotein
LD	-	**L**angevin **d**ynamics
MD	-	**m**olecular **d**ynamics
PrP	-	**pr**ion **p**rotein
PrP^{c}	-	**pr**ion **p**rotein **c**ellular isoform
PrP^{Sc}	-	**pr**ion **p**rotein **s**crapie isoform
ROS	-	**r**eactive **o**xygen **s**pecies
SCC-DFTB	-	**S**elf-**c**onsistent **c**harge **d**ensity **f**unctional **t**ight **b**inding method

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Received 12 March 2003, accepted 3 April 2003