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Increased brain 7-hydroperoxycholesterol in Alzheimer type dementia

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ABSTRACT

Oxidative stress in Alzheimer type dementia (ATD) brains was studied by the analysis of cholesterol-derived hydroperoxide as an index of lipid peroxidation. ATD was diagnosed pathologically using Braak and Braaks' criteria and human brain tissues were collected at forensic autopsy (control, n=5; ATD, n=7). Tissue samples were obtained from frontal, angular and occipital cortex, frontal, angular and occipital white matter, and hippocampus. The extracted membrane lipids were injected into an octyl column for HPLC with post-column chemiluminescence for detection of two cholesterol-derived hydroperoxides, 7α-(7α-OOH) and 7β-hydroperoxycholest-5-en-3β-ol (7β-OOH). The data showed that the concentrations of 7α-OOH and 7β-OOH in the angular gyrus white matter of the dementia group were the highest and approximately 10-fold greater that corresponding value for the controls. Our present findings suggest that oxidative stress, membrane lipid peroxidation in particular, may reflect the extent of neurodegenerative process in AD, and would also argue in favour of the hypothesis that in AD hippocampal atrophy may contribute to oxidative stress in the posterior associate region.

Keywords: 7-hydroperoxycholesterol; Alzheimer type dementia; human brain; HPLC-CL; lipid peroxidation; posterior associate region

Introduction

The brain in Alzheimer's disease (AD) is under increased oxidative stress suggesting that free radicals are involved in the pathogenesis of neuron death.[15] Indeed, free radical-induced lipid peroxidation has been evaluated in a number of studies including the analysis of 4-hydroxynonenal (HNE),[16] malondialdehyde (MDA),[22] thiobarbituric acid-reactive substances (TBARS),[13] and F4-isoprostanes[21] in various AD brain regions compared to control subjects. Little, however, has been done to characterize the oxidized membrane lipids in brains of patients with AD.

We previously developed a method for quantifying cholesterol-derived hydroperoxides using HPLC with chemiluminescent detection (HPLC-CL)[1] and applied this to investigating oxidative stress in a number of models. For example, both paraquat and alcohol administration are well known to produce reactive oxygen species and induce membrane lipid peroxidation. We investigated membrane lipid peroxidation by analyzing the cholesterol-derived hydroperoxides present in the liver and kidneys of rats after administration of a low dose of paraquat.[4] We found significantly elevated concentrations of 7α-(7α-OOH) and 7β-hydroperoxycholest-5-en-3β-ol (7β-OOH).[4] Moreover, elevated concentrations 7α-OOH and 7β-OOH were found in human alcoholic fatty liver indicative of augmented lipid peroxidation due to chronic alcohol intake.[5] We have also identified 7-hydroperoxycholesterol in human liver using liquid chromatography-mass spectrometry[2] and found elevated 7α-OOH and 7β-OOH concentrations in the plantaris as well as the soleus skeletal muscle of rats after ethanol administration[3]. Our findings confirm that 7α-OOH and 7β-OOH are good markers of oxidative stress.

The aim of the study reported here was to evaluate whether lipid peroxidation occurred in the membrane fraction of human brain with Alzheimer type dementia (ATD). We measured 7α-OOH and 7β-OOH, then determined whether individual regions brain were particularly susceptible.

Materials and methods

Table 1. Demographic data for the patient sample studied

Values are mean±SEM		
	Control	Dementia
n	5	7
Age (yrs)	75.0±7.4	81.7±2.6
Body weight (kg)	44.2±3.5	46.3±4.4
Height (cm)	152.4±4.8	148.6±2.0
Brain weight (g)	1266.4±80.6	1249.3±66.1
Brain weight / Body weight	29.3±2.8	28.1±2.5
Postmortem period (hrs)	16.7±1.9	15.5±2.4

Human Brain tissues were obtained from 12 autopsy cases (7 ATD cases and 5 control cases, postmortem interval < 24hours) in the Department of Legal Medicine, Kobe University School of

Medicine, Japan, in compliance with the ethical code of the Ethical Committee of the Japanese Society of Legal Medicine. Demographic data on the subjects are shown in Table 1. There was no significant difference between ATD and control with regard to age, body weight and height, brain weight, brain weight per body weight and postmortem intervals. The control subjects, who had died from causes unrelated to the nervous system, showed no clinical manifestations of dementia or other mental disorders. Historical information of dementia was obtained from the interview to their families. Following macroscopic examination, the frontal lobe (superior frontal gyrus), parietal lobe (post central gyrus) and occipital lobe, hippocampus with entorhinal and transentorhinal areas and adjoining temporal lobe, amygdala, thalamus, substantia nigra and cerebellum were dissected. These tissue blocks were fixed in 10% formalin, embedded in paraffin and sectioned serially at 6 μm. After Gallyus-Braak's silver impregnation, each case was classified neuropathologically respectively, according to Braak and Braaks' staging criteria.[6] Braak and Braaks' staging for all cases is shown in Table 2. There is a close relation between pathological staging of Braak and Clinical Dementia Rating (CDR)[9] scale.[10] When the patients reach Braak and Braaks' stage IV, the severity of neurofibrillary tangles formation is incompatible with CDR of 0.5 or less. Accordingly, we estimated the patient with Braak and Braaks' stage IV - VI to be ATD in this study, whereas individuals with Braak and Braaks' stage 0 were listed up as controls.

Table 2. Classification of pathological stage in the dementia group

Age	Sex	Brain	Episodes of Dementia	Stage
		(g)		
69	F	1200	Apraxia	Ⅳ
80	F	985	Apraxia	Ⅵ
88	F	1160	Poriomania	Ⅴ
82	F	1140	Amnesia	Ⅴ
78	M	1370	Amnesia	Ⅳ
90	M	1460	Poriomania	Ⅵ
85	F	1430	Amnesia	Ⅴ

The right hemisphere was used for all the chemical analysis. Membrane lipids were measured in the frontal cortex (FC), angular gyrus cortex (AGC), occipital cortex (OC), frontal white matter (FW), angular gyrus white matter (AGW), occipital white matter (OW), and hippocampus (H). Total lipids were extracted for the analysis of lipid peroxidation products as follows: Five millilitres of ice-cold chloroform/methanol (2:1, v/v) containing 0.005% (v/v) butylated hydroxytoluene as the antioxidant and 500 pmol β-sitosterol-5α-hydroperoxide as the internal standard was added to approximately 0.1 g of brain tissue, and the mixture homogenized under ice-cold conditions. The homogenate was mixed with 5 ml of chloroform/methanol (2:1, v/v) and 1 ml of distilled water, swirled vigorously for 1 min then centrifuged at 800 g for 20 min. The chloroform layer was aspirated, concentrated in a

rotary evaporator, and dried under a nitrogen stream. The subsequent procedure of purification with Sep-Pak (-NH2) was performed as described previously.[1]

3,5-Di-tert-butyl-4-hydroxytoluene, luminol (3-aminophthaloylhydrazine) and cytochrome c (from horse heart, type VI) were purchased from Wako Pure Chemical Co. (Osaka, Japan). Cholesterol hydroperoxides, 5α-hydroperoxycholest-6-en-3β-ol (5α-OOH), 7α-OOH, 7β-OOH, as well as β-sitosterol 5α-hydroperoxide (the internal standard) were synthesized as described elsewhere.[11]

Table 3. Concentrations of 7α- and 7β-hydroperoxycholesterol and cholesterol in seven areas of brains from the dementia and control groups

	7α-OOH			7β-OOH			Cholesterol	
	Dementia	Control	D/C	Dementia	Control	D/C	Dementia	Control
	(pmol/g)	(pmol/g)		(pmol/g)	(pmol/g)		(mmol/g)	(mmol/g)
FC	493±112 *	155±47	3.1	455±115 *	103±57	4.4	11.1±1.1	11.8±2.3
AGC	278±42 *	109±31	2.6	258±62	89±37	2.8	10.3±0.6	9.2±1.1
OC	1268±887	183±42	6.9	1371±1017	151±48	9.0	9.6±1.0	11.8±2.7
FW	1582±691	545±182	2.9	1894±824	627±235	3.0	11.0±0.6	22.6±7.3
AGW	5421±1549* #	661±221#	8.2	7067±1758* #	555±207#	12.7	27.3±7.0	20.4±7.7
OW	2968±1680	492±71#	6.0	3532±2101	555±97 #	6.3	14.4±2.0	14.6±1.6
H	901±222	384±84	2.3	1225±405	441±83	2.7	23.0±2.2	15.2±3.1

Values are mean±SEM * significantly greater than the corresponding control, $p<0.05$ # significantly greater than the corresponding cortex, $p<0.05$

7α-OOH, 7α-hydroperoxycholest-5-en-3β-ol; 7β-OOH, 7β-hydroperoxycholest-5-en-3β-ol; FC, frontal cortex; AGC, angular gyrus cortex; OC, occipital cortex; FW, frontal white matter; AGW, angular gyrus white matter; OW, occipital white matter; and H, hippocampus; D/C, dementia to control ratio.

The cholesterol hydroperoxides were quantified by reverse phase HPLC-CL as described previously.[18] A TSK gel Octyl-80Ts column (Tosoh, Tokyo, Japan) was used (150 x 4.6 mm internal diameter) with methanol/water/acetonitrile (89:9:2, v/v/v) as a mobile phase. The data values were

standardized by dividing by the area of IS (internal standard). Data for each group are expressed as mean + SEM of seven subjects. Differences between groups were assessed by Student's unpaired t-test.

Results

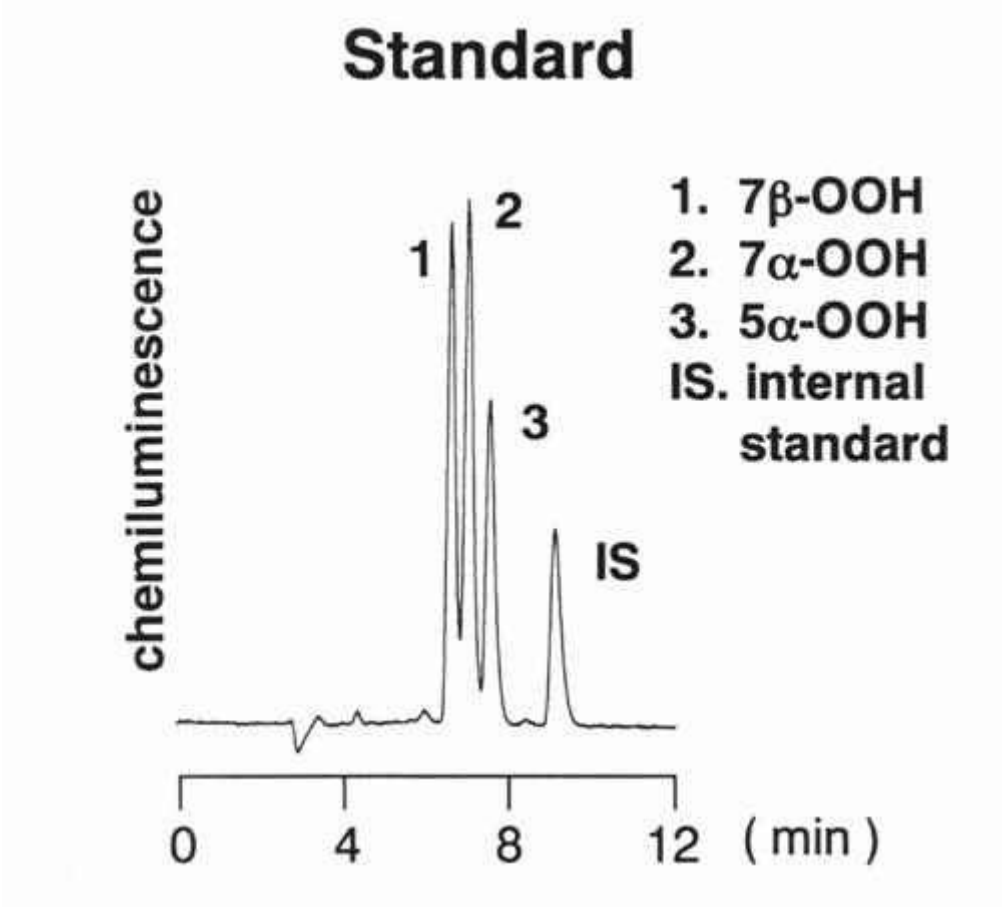

Figure 1. Chromatograms of standard cholesterol hydroperoxides as recorded by HPLC with chemiluminescent detection: 7β-OOH, 7β-hyroperoxycholest-5-en-3β-ol; 7α-OOH, 7α-hydroperoxycholest-5-en-3β-ol; 5α-OOH, 5α-hydroperoxycholest-6-en-3β-ol; IS, β-sitosterol-5α-hydroperoxide.

The retention times of standard 7β-OOH, 7α-OOH, and 5α-OOH and of the internal standard were 6.9, 7.4, 8.0 and 9.7 min. The compounds were clearly separable (Fig. 1). Typical HPLC-CL chromatograms for the cholesterol hydroperoxides in the brain samples from the control and ATD subjects are shown in Fig 2. Peaks 1 and 2 in the samples, which had respective retention times of 6.9 and 7.4 min, corresponded with the peaks of the respective standards for 7β-OOH and 7α-OOH. We detected 7β-OOH and 7α-OOH, but not 5α-OOH. The presence of 5α-OOH would have suggested artifactual formation during processing of the tissue.[1]

The mean 7α-OOH and 7β-OOH concentrations in the seven areas of brains from the dementia and control groups, as well as the values for the dementia to control ratios for each area are given in Table 3. On the whole, the 7α-OOH and 7β-OOH concentrations in all seven areas in the dementia brains were higher than those in the control brains. In particular, 7α-OOH and 7β-OOH in FC and AGW and 7α-OOH in AGC of the dementia group were significantly higher than the corresponding regions in controls ($P<0.05$). The ratios of the 7α-OOH and 7β-OOH concentrations in the dementia

versus the control group ranged from 12.7 to 2.3, indicative of large inter-regional differences. The largest ratio of 7β-OOH in dementia vs. control group was 12.7 in AGW, followed by OC (9.0), OW (6.3), FC (4.4), FW (3.0), AGC (2.8), and H (2.7). The 7α-OOH ratio for the dementia vs control brains decreased in the order of AGW (8.2), OC (6.9), OW (6.0), FC (3.1), FW (2.9), AGC (2.6), H (2.3). The 7α-OOH ratio was virtually identical to that for 7β-OOH.

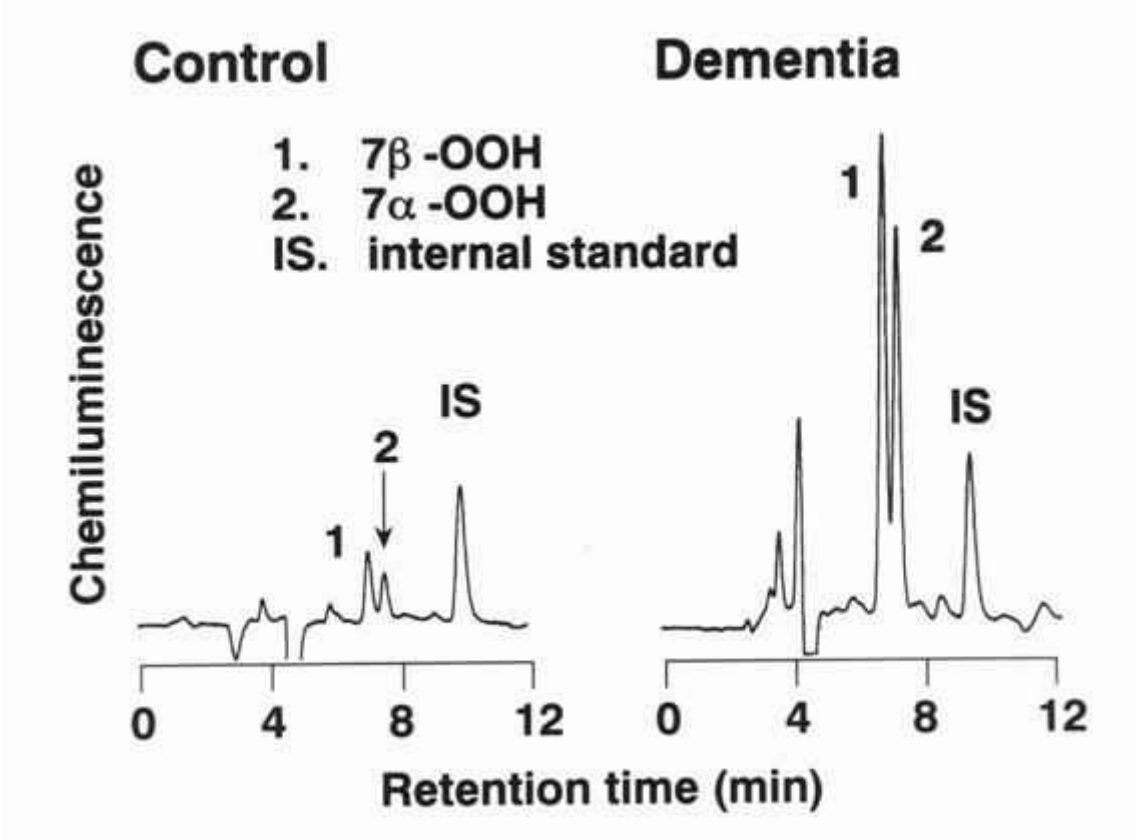

Figure 2. Representative HPLC-CL chromatograms for brain samples of control and dementia patients. 7α-OOH, 7α-hydroperoxycholest-5-en-3β-ol; 7β-OOH, 7β-hyroperoxycholest-5-en-3β-ol.

The highest 7α-OOH and 7β-OOH concentrations in the seven brain areas from the dementia and control groups were 5421 and 7067 pmol/g, respectively, found in lipid extracts from the AGW region of the dementia group. The lowest values were 109 and 89 pmol/g, respectively in the AGC of the control group. The 7α-OOH concentration in the dementia group decreased in the order of AGW, OW, FW, OC, H, FC and AGC: a similar trend was observed for 7β-OOH in the ATD group. The rank order of the 7α-OOH and 7β-OOH concentrations of the control group differed slightly from the dementia group, but the concentrations of the cholesterol hydroperoxides were higher in the white matter than the corresponding cortex. In addition, the 7α-OOH and 7β-OOH concentrations in the AGW from both groups were significantly higher than in AGC and in OW from control group were significantly higher than OC (Table 3). The 7α-OOH and 7β-OOH concentrations for the hippocampus of the control group were between those for the white matter and cortex.

The cholesterol concentrations for each brain area, are shown in Table 3. Mean cholesterol concentrations were higher in the AGW and H of the dementia group compared to the corresponding regions of the control group, but did not reach statistical significance. There was little difference in the cholesterol concentrations of the cortex and white matter regions.

What is already known on this topic

The brain in Alzheimer's disease (AD) is under increased oxidative stress suggesting that free radicals are involved in the pathogenesis of neuron death. Indeed, free radical-induced lipid peroxidation has been evaluated in a number of studies in various AD brain regions compared to control subjects. Little, however, has been done to characterize the oxidized membrane lipids in brains of patients with AD.

What This study adds

This study suggests that oxidative stress, membrane lipid peroxidation in particular, may reflect the extent of neurodegenerative process in AD, and would also argue in favour of the hypothesis that in AD hippocampal atrophy may contribute to oxidative stress in the posterior associate region.

Discussion

A variety of methods have been employed to study oxidative stress and lipid peroxidation, such as HNE and MDA, but many analytes are non-specific and possibly insensitive. Increased isoprostanes levels (metabolites of arachidonic acid formed as a consequence of oxidative stress) in a transgenic mouse model of Alzheimer's disease (AD) amyloidosis have been found.[27] These studies show that amyloid beta deposition in vivo is associated with increased lipid peroxidation.[27] In addition, elevated levels of isoprostanes in urine and blood of patients with AD correlate with functional impairment and established biomarkers of AD pathology (tau and amyloid).[25] 4-Hydroxynonenal has also been shown to be a novel nonprotein mediator of oxidative stress-induced neuronal apoptosis.[12] Membrane lipid peroxidation therefore may reflect the extent of neurodegeneration in AD.

In the present studies, we examined 7-hydroperoxycholesterol, a direct peroxidation product of cholesterol. The products 7α-OOH and 7β-OOH are formed as a consequence of oxidative stress per se rather than by some other metabolic route. For the first time the cholesterol hydroperoxides present in brain were quantified and significantly elevated concentrations were found in subjects with ATD, compared to control brain tissue. Although we used autopsied human brain samples, there is no significant difference of postmortem interval between ATD and controls (Table 1) precluding the possibility that the increased 7α-OOH and 7β-OOH were artifacts of the interval between death and post mortem sampling. We have already investigated many conditions for the artifact formation of cholesterol hydroperoxides in vitro[1], thereby we found 5α-OOH as well as three peaks unknown identity. As we saw neither 5α-OOH nor unknown peaks in any brain sample of the present study, we established that artifactual oxidation was negligible within the postmortem intervals encountered in this study. In previous studies,[2,4,5] we found marked accumulations of 7-hydroperoxycholesterols in human fatty liver, in the kidneys and liver of rats administered paraquat, and in the plantaris and soleus skeletal muscles of rats administered ethanol as well, suggestive of augmented lipid peroxidation in these tissues. This convinces us that 7-hydroperoxycholesterol is as an excellent marker of oxidative stress. The accumulation of lipid peroxidation products was examined in detail in seven brain regions, and the ratio of 7α-OOH and 7β-OOH concentrations in the dementia and control groups calculated. The largest ratios, 12.7 (7β-OOH) and 8.2 (7a-OOH), were in the AGW, and the highest concentrations of these analytes were found in the AGW from ATD (i.e., 5.42 and 7.07 nmol/g, respectively). The rank order of accumulation of 7α-OOH and 7β-OOH in the different regions of ATD brains were identical: AGW, OW, FW, OC, H, FC, AGC. We showed that, of the seven regions brain examined, the greatest

increases in 7-hydroperoxycholesterol were found in the AGW. Research has been carried out to determine which region of the AD brain is subjected to the greatest degree of lipid peroxidation. Isoprostanes were shown to be elevated in the frontal and temporal poles in AD[26], TBARS in the temporal cortex[14], and MDA in the inferior temporal cortex.[22] In 1995 Lovell and collaborators[13] determined TBARS levels and activity of antioxidant enzymes in various regions of the AD brain and showed that oxidative changes were most pronounced in the medial temporal lobe. The following findings also support such regional changes in AD. Weight loss[20] and reduced numbers of neuronal fibers[8] were reported in the supramarginal gyrus of AD patients when compared with control brain tissue. Positron emission tomography (PET) showed that the cerebral glucose metabolic rate was severely reduced in the supramarginal gyrus[23,24] of AD brains. Reiser and collaborators reported that p42IP4/centaurin alpha-immunoreactive neurons were found in temporal and angular cortex in AD patient, having strong relation with neurodegenerative process, [28] and Meguro and collaborators showed metabolic reduction between right hippocampal width and right angular gyrus in AD patients by mean of PET and magnetic resonance imaging.[17] These regional sensitivities in AD would support our present findings. Our present findings suggest that oxidative stress, membrane lipid peroxidation in particular, may reflect the extent of neurodegenerative process in AD, and would also argue in favour of the hypothesis that in AD hippocampal atrophy may contribute to oxidative stress in the posterior associate region such as the supramarginal and angular cortices.

The pathogenesis of white matter lesions in AD is not ascertained clearly. Although vascular changes in mild and moderate white matter lesions have been reported in AD,[29] the present study showed that cholesterol hydroperoxides have a greater accumulation in the white matter than in the corresponding cortex (statistically significant for the AGW in both groups and the OW in the controls). Additionally, white matter changes are often found in patients with vascular dementia, especially of small vessel/subcortical subtypes, including Binswanger's disease, and are generally considered to be a consequence of chronic ischaemia associated with microangiopathy.[7] Thus, chronic ischaemia might be implicated in AD, which might induce oxidative stress in medullary white matter in AD.

In regard to the relationship of senile plaques, neurofibrillary tangles, and lipid peroxidation, Montine and collaborators[19] quantified the F2-isoprostane concentrations in the lateral ventricular fluids of 23 AD patients and controls. They showed that the extent of brain lipid peroxidation is not correlated with the density of neuritic plaques or neurofibrillary tangles in seven brain regions.[19] In contrast, we investigated the relationships of dementia diagnosed by Braak and Braaks' staging, and lipid peroxidation by measuring the 7a-OOH and 7ß-OOH concentrations in several brain regions and found pronounced accumulations of cholesterol hydroperoxides in the angular gyrus in four of seven ATD patients.

In conclusion, when 7-hydroperoxycholesterol is used as an index of lipid peroxidation, the findings support the concept that in ATD the brain is under increased oxidative stress and changes are most pronounced in the angular gyrus.

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References

1. Adachi J, Asano M, Naito T, Ueno Y, Tatsuno Y. Chemiluminescent determination of cholesterol hydroperoxides in human erythrocyte membrane. Lipids 1998; 33: 1235-40. PubMed
2. Adachi J, Asano M, Ueno Y, Naito T. Identification of 7 hydroperoxycholesterol in human liver by liquid chromatography-mass spectrometry. Alcohol Clin Exp Res 2000; 24: 21S-5S. PubMed
3. Adachi J, Asano M, Ueno Y, Reilly M, Mantle D, Peters TJ, Preedy VR. 7α- and 7β-Hydroperoxycholest-5-en-3β-ol in muscle as indices of oxidative stress: response to ethanol dose in rats. Alcohol Clin Exp Res 2000; 24: 675-81. PubMed
4. Adachi J, Tomita M, Yamakawa S, Asano M, Naito T, Ueno Y. 7-Hydroperoxycholesterol as a marker of oxidative stress in rat kidney induced by paraquat. Free Radic Res 2000; 33: 321-7. PubMed
5. Asano M, Adachi J, Ueno Y. Cholesterol-derived hydroperoxides in alcoholic liver disease. Lipids 1999; 34: 557-61. PubMed
6. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 1991; 82: 239-59. PubMed
7. Caplan LR. Binswanger's disease - revisted. Neurology 1995; 45: 626-33. PubMed
8. Duyckaerts C, Kawasaki H, Delaere P, Rainsard C, Hauw JJ. Fibre disorganization in the neocortex of patients with dementia of the Alzheimer type. Neuropathol Appl Neurobiol 1989; 15: 233-47. PubMed
9. Gold G, Bouras C, Kovari E, Canuto A, Glaria BG, Malky A, Hof PR, Michel JP, Giannakopoulos P Clinical validity of Braak neuropathological staging in the oldest-old. Acta Neuropathol 2000; 99: 579-82. PubMed
10. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982; 140: 566-72. PubMed
11. Kulig MJ, Smith LL. Sterol metabolism XXV. Cholesterol oxidation by singlet molecular oxygen. J Org Chem 1973; 38: 3639-42. PubMed
12. Kruman I, Bruce-Keller AJ, Bredesen D, Waeg G, Mattson MP. Evidence that 4-hydroxynonenal mediates oxidative stress-induced neuronal apoptosis. J Neurosci 1997; 17: 5089-100. PubMed
13. Lovell MA, Ehmann WD, Butler SM, Markesbery WR. Elevated thiobarbituric acid-reactive substances and antioxidant enzyme activity in the brain in Alzheimer's disease. Neurology 1995; 45: 1594-601. PubMed
14. Marcus DL, Thomas C, Rodriguez C, Simberkoff K, Tsai JS, Strafaci JA, Freedman ML. Increased peroxidation and reduced antioxidant enzyme activity in Alzheimer's disease. Exp Neurol 1998; 150: 40-4. PubMed
15. Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. Free Radic Biol Med 1997; 23: 134-47. PubMed
16. Markesbery WR, Lovell MA. Four-hydroxynonenal, a product of lipid peroxidation, is increased in the brain in Alzheimer's disease. Neurobiol Aging 1998; 19: 33-6. PubMed
17. Meguro K, LeMestric C, Landeau B, Desgranges B, Eustache F, Baron JC. Relation between hypometabolism in the posterior association neocortex and hippocampal atrophy in Alzheimer's disease: a PET/MRI correlative study. J Neurol Neurosurg Psychiat 2001; 71: 315-21. PubMed
18. Miyazawa T, Suzuki T, Fujimoto K, Yasuda K. Chemiluminescent simultaneous determination of phosphatidylcholine hydroperoxide and phosphatidylethanolamine hydroperoxide in the liver and brain of the rat. J Lipid Res 1992; 33: 1051-9. PubMed

19. Montine TJ, Markesbery WR, Zackert W, et al. The magnitude of brain lipid peroxidation correlates with the extent of degeneration but not with density of neuritic plaques or neurofibrillary tangles or with APOE genenotype in Alzheimer's disease patients. Am J Pathol. 1999; 155: 863-8. PubMed
20. Najlerahim A, Bowen DM. Regional weight loss of the cerebral cortex and some subcortical nuclei in dementia of the Alzheimer type. Acta Neuropathol Berl 1988; 75: 509-12. PubMed
21. Nourooz Zadeh J, Liu EH, Yhlen B, Anggard EE, Halliwell B. F4-isoprostanes a specific marker of docosahexaenoic acid peroxidation in Alzheimer's disease. J Neurochem 1999; 72: 734-40. PubMed
22. Palmer AM, Burns MA. Selective increase in lipid peroxidation in the inferior temporal cortex in Alzheimer's disease. Brain Res 1994; 645: 338-42. PubMed
23. Penniello MJ, Lambert J, Petot Eustache F, Taboue MC, Baree L, Viader F, Morin P, Lechevalier B, Baron JC. A PET study of the functional neuroanatomy of writing impairment in Alzheimer's disease. The role of the left supramarginal and left angular gyri. Brain 1995; 118: 697-706. PubMed
24. Polinsky RJ, Noble H, Di-Chiro G, Nee LE, Feldman RG, Brown RT. Dominantly inherited Alzheimer's disease: Cerebral glucose metabolism. J Neorol Neurosurg Psychiatry 1987; 50: 752-7. PubMed
25. Pratico D, Clark CM, Lee VM, Trojanowski JQ, Rokach J, FitzGerald GA. Increased 8, 12-iso-iPF2alpha-? in Alzheimer's disease: correlation of a noninvasive index of lipid peroxidation with disease severity. Ann Neurol 2000; 48: 809-12. PubMed
26. Pratico D, Lee VM, Trojanowski JQ, Rokach J, Fitzgerald GA. Increased F2-isoprostanes in Alzmeimer's disease: evidence for enhanced lipid peroxidation in vivo. FASEB J 1998; 12: 1777-83. PubMed
27. Pratico D, Uryu K, Leight S, Trojanoswki JQ, Lee VM. Increased lipid peroxidation precedes amyloid plaque formation in an animal model of Alzheimer amyloidosis. J Neurosci 2001; 21: 4183-7. PubMed
28. Reiser G, Bernstein HG. Neurons and plaques of Alzheimer's disease patients highly express the neuronal membrane docking protein p42IP4/centaurin alpha. Neuroreport 2002; 13(18): 2417-9. PubMed
29. Tomimoto H, Akiguchi I, Akiyama H, Ikeda K, Wakita H, Lin JX, Budka H. Vascular changes in white matter lesions of Alzheimer's disease. Acta Neuropathol Berl 1999; 97: 629-34. PubMed