OXIDIZED LOW DENSITY LIPOPROTEINS IN ALZHEIMER'S DISEASE. ROLE FOR PAF-ACETYL HYDROLASE AND PARAOXONASE -1

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INTRODUCTION

Paraoxonase-1 (PON1) and Platelet Activating Factor Acetyl-Hydrolase (PAF-AH) are enzymes associated to HDL and LDL. Alterations of their activities are involved in diseases associated with inflammation and oxidative stress. PON1 is exclusively associated at HDL surface and its activity modulates HDL antiatherogenic functions. PAF-AH is associated mainly to LDL and its biological role is debated: it degrades bioactive phospholipids that express several proinflammatory activities (such as PAF and oxidized phospholipids), but this event results on the formation of inflammatory components (such as lysophosphatidylcoline and isoprostanes), suggesting a possible pro-atherogenic role of PAF-AH. Aim of the study was to investigate the PON1 activity and PAH-AH activity and the levels of oxidized LDL in Alzheimer's disease. In fact, recent studies have reported a physiopathological role of lipid peroxidation of lipoproteins in neurodegerative diseases. Moreover, oxidative stress and lipid peroxidation are recognized to be intimately related to the inflammatory processes and to the pathogenesis of neurodegenerative disorders.

MATHERIALS AND METHODS

Forty-nine Alzheimer's disease patients (20 males and 29 females, 73.3± 6.4 year old) and thirty four gender and age-matched healthy subjects (15 males and 19 females, 74.4 year old) were recruited at the Clinic of Neurology-Ospedali Riuniti di Ancona. In AD patients, the mini-mental state examination (MMSE) assessment was performed to evaluate the clinical severity of the disease (mean value 21.1 ± 5.4).

Serum PON1 activity was evaluated using different substrates: paraoxon for paraoxonase activity, phenylacetate for arylesterase activity and dihydrocoumarin for lactonase. Serum PAF-AH activity was analyzed using the colorimetric method with a commercial kit (Cayman Chemical).

Serum levels of oxidized LDL were evaluated by a sandwich ELISA procedure, as marker of lipoprotein peroxidation (Mercodia).

RESULTS

The levels of TC, HDL-C and LDL-C were not statistically different in the two groups, but the levels of TG and homocysteine levels were higher in the study groups. Enzyme activities and oxidized LDL. The mean value of PON1 activity was significantly lower in serum of AD patients than in control subjects (55.7 ± 35 vs 79.2 ± 29, $p<0.05$). Higher PAF-AH activity was observed in serum AD patients (21.8 ± 5.1 vs 15.2 ± 4.3, $p<0.05$). Also the levels of oxidized LDL were significantly higher in serum of patients compared with controls (65 ± 33.3 vs 46.1 ± 17.5, $p<0.001$ (result not showed). Relationship between enzyme activities, ox-LDL and severity of disease. AD patients with moderate (11<MMSE>24, n=21) and severe AD (MMSE<10, n=9) showed higher ox-LDL levels.

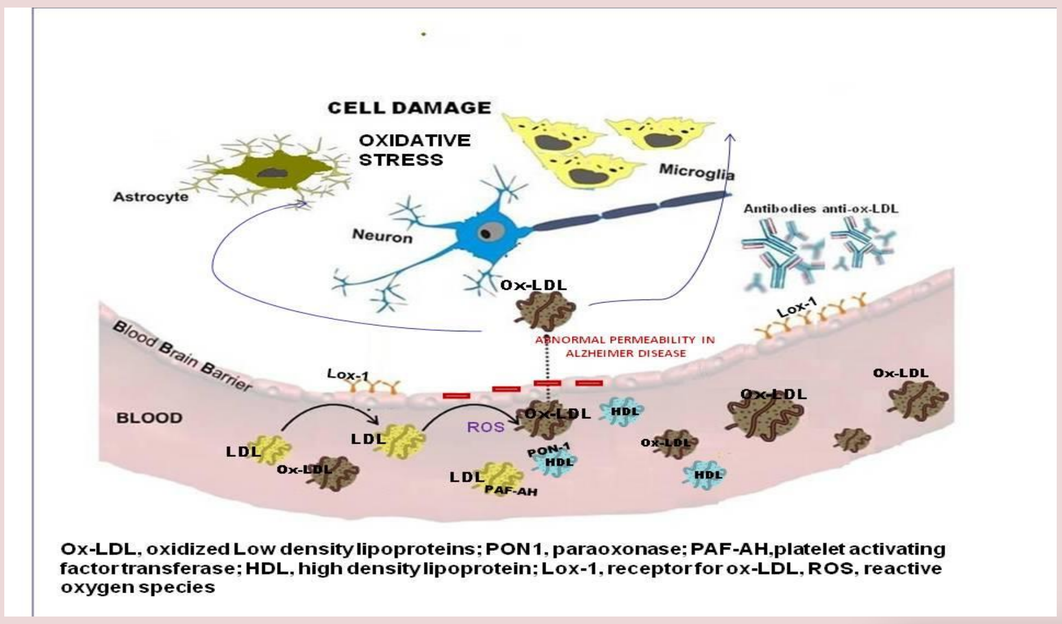
CONCLUSIONS

Some hyphoteses can be advanced to explain the increase of oxidized LDL in AD patients.

Apo B containing lipoproteins are not synthesised by astrocytes. However the presence of antibodies against ox-LDL in cerebrospinal fluid (CSF) of AD patients, suggests a cross of ox-LDL from plasma (Fig.1).

Alterations of Blood brain Barrier (BBB) occur in Alzheimer's disease and would allow the influx of pro-oxidant molecules and/or ox-LDL. Oxidation of lipoproteins not only eliminates their supportive roles in neurite outgrowth and synaptogenesis, but actually transforms them into neurotoxic agents. Ox-LDL show several alterations of their functions, have pro-inflammatory properties and contribute to oxidative stress of astrocytes, microglia and neuronal cells.

In conclusion, we suggest that whether the antioxidant enzyme PON1 is lower and it is not able to prevent the oxidation of LDL, oxidized phospholipids become substrate for PAF-AH which is associated with both HDL and LDL. Hydrolysis of PAF and oxidized phospholipids by PAF-AH generates lysophospholipids such as lysophosphatidylcholine (LPC) and oxidized free fatty acids which are potent bioactive lipids.



Ox-LDL, oxidized Low density lipoproteins; PON1, paraoxonase; PAF-AH,platelet activating factor transferase; HDL, high density lipoprotein; Lox-1, receptor for ox-LDL, ROS, reactive oxygen species

Fig. 2 – Oxidative stress in Alzheimer disease. Roles of oxidized LDL.

Di chi sará il mondo di domani?
Di chi oggi canta in coro.

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