Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Association, Elizabeth Head

b,

-9.7(of)-298.4(Department250.29(Aging),250.26(Univ 17ity42511embrane)-30K(ofucker)-304-30Lexing

Article history:
Received 18 July 2011
Received in revised form 30 September 2011
Accepted 3 October 2011
Available online 8 October 2011

Keywords:
Alzheimer disease
4-Hydroxy-2-nonenal
3-Nitrotyrosine
Oligomer
Protein carbonyl
Trisomy 21

Down syndrome (DS) is the most common genetic cause of intellectual disability in children, and the number of adults with DS reaching old age is increasing. By the age of 40 years, virtually all people with DS have suf cient neuropathology for a postmortem diagnosis of Alzheimer disease (AD). Trisomy 21 in DS leads to lea4515 TAD-140564Tj /F2140bili.1(F21409-28.9(and)-3474com5in)-354068 -n with DS but without signi cant AD pathology, as compared with similarly aged-matched non-DS controls. The frontal cortex was examined in 70 autopsy cases (n=29 control and n=41 DS). By ELISA, we quanti ed soluble and insoluble A 40 and A 42, as well as oligomers. Oxidative and nitrosative stress levels (protein carbonyls, 4-hydroxy-2- trans-nonenal (HNE)-bound proteins, and 3-nitrotyrosine) were measured by slot-blot. We found that soluble and insoluble amyloid beta peptide (A) and oligomers increase as a function of age in DS frontal cortex. Of the oxidative stress markers, HNE-bound proteins were increased overall in DS. Protein carbonyls were correlated with A 40 levels. These results suggest that oxidative damage, but not nitrosative stress, may contribute to the onset and progression of AD pathogenesis in DS. Conceivably, treatment with antioxidants may provide a point of intervention to slow pathological alterations in DS.

1. Introduction

0925-4439/$ …see front matter
doi: 10.1016/j.bbadis.2011.10.001

IgG secondary antibody (1:5000;

the age of 40 years had the highest levels of SDS-extracted A 42 overall ($F(1,69) = 8.23$ $p = 0.006$; Fig. 2E).

The effect of age on FA-extracted A 42 was similar to that of SDS-extracted A

3.4. Association between Aβ and oxidative damage in DS

In all A measures, the DS cases and particularly those over the age of 40 years showed signi cant individual variability. Thus, we hypothesized that individual A measures may re ect differences in the level of oxidative damage. A partial correlation co-ef cient that controlled for PMI was calculated between A measures and measures of oxidative damage. The amount of oligomeric A was not correlated with PCs ($r=0.17$ $p=0.16$), NT ($r=-0.07$ $p=0.55$) or HNE ($r=-0.097$ $p=0.43$). Similarly, there were no correlations between any measure of A 42 and the extent of PCs (PBS A 42 $r=-0.14$ $p=0.27$; SDS A 42 $r=0.02$ $p=0.89$; FA A 42 $r=0.13$

correlated with PCs, although the level of signi cance was marginal (r=0.310 p=0.058 n=36) (Fig. 4C). SDS- (r=0.369 p=0.023 n=36) and FA- (r=0.39 p=0.016 p=36) extracted A 40 were correlated with signi cantly higher PC accumulation, but were not correlated with either HNE or 3-NT levels (Fig. 4D, E).

4. Discussion

An imbalance between pro-oxidant stimuli and cellular antioxidant activity may lead to increased oxidative stress levels that may have an important role in the development of AD neuropathology in DS [9, 11, 37]. Involvement of oxidative and nitrosative stress-induced neuronal damage is a well- established feature during the development of AD [14, 17, 74]. In the current study, we provided new evidence of higher levels of oxidative damage in brains from individuals with DS, although measures of oxidative damage were not increased further with AD pathology. The frontal cortex of DS subjects had signi cantly increased HNE-bound proteins levels, a sensitive marker of lipid peroxidation, compared to non-DS controls. Lipid peroxidation leads to various aldehydic products, with 4-hydroxy-2-nonenal (HNE) being one of the most abundant [76]. HNE is a highly reactive alkenal responsible for the damaging effects of oxidative stress and linked to neurodegenerative diseases such as AD [7, 14, 65].

This study extends earlier studies demonstrating that lipoperoxidation is enhanced in prenatal DS brains compared to non-DS controls [8, 59]. Pratico et al. also demonstrated that another marker of lipid peroxidation, 8,12-iso-iPF2 -VI, was signi cantly increased in the urine of young subjects with DS, as compared to age-matched controls [63]. Furthermore, cortical neurons cultured from prenatal DS cases exhibited the intracellular accumulation of ROS and increased lip,e f lip,

Acknowledgements

This work was supported in part by grants from NIH to D.A.B [AG-05119], and to E.H. and F.S [HD-064993]. Additional funding was provided by NIH to the UCI ADRC (P50 AG16573) and to the UK ADC (P30 AG028383). Human tissue obtained from NICHD Brain and Tissue Bank for Developmental Disorders at the University of Maryland, Baltimore, MD, was under contract HHSN275200900011C, Ref. No. N01-HD-9-0011. This work was also supported in part by a PRIN grant to C.M. and E.B.

References

[1] M.Y. Aksenov, M.V. Aksenova, W.R. Markesbery, D.A. Butter eld, Amyloid beta-peptide (1 ..40)-mediated oxidative stress in cultured hippocampal neurons.

from patients with Alzheimer's disease: implications for neuronal damage, Hum. Mol. Genet. 20 (2011) 2495 ..2509.
[52] D.M. Mann, B. Marcyniuk, P.O. Yates, D. Neary, J.S. Snowden, The progression of the pathological changes of Alzheimer's disease in frontal and temporal neocortex examined both at biopsy and at autopsy, Neuropathol. Appl. Neurobiol. 14 (1988) 177 ..195.
[53] D.M.A. Mann, M.M. Esiri, The pattern of acquisition of plaques and tangles in the brains of patients under 50 years of age with Down's syndrome, J. Neurol. Sci. 89 (1989) 169 ..179.
[54] W.R. Markesbery, Oxidative stress hypothesis in Alzheimer's disease, Free Radic. Biol. Med. 23 (1997) 134 ..147.
[55] B. Mazur-Kolecka, A. Golabek, K. Nowicki, M. Flory, J. Frackowiak, Amyloid-beta impairs development of neuronal progenitor cells by oxidative mechanisms, Neurobiol. Aging 27 (2006) 1181 ..1192.
[56] M. Nistor, M. Don, M. Parekh, F. Sarsoza, M. Goodus, G.E. Lopez, C. Kawas, J. Leverenz, E. Doran, I.T. Lott, M. Hill, E. Head, Alpha- and beta-secretase activity as a function of age and beta-amyloid in Down syndrome and normal brain, Neurobiol. Aging 28 (2007) 1493 ..1506.
[57] A. Nunomura, G. Perry, K. Hirai, G. Aliev, A. Takeda, S. Chiba, M.A. Smith, Neuronal RNA oxidation in Alzheimer's disease and Down's syndrome, Annals NYAS 893 (1999) 362 ..364.
[58] A. Nunomura, G. Perry, M. Pappolla, R.P. Friedland, K. Hirai, S. Chiba, M.A. Smith, Neuronal oxidative stress precedes amyloid- deposition in Down syndrome, J. Neuropathol. Exp. Neurol. 59 (2000) 1011 ..1017.
[59] P. Odetti, G. Angelini, D. Dapino, D. Zaccheo, S. Garibaldi, F. Dagna-Bricarelli, G. Piombo, G. Perry, M. Smith, N. Traverso, M. Tabaton, Early glycoxidation damage in brains from Down's syndrome, Biochem. Biophys. Res. Commun. 243 (1998) 849..851.
[60] M. Perluigi, F. Di Domenico, A. Fiorini, A. Cocciolo, A. Giorgi, C. Foppoli, D.A. Butter eld, M. Giorlandino, C. Giorlandino, M.E. Schinina, R. Coccia, Oxidative stress occurs early in Down syndrome pregnancy: a redox proteomics analysis of amniotic uid, Proteomics Clin. Appl. 5 (2011) 167 ..178.