ELSEVIER

Alzheimer's & Dementia 1 (2005) 51–52

Alzheimer's & Dementia

Commentary: "Ceramide and cholesterol: Possible connections between normal aging of the brain and Alzheimer's disease. Just hypotheses or molecular pathways to be identified?" By Claudio Costantini, Rekha M.K. Kolasani, and Luigi Puglielli

Gemma Casadesus, Mark A. Smith, George Perry*

Institute of Pathology, Case Western Reserve University, Cleveland, OH, USA

The middleman or the missing link: the role of ceramide in Alzheimer's disease—Ceramide, a lipid precursor in the production of a crucial component of membranes called *sphingomyelin*, also plays a key role in the regulation of a multitude of cellular processes. By serving as a potent second messenger, ceramide is implicated in the regulation of proliferation, survival, and differentiation of the cell as well as inflammatory activity and cholesterol metabolism to name but a few of ceramide's key functions. In an eloquently presented review by Costantini et al [1], the pivotal role of ceramide in mediating the relationship between lipid composition and the regulation and production of the amyloid-β peptide, in addition to its link to oxidative stress, senescence, and cell death of neurons in Alzheimer disease (AD) is discussed. As highlighted, the promiscuity of ceramide would allow it to be actively involved in most, if not all, of the pathogenic events occurring in AD.

Of central importance, given the age-related increase in AD, studies have found that ceramide is increased during aging. Moreover, recent data described in the current review, suggest that ceramide can increase amyloid-β protein precursor (AβPP) processing and amyloid-β generation by stabilizing BACE1, a key protease mediating the liberation of amyloid-β from its precursor. These studies, together with additional evidence regarding cholesterol homeostasis and distribution in neurons, as the authors suggest, could provide the missing link between aging and AD. However, an alternative explanation for these findings, based on the stress–response role of the ceramide–sphingomyelin (SM) pathway, should not be ignored [2]. In this regard, the pleuripotent activity of ceramide indicates an intrinsic function in rescue machinery to protect cells subject to stress as shown by the fact that mild increases in ceramide are indeed beneficial [3–5]. With regard to AD, one of the earliest events that occur in AD is oxidative stress [6,7]. Likely, not coincidently, increased ceramide also occurs early in the pathogenesis of AD [8,9]. Therefore, one possibility, in accord with the stress–response activation of the SM pathway, would be that increased oxidative stress would lead to activation of this pathway that could then signal the biochemical messages associated with cell protection [10,11]. Additionally, oxidatively induced ceramide would drive the production of amyloid-β. Although this schema is consistent with the known chronology of the disease, i.e., oxidative stress predating amyloid-β, under the current prevalent belief that amyloid-β is toxic, it would appear to be counterintuitive to a protective response. However, recent evidence suggests that amyloid-β may not only be a consequence of AD but that it may also serve a protective role [12,13] by working as an antioxidant [14–17]. As such, ceramide would serve as the intermediate signal between oxidative stress and the activation of amyloid-β production and other protective pathways to attenuate oxidative damage. Although such an assertion may be provocative, it is consistent with at least one of the known cellular and biochemical functions of ceramide, and, therefore, ceramide (or for that matter, amyloid-β), like many facets of biology, may be important for reasons other than those currently ascribed to it.

*Corresponding author. Tel.: 216-368-2488.
E-mail address: george.perry@case.edu

1552-5260/05/$ – see front matter
doi:10.1016/j.jalz.2005.06.011

References

[1] Costantini C, Kolasani RMK, Puglielli L, et al. Ceramide and cholesterol: possible connections between normal aging of the brain and Alzheimer's disease. Just hypotheses or molecular pathways to be identified? Alzheimer's & Dementia: Journal of the Alzheimer's Association: 2005;1:43–50.

[2] Cutler RG, Mattson MP. Sphingomyelin and ceramide as regulators of development and lifespan. Mech Ageing Dev 2001;122(9):895–908.

[3] Mattson MP, Goodman Y, Luo H, et al. Activation of NF-kappaB protects hippocampal neurons against oxidative stress-induced apoptosis: evidence for induction of manganese superoxide dismutase and suppression of peroxynitrite production and protein tyrosine nitration. J Neurosci Res 1997;49(6):681–97.

[4] Irie F, Hirabayashi Y. Application of exogenous ceramide to cultured rat spinal motoneurons promotes survival or death by regulation of apoptosis depending on its concentrations. J Neurosci Res 1998; 54(4): 475–85.

[5] Ruvolo PP. Ceramide regulates cellular homeostasis via diverse stress signaling pathways. Leukemia 2001;15(8):1153–60.

[6] Nunomura A, Perry G, et al. Neuronal oxidative stress precedes amyloid-beta deposition in Down syndrome. J Neuropathol Exp Neurol 2000;59(11):1011–7.

[7] Nunomura A, Perry G, Pappolla MA, et al. Oxidative damage is the earliest event in Alzheimer disease. J Neuropathol Exp Neurol 2001; 60(8):759–67.

[8] Han X, Holtzman DM, McKeel DW Jr, et al. Substantial sulfatide deficiency and ceramide elevation in very early Alzheimer's disease: potential role in disease pathogenesis. J Neurochem 2002; 82(4):809–18.

[9] Cheng H, Xu J, McKeel DW Jr, et al. Specificity and potential mechanism of sulfatide deficiency in Alzheimer's disease: an electrospray ionization mass spectrometric study. Cell Mol Biol (Noisy-le-grand) 2003;49(5):809–18.

[10] Perry G, Roder H, Nunomura A, et al. Activation of neuronal extracellular receptor kinase (ERK) in Alzheimer disease links oxidative stress to abnormal phosphorylation. Neuroreport 1999;10(11): 2411–5.

[11] Zhu X, Lee HG, Raina AK, et al. The role of mitogen-activated protein kinase pathways in Alzheimer's disease. Neurosignals 2002; 11(5):270–81.

[12] Lee HG, Casadesus G, Zho X, et al. Challenging the amyloid cascade hypothesis: senile plaques and amyloid-beta as protective adaptations to Alzheimer disease. Ann N Y Acad Sci 2004;1019:1–4.

[13] Marlatt M, Lee HG, Perry G, et al. Sources and mechanisms of cytoplasmic oxidative damage in Alzheimer's disease. Acta Neurobiol Exp (Wars) 2004;64(1):81–7.

[14] Cuajungco MP, Goldstein LE, Nunomura A, et al. Evidence that the beta-amyloid plaques of Alzheimer's disease represent the redox-silencing and entombment of abeta by zinc. J Biol Chem 2000; 275(26):19439–42.

[15] Atwood CS, Robinson SR, Smith MA, et al. Amyloid-beta: redox-metal chelator and antioxidant. J Alzheimers Dis 2002;4(3):203–14.

[16] Smith MA, Casadesus G, Joseph JA, et al. Amyloid-beta and tau serve antioxidant functions in the aging and Alzheimer brain. Free Radic Biol Med 2002;33(9):1194–9.

[17] Cuajungco MP, Frederickson CJ, Bush AI, et al. Amyloid-beta metal interaction and metal chelation. Subcell Biochem 2005;38:235–54.