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 pleiotropic 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 coincidentally, 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
References


