

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, Luigi Puglielli

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This excellent review by Costantini et al brings together a series of divergent biological processes that occur during normal aging into an elegant hypothesis for the pathogenesis of Alzheimer’s disease (AD). As correctly noted by Costantini and collaborators, it has been suggested that alterations in dietary lipids may play an important role in cognitive deficits in AD, secondary to their effects on neuronal membrane lipids [1,2]. Most importantly, 2 genetic links between cholesterol and AD have given reasonable proof that this risk factor must be taken seriously. Apolipoprotein E is the main cholesterol transport protein involved in cholesterol recycling in the brain [3]. There are 3 different alleles ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$) of ApoE, of which, the $\epsilon 4$ allele is overrepresented among AD patients [4]. It has been postulated that this risk factor comes into play because of a reduced capability for cholesterol reuptake in the brain. Further proof for a role of cholesterol in AD came recently when investigators found a genetic link between the cholesterol-converting enzyme Cyp46 and incidence of AD [5]. Cyp46, a brain-specific enzyme, acts by regulating the elimination of excess cholesterol in the brain by adding a hydroxyl group to the cholesterol molecule, producing a product that is more soluble than cholesterol and able to be exported from the brain. Several different investigators [5,6] have reported that patients with a Cyp46 polymorphism, exhibit an increase in the plaque load as well as an increase in cerebrospinal fluid (CSF) Ab42. Thus, there are several clinical indications that cholesterol plays a role in AD, but a biological mechanism for this influence has not been fully understood. In animal models, it has also been shown unequivocally that high cholesterol and high-fat diets affect

amyloid production, growth factor levels, and cognitive status. For example, studies using transgenic mouse models have found that $A\beta$ accumulation in plaques is increased by high cholesterol–high lipid diets in mice [7–10]. Cognitive performance has been shown to be diminished in transgenic mice fed this diet [10] and in nontransgenic rats that do not deposit amyloid [11]. Thus, it is not known yet through which mechanisms cholesterol exerts its effects in the aged brain or in Alzheimer pathology. As shown by Costantini and his collaborators, this is, however, a viable novel theory to pursue in future research.

It is possible that the ceramide–cholesterol pathways provide the missing link between the growth factor hypothesis of AD [12] and the amyloid theory. As denoted by Costantini et al, binding of neurotrophins to p75 receptors results in activation of ceramide, leading to increased axonal growth and inhibition of apoptosis. Mufson et al [13] have shown that nerve growth factor (NGF) levels are reduced in basal forebrain and increased in hippocampus of AD patients, suggesting that there is a deficient transport of NGF from the area of production (hippocampus) to the area of need (basal forebrain). Recently we have shown that NGF levels in the CSF of patients with varying cognitive loss correlate with degree of dementia (lower cognitive performance was related to lower NGF levels) in a recognition task, again suggesting that NGF may play a role in AD [14]. This altered growth factor regulation is likely to affect ceramide activation, leading to cell loss or loss of synaptic plasticity as hypothesized in the review. A reduction of NGF in cholinergic neurons, in turn, leads to decreased acetylcholine release from the terminals, and altered processing of amyloid precursor protein (APP) toward the amyloidogenic (BACE) rather than the α -secretase pathway [15]. Thus, it is likely that all of these systems interact

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during both normal aging and AD, leading to neuronal dysfunction, reduced synaptic plasticity, and accumulated aggregation of damaging peptides in the limbic system.

It is clearly described by Costantini et al that both ceramide and cholesterol pathways play an integral role in both normal aging and AD. It is important in continued research to connect these areas of research with existing theories and not restrict ourselves in pursuit of possible treatment avenues for this progressive disease. It is also important to remember that AD is a disease of aging, and, therefore, aging in animal models should be considered an essential paradigm to investigate, even though this may be difficult in the transgenic models. Even though AD is NOT just accelerated aging, it progresses with age and shares common pathologies.

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