Alzheimer’s disease (AD) and Parkinson’s disease (PD) are the most common neurodegenerative disorders. Both diseases are characterized by the deposition in the brain of insoluble protein aggregates: β-amyloid (Aβ) in AD and α-synuclein in PD. The differences in protein aggregate types that accumulate either in AD or PD suggest that these diseases are two distinct entities. However, a significant proportion of dementia brains showing features of AD also exhibit α-synuclein inclusions. As well, a subset of PD patients has Aβ aggregates in addition to α-synuclein load. The concomitant presence of the two proteins indicates that AD and PD overlap, and that this overlap may be caused by factors that can converge to trigger the overlapping features (i.e., Aβ and α-synuclein). However, currently no genetic or environmental factor that can generate both Aβ and α-synuclein in vivo or in vitro has been identified. Thus, while the pathogeneses of AD, PD, and mixed AD/PD are still to be determined, identification of signaling mechanisms that can be modulated to trigger the overproduction of Aβ and α-synuclein may help design strategies that prevent or slow the accumulation of these aggregates.

The identification of genetic mutations linked to familial forms of AD and PD has led to the development of cellular and animal models that have helped in understanding aspects of the pathophysiology of the inherited, early onset AD and PD forms. However, the majority of AD and PD cases are sporadic. While genetic mutations are responsible for the accumulation of Aβ in familial AD and α-synuclein in familial PD, the causative factors for the accumulation of Aβ and α-synuclein in sporadic AD are not known. This raises the possibility that the accumulation of Aβ and α-synuclein in the absence of genetic mutations might result from abnormalities in specific signaling pathways that lead to an increase in Aβ and α-synuclein production and/or a decrease in their clearance. Factors such as the environment and diet may be implicated in the pathogenesis of sporadic forms of AD and PD. The first identified risk of AD is apolipoprotein E (ApoE) [1]. Some but not all people who have one or two copies of the ApoE ε4 allele are at increased risk of AD. ApoE is a specific type of lipoprotein that plays an important role in the distribution of cholesterol in blood and brain. Carrying ApoE ε4 is associated with high plasma cholesterol [2,3]. The association between ApoE and cholesterol has put cholesterol up front as a potential risk factor for sporadic forms of AD. Both the pioneer studies by Sparks et al. [4] showing that rabbits fed a diet rich in cholesterol exhibit increased Aβ accumulation and the epidemiological studies by Solomon et al. [5] demonstrating that high cholesterol at mid-age increases the risk for AD by 66% later in life link cholesterol to the pathophysiology of AD. For the last few years, high dietary fat intake has also been under scrutiny as a risk factor for PD. A standardized food frequency questionnaire has shown an association of PD with high intake of total fat, saturated fats, and cholesterol [6]. A recent large prospective study has suggested that total serum cholesterol at baseline is associated with an increased risk of PD [7]. In other studies however, elevated serum levels of cholesterol were either not associated with PD risk [8] or were related to a decreased PD risk [9,10].

Thus, to date, the extent to which disturbances in cholesterol metabolism play a role in the pathogenesis of AD or PD is still unclear. The absence of a consensus on a role of cholesterol in AD or PD may be explained by the following: First, it may be possible that abnormalities in cholesterol metabolism take part in AD and PD pathogenesis early at mid-age when the disease is initiated; at late-age when symptoms manifest and PD progresses, the correlation between AD/PD and cholesterol status is no longer consistent. Indeed, AD or PD patients may have normal, low or high cholesterol levels. Second, fluctuations in cholesterol oxidation products (oxysterols), rather than cholesterol per se, may correlate better with the onset of AD and PD. Some oxysterols may place the brain at risk of injury following disturbances in their levels. Of these oxysterols, 27-hydroxycholesterol (27-OHC) has the ability to cross lipophilic membranes into and out of the brain [11,12]. As 27-OHC originates almost exclusively from oxidation of cholesterol in the circulation, one can expect that hypercholesterolemia increases turnover of cholesterol to 27-OHC, thus increasing its levels in the circulation and potentially in the brain. Circulating 27-OHC levels are 0.15-0.73 μM, and these concentrations can be in the millimolar range in some pathological situations such as atherosclerosis [13,14]. A marked accumulation of 27-OHC in the brains of Alzheimer’s patients with the Swedish APP 670/671 mutation has been recently demonstrated [15]. Oxysterols were also shown to be elevated in the cerebral cortex of individuals with Lewy body dementia where they are suggested to accelerate α-synuclein aggregation [16]. A recent study also showed increased levels of several oxysterols including 27-OHC in cortex of PD brains [17]. These studies, together with the known toxic effects of high levels of oxysterols suggest a possible role of these cholesterol metabolites in AD and PD.

The question as to what are the potential cellular pathways and mechanisms that mediate the deleterious effects of oxysterols is however still to be answered. Binding to and activating liver X receptors (LXRs) is one of the major mechanisms by which 27-OHC and other oxysterols exert their major functions [18]. LXRs bind to promoters of specific genes to recruit co-activators or co-repressors, thus impacting expression of target genes. We have recently found that treatment with the oxysterol 27-OHC increases α-synuclein production [19] and reduces tyrosine hydroxylase (TH), the rate limiting enzyme in dopamine synthesis, and increases α-synuclein levels [20,21]. In support of our data, another independent study also showed that 27-OHC regulates α-synuclein expression levels, and provided further evidence that 27-OHC modulates α-synuclein through activation of LXRs [22]. We also

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investigated the potential of estrogen receptors (ERs) as the target for 27-OHC as it has been recently discovered that 27-OHC, in addition to being an LXR agonist, is also a selective estrogen receptor modulator (SERM) [23] and ERs were also shown to regulate the expression levels of TH [24]. We speculated that 27-OHC acts as an inverse agonist of ERs, competitively antagonizes ERs and reduces TH levels. We incubated SH-SY5Y cells for 24 h with 27-OHC and/or estradiol (E2), the most abundant and potent endogenous estrogen that activates ERs, and found that while 27-OHC reduces TH expression, E2 increases basal levels and opposes 27-OHC effects on TH [20].

Overall, the involvement of cholesterol metabolism in AD and PD needs to be re-examined. Oxysterols, normal lipid components in the brain, can regulate Aβ, TH and α-synuclein through LXRs and ERs in vitro. Modulation of LXR and ERs in vivo models remain to be carried out to determine their potential in causing or protecting against AD and PD. More importantly, further studies demonstrating the accumulation of 27-OHC in brains exhibiting overlapping AD and PD pathologies are needed. Confirmation of involvement of LXR and ER pathways in the regulation of Aβ, TH and α-synuclein levels may lead to novel therapeutic avenues that consist in the use of an LXR antagonist to reduce Aβ and α-synuclein accumulation and an ER agonist to prevent TH reduction. These agents, used as mono or combined therapies, may be a promising therapeutic strategy to protect against AD/PD overlap.

References