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Mitochondria, cholesterol and amyloid β peptide: a dangerous trio in Alzheimer disease

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Abstract The molecular mechanisms of Alzheimer's disease (AD) are not fully understood. Extensive evidence from experimental models has involved the overgeneration and accumulation of toxic amyloid β peptides (Aβ) in the onset and progression of the disease. The amyloidogenic processing of amyloid precursor protein into pathogenic Aβ fragments is thought to occur in specific domains of the plasma membrane and favored by cholesterol enrichment. Intracellular Aβ accumulation is known to induce oxidative stress, predominantly via mitochondria targeting of toxic Aβ. Recent evidence using mouse models of cholesterol loading has demonstrated that the specific mitochondrial cholesterol pool sensitizes neurons to Aβ-induced oxidant cell death and caspase-independent apoptosis due to selective mitochondrial GSH (mGSH) depletion induced by cholesterol-mediated perturbation of mitochondrial membrane dynamics. mGSH replenishment by permeable precursors such as glutathione ethyl ester protected against Aβ-mediated neurotoxicity and inflammation. Thus, these novel data expand the pathogenic role of cholesterol in AD indicating that in addition to fostering Aβ generation, mitochondrial cholesterol determines Aβ neurotoxicity via mGSH regulation.

Keywords Alzheimer disease · Lipid rafts · Cholesterol · GSH · Glycosphingolipids · Mitochondria

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Abbreviations

AD	Alzheimer's disease
Aβ	amyloid β peptide
APP	amyolid precursor protein
ACAT-1	acyl-coenzyme A:cholesterol acyl transferase
IDE	insulin degrading enzyme
KGDHC	α-ketoglutarate dehydrogenase
GSH	reduced glutathione
mGSH	mitochondrial GSH
GEE	GSH ethyl ester
HP	3-hydroxy-4-pentenoate
NPC-1	Niemann-Pick type C1
ROS	reactive oxygen species
SREBP-2	sterol regulatory binding protein-2

Introduction

Alzheimer's disease (AD) is a major neurodegenerative disorder, characterized by progressive memory loss and cognitive impairment, whose incidence increases with age. Despite intense research, our current understanding of the pathogenesis of the disease is incomplete, which limits the prospects for treatment and management of this devastating disease. The current recommended therapies for the treatment of AD typically include acetylcholinesterase inhibitors and the *N*-methyl-d-aspartate antagonist memantine. Unfortunately their benefits are very modest and ultimately do not prevent disease progression (Vardy et al. 2006). Thus, given the lack of effective therapy and its association with aging the number of patients worldwide that potentially can develop AD is large and rising, hence illustrating the urgent need for the discovery of novel therapies. AD is characterized by the deposition in the brain

of senile plaques, consisting predominantly of the amyloid β (Aβ) peptide of 40–42 amino acids forms, which is thought to play a key role in AD (Taylor et al. 2002; Tanzi et al. 2004; Deane and Zlokovic 2007; Haass and Selkoe 2007). Accumulation of oligomeric Aβ, particularly the longer Aβ1–42, initiates a cascade of events resulting in the neurodegeneration seen in AD (Shankar et al. 2008). The pathogenic processing of the amyloid precursor protein (APP) into toxic Aβ fragments occurs in cholesterol-enriched membrane domains of the plasma membrane, underlying the recognized role of cholesterol in AD pathogenesis (Notkola et al. 1998; Wolozin et al. 2000). Although the molecular mechanisms of Aβ-induced neurotoxicity are not fully known, a crucial factor is the generation of reactive oxygen species (ROS) originating from the mitochondrial targeting of Aβ (Lin and Beal 2006; Manczak et al. 2006). In this review, we summarize recent evidence linking mitochondria, cholesterol and Aβ, in a relationship in which the specific mitochondrial cholesterol pool determines the susceptibility of neurons to Aβ-mediated neurotoxicity and inflammation via regulation of mitochondrial GSH (mGSH). This scenario suggests that therapeutic avenues aimed to specifically boost mGSH may be of potential relevance in AD.

Aβ and cholesterol

Aβ is generated by a specific proteolytic cleavage of APP. In the amyloidogenic pathway, the β- and γ-secretases cleave APP at the N- and C-termini of the Aβ peptide, respectively. β-Secretase has been characterized as a membrane-bound aspartic protease termed BACE1 (beta-site APP-cleaving enzyme 1), while γ-secretase is a complex comprised of presenilin-1 or -2, nicastrin, Aph-1 (anterior pharynx-defective 1) and Pen-2 (presenilin enhancer 2) (Haass 2004). Inhibition of the β- and γ-secretases is considered a viable therapeutic approach for AD treatment and compounds that inhibit one or the other protease are currently under clinical trials (Vardy et al. 2006; Shah et al. 2008). In addition to its amyloidogenic processing by β- and γ-secretases, APP can be cleaved within the Aβ domain by α-secretase. This non-amyloidogenic processing prevents the deposition of intact Aβ peptide and results in the release of a large soluble ectodomain, sAPPα, from the cell, which has neuroprotective and memory-enhancing effects. Members of the ADAMs, a disintegrin and metalloprotease family of proteases, have been shown to possess α-secretase activity (Hooper and Turner 2002).

Epidemiological evidence established a link between plasma cholesterol levels and AD development (Notkola et al. 1998; Wolozin et al. 2000; Anstey et al. 2008). High cholesterol levels correlated with Aβ deposition and the risk of developing AD, while conversely, patients taking the cholesterol-lowering drug statins were found to have a lower incidence of the disease (Notkola et al. 1998; Wolozin et al. 2000). Although recent reports examining statin usage have produced mixed conclusions, the epidemiological data linking high cholesterol levels with increased Aβ production and prevalence of AD have been supported by a number of *in vivo* and *in vitro* studies. For instance, animals fed a high cholesterol diet showed increased Aβ accumulation and increased BACE1 activity, whereas treatment with cholesterol-lowering drugs resulted in lower Aβ levels (Refolo et al. 2000; Fassbender et al. 2001; Refolo et al. 2001). The differential localization of APP and its secretases in cholesterol-rich lipid rafts is thought to regulate the production of the neurotoxic Aβ peptide. Increasing evidence supports the hypothesis that the amyloidogenic processing of APP occurs in cholesterol-rich lipid rafts, while non-amyloidogenic processing occurs mainly in other regions of the membrane. Thus, altering cellular cholesterol levels regulates the processing of APP through these two pathways (Kojro et al. 2001; Wahrle et al. 2002; Ehehalt et al. 2003). Several studies have examined the localization of APP, the α-, β- and γ-secretases in rafts, mainly by exploiting the relative detergent insolubility of such domains. Varying proportions of the presenilins and the other components of the γ-secretase complex (nicastrin, Aph-1 and Pen-2), along with γ-secretase activity, as well as minor amounts of the β-secretase BACE1, are present in detergent-resistant rafts (Riddell et al. 2001; Wahrle et al. 2002; Vetrivel et al. 2005; Hur et al. 2008). In addition, the activities of BACE1 and γ-secretase are stimulated by some lipid components of rafts, such as glycosphingolipids and cholesterol (Sawamura et al. 2004; Osenkowski et al. 2008; Kalvodova et al. 2005; Ariga et al. 2008). Intriguingly, although the presence of APP in detergent-resistant rafts is relatively minor (Lee et al. 1998), once localized to the raft, the APP may be rapidly cleaved by β- and γ-secretases, thus contributing to Aβ generation. Several studies have demonstrated the requirement of APP internalization and its subsequent processing in endosomes (Koo and Squazzo 1994; Ehehalt et al. 2003; Kinoshita et al. 2003). A recent study indicates that the cytoplasmic domain of the low-density lipoprotein receptor-related protein (LRP) might promote APP trafficking to lipid rafts in the endocytic pathway enhancing its association with BACE1 (Yoon et al. 2007). In addition to free cholesterol, cholesterol-esters have also been shown to regulate Aβ generation. Thus, cholesterol-ester levels directly correlate with Aβ production (Puglielli et al. 2001), and antagonism of acyl-coenzyme A: cholesterol acyl transferase 1 (ACAT1) reduces the amiloidogenic processing of APP by regulating its intracellular trafficking in the early secretory pathway (Huttunen et al. 2007, 2009). Thus, cholesterol plays a pathogenic role in AD by fostering toxic Aβ generation (Fig. 1).

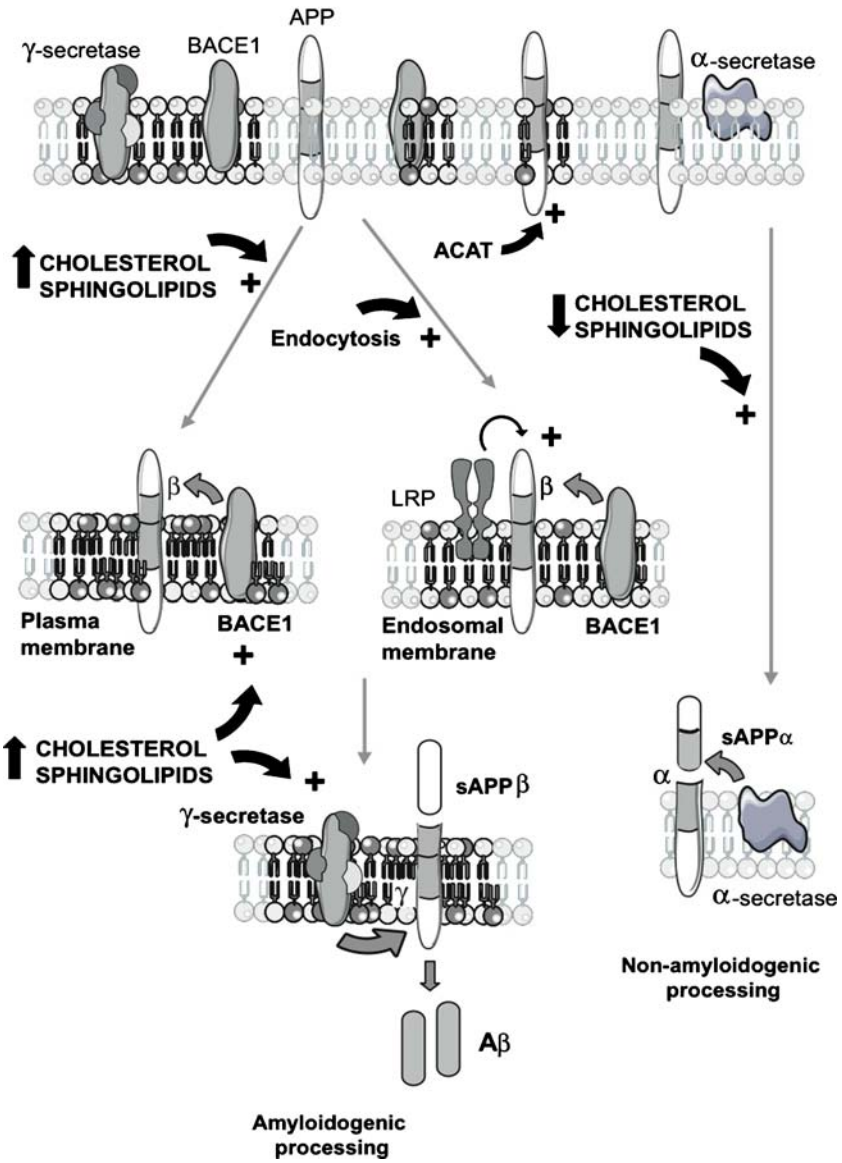

Fig. 1 Model of regulation of Aβ peptide production by cholesterol and sphingolipids. The differential localization of APP and its secretases in cholesterol-rich lipid rafts is thought to regulate the production of the neurotoxic Aβ peptide. Lipid rafts are the preferential sites for the amyloidogenic processing through a sequential proteolytic cleavage of APP, first by the β-secretase BACE1 followed by the γ-secretase. Under normal conditions, while mature γ-secretase complexes are mainly present in lipid rafts, APP and BACE1 molecules are distributed in both lipid rafts (*depicted in dark grey*) and phospholipid domains (*depicted in light grey*). Due to the small size of the rafts, individual APP and BACE molecules are rarely present in the same raft. In this situation, APP is mostly cleaved by α-secretase present in non-raft domains releasing the secreted (s)APPα fragment from cell surface. Elevated levels of cholesterol and sphingolipids, that increase the number and size of rafts, or clustering of rafts upon endocytosis would bring APP and BACE molecules into contact enhancing the amyloidogenic processing. Conversely, decreased levels of cholesterol or sphingolipids would result in the disorganisation of rafts and favour the non-amyloidogenic pathway. β- and γ-secretases are both stimulated by changes in cholesterol and sphingolipid content. In addition, low-density lipoprotein receptor-related protein (LRP) promotes APP translocation to lipid rafts in the endocytic pathway enhancing its association with BACE1. Amyloidogenic processing may also be stimulated by changes on the acyl-coenzyme A: cholesterol acyl transferase 1 (ACAT1) activity, which modulates APP intracellular trafficking in the early secretory pathway and thus, its availability in the plasma membrane

Mitochondria, APP and Aβ neurotoxicity

In addition to its extracellular deposition, current evidence indicates the processing and targeting of APP and Aβ to intracellular sites, including mitochondria (Lin and Beal 2006). Well before plaques are observed, intracellular aggregates of Aβ form early in mice overexpressing APP, and these aggregates seem to congregate in synaptic compartments and correlate with cognitive impairment (Oddo et al. 2003). Moreover, nonglycosylated full-length

and C-terminally-truncated APP were associated with mitochondria in samples from the brains of individuals with AD, but not with mitochondria in samples from subjects without the disease. Furthermore, within AD brain samples, levels of mitochondrial APP were higher in more affected brain areas and in subjects with more advanced disease (Devi et al. 2006). Immunoelectron microscopy analyses indicated the stably association of APP with mitochondrial protein translocation components, TOM40 and TIM23, which correlated with decreased import of respiratory chain subunits *in vitro*, decreased cytochrome oxidase activity, increased ROS generation and impaired mitochondrial reducing capacity (Devi et al. 2006). Moreover, mitochondria have been described to interact with factors involved in Aβ metabolism. Functional complexes with γ-secretase activity have been found in mitochondria (Hansson et al. 2004) and insulin degrading enzyme (IDE), which is important for Aβ removal, can be targeted to mitochondria by alternative translation initiation (Leissring et al. 2004).

Although it is currently unclear whether APP processing and subsequent Aβ generation occur actually in mitochondria (Falkevall et al. 2006; Manczak et al. 2006), it has been shown that Aβ can target mitochondria to stimulate ROS generation, contributing to Aβ toxicity in neurons (Behl et al. 1994; Casley et al. 2002; Lustbader et al. 2004). Consistent with the mitochondrial generation of ROS, MnSOD overexpression has been shown to reduce oxidative stress, Aβ deposition and memory loss in Tg19959 mice (Dumont et al. 2009a). In addition, the activity of the mitochondrial α-ketoglutarate dehydrogenase complex (KGDHC), which is involved in NADH regeneration and ROS regulation, is reduced in human AD brains. Interestingly, recent observations indicated that the mitochondrial dihydrolipoyl succinyltransferase, a key subunit of the KGDHC complex, regulates mitochondrial ROS generation, Aβ burden and AD pathology in a transgenic AD mouse model (Dumont et al. 2009b). Thus, collectively these data indicate that the regulation of mitochondrial generated ROS by Aβ may be of potential relevance in AD.

Mitochondrial cholesterol, GSH and AD

The plasma membrane is a predominant site of cholesterol distribution in cells and increased cholesterol levels have been described in membranes from brain tissue of AD patients (Cutler et al. 2004; Bandaru et al. 2009). Although mitochondria are cholesterol-poor organelles, the uncontrolled trafficking of cholesterol into mitochondria has emerged as a critical factor in oncology and liver diseases (Garcia-Ruiz et al. 2009; Montero et al. 2008). Since the specific pool of mitochondrial cholesterol has not been previously examined in AD, we have recently used genetic mouse models of cholesterol loading to address the role of mitochondrial cholesterol in Aβ sensitization and AD pathology (Fernandez et al. 2009). Isolated mitochondria from brain or cortical neurons of transgenic mice overexpressing sterol regulatory element binding protein 2 (SREBP-2) or Niemann-Pick type C1 (NPC-1) knockout mice exhibited mitochondrial cholesterol loading. Following exposure to toxic Aβ we observed enhanced ROS generation and release of apoptogenic proteins (Fernandez et al. 2009). Inhibition of complex III of the respiratory chain enhanced Aβ-mediated ROS generation, while preincubation with rotenone and TTFA (2-thenoyltrifluoroacetone), which block complex I and II respectively, prevented the Aβ-mediated increase in hydrogen peroxide, suggesting complex III as a major source of ROS generation by Aβ. Consistent with our previous studies in cholesterol-enriched mitochondria from rat liver indicating impaired GSH transport of cytosolic GSH into mitochondria, brain mitochondria from SREBP-2 and NPC-1 mice exhibited mGSH depletion. To address a cause-and-effect relationship between mGSH depletion and enhanced Aβ susceptibility, selective mGSH depletion was accomplished pharmacologically in neuronal and glial derived cell lines by incubation with 3-hydroxy-4-pentenoate (HP), which is first biotransformed within mitochondria into a Michael acceptor followed by its conjugation with matrix GSH, resulting in the depletion of mGSH. HP pretreatment sensitized the human neuroblastoma SH-SY5Y cell line to Aβ-mediated ROS generation, apoptosome assembly, caspase activation and cell death. While caspase inhibition prevented the morphological features of apoptosis in mGSH-depleted SH-SY5Y cells, it failed to protect against Aβ-mediated cell death. However, the combined treatment with caspase inhibition and antioxidants abolished Aβ-mediated ROS generation, rescuing SH-SY5Y cells from Aβ-induced cell death. Overall, these findings indicate that mGSH plays a key role in controlling Aβ-induced ROS generation and that mGSH depletion sensitizes to Aβ by stimulating oxidant-dependent cell death and caspase-independent apoptosis (Fernandez et al. 2009). The relevance of these *in vitro* findings were examined *in vivo* following the intracerebroventricular delivery of human Aβ1-42, indicating glia activation, inflammation, neurotoxicity and synaptodendritic degeneration that were markedly aggravated in SREBP-2 mice compared to wild type mice. Moreover, we observed enhanced mitochondrial cholesterol accumulation and mGSH depletion in APP/PS1 transgenic mice. An interesting observation was that these changes in brain mitochondria from APP/PS1 mice, namely cholesterol accumulation and subsequent mGSH depletion, were preceded by enhanced Aβ levels, raising the intriguing possibility of a mutual regulation between cholesterol and Aβ. Although this

specific question needs to be critically established, consistent with this possibility previous studies described that the Aβ1-40/1-42 ratio altered lipid homeostasis and that familial presenilin mutations decreased the Aβ1-40/1-42 ratio resulting in enhanced cholesterol levels (Grimm et al. 2005). Another important recent finding is the description that hydrogen peroxide promotes Aβ production through a JNK-dependent activation of γ-secretase (Shen et al. 2008). Thus, in view that mGSH controls the extent of hydrogen peroxide generation by Aβ, it is tempting to speculate that besides regulating Aβ susceptibility the mitochondrial pool of GSH may also indirectly contribute to the regulation of Aβ generation via mitochondrial generation of hydrogen peroxide, establishing a vicious cycle of nefarious consequences for neurons. To further demonstrate the role of mGSH in AD pathogenesis, we tested the therapeutic efficacy of glutathione ethyl ester (GEE), a permeable GSH precursor, in SREBP-2 mice challenged with the delivery of human Aβ into the brain. GEE intraperitoneal therapy protected against Aβ-mediated neurodegeneration in SREBP-2 mice due to the recovery of the mitochondrial pool of GSH. These findings are of particular significance in AD as they suggest that specific strategies aimed to boost mGSH should be further assessed for potential application in patients with AD. They also imply that the use of precursors that promote GSH synthesis in the cytosol of neurons, such as N-acetylcysteine (NAC), may not be particularly effective in increasing the mGSH due to the impairment of GSH transport into mitochondria imposed by cholesterol loading (Fernandez-Checa and Kaplowitz 2005; Mari et al. 2009). Consistent with these notions, it has been recently shown that NAC failed to attenuate the astroglial activation and to improve the reduced cortical cholinergic innervation in APP transgenic mice (Nicolakakis et al. 2008). Thus, taken collectively, mitochondrial cholesterol emerges as a novel pathogenic factor in AD by modulating Aβ toxicity via mGSH regulation (Fig. 2), and that strategies boosting the particular pool of mGSH may be of relevance to slow down AD progression.

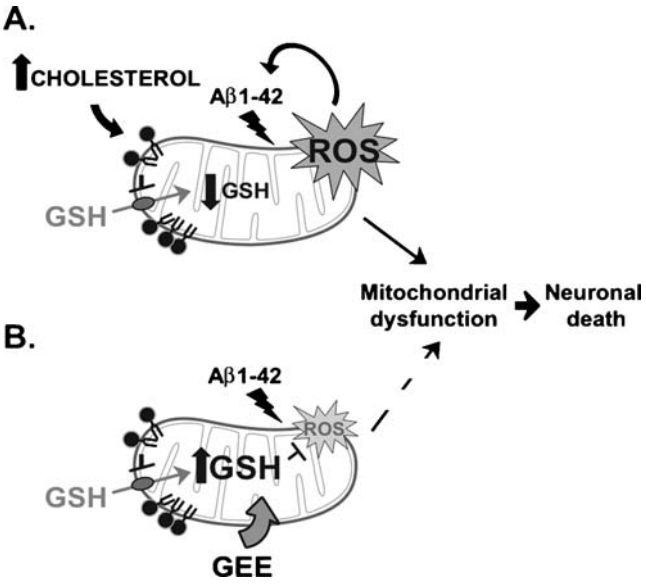

Fig. 2 Regulation of Aβ cytotoxicity by mitochondrial cholesterol. Mitochondria are primary sites of ROS generation induced by intracellular Aβ. (**A**). Cholesterol enrichment of mitochondria (by enhanced synthesis or exogenous supply) impairs the GSH carrier resulting in decreased GSH levels. Mitochondrial GSH plays a key role in controlling Aβ-induced ROS generation and its depletion sensitizes to Aβ toxicity not only by stimulating oxidant-dependent cell death but also by inducing its synthesis via JNK-dependent activation of γ-secretase. (**B**). Glutathione ethyl ester (GEE), a permeable GSH analog that can cross the mitochondrial membranes independently of cholesterol content, recovers the mitochondrial pool of GSH and prevents Aβ-induced oxidative stress

Gangliosides and AD

In addition to cholesterol, another key component of lipid rafts are glycosphingolipids. In particular, gangliosides are acidic glycosphingolipids that are enriched in lipid rafts which are essential in many cellular functions in the brain. Due to the role of lipid rafts in APP processing, it is conceivable that glycosphingolipids, specifically gangliosides, may also regulate Aβ metabolism, and potentially also Aβ toxicity. For instance, gangliosides have been shown to be required for Aβ binding and aggregation, at least in prepared vesicles (Kakio et al. 2002; Gellermann et al. 2005). The binding affinity and tendency of Aβ to induce a β-sheet conformation correlates with the number of sialic acid residues in the carbon backbone of gangliosides (Ariga et al. 2001). Cholesterol enhances Aβ binding by facilitating the clustering of GM1 ganglioside within lipid rafts, and the depletion of cholesterol significantly reduces Aβ binding to gangliosides. Central administration of GM1 increased Aβ load in a mouse model of Aβ overexpression (Matsuoka et al. 2003), illustrating the role of gangliosides in regulating Aβ metabolism *in vivo*. Recent observations indicated a role for ganglioside GD3 in AD, as the genetic downregulation of GD3 synthase, the enzyme responsible for the synthesis of GD3 from GM3, reduced Aβ plaque load and improved memory in the APP/PSEN1 transgenic AD model (Bernardo et al. 2008). In addition to potentially control the processing of APP and Aβ generation, GD3 may also modulate Aβ toxicity. Consistent with this possibility, GD3 has been shown to play a proapoptotic role by a dual mechanism including its trafficking to mitochondria to induce mitochondrial membrane permeabilization, ROS generation, release of cytochrome c and apoptosome assembly (Garcia-Ruiz et al. 2000, 2002; Colell et al. 2001; Garofalo et al. 2005). Thus, it is conceivable that GD3, like cholesterol, may play a dual

role in AD not only by modulating Aβ generation but also by regulating Aβ toxicity, especially with the association of mGSH depletion as shown previously in rat liver mitochondria (Garcia-Ruiz et al. 2000). Moreover, whether cholesterol/GD3 and mitochondrial raft-like domains play a role in the targeting of Aβ to mitochondria deserves further investigation. These hypotheses are currently being tested in transgenic mouse AD models and may open novel therapeutic opportunities in AD.

Concluding remarks

Biochemical, epidemiological and genetic evidence have involved cholesterol, mitochondria and Aβ in the pathogenesis of AD. While the role of cholesterol in AD has been described mainly in the amyloidogenic processing of APP, we have unraveled a critical relationship of this trio in AD. In this scenario, the mitochondrial pool of cholesterol plays a fundamental role in determining the susceptibility of neurons to Aβ-mediated cell death by favoring the generation of ROS by Aβ from the mitochondrial electron transport chain due to the depletion of mGSH. The transport of mGSH has been well characterized in non-neuronal cells, in particular in liver mitochondria, with the sensitivity of mitocondrial carriers to the loss of membrane fluidity. Although the molecular mechanisms of GSH transport into brain mitochondria have not been well characterized, our data indicate a similar susceptibility to cholesterol-mediated perturbations in membrane dynamics. A key aspect of future research will be to describe and characterize the molecular carrier of the brain mitochondrial inner membrane responsible for the import of GSH into the matrix. Strategies using fluidizing agents, such as tauroursodeoxycholic acid, have been shown useful to prevent inflammatory cytokines-mediated hepatocellular death by restoring the mGSH pool size, which is of significance in alcoholic and non-alcoholic liver disease. Whether or not a parallel approach may be of relevance in AD models remains to be explored. A key finding is that AD mouse models (e.g. APP/PS1, Fernandez et al. 2009) exhibit increased mitochondrial cholesterol loading and subsequent mGSH depletion. Although this specific pool has not yet been described in patients with AD, it is interesting to note that immunocytochemical analyses described the expression of the steroidogenic acute regulatory protein (StAR), a cholesterol transporting polypeptide, in mitochondria strongly suggesting the possibility to find enhanced cholesterol levels in this organelle. Collectively, these findings point to the specific pool of mitochondrial cholesterol as a potential target for therapy in AD. Using strategies that modulate the levels and/or trafficking of cholesterol to mitochondria, such as statins, along with pharmacological use of permeable GSH precursors, like GEE, may stand as a promising combinational therapy to slow down the progression of AD. Given the pressing health challenge of AD in the future, we hope that the proposal to target mitochondrial cholesterol to modulate mGSH may gain a niche in the therapeutic armamentarium for AD.

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