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# Apolipoprotein E and Apolipoprotein E Receptors: Normal Biology and Roles in Alzheimer Disease

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Apolipoprotein E (*APOE*) genotype is the major genetic risk factor for Alzheimer disease (AD); the  $\epsilon 4$  allele increases risk and the  $\epsilon 2$  allele is protective. In the central nervous system (CNS), apoE is produced by glial cells, is present in high-density-like lipoproteins, interacts with several receptors that are members of the low-density lipoprotein receptor (LDLR) family, and is a protein that binds to the amyloid- $\beta$  (A $\beta$ ) peptide. There are a variety of mechanisms by which apoE isoform may influence risk for AD. There is substantial evidence that differential effects of apoE isoform on AD risk are influenced by the ability of apoE to affect A $\beta$  aggregation and clearance in the brain. Other mechanisms are also likely to play a role in the ability of apoE to influence CNS function as well as AD, including effects on synaptic plasticity, cell signaling, lipid transport and metabolism, and neuroinflammation. ApoE receptors, including LDLRs, Apoer2, very low-density lipoprotein receptors (VLDLRs), and lipoprotein receptor-related protein 1 (LRP1) appear to influence both the CNS effects of apoE as well as A $\beta$  metabolism and toxicity. Therapeutic strategies based on apoE and apoE receptors may include influencing apoE/A $\beta$  interactions, apoE structure, apoE lipidation, LDLR receptor family member function, and signaling. Understanding the normal and disease-related biology connecting apoE, apoE receptors, and AD is likely to provide novel insights into AD pathogenesis and treatment.

Alzheimer disease (AD), specifically the late-onset form of AD (LOAD), is the most common cause of dementia in individuals older than 60 years of age. Although mutations in the genes *PS1*, *PS2*, and *APP* cause less common forms of early-onset, autosomal dominant

familial AD (FAD), these cases represent <1% of AD. In addition to the genes that cause FAD, LOAD also has a strong genetic component. Although several susceptibility genes for AD have been reported, by far the strongest genetic risk factor for LOAD is apolipoprotein

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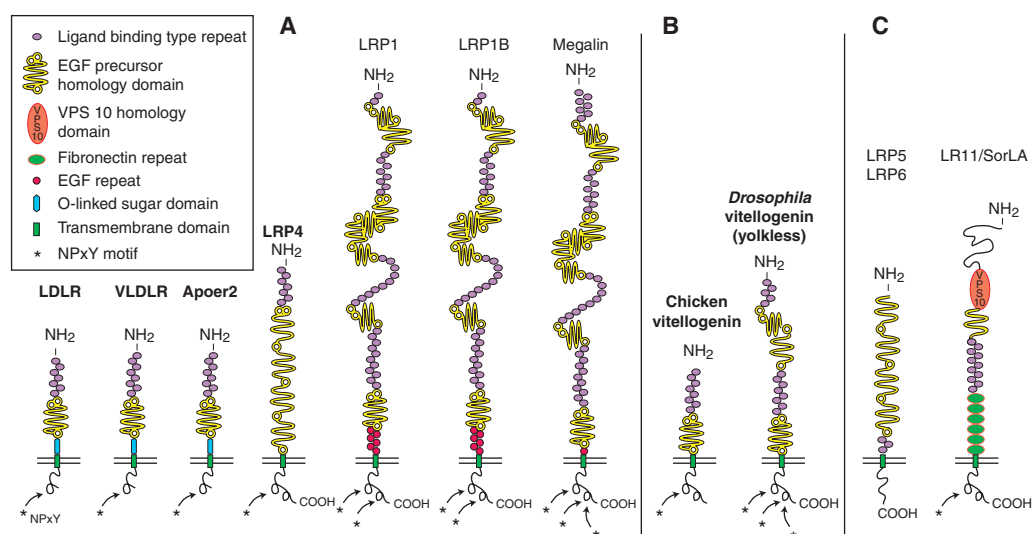
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E (*APOE*) genotype, with the  $\epsilon 4$  allele being an AD risk factor and the  $\epsilon 2$  allele being protective relative to the prevalent  $\epsilon 3$  allele (Corder et al. 1993; Strittmatter et al. 1993a). Strong evidence suggests a major mechanism by which apoE influences AD and cerebral amyloid angiopathy (CAA) is via its effects on A $\beta$  metabolism (Kim et al. 2009a; Castellano et al. 2011). Current understanding of apoE biology in the CNS and how apoE/A $\beta$  interactions are relevant to AD will be reviewed in the first section. There are several apoE receptors that are members of the LDLR family (Fig. 1). Some of these receptors, such as LDLR and LRP1, influence apoE levels (Fryer et al. 2005a; Liu et al. 2007). Others, such as Apoer2 and VLDLR, although apoE receptors, are also receptors for other ligands such as the neuromodulatory signaling protein

Reelin, which plays an important role in neurodevelopment and synaptic function. These receptors are involved in neural signaling and tau phosphorylation, and there is evidence that apoE can counteract some of the neurotoxicity caused by A $\beta$ . Apoer2 and VLDLR will be reviewed in the second section. LDLR and LRP1 are important receptors for apoE in the brain that regulate CNS apoE levels. Although LDLR has no known ligand other than apoE in the CNS, LRP is somewhat unique in that it has multiple ligands, binds to both APP and A $\beta$ , and influences APP and A $\beta$  metabolism. LDLR and LRP1 will be reviewed in the third section. Although there are currently no apoE-based therapies for AD, given the effects of apoE and apoE receptors on both A $\beta$  and CNS development and function, a variety of



**Figure 1.** The low-density lipoprotein (LDL) receptor gene family. (A) The core LDL receptor gene family as it exists in mammalian species. These family members are characterized by one or more ligand-binding domains, epidermal growth factor (EGF), homology domains consisting of EGF repeats and YWTD propeller ( $\beta$ -propeller) domains involved in pH-dependent release of ligands in the endosomes, a single transmembrane domain and a cytoplasmic tail containing at least one NPxY motif. The latter represents both the endocytosis signal as well as a binding site for adaptor proteins linking the receptor to intracellular signaling pathways. Furthermore, LDLR, VLDLR, and Apoer2 carry an O-linked sugar domain. (B) Equivalent receptors that are structurally and functionally distinct family members in nonmammalian species. (C) A subgroup of functionally important, but more distantly related family members that share some, but not all, of the structural requirements of the “core members.” In addition, they could also contain domains, e.g., vacuolar protein sorting (VPS) domains, which are not present in the core family. (From Dieckmann et al. 2010; reprinted, with permission, from Walter de Gruyter GmbH © 2010.)

apoE/apoE receptor-based approaches will be discussed.

## ApoE: POTENTIAL ROLE IN AD

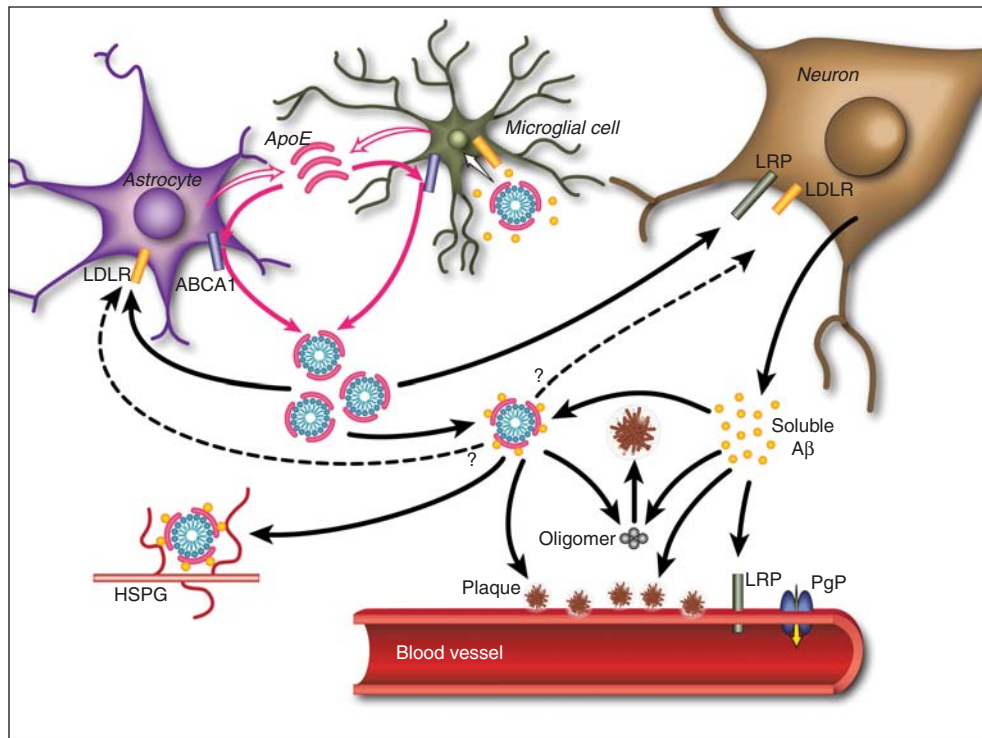
### Neurobiology of ApoE

The human apoE protein is a 299 amino acid glycoprotein that is expressed by several cell types, but with highest expression in the liver and in the CNS (Mahley 1988). In the brain, apoE is expressed predominantly by astrocytes but also by microglia (Fig. 2) (Pitas et al. 1987; Grehan et al. 2001). Under certain conditions, such as after excitotoxic injury, some neurons appear to be able to synthesize apoE (Xu et al. 1999; Xu et al. 2006). Under physiological conditions, apoE is present in lipoprotein particles (Fig. 2). Although it is present in lipoproteins of different size classes in plasma, in the CNS, it is the most abundantly produced apoprotein and is secreted by glial cells in nascent high-density lipoprotein (HDL)-like particles (Pitas et al. 1987; DeMattos et al. 2001) that are discoidal in shape and contain phospholipids and cholesterol. ApoE is also present in cerebrospinal fluid (CSF) at a concentration of  $\sim 5 \mu\text{g/ml}$ , in spherical particles that are similar to glial-secreted HDL, except that they also contain a cholesteryl ester core (LaDu et al. 1998). Although apoE-containing lipoproteins may play a role in reverse cholesterol transport as well as in cholesterol and lipid delivery, their role in CNS lipid and cholesterol homeostasis is not yet clearly defined. As in the periphery, apoE functions as a ligand in receptor-mediated endocytosis of lipoprotein particles in the CNS. In vitro studies have shown that cholesterol released from apoE-containing lipoprotein particles is used to support synaptogenesis (Mauch et al. 2001) and the maintenance of synaptic connections (Pfrieger 2003). Although there is some in vitro (Nathan et al. 1994; Holtzman et al. 1995) and in vivo (Masliah et al. 1995; Poirier 2003) data suggesting that apoE can play a role in neuronal sprouting after injury, whether apoE plays a major role in supporting synaptogenesis and maintenance of synaptic connections in vivo in the uninjured brain has not

yet been proven. For example, several studies have shown that the brain of apoE knockout mice, for the most part, appears normal in the absence of injury (Anderson et al. 1998; Fagan et al. 1998). Moreover, no overt cognitive defects have been reported in humans with genetic ApoE deficiency. In addition to apoE, several other apolipoproteins are present in the CNS, the most abundant being apoAI and apoJ, also called clusterin. ApoE in the CNS is derived from the CNS; the same appears to be true for clusterin. In contrast, apoAI in CNS is derived from the periphery (Sorci-Thomas et al. 1988). Whether apoAI and clusterin play a role in CNS lipid metabolism, or in normal brain function, is not clear. Genetic deficiency of either protein in humans or mice does not result in an obvious CNS phenotype (Schaefer et al. 1982; McLaughlin et al. 2000). Interestingly, single-nucleotide polymorphisms in clusterin have been shown to be a risk factor for AD (Harold et al. 2009; Lambert et al. 2009). The mechanism for this is unclear, although animal model data have shown that clusterin strongly influences A $\beta$  aggregation and toxicity in vivo (DeMattos et al. 2002; DeMattos et al. 2004).

### Genetic, Clinical, and Biomarker Observations on Relationship of ApoE and AD

The human apoE gene contains several single-nucleotide polymorphisms (SNPs) distributed across the gene (Nickerson et al. 2000). The most common three SNPs lead to changes in the coding sequence and result in the three common isoforms of apoE: apoE2 (cys112, cys158), apoE3 (cys112, arg158), and apoE4 (arg112, arg158). Although the three common isoforms differ by only one or two amino acids at residues 112 or 158, these differences alter apoE structure and function (Mahley et al. 2006). In regard to the connection between apoE and AD, apoE was found to colocalize with amyloid plaques in the early 1990s (Namba et al. 1991; Wisniewski and Frangione 1992). After that, the  $\epsilon 4$  allele of the *APOE* gene was discovered to be a strong genetic risk factor for AD (Corder et al. 1993; Strittmatter



**Figure 2.** Pathways by which apoE and A $\beta$  interact in the brain. ApoE is primarily produced by both astrocytes and microglia and is subsequently lipidated by ABCA1 to form lipoprotein particles. In the extracellular space, lipidated apoE binds to soluble A $\beta$  in an isoform-dependent pattern ( $E2 > E3 > E4$ ) and influences the formation of parenchymal amyloid plaques and transport of A $\beta$  within the CNS. ApoE is endocytosed into various cell types within the brain by different members of the LDL receptor family, including LDLR and LRP1. ApoE may also facilitate the cellular uptake of A $\beta$  through the endocytosis of a complex of apoE-containing lipoprotein particles bound to A $\beta$  in a manner that likely depends on the isoforms and its level of lipidation. Furthermore, apoE has been shown to directly enhance both the degradation of A $\beta$  within microglial cells and the ability of astrocytes to clear diffuse A $\beta$  deposits (Koistinaho et al. 2004; Jiang et al. 2008). A $\beta$  associated with apoE-containing lipoprotein particles may also be retained within the CNS through their binding to heparin sulfate proteoglycan (HSPG) moieties present in the extracellular space (Mahley and Rall 2000). At the blood–brain barrier (BBB), soluble A $\beta$  is predominantly transported from the interstitial fluid into the bloodstream via LRP1 and P-glycoprotein (Cirrito et al. 2005; Zlokovic 2008). ApoE has been shown to slow the transport of A $\beta$  across the BBB in an isoform-dependent manner ( $E4 > E3 > E2$ ) (Bell et al. 2007; Ito et al. 2007; Deane et al. 2008). In addition, apoE can influence the pathogenesis of CAA in an amyloid protein precursor (APP)-transgenic mouse model, with apoE4 increasing the amount of vascular plaques in comparison to apoE3 (Fryer et al. 2005b). (From Kim et al. 2009; reprinted, with permission, from Elsevier © 2009.)

et al. 1993a). Since then, numerous studies have confirmed that the  $\epsilon 4$  allele is the strongest genetic risk factor for both AD and CAA, or a combination of both disorders (Schmechel et al. 1993; Greenberg et al. 1995; Bertram et al. 2007). As compared to individuals with no  $\epsilon 4$  alleles, the increased risk for AD is approximately threefold in people with one  $\epsilon 4$

allele and  $\sim 12$ -fold in those with two  $\epsilon 4$  alleles. The odds ratio for  $\epsilon 4$  versus  $\epsilon 3$  alleles by meta-analysis of multiple studies is 3.68 as of June 2011 (www.alzgene.org). Importantly, the  $\epsilon 2$  allele of apoE is associated with a lower risk for AD (Corder et al. 1994; Farrer et al. 1997) with an odds ratio of  $\epsilon 2$  versus  $\epsilon 3$  of 0.62 as of June 2011 (www.alzgene.org).



## Evidence of a Key Role for ApoE on A $\beta$ Metabolism in AD Pathogenesis

In vitro and in vivo data including data in humans and animal models suggests that the physical interaction of apoE with A $\beta$  plays an important role in AD and CAA pathogenesis (Fig. 1). It was first proposed that apoE was an A $\beta$ -binding protein in the brain that induces a pathological  $\beta$ -sheet conformational change in A $\beta$  (Wisniewski and Frangione 1992). Pathological studies showed a positive correlation between plaque density and  $\epsilon$ 4 allele dose in AD patients at autopsy (Rebeck et al. 1993; Schmechel et al. 1993). Although some studies reported conflicting findings (Benjamin et al. 1995; Heinonen et al. 1995), a large autopsy study strongly suggested that  $\epsilon$ 4 dosage is associated with increased neuritic plaques in AD (Tiraboschi et al. 2004). If the effect of apoE4 is to accelerate the average onset of A $\beta$  deposition in the brain, an expectation would be that middle-aged individuals at risk to develop AD in the future who are still cognitively normal would have larger amounts of A $\beta$  deposition in the brain. This has now been shown to be the case as evidenced by amyloid-imaging studies with Pittsburgh compound B as well as CSF studies using CSF A $\beta$ 42 in which a decrease has been shown to indicate brain amyloid deposition. Cognitively normal apoE4-positive middle-aged and elderly individuals are much more likely to have brain amyloid (Reiman et al. 2009; Morris et al. 2010) and low CSF A $\beta$ 42 (Sunderland et al. 2004; Morris et al. 2010) than apoE4-negative individuals. Further, apoE2-positive individuals rarely develop fibrillar A $\beta$  as defined by a positive amyloid-imaging scan (Morris et al. 2010).

Whereas human data supports the idea that apoE isoforms result in differential susceptibility to A $\beta$  aggregation in the brain, animal studies utilizing genetically modified mice that develop A $\beta$  deposition and express human apoE isoforms show more directly that human apoE isoforms have a strong effect on the time of onset of A $\beta$  aggregation as well as the amount, location, and conformation of A $\beta$  in the brain. Early studies with APP-transgenic

(Tg) mice that develop A $\beta$  deposition in the brain (PDAPP and Tg2576 models) showed that when these mice were crossed with apoE<sup>-/-</sup> mice, there was less A $\beta$  deposition and a virtual abolishment of true amyloid plaques, plaque-associated neuritic dystrophy, CAA, and CAA-associated microhemorrhage in the absence of apoE (Bales et al. 1997; Bales et al. 1999; Holtzman et al. 2000b; Fryer et al. 2003). In addition, the anatomical pattern of A $\beta$  deposition differs in the absence of apoE (Holtzman et al. 2000a; Irizarry et al. 2000). The expression of human apoE isoforms in either PDAPP or Tg2576 Tg mice resulted in a marked delay in the deposition of A $\beta$  and formation of neuritic plaques, compared with APP Tg mice expressing no apoE or mouse apoE (Fagan et al. 2002; Fryer et al. 2005b). Importantly, expression of human apoE isoforms in APP Tg mice results in an isoform-specific effect on the amount of A $\beta$  accumulation as well as true amyloid deposits (E4 > E3 > E2) (Holtzman et al. 2000a; Fagan et al. 2002; Fryer et al. 2005b). In addition to the isoform-specific effects of human apoE on parenchymal A $\beta$  pathology, crossing human apoE knockin mice to Tg2576 mice resulted in a relative shift of A $\beta$  deposition from the brain parenchyma to arterioles in the form of CAA in apoE4 expressing mice relative to apoE3 or mouse apoE (Fryer et al. 2005b). A similar effect of apoE4 predisposing to CAA is seen in humans. These data strongly suggest that understanding the in vivo mechanisms underlying the apoE isoform-mediated difference in A $\beta$  accumulation is critical for relating these findings to the pathogenesis of AD.

The underlying mechanism underlying how apoE influences A $\beta$  aggregation and accumulation in the brain is on its way to being elucidated. In vitro and in vivo studies suggest that apoE may influence A $\beta$  seeding and fibrillogenesis, as well as soluble A $\beta$  clearance. Lipid-free and lipidated (physiological) forms of apoE can interact with A $\beta$  in vitro (Strittmatter et al. 1993b; LaDu et al. 1994; Sanan et al. 1994; Aleshkov et al. 1997; Yang et al. 1997; Tokuda et al. 2000). Most studies show that the efficiency of complex formation between lipidated

apoE and A $\beta$  follows the order of apoE2 > apoE3 > apoE4. The effect of apoE isoforms on A $\beta$  aggregation has also been investigated extensively in vitro. Some studies show apoE causing greater fibrillization (E4 > E3 > E2) (Ma et al. 1994; Wisniewski et al. 1994; Castano et al. 1995), whereas others show that apoE inhibits fibrillization (Evans et al. 1994; Wood et al. 1996). Conflicting results between in vitro studies may be owing to the differences in apoE and A $\beta$  preparations or other factors. Altering the lipidation state of apoE in the brain is associated with strong effects on A $\beta$  fibrillization in vivo. ATP-binding cassette A1 (ABCA1) normally lipidates apoE in the brain. When APP Tg mice are crossed onto an *Abca1*<sup>-/-</sup> background, this decreases apoE lipidation and increases amyloid deposition (Hirsch-Reinshagen et al. 2005; Koldamova et al. 2005a; Wahrle et al. 2005), whereas increasing ABCA1 increases apoE lipidation and decreases amyloid deposition (Wahrle et al. 2008).

In addition to the effects of apoE on fibrillogenesis, there is evidence that apoE alters both the transport and clearance of soluble A $\beta$  in the brain (Fig. 1). A recent study shows that apoE isoforms do not differentially influence A $\beta$  production in vivo; however, apoE isoforms differentially affect A $\beta$  clearance before A $\beta$  deposition with E4 resulting in clearance that is slower than E3 and E2 (Castellano et al. 2011). These results suggest the difference in A $\beta$  accumulation between apoE isoforms is likely because of isoform-specific differences in A $\beta$  clearance. ApoE seems to play an important role in the clearance of A $\beta$  through several possible mechanisms. ApoE-containing lipoprotein particles may sequester A $\beta$  and modulate the cellular uptake of an apoE-A $\beta$  complex by receptor-mediated endocytosis. Alternatively, apoE may modulate A $\beta$  removal from the brain to the systemic circulation by transport across the blood-brain barrier. Data from in vitro studies support the idea that apoE facilitates the binding and internalization of soluble A $\beta$  by cells or its clearance via enzymes such as neprilysin (Beffert et al. 1998; Yang et al. 1999; Cole and Ard 2000; Koistinaho et al. 2004; Jiang et al. 2008). Although in vitro studies suggest

that apoE enhances cellular A $\beta$  uptake and degradation (Kim et al. 2009a), there is in vivo evidence that apoE retards A $\beta$  clearance from the brain (DeMattos et al. 2004; Bell et al. 2007; Deane et al. 2008), possibly via an effect at the blood-brain barrier (BBB) (Fig. 1) (Zlokovic 2008). More work is clearly needed to determine the exact role that apoE has in modifying brain A $\beta$  clearance, the role of the BBB in the process, and whether isoform-specific effects exist.

Several key questions remain to be further addressed regarding the effect of apoE on A $\beta$ . Whether it is better to increase or decrease human apoE levels (regardless of isoform) to reduce A $\beta$  levels is still unanswered. Analyzing whether, and to what extent, altering human apoE level affects A $\beta$  pathology will help determine whether targeting apoE levels may be a viable therapeutic option for influencing A $\beta$  levels and toxicity, and ultimately treating AD.

## ApoE RECEPTORS AND SYNAPTIC PLASTICITY

The strong association of ApoE4 with late-onset AD raised the possibility that ApoE is mediating its powerful effect on the average age of disease onset at least in part through the receptors to which it binds. These ApoE receptors include the core, as well as potentially several more distantly related members of the LDLR gene family (Fig. 1). LRP1 has been repeatedly, albeit weakly, associated with AD risk (Beffert et al. 1999; Vazquez-Higuera et al. 2009), and a coding polymorphism in the distantly related Wnt coreceptor LRP6 has also been implicated (De Ferrari et al. 2007). None of the other family members have so far been convincingly associated with AD by human genetic data. The absence of genetic association, however, does not preclude important roles for these multifunctional receptors in the molecular mechanisms that underlie the disease process. The very nature of their essential functions during the development of the embryo in general (Herz et al. 1992; Johnson et al. 2005; Dietrich et al. 2010; Karner et al. 2010), and the brain, in particular (Willnow et al. 1996; Trommsdorff



et al. 1999; May et al. 2004; Boycott et al. 2005; Boycott et al. 2009), may occlude their participation in AD pathogenesis, which would manifest itself much later in life.

Mechanisms by which ApoE receptors may contribute to AD development and progression may include roles in the control of inflammation (Lillis et al. 2008; Zurhove et al. 2008), cholesterol metabolism (reviewed in Herz et al. 2009), neurogenesis (Gajera et al. 2010), or the generation and trafficking of APP and A $\beta$  (reviewed in the third section). Other potential mechanisms by which ApoE receptors may promote neuronal survival (Beffert et al. 2006b) during aging involve signaling pathways that control microtubule and actin dynamics (Beffert et al. 2002; Assadi et al. 2003; Brich et al. 2003; Ohkubo et al. 2003; Chai et al. 2009; Forster et al. 2010; Rust et al. 2010), dendritogenesis (Niu et al. 2004), spine formation (Niu et al. 2008), glutamate receptor function and synaptic plasticity (Zhuo et al. 2000; Weeber et al. 2002; Beffert et al. 2005; Chen et al. 2005; D'Arcangelo 2005; Sinagra et al. 2005; Groc et al. 2007; Durakoglugil et al. 2009; Korwek et al. 2009; Chen et al. 2010), as well as learning and memory (reviewed in Herz and Beffert 2000; Herz and Chen 2006; Bu 2009; Herz 2009). In this section we will mainly focus on the role of the ApoE receptors Apoer2 and Vldlr and their ligand Reelin in these processes.

### Molecular Basis of Signal Transduction by Neuronal ApoE Receptors

ApoE receptors contain only short cytoplasmic tails, which lack functional enzymatic domains through which many cell-surface receptors transmit extracellular signals into the cell. However, they harbor a variety of short conserved sequence stretches, such as the tetra-amino acid NPxY motif, which serve as docking sites for a wide array of cytoplasmic adaptor and scaffolding proteins (Trommsdorff et al. 1998; Gotthardt et al. 2000; Beffert et al. 2005; Hoe et al. 2006a; Hoe et al. 2006b). The receptors can also interact as coreceptors through their extracellular domains with other types of signaling

proteins and modules, and thereby modulate their intrinsic activity (Boucher et al. 2002; Loukinova et al. 2002; Huang et al. 2003; Lillis et al. 2008; Zurhove et al. 2008), including that of the *N*-methyl-D-aspartate (NMDA) receptor (May et al. 2004; Beffert et al. 2005; Hoe et al. 2006b).

Apoer2 and Vldlr are a notable exception, inasmuch as they do not need to associate with another protein with intrinsic signal transduction activity to elicit an intracellular signal. Both receptors bind the large homo-oligomeric signaling protein Reelin with high affinity (D'Arcangelo et al. 1999; Hiesberger et al. 1999), resulting in their clustering at the plasma membrane (Strasser et al. 2004). The simultaneous interaction of the adapter protein Disabled 1 (Dab1) with NPxY motifs in their intracellular domains (ICDs) (Trommsdorff et al. 1998; Stolt et al. 2005) results in the progressive recruitment and transphosphorylation of Src family tyrosine kinases (SFKs) (Howell et al. 1997; Arnaud et al. 2003; Bock and Herz 2003). This in turn initiates a kinase cascade inside the neuron, starting with the activation of phosphoinositide-3-kinase (PI3K), which subsequently activates protein kinase B (also known as Akt), and ending with the inhibition of glycogen synthase 3 $\beta$  (GSK3 $\beta$ ) (Beffert et al. 2002), one of the primary kinases that phosphorylate the microtubule stabilizing protein tau on the same sites that are typically abnormally phosphorylated in the neurofibrillary tangles in the AD-afflicted brain.

Reelin signaling is essential for normal brain development by regulating a pathway that controls the migration and positioning of the neuronal cell bodies in their appropriate cortical layers of the neocortex and the cerebellum (Tissir and Goffinet 2003), as well as neuronal connectivity (Del Rio et al. 1997). Activation of SFKs is the "master switch" that is required for the initiation of all subsequent downstream signaling events, which are not limited to the control of GSK3 $\beta$  activity but also involve the regulation of Lis1-dependent nuclear translocation (Shu et al. 2004), n-cofilin-mediated actin reorganization (Chai et al. 2009; Frotscher 2010), and tyrosine phosphorylation of NMDA



receptor subunits (Beffert et al. 2005; Chen et al. 2005).

### Regulation of Tau Phosphorylation

Genetic disruption of any component of this Reelin-Apoer2/Vldlr-Dab1 signaling pathway in the mouse, i.e., loss-of-function mutations in the ligand, the receptors, or the adaptor protein, results in reduced phosphorylation of GSK3 $\beta$  on an inhibitory serine residue, which leads to disinhibition of the enzyme and hyperphosphorylation of tau (Hiesberger et al. 1999; Beffert et al. 2002; Brich et al. 2003; Ohkubo et al. 2003). High levels of tau phosphorylation disrupt neuronal vesicle transport by compromising microtubule stability (Mudher et al. 2004), and consequently lead to variable degrees of neuronal dysfunction and premature death of signaling defective mutant mice (Sheldon et al. 1997; Trommsdorff et al. 1999; Brich et al. 2003). Intriguingly, genetic deficiency of tau prevents APP/A $\beta$ -induced cognitive defects as well as excitotoxicity in mice (Roberson et al. 2007), indicating that the presence of abnormally phosphorylated tau, rather than its functional loss, is the likely reason for the severe motor defects that cause the premature death in the Reelin pathway mutants. This is further supported by a series of recent studies that showed a broad effect of mislocalized, phosphorylated tau on the spinodendritic targeting of Fyn (Ittner et al. 2010) and of the scaffolding protein JIP1 (Ittner et al. 2010), as well as on the disruption of glutamate receptor trafficking and recycling (Hoover et al. 2010). Intriguingly, the tau-induced synaptic defects are prevented or reversed by reducing the tau levels (Roberson et al. 2011; Sydow et al. 2011).

Loss of LRP1 also results in increased GSK3 $\beta$  activity, at least in fibroblasts and adipocytes, as a result of a loss of autocrine Wnt5a expression (Terrand et al. 2009). Conditional LRP1 knockout mice, lacking LRP1 expression exclusively in postmitotic neurons, also display severe locomotor abnormalities (May et al. 2004), raising the possibility that these dysfunctions could also be caused in part by defective regulation of tau phosphorylation, although

this has not been explored at the time of this writing.

Tau hyperphosphorylation in Reelin signaling defective animals on a mixed strain background is highly variable (Hiesberger et al. 1999) and strongly dependent on the background strains. This observation was exploited in an unbiased approach to map genetic modifiers of ApoE receptor/Dab1-dependent tau phosphorylation in the mouse (Brich et al. 2003). Surprisingly, the strongest modifier mapped to a narrow genomic region centered around APP on mouse chromosome 16, in addition to a suggestive quantitative trait in the vicinity of Presenilin 1 on chromosome 12. Together these findings add further support to a model in which ApoE receptors functionally interact with APP, A $\beta$ , and tau to control the molecular mechanisms that underlie the pathogenesis of AD.

### Regulation of Dendritic Spines, Glutamatergic Neurotransmission, and Synaptic Plasticity

Numerous independent studies and observations point toward a role for Reelin and ApoE receptors in the formation of neuronal connections (Del Rio et al. 1997; Borrell et al. 2007) and the generation of dendritic complexity (Trommsdorff et al. 1999; Costa et al. 2001; Niu et al. 2004; Matsuki et al. 2008; Hoe et al. 2009). The latter may, however, not be entirely dependent on Apoer2 and Vldlr (Chameau et al. 2009) and may also involve interactions with APP (Hoe et al. 2009). Reelin signaling also regulates dendritic spine morphology (Costa et al. 2001; Niu et al. 2008; Pujadas et al. 2010), which likely involves regulation of actin dynamics and the participation of n-cofilin (Chai et al. 2009; Rust et al. 2010). It activates LIM kinase (LIMK), which inhibits the actin-depolymerizing activity of n-cofilin. The dynamic remodeling of synaptic connections requires constant reorganization of actin filaments (Dillon and Goda 2005). Consequently, postnatal disruption of n-cofilin in mice leads to increased synapse density and enlargement of axospinous synapses (Rust et al.

2010) with defects in long-term potentiation (LTP) and long-term depression (LTD). Although synaptic AMPA receptor mobility is not affected, diffusion of extrasynaptic AMPA receptors is reduced owing to F-actin stabilization, preventing efficient egress of AMPA receptors from the synaptic into the extrasynaptic domain, and thus LTD, in the n-cofilin mutants. Similarly, Reelin has been shown to regulate surface mobility and synaptic residency of NMDA receptor NR2B subunits (Groc et al. 2007). It is thus required for NMDA receptor maturation (Sinagra et al. 2005) and for the maintenance of normal NR2A/B ratios (Campo et al. 2009).

These findings explain the profound effect of Reelin on glutamatergic neurotransmission and synaptic plasticity *ex corpore* (Weeber et al. 2002; Beffert et al. 2005; Beffert et al. 2006b; Qiu et al. 2006; Campo et al. 2009) and *in vivo* (Pujadas et al. 2010) (E Weeber, pers. comm.). Reelin potently increases LTP, which requires the presence of both receptors, Apoer2 and Vldlr (Weeber et al. 2002). This increase of synaptic plasticity is mediated by the effect Reelin has on NMDA and AMPA receptor trafficking and conductance, which determine the synaptic activity of these glutamate receptors (Qiu et al. 2006). It further requires the presence of a 59 amino acid insert encoded by an alternatively spliced exon in the cytoplasmic domain of Apoer2 (Beffert et al. 2005). Only when the insert is present can Apoer2 functionally couple with NMDA receptors and induce tyrosine phosphorylation of NR2 subunits in response to Reelin. Increased tyrosine phosphorylation of the NMDA receptor increases ion gating and reduces its endocytosis, thereby increasing NMDA receptor activity overall (Salter and Kalia 2004; Snyder et al. 2005). Intriguingly, differential splicing of this exon is regulated in a circadian, activity-driven manner (Beffert et al. 2005), suggesting that periodic variation of NMDA receptor activity by Reelin is physiologically significant for synapse function, learning, and memory (Beffert et al. 2002; Weeber et al. 2002; Beffert et al. 2005; D'Arcangelo 2005; Beffert et al. 2006b; Pujadas et al. 2010).

### ApoE Receptors as Antagonists of A $\beta$ -Induced Synaptic Suppression

A $\beta$ <sub>1-42</sub> oligomers are strong inducers of synaptic suppression, and several mechanisms have been proposed to explain this effect (Lambert et al. 1998; Walsh et al. 2002; Lacor et al. 2004; Snyder et al. 2005; Lesne et al. 2006; Townsend et al. 2006; Haass and Selkoe 2007; Shankar et al. 2007; Berman et al. 2008; Puzzo et al. 2008; Shankar et al. 2008; Nygaard and Strittmatter 2009; Gimbel et al. 2010; Palop and Mucke 2010; Renner et al. 2010; Ronicke et al. 2010) (see Mucke and Selkoe 2011). Synaptic suppression by the oligomers correlates with reduced NMDA receptor activity (Snyder et al. 2005; Shankar et al. 2007), which is caused by NMDA receptor dephosphorylation and accelerated endocytosis (Snyder et al. 2005). Snyder, Greengard, and colleagues (Snyder et al. 2005) proposed that this is mediated by the A $\beta$ -mediated activation of phosphatases (STEP and calcineurin). The concomitant reduction of NMDA receptor activity induces dendritic spine loss and, intriguingly, this requires calcineurin, as well as the active, *i.e.*, Ser3-unphosphorylated form of n-cofilin (Shankar et al. 2007). A dominant negative form of n-cofilin, in which Ser3 is replaced with a phosphomimetic amino acid (Ser3Asp), prevents oligomer-induced spine loss (Shankar et al. 2007).

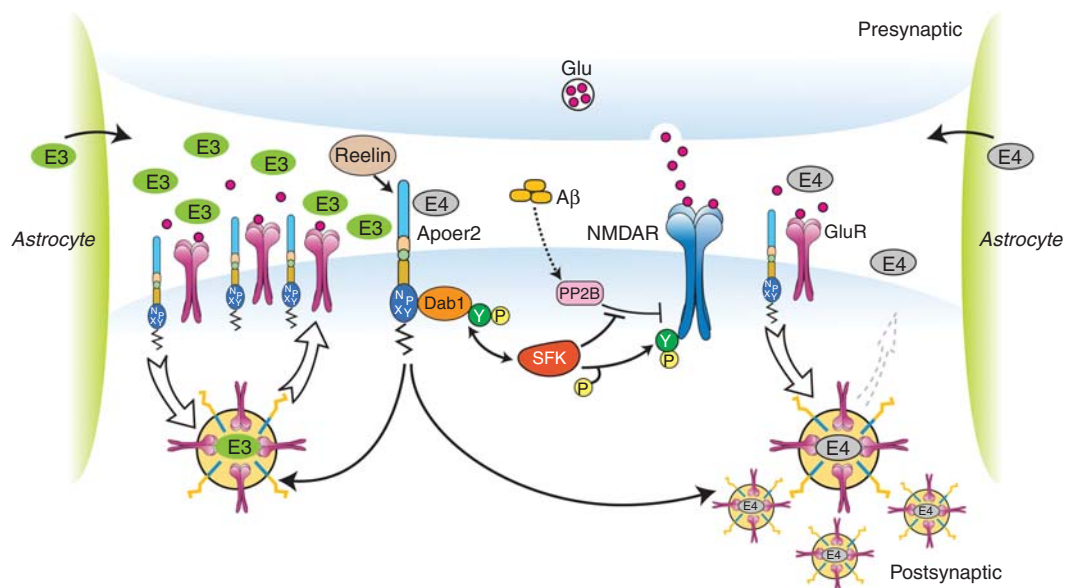
Reelin induces the phosphorylation of n-cofilin at the inhibitory Ser3 residue, thereby promoting spine stability (Chai et al. 2009; Frotscher 2010). Moreover, Reelin signaling activates SFKs (Chen et al. 2005), which would directly oppose the activity of the phosphatases on the NMDA receptor (Snyder et al. 2005). This hypothesis was tested by measuring the effect of different A $\beta$  preparations, including A $\beta$ -containing extracts from human AD brain, on hippocampal synaptic plasticity, NMDA receptor tyrosine phosphorylation, and activity in response to Reelin (Durakoglugil et al. 2009). At low to intermediate, but not at unphysiologically high (>400 nM) A $\beta$  concentrations, activation of Reelin signaling can completely prevent the synaptic suppression induced by the oligomers, suggesting that Reelin

is a physiological mediator of neuroprotection. Importantly, ApoE4 strongly interferes with these synapse-enhancing functions of Reelin by sequestering ApoE receptors in intracellular compartments (Chen et al. 2010) (Fig. 3), thus providing a novel mechanism by which accelerated spine loss, increased tau phosphorylation (Kocherhans et al. 2010), loss of network homeostasis (Palop et al. 2007; Palop and Mucke 2010), and earlier disease onset through loss of neuroprotective compensatory bandwidth (Korwek et al. 2009) can be readily explained. This mechanism is also consistent with the finding that ApoE4 reduces spine density and dendritic complexity in cortical neurons in vivo (Dumanis et al. 2009). Moreover, Reelin expression levels are reduced in the brains of AD patients and in the entorhinal

cortex of APP overexpressing mice (Chin et al. 2007), suggesting that A $\beta$  can reduce Reelin expression in a subset of entorhinal pyramidal neurons, thereby adding further support to a role of diminished Reelin signaling in AD progression (Herz and Chen 2006).

### ApoE Receptors Protect against Neurodegeneration

Recent evidence shows that ApoE receptors, specifically Apoer2 and LRP1, directly protect against the loss of neurons and dendrites in vivo (Beffert et al. 2006b). Apoer2 was found to protect against the loss of corticospinal neurons during the normal aging process (Beffert et al. 2006b). This protection requires the presence of the alternatively spliced cytoplasmic



**Figure 3.** ApoE isoforms differentially impair ApoE receptor and glutamate receptor recycling at the synapse. Apoer2 induces *N*-methyl-D-aspartate receptor (NMDAR) tyrosine phosphorylation by activating Src family tyrosine kinases (SFKs) in response to Reelin in the postsynaptic neuron. Astrocyte-derived ApoE3 (green ovals) or ApoE4 (gray ovals) bind to Apoer2 and are constitutively but slowly internalized. Apoer2 undergoes accelerated endocytosis in response to Reelin signaling. ApoE4 sequesters Apoer2 in intracellular compartments along with glutamate receptors (NMDAR and GluR), thereby reducing the ability of the postsynaptic neuron to recycle these proteins with normal kinetics, whereas ApoE2 or ApoE3 efficiently recycle back to the cell surface and thus deplete surface Apoer2 and glutamate receptor levels to a lesser extent (illustrated on the left for ApoE3). A $\beta$  oligomers interfere with NMDAR tyrosine phosphorylation by activating tyrosine phosphatases (Snyder et al. 2005). (Modified from Chen et al. 2010; reprinted, with permission, from the National Academy of Sciences © 2010.)

insert, which functionally couples Apoer2 to NMDA receptors, presumably through a PSD95-mediated interaction (Beffert et al. 2005; Hoe et al. 2006b), but also serves to recruit a c-jun amino-terminal kinase (JNK) signaling complex to the cytoplasmic tail of Apoer2 (Gotthardt et al. 2000; Stockinger et al. 2000). Intriguingly, JNK3 knockout mice and Apoer2 mutants lacking the alternatively spliced insert are resistant to lesion-induced neuronal death, suggesting that JNK recruitment to the Apoer2 cytoplasmic domain can promote both, neuronal loss or survival, depending on context (Beffert et al. 2006b).

Apoer2 also protects against neurodegeneration through another, mechanistically distinct mechanism, which involves its role in the uptake of essential selenoproteins into the brain (Burk et al. 2007). Loss of Apoer2 sensitizes the animals to low dietary selenium levels resulting in death from rapid and severe neurodegeneration. Selenoprotein 1 (Sepp1)-deficient animals show a pronounced LTP defect owing to selenium deficiency in the CNS when fed a selenium-reduced diet (Peters et al. 2006). However, the synaptic defects of Apoer2 knockin mutants (Beffert et al. 2005; Beffert et al. 2006a; Beffert et al. 2006b) are not caused by selenium depletion, but by the loss of NMDA and AMPA receptor regulation (Masiulis et al. 2009). LRP2 also mediates transport of this essential micronutrient (Chiu-Ugalde et al. 2010).

Neuroprotection by Apoer2 is further likely to involve its potent ability to mediate phosphorylation of cyclic AMP response element binding protein (CREB), a neuroprotective transcription factor that is also involved in long-term memory formation.  $\text{Ca}^{2+}$  influx through synaptic NMDA receptors stimulates CREB phosphorylation and promotes neuronal survival, whereas excitotoxic stimulation of extrasynaptic NMDA receptors shuts off CREB phosphorylation and promotes neuronal death (Hardingham et al. 2002). Reelin signaling strongly promotes CREB phosphorylation in cultured primary cortical neurons and this requires NMDA receptor activity (Chen et al. 2005). However, this is almost completely prevented by ApoE4 (Chen et al. 2010), suggesting

another potential mechanism by which this apolipoprotein may contribute to the premature onset of neurodegeneration in ApoE4 carriers.

## LRP1: EFFECTS ON APP, $\text{A}\beta$ , AND ApoE METABOLISM

### Regulation of APP Trafficking and Processing by LRP1 and Other ApoE Receptors

The  $\beta$ -secretase BACE1 is abundantly present and active in acidic endosomes (Cole and Vassar 2007). Consequently, increased APP endocytosis and distribution in endosomes lead to increased amyloidogenic processing and  $\text{A}\beta$  production. Conversely, if APP is retained at the cell surface, it has a greater availability for the cell-surface-localized  $\alpha$ -secretase and is cleaved to sAPP $\alpha$  and a minimally toxic peptide p3 (see Haass et al. 2011 for details). Therefore, APP-interacting proteins or cellular conditions that alter APP trafficking and/or distribution are expected to impact APP processing to  $\text{A}\beta$ . Indeed, several apoE receptors interact with APP and modulate its trafficking and processing. LRP1 interacts with APP extracellularly by binding to the Kunitz-type protease inhibitor (KPI) domain that is present in the longer forms of APP (APP751 and APP770) (Kounnas et al. 1995). Further studies showed that LRP1 also interacts with the neuronal isoform of APP lacking the KPI domain (APP695). Two different phosphotyrosine-binding (PTB) domains within the adaptor protein FE65 bind to the NPxY motifs within APP and LRP1, thus bridging an interaction between these two membrane proteins intracellularly (Trommsdorff et al. 1998; Kinoshita et al. 2001; Pietrzik et al. 2004). Because of the rapid endocytosis rate of LRP1 compared with that of APP (Cam et al. 2005), the consequence of APP and LRP1 interaction is accelerated APP endocytic trafficking and processing to  $\text{A}\beta$  (Ulery et al. 2000; Zerbinatti et al. 2004; Cam et al. 2005; Zerbinatti et al. 2006). The in vivo role of LRP1 in APP trafficking and processing requires further investigation.



Several other apoE receptors also interact with APP and regulate its trafficking and processing to A $\beta$ . LRP1B, which shares high sequence homology with LRP1 but has a significantly slower rate of endocytosis retains APP at the cell surface and reduces its processing to A $\beta$  (Cam et al. 2004). Apoer2 either decreases or increases A $\beta$  production depending on the experimental conditions. In the presence of F-spondin, a common ligand that bridges APP and Apoer2 extracellular interaction, the slow endocytosis rate of Apoer2 inhibits APP endocytic trafficking and reduces A $\beta$  production (Hoe et al. 2005). However, in the absence of common ligands, Apoer2 increases the distribution of APP into lipid rafts and APP processing to A $\beta$  (Fuentealba et al. 2007). A third apoE receptor that modulates APP trafficking and processing to A $\beta$  is sorLA/LR11 whose expression is significantly reduced in AD brains (Scherzer et al. 2004). Cell biological studies show that sorLA in neurons shifts APP distribution to the Golgi compartment and decreases its processing to A $\beta$  (Andersen et al. 2005). Importantly, a deletion of the *Sorla* gene in mice increases concentration of A $\beta$  in the brain (Andersen et al. 2005). Supporting a role for sorLA in AD pathogenesis, a genetic study showed that inherited variants in the *SORL1* gene (which encodes sorLA) are associated with LOAD (Rogaeva et al. 2007). Collectively, these studies show that apoE receptors are intimately associated with APP in neurons and regulate APP trafficking and processing.

### LRP1 and LDLR in Cellular and Brain A $\beta$ Metabolism

Impaired A $\beta$  clearance is likely a major pathogenic event for LOAD. There are two major pathways by which A $\beta$  is cleared from the brain: (1) receptor-mediated clearance by cells in brain parenchyma (microglia, astrocytes, neurons), along the interstitial fluid (ISF) drainage pathway or through the BBB and (2) through endopeptidase-mediated proteolytic degradation (see Saido and Leissring 2011 for details on proteolytic degradation of A $\beta$ ). Receptor-mediated clearance of A $\beta$  in the brain is at least

partially mediated by the apoE receptors LRP1, LDLR, and VLDLR, which are widely expressed in neurons, astrocytes, and microglia of brain parenchyma, as well as in endothelial cells, astrocytes, and smooth muscle cells at the BBB and cerebral arteries.

The best-characterized A $\beta$  clearance receptor in the brain is LRP1, which along with several of its ligands are present in amyloid plaques (Rebeck et al. 1995). The important function of LRP1 in brain A $\beta$  clearance was shown in amyloid mouse model with decreased LRP1 expression owing to a deletion of their chaperone RAP (Van Uden et al. 2002). Recombinant RAP and LRP1 antibody also reduce A $\beta$  efflux from mouse brain (Shibata et al. 2000). In humans, a decreased LRP1 expression in the brain capillaries in AD brains may contribute to impaired A $\beta$  clearance (Deane et al. 2004), whereas circulating soluble LRP1 (sLRP) might provide peripheral “sink” activity for A $\beta$  clearance through the BBB (Sagare et al. 2007).

LRP1 binds A $\beta$  directly (Deane et al. 2004) or indirectly via its ligands, which include  $\alpha$ 2-macroglobulin (Narita et al. 1997), RAP (Kaneakiyo and Bu 2009), and apoE (Bu 2009; Kim et al. 2009a). ApoE is the best-characterized A $\beta$  chaperone. Because apoE immunoreactivity is commonly found in amyloid plaques (Namba et al. 1991; Wisniewski and Frangione 1992), it is likely that apoE interacts with A $\beta$  directly in the human brain. The region of apoE that is responsible for A $\beta$  binding is in the carboxy-terminal domain overlapping with the lipid-binding region (Strittmatter et al. 1993b; Tamamizu-Kato et al. 2008), suggesting that the lipophilic A $\beta$  peptide associates with apoE in a process that is analogous to lipid binding. Indeed, A $\beta$  binding to apoE compromises its lipid-binding function (Tamamizu-Kato et al. 2008). Furthermore, A $\beta$  peptides modulate the binding of apoE isoforms differently to apoE receptors (Beffert et al. 1998; Hone et al. 2005). These results show that A $\beta$  peptides can interfere with the normal function of apoE under in vitro conditions. It is unclear if in vivo this is the case. A fraction of apoE3/lipoprotein binds to A $\beta$  with higher affinity than apoE4/lipoprotein (LaDu et al. 1994). How-



ever, whether A $\beta$  binding to apoE/lipoprotein leads to enhanced or reduced A $\beta$  clearance, has not yet been clarified (Kim et al. 2009a). If A $\beta$  is cleared more efficiently through apoE/lipoprotein-independent pathway, one would expect that A $\beta$  binding to apoE/lipoprotein will impede its clearance. On the other hand, if apoE/lipoprotein/A $\beta$  complexes enter cells via apoE receptor (e.g., LRP1 and LDLR) pathways more efficiently than A $\beta$  alone, apoE/lipoprotein likely promotes A $\beta$  clearance. The in vivo role of apoE/lipoprotein in A $\beta$  clearance is likely influenced by apoE lipidation state, receptor expression, and local A $\beta$  concentration (Bu 2009; Kim et al. 2009a). Interestingly, a recent study shows that A $\beta$  binding to apoE4 redirects its clearance from LRP1 to VLDLR, which internalizes A $\beta$ -apoE4 complexes at the BBB more slowly than LRP1 (Deane et al. 2008). In contrast, A $\beta$ -apoE2 and A $\beta$ -apoE3 complexes are cleared at the BBB via both VLDLR and LRP1 at a substantially faster rate than A $\beta$ -apoE4 complexes.

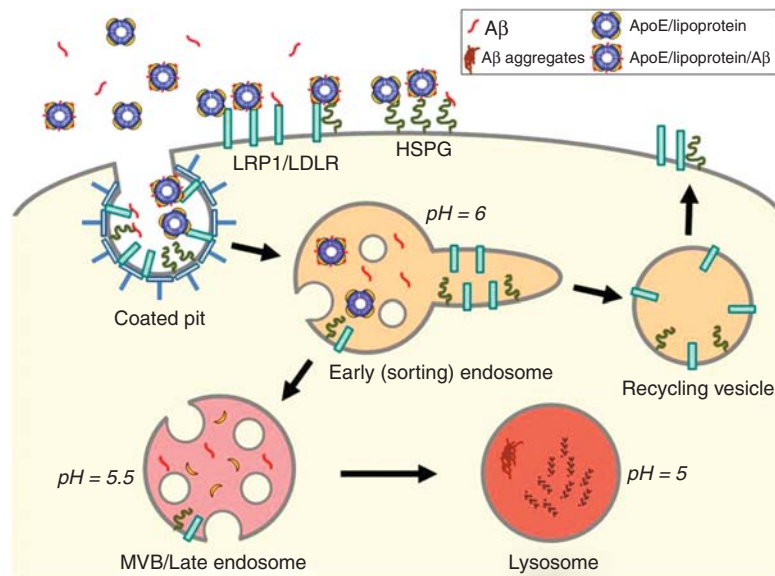
LDLR is another receptor that is implicated in brain A $\beta$  clearance, although the effects of LDLR loss-of-function on A $\beta$  clearance are still being worked out. One study showed that LDLR deficiency was associated with increased amyloid deposition in Tg2576 APP-transgenic mice (Cao et al. 2006). In contrast, another study using PDAPP-transgenic mice did not find a significant effect of *Ldlr* deletion on A $\beta$  level or deposition although there was a trend for increased A $\beta$  in the absence of LDLR (Fryer et al. 2005a). Using a gain-of-function approach, a more recent study showed that overexpression of the LDLR in the brain of transgenic mice enhanced A $\beta$  clearance and decreased A $\beta$  deposition (Kim et al. 2009b). It is not clear whether the effect of LDLR overexpression on A $\beta$  clearance is because of the reduced level of apoE in the LDLR transgenic mice, or a direct effect on A $\beta$ , or both. Nonetheless, these findings indicate that increasing LDLR expression may represent a novel therapeutic strategy to treat AD.

The receptor-mediated clearance is, in principle, an efficient way of reducing brain A $\beta$  because most A $\beta$  that is internalized by apoE

receptors is delivered to lysosomes for degradation (see Fig. 4) or transcytosed into the plasma via BBB. However, it is possible that receptor-mediated clearance of A $\beta$  into neurons can lead to intraneuronal accumulation of A $\beta$  (Fig. 3), which under certain conditions may be toxic (Billings et al. 2005). A portion of A $\beta$  that is internalized by neurons, in particular oligomeric A $\beta$ 42, accumulates in multivesicular bodies (MVBs)/late endosomes and lysosomes, and contributes to lysosomal dysfunction and neuronal toxicity. In contrast, receptor-mediated internalization of A $\beta$  by astrocytes (Koistinaho et al. 2004) and microglia (Mandrekar et al. 2009) is likely to represent a more functional pathway to clear and eventually degrade A $\beta$ .

### Evidence that LRP1 and LDLR Are Key Metabolic Receptors for ApoE/Lipoprotein in the Brain

Although several LDLR family members are expressed in the brain, accumulating evidence indicates that the LDLR and LRP1 are the two primary metabolic receptors for apoE/lipoprotein. Deletion of the *Ldlr* gene in mice increases apoE levels in brain parenchyma and CSF (Fryer et al. 2005a), suggesting impaired metabolism of apoE. In contrast, overexpression of the LDLR in the brain decreases apoE levels, reflecting an increased metabolism of apoE (Kim et al. 2009b). Similarly, conditional deletion of the *Lrp1* gene in mouse forebrain neurons increases apoE levels (Liu et al. 2007) and overexpression of a functional LRP1 minireceptor in mouse brain decreases brain apoE levels (Zerbinatti et al. 2006). Although both LDLR and LRP1 play roles in brain apoE/lipoprotein metabolism, there are important differences between them. First, whereas LRP1 is highly expressed in neurons and to a lesser degree in glia, LDLR is more prominently expressed in glia than neurons (Rebeck et al. 1993; Rapp et al. 2006). Second, deletion of the *Lrp1* gene in mouse forebrain neurons reduces brain cholesterol levels (Liu et al. 2007), whereas cholesterol levels in *Ldlr* knockout mice are unchanged (Fryer et al. 2005a). Third, apoE/lipoprotein



**Figure 4.** Schematic model of LRP1/LDLR-mediated cellular transport of apoE/lipoprotein and A $\beta$ . Three cell-surface receptors, LRP1, LDLR, and HSPG, are capable of binding to apoE/lipoprotein, A $\beta$ , and apoE/lipoprotein/A $\beta$  complexes. On clathrin-mediated endocytosis, ligands are mostly dissociated from the receptors within the early/sorting endosomes owing to lower pH. Whereas receptors are typically recycled back to the cell surface, ligands are delivered to multivesicular bodies (MVBs)/late endosomes and eventually to lysosomes for degradation. Lipid components are transported out of the lysosomes for storage or reutilization. Depending on the concentrations and cellular conditions, some A $\beta$  molecules might aggregate within the lysosomes as intracellular A $\beta$ , which could eventually serve to seed amyloid plaques (Hu et al. 2009).

particles secreted by astrocytes have higher affinity for LDLR than LRP1 (Fryer et al. 2005a), whereas recombinant apoE (Narita et al. 2002), apoE-enriched lipoprotein particles (Kowal et al. 1990), and CSF-isolated HDL particles (Fagan et al. 1996) bind more avidly to LRP1. The receptor-binding specificity of apoE is likely influenced by its conformation and lipidation state. It is possible that apoE/lipoprotein particles secreted by astrocytes recruit additional apoE molecules, perhaps bound to heparan sulfate proteoglycan (HSPG), before being transported to the CSF or binding to LRP1 at the neuronal cell surface.

There is some evidence that apoE isoforms may differ in their function in regard to cholesterol transport and efflux (Michikawa et al. 2000; Gong et al. 2002; Rapp et al. 2006), although not all studies show this (Hirsch-Reinshagen et al. 2004). Thus the roles of apoE isoforms in brain cholesterol metabolism require

further investigation. The structural differences among apoE isoforms that determine their lipid- and receptor-binding specificities in the brain environment could account for their differences in modulating brain cholesterol metabolism. It is important to note that there are likely LRP1-mediated cholesterol transport mechanisms in the brain that are independent of apoE because LRP1 deficiency in the brain, but not apoE deficiency, leads to decreased brain cholesterol levels. Other LRP1 ligands such as lipoprotein lipase might also play a role. Alternatively, LRP1 may serve as a cholesterol sensor that influences cholesterol synthesis and/or intracellular transport.

In addition to cholesterol, apoE also mediates the transport of other brain lipids, some of which are not produced in astrocytes. For example, sulfatide, an oligodendrocyte-synthesized lipid that is crucial for neuronal spine and myelin sheath integrity, is actively transported

by an apoE- and LRP1-dependent mechanism (Han 2007). It is possible that apoE/lipoprotein particles are modified by myelin-associated lipids before being transported into neurons. Interestingly, sulfatide is a potential biomarker for AD diagnosis as its levels are decreased in AD brains (Han 2007). Whether LRP1/LDLR-mediated apoE/cholesterol transport is impaired in AD brains and how this in turn contributes to AD pathogenesis is currently not clear. However, because of the important role of apoE/cholesterol in injury repair, the cholesterol transport pathway should be considered when apoE/LRP1/LDLR pathways are explored as therapeutic targets for AD.

## SUMMARY

*APOE* genotype is the strongest genetic risk factor for AD, and understanding the mechanism underlying this relationship has the potential to lead to new therapeutic approaches. A major reason that appears to underlie this relationship is the fact that apoE isoforms result in differential onset of A $\beta$  accumulation in the brain with the onset E4 earlier than E3, which is earlier than E2. There is direct in vivo evidence that differences in A $\beta$  clearance is one factor that accounts for this (Castellano et al. 2011), although effects of apoE on A $\beta$  aggregation independent of clearance may also be important. From a therapeutic standpoint, pathways that stimulate A $\beta$  clearance via apoE-dependent mechanisms are one possible approach to decrease A $\beta$  accumulation and its toxic effects. Targeting the liver X receptor (LXR) pathway (Koldamova et al. 2005b), apoE lipidation state via ABCA1, as well as LDLR, LRP1, and other apoE receptors are potential ways to stimulate apoE-dependent A $\beta$  clearance. In terms of apoE-dependent A $\beta$  aggregation, interrupting the apoE-A $\beta$  interaction may also have therapeutic potential (Sadowski et al. 2006). In addition to effects on the apoE/A $\beta$  pathway, apoE receptors such as Apoer2 and Vldlr play important roles in synaptic plasticity, tau phosphorylation, and neuroprotection. Determining ways to activate these receptors may be

## Apolipoprotein E and Apolipoprotein E Receptors

another strategy to delay or halt the progressive neurodegenerative process that occurs in AD.

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