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ApoE Receptors in the Nervous System

Joachim Herz

Department of Molecular Genetics, UT Southwestern, Dallas, TX 75390-9046

Abstract

Purpose of review—Over the last few years ApoE receptors, also known as LDL receptor related proteins, have distinguished themselves as functionally diverse signaling receptors with pivotal roles not only in the vascular system, but also in the nervous system and during development.

Recent findings—The expanding roles of ApoE receptors for cellular signal transduction at the same time transcend and integrate their lipid transport roles into a larger biological and clinical context. ApoE receptors are essential for the development of the nervous system, the regulation of synaptic plasticity, neuroprotection, and the innervation of the muscle. They also regulate the metabolism of the amyloid precursor protein on multiple levels, implicating them in the pathogenesis of Alzheimer's disease (AD).

Summary—ApoE, a common ligand for all members of the evolutionarily ancient LDL receptor gene family, is the major genetic modifier of the age of onset of Alzheimer's disease. The underlying molecular mechanisms remain shrouded in mystery, but the numerous critical functions of ApoE receptors within and outside the nervous system that have recently emerged make it likely that these multifunctional signal modulators participate in AD pathogenesis. This review attempts to summarize the most recent and relevant findings in this area.

Keywords

LDL receptor family; dementia; synaptic plasticity; neuronal survival

Introduction

The last decade has seen a role reversal for lipoprotein receptors, and in particular the LDL receptor related proteins (LRPs, Figure 1). Rather than being perceived as mere transporters of lipoproteins, lipids and other macromolecules in the circulation, these multifunctional and evolutionarily ancient cell surface proteins were first recognized for what initially appeared to be isolated and specialized functions as intercellular signal transducers. More recently, this image has further evolved to reveal that ApoE receptors cannot only act as direct signal transducers, but that they function also on a much broader scale as signal modulators as well as integrators of several distinct and independent signaling pathways. Here I am going to review the most recent findings with particular emphasis on the role of ApoE receptors in the nervous system.

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Control of Brain Development and Architecture

That ApoE receptors have critical functions during brain development became apparent during the analysis of knockout mice lacking megalin/LRP2, and from animals deficient for both Apoer2/LRP8 and Vldlr. The latter are phenotypically identical to mice lacking the developmental signaling protein Reelin and to another strain of mice carrying mutations in the cytoplasmic adapter protein Disabled-1 (Dab1). This immediately suggested that both of these ApoE receptors function together in a linear signaling pathway that is dependent upon the extracellular ligand Reelin and the intracellular adaptor Dab1 for initiating a signaling cascade that regulates the migration and positioning of neurons during development [1]. The power of mouse genetics has been invaluable for the initial discovery of the basic frame work of this essential and evolutionarily highly conserved signaling pathway (Figure 2). This subsequently allowed for the rapid elucidation of the intracellular branches of a signaling cascade that is initiated by Reelin induced receptor clustering and followed by the activation of Src family tyrosine kinases (SFKs) through proximity triggered transphosphorylation. These include activation of PI3 kinase, Akt and inhibition of GSK3 β resulting in reduced phosphorylation of the microtubule stabilizing protein tau, regulation of microtubule dynamics through Reelin triggered interaction of Dab1 with Lis1 (Pafah1b1), direct interaction of the Pafah1b complex with Vldlr [2], interaction of phosphorylated Dab1 with the adapter proteins Crk and CrkL [3,4], and stabilization of the actin cytoskeleton of neuronal processes by phosphorylation of the actin depolymerizing protein N-cofilin [5]. Recently, Thrombospondin-1 has been recognized as a novel ligand for Apoer2 and Vldlr in the brain where it participates in the chain migration of postnatal neurons along the rostral migratory stream [6].

These novel interactions, which take place downstream of, or in parallel with, the activation of SFKs and which are partly dependent upon unique interaction motifs within the cytoplasmic domains of the receptors help to explain the specific and non-redundant roles Apoer2 and Vldlr have in shaping different regions of the brain in response to the binding of the same ligand or ligands. For instance, Apoer2 and Vldlr play different roles in the patterning of the cerebellum, in particular the topography of the Purkinje cell layer [7]. Similarly, in the neocortex Vldlr provides a stop signal for migrating neurons, preventing them from entering the marginal zone, while Apoer2 regulates the migration of later-born neurons and is essential for proper lamination of neocortex and hippocampus [8]. Intriguingly, regulation of neuronal migration by Reelin also involves interaction with Notch proteins, where stabilization of the intracellular (signaling) domain of Notch requires Reelin and Dab1 [9]. Reelin signaling through Apoer2 and Vldlr is also necessary for neuronal positioning in the spinal cord and for the processing of nociceptive input, although the alternative splicing of the Apoer2 cytoplasmic domain [1] does not seem to contribute to the neuronal plasticity of pain processing [10].

Synapse Development and Regulation of Synaptic Plasticity

In addition to the activation or inhibition of pathways that regulate cell shape or migration, Reelin signaling through Apoer2 also induces the tyrosine phosphorylation of NMDA receptor (NR2) subunits, which changes the surface distribution and activity of this glutamate receptor and synaptic ion channel. This results in the Reelin-dependent regulation of synaptic plasticity over a wide physiological range, and this is further modulated by differential splicing of the Apoer2 cytoplasmic domain [1]. The importance of Reelin signaling for NMDA receptor function is further emphasized by its role in the regulation of NMDA receptor maturation, which requires the participation of β 1-integrins [11]. Moreover, Reelin has a powerful effect on the function of synapses in postmitotic neurons where it promotes dendritic spine development [12] and Apoer2 is required to ensure long-term neuronal survival in vivo [13]. LRP1 can also modulate NMDA receptor function through a tissue-type plasminogen activator dependent mechanism that involves the second NPxY motif in LRP1 [14].

The fundamental importance of ApoE receptors for synapse function and development is also illustrated by recent findings from two independent groups who revealed the mechanism by which LRP4 controls the development of a specialized peripheral synapse, the neuromuscular junction [15,16]. LRP4 deficient newborn mice completely lack neuromuscular junctions and consequently they are still-born. The underlying mechanism that is disrupted by the absence of LRP4 involves a role of LRP4 as an obligate coreceptor for the muscle specific tyrosine kinase MUSK and the neuronally produced ligand agrin. Binding of agrin to LRP4 induces clustering and transphosphorylation of MUSK. The latter does not bind agrin and therefore the neuron-to-muscle signal is disrupted in the absence of LRP4. As a result, acetylcholine receptors fail to form postsynaptic clusters, a process that requires MUSK activation (Figure 3).

Taken together, these independent findings have revealed distinct, but nevertheless molecularly similar mechanisms by which ApoE receptors function in neurons and which are critical for the formation or function of central as well as peripheral synapses.

ApoE receptors and Alzheimer's Disease

ApoE is the major risk factor/modifier of age of onset of late-onset Alzheimer's disease (AD). ApoE4 carriers develop AD in a dose-dependent manner on average up to 10 years earlier than the remainder of the population. Mechanisms that have been suggested by which ApoE exerts its strong isoform-specific effect on amyloid plaque formation include increased fibrillogenesis of b-amyloid, impaired clearance of the amyloid-b peptide from the extracellular space [17, 18] and diminished export across the blood-brain-barrier [19]. An alternative mechanism our laboratory has proposed involves a direct effect of ApoE on its own receptors, which interferes with the ability of these multifunctional ApoE receptors to signal to neurons, thereby impairing synaptic plasticity [1], spine formation [12], learning and memory [1] and neuronal survival [13]. Ab oligomers have been shown to induce synaptic dysfunction, which precedes neuronal loss in AD patients [20,21].

Another mechanism by which ApoE receptors can potentially influence the production of b-amyloid is by altering the subcellular trafficking of the amyloid precursor protein (APP) [22]. A large amount of evidence has accumulated over the last few years that shows that ApoE receptors can directly as well as indirectly alter the expression, distribution and routing of APP and thereby influence the pathways that control APP processing and thus Ab production. LRP1 regulates the expression of ApoE in the CNS while conversely disruption of APP and its close relative APLP2 increases LRP1 expression [23]. Upregulation of LRP1 expression is reversed by overexpression of the APP intracellular domain. Apoer2 can increase Ab production by decreasing APP endocytosis through altering APP partitioning [24]. On the other hand, ApoE binding to Apoer2 increases APP endocytosis and Ab production in an isoform specific manner [25]. Intriguingly, nuclear liver X receptor (LXR) agonists which regulate cholesterol homeostasis and which also have anti-inflammatory activity, reduce Ab production by increasing metalloproteinase dependent a-cleavage of APP as well as ectodomain release of Apoer2 through inhibition of metalloproteinase inhibitor TIMP-3 expression [26].

Another LDL receptor family member that has a major effect on the subcellular trafficking of APP and on its processing to b-amyloid is SORL1 (a.k.a. LR11) through interaction with intracellular adaptor proteins [27]. Loss of SORL1 in the mouse increases APP cleavage and Ab production [28,29]. Increased production of soluble APP ectodomain (APPs) increases ERK activation and neurogenesis [30]. Taken together, these findings emphasize the close functional relationship between ApoE receptors, APP and the regulation of the b-amyloid producing machinery, consistent with a model in which ApoE exerts its effect on AD age-of-onset through interaction with ApoE receptors.

Human Genetics

The genes for all members of the LDL receptor gene family shown in Figure 1 have been disrupted in the mouse. Aside from the LDL receptor, where mutations cause familial hypercholesterolemia (FH), confirmed human gene defects have so far only been identified in LRP2 (a.k.a. Megalin) and VLDLR, while a sequence variant that is associated with coronary artery disease and myocardial infarction has been found in LRP8 [31]. Defects in LRP2 are the cause for Donnai-Barrow syndrome, a congenital malformation that includes agenesis of the corpus callosum, diaphragmatic hernia, facial dysmorphology, ocular anomalies, sensorineural hearing loss and developmental delay [32,33]. The defects seen in these patients are similar, but not identical to those seen in C57BL/6 $\times$ 129 hybrid LRP2 deficient mice, indicating that genetic modifiers influence the relative developmental importance of this large ApoE receptor between different mammalian species and between different mouse strain backgrounds over a wide range.

VLDLR-deficiency in humans was first identified by Boycott et al. [34] in the Canadian Hutterite population by a combination of a gene mapping and candidate gene approach. Conversely to LRP2 deficiency, this fully autosomal recessive gene defect manifests itself also with a similar, but more severe phenotype in humans compared to the mouse. While the latter present with relatively mild cerebellar hypoplasia and primarily rostral cerebellar malformation with no recognizable ataxia, humans lacking VLDLR show severe cerebellar vermal hypoplasia, accompanied by delayed motoric development and persistent truncal ataxia. Additional genetically distinct mutations in human VLDLR have been reported in independent pedigrees in Middle Eastern populations [35–37]. Neuroanatomically, the affected patients are indistinguishable from the initially reported Hutterites. By contrast, considerable variations between the two geographically separated populations, but also between individuals, are seen with respect to motor development. Several, but not all, affected individuals of a large Turkish pedigree were reported to be habitually quadrupedal, prompting the authors to attribute VLDLR as a crucial gene for the evolution of bipedal gait [36]. This conclusion has been drawn into question, however, since even within the same families this behavioral phenotype is not penetrant and the presence of adverse environmental and societal conditions offer far simpler and straightforward explanations [38,39].

Recently, the first compound heterozygous case has been reported in a young child with developmental delay [40] where loss of VLDLR function is caused by two novel and genetically independent mutations in the VLDLR extracellular domain, resulting in premature translational truncation of the gene product from one allele and a missense mutation in the other, which matches a known FH causing mutation in LDLR, mostly likely through ER retention and degradation of the misfolded protein.

Other human autosomal recessive defects with phenotypes that are virtually identical, but non-allelic to, VLDLR deficiency have also been reported [36,37]. One of these loci has been narrowed to a short minimal region on Chr. 17 [37]. This region contains Crk, a downstream component of the Reelin signaling pathway [3,4] (Figure 2), prompting Boycott et al. [40] to propose Crk as a highly likely candidate gene for the Chr. 17 defect.

SORL1 (a.k.a. LR11) is an LDL receptor family member that combines most of the structural features of the core family members (Figure 1A) with functional domains found in other not related proteins, most notably a vacuolar protein sorting (VPS) domain [41]. Some of the in vivo functions of SORL1 resemble those of LRP1, in particular with respect to its role in regulating the trafficking of APP and as a signal modulator in the vascular wall, where it regulates AngII dependent smooth muscle cell migration [42]. SORL1 expression is dramatically reduced in the brains of AD patients [28] and intronic variants within SORL1 are

genetically associated with AD [43]. Postmortem expression analysis also showed a statistically significant inverse correlation between SORL1 expression and cognitive impairment, suggesting SORL1 expression as a marker for prodromal AD [44]. Intriguingly, docosahexanoic acid, an essential omega-3 fatty acid, increases SORL1 expression in vitro and in mice in vivo [45], providing a potential mechanism for a role of diet in AD prevention.

LRP6 is a 'distant' member of the LDL receptor gene family and functions as an obligate component of the Wnt signaling complex at the plasma membrane which also includes Frizzled (Fz) receptors. A particular LRP6 variant (Ile1062Val) has previously been shown to have decreased canonical Wnt signaling associated with reduced bone mass. The same variant was found to convey an increased risk for late-onset AD in an ApoE4 dependent manner suggesting a role for Wnt signaling in AD pathogenesis [46].

Conclusions

Over the last decade the nervous system has morphed from a sideshow of lipoprotein receptor research to main stage act. ApoE receptors in particular have distinguished themselves as pivotal regulators of crucial developmental and synaptic processes that control neuronal migration and positioning, learning and memory, synaptogenesis and neuronal survival. As we continue to peel away the layers that shroud their increasingly complex functions in the central nervous system, we may ultimately arrive at a comprehensive understanding of the fundamental roles of this remarkable, multifunctional and ancient gene family in the maintenance and operation of our most complex organ, the brain.

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Figure 1. The LDL receptor family of ApoE receptors (modified from 1, 47)

Panel A, the core of the family in mammals. *Panel B*, physiologically and functionally important, related family members that do not share all the structural requirements of the ‘core members’, including a ligand binding domain of variable repeat length at the amino terminus, followed by an EGF precursor homology (β -propeller) domain, which in turn is followed by either another ligand binding domain, an O-linked sugar domain, or a ligand binding segment. All receptors are type I transmembrane proteins that are anchored by a single transmembrane segment. Core members contain short cytoplasmic tails with at least one ‘NPxY’ tetraamino acid motif that combines endocytosis with adapter protein docking functions.

Figure 2. Vldlr and Apoer2 function as signal transducers in neurons (modified from 1, 47)

Panel A, The large oligomeric high affinity signaling protein Reelin binds to Vldlr and Apoer2 and induces receptor clustering. Transactivation of Src family tyrosine kinases (SFK) results in phosphorylation and thereby activation of Disabled-1 (Dab1), an adaptor protein that interacts with NPxY motifs in both receptor tails. This activates phosphatidylinositol 3-kinase (PI3K) and protein kinase B (PKB, Akt), which in turn inhibits glycogen synthase kinase-3 β (GSK3 β) and reduces phosphorylation of the microtubule stabilizing protein tau. Crk and Crk-like (CrkL) function downstream of Dab1, regulating actin cytoskeleton rearrangement. Actin depolymerization is also controlled by LIM kinase (LIMK) which inhibits n-cofilin, an actin depolymerizing protein. Lis1 binds to tyrosine-phosphorylated Dab and as part of a Pafah1b complex regulates microtubule functions. Cyclin-dependent kinase 5 (Cdk5) and its activators p35 and p39 function parallel to Reelin. In the synapse, Apoer2 interacts with PSD95 through its cytoplasmic exon 19, thereby functionally coupling the Reelin signaling complex to the NMDA receptor (NMDAR). Reelin-activated SFKs phosphorylate the NMDA receptor NR2 subunits, thereby potentiating NMDAR-mediated Ca^{2+} influx. Phosphorylation of survival factor cAMP-response element binding protein (CREB) ensues. This phosphorylation event initiates the expression of genes that are important for synaptic plasticity, neurite growth and dendritic spine development.

Panel B, Reelin potentiates long-term potentiation (LTP) and enhances NMDAR-mediated currents in wild type CA1 pyramidal neurons.

Figure 3. LRP4 is a receptor for agrin and a coreceptor for the tyrosine kinase MUSK in muscle (modified from 47)

The membrane tyrosine kinase MUSK is required for acetylcholine receptor (AChR) clustering in neuromuscular endplates. However, MUSK does not bind the obligate signaling protein agrin directly. Instead, MUSK must form a complex with LRP4, which is a receptor for agrin. This in turn enhances complex formation of MUSK with LRP4 and induces transphosphorylation and activation of MUSK, followed by AChR clustering.