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Chapter 6

Lipoproteins and Diseases of the Brain

Kwang-Min Kim and G. Tayhas R. Palmore

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Abstract

Apolipoprotein E4 (apoE4) and outer surface protein A (ospA) are pathogenic lipoproteins involved in the progression of Alzheimer's disease and Lyme neuroborreliosis, respectively. Results from previous studies indicate that apoE4 exhibits neurotoxicity by activating amyloid beta pathways, and ospA causes damage to the brain by stimulating immune activity of microglia and astrocytes. These results, however, lack information about the specific interactions that develop between neurons and these two lipoproteins. It is essential to investigate the effect of these lipoproteins on neuronal morphology and function to better understand the mechanism of damage and disease of the brain. This chapter summarizes previous studies on the role of apoE4 and ospA in diseases of the brain and discusses experimental results from our own work that suggests new roles for apoE4 and ospA in neuronal outgrowth and synaptic loss.

Keywords: apolipoprotein E4, bacterial outer surface protein A, neurodegeneration, neuroinflammation, nerve regeneration, synaptic loss

1. Introduction

Lipoproteins in the brain are involved in the onset and progression of neurodegenerative diseases (e.g., Alzheimer's disease) [1, 2] and neuroinflammatory disorders (e.g., neuroborreliosis) [3, 4]. These lipoproteins are either endogenously expressed by astrocytes [5] and microglia [6, 7] or exogenously produced by bacterial pathogens (e.g., *Borrelia burgdorferi, Streptococcus pneumoniae*) [8].

The most abundant endogenous lipoproteins in the brain include apolipoprotein E (apoE) and apoJ [2]. These endogenous lipoproteins mediate transport of lipids between various cells in the brain to maintain and regulate the brain structure and function [9, 10]. The apoE isoform, apoE4, has been investigated intensively because previous studies showed that lipidation of

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apoE4 (i.e., apoE4 carrying cholesterol and phospholipids) is the major risk factor indicative of the onset of Alzheimer's disease (AD) [11].

The exogenous lipoprotein most studied in the brain is the bacterial outer surface protein A (ospA), which is produced by *B. burgdorferi* [12, 13]. *B. burgdorferi* causes Lyme disease, which is the most common tick-borne infection in Europe and in North America [14]. A recent study using rats infected with *B. burgdorferi* demonstrated that *B. burgdorferi* was observed across the blood-brain barrier (BBB) and that the expression level of ospA was augmented significantly in the brain [4].

Thus, apoE and ospA have been of interest to both scientists and clinicians who seek to develop new strategies for treatment of brain injuries and brain disorders induced by these pathogenic lipoproteins. It still remains unclear however, if apoE and ospA interact directly with neurons to disrupt the structure and function of the brain, whereas it is documented extensively that these lipoproteins induce pathological states via amyloid beta (Aβ) aggregation [15, 16] and immune activation of microglia and astrocytes [17, 18]. To address the absence of direct evidence of interaction between lipoproteins and neurons, we have studied the effect of apoE4 and ospA on neurons in terms of axonal outgrowth and synaptic loss. This chapter discusses these findings and the potential new roles of apoE4 and ospA in the context of previous studies on these lipoproteins in neurodegeneration and neuroinflammation.

2. ApoE4 and neuronal outgrowth

2.1. Lipidation of apoE isoforms

ApoE transports and clears lipids from one cell to another to maintain lipid homeostasis of the brain [9, 10]. To carry lipids (e.g., cholesterol, phospholipids, and lipoproteins), apoE is lipidated (i.e., lipid-bound apoE) by adenosine triphosphate (ATP)-binding cassette A1 (ABCA1) transporters on astrocytes [19] (**Figure 1a**). The lipidation status of apoE depends on its three isoforms (i.e., apoE2, apoE3, and apoE4) coded by three alleles (ε2, ε3, and ε4 of *APOE* gene) on chromosome 19 [20]. The three isoforms of apoE differ from one another by amino acid interchanges at two residue sites (**Table 1**).

These minor variations cause a change in the structure and function of apoE, which eventually leads to distinct disease mechanisms in AD [21]. ApoE4 has an arginine at residue 112 that connects the N terminus (Arg 61) to the C terminus (Glu 255) to form a folded structure of apoE called *domain interaction* [22]. ApoE2 and apoE3 have a cysteine at residue 112, which is less likely to create the folded structure of domain interaction. The presence of domain interaction results in distinct lipid-bound forms among apoE isoforms. ApoE4 binds preferentially to larger lipid particles due to its folded structure, which interferes with internalization of lipids into neurons [11]. In contrast, apoE2 and E3 bind to various sizes of lipids in more ways that are efficient and thus facilitate lipid transport between cells in the brain. The lipidated apoE can be internalized into cells in the brain (i.e., astrocytes, microglia, and neurons) through the family of low-density lipoprotein receptors (LDLR), low-density lipoprotein receptor-related protein 1 (LRP1), or heparan sulfate proteoglycans (HSPGs) [11, 16].

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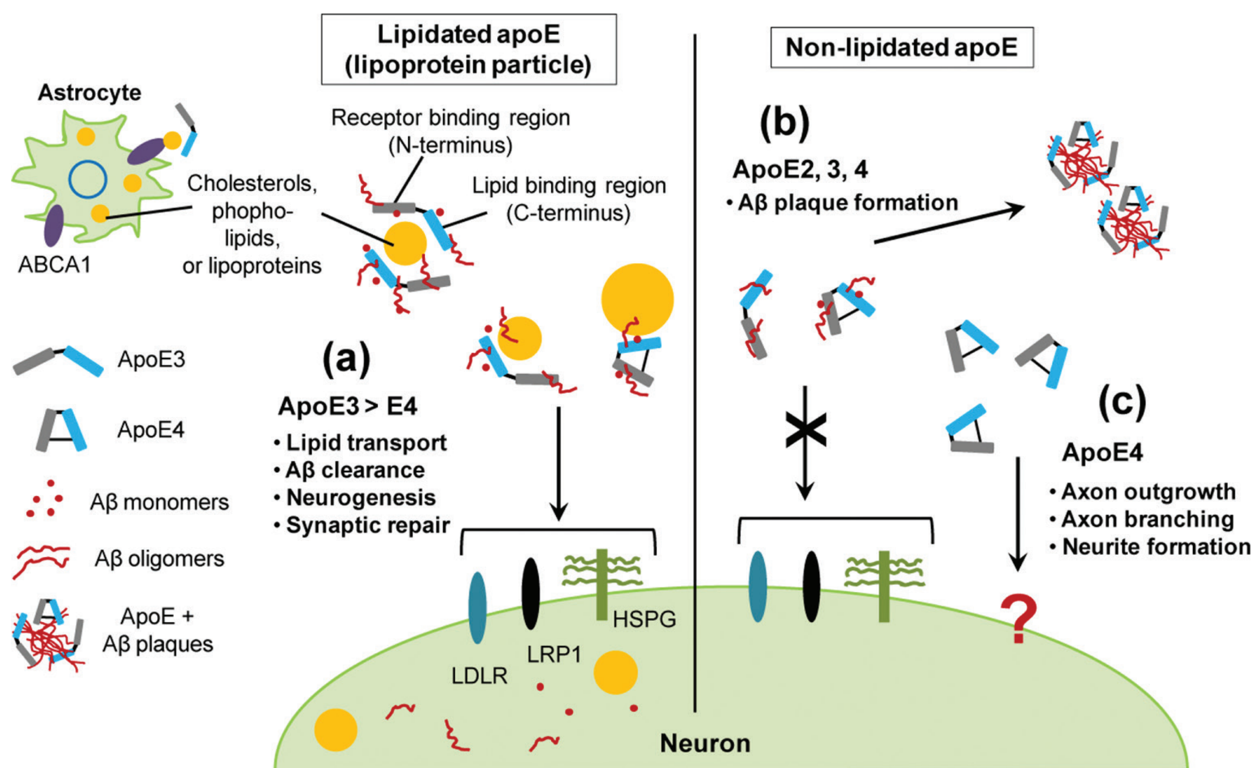

Figure 1. The interaction between apoE and neurons illustrated. (a) ApoE transports lipids to neurons by forming lipopeptide particles (i.e., lipidation of apoE). ApoE is lipidated by ATP-binding cassette A1 (ABCA1) transporters of astrocytes. The lipid-binding affinity of apoE4 is different from that of apoE2 and apoE3 because of structural differences in its *domain interaction*. Both lipid and apoE can bind to Aβ monomers and oligomers. The Aβ-lipidated apoE2/3 complex can be internalized by LDLR, LRP1, or HSPG, which clears Aβ. The efficiency of internalizing large lipid-bound apoE4 into cells is low, which increases the probability of Aβ plaque formation because of poor Aβ clearance. (b) ApoE alone can bind to Aβ monomers and oligomers regardless of its isoforms. The Aβ-nonlipidated apoE complex increases the probability of forming Aβ plaques because nonlipidated apoE cannot be internalized via LDLR or LRP1. (c) Nonlipidated apoE4 enhances neuronal adhesion, axon outgrowth, and neurite branching. The receptor in neurons that regulates growth-enhancing effects of nonlipidated apoE4 remains unknown. Abbreviations: ABCA1, ATP-binding cassette A1 transporter; LDLR, low-density lipoprotein receptor; LRP1, low-density lipoprotein receptor-related protein 1; HSPG, heparan sulfate proteoglycans.

ApoE isoforms	ApoE amino acid residue	
	112	**158**
ApoE2	Cys	Cys
ApoE3	Cys	Arg
ApoE4	Arg	Arg

Table 1. Differences of apoE isoforms in amino acid residues.

When the lipidated apoE is internalized into cells, Aβ monomers and oligomers are also cleared because they bind to both lipids and apoE at residues 12–28 [23]. Thus, Aβ clearance is dependent on the structural difference of apoE isoforms, and this mechanism helps to prevent

the Aβ aggregation that is associated with the progression of AD. The Aβ-bound apoE, however, forms aggregates regardless of the isoform of apoE when they are not lipidated and thus, are not internalized [16, 23] (**Figure 1b**).

2.2. Nonlipidated apo E4 and neuronal outgrowth

When lipidated, apoE4 is known to be toxic to neurons through various pathogenic pathways such as Aβ aggregation and apoE fragment formation [21]. The effect of apoE4 on neurons when it is not lipidated, however, remains unclear. To address this knowledge gap, the effect of apoE4 on neuronal outgrowth was studied *in vitro* without lipids in the medium [24]. This study compared neuronal responses to various culture substrates including glass, laminin-coated glass, and apolipoprotein E4-coated glass by quantifying key neuronal outgrowth parameters in terms of cell adhesion, axon length, number of neurites, and number of branches on axons. The results of this study demonstrated that apoE4 not only enhances neuronal adhesion but also significantly increases axon outgrowth and branching when compared to laminin, a protein that is recognized as one of the best extracellular matrix (ECM) proteins for enhancing neuronal growth [25]. As such, results from this study contradict the prevailing view that apoE4 has only a degenerative effect on cells in the brain. Although apoE4 when lipidated predominantly exhibits neurotoxicity when studied *in vivo* and in clinical models, it should be considered that both lipidated and nonlipidated apoE in these models constantly interact with neurons to mediate brain activity. Thus, the results from this study provide a complementary mechanism of action of apoE. In addition, the neuron-growing potential of apoE4 can be applied to transplantable therapeutic systems using stem cells or microstructure devices prior to interaction of lipids *in vivo*.

The mechanism by which nonlipidated apoE mediates axon outgrowth and branching remains elusive, whereas lipidated apoE is known to interact with cells via LRP1, LDLR, or HSPG [16]. It has been reported that apoE does not bind to LDLR or LRP1 without lipidation [26, 27]. Integrin and HSPGs also were tested for their involvement in apoE4-induced axon outgrowth by inhibiting these receptors. Neither of these receptors was found to be responsible for apoE4-induced neuronal outgrowth (**Figure 1c**). The mechanism of interaction between neurons and nonlipidated apoE4 is the subject of ongoing studies.

3. Bacterial lipoprotein and synaptic loss

3.1. Bacterial lipoproteins and neuroinflammation

Bacterial surface components including lipoproteins and lipopolysaccharide (LPS) have been reported to be elevated in the cerebrospinal fluid (CSF) of patients suffering from a bacterial infection such as bacterial meningitis [28]. These components can cause neuropsychiatric manifestations such as lymphocytic meningitis, cranial and peripheral neuropathy, and cerebral infarcts [29, 30]. When compared to LPS, bacterial lipoproteins activate inflammatory pathways more vigorously [31], leading to more severe damage to tissue [32]. Bacterial lipoproteins still remain in the tissue even after the degradation of bacteria by antibiotic

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therapies [33, 34]. As a result, many studies suggest that minimizing the production of bacterial proteins or inhibiting bacterial protein synthesis is more effective at preventing neural injury from bacterial infections in animal models or patients [35, 36] than simply using antibiotics to kill bacteria. Bacterial lipoproteins in the brain trigger microglia activation via the toll-like receptors (TLRs) to produce inflammatory mediators (e.g., cytokines and reactive oxygen species) [37–39] and induce migration of immune cells across the BBB [40, 41]. The result is damaged brain tissue including cell death of astrocytes, oligodendrocytes, and neurons [42, 43].

The outer surface protein (osp) is the most studied bacterial lipoprotein that includes ospA, ospB, and ospC from *B. burgdorferi* [12, 44, 45]. Three palmitoyl groups (i.e., the lipid portion) at the N-terminus of the peptide is responsible for immune activation and tissue injury [46, 47], whereas the peptide portion of ospA is not effective at activating immune pathways [32]. Thus, tripalmitoyl-S-glyceryl-cysteine (Pam3-Cys), a synthetic lipopeptide mimicking the N-termini of osp, is often used for studying bacterial infection in a wide range of research fields involving immunology and neuroscience [48, 49]. Although all of ospA, ospB, and ospC share common immune pathways (e.g., NF-κB activation) via TLR2, ospA shows higher toxicity to tissues when compared with ospB and ospC [32]. The reason for distinct toxic effects among these different lipoproteins continues to remain elusive.

3.2. OspA and presynaptic loss

OspA from *B. burgdorferi* is able to cross the BBB by binding to CD40 of brain-microvascular endothelial cells [4]. OspA in the brain activates TLR2 on microglia and astrocytes, which initiates immune activity and causes damage to brain tissue [14, 50]. However, information regarding the interaction between ospA and neurons is lacking because the expression level of TLR2 in neurons is extremely low when compared with that of microglia or astrocytes. Thus, the interaction between ospA and neurons has been overlooked [51, 52]. To address this question, the effect of ospA on neurons has been investigated with a specific focus on synaptic loss. The density and transmission of synapses are considered to be the key parameters in determining the functional state of brain tissue (e.g., information processing and storage) because neurons transmit electrical and biochemical signals to adjacent neurons through the synapse. The signal-sending synapse (i.e., presynapse) is located on the axon and the signal-receiving synapse (i.e., postsynapse) is located on the dendrite of a neuron. If neurons lose one of these synapses or have misaligned synapses, the brain cannot function properly even when neurons survive from brain injuries or diseases. Thus, the change in pre- and postsynaptic density was quantified following treatment of cultures of rat E18 hippocampal neurons with ospA (2 μM) for 24 h (**Figure 2**). The quantification of synaptic density was determined by counting the number of synaptic sites (i.e., synapsin or postsynaptic density protein 95 (PSD-95)) in a randomly selected secondary dendrite. OspA expressed from *Escherichia coli* (prepared by the Biomaterials and Advanced Drug Delivery Laboratory at Stanford University) showed that ospA significantly decreased the number of presynaptic sites (i.e., synapsin) ($p = 0.04$), whereas it did not affect the number of postsynaptic sites (i.e., PSD-95) ($p > 0.05$) (**Figure 2**). This result suggests that ospA directly disrupts neuronal function by damaging presynapses exclusively.

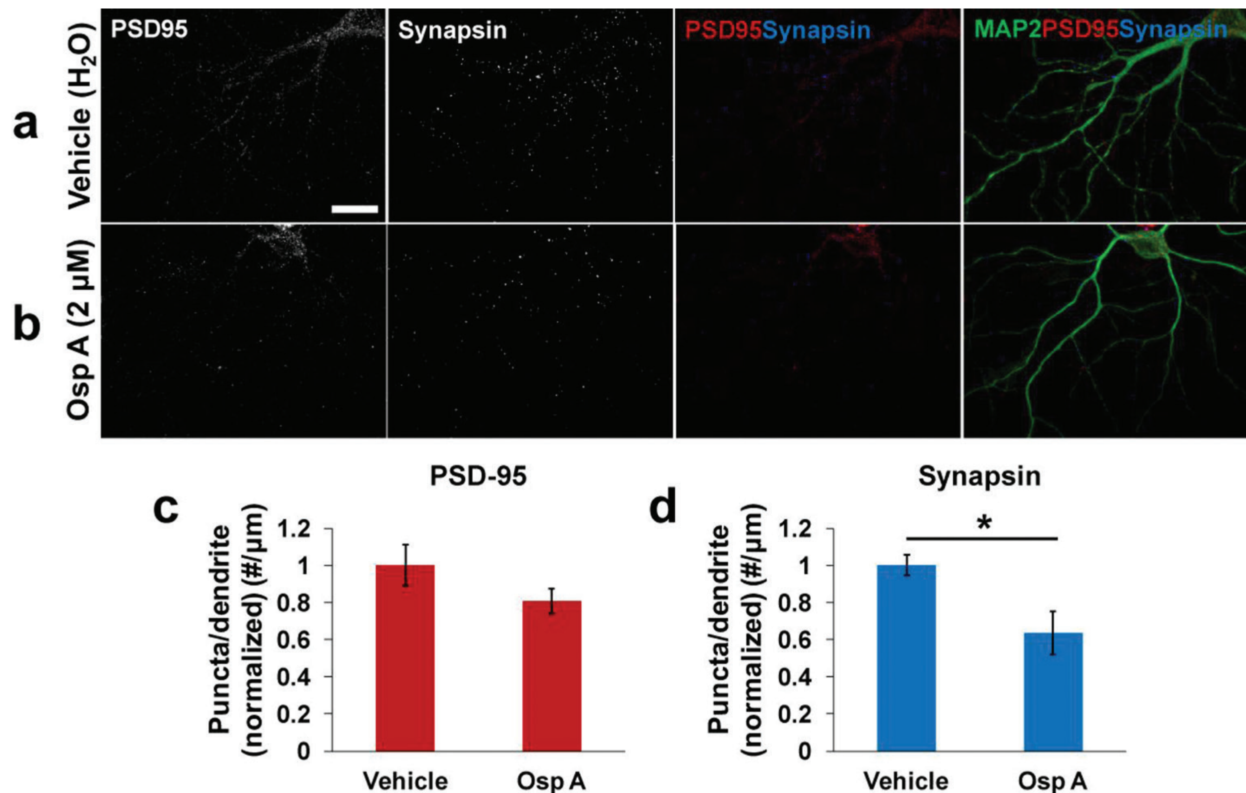

Figure 2. OspA and synaptic density. (a) Fluorescent images showing rat primary hippocampal neurons treated with vehicle (endotoxin-free water). (b) Fluorescent images showing rat primary hippocampal neurons treated with ospA (2 μM). (a) and (b) Neurons stained with anti-PSD-95 (postsynaptic protein), anti-synapsin (presynaptic protein), merge of PSD-95 and synapsin, merge of PSD-95, synapsin, and MAP2 (dendrite) from left to right are shown. (c) The postsynaptic density was measured by the number of postsynaptic sites (puncta) per length of selected dendrite. The postsynaptic density was not affected by ospA ($P > 0.05$). (d) The presynaptic density was measured by the number of presynaptic sites (puncta) per length of selected dendrite. The presynaptic density decreased significantly by ospA ($P = 0.041$).

3.3. Mechanism of synaptic dysfunction induced by bacterial lipoproteins

A recent study demonstrated that viral infection leads to cognitive dysfunction by microglial engulfment of presynapses via the complement C3 pathway [53]. Another recent study showed that viral infection impairs synaptic function via glycogen synthase kinase 3 (GSK-3) activation and intracellular accumulation of Aβ [54]. Thus, an increasing number of studies are being reported that elucidate the mechanism underlying synaptic dysfunction induced by viral infection. Although there is evidence that bacterial lipoprotein ospA also damages presynapses (**Figure 2**), information as to how bacterial infection impairs synaptic function is lacking. Three possible mechanisms may account for synaptic dysfunction during bacterial infection. First, bacterial lipoproteins damage synapses via activation of inflammatory pathways (e.g., TLR2 and TLR4) as discussed in Section 3.1. Second, bacterial lipoproteins damage synapses through neurotransmitter-mediated excitotoxicity. It has been demonstrated that the level of quinolinic acid, the N-methyl-D-aspartate (NMDA) receptor agonist, was elevated significantly in the CSF of Lyme neuroborreliosis patients [55]. The

NMDA receptor mediates synaptic transmission, plasticity, and excitotoxicity in the central nervous system (CNS) and it exhibits excitotoxic effects when an excessive flux of calcium occurs by the increase of a neurotransmitter such as glutamate [56]. However, it is yet to be determined whether the presence of bacterial lipoproteins directly mediates the elevation of quinolinic acid. Third, bacterial lipoproteins damage synapses through physical interaction with synapses independent of biochemical pathways (i.e., inflammation and receptor activation). It has been suggested that the physical properties of proteins (e.g., aggregate pattern and size) is a crucial determinant in mediating pathogenic toxicity [57, 58]. This toxicity occurs independent of their sequences or lengths [59] in a manner that is similar to the aggregation of Aβ in Alzheimer's disease [60] or α-synuclein in Parkinson's disease [61]. Previous studies showed that Pam3-Cys, the synthetic N-terminus of ospA, self-assembled and showed aggregating potential *in vitro* assays [58, 62], which can be related to brain tissue damage including the disruption of synaptic function.

4. Conclusions

This chapter describes the new roles of apoE4 and ospA as major pathogenic endogenous and exogenous lipoproteins, respectively, in neuronal outgrowth and function by discussing recent experimental data in the context of previous reports. Recent studies show that apoE4 enhances neuronal adhesion and axonal outgrowth *in vitro* when it acts alone without lipids. New studies also demonstrate the possibility that ospA can induce synaptic dysfunction by damaging exclusively presynaptic sites. These results contribute to a new understanding of how lipoproteins are involved in developing neuropathology by interacting with neurons. Future studies should focus on the specific mechanism of interaction between apoE4 and neurons and the effect of ospA on synaptic function using *in vivo* models. Along with many pathogenic pathways governed by various cell types in the brain (e.g., microglia, astrocytes, and oligodendrocytes), the effect of pathogenic factors on neuronal activity provides a deeper understanding of structural and functional abnormality in neurodegeneration and neuroinflammation [63]. Understanding the interaction between lipoproteins and neurons in the brain should yield new approaches to the treatment of brain injuries and brain disorders.

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