Published in final edited form as:

Clin Lipidol. 2010 August 1; 51(4): 555–573. doi:10.2217/CLP.10.37.

Apolipoproteins in the brain: implications for neurological and psychiatric disorders

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Abstract

The brain is the most lipid-rich organ in the body and, owing to the impermeable nature of the blood–brain barrier, lipid and lipoprotein metabolism within this organ is distinct from the rest of the body. Apolipoproteins play a well-established role in the transport and metabolism of lipids within the CNS; however, evidence is emerging that they also fulfill a number of functions that extend beyond lipid transport and are critical for healthy brain function. The importance of apolipoproteins in brain physiology is highlighted by genetic studies, where apolipoprotein gene polymorphisms have been identified as risk factors for several neurological diseases. Furthermore, the expression of brain apolipoproteins is significantly altered in several brain disorders. The purpose of this article is to provide an up-to-date assessment of the major apolipoproteins found in the brain (ApoE, ApoJ, ApoD and ApoA-I), covering their proposed roles and the factors influencing their level of expression. Particular emphasis is placed on associations with neurological and psychiatric disorders.

Keywords

apolipoprotein; brain; CNS; lipid; neurological disease

Structure & function of apolipoproteins

The definition of ‘apolipoprotein’ can be some-what misleading. Textbooks and medical dictionaries tend to define apolipoproteins as “Any of various proteins that combine with a lipid to form a lipoprotein, such as HDL and LDL” [301], or “The protein components of lipoproteins, which remain after the lipids to which the proteins are bound have been removed” [302]. However, there are apolipoproteins, such as ApoD and Apo(a), that are not capable of forming even a nascent lipoprotein particle on their own, but rather associate with lipoproteins via hydrophobic surface features or through disulfide linkage to another

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Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

‘integral’ apolipoprotein [1,2]. For example, ApoD is structurally related to the lipocalin family, and its function as a lipid-transport protein and its identity as a component of either peripheral or CNS lipoproteins is still not completely resolved. However, it is clear that a hydrophobic ligand-binding pocket is a prominent feature of ApoD, which is important for high-affinity binding of arachidonic acid and certain steroid hormones [3]. It may be argued that if we are to consider ApoD as an ‘apolipoprotein’, then possibly other lipid-binding proteins, such as α -synuclein (fatty acid binding) and the Niemann Pick type C1 protein (lysosomal cholesterol transport), could be similarly considered to have ‘apolipoprotein functions’ [4,5]. For the purpose of this article, we have not discussed all proteins that may bind/transport lipid, rather, we have focused on those proteins that have both been historically referred to as apolipoproteins and have been clearly detected in the brain or cerebrospinal fluid (CSF) at the protein level.

We should also acknowledge that a great volume of data related to apolipoprotein mRNA or protein expression, especially when the human brain is considered, may only be relevant for a specific brain region at a specific time in development or aging. Related to this, we have assembled apolipoprotein gene microarray data from a study, first described by Weickert *et al.* in 2009 [6], accessible at the National Center for Biotechnology Information Gene Expression Omnibus data-base [7,8,303], which highlights the dramatic changes in the expression of the quantitatively major apolipoproteins expressed in the human brain (Figures 1–5). These data indicate that, of the 22 apolipoprotein genes analyzed in the prefrontal cortex, only three (*APOD* [Figure 3C], *APOE* [Figure 3D] and *CLU* [Figure 4C]) are expressed at high levels. Furthermore, the expression of all three of these genes is dramatically affected by age, with *APOD* and *CLU* increasing five- to ten-fold from neonatal to adult ages, and *APOE* levels dropping by approximately 50% over the same period (Figures 3 & 4). These changes have also been confirmed previously at the protein level [9,10]. Four other genes are expressed at levels above background (~60 arbitrary expression units). We found that *APOC1* mRNA levels (Figure 2C), while quite variable, are higher within the first 5 years of life, gradually dropping to adult levels. By contrast, *APOC2* (Figure 2D) is at the limit of detection in most babies, but increases during the school-age period, suggesting that while *APOC1* is being downregulated *APOC2* may be upregulated. *APOL2* mRNA (Figure 5A) increases gradually within the first decade of life, while *APOL3* mRNA (Figure 5B) is expressed at lower levels, but follows a similar trend. Furthermore, it must be considered that just because a result may be at or below the limit of detection by microarray, it does not conclusively mean that a gene is not being expressed, albeit at lower levels. With these caveats in mind, we focus our attention to what is known about the major apolipoproteins in the brain regarding their role in neurological disorders.

The apolipoprotein family of proteins play an essential role in physiology by facilitating the transport of lipids and lipophilic substrates throughout the aqueous fluids of the body. In general, a key feature of apolipoproteins (aside from ApoD and Apo[a]) is that they possess highly conserved amphipathic α -helices, which are responsible for their lipid-binding capability [11,12]. Most apolipoproteins also contain specialized functional domains, such as a signal peptide (that directs newly translated peptides towards the secretory pathway) and a receptor binding domain (RBD). The major binding partner for the apolipoprotein RBD in the CNS is the LDL receptor (LDLR) family of receptors (which includes LDLR, ApoER2, VLDLR, MEGF7, LRP1, LRP1b and LRP2) [13,14], and this interaction facilitates the tightly regulated delivery of lipids and substrates to specific cells in the brain, as well as regulating signal transduction pathways [15]. It is now also recognized that apolipoproteins are involved in several functions beyond lipid transport (discussed in detail later) [12].

Unique features of CNS lipid/cholesterol & apolipoprotein metabolism

The brain is the most cholesterol-rich organ in the body. While the brain is only 2% of total body mass, it contains 25% of total unesterified cholesterol in the body [16]. Virtually all cholesterol produced in the brain (>99.5%) remains unesterified, and the majority of this is present within myelin sheaths and, to a lesser degree, plasma membranes of glial and neuronal cells [17]. Lipid metabolism in the CNS is unique in that there is virtually no exchange of cholesterol and lipoproteins from the peripheral circulation, owing mostly to the impermeable nature of the BBB [18,19]. Thus, cholesterol in the CNS exists in a compartment distinct from the rest of the body. This has been clearly demonstrated in numerous studies, where radiolabelled cholesterol injected into the periphery cannot be detected in the CNS [20–22]. Thus, practically all cholesterol present in the CNS is synthesized *de novo* in brain cells, and is efficiently recycled within the CNS, having a half-life of between 1 and 5 years in comparison with a few hours in the periphery [23,24].

Distinct differences also exist in the composition of lipoprotein particles and the apolipoproteins present in the CNS compared with the plasma and peripheral tissues. The transport of lipids throughout the CNS is carried out predominantly by specialized HDL-like lipoproteins, unlike the rest of the body, where a broad range of lipoprotein densities are utilized [25–27]. The most abundant apolipoproteins in the CSF are ApoE (0.3 ± 0.2 mg/dl) and ApoA-I (0.37 ± 0.08 mg/dl) with lower quantities of ApoJ, ApoD, ApoA-II and ApoA-IV [27,28]. The apolipoproteins ApoA-I, ApoE and ApoJ are predominantly located on distinctly independent lipoprotein particles within the CSF. ApoJ lipoproteins are typically smaller, and contain less lipid than ApoA-I and ApoE lipoproteins [29]. Astrocytes are the major source of ApoE and ApoJ in the CSF, and *in vitro* studies, examining the profile of lipoproteins secreted by murine astrocytes, have corroborated these *in vivo* observations [30]. A review focusing on lipoprotein biogenesis in the brain compared with the plasma compartment provides information on similarities and differences regarding lipid-transfer proteins and other factors [31].

Of the 22 known apolipoproteins, nine have been detected at the protein level, to varying degrees, in the CNS, and evidence of significant mRNA expression has only been found for eight (*APOC1*, *APOC2*, *APOD*, *APOE*, *CLU*, *APOL2* and *APOL3* [Figures 2C, 3C, 3D, 4C, 5A & 5B] and text regarding *APOA4*). It is possible that some brain apolipoproteins were actually synthesized outside the CNS; thus, we would not expect their encoding mRNA to be found in brain cells. For example, the transit of peripherally derived apolipoproteins into the CNS has been suggested for ApoA-I and ApoA-II, as they may enter the CSF via the choroid plexus [26].

Altered cholesterol metabolism and polymorphisms within the apolipoprotein genes have been associated with several neurological and psychiatric conditions, thus emphasizing the important role these factors play in CNS physiology. The purpose of this article is to provide an up-to-date account of the most abundant apolipoproteins present within the CNS.

ApoE

ApoE is highly expressed in the CNS, and the brain is the second largest site of ApoE synthesis in the body [32]. There is no exchange of brain-derived and peripheral ApoE; therefore, the CNS represents a distinct compartment in terms of ApoE metabolism [19]. Astrocytes are the primary source of ApoE in the brain; however, ApoE is also expressed by oligodendrocytes, ependymal layer cells, microglia and, under certain physiological circumstances, in neurons [33–41]. The upstream promoter region of the *APOE* gene contains several regulatory regions that can bind a variety of different transcription factors (TFs) [42–49]. One of the best characterized mechanisms of *APOE* upregulation is

regulation by the liver X receptors (LXRs) and retinoid X receptors (RXRs), usually in response to increased levels of cellular cholesterol and oxy-sterols [44]. LXR and RXR also activate expression of the membrane-bound lipid-transport proteins ABCA1 and ABCG1, which are involved in transferring lipids to ApoE in the brain [50–52]. Importantly, a lack of these transport proteins results in poorly lipidated ApoE, which is turned over more rapidly in the brain [53].

ApoE plays a major role in cholesterol and phospholipid transport in the CNS. However, *APOE*^{-/-} mice display only a mild phenotype, and there is evidence to suggest that ApoD may play a compensatory role, as this protein is increased 50-fold in these animals [54,55]. Briefly, ApoE is secreted by astrocytes as a nascent lipoprotein [56–58], cholesterol is then transferred to ApoE, predominantly via ABCA1, which is expressed on astrocytes, microglia and neurons [50,52]. ABCG1 may also play a role in transferring lipids to ApoE, as it matures into a lipidated lipoprotein particle [52], and there is evidence that ABCG1 can regulate brain lipid homeostasis [51,59–61]. It has been proposed that, in astroglial cells, endogenously synthesized ApoE-containing lipoproteins, and partially lipidated ApoA-I-containing lipoproteins formed via the action of ABCA1, accept additional lipids via ABCG1, which promotes maturation of a larger lipoprotein particle [51]. However, *in vivo* studies in mice suggest that ABCG1 may not play the major role in ApoE lipidation [60].

The transport of cholesterol to cells within the CNS is then mediated by the interaction of ApoE with cell surface receptors, which are abundant in the brain (including LDLR, LDL receptor-related protein [LRP1], VLDL receptor [VLDLR], LR8/ApoE receptor-2 and LRP2), followed by endocytosis (reviewed in [62]).

In humans, ApoE exists as three major isoforms – ApoE2, ApoE3 and ApoE4 – which differ in their Cys/Arg composition at positions 112 and 158. ApoE2 contains Cys¹¹², Cys¹⁵⁸; ApoE3 contains Cys¹¹², Arg¹⁵⁸; and ApoE4 contains Arg¹¹², Arg¹⁵⁸ [63]. Inheritance of ApoE4 results in a dose-dependent increase in the risk of developing late-onset Alzheimer's disease (AD), and is the most important genetic risk factor known for this illness, whereas ApoE2 is associated with decreased risk [64,65]. This finding has been replicated in many studies, including two recent genome-wide association studies [66,67]. Additionally, possession of ApoE4 is associated with adverse outcomes in several CNS pathological states, including traumatic brain injury (TBI), spinal cord injury (SCI) and stroke [68–70]. Interestingly, a meta-analysis study of ApoE and Parkinson's disease (PD) found that the *APOE* ε2 allele is associated with a higher disease risk [71]. These findings highlight the importance of ApoE in neurobiology. The precise mechanism by which differences in ApoE isoform increase risk in these circumstances is not completely understood; however, ApoE is known to play a variety of roles in the brain, in addition to lipid transport, which may be of relevance.

ApoE is found to colocalize with amyloid-β (Aβ) in the AD brain, and this occurs primarily through interaction with the lipid-binding amphipathic α-helical region of ApoE [65,72–75]. ApoE plays a role in enhancing the clearance and degradation of Aβ in the brain. The binding of ApoE to Aβ forms a complex that can interact with ApoE receptors, resulting in endocytosis of Aβ, and either removal across the BBB or intracellular degradation in microglia and astrocytes [76–84]. *In vitro* studies using lipid-associated ApoE (which is physiologically more relevant than lipid-free ApoE) have found that ApoE3 binds Aβ with approximately 20-fold greater avidity than ApoE4, and this is hypothesized to result in ApoE4 being less efficient at Aβ clearance [85]. In accordance with this, total Aβ levels are increased in the brain tissue of AD and TBI patients who carry ApoE4 [86,87].

In transgenic mouse models of AD, expression of mutant human amyloid precursor protein (*hAPP*) results in intense A β deposition, which, interestingly, is reduced on an *APOE*^{-/-} background [88]. This indicates that murine ApoE facilitates A β plaque formation. In stark contrast, the addition of human ApoE isoforms to this mutant *hAPP/APOE*^{-/-} model results in a further delay in A β deposition (ApoE2 > ApoE3 > ApoE4) [89–91]. The cellular mechanism(s) underlying these effects and the observed interspecies difference are not entirely understood; however, these findings highlight the influential role ApoE plays in modulating A β deposition.

Following peripheral nerve injury, secretion of ApoE by resident macrophages is dramatically increased, resulting in a 100–200-fold increase in ApoE levels at the site of injury, where it plays an important role in the redistribution of lipids to regenerating neurites [32,36,92]. ApoE is increased following TBI, and experimentally induced brain lesions and CNS neurons are capable of synthesizing ApoE in response to stressful stimuli, such as cerebral infarction and hypoxia [41,93–97]. Several lines of evidence indicate this increase may be conferring a neuroprotective and regenerative effect in the CNS [95,98,99]. Of potential relevance to this, the regulatory region of the *APOE* gene contains binding sites for several inflammatory response-associated TFs (reviewed in [46]), most notably nuclear factor κ B (NF- κ B) [47]. NF- κ B regulates the expression of over 200 genes, thus enabling it to coordinate the cellular response to a wide range of stressful stimuli. The regulatory pathways of NF- κ B are elaborate, and this TF can play a major role in several responses, including cell survival, inflammation and immune regulation [100]. Several studies have searched for differences in ApoE expression associated with AD status or ApoE isoform with varying results [101–112]. However, overall, it appears that the ApoE isoform is the more influential regulator of ApoE protein level, with lower total ApoE levels associated with the $\epsilon 4$ allele [110,113].

ApoE is proposed to be involved in several other functions, including immunomodulation, oxidative stress, stabilization of neuronal microtubules, synaptic plasticity and apoptosis [114–119]. The contributions that these ApoE-related functions may make toward normal physiology and AD remain to be established.

ApoJ/clusterin

ApoJ, also known as clusterin (encoded by the *CLU* gene), is a predominantly secreted 75–80-kDa disulfide-linked heterodimeric glycoprotein, which serves as both a lipid-transport protein (with the ability to induce cholesterol efflux) and a molecular chaperone in the cellular stress response [120–122]. In addition, lower mass versions of ApoJ (~49–60 kDa) are observed in the cytosol and nucleus, particularly during cellular stress (reviewed in [123]). The promoter region of the *CLU* gene contains several response elements for transcription factors involved in the response to cellular stress [124–127]. ApoJ is dramatically upregulated during cellular stress, and is able to bind and stabilize a diverse range of misfolded proteins, including several involved in neurodegenerative conditions, such as A β , Lewy bodies and prion deposits [128–130]. In the extracellular space, ApoJ binds these substrates, inhibiting an inflammatory response and promoting endocytosis by phagocytic cells via interaction with the megalin/LRP-2 receptor [131,132]. ApoJ also promotes the phagocytosis of apoptotic debris by this same mechanism [133,134].

ApoJ is produced in several regions of the brain, primarily by astrocytes, but also in pyramidal neurons of the hippocampus and Purkinje neurons in the cerebellum [135,136]. Neuronal levels of ApoJ protein can increase significantly following stressful conditions [137,138]. Furthermore, increased expression of brain ApoJ is observed in several pathological conditions; AD, multiple sclerosis, TBI, SCI, gliomas, ischemia, epilepsy,

chemically induced lesions and aging [94,95,139–142]. It seems likely that ApoJ is playing a protective role in these injurious states, as *APOJ*^{-/-} mice display significantly impaired recovery to cerebral ischemic insult [143].

In AD, ApoJ levels are particularly increased in regions most afflicted with AD pathology: the hippocampus and entorhinal cortex [144,145]. ApoJ can bind Aβ fibrils, and is associated with Aβ plaques, neuropil threads and cerebrovascular amyloid deposits [144,146,147]. *In vitro* and experimental animal models have demonstrated that ApoJ is able to inhibit Aβ aggregation and facilitate its clearance across the BBB [148,149]. There is evidence that some of these processes are regulated in a cooperative manner with ApoE [150]. Interestingly, *APOJ*^{-/-} on a mutant hAPP mouse background results in decreased levels of Aβ deposition, analogous to the result observed with *APOE*^{-/-} mice (see previously). By contrast, double knockout of both *APOE* and *APOJ* on this hAPP background results in dramatically increased Aβ deposition [150]. The mechanism(s) responsible for this paradoxical observation is not entirely understood. The importance of ApoJ in AD pathogenesis is further underlined by two recent genome-wide association studies linking polymorphism within the *CLU* gene with a significantly increased risk of AD [66,67]. In fact, after *APOE* ε4, this polymorphism is the second most influential genetic risk factor for late-onset AD.

In addition, there is emerging evidence to suggest that ApoJ may play a role in neuritic outgrowth. Similar to ApoE and ApoD, ApoJ can escape the secretory pathway and enter the cytosol under certain stressful conditions [151–154], and experiments by Kang *et al.* [155], have reported that cytosolic ApoJ can bind with the microtubule-destabilizing protein superior cervical ganglia neural specific 10-like protein SCLIP, resulting in enhanced neurite outgrowth. This is of interest when it is considered that neuritic dysfunction is a major part of many neurodegenerative illnesses [156,157]. Therefore, this finding may represent another potential mechanism by which ApoJ may exert a neuroprotective effect.

ApoD

ApoD is a 27–33-kDa glycoprotein that does not share significant degrees of homology with other apolipoproteins but, instead, is structurally more similar to the lipocalin family (which includes ApoM). Thus, ApoD cannot support the synthesis of nascent lipoprotein particles [3,158,159]. Early studies suggested that ApoD binds lipids, including cholesterol, arachidonic acid and a variety of steroids such as pregnenolone, dihydrotestosterone, testosterone, dehydroepiandrosterone and estradiol [160–163]. The ApoD crystal structure reveals an eight-stranded, antiparallel β-barrel flanked by an α-helix [3]. ApoD contains a binding pocket that is highly specific for certain lipids (progesterone and arachidonic acid). However, other lipids may interact via an alternate mechanism [164]. ApoD has a number of ‘exposed’ hydrophobic residues residing in three out of its four extended loops [3]. This generates a region of surface hydrophobicity close to the open end of the binding pocket, which facilitates ApoD association with HDL particles, and also permits insertion of ApoD into cellular lipid membranes [3]. These exposed hydrophobic residues may also permit low-affinity binding with many of the lipids mentioned previously.

ApoD is expressed in several regions of the brain in both cortex and cerebellum. Various human and mammalian studies, utilizing northern and western blotting analyses, have demonstrated that the majority of ApoD is produced in white matter and the subarachnoid space [165,166], but also in the dorsolateral prefrontal cortex, occipital cortex, substantia nigra, hippocampus and cerebellum [9,167]. Brain ApoD is synthesized and excreted predominantly by oligodendrocytes and astrocytes. Under normal circumstances, neuronal

ApoD protein, but not mRNA, is also observed in Purkinje neurons and, to a lesser degree, in cortical neurons; however, this may be increased under pathological conditions [168].

Interestingly, ApoD expression is altered in several disease states and normal aging. ApoD expression is increased in the dorsolateral prefrontal cortex during normal aging and in patients with schizophrenia [9,167]. The dorsolateral prefrontal cortex is a region that plays a critical role in attention and working memory and is implicated in psychiatric disorders, such as schizophrenia, autism and depression [169,170]. In AD, ApoD is increased in the CSF and affected brain regions (including hippocampus, frontal cortex and temporal cortex) [103,171,172], plus an increased incidence of neuronal ApoD immunostaining, is observed in cortical neurons, and appears to correlate with neurofibrillary tangle density (a hallmark of AD pathology) [168,173]. ApoD is also increased in the substantia nigra of PD patients, and in the CSF of patients with meningoencephalitis, stroke, dementia and motor neurone disease [171,174]. Furthermore, animal models have demonstrated an increase in ApoD expression following TBI, stroke, kainic acid injection and an entorhinal cortex lesion, and an approximately 30-fold increase in murine models of the human cholesterol-storage disorder, Niemann–Pick disease [55,175–179].

The increased expression of ApoD observed in such a diverse range of injurious/pathological conditions may reflect a general role of ApoD in the stress response and neuroprotection. In accordance with this theory, the promoter region of the *APOD* gene contains several consensus sites for factors involved in the stress response, including NF- κ B and AP1 (for reviews see [154,180]).

Increased oxidative stress is a key feature in both normal aging and many neurological disorders [9,181–183], and recent studies strongly support an antioxidant role of ApoD in the brain that is correlated with its ability to prevent lipid peroxidation [184]. Knockout of *APOD* in mice, and glial lazaro, its homolog in *Drosophila*, results in increased peroxidation of brain lipids, decreased life expectancy and impaired performance in tests of behavior and learning [184,185]. Conversely, overexpression of human ApoD in these animal models has been demonstrated to decrease lipid peroxidation, plus enhance neuroprotection and life expectancy in response to experimentally induced stressors [184,186–188].

There is also evidence suggesting that ApoD may play a role analogous to ApoE in the redistribution of cholesterol and phospholipids during nerve regeneration and remyelination. Nerve-crush injury to the rat sciatic nerve results in an approximate 500-fold increase in ApoD protein and an approximate 40-fold increase in mRNA [189,190]. Similarly, following stroke, ApoD is increased in pyramidal neurons and oligodendrocytes within the infarct area [176]. In fact, there are several lines of evidence indicating a similar or complimentary/overlapping function of ApoD with ApoE. These are that ApoD can also bind with A β plaques [191], ApoD protein is increased approximately 50-fold in the frontal cortex of *APOE*^{-/-} mice [55], both ApoD and ApoE are increased in the hippocampus following an entorhinal cortex lesion [55] and kainic acid exposure [177], and ApoE isoform may influence the concentration of ApoD in the hippocampus and CSF [171]. It has been speculated that colocalization with compact A β plaques may indicate a role for ApoD in the aggregation and/or removal of A β ; however, this is yet to be demonstrated [191].

The importance of ApoD in AD pathophysiology is reinforced by genetic studies [192–194]. Interestingly, an intronic polymorphism within the *APOD* gene, found exclusively in people of African heritage, is significantly associated with increased AD risk [194], but only when the *APOE* ϵ 4 allele is also present. Since this sequence change linked to AD risk is not in a

coding region, it would be interesting to determine if this polymorphism can alter *APOD* mRNA splicing and/or gene regulation.

In addition to the association of ApoD with neurodegenerative disease, the region on chromosome 3 encoding *APOD* has been tightly linked with schizophrenia in a genome-scan meta-analysis [195], and an *APOD* polymorphism is associated with long-term clinical outcome [196]. Interestingly, the atypical antipsychotic drug, clozapine, has been demonstrated to increase ApoD levels in the rodent brain, and it remains possible that this increase plays an underlying therapeutic role in this drug's mechanism of action [197,198].

ApoA-I

ApoA-I is a 27-kDa protein, which is one of the most abundant apolipoproteins in the CSF, and ApoA-I protein, but not mRNA, has been detected in brain tissue [25,26,199–201]. In support of this, we find that *APOA1* mRNA is at very low/absent levels throughout human development and adulthood (Figure 1A). ApoA-I in the CNS is believed to be plasma derived, crossing the BBB at the choroid plexus [25,26]. There is also evidence to suggest brain endothelial cells are able to synthesize ApoA-I and contribute to the CNS pool [202,203].

Decreased levels of ApoA-I have been reported in the brain tissue and CSF of schizophrenic patients [201]. Decreased levels were also observed, on average, in the liver, red blood cells and serum; however, there was no correlation between peripheral and CNS levels within individual patients. This indicates that, although brain ApoA-I originates in the periphery, the mechanisms regulating ApoA-I concentration and metabolism in CNS are clearly independent.

Interestingly, a polymorphism in the promoter region of the *APOA1* gene (−75 A/G) has been linked with an earlier age of AD onset, whereby individuals homozygous for the A allele (at this location) develop AD, on average, 8 years earlier than heterozygotes [204]. This allele is associated with a modest increase in plasma ApoA-I and, depending on the *in vitro* model used, an increased rate of ApoA-I expression [205–208]. Altered levels of ApoA-I in the AD brain have not yet been clearly established. One study has observed an increase of ApoA-I in the CSF of AD and dementia patients [209], while another study found no difference [200]. We have found that ApoA-I protein is significantly decreased in cortical homogenates from AD patients (n = 15), compared with controls (n = 8) [ELLIOTT DA & GARNER B, UNPUBLISHED DATA].

The function(s) of brain ApoA-I are not entirely clear. ApoA-I plays a major role in peripheral cholesterol transport and it seems probable that ApoA-I plays an analogous role in the CNS [199]. In support of this, ApoA-I is an important lecithin-cholesterol acyltransferase (LCAT) activator and, as LCAT is expressed in the brain [166], this provides a plausible mechanism for CNS cholesterol transport. ApoA-I has also been demonstrated to bind with the extra-cellular domain of APP (which can be cleaved to produce Aβ [210]), and has been found to co-localize with occasional Aβ plaques in the cortex of AD patients [200,211]. This raises the possibility that ApoA-I could influence APP cleavage and Aβ aggregation and/or clearance; however, this is yet to be clarified. A greater understanding of both the functions ApoA-I fulfills in the brain, and the mechanisms regulating ApoA-I metabolism in the CNS, should yield insights into its association with schizophrenia and AD.

Less-abundant brain apolipoproteins

Other apolipoproteins have been detected in the brain, albeit at much lower levels than those discussed. Of particular interest, ApoC-I mRNA and protein has been detected in brain astrocytes and polymorphisms of the *APOC1* gene are associated with altered transcription and increased incidence of AD [212–217]. Interestingly, ApoC-I is known to block ApoE receptor interaction, and expression of *APOC1* decreases with age (Figure 2C) [218–220].

ApoA-IV is synthesized in the hypothalamus and colocalizes predominantly with neurons and, to a lesser extent, glia in this brain region [221,222] (of note, data presented in Figure 1C, where *APOA4* expression is negligible, is from the prefrontal cortex [Brodmann area 46], not hypothalamus). Expression of ApoA-IV is increased following a high-fat meal, and ApoA-IV has been demonstrated to play a centrally acting role in satiety [223–225]. There is also evidence to suggest that a polymorphic version of ApoA-IV, which is more efficient at activating LCAT, may be associated with increased AD risk [226].

APOL2 is expressed in the brain (Figure 5A), with the level of expression being increased in schizophrenia [227]. In addition, polymorphisms in this gene have been linked to schizophrenia risk [228]. However, the biological function of ApoL-II in the brain is currently unclear [229].

ApoA-II, ApoC-II, ApoC-III and ApoH proteins have all been detected in the CNS [25,27,28,200,230–232]. However, the regulation and possible roles of these apolipoproteins in the CNS is poorly understood [222,226,233].

Future perspective

Our current understanding of the major apolipoproteins in the brain strongly suggests that ApoD, ApoE and ApoJ exert beneficial effects in several neurological conditions. Thus, it is tempting to speculate that a therapeutic intervention aimed at increasing expression of these apolipoproteins may be of clinical benefit. Brain ApoE levels in mice are increased upon administration of the LXR agonist, TO-901317, and in transgenic models of AD, this is associated with decreased A β production [234–236]. As discussed previously, the antipsychotic drug clozapine is able to increase brain ApoD levels, and investigations are ongoing to see whether this clozapine-induced ApoD increase may be of benefit in a broader range of neurological conditions [237].

A greater understanding of brain apolipoprotein biology and the mechanisms responsible for polymorphism-associated disease risk, should provide fresh insight into the underlying mechanisms of neurological disease and uncover novel therapeutic targets. More specifically, further elucidation of apolipoprotein interactions with the LDLR family of receptors, and the role this plays in neurological and psychiatric conditions, may lead to therapeutics that directly target these receptors. Of relevance to this, it has been found that mimetic peptides, derived solely from the receptor-binding domain of ApoE, are able to exert strong bioactive effects [238–240]. These peptides have been demonstrated to confer a neuroprotective effect in animal models of TBI, multiple sclerosis, cerebral hemorrhage and AD [241–246]. Furthermore, these studies highlight that the entire holoprotein of an apolipoprotein does not necessarily need to be present in order to confer a beneficial effect, and it is conceivable that future research may identify small functional peptides derived from ApoD and ApoJ [247]. In addition, technology is currently being developed that aims to promote the transport of therapeutic peptides across the BBB and make them more resistant to degradation [247–250].

Acknowledgments

Brett Garner is supported by a Research Fellowship from the Australian Research Council (ARC Grant No. FT0991986). David A Elliott is supported by a Viertel Postdoctoral Fellowship awarded by Alzheimer's Australia. Cyndi Shannon Weickert is supported by the Schizophrenia Research Institute, New South Wales Health, Macquarie Group Foundation, Prince of Wales Medical Research Institute and the University of New South Wales. The authors would like to thank their collaborator Maree J Webster for her valuable contribution to the construction of the developmental microarray results. This work was supported by funding from the NIH National Institute of Mental Health Intramural Research Program.

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Figure 1. Expression of apolipoproteins APO-A1, -A2, -A4 and -A5 during development of the human prefrontal cortex

(A) Expression of APOA1. (B) Expression of APOA2. (C) Expression of APOA4. (D) Expression of APOA5. Data are derived from an Affymetrix GeneChip (HG-U133_Plus_2) microarray study conducted by Harris *et al.* [8] and accessible at the National Center for Biotechnology Information Gene Expression Omnibus database [7,303]. Fresh-frozen post-mortem prefrontal cortex tissue (Brodmann area 46) was obtained from 44 individuals varying from 0 to 49 years of age. RNA was extracted from these samples and hybridized to HG133plus2.0 GeneChips. The data were used to examine patterns of gene expression over the course of human postnatal developmental and aging. Seven developmental periods are defined as neonate (<3 months: black), infant (3 months to <1 year: green), toddler (1 year to <5 years: red), school age (5 years to <13 years: dark blue), teenage (13 years to <20 years: light blue), young adult (20 years to <26 years: yellow) and adult (35 years to <50 years: purple). Data are plotted for both sexes (males: circles; females: triangles). Gene expression values that are less than 60 are below the limit of reliable detection, and genes with expression values in this range are, therefore, considered not to be expressed in the brain. The p-values shown were calculated as follows. Affymetrix Microarray Suite (MAS5.0) was used for image processing and data acquisition. The Bioconductor package was used to compute normalized expression values from the Affymetrix.cel files. Statistical analysis was performed using R and Bioconductor software (Free Software Foundation, Boston, MA, USA). Probe sets that met the criteria of being 50% present in at least one of the age subgroups were retained in the analysis (33,210 probe sets retained; 61% of total number). Differential gene expression across chronological age was analyzed by linear regression comparing age (log scale) with gene expression (log scale) as the dependent variable. Statistical models in Supplemental Affymetrix Microarray Suite (MAS 5.0) was used for image processing and data acquisition.

Figure 2. Expression of apolipoproteins *LPA* and *APO-B*, *-C1* and *-C2* during development of the human prefrontal cortex

(A) Expression of *LPA*. **(B)** Expression of *APOB*. **(C)** Expression of *APOC1*. **(D)** Expression of *APOC2*. See caption from Figure 1 for details of how these graphs were obtained.

Figure 3. Expression of apolipoproteins APO-C3, -C4, -D and -E during development of the human prefrontal cortex

(A) Expression of APOC3. (B) Expression of APOC4. (C) Expression of APOD. (D) Expression of APOE. See caption from Figure 1 for details of how these graphs were obtained.

Figure 4. Expression of apolipoproteins *CLU* and *APO-F*, *-H* and *-LI* during development of the human prefrontal cortex

(A) Expression of *APOF*. (B) Expression of *APOH*. (C) Expression of *CLU*. (D) Expression of *APOLI*. See caption from Figure 1 for details of how these graphs were obtained.

CLU: Clusterin.

Figure 5. Expression of apolipoproteins APO-L2, -L3, -L4, -L5, -L6 and -M during development of the human prefrontal cortex

(A) Expression of APO-L2. (B) Expression of APO-L3. (C) Expression of APO-L4. (D) Expression of APO-L5. (E) Expression of APO-L6. (F) Expression of APO-M. See caption from Figure 1 for details of how these graphs were obtained.