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The neurobiology of APOE in schizophrenia and mood disorders

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1. ABSTRACT

APOE is a major component of several lipoproteins. In addition to its role as a lipid transport protein APOE also serves a dual role as a glial derived, synaptic signalling molecule and thought to play an important role in synaptic plasticity and cognition. Polymorphisms within the *APOE* gene have been associated with the incidence of Alzheimer's disease. In light of the similarities in the cognitive deficits experienced in both Alzheimer's disease and schizophrenia as well as the comorbidity of depression in Alzheimer's disease, aberrant APOE signalling has been implicated in the pathologies of schizophrenia and mood disorders. The schizophrenia candidate gene, reelin, also shares common receptors with APOE, further supporting a role for APOE in the pathology of these disorders. This review will summarise the current understanding of the involvement of APOE and its receptors in the symptomatology and pathology of schizophrenia and mood disorders and the implications of this involvement for drug treatment.

2. INTRODUCTION

Apolipoprotein E is a constituent of several lipoproteins and serves a primary role in facilitating the transport and uptake of lipids. Beyond this role, APOE is also involved in cytoskeletal and microtubule restructuring (1, 2), neurite outgrowth and synaptic plasticity (3, 4), cell migration (5) and activation of the WNT pathway (6). This wide reaching role in neuronal signalling pathways has made APOE a focus for understanding the pathology of several neurological disorders. Most notably the APOE polymorphic variant, APOEε4 is associated with a dramatically increase in the risk of developing Alzheimer's disease (AD) (7) and decreasing the age of onset (8), while allele APOEε2 is negatively associated with development of AD (9). The similarities between the cognitive decline in patients with AD and those with schizophrenia (10) and the co-morbidity of AD and depression (11) have resulted in the investigation into the role APOE plays in the pathologies of schizophrenia, major depressive disorder (MDD) and bipolar disorder (BPD). In order to understand

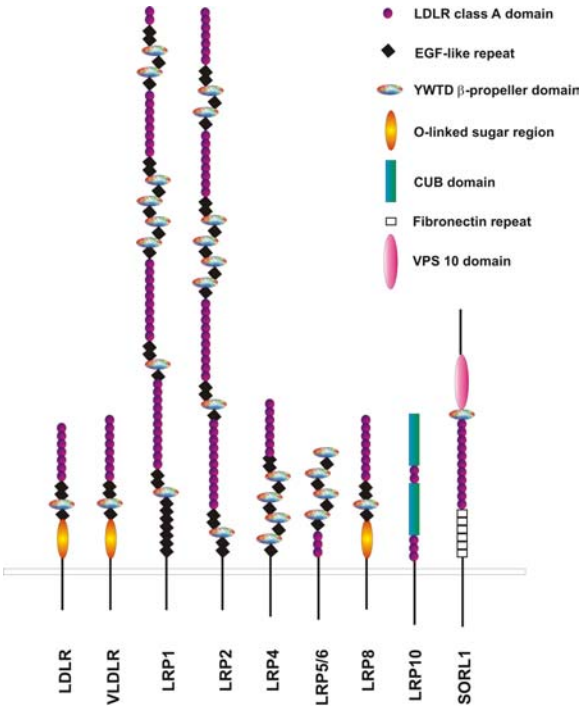

Figure 1. he LDLR class receptors that are known to interact with APOE in the CNS. The major extracellular structural domains of the receptors are shown. Receptors within the LDLR family are characterised by a series of LDLR class A repeats which facilitate apolipoprotein binding.

how APOE dysfunction is associated with the pathology of psychiatric disorders such as schizophrenia and mood disorders it is first necessary to understand the molecular function of APOE and its involvement in the central nervous system (CNS).

3. APOE and its receptors

3.1. The *APOE* gene and its allelic variants

The human APOE is encoded by a single gene located on chromosome 19q13.2. The *APOE* gene encodes a 317 amino acid peptide, from which an 18 signal peptide is cleaved to produce a 34kDa active peptide (12). Tissue specific localisation has been shown to depend upon transcriptional and post-transcriptional regulatory mechanisms (13, 14). Two domains within the APOE peptide facilitate lipid binding. Within the N-terminal domain, residues 140-150 serve as a recognition site for binding to low density lipoprotein receptor (LDLR) class of receptors (15, 16).

Three major pathologically important allelic variants of the APOE protein with differing biochemical properties have been characterised based on isoelectric focusing; APOE e2, APOE e3 and APOE e4 (17). APOE e3 represents the most frequent variant in normal populations and is the most functionally intact of the three alleles (18). APOE e2 differs from APOE e3 by an arginine to cysteine substitution at residue 158 in the peptide sequence. *In vitro* experiments have found that APOE e2 exhibits a dramatically reduced ability to bind surface LDLR class of receptors, compared to either the APOE e3 or APOE e4 isoforms (19). As such, APOE e2 has been associated with disorders of lipid metabolism. By contrast, APOE e4 contains a cysteine to arginine substitution at residue 112 when compared with APOE e3. APOE e3 and APOE e4 have been shown to elicit markedly different functions in the CNS. Most notably, *in vitro* numerous studies have reported enhanced neurite outgrowth in response to APOE e3 expression, while APOE e4 has been shown to inhibit neurite outgrowth (20-22). Since the initial characterisation of the APOE variants, further allelic subtypes within the major allelic classes have been described based in variation in the nucleotide sequence (23) and several disease related alleles have been characterised within the APOE e3 class (24, 25). This underlying allelic complexity within the classic three allele model, by which APOE-related pathologies are often viewed, may account for some of the discrepancies seen in genetic association studies of schizophrenia and mood disorders.

3.2. The LDLR superfamily

The LDLR superfamily mediates the lipid uptake and signalling pathways of apoliproteins with individual receptors having affinity for multiple ligands. LDLR class receptors exhibit considerable structural diversity but are characterised by the presence of a series of ligand binding modules (LDLR class A modules) within the extracellular domain. The ligand binding modules are the major domains that facilitate the binding of apolipoproteins to the receptors (26). Other modules, including EGF-like repeats, beta-propeller domains and CUB domains are shared by several but not all LDLR class receptors and underlie the functional diversity exhibited by this class of receptors.

Amongst the receptors that have been shown to mediate APOE signalling are LDLR, very low density lipoprotein receptor (VLDLR) (27), lipoprotein receptor-related protein (LPR) 1, (LRP1) (28), LRP2 (Megalin) (29), LRP4 (MEG7) (30), LRP5/6, LRP8 (APOER2) (31), LRP10 (32), SORL1 (SORLA/LR11) (33) and LSR (34) (Figure 1). The affinity of APOE for other LRP's is largely undefined, although evidence suggests APOE is not a ligand for LRP3 (35), a molecule that displays high structural homology to LRP10. However, common domain structures of the LDLR class receptors suggest APOE may act as a ligand for most of the LDLR class receptors. The affinity of APOE for multiple receptors within the LDLR family accounts for the broad range of signal transduction pathways that APOE is known affect (Figure 2). Extensive discussion of the signal transduction pathways of the LDLR class receptors have been reviewed elsewhere (36-39).

Amongst the LDLR class receptor signalling pathways with major significance to the pathology of schizophrenia are the VLDLR and LRP8 mediated reelin signalling pathways (40, 41). APOE competes with Reelin for available binding sites on the VLDLR and LRP8 receptors regulating Disabled-1 (DAB1)-mediated signal

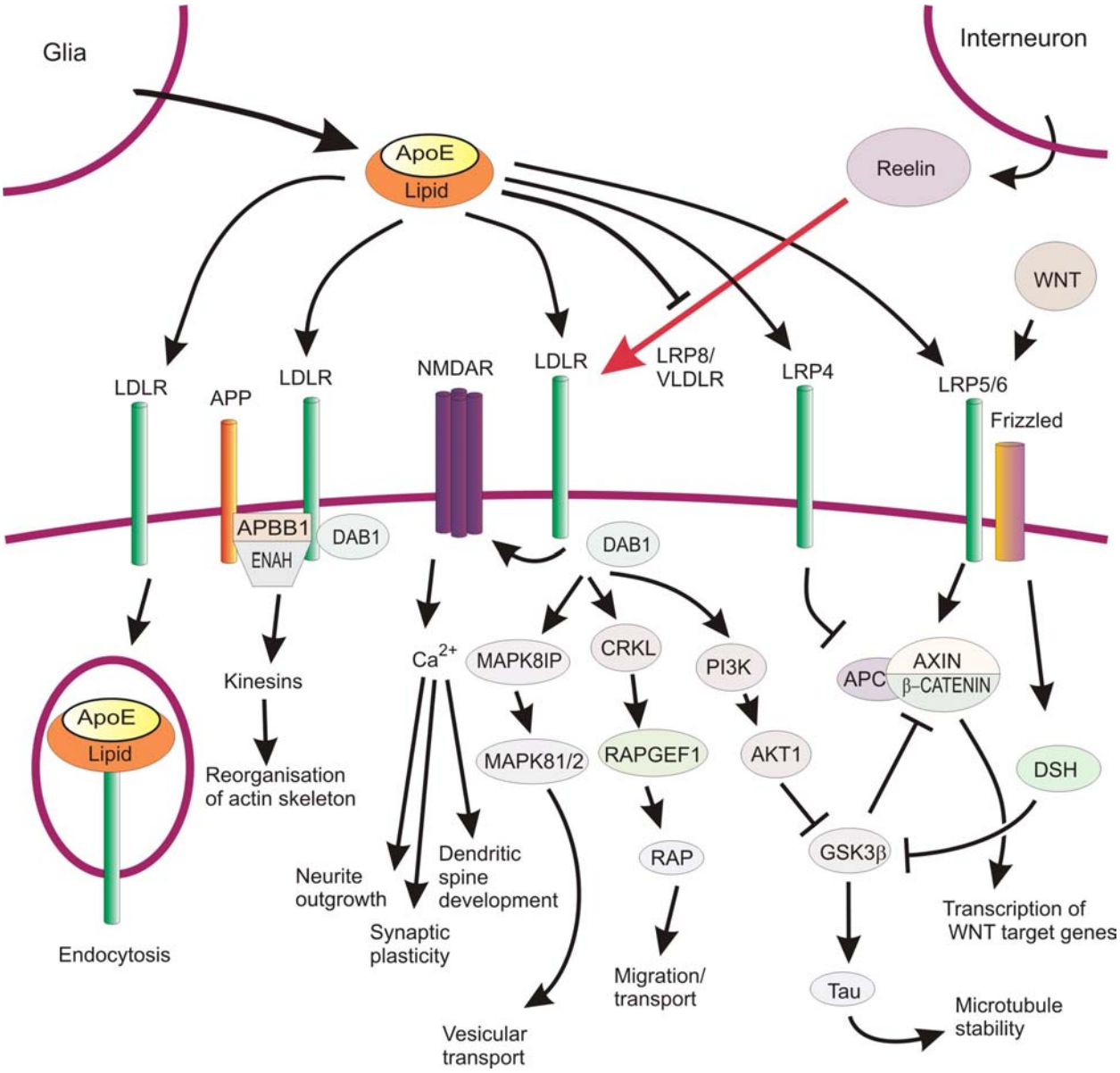

Figure 2. A summary of the major molecular pathways through which LDLR class receptors mediate APOE signalling. Receptor specific interactions are highlighted.

transduction pathways. APOE/reelin mediated control of DAB1 signalling has been shown the regulate glutamate signalling through the NMDA receptor, affecting neurite outgrowth and synaptic plasticity and it is likely that this mechanism underlies the impact of aberrant APOE signalling on cognition (42, 43).

4. THE ROLE OF APOE IN CNS LIPID METABOLISM

A major role of APOE in both the nervous system and non-neural systems is in the transport and metabolism of lipids. APOE is the core molecule of several classes of lipoproteins including very low density lipoproteins (VLDLs), intermediate-density lipoproteins (IDL), high-density lipoproteins (HDLs) and chylomicrons, and is the pivotal ligand LDLRs LRPs in the periphery and the CNS. APOE e4 is associated with triglyceride (TG)-rich VLDLs, whereas APOE e2 and APOE e3 predominantly bind to phospholipid-rich HDLs (44). It is thought that the structural changes of the APOE isoforms and changes of their expression levels are important to maintain brain lipid homeostasis and metabolism.

In the CNS, APOE plays an important role in the delivery and clearance of lipids, such as cholesterol, phospholipids and triglycerides, by mediating their binding and internalization through LDLR receptors in the brain (45, 46) and acting to both promote and prevent abnormalities in lipid metabolism. Thus, altered lipid

homeostasis within the CNS may influence cellular damage, and synaptic loss. APOE is required for the uptake and redistribution of lipids and cholesterol in the CNS (47). Furthermore, the inability of most plasma lipoproteins to cross the blood-brain barrier suggests the regulation cholesterol homeostasis within the CNS is likely to act independently of the periphery (48). Cholesterol synthesis is repressed and APOE expression is increased following injury to neurons suggesting APOE plays a neuroprotective role. This neuroprotective ability varies between the APOE isoforms. Following injury, APOE e3 (and APOE e2) and cholesterol are transported from the glia to neuronal cells via APOE transport systems in order to repair the injured neurons. The APOE e4 isoform is thought to be detrimental in this process due to the increased formation of APOE e4 fragments that cause alterations of cytoskeleton and mitochondria, causing cell death in the CNS (49-51). Thus, the role of APOE in lipid metabolism and neuronal protection is paramount to that of any other lipoprotein in the CNS, and the levels of APOE expression and redistribution of cholesterol can influence development and maintenance of neurons and their connections.

5. THE ROLE OF APOE IN NEURAL FUNCTION

5.1. Glial signalling and the tripartite synapse

APOE expression in the brain is comparably high compared to most other organs (52). Of paramount importance to the role APOE plays in psychiatric disorders is its involvement in synaptic signaling. The involvement of APOE signaling in synaptic plasticity and consequently cognition is pertinent in light of the cognitive deficits that are widely reported in schizophrenia, BPD and MDD. At the centre of this association is the involvement of APOE in glial-neuronal interactions within the synapse. Within the CNS, expression of APOE is a predominantly localised to glia (53, 54), with markedly lower levels of neuronal expression reported under certain physiological and pathological conditions (55-58). It is well established that glia are not simply support elements for neurons, as they were once regarded, but are actively involved in neuronal signaling. Thus the concept of the tripartite synapse, which incorporates the glial cell as a part of the synaptic junction between the pre- and post-synaptic neurons, has emerged to incorporate glial cells as crucial elements in synaptic function (59). The deficits in synaptic plasticity and cognition reported in both APOE knockout mice and APOE receptor knockout mice suggests that APOE plays an important role in neurotransmission within the tripartite synaptic complex (60, 61). Furthermore, in vitro studies have also shown that astrocyte-derived, cholesterol/APOE complexed lipoproteins promote synaptogenesis in purified neurons and that blocking APOE receptors reduced the synaptic activity induced by this lipoprotein complex (62). Notably APOE has been reported to interact with glutamatergic, cholinergic and adrenergic neurotransmission, which are purportedly involved in the pathology of schizophrenia and mood disorders (63-67) and may underlie the glial mediated, consolidation of synaptic strength and plasticity in neurons expressing these neurotransmitters.

5.2. APOE involvement in synaptic plasticity

Numerous studies have demonstrated the importance of APOE in synaptic plasticity. Several *in vitro* studies have illustrated the necessity of APOE-lipoprotein complexes in neurite outgrowth and synapse formation (4, 68). *In vitro* studies of APOE have examined its isoform specific effects on signal transduction pathways critical to synaptic plasticity such as ERK, c-jun N-terminal kinase (JNK) and DAB1 (69). In primary neuronal cell culture, application of either the full length APOE or a peptide consisting of a tandem repeat of the receptor binding domain of APOE significantly increased the activation levels of ERK and DAB1 and decreased the activation of JNK. In addition, both APOE-induced ERK1/2 phosphorylation and DAB-1 regulation were shown to be dependent on NMDA receptor function. Interestingly, in primary neuronal cell culture, the APOE-mediated reduction in JNK1/2 phosphorylation required activity of α-secretase (69, 70). Recent studies revealed that APOE promotes α-secretase-dependent receptor processing to varying degrees in an isoform-dependent manner, with APOE e2 having a greater effect than APOE e4 (69).

While *in vitro* studies have facilitated an understanding of the acute cellular response to specific APOE isoforms, understanding how cellular responses to specific APOE isoforms correspond to physiological and behavioural responses has necessitated the use of animal model systems to better address how these isoforms may behave within the human brain. Such studies have involved the administration of human recombinant APOE isoforms to *APOE*-deficient mice or the use of targeted replacement, APOE isoform-expressing mice (APOE-TR) which express one of the three human APOE isoforms under the control of an endogenous murine promoter (71). Comparison of the physiological role of APOE isoforms between mice and humans is, however, complicated by the fact that the APOE isoforms that occur in humans do not occur naturally in the mouse. Thus, the physiological responses in the mouse to the different APOE isoforms may not truly reflect the human brain which may have evolved to compensate for APOE polymorphisms.

In mice, the different isoforms of APOE do not appear to change overall baseline synaptic transmission or short-term plasticity. However, APOE isoform effects on long-term potentiation (LTP) appear to differ depending upon the region examined. Examination of the electrophysiological response to hippocampal perforant path stimulation revealed that LTP induction in APOE e3-TR mice was equivalent to the wild-type controls, but APOE e2-TR and APOE deficient animals showed significant reduction in LTP induction with further decreases observed in APOE e4-TR animals (72). These results suggest that specific APOE isoforms have a differential consequence on signal transduction regulation involved in LTP induction and are consistent with the cognitive decline associated with APOE e4 that implicates a role for this allele in schizophrenia (10, 73).

By constrast, application of APOE e4 increases long-term potentiation (LTP) induction from control levels

in the hippocampal CA1 region of the APOE knockout mouse, while APOE e2 decreases LTP induction and APOE e3 does not appear to alter LTP induction (3). This effect is associated with increased receptor mediated signalling when APOE is added. Furthermore, there is also a change in NMDA receptor signalling with APOE e2 and APOE e4 causing a significant decrease in conductance. These findings are consistent with studies suggesting the signal transduction via APOE receptors in related to NMDA receptor maturation during certain forms of neurotoxicity (74). The enhancement of LTP in CA1 of the hippocampus in response to APOE e4 does, however, appear to be age dependant. Thus, while young APOE e4-TR mice display increased LTP these effects are not discernable in older animals, which may have implications for the pregression of cognitive deficits in psychiatric disorders.(75). While these data suggest that the action of APOE isoforms can alter synaptic plasticity in subregion-specific manner, APOE isoforms are indeed acting as signalling molecules and mediated in a way that is sufficient to affect synaptic plasticity.

5.3. APOE involvement in cognition

Consequent to its role in synaptic plasticity, APOE is thought to play an important role in brain cognitive function, including attention (76) and memory (77). Investigations into the effects of APOE gene on spatial attention, including attention shifting, attention scaling, vigilance and spatial working memory, in middle-aged adults without clinical signs of dementia revealed impairments in attention shifting from an invalid location and a reduction in the scaling of attention associated with the APOE e4 allele. However, the vigilance test showed no difference with APOE genotype (76). In addition, spatial working memory experiments showed that APOE e4 homozygotes without dementia are impaired in components of spatial working memory (76), suggesting that APOE genotype can influence component operations of spatial selective attention and working memory in non-disease states. Interestingly, recent studies have reported that the presence of the APOE e4 allele increased the risk of developing cognitive impairments in attention and working memory compared with the APOE e2 and APOE e3 alleles. Behavioural studies in mice have revealed a differential effect of APOE isoforms on spatial memory (78). Mice expressing the APOE e3 isoform are identical to wild type mice in spatial learning. In contrast, mice expressing the APOE e4 isoform demonstrate compromised spatial learning. Furthermore, expression of APOE e4-TR leads to age and sex dependent impairment in spatial learning and memory and this memory defect is exacerbated in female mice, which supports evidence from human studies, which demonstrate increased susceptibility to the detrimental effects of the APOE e4 allele in women (79). At 6 months of age, female APOE e4-TR mice showed impairments in hippocampus-dependent spatial learning and memory in the water maze. These impairments were observed in mice that express APOE e4 in neurons (79, 80) or astrocytes (81). In addition, the impaired spatial learning exhibited by APOE-deficient mice can be rescued by infusion of human APOE e3 or APOE e4 isoforms (82). APOE is associated with mechanisms that are essential for cognition, learning and memory. Thus, abnormal APOE signalling may underpin the cognitive deficits observed in schizophrenia and mood disorders.

6.0 APOE IN SCHIZOPHRENIA

6.1 APOE allelic variation in schizophrenia

Schizophrenia is a debilitating mental illness, affecting approximately 1% of the population characterised by a symptomatology that includes positive symptoms, such as delusions, hallucinations and thought disorder; negative symptoms, such as blunted affect, alogia, anhedonia and avolition; and deficits in cognition (83). The disorder is suggested to be a neurodevelopmental and progressive disorder, and is associated with both functional and structural changes in the brain (84-89). It is believed that schizophrenia is brought about by both genetic and environmental factors (90, 91). Several genes have been implicated in this disorder, including those involved in glutamatergic neurotransmission (92-94), regulation of presynaptic function (92, 95) G-protein signalling, (92, 96), GABAergic function (97), and synapse plasticity (98), however precise mechanisms underlying the pathophysiology are still unknown. Since APOE is important in CNS functions such as modulating intraneuronal calcium (99), cell signaling (69), protein phosphorylation (100) and storage-induced synaptic sprouting (101), alterations in APOE expression may have consequences in either the risk of developing schizophrenia or the clinical manifestations.

Due to the similar decline in cognitive symptoms in some patients with schizophrenia to those with Alzheimer's disease, Harrington *et al* (10) first hypothesized that APOE may also play a role in schizophrenia, and showed, using DNA from post-mortem brain tissue, an increased frequency of the APOEε4 allele in 42 patients with schizophrenia compared to controls, with a similar frequency to that seen in patients with AD. This finding was corroborated by a study in a Chinese population of 479 subjects with the disorder (102). However subsequent studies in various other Caucasion and Asian populations failed to replicate these findings (103-107), suggesting that, in contrast to AD, APOEε4 polymorphism is unlikely to be a strong risk factor for developing schizophrenia.

Examination of APOE APOEε4 in relation to clinical variables revealed in some studies that, while the APOEε4 allele frequency was not different in schizophrenia compared to control, it may be associated with clinical features (104, 107). Patients with schizophrenia that had the APOEε4 allele showed altered scores for psychotic symptoms (108, 109) and there was indication of poorer outcome associated with this polymorphism (104). In addition, subjects with the APOEε4 allele displayed significantly reduced ketamine-induced psychosis compared to those without the APOEε4 allele, indicating APOE genotype plays a role in modifying the expression of positive symptoms (110). However the outcomes of some of these studies were mixed. For

example allele APOEε4 was associated with a younger age of onset in some studies(104), which is opposite to what was shown in a Japanese population of schizophrenia patients (107) In an attempt to clarify discrepancies across the various studies, a large study was performed in 365 patients with schizophrenia, and showed that, while there was no increase in the APOEε4 allele frequency in patients compared to controls, in female patients only, APOEε4 was associated with a lower age of onset and greater risk of suffering negative symptoms (111), suggesting that while this polymorphism may not increase the risk of developing schizophrenia it plays a role in modifying the phenotypic expression of the disease in a sex-dependent manner. Various studies have since postulated that the genetic impact of APOE on schizophrenia may be race specific (105, 112-114), with some indication that it may also be influence by famine (102, 115). Evidence linking the relationship between APOEε4 and schizophrenia with additional demographic factors such as gender or race, or to the response to metabolic challenge suggests the APOEε4 allele may confer vulnerability to developing schizophrenia in individuals challenged by other genotypic or environmental influences. Nonetheless, due to the lack of concurrent results from the various studies performed, the precise role for the APOE e4 polymorphism in schizophrenia susceptibility and pathogenesis remains unclear.

Like in AD, allele APOEε2 frequency was decreased in schizophrenia, particularly in the late-onset form, suggesting it to have a protective effect against developing the illness (105, 107, 112). Again there are conflicting results from different studies, where some showed no association between the APOEε2 polymorphism and schizophrenia (104, 116-118), even when subjects were divided into clinical subgroups (119, 120). A positive associating between the APOEε3 allele and schizophrenia has also been demonstrated (105, 120, 121), however this was not shown in all populations studied (104, 112, 116, 117, 122), again conflicting results from different studies (123). Due to the apparent many number of genes involved in this disorder, effects of each individual gene may be modest and therefore difficult to detect, particularly in small samples. With all three isoforms for APOE there is still uncertainty of their influence in schizophrenia susceptibility and pathophysiological manifestations and further investigation is required.

Due to the various functions of APOE in the CNS, allelic variation in APOE could have implications in schizophrenia through several possible pathways. The APOEε4 allele has been linked to decreased hippocampal volume (124) and it was shown in a small sample size that carriers of the APOEε4 allele had reduced right hippocampal volume and altered hypocampus symmetry in schizophrenia (125). Another study was unable to show an association between APOE ε4 and hippocampal or temporal lobe volume in childhood onset schizophrenia (126), however the mean age of the subjects of this study was much younger, indicating volume abnormalities may only manifest later in the illness, which fits with the progressive nature of the disease. The different APOE isoforms have differences in lipid metabolism, which is largely implicated in schizophrenia pathophysiology (127). Abnormalities in cholesterol metabolism have been suggested to affect treatment resistance in schizophrenia (128). Allele APOEε2 was negatively associated with treatment responders in one study, (129), although the opposite was apparent in another study (119). APOE is also known to neutralize free radicals, where APOEε4 is less effective than APOEε2 or APOEε3 (130), and there is evidence that oxidative injury contributes to schizophrenia pathophysiology (131-133). Finally, *APOE* knock-out mice show enhanced pro-inflammatory markers, indicating the inflammatory pathway may also be a mechanism for the involvement of APOE in schizophrenia (134, 135). Abnormalities in this protein is, therefore, likely to have effects on schizophrenia pathology and treatment.

Besides investigating the protein major isoforms of APOE, the -491A/T and -219G/T polymorphisms in the promoter region of the *APOE* gene have been shown to modulate the risk for AD (136) and have therefore also been examined in schizophrenia. The -419A/T polymorphism at position is a significant factor in determining levels of APOE in serum (137), and CNS (138). The allele frequency at this position was not changed in schizophrenia compared to control in two studies (123, 139). However, the *APOEε3/APOE-219G* haplotype combination, has been shown to be associated with schizophrenia in a study of 60 families from a Mexican population (121).

6.2. APOE expression abnormalities in schizophrenia

Despite a wide number of studies that have examined APOE polymorphisms in schizophrenia, comparatively a limited number of studies have examined how the expression of APOE is affected in the CNS of individuals with the disorder. Studies that have examined the post-mortem brain, which provides a closer molecular model of the pathological changes in schizophrenia than the mouse or cell line while allowing greater experimental flexibility than the live human subject, have reported increased APOE protein levels in Brodmann's Area (BA) 9 and 46 of the dorsolateral prefrontal cortex from patients with schizophrenia, but not in the frontal pole or the supramarginal gyrus (123, 140, 141). Such observations suggest these changes are not only regionally specific but, as the dorsolateral pre-frontal cortex is largely implicated in schizophrenia where it is thought to be responsible for the cognitive impairments associated with this disorder, are also specific to a part of the brain involved executive function, supporting a cognitive role for APOE in schizophrenia. This increase in APOE expression was not likely due to antipsychotic effects as rats treated with haloperidol showed decreased APOE levels (123), indicating that antipsychotic drugs may be decreasing APOE levels as part of their therapeutic actions. Importantly, these changes in expression appeared to be independent of APOE polymorphism frequency (123). Interestingly, plasma levels of APOE are reported to be decreased in treatment free subjects with the disorder compared to controls suggesting that CNS and peripheral

APOE expression are under different regulatory mechanisms and, thus, expression studies in the periphery may not reflect APOE dysfunction in the brain (142). These results further support the notion that APOE is involved in schizophrenia pathophysiology and may have an impact on treatment.

6.3. The potential role for APOE in myelin abnormalities in schizophrenia

As a transport molecule for cholesterol, APOE is thought to play a role in myelin synthesis and may be associated with the loss of integrity of the myelin sheath surrounding the neurons seen in AD (143). Thus, the APOE e4 polymorphism has been associated with an increase in myelin breakdown and accelerated development of cognitive deficits (144). Evidence of myelin disruption has been reported in both schizophrenia and mood disorders. Myelin damage and oligodendrocyte loss has been reported in the frontal pole and caudate putamen in schizophrenia (145). Oligodendrocyte density has been reported to be decreased in dorsolateral prefrontal cortex in schizophrenia, BPD and MDD (146). Furthermore, microarray studies have reported altered expression of several genes involved in myelination and myelin-related processes in the dorsolateral prefrontal cortex associated with schizophrenia (147). It is currently unclear whether the APOE dysfunction seen in schizophrenia plays a role in this apparent disruption of myelin integrity or how localised increases in APOE expression could account for broader deficits in myelin and oligodendrocytes. However, rat studies suggest APOE is involved in myelin cholesterol salvage following neurodegeneration (148). Thus, the localised increase as APOE within the dorsolateral prefrontal cortex could be a response to myelin degradation in an attempt to upregulate recycling of cholesterol back into myelin.

6.4. APOE receptors in schizophrenia

Despite a considerable body of evidence implicating APOE in the pathology of schizophrenia, few studies have examined the how the APOE receptors are affected in the disorder. Analysis of the polymorphic CGG repeat in the 5' untranslated region of *VLDLR* gene has shown no association with the incidence of schizophrenia (149). However, the expression *VLDLR* mRNA has been reported to be decreased in blood lymphocytes from drug-naive patients with schizophrenia compared to controls (150). Additionally, there was a negative correlation between *VLDLR* mRNA level and severity of clinical symptoms. While *VLDLR* levels are influenced by diet, patients in this study were fasted prior to the study to control their nutitional status. Furthermore, six months of antipsychotic treatment in these subjects resulted in an increase in *VLDLR* mRNA expression (150). For *LRP8*, results indicated that while there was no difference between mRNA levels in non-medicated patients and controls, antipsychotic treatment potentially decreases its expression in peripheral lymphocytes (150). Microarray analysis of gene expression in schizophrenia throughout the progression of the illness detected an increased in LRP2 mRNA expression in the schizophrenia during a period between 7 and 18 years following diagnosis (151). Furthermore, a decrease in the expression of *LRP10* mRNA and an increase in the mRNA expression of *LRP12*, a poorly characterised LDLR class receptor structurally related to LRP10, was also reported to be decreased during the first 7 years following diagnosis with schizophrenia (129). Whether APOE is a ligand for LRP12 has yet to be determined. However, these data suggest the effects of abnormal APOE signalling may be preferentially mediated by distinct receptor types.

6.5. Reelin and its receptors in schizophrenia

APOE and reelin are thought to interact through competition for their common receptors, VLDLR and LRP8. This interaction between APOE and reelin signalling is pertinent in light of a significant body of research implicating reelin in the pathology of schizophrenia. Reelin is a glycoprotein that also binds to LDLR class receptors to activate signaling. It plays important roles in both neurodevelopment and in the adult brain. Embryologically, it is secreted from Cajal Retzius cells to guide neurons and radial glial cells to their correct positions (152-154), while in the adult brain it is secreted by GABAergic interneurons and is involved in neurotransmission, memory formation and modulating synaptic plasticity (155-157), making it a likely candidate for genes involved in schizophrenia.

Reelin was first shown in 1998 to be decreased in the pre-frontal cortex, temporal cortex, cerebellum, hippocampus and caudate nucleus from people with schizophrenia compared to controls (41). Both mRNA and protein were decreased, as well as the number of interneurons expressing Reelin protein in layers I and II in the pre-frontal and temporal cortex, without total neuronal loss. Though the sample size was small (n=18 schizophrenia, 18 control) these findings were supported by several studies using various techniques, including RT-PCR, Western blot, in-situ hybridization and immunocytochemistry (158-161). Furthermore, the change in expression did not correlate with confounding factors such as sex, age of onset, postmortem interval or antipsychotic exposure (41, 160, 161). Taken together with mouse studies that show reduced reelin expression results in behavioral and anatomical abnormalities, such as deficits in prepulse inhibition and sensory gating, reduced neuropil density and reduced dedritic spine density in cortical pyramidal neurons, similar to those seen in patients with schizophrenia (162-166), the above studies suggest that this protein is involved in schizophrenia pathophysiology. Micelacking the two APOE/reelin receptors, VLDLR and LRP8, also show neuroanatomical changes similar to those seen in reelin defective mice (167, 168), suggesting the receptors for reelin may also important in the pathophysiology of schizophrenia.

Evidence suggests that decrease reelin expression in schizophrenia is a result of increased methylation, as DNA methyltranseferase 1 mRNA is up-regulated in schizophrenia in the same neurons that express reelin, and the reelin promoter is more heavily methylated in patients with schizophrenia compared to control subjects (169-171). Furthermore, treatment with the histone deacetylase inhibitor valproate, reversed methionine-

induced hypermethylation of the reelin promoter as well as schizophrenia-like behavior in mice (171, 172).This influence of valproate is pertinent as valproate has been used as an adjunct treatment for schizophrenia particularly for the treatment of affective symptoms that can be associated with the disorder. However, meta-analyses have questioned the benefit of valproate as an adjunct to antipsychotic treatment over antipsychotics alone (173). Despite increased methylation of the reelin promoter in the CNS, blood levels of reelin was significantly increased in subjects with schizophrenia (174), indicating reelin could potentially be used as a biological marker for schizophrenia. Whether abnormal APOE and reelin expression in schizophrenia represents a compensatory change in expression to counter the effects of dysregulation of either APOE or reelin, or whether it reflects independent molecular challenges on the same LRP signalling system in discrete subtypes of schizophrenia that results in a similar pathophysiological outcome requires further investigation.

7. EVIDENCE FOR APOE ABNORMALITIES IN MDD AND BPD

7.1. APOE allelic variation in MDD and BPD

In addition to schizophrenia, several studies have also examined the relationship between the APOEε4 allele and mood disorders with varying results. Some show no association between this allele and either MDD or BPD even with regard to onset of symptoms, age of first admission, number of affective episodes, psychotic features or familial connection (175). Conversely, an increase in APOEε4 frequency has been reported in early onset BPD compared to either control or intermediate or late onset BPD. The discrepancy between these two findings may have resulted from the increased statistical power arising from the considerably larger cohort size used in the latter study (176). A strong association is evident between APOEε4 and affective symptoms resulting from interferon α therapy for chronic hepatitis C (177). Patients with the APOEε4 allele were more likely to be referred to a psychiatrist during treatment, had more psychiatric symptoms although, notably, APOEε4 was associated with symptoms of anger, irritability, short temper and anxiety, while symptoms of depression were not significantly affected. Thus, APOEε4 may serve as a risk factor for psychotic features of mood disorders.

APOEε2 has been reported to elicit greater neuroprotective effects compared to APOEε3 and APOEε4 in *in vitro* studies (178). In agreement with this varying allelic neuroprotective effect, a protective effect of the APOEε2 allele on MDD has been observed in a Taiwanese population (179), with a meta-analysis of 7 studies showing a significant protective effect of the APOEε2 allele in Caucasian populations (180). However, this effect became non-significant upon after of one of the studies was removed from the analysis. Further studies would need to evaluate whether the APOEε2 allele provides a similar neuroprotective effect in BPD.

7.2. APOE expression alterations in MDD and BPD

Studies into APOE expression in bipolar 1 disorder (BPD1) reveal regional changes in expression in postmortem tissue. APOE was found to be increased in BA 9 and the caudate putamen (CPu) in brains of subjects with BPD1, when compared with controls, but decreased in BA 10 and plasma and unchanged in BA 40 (181, 182). As this study also found the frequency of the APOEε2 allele to be extremely low in the BPD1 group it is likely the regional variation in APOE expression is due to APOEε3 and/or APOEε4. However further investigation would be required to assess the contribution of various isoforms to the observed effects. APOE complexed with cholesterol has been shown to play a role in synaptogenesis (62) in addition to its previously mentioned role in the repair and synthesis of cell membranes and synapses and the reduction of oxidative stress. As mood disorders are associated with impairments of synaptic plasticity in regions of the CNS (183, 184) it is possible that there may be altered expression of APOE in various brain regions associated with this change in synaptic plasticity.

8. APOE, metabolic disturbances and peripheral drug effects

The role of APOE as a lipid transport molecule is important as it may be involved with the metabolic disturbances reported in schizophrenia and mood disorders (185, 186) and, importantly the metabolic side effects of psychiatric medication, which can affect therapeutic compliance (187). Murine knockout studies have highlighted the role APOE plays in the development of obesity insulin resistance suggesting it may play a role in the increased comorbidity of dyslipidemia and diabetes amongst individuals with schizophrenia and mood disorders (188). Furthermore, APOE e4 has been associated with an increase in metabolic syndrome in non-psychiatric subjects (189) and in cognitively impaired subjects (190). However, the incidence of metabolic disorders in schizophrenia and mood disorders is confounded by the influence of environmental factors and any potential for APOE dysfunction to impact lipid metabolism in these disorders must be viewed in light of these confounds.

Obesity in schizophrenia and mood disorders is commonly attributed to the peripheral side effect of the use of psychiatric medication (191, 192). Whether the prevalence of obesity in medicated individuals is solely a side effect of psychiatric drug use or whether it reflects an underlying predisposition to abnormal lipid metabolism potentially resulting from APOE dysfunction that is exacerbated in the periphery upon challenge with medication is difficult to interpret. The extent to which the atypical antipsychotic clozapine induces weight gain is reportedly influenced by the baseline body mass index of the individual. Racial differences between the incidence of weight gain and clozapine treatment also point to underlying genetic predisposition to antipsychotic induced dyslipidemia (193, 194). Drug naïve subjects with schizophrenia have been reported to have a lower incidence of obesity compared to controls (195) and higher incidences of underweight individuals have been reported amongst long term sufferers of the disorder (196). Furthermore, subjects with schizophrenia have also been

reported to have lower body mass indices prior to diagnosis (197).

Contrasting schizophrenia, higher incidences of obesity are associated with drug naïve individuals with mood disorders. While plasma APOE levels have also been shown to be significantly decreased subjects with BPD who have been treatment free for at least 1 month compared to healthy controls, plasma APOE expression significantly increased following the subsequent treatment of these subjects with mood stabilizers (182). Thus, while mood stabilisers may to influence APOE expression, aberrant APOE expression does appear to be intrinsic to the underlying aetiology of BPD. While this data would suggest abnormal lipid metabolism could underlie the pathology of these psychiatric disorders, such observations may be attributed to poor nutritional patterns and more sedentary habits amongst individuals with schizophrenia and mood disorders (198, 199).

The impact of APOE genotype on peripheral drug metabolism is poorly understood. APOE genotype does not appear to impact the therapeutic effects of antipsychotics on individuals with schizophrenia (200) By contrast, APOE e4 has been associated with the efficacy of antidepressants in cognitively intact subjects, although this effect varies between different drugs [201]. Genetic association studies have identified two SNPs in the *APOE* gene associated with high BMI in a cross section of individuals with schizophrenia and mood disorders who had been receiving risperidone treatment. The SNP rs405509 was less prevalent in individuals classified as overweight while rs439401 was more prevalent in overweight individuals. This association was not seen in individuals classified as obese, nor were these SNPs associated with the incidence of hyperlipidemia or hypercholesterolemia (202). However, the genetic heterogeneity within a combined cohort of subjects with varying psychiatric disorders may have impacted the clarity with which the SNP associations with metabolic dysfunction could be assessed.

9. CONCLUSIONS AND PERSPECTIVES

The role APOE plays in the pathologies of schizophrenia and mood disorders is still unclear. Contrasting the strong association between APOE e4 and the incidence of Alzheimer's disease, associations between specific APOE polymorphisms in incidence of schizophrenia, MDD or BPD remain inconclusive and may be reliant upon secondary environmental and genetic triggers to exert a disease effect. Attempts to associate the 3 major isoform classes with these disorders may be a simplistic approach and the characterisation of 30 polymorphic variants by Deknijff *et al*, many of which were associated with abnormal function of the protein (24), offers the potential for classically non-pathological isoforms to also display aberrant signalling. Whether these isoforms could account for discrepancies in the allelic association studies has yet to be addressed. By contrast, expression studies have yielded more convincing evidence of the involvement of APOE in the pathologies of schizophrenia and mood disorders. However, current evidence points to regionally specific alterations in APOE expression and comparably little attention has been directed towards characterising the changes in APOE expression in the brains of individuals with these disorders or how these changes affect receptor signalling in the pathological state. The regional differences in APOE expression in schizophrenia and bipolar disorder, both within the CNS and between the CNS and the periphery, suggest the aberrant expression of APOE involves complex regulatory dysfunction of this molecule (106, 181, 182). This is further complicated by the influence antipsychotics, antidepressants and mood stabilisers have on the expression of APOE. While abnormal metabolism is a common symptom of schizophrenia and mood disorders, the extent to which these symptoms are solely a consequence of the adverse effects of medication is unclear. Indeed, the poor dietary habits commonly associated with schizophrenia and mood disorders can often prevent the establishment of any form of metabolic baseline from which to assess the impact of medication and it is unknown whether abnormal APOE expression associated with these disorders reflects a response to abnormal metabolism or an underlying predisposition to abnormal lipid metabolism that is exacerbated by medication and diet. Given that weight gain is a significant hindrance to medication compliance individuals suffering with schizophrenia and mood disorders, understanding how APOE dysfunction contributes to the pathologies of schizophrenia, MDD and BPD remains a high priority for psychiatric research.

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