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Apolipoprotein E alleles can contribute to the pathogenesis of numerous clinical conditions including HSV-1 corneal disease

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Abstract

Apolipoprotein E (ApoE) alleles have been reported to affect the clinical outcome of numerous cardiovascular, neurodegenerative, and viral infectious diseases, including atherosclerosis, Alzheimer's disease (AD), hepatitis C, and HIV. The major alleles of ApoE are ϵ 2, ϵ 3, and ϵ 4. ApoE genotypes have been hypothesized to regulate many biological functions, resulting in significant changes in the onset and/or outcome (severity and duration) of several clinical conditions. Based on genetic analyses in human and animal studies using knockout (ApoE $-/-$) mice and mice transgenic for human ϵ 3 and ϵ 4, we present evidence that strongly suggests that the ApoE alleles can regulate the pathogenesis of ocular herpes simplex virus type 1 (HSV-1) infections. This review will summarize the major studies that support this hypothesis. Significant gender based differences in HSV-1 pathogenesis have also been reported, suggesting that hormonal regulation combined with ApoE genotype plays a significant role in HSV-1 pathogenesis. Identification of specific mechanisms in ocular HSV-1 infections related to the ApoE alleles and gender could lead to therapeutic intervention based on the properties of the apoE isoforms. While many clinical investigations have been reported and, to a lesser extent, transgenic mouse studies have been conducted, no specific mechanisms of how ApoE induces or alters clinical disease are known.

Keywords

ApoE; ARMD; chemotherapy; HSV; ocular; pathogenesis; Alzheimer's disease

1. Introduction

The association of the ApoE allele ϵ 4 and cardiovascular diseases, namely atherosclerosis, was reported over a decade ago and is now widely accepted (Alber et al., 2000; Elosua et al., 2004; MacKensen et al., 2004; Scuteri et al., 2005). Furthermore, the risk association of the ApoE ϵ 4 allele and Alzheimer's disease (AD) has become almost universally accepted (Baxter et al., 2003; Bennett et al., 2003; Craig et al., 2004; Hoyt et al., 2005; Huang et al., 2004; Messier, 2003; Mosconi et al., 2005; Roses et al., 1995; Roses, 1996; Rubinsztein and Easton, 1999). This review will highlight clinical studies and experimental mouse studies that have shown significant disease risk (increased susceptibility) and/or protection (reduced susceptibility) associated with one of the three isoforms of apoE. Growing evidence suggests that one isoform of apoE (ϵ 4) increases the susceptibility and/or severity of infection with respect to HSV-1. This suggests that HSV-1 pathogenesis can be regulated by a specific isoform

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of apoE. This review will accentuate the possible relationship between the ApoE ϵ 2, ϵ 3 and ϵ 4 alleles and ocular HSV-1 infection, focusing on the hypothesis that isoforms of apoE regulate many molecular events occurring during the pathogenesis of ocular HSV-1 infections.

1.1. Chemistry and genetics of human ApoE

Apolipoprotein E is a 34,200 D protein that consists of 299 amino acid residues. There are three major alleles (ϵ 2, ϵ 3, and ϵ 4) of the human ApoE gene that code for three protein isoforms: apoE ϵ 2, apoE ϵ 3, and apoE ϵ 4 (Huang et al., 2000; Mahley and Rall, 2000). These three apoE isoforms are all products of the same gene located on chromosome 19. The isoforms differ at only 2 amino acid residues, namely residues 112 and 158. While the apoE ϵ 3 isoform consists of a cysteine at position 112 and an arginine at position 158, the apoE ϵ 4 isoform consists of an arginine at both positions. The apoE ϵ 2 isoform has a cysteine at both positions. The predominant allele for most populations is the ϵ 3 allele (~70%–80%), while the ϵ 4 allele accounts for ~10–15% and the ϵ 2 allele accounts for ~5–10%. Table 1 gives the estimated frequencies of the six human ApoE genotypes. While the primary role of apoE is to function as a lipid transporter, there have been numerous reports that this protein has many other roles (Mahley and Rall, 2000). The alleles of ApoE have been linked to atherosclerosis, AD, cognitive function, neurite outgrowth, head trauma severity, and brain trauma. Our review will highlight the clinical studies and experimental mouse studies on the ApoE alleles and the protective or detrimental effects associated with various diseases related to ApoE genotype.

1.2. ApoE alleles: related to cardiovascular and other clinical conditions

Table 2 summarizes and categorizes a wide range of clinical conditions, the ApoE genotype, and the risk associated with a specific isoform to the designated diseases. In each selected clinical study (Table 2), a correlation can be made between an adverse or high-risk association, a low-risk or protective effect, or no association relative to the ApoE genotype. For example, hepatitis B (Percy et al., 2003), multiple sclerosis (Minagar et al., 2004), Huntington's disease (Saft et al., 2004), and Parkinson's disease (Hemling et al., 2003) are conditions in which, to date, no association or risk factor involvement has been proven to exist between any ApoE genotype and disease severity or protection. While it is assumed that these diseases are not related to the presence or absence of specific ApoE alleles, in any clinical condition, subsets of clinical patients and more stringent definitions might identify an association.

Table 3 lists selected clinical conditions for experimental mouse studies that have shown increased risks and adverse effects associated with the presence of the ϵ 4/ ϵ 4 allele, while the ϵ 2/ ϵ 2 genotype exhibits lower risk potentials and protective effects for the same clinical conditions. As noted in Table 2, there are suggested associations between AD, ApoE alleles, and HSV-1. The ϵ 4/ ϵ 4 allele has also been reported to reduce the severity of hepatitis C but not onset, whereas with HIV infections, the ϵ 4/ ϵ 4 allele increases the severity both of the infection and dementia (Corder et al., 1998b; Minagar et al., 2004; Mueller et al., 2003; Toniutto et al., 2004; Wozniak et al., 2002).

In cardiovascular and cerebrovascular disease, there are many examples noted in which the ϵ 4 allele increases the risk factor associated with the disease, while the ϵ 2 allele decreases the risk (Table 2). For other central nervous system (CNS) conditions, such as head injury, cerebrovascular disease, stroke, learning, and intracerebral hemorrhage, the outcome has been reported to be more detrimental when associated with ApoE ϵ 4. A number of studies in both humans and mice have reported risk factors associated with age-related macular degeneration (ARMD). This is a subject of a separate discussion later in this review (see Section 1.7).

Over the past 15 years, there has been a significant increase in the number of studies focusing on the role of ApoE in various clinical conditions. These studies also focused on defining the

mechanisms involved in the manifestations of those conditions. The precise mechanism(s) by which apoE isoforms can compromise any of these clinical conditions is unknown, and investigators are searching for answers to the following questions: How do apoE isoforms in humans and in mice alter development, neuronal repair, and susceptibility to infectious agents? Is there a common mechanism associated with the apoE isoforms that is related to listed conditions (Table 2), or are there different mechanisms for the cardiovascular system, the nervous system, and the onset of viral infections? In any case, the importance of basic biomedical research on transgenic mice with various alterations in ApoE genotype is critical to developing an understanding of how these could be applied to clinical diseases, especially ocular diseases.

1.3. ApoE ϵ 4 is a risk factor for AD

Alzheimer's disease (AD) is a devastating neurodegenerative disease of unknown etiology. Many studies have described the epidemiological, clinical, biochemical, and pathological aspects of AD. Certainly, genetic and environmental factors play a role in the etiology of AD. Familial AD cases, which represents less than 5% of all AD, is primarily due to a genetic factor. However, in sporadic AD, a clinical condition representing greater than 95% of the current AD population, at least 3 factors can be associated with the onset of the disease. These factors include gender (females are more susceptible than males), age, and at least one genetic factor (the presence of the ApoE ϵ 4), which has been suggested as being a significant risk factor for the onset of AD. However, the nature of the involvement of ApoE ϵ 4 in this devastating neurodegenerative disease requires further investigation. While the etiology of sporadic AD is unknown, one hypothesis currently being tested is that an infectious/inflammatory agent, such as HSV-1, combined with the presence of the ApoE ϵ 4 allele could significantly increase the risk factor for AD (Tables 2 and 4). The following section addresses HSV-1 neuronal infections coupled with the ApoE alleles.

1.4. HSV-1, apoE isoforms and AD

Fraser et al. (1981) was the first to report evidence of HSV-1 DNA in a human brain; a possible relationship between HSV-1 and AD was first suggested by Ball et al. (1982). Despite a few early reports being negative, with respect to the detection of HSV-1 DNA in human brains (Middleton et al., 1980; Roberts et al., 1986; Taylor and Crow, 1986), there has been a continuous increase in the percentages of brains and trigeminal ganglia (TG) from both AD and non-AD patients reported to harbor HSV-1 DNA. Subsequently, Professor Ruth Itzhaki has extensively investigated the roles of HSV-1 and the ApoE allele genotype in AD. Table 4 summarizes the results of these human studies relating to HSV-1, the ApoE genotype, TG, and the brain (Itzhaki et al., 1997; Itzhaki and Lin, 1998; Lin et al., 1995, 1996, 2002). Although there have been reports that did not show a statistical relationship among HSV-1 DNA, AD, and the presence of the ApoE allele ϵ 4 (Beffert et al., 1998; Itabashi et al., 1997), it is important to note that these studies were limited by sample size, thus hampering the possibility of conclusively determining whether the ApoE ϵ 4 allele in combination with the presence of HSV-1 DNA was indeed a risk factor in the onset of AD. Regardless, the intriguing evidence favors the hypothesis that the ApoE allele ϵ 4 and HSV-1 DNA are, together, a risk factor for the onset of AD. Furthermore, there is evidence that the ApoE ϵ 2 allele offers protection/decreased risk for AD (Colangelo et al., 2002; Compton et al., 2002; Corder et al., 1993; Farrer et al., 1997; Roses et al., 1995; Roses, 1996; Rubinsztein and Easton, 1999).

1.5. ApoE alleles: risk factors associated with increased susceptibility and/or severity to HSV-1 infections

1.5.1. Human studies—Specific ApoE genotypes have been strongly suggested to be involved as a risk factor in certain viral infections. Two studies have assessed the role of ApoE

genotypes on two frequent HSV-1 diseases: herpes labialis and ocular HSV-1 keratitis. Lin et al. (1995, 1998) reported that the presence of the apoE ϵ 4 isoform could be a risk factor for herpes labialis, an oral-facial lesion caused primarily by HSV-1. The ApoE ϵ 4 allele frequency was reported to be significantly higher in subjects with HSV-1 labialis in comparison with age-matched subjects. In a clinical study of herpes keratitis in 46 patients, no association with the frequency of ApoE ϵ 4 allele was found (Lin et al., 1999). In this study, the patients evaluated presented with heterogeneous herpetic ocular diseases, including dendritic, geographic, and stromal keratitis. This study lacks a detailed clinical description and characterization of the ocular herpetic lesions and also has a small sample size. However, a higher frequency of association of ApoE ϵ 2 was reported (13%), which was almost twice that predicted in the general population (approximately 7%). No other study has been done to confirm these results. To the best of our knowledge, there have been no other studies in herpes labialis or herpes keratitis on the status of the possible risk factors of ApoE alleles and any other human HSV infections. Thus, more clinical and experimental studies are needed.

1.5.2. Mouse studies: ApoE alleles—A study by Burgos et al. (2002) reported the acute pathogenesis of HSV-1 in knockout and wild type mice using: (1) C57BL/6J; (2) C57BL/6J-ApoE^{tm1anc} (ApoE $-/-$); and (3) the hemizygote ApoE (+/-) mice. All mice were given IP injections of HSV-1 strain KOS. Viral quantitation was determined at various times post-inoculation. The study concluded that the ApoE gene dose is directly proportional to the neuroinvasiveness of HSV-1. Comparing the three phenotypes, the ApoE +/+ was more susceptible (higher viral load) than the hemizygote ApoE +/- (lower viral load), and the homozygote ApoE $-/-$ was the least susceptible (lowest viral load). In another study, Burgos et al. (2005) reported using male and female homozygous knock-out [ApoE ($-/-$)] and hemizygote (+/-) mice derived from breeding the C57BL/6J parent with the ApoE ($-/-$) knockout. This study concluded that these female mice were more susceptible to HSV-1 than the males since, during acute infection, there was significantly more HSV-1 DNA in the TG of female mice compared to the males. In studies using “knock-in” mice of human ApoE ϵ 3 (B6.129P2-TgH^{APOE3} N8) and human ApoE ϵ 4 (B6.129P2-TgH^{APOE4}), the ϵ 4 bearing mice had a higher burden of HSV-1 DNA in neural tissues, while the ApoE ϵ 3 mice had viral DNA loads that were low or not detectable (Burgos et al., 2003). Specifically, the mouse brains of ApoE ϵ 4 mice had significantly higher loads of HSV-1 than the ApoE ϵ 3 in all four brain regions (mid-brain, ventricles, cortex, and cerebellum). This report supplies direct evidence that the human ϵ 4 increases the susceptibility, severity, and neuroinvasiveness of HSV-1 compared to mice possessing human allele ϵ 3. Based on recent results reported (Bhattacharjee et al., 2006) from our lab and our understanding of the current concepts of ocular HSV-1 neurovirology, we have hypothesized, in Figs. 1 and 2, the pathogenesis of acute infection, development of latency, and neuronal reactivation based on ApoE genotypes.

1.6. ApoE alleles: risk factors associated with protective effects – reduced severity – against viral infection other than HSV

In other studies examining the affects of the ApoE genotype on viral infection, Toniutto et al. (2004) and Wozniak et al. (2002) reported that the ApoE ϵ 4 allele protects against severe liver damage caused by the hepatitis C virus (HCV). Both reports agree that there is no correlation with any ApoE genotype, relative to HCV susceptibility. In the study of Wozniak et al. (2002), gender differences were not assessed, and Toniutto et al. (2004) noted that the ApoE ϵ 4 allele in male patients resulted in significantly less progression of liver fibrosis. This, to the best of our knowledge, is the first clinical report of a contribution of gender and ApoE alleles altering – reducing in this case – the severity of a viral disease, such as HCV. Although the mechanism(s) of the HCV and ApoE ϵ 4 interaction are not known, Wozniak et al. (2002) speculated that repair mechanisms and/or HCV uptake and/or spread into liver cells could be the major mechanisms involved in reducing the severity of liver fibrosis. Gender was

not evaluated relative to liver damage by Wozniak et al. (2002), and no association of age or ethnicity was given in either report, indicating the need for more comprehensive studies involving multiple factors.

1.7. ApoE alleles: risk factors associated with ARMD

Numerous clinical investigations (Baird et al., 2004; Klaver et al., 1998; Lucotte et al., 1997; Pang et al., 2000; Schmidt et al., 2000; Schultz et al., 2003; Simonelli et al., 2001) have been conducted to determine if there is a risk factor associated with ApoE alleles and ARMD. Baird et al. (2004) reported a statistically significant association showing that the ϵ 4 allele is protective against ARMD because it delays the onset of the disease, while the ϵ 2 allele has a modifier effect, which decreases the mean age of onset of ARMD. These studies are supported by others, such as Klaver et al. (1998). But there are contradictory reports that suggest a lack of association of the ApoE alleles with ARMD (Pang et al., 2000; Schmidt et al., 2002; Schultz et al., 2003). The reason for these contradictory findings is not known. In studies to determine the effects of apoE and cholesterol on retinal abnormalities in ApoE-deficient mice, ARMD is thought to occur, in part, because there is an accumulation of lipid-rich debris in Bruch's membrane (Malek et al., 2005; Ong et al., 2001). These studies showed significant retinal abnormalities, as well as abnormal changes, in cellular morphology in cholesterol-treated ApoE-deficient mice. To date, no ARMD studies have been done in mice with the knock-in of human allele's ϵ 4 or ϵ 2; however, Kliffen et al. (2000) used ApoE- ϵ 3-Leiden mice and reported the pathogenesis of the basal laminar (drusen), primarily when mice were fed a high fat (cholesterol) diet (Table 4). This animal study supports the involvement of ApoE alleles in the accumulation of extracellular deposits characteristic of ARMD. Dithmar et al. (2000) reported ultrastructural changes in Bruch's membrane of ApoE ($-/-$) deficient mice. Further studies with knock-in mice of ApoE human allele's ϵ 2, ϵ 3, and ϵ 4 could result in a more definitive determination and identification of the role(s) of ApoE alleles in ARMD.

In summary, there are clinical studies that support findings of alterations in pathogenesis related to ApoE alleles. The ϵ 4 may offer protection (low risk), while the ϵ 2 has detrimental effects, especially for age of onset of ARMD. However, other clinical investigations have reported no association, i.e. no change in risk factors related to any of the ApoE alleles. An important question to consider is, how can these apparently contradictory results be resolved? There are no specific animal models that fulfill all the criteria for human ARMD; however, mouse studies have linked cholesterol and ApoE alleles as potent factors in the modulation and/or contribution to retinal abnormalities (Malek et al., 2005). Thus, more human and animal studies are needed to definitively establish whether any ApoE allele is a risk factor for ARMD. Detailed statistical analysis (meta-analysis) of risk factors with a large, well-defined ARMD population should ultimately determine if there is a specific genetic risk factor between any ApoE allele and ARMD, as well as possible relationships of other factors associated with the onset, severity, and duration of ARMD.

1.8. ApoE isoform-dependent effects and hormones (estrogens and androgens)

In a review of ApoE alleles, hormones, and AD, Raber (2004) cites many examples of how androgens and estrogen coupled with apoE isoforms can contribute to significant alterations relative to cognitive impairment and the onset of AD. His review proposes 15 possible mechanisms that could be involved in the isoform-dependent effects of ApoE. We suggest at least 5 of these proposed mechanisms could be involved the regulation of HSV-1 isoform-dependent effects of apoE. These 5 possible mechanisms are: 1) the brain's ability to recover from environmental challenges, i.e. injury, inflammation, and oxidative damage; 2) neuronal apoptosis; 3) androgen receptor function; 4) endosomal trafficking; and 5) testosterone concentration. Examples of each possible mechanism and the relationship to HSV are: 1) Environmental challenges could include stress, trauma, chemical toxicity (lipid peroxidation

resulting in formation of 4-hydroxy-2-nonenal (HNE) and 8-hydroxyguanine (8OHG)), and fever (Valyi-Nagy and Dermody, 2005; Valyi-Nagy et al., 2000). 2) Apoptosis of neurons has been suggested to play a role in the establishment and maintenance of HSV-1 latency (Perng et al., 2000). 3) Androgen receptor function – Raber et al. (2002) have shown that androgen receptors can act against ApoE ϵ 4 induced defects and thus, reduce or block the cognitive defects. These receptors could be involved in reducing susceptibility and/or severity of HSV infection. This suggests that androgen receptors can overcome whatever mechanisms or regulations the apoE imposes on the transgenic mouse harboring the human ϵ 4 allele. Yirrell et al. (1987) reported that androgens offered protection against systemic HSV-1 infection in mice. 4) Endosomal trafficking (endocytosis) and lipid rafts have been suggested by us (Hill et al., 2004) as playing a role in anterograde and retrograde transport of HSV. One hypothesis is that the ApoE ϵ 4 allele could increase the transport of HSV to and from neural tissues to the peripheral sites of acute or recurrent infection. 5) Testosterone could reduce the susceptibility and/or severity of HSV-1 infection (Han et al., 2001). We suggest that the testosterone and the androgen functions could be overlapping with similar or different mechanisms. As noted earlier, testosterone (androgen) has been shown to reduce HSV susceptibility (Yirrell et al., 1987). The gender studies by Burgos et al. (2005) have shown that female mice are more susceptible than the males with the same ApoE genotype.

1.9. HSV-1, hormones, and ApoE

We know of no studies that have correlated apoE isoforms and HSV-1 infection with hormonal treatments in normal or neutered mice. Sex hormones have been reported to modulate the susceptibility of HSV-2 in a mouse genital model of acute infection. These studies showed that in ovariectomized mice, estradiol was protective (reduced severity) while progesterone increased severity (Gallichan and Rosenthal, 1996; Gillgrass et al., 2005a, b; Kaushic et al., 2003; Yirrell et al., 1987). The *in vivo* studies involving hormones and HSV are complex. For example, in combination, estrogen and progesterone offer protection at low inoculation doses of HSV-2. However, a high titer of HSV-2 overcomes the protective effect that the combined estrogen and progesterone exhibited (Kaushic et al., 2003). Han et al. (2001) reported that there were significant differences, based on gender, following ocular inoculation of HSV-1 in normal and gamma interferon mutant mice in a background of strain 129/SV/EV. In this genetic background, gamma interferon knockout and gamma interferon receptor knockout mice were used, and a gender difference with a significantly worse outcome for the male mice was reported. Additionally, both types of male knockout mice showed increased viral pathogenesis. This suggested that gamma interferon, a key neuroregulator, could be gender specific. Yirrell et al. (1987) showed that castration of male mice increased their susceptibility to HSV compared to female mice of the same strain. More importantly, testosterone administration to castrated males reversed this change. The conclusion was that testosterone reduced susceptibility and severity of HSV infection. Taken together, these reports support the hypothesis that gender (hormones) can significantly influence HSV susceptibility and/or severity. Most herpes virologists agree that viral strains, titers, mouse strains, gender, age, and route of inoculation can all significantly influence susceptibility and/or severity of HSV infections. In summary, current evidence in mouse models strongly suggests that ApoE ϵ 4 in female mice in a background of C57BL/6 exhibits the highest sensitivity and the most significant neuroinvasiveness when compared to the ApoE ϵ 3 genotype in the same genetic background.

1.10. Exogenous administration of apoE decreases neuronal damage caused by brain injuries

Horsburgh et al. (2000) assessed the ability of intraventricular infusion of apoE to reduce neuronal damage after global ischemia in ApoE knockout mice ($-/-$) compared to C57BL/6J mice ($+/+$). The apoE protein infusion reduced the neuronal damage by 50% in both the ApoE

knockout and the C57BL/6J mice when both were subjected to global ischemia. The ApoE knockout mice had significantly more damage relative to the parental C57BL/6 mice. This reduction in neuronal damage matched a reduction in lipid peroxidation in the ApoE deficient mice. Thus, this was the first report of the potential for the apoE protein to be used pharmacologically. We know of no other study that has administered the apoE protein to achieve a positive chemotherapeutic outcome. This study by Horsburgh et al. (2000) also demonstrates that the concentration of apoE available (exogenous source) can be a key factor in response to acute brain injuries, as noted by the effect of the administered protein in the C57BL/6J mice who also produce endogenous apoE. This study supports a critical role for the apoE concentration in the CNS, in response to injury, and demonstrates the unique potential of the apoE protein administration for the reduction of neuronal brain damage following acute injury.

In a related study, Lynch et al. (2005) tested a peptide derived from the apoE receptor binding region for therapy for brain injury. This apoE-mimetic peptide can cross the blood–brain barrier and can be given systemically. Lynch et al. (2005), similar to Horsburgh, showed in a mouse model that their apoE-mimetic peptide significantly reduced brain inflammation and improved functional outcomes after traumatic brain injury. These two studies provide evidence of the importance of apoE in brain injury and the chemotherapeutic usefulness of this unique protein (Lahiri, 2004).

1.11. Oxidative damage to neurons by HSV-1 may be correlated to the ApoE genotype

Valyi-Nagy et al. (2000) assessed the extent of oxidative damage in the mouse TG and brain studied over a long time (200 days). Even at 200 days post-inoculation, oxidative damage was documented by immunoreactive assays specific for HNE and 8OHG, markers of oxidative neuronal damage. In the acute and latent phase of HSV-1 infection, the TG and brain had focal, chronic inflammation and consistently detectable documentation of oxidative damage primarily involving neurons. Since the mouse apoE has been suggested to function phenotypically similar to the human apoE, we further suggest that the ApoE (–/–) knockout mice will exhibit reduced oxidative damage, compared to the ApoE (+/+) C57BL/6 mice.

Cellular injury can be caused by free radicals. When these cellular injuries occur, lipids undergo peroxidation and yield reactive by-products such as HNE and 8OHG, noted above. Antisera to HNE and 8OHG allow for assessment of oxidative damage in the TG and brain harboring latent HSV-1. Valyi-Nagy et al. (2000), using immunohistochemistry, showed that the oxidative damage following HSV-1 infection was due in part to these two compounds. Valyi-Nagy and Dermody (2005) recently reviewed the role of oxidative damage in the pathogenesis of viral infections of the neuronal system. They summarized the current evidence of active oxidative damage during HSV-1 neuronal latency. We have summarized the protective effects of ApoE e3 and the detrimental effects of ApoE e4 related to HSV-1 infection (Table 5).

In summary, we suggest that the anti-oxidative properties of apoE ε 3 relative to apoE ε 4 could reduce the oxidative damage, i.e., increased oxidative stress, caused by HSV-1. Conversely, the human apoE ε 4 would have less anti-oxidative properties and would increase susceptibility to oxidative damage. These biochemical studies, coupled with the therapeutic studies (Section 1.10), suggest dynamic neuronal activity in both HSV-1 neuronal infections and CNS injury. Chemotherapeutic administration of protective apoE molecules might reduce the HSV-mediated cellular injuries and even block or reduce HSV-1 neuronal reactivation.

2. Summary

This review has provided an overview of ApoE allele genetic associations (positive and negative) with specific clinical conditions (Table 2), as well as examples in mouse genetic

studies that also provide evidence of a positive or negative association relative to apoE isoforms, especially HSV-1 ocular infection. The mouse studies using genetic variations such as ApoE knockout (−/−), ApoE hemizygote (+/−), and human ε 3 or ε 4 knock-ins have been important in assessing association of genotype with phenotypic outcomes. Clinical studies, by their very nature, utilizing a very heterogeneous population, must accumulate extensive pertinent clinical information to allow a large-scale statistical analysis. All studies have limitations, whether they are with transgenic mice or clinical evaluations assessing an ApoE allele relative to susceptibility and/or severity of infection. However, by the force of experiments including both mouse genetic models and clinical studies, information about the relationship between a particular host factor (ApoE alleles) and a clinical condition, for example HSV-1 infection, and risk association can be statistically determined. One prediction about the differential outcome of HSV-1 pathogenesis between ApoE allele types ε 3 and ε 4 in mouse strain background C57BL/6J has been depicted in Figs. 1 and 2. Using these predictions, one can develop strategies for early identification of clinical problems, as well as the potential for early drug therapy and intervention, even when the clinical condition coupled with a specific genetic factor is associated with increased severity and/or longer duration.

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Fig. 1.
Hypothesis of the viral and host characteristics based on ApoE genotype for acute HSV-1 pathogenesis and establishment of neuronal latency.

Fig. 2.

Hypothesis of viral and host characteristics based on ApoE genotypes for HSV-1 latency and neuronal reactivation.

Table 1

Estimated human genotype frequency of ApoE

$\epsilon 3/\epsilon 3$	$\epsilon 3/\epsilon 4$	$\epsilon 3/\epsilon 2$	$\epsilon 4/\epsilon 4$	$\epsilon 2/\epsilon 2$	$\epsilon 4/\epsilon 2$
~55%	~25%	~15%	~1–2%	~1–2%	~1–2%

These frequencies are generally accepted for most populations, especially with regard to the USA. Numerous reports (Farrer et al., 1997; Gerdes, 2003; Lucotte et al., 1997) have also noted some variations in genotypes based on gender, nationality, and geographic regions.

Table 2
Risk association with ApoE alleles in clinical groups with specific clinical conditions

Risk association	Genotype	Clinical condition or infection	Authors
High	e4/e4	Alzheimer's	Bennett et al. (2003), Corder et al. (1993), Huang et al. (2004), Hoyt et al. (2005), Mosconi et al. (2005), Roses et al. (1995), Roses (1996), Rubinsztein and Easton, 1999
		Alzheimer's + HSV	Cheon et al. (2001), Corder et al. (1998a), Federoff (1999), Hendrie (1998), Itzhaki et al. (1997); Itzhaki and Lin (1998), Itzhaki et al. (2002); Lin et al. (1996, 2002)
		HIV	Corder et al. (1998b)
		Cardiovascular disease	Frank et al. (2002)
		Diabetic neuropathy	Bedlack et al. (2003), Messier (2003)
		Stroke	Gorelick (2004)
		Cerebral vascular disease	Kim et al. (2003), McCarron et al. (1998)
		Head (brain) injury severity	Blackman et al. (2005), Friedman et al. (1999), Leclercq et al. (2005)
		New learning	Baxter et al. (2003)
		Aggressive behavior	Craig et al. (2004)
Low or protective	e2/e2	Intracerebral hemorrhage	McCarron et al. (1998)
		Kidney transplantation	Hertzberg and Pope (2000)
		Alzheimer's	Compton et al. (2002), Corder et al. (1993, 1994), Farrer et al. (1997), Hoyt et al. (2005), Roses et al. (1995), Roses (1996), Rubinsztein and Easton (1999)
		HSV-1 encephalitis	Lin et al. (2001)
		Cardiovascular disease	Frank et al. (2002), Freitas et al. (2002)
		Macular degeneration	Baird et al. (2004)
		HSV-1	Prober (2005)
		Cardiovascular disease	Frank et al. (2002), Freitas et al. (2002)
		Macular degeneration	Klaver et al. (1998), Baird et al. (2004)
		Wilson's disease	Schiefermeier et al. (2000)
None	e2/e2 e4/e4	Hepatitis C	Toniutto et al. (2004), Wozniak et al. (2002)
	e3/e3	Hepatitis B	Percy et al. (2003)
	e4/e4	Multiple sclerosis	Minagar et al. (2004)
	All genotypes	Huntington disease	Saft et al. (2004)
		Parkinson's disease	Hemling et al. (2003)

Table 3

Summary of selected studies using transgenic mice models with different ApoE genotypes that alter clinical conditions

Clinical condition or infection	Genotype	Adverse risk association	Protection/ lack of association	Authors
HSV-1 CNS	ApoE (-/-)		Low	Burgos et al. (2002)
HSV-1 CNS	ApoE e3		Low	Burgos et al. (2003)
HSV-1 CNS	ApoE e4	High		Burgos et al. (2005)
HSV-1 CNS	Female	Very high		Burgos et al. (2003)
	ApoE e4			Burgos et al. (2005)
Macular degeneration	ApoE (-/-)	High		Dithmar et al. (2000), Malek et al. (2005), Ong et al. (2001)
Cardiovascular disease + HSV	ApoE (-/-)	High		Alber et al. (2000)
Cardiovascular disease + estrogen	ApoE (-/-)		Relative protection	Hodgin et al. (2001)
Global ischemia	ApoE (-/-)	High		Horsburgh et al. (1999, 2000)
Global ischemia + estrogen	ApoE (-/-)		Neuroprotective	Hodgin et al. (2001)
Atherosclerosis + CMV	ApoE (-/-)	High		Hsich et al. (2001)
Ischemic brain injury	ApoE (e4/e4)	High		Mori et al. (2003)
Retinal abnormality	ApoE (-/-)	High		Ong et al. (2001)
Astrocyte activity	e3/e3		Relative protection	Cheon et al. (2001)
Brain function	ApoE (-/-)	Increased dysfunction		Raber et al. (2000)
Anxiety	ApoE (-/-)	Increased anxiety		Robertson et al. (2005)
Atherosclerosis + IFN- γ	ApoE (-/-)	Potentiates		Gupta et al. (1997)

Table 4

Summary of studies assessing human brain and TG for HSV-1 DNA

Methods	HSV-1 positive/total		Anatomical regions/comments	Year	Authors
	AD	Non-AD			
Fluid hybridization	0/5	NT	Temporal & frontal neocortex	1980	Middleton et al. (1980)
Southern blots	NT	6/11	Total brain	1981	Fraser et al. (1981)
Southern blots	0/7	0/29	Frontal neocortex	1986	Taylor and Crow (1986)
Antigen detection	0/25	0/32	Temporal neocortex	1986	Roberts et al. (1986)
RNA in situ hybridization for LAT	0/21	0/19	Hippocampus, pons & medulla	1990	Deatly et al. (1990)
TK PCR	17/21	9/19	TG		
TK PCR	8/8	6/6	Temporal & frontal neocortex; hippocampus	1991	Jamieson et al. (1991)
TK PCR	14/21	9/15	Frontal & temporal neocortex; hippocampus	1992	Jamieson et al. (1992)
TK PCR	0/9	0/5	Occipital region(s) in elderly	1992	Jamieson et al. (1992)
TK PCR	NT	0/15	Occipital region(s) in infants	1992	Jamieson et al. (1992)
Four PCR targets	NT	14/40	Frontal neocortex	1994	Hertzberg and Pope (2000)
Four PCR targets	NT	26/40	TG	1994	Baringer and Pisani (1994)
TK; ICP-0 PCR	28/36	23/36	Frontal neocortex	1996	Lin et al. (1996)
gD PCR	14/46	5/23	Brain	1997	Itabashi et al. (1997)
TK PCR	14/17	8/10	Frontal & temporal neocortex	1997	Lin et al. (1997)
PCR	49/84	41/75	Brain	1997	Itzhaki and Lin (1998)
gD PCR	24/33	54/73	Brain	1998	Beffert et al. (1998)
gD PCR	10/10	10/10	Frontal neocortex & cerebellum	2001	Cheon et al. (1998)
PCR (quantitative)	10/22	8/20	TG	2001	Ball et al. (2001)
gB PCR	45/61	20/48	Frontal & temporal neocortex	2002	Lin et al. (2002)

Modified from Pyles (2001). **Bold** print indicates studies that examined for both HSV-1 and ApoE allele status. References (Hendrie, 1998; Lin et al., 1996, 2002) in this table, were suggestive of a positive relationship between HSV-1 plus ApoE e4 and development of AD. HSV-1, herpes simplex virus; AD, Alzheimer's disease; NT, not tested; LAT, HSV-1 latency-associated transcript; TG, trigeminal ganglion; TK PCR, polymerase chain reaction-based detection for viral thymidine kinase; gB & gD, HSV-1 glycoproteins.

Table 5

Protective effects of ApoE e3 and detrimental effects of ApoEe4 in neural tissue related to HSV-1 infection (Huang et al., 2004)

ApoE3: protective effects	ApoE4: detrimental effects
Stimulates neurite outgrowth [*]	Inhibits neurite outgrowth [*]
Protects from neurodegeneration [†]	Causes neurodegeneration [†]
Antioxidative effect (protective)	Oxidative stress
	Potentiates A β -induced lysosomal leakage
Protects from cognitive decline	Causes cognitive decline
Maintains androgen receptors	Decreases androgen receptor [‡]

^{*} This factor could be involved in neuronal response after HSV-1 infection (latency).

[†] This factor could be involved in neuronal response during acute HSV-1 infection.

[‡] The decline in androgen receptors could increase susceptibility to HSV-1 infection and/or neuroinvasiveness of HSV-1.