Apolipoprotein E: A Meta-Analysis its Effects on Children and Adults

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Abstract:

More than 500,000 children in the United States suffer a brain injury requiring medical evaluation annually[1]. Different isoforms of the protein, apolipoprotein E (ApoE), have been shown to impact the outcome of traumatic brain injuries (TBI) in adolescents and adults.[2] Specifically, the ApoE4 allele is a strong risk factor for late-onset Alzheimer's disease (AD), while ApoE2 and ApoE3 have been shown to be protective against the neurodegenerative disease later in life.[3,4] Adolescents who experience TBI and carry the ApoE4 allele have been shown to develop a variety of disorders later in life, one of which being AD.[5] In several studies, the presence of the ApoE4 gene has been identified as one of the factors that influences the long term effects of TBI.[6] A meta-analysis that examined over 300 cases of pediatric TBI found that at six months post-injury, there is a 2.6 times higher odds of poor outcomes in children that had at least one ApoE4 allele in comparison to children without the allele.[7] Although ApoE4 has been extensively researched in the context of neurodegeneration in adults, new studies suggest the importance of studying this protein in the context of TBI in children.[8] This review discusses recent research regarding the relationship between TBI and ApoE4-related neurodegeneration in adolescents and adults. This review addresses the question: How does ApoE4 affect the likelihood of neurodegenerative disease for those who have experienced TBI?

Introduction:

Traumatic brain injuries (TBI) are a leading cause of disability in children with more than 500,000 children suffering a brain injury requiring medical evaluation annually.[9] Moderate to severe TBI result in disability in more than 60% of cases.[10] While the ApoE2 and ApoE3 genes are not associated with premature neurodegeneration, ApoE4 has been strongly linked to Alzheimer's disease (AD) development.[3] Furthermore, recent evidence has shown that TBI may worsen the clinical outcomes for those who carry the ApoE4 gene.[6] Specifically, TBI patients who carry ApoE4 are at increased risk for accelerated neurodegeneration.[2,6]

Molecular Biology:

Apolipoprotein E (ApoE) is a lipid transport protein in the brain, which is made by astrocytes.[9,11] Astrocytes are an essential cell type that plays a critical role in lipid production and transport in the central nervous system.[9,11] After ApoE is produced, it binds to lipids such as cholesterol and phospholipids, which are then utilized in different metabolic pathways in the

brain.[4,9] The ApoE protein is used to repair neurons and grow neuronal pathways. When the brain is exposed to traumatic brain injuries (TBI) and other neurological stressors, the brain has been shown to increase lipid metabolism.[2] In response to these injuries, ApoE has been found to accumulate in cortical synapses.

Three different isoforms of ApoE are known to have different roles in various neurological conditions.[3,4,9] The three isoforms of ApoE are ApoE2, ApoE3, and ApoE4. Many studies have shown that ApoE2 and ApoE3 have more efficient lipid metabolism relative to the ApoE4 protein.[2] In a study that used ApoE4 knockout mice, researchers tested how the absence of this protein affected the response to oxidative stress.[3,12] Oxidative stress is how harmful oxidative species accumulate in the brain.[3,12] This state is usually due to the imbalance of production and reduction of reactive oxygen species (ROS) in the brain by oxidative and antioxidative processes, respectively. [3,12] In this study, researchers used diets of increased iron or decreased folate to induce oxidative stress. They found that the brains of the ApoE-knockout mice had increased levels of antioxidants, yet they had more oxidative damage.[3] This suggested that increased antioxidant levels could not rescue the oxidative damage in ApoE-knockout mice.[3,13]

ApoE2 and ApoE3 have also been shown to have more promising results in neurodegenerative recovery.[3,13] The mice were used to demonstrate the greater lipid metabolism that ApoE isoforms could affect. In addition to this impaired lipid metabolism, ApoE4 has been linked to oxidative stress in other neurological conditions such as Alzheimer's Disease (AD).[3,4,9] TBI are one mechanism that increases oxidative stress in the brain.[3,13] Accumulated evidence has also shown ties between ApoE4 and TBI-related premature neurodegeneration.[2,3,13]

ApoE2 and ApoE3 alleles have minimal impacts on neurodegenerative risk, with a total of 86% of the studied Caucasian population carrying one of these two alleles. [1,4] In the same study, 14% of this studied population who had the ApoE4 isoform were shown to have a higher frequency of neurodegenerative disease.[1] While many questions remain regarding the precise role of ApoE4, apolipoprotein E clearly is involved in many metabolic processes and injury responses.

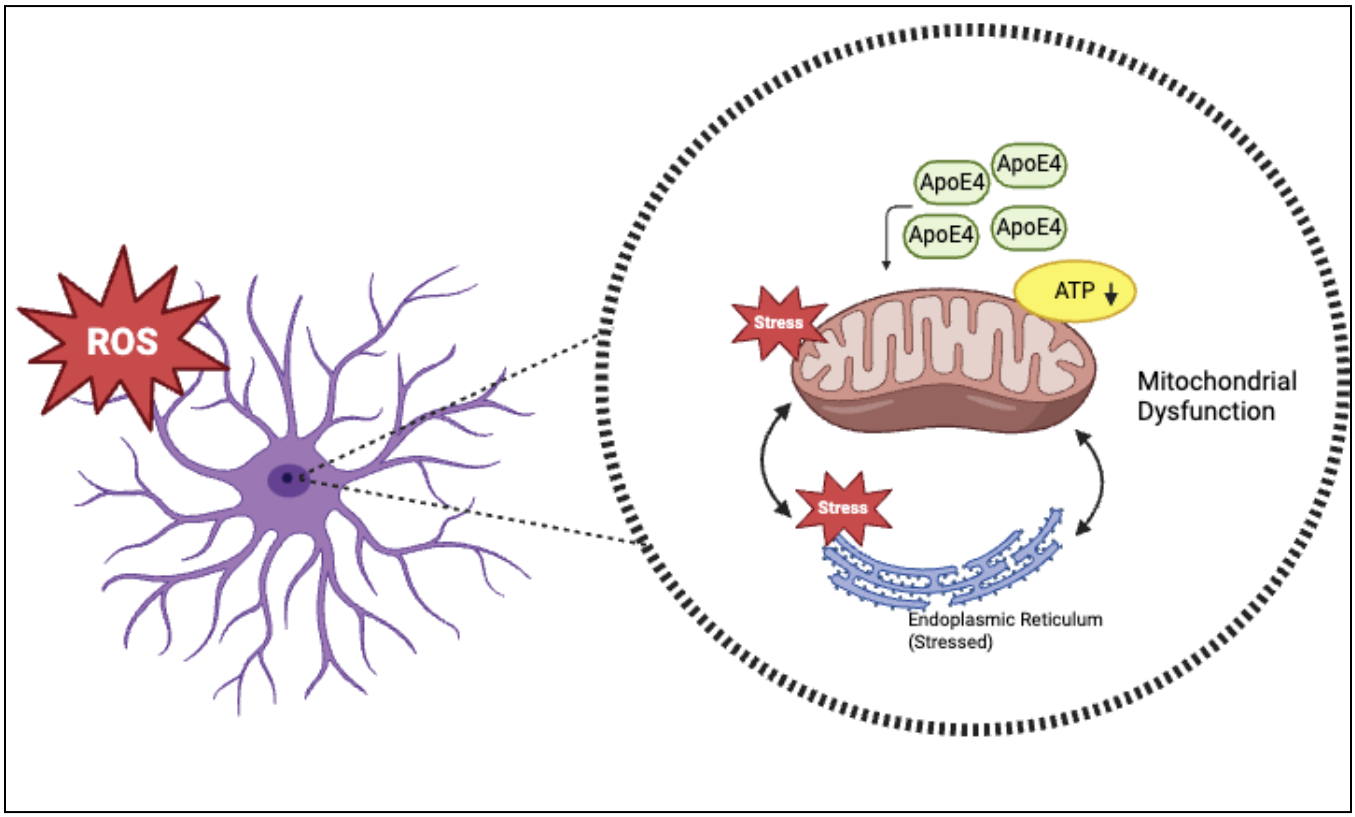

Figure 1. Current Model of Cellular Response to Stress. *When neurons experience oxidative stress, the ApoE4 protein reduces the efficiency of the mitochondria. This reduction in efficiency leads to a decreased production of ATP. Following the dysfunction in the mitochondria, many other cellular organelles are affected, such as the endoplasmic reticulum.*

ApoE in adults and children;

Many studies have shown that Apolipoprotein E4 (ApoE4) is a risk factor for developing Alzheimer's disease (AD).[3,4,9,14,15] AD is one of many genetic disadvantages that ApoE4 can influence. Many studies have been conducted in which neuronal changes from injury impact the ability for the brain to recover, thus having an increased chance of AD development.[3,14] Patients with Alzheimer's disease often have abnormal protein deposits (amyloid beta and Tau) in their brains.[9] Though the exact role is unclear, studies have suggested a connection between deposits of these two proteins in the brain and the development of AD.[9] One study examined the sequelae of temporal changes that occur in the brains of gerbils after they experienced traumatic brain injuries (TBI).[14] After about a week, researchers found that ApoE was present and active in the brain tissue that was injured.[14] This study demonstrates that ApoE pools around injury sites and plays a role in the neuronal degeneration process.[14] However, a limitation of this study is that the authors did not express which isoform of ApoE

was analyzed.[14] In another study, done in 2003, researchers tested the outcomes of injuries with a population that consisted of 100 patients who experienced intracranial injuries.[7] Of these injuries, the patients with ApoE4 had increased outcomes of death, vegetative states, and disability.[7] All outcomes of this experiment, including the patients who recovered, experienced a loss in neuroplasticity and aspects of brain function.[7]

In adults, neuroplasticity describes a complex process of synapse formation and some degree of regeneration of neurons.[16,17] Specifically, this process becomes crucial after injury.[16,17] One common theory to describe neuroplasticity in the field of neuroscience is Hebb's postulate.[18] This theory states the “neurons that fire together, wire together.” In other words, neuronal pathways are formed when signals are sent out between them. The synthesis of these new neuronal pathways is a sign of increased neuroplasticity in the brain.[17,18] The ApoE4 allele is thought to hinder neuroplasticity. Given the role that ApoE plays in facilitating neuronal communication in the brain, many studies have drawn connections between the protein and TBI.

As TBI and many other neurodegenerative diseases become more known, the effects that ApoE can have on children are much less researched in comparison to adults. Although there has been an increase in studies examining ApoE, many of these studies are conducted in vitro using adult cells.[19] Very few studies have examined the role of ApoE4 in children or models of children. One study from 2015 examined the role of different isoforms of ApoE on the morphology of dorsal root ganglia.[19] This study shows that ApoE4 restricts the growth of neurons while ApoE3 promotes the growth of neurons.[19] The neurons that had ApoE3 displayed increased ramification, or branching.[19] While this was an in vitro study, this suggests that neuronal recovery after childhood TBI may be restricted or completely inhibited in children that carry the ApoE4 allele.[6,19] Other studies have shown that these children also have an increased risk of developing AD.[6,10,20] In neurobiology, ApoE is critical in lipid production and transport, with lipids playing an essential function in neural membrane composition.[2,9,13] In children who have had TBI, capacity for neuron repair is extremely important to allow optimal healing from the injury.[5,10,21] Similar to the association between Alzheimer’s dementia and ApoE4, the presence of the ApoE4 allele in people with a history of TBI correlates with worse clinical outcomes.[13,14,20] Studying the role between ApoE4 and TBI in children will be critical to advance treatments and prognosis for kids who undergo TBI.

Public Opinion:

Advancements in understanding the function of Apolipoprotein E (ApoE) point toward its potential role in modulating healing from traumatic brain injuries (TBI). This has potential implications regarding screening for the presence of ApoE4 in children, given its association with worse clinical outcomes after TBI. Contact sports have been a significant risk for TBI in children with many TBI cases coming from football and wrestling.[8] A 2016 study asked 846 student-athletes from 26 schools across 20 states if they had heard about genetic testing for ApoE.[8] Most questioned athletes showed little to no knowledge about ApoE testing while about half of the athletes also had little to no concern about genetic risks in contact sports.[8] As more children enter sports with the genetic code for ApoE4, there will in turn be an increased number of worse clinical outcomes relating to TBI cases.[8,21] In comparison to athletes, another study has shown that TBI has become the leading cause of disability for all children, regardless of athletic background.[12] A combination of disability and the frequency of ApoE4 in children who play contact sports could be detrimental to the future generation of athletes and generations as a whole. Many researchers have proposed genetic testing, although as ApoE is further researched, many parents of children are fearful of the restrictions that their children may face.[8] Recognition of the severe implications of TBI can be seen through recent advancements and public attention to protective gear for athletes. One viable option would be to use this research to influence public policy on genetic testing as a source of prevention. A more conservative resolution to this growing issue would be to stop at-risk children from playing contact sports at all. This points to the importance of further research into the role of ApoE in children with TBI to further understand the importance of this issue, with the ultimate goal of influencing and improving public policy.

Conclusion:

The functions of apolipoprotein E (ApoE) have been shown by various studies to have many effects on the brain which is very dependent on specific isoforms that a person may carry.[4,6,13] Though ApoE has not been thoroughly studied to the point of certainty to worsen outcomes in the context of children with traumatic brain injury (TBI), extensive research has reinforced the importance of ApoE in neurodegeneration.[2] A multitude of neurodegenerative diseases, such as Alzheimer's disease (AD) have been found to have much worse outcomes when patients are carriers of the ApoE4 isoform in relation to ApoE2 and ApoE3.[3,4,9] The effect of ApoE on children has had many researchers suggest that TBI acquired in childhood could lead to disability and neurodegeneration later in a child's life.[6,22,23] This points to the importance of further research being done on this topic with the ultimate goal of improving public policy. This course of action could prevent disability in children, especially those who play contact sports.

Citations

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