The neuronal functions of human apolipoprotein E

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Abstract

Introduction
Genetic polymorphisms modulate the function of human apolipoprotein E and disease susceptibility. Inheriting the apolipoprotein E4 allele is linked to higher peripheral cholesterol levels and increased risk for atherosclerosis. This gene allele is also a major genetic risk factor for Alzheimer’s disease, but it is unclear how harbouring the apolipoprotein E4 allele causes earlier disease manifestation. This is because little is known about the function of human apolipoprotein E in the brain. While intranasal insulin can improve cognition, this has little effect on apolipoprotein E4 non-demented elderly subjects. These subjects are also found to have lower cerebral glucose metabolic rate.

This critical review discusses the neuronal functions of human apolipoprotein E.

Conclusion

Put together, this suggests that apolipoprotein E isoforms could modulate brain metabolism. In this article, we have discussed a possible role for apolipoprotein E in regulating brain insulin signalling.

Introduction

Human apolipoprotein E (ApoE) is located on chromosome 19 and encodes a 35 kDa glycoprotein that exists in three isoforms: E2, E3 and E4. These isoforms differ by amino acid substitutions at two positions (residues 112 and 158). The amino acid changes are believed to alter the protein charge and stability, thereby contributing to its distinctive physiological functions.

Although sequence analysis has shown that ApoE4 is in the ancestral state in humans, ApoE3 has increased in frequency through evolution as the most common isoform, occurring in 70% of most populations, whilst human ApoE4 and human ApoE2 represent 16% and <10% of the human population, respectively.

ApoE belongs to a group of lipid carrier molecules and is vital in the cholesterol homeostasis of the body. It is one of the key components of lipoproteins that regulate the metabolism of lipids in the body through ApoE receptors and related proteins. ApoE is widely expressed in various tissues with the highest expression in the liver and brain.

Emerging studies have suggested that its functions may extend beyond lipid metabolism to include maintenance of normal brain function. Structural variations in the ApoE isoforms might affect its preferential binding to lipoprotein receptors that in turn could potentially remodel the lipid metabolism and/or neuronal signalling. In this critical review, we have discussed the neuronal functions of human ApoE.

Discussion

The authors have referenced some of their own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. Animal care was conducted in accordance with the institutional guidelines.

What are the functions of ApoE in the central nervous system (CNS)?

The human brain contains up to 25% of cholesterol. Since it is essential for myelin production, function and integrity, it is an important task to maintain the cholesterol homeostasis in the CNS. In the CNS, cholesterol is regulated by glial cells and transported to the neurons. Cholesterol dysfunction has been associated with ageing and the development of neurodegenerative diseases including Alzheimer’s disease (AD).

The blood brain barrier restricts the exchange of lipoproteins and ApoE between the peripheral nervous system and the CNS. Hence, lipid metabolism in both systems is mutually exclusive. In the CNS, lipoproteins are primarily synthesised by glial cells, especially astrocytes, and ApoE may play a significant role in the transportation of these lipoprotein complexes. These ApoE-containing lipoproteins can also interact with ApoE receptor-rich neurons for neuronal repair.

Inheriting the ApoE4 isoform is a strong genetic risk factor for human diseases like atherosclerosis and AD. In AD, ApoE4 is linked to early disease onset. In addition, altered neuronal ApoE expression is linked to neurological disorders such as Niemann-Pick Type C (NPC) and AD. In AD, ApoE expression may regulate the clearance of amyloid beta (Aβ).

The role of ApoE in AD

AD is a widespread neurodegenerative illness and also the leading cause of dementia. The most prominent symptom of AD is decline of recent memory. As the disease develops, other cognitive abilities such as language, movement and sightedness, begin to deteriorate and eventually the disease results in global cognitive decline. The classical hallmarks of AD include extracellular amyloid plaques consisting of Aβ aggregates and intracellular neurofibrillary tangles.
ApoE is the second major risk factor (after ageing) and the most important genetic factor related to AD. Inheriting the ApoE4 allele is linked to early AD onset and an accelerated rate of disease progression. Changes in ApoE expression are also thought to be involved in the development of AD. The lower ApoE expression in AD is believed to be due to degradation as ApoE4 is more susceptible to chemical and thermal modification. While ApoE has been suggested to be involved in Aβ catabolism, the underlying molecular events that precede dementia and involve the role of ApoE, remain elusive.

The role of ApoE in NPC disease
NPC is an inherited autosomal recessive disorder caused by a failure in cholesterol trafficking due to mutations in the NPC1 or NPC2 proteins. NPC1 is a large transmembrane protein of 1278 amino acids. It is localised to the late endosomal membrane and has been associated with cholesterol trafficking. Mutations on the NPC protein will result in the accumulation of unesterified cholesterol and other lipids in the peripheral tissues, particularly in the liver and spleen.

However, this NPC1 deficiency has little effect on the plasma cholesterol, only increasing plasma triglyceride. Interestingly, the CNS is uniquely spared from this lipid accumulation and a significant reduction in the cholesterol is observed. As the disease progresses, the subjects develop extensive neurodegeneration of the cerebellum, especially in the thalamus and the purkinje cells layer.

Several studies have also noted that both AD and NPC bear strong pathological resemblances such as neurofibrillary tangles, tau pathology and increased Aβ generation. Furthermore, NPC subjects bearing the ApoE4 allele display faster disease progression. Researchers, including us, have also observed increased ApoE expression in the brain of NPC transgenic mice. Recently, we reported that the altered ApoE expression is linked to impaired brain insulin signalling in the NPC mice. Collectively, these studies suggest a pathogenic role for ApoE in the neurodegenerative process in NPC.

The role of ApoE in brain insulin signalling
Insulin is an important modulator of growth and metabolic function. A reduction in insulin signalling activity can result in diseases such as diabetes and AD. Most of our knowledge on insulin function is derived from observations in the peripheral organ systems. However, a recent study has shown a functional separation between brain insulin and peripheral insulin. Although studies have shown that insulin receptors are abundantly expressed in the brain, little is known about brain insulin function.

Insulin is able to enhance cognitive performance in non-diabetics, but this effect is weaker in ApoE4 carriers. It is unclear if this is due to, or possibly leads to, lower cerebral glucose metabolic rates (CMRglu) detected in non-demented ApoE4 subjects. However, it is possible that this impairment could nullify the response to the administered insulin (Figure 1). Since brain ApoE levels are known to be isoform-dependent, it is possible that the altered expression can contribute to the changes in brain glucose metabolism.

The role of ApoE in brain glucose metabolism and cognition
Glucose is the most common source of energy for the body and it is important to maintain its regulation. In the peripheral system, an overdose of hyperphosphorylated tau protein. Clinical diagnosis of AD is still in its infant phase with the lack of an established and non-invasive approach to accurately determine the severity or progression of the illness.

Figure 1: Role of ApoE in neuronal insulin signalling. ApoE4, but not ApoE3, inhibits the function of the insulin receptor, impairs the activation of the insulin-signalling cascade. This impairment affects the trafficking of the glucose transporter to the plasma membrane and reduces the movement of glucose molecules into the cell.
blood glucose may lead to diabetes mellitus while low blood glucose can cause hypoglycaemia\(^4\).

As the human brain consumes approximately 30% of the total body glucose, any disruption may affect the health of the CNS\(^4\). It is widely recognised that hypometabolism occurs in a certain region of the brain with AD and ageing\(^{45,46}\). For long, there has been contention as to whether this phenomenon precedes neurodegeneration or results from the lower brain activity observed in these groups of people\(^45,46\).

Emerging studies in population and animals seem to show inclination towards the idea that lower brain glucose metabolism may be indicative of cognitive decline later in life\(^7,46\). It is also noteworthy that most studies have associated ApoE4 as one of the major genetic risk factors for AD with glucose metabolism.

Epidemiological studies have shown that diabetes is a risk factor for memory and learning impairment diseases such as AD\(^{49,50}\). Line with these findings, a recent clinical publication has detected higher phosphorylation of tau and its relevant enzyme in diabetics and AD patients\(^51\).

Fluorodeoxyglucose-positron-emission tomography studies have detected lower CMRglu in non-demented ApoE4 elderly subjects\(^42\). Since cerebral blood flow (CBF) is known to be tightly correlated with the metabolic rate\(^2\), changes in brain metabolism are likely to affect CBF. Interestingly, a recent study has shown that peripheral insulin resistance and peripherally administered insulin do not affect CBF\(^38\), suggesting a functional separation between neuronal and non-neuronal metabolism. However, is this lower CMRglu (and possibly CBF) a reflection of poorer response of ApoE4 non-demented subjects to intranasal insulin\(^49\)? Is the lower CMRglu due to reduced glucose transportation due to the impairment of insulin signalling (Figure 1)? What is the difference in the effect of intranasal insulin on the brain structure and function between ApoE3 and ApoE4 human subjects and mouse models?

The ApoE4 allele is also linked to accelerated memory decline in ageing and AD\(^{24,53,54}\), but the underlining mechanism remains unclear. Although intranasal insulin can improve cognition\(^55,56\), this has little effect in ApoE4 non-demented elderly subjects\(^46\). One possibility could relate to the detected lower CMRglu in ApoE4 subjects\(^41,42\).

**Conclusion**

In this review, we suggest that ApoE has a role in regulating brain insulin signalling, and this functional role could affect the cognitive process during ageing and in AD.

**Abbreviations list**

AD, Alzheimer’s disease; ApoE, apolipoprotein E; Aβ, amyloid beta; CBF, cerebral blood flow; CMRglu, cerebral glucose metabolic rates; CNS, central nervous system; NPC, Niemann-Pick Type C.

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**References**

Critical review


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