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Review

Apolipoproteins and Suicide: a Potential Psychiatry Biomarker

María Fernanda Serna-Rodríguez[1], Miguel Zambrano-Lucio[1], Jorge Luis Trejo-Luevanos[1], Iván Alberto Marino-Martínez[2], Ana María Rivas-Estilla[1], José Alfonso Ontiveros-Sánchez de la Barquera[3] and Antonio Alí Pérez-Maya[1,*]

[1] Universidad Autónoma de Nuevo León, Facultad de Medicina, Departamento de Bioquímica y Medicina Molecular. Monterrey, N.L., México. CP. 64460
[2] Universidad Autónoma de Nuevo León, Centro de Investigación y Desarrollo en Ciencias de la Salud. Monterrey, N.L., México. CP. 64460
[3] Universidad Autónoma de Nuevo León, Facultad de Medicina Monterrey, Departamento de Psiquiatría. Monterrey, N.L., México. CP. 64460
*Corresponding author: antonio.perezmy@uanl.edu.mx or bioquimicomty@gmail.com

Abstract: Every year around 800 000 people commit suicide, this represents one death every 40 seconds. In the search for possible biological biomarkers associated with suicide and/or psychiatric disorders, serum cholesterol levels have been extensively explored. Several studies have indicated that cholesterol and associated proteins, especially apolipoproteins (Apos), may play an important role in the diagnosis, prognosis, and susceptibility of suicide. Here, we describe the current knowledge and findings in the relationship between apolipoproteins and suicide.

Highlights:

- This is the first systematic review of Apos in relation to suicidal behavior.
- Dysregulations of Apos expression has been observed in patients with suicidal behavior.
- Apos seem to be associated with cognitive dysfunction in suicide attempters.
- ApoE is a potential biomarker regarding suicidal behavior.

Keywords: apolipoprotein; suicide; biomarker; psychiatry; risk factor

1. Introduction

Suicide is death caused by injuring oneself with the intent to die (Centers for Disease Control and Prevention, 2020). This includes all deaths that are the result of suicidal behavior by the victims, who most of the time are aware of the goal they want to achieve (Nogales, 2011). Every year around 800 000 people commit suicide, this represents one death every 40 seconds. In 2016, suicide was the second leading cause of death among young people aged 15-29 years (World Health Organization, 2019). There is evidence that for every person who commits suicide, more than 20 others had a suicide attempt (PAHO, 2014).

To date, no true biomarker is currently used as a tool to diagnose or to identify suicide risk. Finding biomarkers that are associated with suicidal behavior are extremely necessary because people at risk often choose not to share their intentions with others (Le-Niculescu et al., 2013).

A biomarker can be defined as "a biological molecule found in blood, other body fluids, or tissue that is a sign of a normal or abnormal process, or of a condition or disease" (National Institutes of Health, 2019). To be widely used, these must be simple to detect, use non-invasive methods, and be inexpensive. A potential molecular biomarker may consist of a difference in a measurable biochemical parameter, either intracellular or extracellular, between physiological and pathological states (Woods et al., 2012). When focused on suicide, biomarkers could also be divided into *diathesis biomarkers* (to assess if the subject is at risk for suicide) and *stress biomarkers* (to evaluate when the subject will attempt

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suicide) (Califf, 2018; Faqi et al., 2017). One potential avenue for improving the clinical management of suicidal behavior is the use of peripheral biomarkers rather than subjective symptom scoring. It could be an objective, cost-effective, time-efficient and non-invasive method of diagnosing and monitoring suicide risk (Parekh et al., 2017). Because of the inaccessibility of the human brain, initial studies of the biology of suicidal behavior and development of biomarkers focused on peripheral tissue such as cerebrospinal fluid (CSF), urine, platelets, serum, etc. (Dwivedi, 2012)

In the search for possible biological biomarkers associated with suicide and/or psychiatric disorders, serum cholesterol levels have been extensively explored. The association between the cholesterol system with suicide and/or psychiatric disorders has been researched since the 1900s. Several studies have suggested that an alteration in the cholesterol system can occur in people with mental disorders and in those more likely to score higher on measures of aggression, anger, and a higher risk of displaying violent suicidal behaviors (Knowles et al., 2018; Magadum & Kishore, 2020; Messaoud et al., 2017; Tomson-Johanson & Harro, 2018). There is a theory that serum lipid levels play an essential role in the pathogenesis of suicide, assuming that lower cholesterol level may decrease membrane fluidity and cause instability of the membrane lipid bilayer; this might decrease serotonergic neurotransmission (Kułak-Bejda et al., 2021). The association between low cholesterol levels and suicidal behavior has not yet been established clearly; however, most studies have shown that patients with a history of suicide attempts have significantly lower cholesterol levels than those who have not presented any type of suicidal behavior (Da Graça Cantarelli et al., 2015; Dwivedi, 2012; Kułak-Bejda et al., 2021).

The association between the cholesterol system with suicidal risk and/or suicidal disorders has been studied by analyzing candidate genomic biomarkers; however, gene information does not necessarily reflect protein activity or levels. Recently, some studies have found that apolipoprotein E (ApoE), ApoA1, ApoB, and ApoD may play an important role in the diagnosis, prognosis and susceptibility of suicide (Asellus et al., 2016; Edgar et al., 2007; Hui et al., 2017; Lee et al., 2016; Y. R. Song et al., 2015; Vila-Rodriguez et al., 2011; Zhan et al., 2014). The present review will describe the current knowledge and findings in relation between apolipoproteins and suicide.

1.1. Apolipoprotein superfamily

Apolipoproteins (Apos) are the protein component of lipoproteins that are mostly formed in the liver and intestine. It is known that apolipoproteins regulate lipoprotein metabolism and determine their role in lipid metabolism (Mahley et al., 1984). They function as keys by allowing lipoproteins to access to specific sites for delivery, acceptance or modification of lipids (Semenkovich, 2011).

The brain is the most lipid-rich organ, containing 20-25% of the total cholesterol in the human body (Walker et al., 2020). Disruption of Apos expression in the central nervous system (CNS) can have serious effects on membrane fluidity and neurotransmitter functions, leading to severe neurological disorders such as Niemann-Pick, disease, schizophrenia, Parkinson's disease, mood disorders, as well as unipolar and bipolar depression. Dysregulations of Apos levels has been observed in patients with suicidal behavior and/or psychiatric disorders, where they might be involved in affectation in the CNS disorders (Fig. 1) (Li et al., 2017; Y. R. Song et al., 2015; Walker et al., 2020; Woods et al., 2012). Serum measurements of Apos may have clinical utility; however, their role in the mechanism of suicide remains uncleared.

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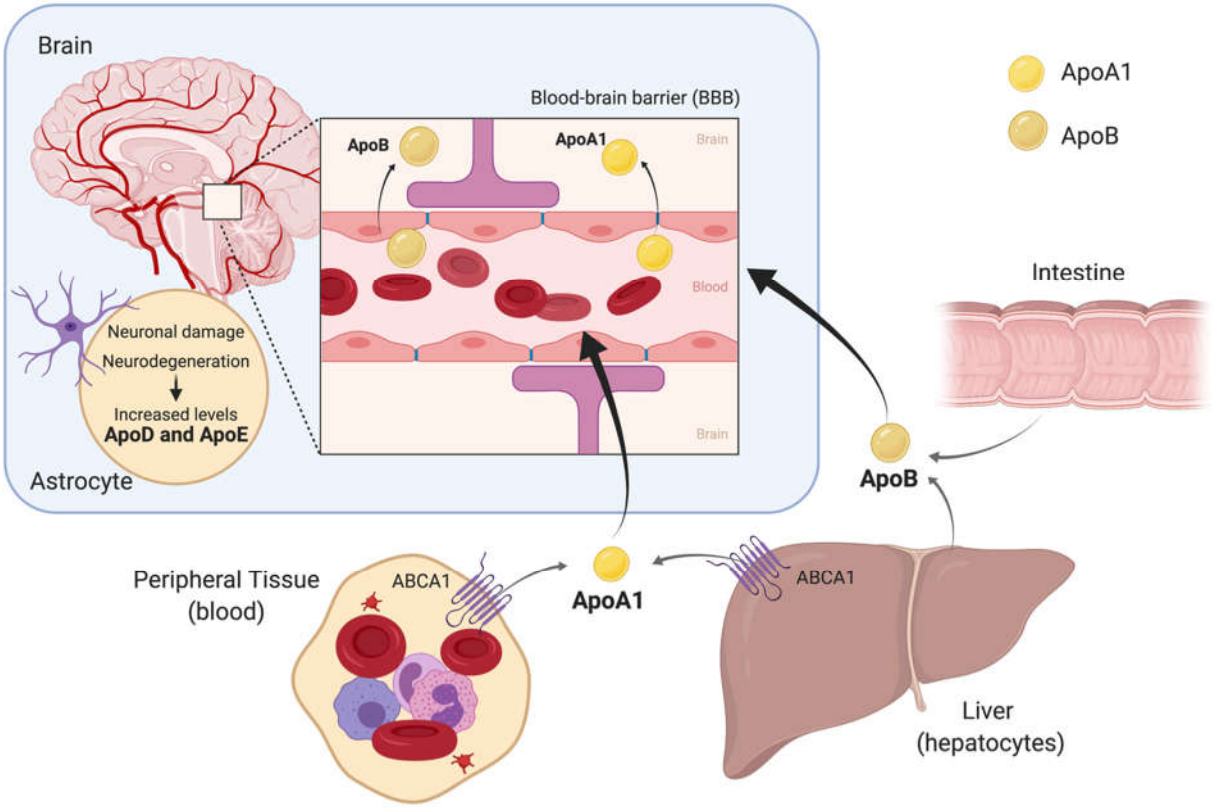

Figure 1. Apolipoproteins in central nervous system (CNS). Apolipoproteins are the protein component of lipoproteins that are mostly formed in the liver and intestine. Dysregulations of Apos expression might be involved in adverse effects in CNS disorders. ApoA1 is the main protein component of high-density lipoprotein (HDL) and ApoB is the principal protein of chylomicrons and low-density lipoproteins (LDL) in plasma. It is known that ApoA1 and ApoB are capable of crossing through the blood-brain barrier (BBB) from plasma indicating that they may play a possible role in cognition and mental processes. ApoD and ApoE expression has been observed in cells of the CNS, and it has been found that during the process of neurodegeneration and aging, levels of these proteins increase. High levels of ApoD and ApoE in the brain suggest that increased secretion of these proteins might occur during periods of increased cellular stress or injury.

2. Materials and Methods

2.1. Search strategy

Following PRISMA methodology (PRISMA), eligible studies were systematically identified by searching electronic databases PubMed, Google Scholar, and Web of Science for relevant literature (2004 – January 2021). Our search terms included "Apolipoproteins AND suicide", apolipoproteins AND psychiatry", "cholesterol AND suicide" and "cholesterol AND psychiatry". In addition, reference lists of included studies were scanned to identify additional studies.

To be eligible, studies had to meet the following criteria: cohort studies in adults (age>18), including association of apolipoproteins with suicidal ideation, suicide attempts, or completed suicide. Both prospective and cross-sectional studies were included. As no human participants or animals had been recruited, ethical approval was not required.

3. Results

3.1. Search strategy and study selection

A flow chart of the study identification and selection process is presented in Fig 2. We identified twenty-nine research articles for inclusion. The search of PubMed, Google Scholar, and Web of Science provided 2,771 articles, after removal of duplicates. After

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reviewing titles and abstracts 99% of these did not meet our inclusion criteria, mostly due to the articles not examining the association between apolipoproteins and suicidal ideation, suicide attempts, or completed suicide.

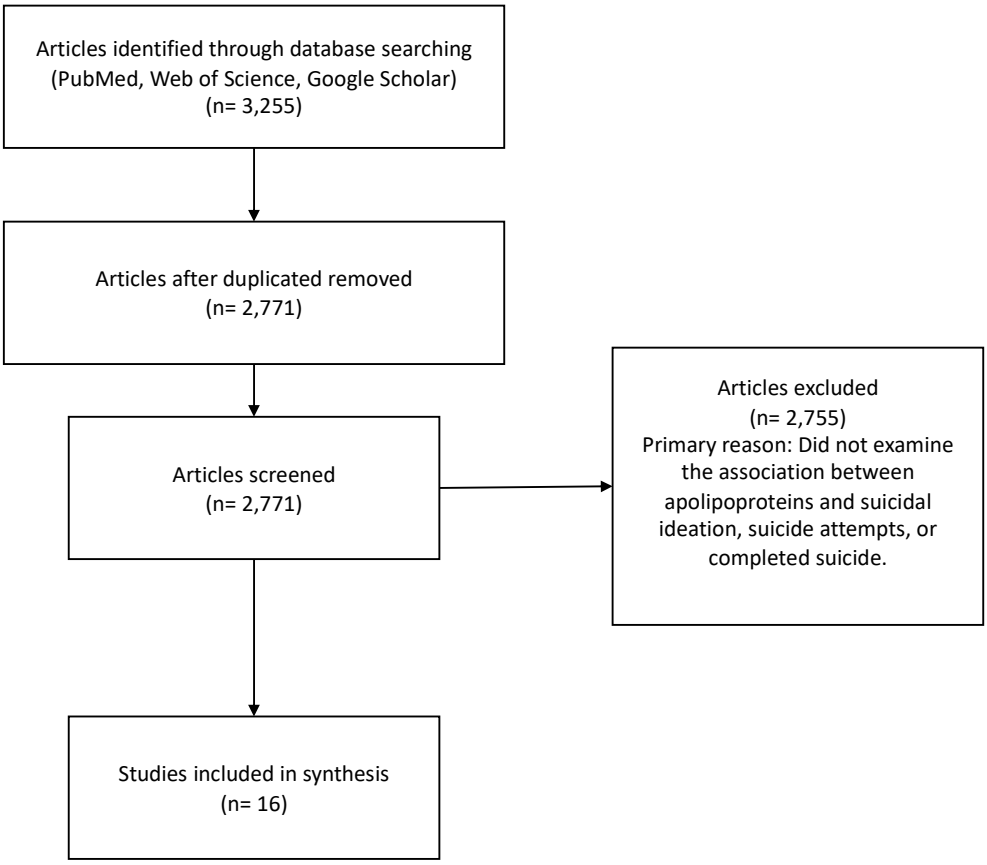

Figure 2. Flow chart of study identification and selection.

3.2. Study characteristics

We identified 16 studies (Table 1). Studies included general population samples and patient populations, with a wide age range. Thirteen studies reported on the association of ApoE with suicide (Asellus et al., 2016, 2018; Baca-Garcia et al., 2004; Bogner et al., 2009; Calderón-Garcidueñas, González-Maciel, et al., 2018; Calderón-Garcidueñas, Gónzalez-Maciel, et al., 2018; Hwang et al., 2006; Kim et al., 2011; Lalovic et al., 2004; Merritt et al., 2018; Saiz et al., 2011; Vila-Rodriguez et al., 2011; Yoshida et al., 2019) two studies reported the association of ApoB with suicide risk (Edgar et al., 2007; Hui et al., 2017), and one study reported on ApoA1 association with suicide attempt (Mathew et al., 2019).

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Table 1. Overview of Studies that Examined the association of apolipoproteins with suicidal ideation, suicide attempts, or completed suicide.

Author	*Country*	*Population total*	*Apolipoprotein*	*Suicidality*	*Results*
Asellus et al. (2015)	Sweden	100	ApoE	Suicide attempt	- The mean plasma ApoE level in suicide attempters was 36.6 mg/l (n=74, SD= 10.7, range 17-65, median 35 mg/l) - Patients with at least one earlier suicide attempt had significantly higher ApoE levels (mean= 41.2mg/l, SD= 11.6, range 17–65, median 42.5 mg/l, n= 22) compared to suicide attempters debuting with suicidal behaviour at inclusion in the study (mean= 34.9 mg/l, SD= 9.5, range 20–64, median 34 mg/l, n= 43). - A higher number of earlier suicide attempts was significantly correlated with higher plasma ApoE levels in suicide attempters (rho= 0.34, p= 0.0051).
Asellus et al. (2017)	Sweden	42	ApoE	Suicide attempt	- The mean CSF ApoE level in suicide attempters was 3.27 mg/l, (n = 41, SD = 1.05, range 1.35-5.21, median 3.33mg/l). - Suicide attempters with a violent suicide attempt showed a trend for lower CSF ApoE level (mean = 2.74 mg/l, SD =0.64, range 1.54-3.52, median 2.79 mg/l, n = 9) compared to suicide attempters with a non-violent method (mean = 3.41 mg/l, SD = 1.10, range 1.35-5.21, median 2.42 mg/l, n = 32).
Baca-Garcia et al. (2004)	Spain	556	ApoE	Suicide attempt	This study with a relatively large sample of representative suicide attempters suggests that plasma apolipoprotein E levels may not be associated with suicide attempts despite low cholesterol levels having been associated with suicide attempts.
Bogner et al. (2009)	United States	305	ApoE	Suicidal ideation	Findings indicate that depression may be related to the presence of APOE-ε4 and that the presence of APOE-ε4 increases the risk of cognitive impairment.
Calderon-Garcidueñas et al. (2018)	Mexico	203	ApoE	Completed suicide	- In a model where $CPM_{2.5}$, age and APOE status were included as suicide predictors, having an APOE4 significantly increases the odds of dying by suicide (p = 0.0006). - APOE4 carriers 25.2 ± 8.48 y-with accelerated NFT V and amyloid-β phase 3, had the highest suicide risk, opening the possibility advanced Htau and amyloid stages contributed to depression and suicide at this early age.
Calderon-Garcidueñas et al. (2018)	Mexico	179	ApoE	Completed suicide	In a model where $CPM_{2.5}$, age and APOE status were included as suicide predictors, having an APOE4 significantly increased the odds of dying by suicide 4.57 times (p = 0.0025).
Edgar et al. (2007)	New Zealand	3	ApoB	Suicidal behavior	- The index patient had low plasma LDL-cholesterol, vitamin E and ApoB concentrations. - ApoB-29.4 mutation was the sole cause of the index patient's hypocholesterolemia. - *APOB* (2p24) may be important to the development of psychosis, a symptom often linked to suicide and violent behavior.
Hui et al. (2017)	China	180	ApoB	Suicide risk	- Higher serum ApoB levels on delayed memory decline of depressive disorder.

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					- Depressive patients also have poorer cognitive functions than healthy controls, especially in delayed memory and language.
Hwang et al. (2006)	Taiwan	255	ApoE	Suicide attempt	- A significant association of APOE status with suicide attempt history was observed in the depressed group (p= 0.012) in that subject carrying the APOE4 allele were at an increased risk of suicide. - Using non-APOE4 carriers as a baseline comparison, we found this risk to be 4.32 times higher in APOE4 carriers (95% CI 1.51-12.36). - Patients carrying the APOE4 allele have increased suicidality.
Kim et al. (2010)	Korea	625	ApoE	Suicidal ideation	There were synergistic interactions between depression and APOE e4 on incident dementia independent of covariates. This interaction was particularly strong for four depressive symptoms: depressed mood, worthlessness, concentration difficulty, and suicidal ideation.
Lalovic et al. (2004)	Canada	305	ApoE	Completed suicide	- No significant differences were found in allele or genotype frequency distributions between the suicides and controls. - No significant differences were found between suicide cases and controls with respect to the frequency of each allele.
Mathew et al. (2019)	India	31	ApoA1	Suicide attempt	ApoA1 was significantly downregulated by 2.68-fold (p5% CI= 1.83-3-937) in individuals with deliberate self-harm compared to controls.
Merritt et al. (2018)	United States	133	ApoE	Suicide risk	ApoE-e4 allele is a risk factor for the development of neuropsychiatric symptoms in veterans with history of traumatic brain injury.
Vila-Rodriguez et al. (2010)	Canada	105	ApoE	Completed suicide	Death by suicide had no influence on cholesterol or ApoE levels, with this finding remaining when cases were stratified into violent and non-violent suicides.
Yoshida et al. (2019)	Japan	189	ApoE	Completed suicide	- A history of psychiatric disease was significant risk factor of suicide in subjects >20 years old (p< 0.001 in 20-29 years old subjects and p< 0.0001 in 30-39 years old subject). - Neither *APOE* genotype nor allele frequency were associated with a history of psychiatric disorder. - Investigation of *APOE* genotypes revealed the e4 genotype in 14 cases (5.2%). Significantly higher prevalence of e3 in suicide cases (p< 0.05) and e2 in natural death cases (p< 0.01) were found.
Saiz et al. (2011)	Spain	1,333	ApoE	Suicide attempt	- There was evidence of an association between lethality in the presence of the APOE ε3/ε3 genotype and when only one of the APOE genotype alleles was ε3. - Higher lethality in the presence of APOE ε2ε3 or ε3ε4 genotypes.

Note. APOE= apolipoprotein E; CSF= cerebrospinal fluid; $CPM_{2.5}$= cumulative particulate matter; NFT V= neurofibrillary tangles stage V; LDL= low-density lipoprotein; *APOB*= apolipoprotein B; ApoA1= apolipoprotein A1;

In ten of the ApoE studies reported, the association of suicide with ApoE genotype was analyzed; the rest of the studies evaluated ApoE serum or CSF levels with suicide

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attempt. In all ApoB and ApoA1 studies, serum or plasma concentrations were measured as an indicator of suicidal behavior in 3 studies.

3.3. Structure and function of apolipoproteins

3.3.1. Apolipoprotein A1

ApoA1 is a 27-kDa protein, consisting of 243 amino acids, which is the main protein component of high-density lipoprotein (HDL) in plasma. It is responsible for promoting the release of cholesterol from peripheral tissues to the liver. ApoA1 is a cofactor of lecithin cholesterol acyltransferase (LCAT) and plays a role in suppressing inflammatory reactions, protecting vascular endothelium, and regulating the immune responses. The functions of ApoA1 in the CNS are not entirely clear, but it is known that this protein is capable of crossing through the blood-brain barrier from plasma. ApoA1 has been reported to be present in neurons in the brain and spinal cord indicating that it may play a possible role in cognition and mental processes (Boiko et al., 2019; Li et al., 2017; Swanson et al., 2015; Woods et al., 2012).

3.3.2. ApoB

ApoB is the principal protein of chylomicrons and low-density lipoproteins (LDL). ApoB can be found in two isoforms, ApoB48 and ApoB100, the first is synthesized exclusively in the intestine and the second in the liver (Hui et al., 2017; NCBI, 2020; Woods et al., 2012). ApoB might not be produced in the brain; however, studies have shown expression of human ApoB100 in the brain of transgenic mice causing the formation of amyloid plaques and extensive neuronal death, indicating that serum ApoB levels may be involved in cognitive dysfunction (Hui et al., 2017; Martins et al., 2009; F. Song et al., 2012).

3.3.3. ApoD

ApoD, a 29-kDa glycoprotein, is a component of plasma HDL and belongs to lipocalins, a superfamily of proteins involved in the transportation of small hydrophobic molecules such as cholesterol. ApoD can be found in most body fluids as well as in different organs and tissues, such as the brain. The expression of this protein has been observed in neurons, oligodendrocytes, astrocytes, and perivascular cells in the CNS, and it has been found that during the process of neurodegeneration and aging, its levels increase. High levels of ApoD in the brain suggest a role of this protein in lipid transport and in maintaining cholesterol homeostasis (Del Valle et al., 2003; Li et al., 2017; Martins et al., 2009; Navarro et al., 2008).

3.3.4. ApoE

ApoE is a glycoprotein of 299 amino acids with a molecular weight of 34-kDa. The ApoE gene is located on chromosome 19q13.32 and is composed of four exons and three introns (Forero et al., 2018; NCBI, 2014). ApoE is found in all plasma lipoproteins and is a crucial element in the lipoprotein metabolism, lipid transportation, and clearance of amyloid proteins in the brain. This protein is mainly synthesized by brain astrocytes in the CNS, controlling cholesterol efflux from cells with ApoA1 (Dominiczak & Caslake, 2011; Li et al., 2017; Martins et al., 2009; Woods et al., 2012).

There are 3 main alleles of the human *APOE* gene, ε2, ε3, and ε4, which specify three protein isoforms, ApoE2, ApoE3, and ApoE4. The differences between ApoE isoforms are due to the amino acids at positions 112 and 158 (Dominiczak & Caslake, 2011; Vila-Rodriguez et al., 2011). Allele ε3 is the most common with a frequency of 70-80% and is considered to be the normal allele with a cysteine at position 122 and arginine at position 158. Alleles ε2 and ε4 are not that common and have been associated with the progression of Alzheimer's disease (AD). ApoE4 (frequency 15-20%) has arginine at both positions, and ApoE2 (frequency 5-10%) has cysteine. Individuals with allele ε4 have higher plasma cholesterol concentration than those with ε2 (Dominiczak & Caslake, 2011; Feng et al.,

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2015). Evidence suggests that ApoE4 carries the highest risk of neurodegeneration; however, little support for an association of ApoE and suicide has been found (Su et al., 2015).

3.4. Apolipoproteins in suicide

3.4.1. ApoA1 and neurodegeneration

The role of ApoA1 in cognition and mental processes is unclear; however, several studies have shown that down regulation of ApoA1 may be a strong risk factor involved in neurodegeneration and cognitive decline (F. Song et al., 2012; Y. R. Song et al., 2015). Swanson et al. report a correlation between lower ApoA1 plasma levels and decreased dopamine transport, indicating a disruption to the dopaminergic system (Swanson et al., 2015, 2016). Dopamine plays an important role in the pathophysiology of depression. Impaired neurotransmission of dopamine may cause anhedonia, loss of motivation, and psychomotor retardation in patients with severe depression (Amidfar, 2018).

This protein also acts as an anti-inflammatory factor (Sadeghi et al., 2011). Swanson et al. overexpressed ApoA1 in a mouse model and observed a reduction in neuroinflammation by attenuating astrogliosis and pro-inflammatory cytokines, suggesting a potential mechanism of action (Swanson et al., 2016). Inflammation is known to be a risk factor, playing a major role in the pathophysiology of many psychiatric disorders (Sadeghi et al., 2011). Also, Lin Li et al. report that ApoA1 may take part in delaying dopaminergic neurodegeneration, promoting the repair of damaged neurons, and maintaining the integrity of neurons with anti-inflammatory and antioxidants properties, indicating that this protein may be a neuroprotective factor (Li et al., 2017).

Mathew B. et al. used proteomics and found that expression of ApoA1 was reduced among patients with deliberate self-harm as compared to healthy controls. This study concluded that downregulation of ApoA1 may be the biochemical link between low cholesterol levels and deliberate self-harm (Mathew et al., 2019).

3.4.2. ApoB and violent behavior

Several human studies indicate that ApoB serum levels may be involved in cognitive dysfunction (Hui et al., 2017). Locus 2p25 has been identified as a putative locus for psychosis. This indicates that genes in this area, such as *APOB* (2p24), may be important in the development of psychosis, a symptom linked to violent behavior and suicide. P.F Edgar et al. described a family with hypocholesterolemia caused by a novel mutation of *APO.B* (apoB-29.4). In this study, an association, with an odds ratio of 16.9, between low plasma cholesterol status and violent behavior of family members was reported (Edgar et al., 2007). This suggests that the inheritance of a molecular defect of lipoprotein metabolism could predispose individuals to violent behavior.

3.4.3. ApoD expression in response to neural damage

ApoD is highly expressed in peripheral nerves and the brain. It is also a protein that can be found in a variety of body fluids, such as CSF (Lee et al., 2016). ApoD is thought to act as a response protein, where an increased level of this protein may be a natural response to neuronal damage. Over the years, ApoD has been related to several neuropathologies, but its physiological functions remain unknown (Navarro et al., 2008). Increased levels of ApoD suggest that this protein could be a good marker of pathologies induced as soon as any type of injury occurs. It has been speculated that ApoD might be involved in repair and regeneration after neurodegeneration or in the removal of neurotoxic molecules after neuronal loss (Del Valle et al., 2003; Navarro et al., 2008).

ApoD has not yet been linked to suicide/suicidal ideation; however, Navarro et al. reported increased levels in plasma and certain brain regions of schizophrenic patients. Lee et al. also found significantly upregulated ApoD levels in brain tissue of schizophrenic and bipolar patients (Lee et al., 2016; Navarro et al., 2008).

3.4.4. ApoE as a potential suicide risk factor

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ApoE is involved in the transport and uptake of cholesterol, lipoproteins and triglycerides in both the periphery, and in the CNS (Asellus et al., 2016). Several studies suggest that ApoE might be a potential biomarker regarding suicidal behavior. ApoE and cholesterol play an important role in synaptogenesis, membrane repair, and maintenance, indicating that increased ApoE secretion might occur during periods of increased cellular stress or injury. ApoE also plays a significant role in the hypothalamic-pituitary-adrenal (HPA) axis activity and immune regulation, both being biological systems implicated in suicidal behavior (Asellus et al., 2016; Vila-Rodriguez et al., 2011).

Calderon-Garcidueñas et al. analyzed individuals according to their cause of death by assigning them to three major groups: accidents, homicides, and suicide. They identified ApoE4 carriers as individuals that had the highest risk of committing suicide at an early age (Calderón-Garcidueñas, Gónzalez-Maciel, et al., 2018). In another study, the same group of investigators reported that the odds of dying by suicide in individuals with Alzheimer's Disease (AD) increased 4.57 times by being ApoE4 carriers (Calderón-Garcidueñas, González-Maciel, et al., 2018).

Asellus et al. evaluated patients with a history of suicide attempts and reported that patients with earlier suicide attempts had higher plasma ApoE levels compared to individuals with no previous history of suicide attempts (Asellus et al., 2016). Later in 2018, Asellus et al. showed that suicide attempters with a violent suicide attempt showed lower CSF ApoE levels (mean= 2-74 mg/l) compared with a non-violent method (mean= 3.41 mg/l) (Asellus et al., 2018).

The ApoE4 allele has been implicated in neuropathological processes such as mitochondrial dysfunction, increased production/accumulation of amyloid β-peptide (Aβ), and inflammation (Merritt et al., 2018). ApoE ε4 has also been reported as a risk of incident dementia, with a particularly strong association with four depressive symptoms such as depressed mood, worthlessness, difficulty concentrating, and suicidal ideation (Kim et al., 2011). The presence of ApoE4 allele alters the normal function of astrocytes, as well as other glial cell types, and may therefore represent a pathogenic mechanism that contributes to neurodegenerative pathways in AD and other disorders (Walker et al., 2020). Bogner et al. findings indicate that depression may be related to the presence of ApoE ε4 and that it increases the risk of cognitive impairment (Bogner et al., 2009).

Evidence suggests that ApoE2 may be the most beneficial ApoE isoform, while ApoE4 carries the highest risk of neurodegeneration and suicide (Su et al., 2015). Hwang et al. found a significant association of ApoE status with suicide, where subjects carrying the ApoE4 allele had a 4.32 times higher risk of committing suicide. This allele is significantly associated with a reduced volume of the hippocampus, a brain region that is important for cognitive performance (Hwang et al., 2006).

Other studies failed to support an association between ApoE4 carriers and suicide. Yoshida et al. evaluated the presence of two single nucleotide polymorphisms (SNPs) of the *APOE* gene; neither *APOE* genotype nor allele frequency were associated with a history of psychiatric disorder (Yoshida et al., 2019). Also, a case-control study by Su et al. did not show any relation between ApoE ε4 frequencies and depression (Su et al., 2015). Saiz et al. suggest that ApoE genotypes ε2ε3 and ε3ε4 were associated with high lethality in suicide attempters; however, plasma APOE levels may not be associated with suicide attempts despite low cholesterol being associated with suicide attempts (Saiz et al., 2011). Both Lalovic et al. and Baca-Garcia et al. found no significant differences in *APOE* allele or genotype distributions between suicide cases and controls (Baca-Garcia et al., 2004; Lalovic et al., 2004). Yoshida et al. found a higher prevalence of ε3 in suicide cases and ε2 in natural death cases. In this study, no clear association between the ε4 allele and suicide history was evident in younger subjects, indicating that ε4 allele might be significantly associated with suicide attempters in the elderly population (Yoshida et al., 2019).

To date, results of studies looking for an association between *APOE* alleles and suicide have been inconsistent, and some studies did not detect a significant association with ApoE4 frequencies between suicidal attempters and controls. Therefore, no clear agreement on the nature of the relation between *APOE* alleles and suicide risk has been reached.

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4. Discussion

Many studies have tried to identify lipids as a biological marker in the prediction, prognosis and management of suicidal behavior(Freemantle et al., 2013; Kułak-Bejda et al., 2021; Lütjohann, 2007; M. Daray et al., 2018; Shaker et al., 2020; Tomson-Johanson & Harro, 2018). However, preliminary conclusions such as ApoB is associated with violent behavior and ApoE4 carriers have higher risks of committing suicide remain to be further analyzed to sufficiently understand the relationship before using these proteins as biomarkers of suicidal behavior.

Proteomics has been a valuable tool for studying changes in the cholesterol system in CNS disease states. Extensive evidence shows that apolipoprotein levels are disturbed in several psychiatric disorders, suggesting that the cholesterol system may lead to promising psychiatric biomarkers (Boiko et al., 2019; Muenchhoff et al., 2017; Y. R. Song et al., 2015; Vila-Rodriguez et al., 2011). Apos are a great prospect to be biomarkers with the capabilities of identifying patients with suicidal behavior, the severity of suicidal ideation, and providing viable treatments (Fig. 3).

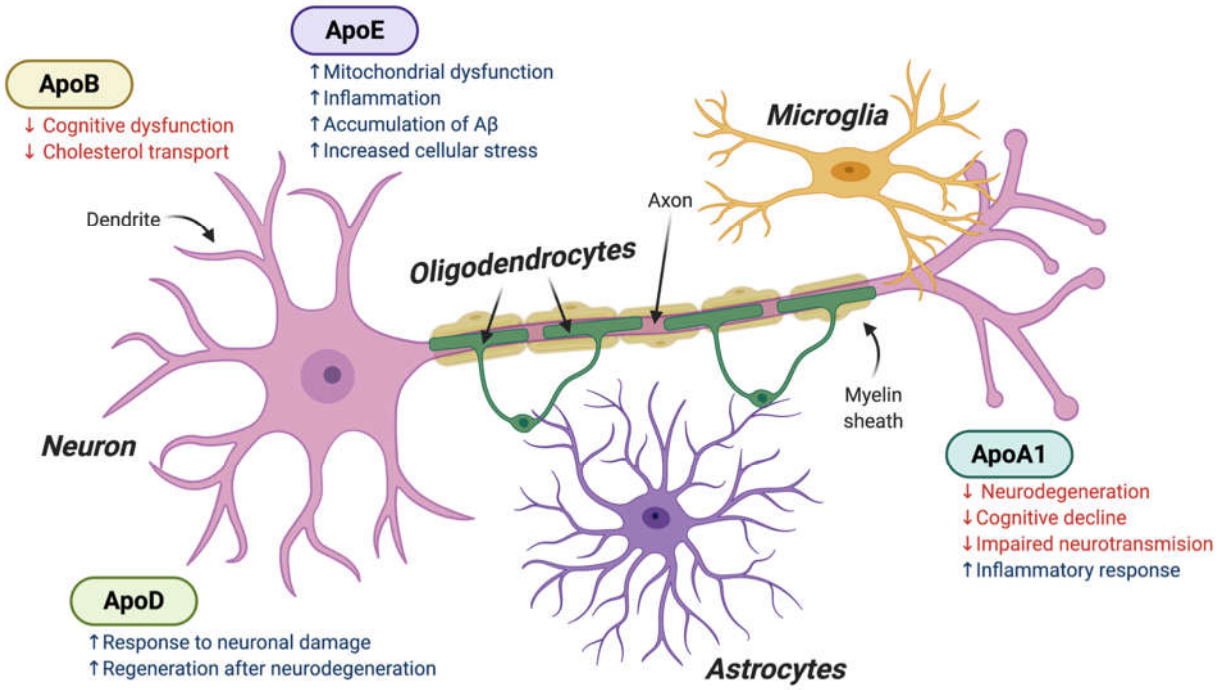

Figure 3. Potential pathological role of Apos dysregulation in suicidal behavior. Cholesterol dysregulation by apolipoproteins could lead to functional abnormalities in the brain such as impaired neurotransmission, cognitive decline, neurodegeneration, increased cellular stress causing neuronal loss, Aβ accumulation and inflammatory response in microglia.

There are other studies focused on the relationship between psychiatric disorders and serum Apos levels, like Alzheimer's disease, bipolar disorder, schizophrenia, mayor depression, or personality disorders. However, in our review we have limited our research by only including articles with Apos relationship with suicidal behavior.

5. Limitations, strengths, and conclusions

Some limitations and strengths to the reviewed literature should be noted. So far, only sixteen studies have explored the association between apolipoproteins with suicidal ideation, suicide attempts, or completed suicide. Another limitation is the wide diversity among the studies since result may vary depending on ethnicity. Also, limited studies were found on ApoB and ApoA1 association with suicide.

The search for biomarkers in psychiatry is continuously expanding with the discovery of novel targets based on diverse neurobiological processes. However, this process is particularly challenging for psychiatric disorders due to significant overlap of symptoms within the same diagnostic groups and lack of precise understanding of exact causation. Our review supports the proposition that Apos may play an important role in the diagnosis, prognosis, and susceptibility of suicide. ApoE, ApoB, and ApoA1 might be a potential biomarker regarding suicidal behavior. The identification of useful and reliable biological markers of suicidal behavior remains a critical need, and, thereby, suggest a field for future research.

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