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The Relationship Between Lipids and Lipoproteins in Spinal Cord Injury: A Review

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ABSTRACT

Spinal cord injury (SCI) results in disrupted neuronal communication between the brain and the peripheral organs due to impairment of neuronal function below the site of injury. SCI triggers a cascade of molecular events, including an imbalance in lipid metabolism, which can exacerbate tissue damage and impede neurological recovery. Lipids are crucial for cellular and tissue maintenance in the central nervous system (CNS). They are physical and structural elements of cell membranes, offering fluidity and integrity, and myelin sheaths, allowing for more rapid propagation of electrical signals and enabling the nervous system to function properly. Lipids also function as signaling and energy storage molecules essential for proper CNS function and health. Lipid dysregulation in CNS following spinal cord injury (SCI) is a critical area of study due to its significant impact on cellular environments and subsequent recovery processes. Research indicates that targeting lipid dysregulation could offer a promising avenue for mitigating the secondary damage resulting from SCI and improving overall recovery. Understanding the intricate link between SCI and lipids is important to the development of targeted therapies that modulate lipid metabolism for improved outcomes. This article reviews the current understanding of the relationship between SCI, lipids, and lipoproteins and the potential to target lipids in future SCI treatment mechanisms.

Introduction

Spinal cord injury (SCI) is an injury to the spinal cord, a bundle of nerves that allows the brain to communicate sensory and motor information with the body (National Institute of Neurological Disorders and Stroke (NINDS), 2021). SCI has ramifications on both individuals and society, presenting a formidable challenge to healthcare systems. Every year, between 250,000 and 500,000 people suffer from spinal cord injury worldwide (World Health Organization, 2013). SCI is usually caused traumatically by motor accidents, falls, violence, and sports injuries, but can also be caused by disease (Mayo Clinic, 2023). In SCI, nervous function is impaired below the site of the injury, with injuries at higher levels in the spinal cord and closer to the brain, incurring greater physical, economic, and social costs (NINDS, 2021; World Health Organization, 2013). Traumatic spinal cord injuries occur in two stages: the primary injury is defined by mechanical damage from the initial injury, and the secondary injury is characterized by prolonged cellular, molecular, and biochemical responses that worsen the damage inflicted by an injury (Alizadeh *et al.*, 2019). SCI can result in complications in breathing, circulation, muscle tone, bladder function, and sexual function and can cause pressure sores, pain, and autonomic dysreflexia (NINDS, 2021). Additionally, 20-30% of people with SCI show signs of depression (World Health Organization, 2013). Ultimately, SCI can result in high socioeconomic costs, which are higher than those of comparable neurological conditions, such as dementia, multiple sclerosis, and cerebral palsy. Children with SCI are less likely to start and advance in school, while adults with SCI face a 60% global unemployment rate. SCI can make people dependent on caregivers, and individuals with SCI are 2-5 times more likely to die prematurely when compared to those without (World Health Organization, 2013).

Currently, there are no known cures for SCI, although there is a range of existing treatments to improve recovery after an injury. Researchers are studying the cellular and molecular processes related to SCI to identify potential targets for future treatments. Lipids and lipoproteins have shown promise of being useful targets for such treatments because of their essential role in cell structure and metabolism. This review article aims to provide an overview of the current understanding of the relationship between lipids/lipoproteins and spinal cord injury. Firstly, an overview of spinal cord injury and lipids/lipoproteins will be discussed. Next, the role of lipids/lipoproteins in the central nervous system and lipids/lipoprotein dysregulation after SCI will be reviewed. Finally, current research on potential therapeutic strategies for SCI recovery will be presented.

Overview of Spinal Cord Injury

Spinal cord injury (SCI) leads to impairment of neuronal function below the site of injury, resulting in loss of function or range of disability. Depending on the severity, SCI can lead to paralysis, impairing movement of the body. In turn, it puts individuals with SCI at a higher risk of living sedentarily and predisposes them to other conditions, such as cardiovascular disease. SCI can also result in chronic pain and has high living costs (Ahuja *et al.*, 2017; Sterner & Sterner, 2023).

The pathophysiology of SCI is complex, and researchers continue to study cellular and molecular processes during recovery to develop potential treatments. Spinal cord injury occurs in two phases, primary and secondary. In the preliminary injury phase, the initial trauma due to physical forces causes neuronal cell dysfunction and death. During the secondary phase, a cascade of responses follows, triggering reactions resulting in exacerbated damage to the spinal cord (Ahuja *et al.*, 2017; Sterner & Sterner, 2023). Various research is being conducted to address how to recover from spinal cord injury but there is no complete treatment yet. Currently, patient care is focused on managing physical condition through recovery, therapy, and pharmaceutical strategies. Furthermore, research is focused on key aspects of spinal cord repair of neuroprotection, repair and regeneration, cell-based therapies, and retraining central nervous system circuits (NINDS, 2021).

Primary Injury and Secondary Injury

Primary injury involves direct physical damage to the spinal cord, including compression, laceration, and impact. This damage directly impairs the proper spinal cord function as well as the blood vessels and cell membranes that accompany it, which can lead to secondary injury complications (shock, neurotransmitter accumulation, ischemia, and hypotension) (Alizadeh *et al.*, 2019; Hu *et al.*, 2023). Secondary injury occurs following the primary injury and is marked by cellular, molecular, and chemical changes in the spinal cord that continue to impair its function. Secondary injury encompasses numerous processes, including inflammation, glial scarring, cell death, and ischemia (Alizadeh *et al.*, 2019; Hu *et al.*, 2023).

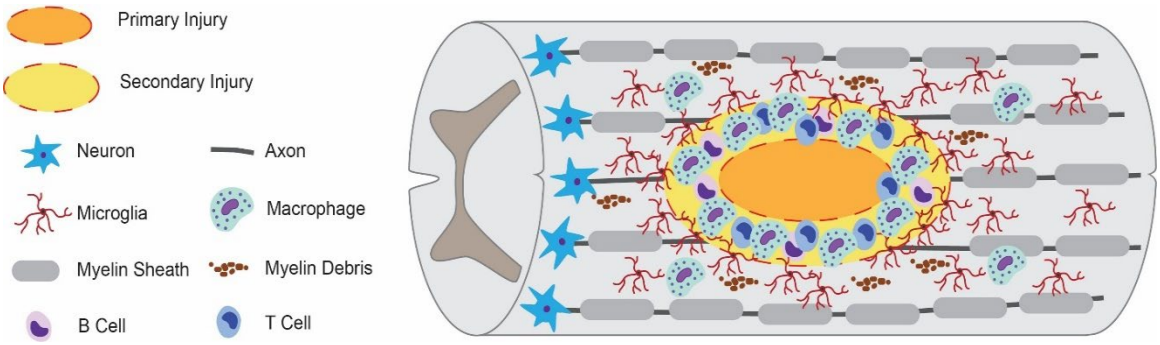

Figure 1. Simplified diagram of cellular infiltration and damage after spinal cord injury (Adapted from Hellenbrand *et al.*, 2021)

Neuroinflammation

Neuroinflammation is the immune response to spinal cord injury, and it is an important part of secondary injury. In the neuroinflammatory response, many types of immune cells are recruited to the site of the injury, including neutrophils, microglia, dendritic cells, macrophages, B cells, and T cells. Neuroinflammation is characterized by the release of both pro- and anti-inflammatory cytokines, and it is known that microglia, macrophages, B cells, and T cells can take a pro- or anti-inflammatory role following SCI. Neuroinflammation is known to have detrimental effects after SCI. For example, researchers found that activated macrophages actively infiltrate cavities of injury and phagocytize myelin and red blood cells (Kwiecien *et al.*, 2020). However, neuroinflammation can also be beneficial after SCI, depending on the phase of recovery and strength of the inflammatory response (Alizadeh *et al.*, 2019). Due to varied findings, further research needs to be conducted to elucidate the role of neuroinflammation in SCI and to develop potential treatments accordingly.

Glial Scarring

Shortly after a traumatic SCI occurs, glial scar tissue surrounds the site of the injury and is known to remain in the spinal cord into the chronic stages. This scar is comprised of multiple types of cells, including astrocytes, oligodendrocyte precursor cells, microglia, macrophages, fibroblasts, and pericytes. Of these cells, astrocytes, which become activated, play an especially considerable role in glial scar formation by forming a barrier, protecting surrounding tissue from immune cell infiltration. However, it also prevents regeneration in the spinal cord since it contains chondroitin sulfate proteoglycans (CSPGs), which are known to assist the glial scar in limiting neuron growth and regeneration (Alizadeh *et al.*, 2019). Thus, researchers are searching for ways to overcome the barrier that the glial scar poses to neuron regeneration to improve functional recovery.

Cell Death

Cell death is another important component of secondary injury in SCI. The mechanical damage arising from the primary injury causes cell death in neurons and glia, and this cell death is continued into the secondary phase of SCI via multiple mechanisms that contribute to cell death following SCI, including apoptosis, necrosis, and autophagy disruption. Necrosis is a non-programmed form of cell death, and after SCI, it is triggered by multiple factors, including pro-inflammatory cytokines, free radicals, and ionic imbalance. Necroptosis, a programmed form of necrosis, also occurs after SCI triggered by tumor necrosis factor receptor 1, along with the kinase receptor-interacting serine/threonine kinase 1 and 3 (RIPK1 & RIPK3), which both accumulate after SCI. Apoptosis is a programmed form of cell death, and in SCI, it occurs in cells further away from the injury center that survives the mechanical damage from the primary injury. It is triggered through the activation of caspases and calpains (enzymes that break down proteins) and can be furthered by free radicals, excitotoxicity, and cytokines. Oligodendrocytes are particularly affected by apoptosis, contributing to the demyelination of axons, but apoptosis also affects microglia and astrocytes. Autophagy is the process where harmful cellular components are removed. However, after SCI, autophagy is dysfunctional because of stress to the endoplasmic reticulum, making neurons more prone to cell death (Alizadeh *et al.*, 2019). Altogether, cell death mitigation has become an important target for therapeutic treatments aiming to increase neuroprotection and improve functional recovery.

Ischemia

Following SCI, blood flow to the spinal cord is severely disrupted, and increased pressure on injured tissue exacerbates ischemia. Small blood vessels rupture, causing hemorrhage in the surrounding tissue. In white mat-

ter, blood flow is normalized within 15 minutes of the injury. On the other hand, grey matter is impacted significantly more by ischemia as gray matter is more abundant in capillaries. Ischemia leads to multiple mechanisms, including decreased oxygen flow, free radical release, and excitotoxicity, which contribute to tissue damage and death. Additionally, the restoration of blood flow to previously ischemic tissue can release free radicals and cause further exacerbated inflammation, worsening tissue damage (Alizadeh *et al.*, 2019). Preventing ischemia will prevent tissue damage inflicted by decreased oxygen, free radicals, and excitotoxicity, therefore, researchers are looking for effective treatments to prevent ischemia.

Overview of Lipids and Lipoproteins

Lipids are important components of cell membranes, signaling molecules, energy reserves, and absorbers of certain vitamins, including fats, oils, hormones, and vitamins that are insoluble in water. The main types of lipids are triglycerides, phospholipids, and steroids. Triglycerides are made up of 3 fatty acids and a glycerol molecule that are used to store energy, provide insulation for cells, and can help absorb certain types of vitamins (Ahmed *et al.*, 2023). Phospholipids are made up of a glycerol molecule, two fatty acids, and a phosphate group. The fatty acid tails are hydrophobic, while the phosphate group is hydrophilic, making phospholipids amphipathic. Due to this property of phospholipids, they make up cell membranes and are arranged in bilayers with the hydrophilic phosphate group facing outwards (Ahmed *et al.*, 2023; Dowhan & Bogdanov, 2002). Steroids have a structure of four fused rings and include cholesterol, which can be found in cell membranes and affects membrane permeability. All steroid hormones, including cortisol and sex hormones, are derived from cholesterol (Ahmed *et al.*, 2023; Craig *et al.*, 2023; Roy & Tedeschi, 2021; Dowhan & Bogdanov, 2002). Lipids play multiple roles in structural components and cellular processes and, thus, are essential to the healthy functioning of the body.

As lipids are insoluble in water, they need to be transported in the bloodstream with the assistance of lipoproteins to be appropriately utilized. Lipoproteins have a hydrophobic lipid core mainly comprised of triglycerides and cholesteryl esters and a hydrophilic outer membrane made up of phospholipids, apolipoproteins, and cholesterol. The main function of lipoproteins is to transport lipids, but they are thought to have additional disease protection functions such as reducing the toxic effects of gram-negative and gram-positive bacteria. Lipoproteins are categorized based on their size, what lipids they carry, and what apolipoproteins are attached. They include chylomicrons, very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), high-density lipoproteins (HDL), and lipoprotein (a) (Ahmed *et al.*, 2023; Feingold, 2024).

Chylomicrons

Chylomicrons are large lipoproteins that contain both triglycerides and cholesterol, both on recent dietary consumption. They are synthesized in the small intestine and deliver triglycerides and cholesterol to the liver and peripheral tissues. Chylomicrons contain ApoB-48 apolipoproteins, which are involved in chylomicron assembly and structure, but also contain other apolipoproteins. They are by far the largest class of lipoproteins in size. When muscle and adipose lipoprotein lipase breaks down triglycerides and releases subsequently created fatty acids from chylomicrons, chylomicrons remnants are formed, which are smaller than chylomicrons. Both chylomicrons and chylomicron remnants contribute to atherogenesis, the formation of plaques on artery walls that can create many cardiovascular complications (Ahmed *et al.*, 2023; Björkegren & Lusis, 2022; Feingold, 2024).

Very-Low-Density Lipoproteins

Very-low-density lipoproteins (VLDL) contain triglycerides and incorporate ApoB-100 as the core apolipoprotein. VLDLs are produced in the liver, and their size depends on liver triglyceride production. VLDL particles are smaller than chylomicrons. Like chylomicrons, VLDLs contribute to atherogenesis (Ahmed *et al.*, 2023; Feingold, 2024).

Intermediate-Density Lipoproteins

When muscle and adipose tissue lipoprotein lipase removes triglycerides from VLDL particles, the remnants become intermediate-density lipoproteins (IDL). IDL particles contain triglycerides, cholesterol, and apolipoproteins B-100 and E. Half of IDL in circulation is turned into low-density lipoprotein particles via the hepatic lipase while the other half returns to the liver. IDL is atherogenic (Ahmed *et al.*, 2023; Feingold, 2024; Juarez Casso & Farzam, 2022).

Low-Density Lipoproteins

Low-density lipoproteins (LDL) are derived from VLDL and IDL particles and carry most cholesterol in the bloodstream. LDL particles also carry most apolipoprotein B particles in the bloodstream, with ApoB-100 being the main apolipoprotein. LDL particles are known to be atherogenic and are colloquially referred to as "bad." Small, dense LDL particles have a stronger atherogenic effect because they stay in circulation for longer, get trapped on artery walls more easily, and are more easily uptaken by macrophages. Higher levels of small, dense LDL particles are linked with certain conditions, including obesity and type 2 diabetes. One form of LDL is lipoprotein (a) (Lp(a)), which contains apolipoprotein (a) particles that are attached to ApoB-100 particles. Lp(a) increases macrophage lipoprotein uptake and prevents fibrinolysis. LDL and Lp(a) are both pro-atherogenic (Ahmed *et al.*, 2023; Feingold, 2024).

High-Density Lipoproteins

High-density lipoproteins (HDL) are comprised of cholesterol and phospholipids, with its core apolipoprotein being ApoA-I. They are the smallest-sized class of lipoproteins. HDL particles transport cholesterol from peripheral cells to the liver, making it the only anti-atherogenic lipoprotein class in this list and is thus colloquially referred to as "good." HDL is also known to combat inflammation linked with atherosclerotic plaques (Ahmed *et al.*, 2023; Bailey & Mohiuddin, 2022; Feingold, 2024).

Apolipoproteins

Apolipoproteins have multiple roles in lipoprotein function and metabolism. These include assisting the formation of lipoproteins, helping maintain the structure of lipoproteins, being cofactors for lipoprotein metabolism enzymes, binding to lipoprotein receptors, and facilitating the exchange of lipid components between lipoproteins. The apolipoproteins involved in lipoprotein function are ApoA-I, ApoA-II, ApoA-IV, ApoA-V, ApoB-48, ApoB-100, ApoC-I, ApoC-II, ApoC-III, ApoE, and Apo(a). All of these forms of apolipoproteins are primarily synthesized in the liver or intestine (Ahmed *et al.*, 2023; Feingold, 2024).

Since lipoproteins are involved in atherogenesis, they are useful targets for treatments addressing SCI-linked cardiovascular complications. In particular, researchers might seek to develop treatments that promote HDL synthesis, as it is anti-atherogenic, while also developing treatments to suppress levels of chylomicrons,

VLDL, IDL, and LDL. Additionally, as apolipoproteins are crucial to the structure and function of lipoproteins, potential treatments could also target the synthesis of apolipoproteins to reduce atherosclerosis and other lipid-related complications.

Lipids and Lipoproteins in the Central Nervous System (CNS)

Lipids serve multiple important functions in the central nervous system. They are involved in neuron development, synapse formation, signaling, and other vital functions that help maintain proper nervous function. Cell membranes contain three main forms of lipids: phospholipids which form the lipid bilayer cell membrane; glycolipids, which are involved in cell communication and signaling; and cholesterol, which influences membrane permeability. In the central nervous system (CNS), new membrane synthesis is crucial for axon elongation during development. In dendrites, sterol regulatory element binding protein (SREBP, transcriptomic factors that influence lipid synthesis) levels need to be balanced for optimal formation and growth. Additionally, cholesterol from glial cells helps drive synapse formation in the CNS, while a derivative of cholesterol, 24S-hydroxycholesterol, modulates N-methyl-D-aspartate receptors, which are involved in synaptic plasticity (Cermenati *et al.*, 2015; Bertolio *et al.*, 2019; Roy & Tedeschi, 2021).

Lipids are also very important components of myelin sheaths, which consist of layers of membrane wrapped around axons. Myelin provides insulation to the axon, creating nodes of Ranvier that have high densities of sodium channels that allow neuronal signals to travel quickly to improve nervous system function. Myelin is primarily made up of a variety of lipids which make up 70-80% of the total weight. Cholesterol and glycosphingolipids are the main lipid forms present in myelin membranes. During brain development, fatty acids derived from astrocytes are also important components of myelin in the CNS, although oligodendrocytes can directly utilize circulating lipids if astrocyte lipid levels are low (Roy & Tedeschi, 2021).

Lipids are known to play additional roles in the CNS such as in energy storage. Glucose is preferred over fatty acids in the brain for energy metabolism because of increased ATP production, decreased oxygen usage, and decreased release of reactive oxygen species. However, neurons and astrocytes use fatty acids as energy under pathological conditions. The use of fatty acids in metabolism impairs oxidative phosphorylation during cellular respiration, ultimately leading to oxidative stress and impaired neuronal function (Cermenati *et al.,* 2015; Roy & Tedeschi, 2021).

Lipids are also involved in signaling which is important for maintaining proper CNS functioning. Certain signaling molecules, including neuroactive steroids and oxysterols, are derived from cholesterol. Neuroactive steroids can activate gene transcription and, in the CNS, are known to influence neuronal survival during neurodegeneration. Oxysterols can inhibit cholesterol synthesis and trigger the expression of liver X receptors, which are important in maintaining homeostatic lipid levels (Patel *et al.*, 2008). 24S-hydroxycholesterol, a form of oxysterol, was found to limit beta-amyloid synthesis (the accumulation of amyloid-beta in plaques is a key mechanism in Alzheimer's disease) in human neuroblastoma cells through the triggering of the endoplasmic reticulum stress marker glucose-regulated protein 78 (Urano *et al.*, 2013; Rukmangadachar & Bollu, 2023). Overall, abnormal levels or distributions of oxysterols are linked with neurodegenerative disease (Cermenati *et al.*, 2015).

Lipids play a wide range of crucial roles in the CNS, from being components of myelin and cell membranes to acting as energy sources and signaling molecules. As a result, maintaining a proper balance of lipids is crucial for proper CNS function and health.

Lipids and Lipoproteins after SCI

Multiple studies have investigated altered lipid profiles in individuals with spinal cord injuries. One such study found that individuals with SCI had significantly lower levels of total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C), as well as a significantly higher TC/HDL-C ratio (Gilbert *et al.*, 2013). Lower HDL-C levels have been associated with a higher risk of cardiovascular disease morbidity, and individuals with SCI have a 2.5 times higher rate of ischemic heart disease along with a higher rate of cardiac-caused mortality, making HDL-C levels a point of interest for SCI research (Yekutiel *et al.*, 1989). Researchers also found other demographic associations in individuals with SCI. For example, active individuals and women with SCI had significantly lower ratios of TC/HDL-C, while women also had significantly higher levels of HDL-C (Gilbert *et al.*, 2014). Another study found that lower low-density lipoprotein (LDL) to high-density lipoprotein (HDL) ratios and TC/HDL ratios were linked with better respiratory and muscular capacity after SCI (Groot *et al.*, 2007).

Other studies have looked at the molecular underpinnings of lipids and lipoproteins in SCI. For example, when axons are severed due to SCI, they require the resealing of the ruptured membrane to restore proper ion concentration and mitigate osmotic stress. In smaller injuries, the lipids in the membrane can reposition themselves to reseal the membrane, but in larger injuries, vesicles (which also have lipid bilayer membranes) are needed to fuse with the severed neuronal membrane (Cooper, 2000). SCI also causes damage to myelin sheaths and cell membranes. As cholesterol is an integral component of both structures, SCI leads to cholesterol accumulation in the extracellular space. A study conducted in CNS myelin-deficient mice found that CNS myelin lipids (mainly cholesterol and sphingomyelin) impede axon regeneration after axon severance, suggesting that SCI-induced cholesterol accumulation hinders regeneration (Mar *et al.*, 2015). For proper remyelination to occur, fatty acid synthesis must occur. Additionally, studies have found that cholesterol limiting agents inhibit remyelination post-SCI, suggesting that proper cholesterol synthesis is necessary for remyelination (Roy & Tedeschi, 2021). A study in old mice found that myelin damage caused large quantities of myelin debris, which is rich in lipids, to impede clearance, trigger the creation of cholesterol crystals that induce lysosome rupture, and activate inflammasomes, which can induce inflammation (Cantuti-Castelvetri *et al.*, 2018).

Lipids are also implicated in altered energy metabolism post-injury. Under pathological conditions from CNS injuries like SCI, neurons and astrocytes use fatty acids for energy metabolism. This lipid metabolism disrupts oxidative phosphorylation, binds to parts of the electron transport chain, and generates free radicals, which promotes oxidative stress (Phaniendra *et al.*, 2015; Roy & Tedeschi, 2021). Macrophages also exhibit altered energy metabolism, with their primary function being lipid metabolism at 7 days post-SCI. These macrophages closely resemble foam cells, lipid-enriched macrophages that make up atherogenic plaques (Zhu *et al.*, 2017). Additionally, rat models have shown that polyunsaturated fatty acid metabolism in spinal cord astrocytes leads to inflammation and cellular stress (Roy & Tedeschi, 2021).

Lipid metabolism is also dysregulated outside the spinal cord following a spinal cord injury. White adipose tissue (WAT), which is made up of triglycerides, stores extra energy. WAT is innervated by sympathetic neurons, which is needed to break down stored triglycerides into their component fatty acids and glycerols and maintain proper energy balance. WAT is also innervated by sensory neurons. This sensory circuit is sensitive to the adipose hormone leptin, which is involved in energy metabolism by suppressing appetite (Al-Hussainy *et al.*, 2021). After SCI, innervation of adipose tissue is severed, which compromises leptin signaling and leads to the accumulation of excess lipids in adipose tissue. This increased adiposity poses problems for the overall health of individuals with SCI. In more than half of individuals with SCI, more than 30% of body mass comes from adipose tissue, putting them at increased risk for metabolic conditions (Gorgey *et al.*, 2011). Individuals with SCI have increased adiposity in bone marrow, which can increase the risk for osteoporosis and cause inflammation while impeding immune function. They also have increased adiposity in non-adipose tissues like the liver, heart, and skeletal muscles. Increased lipid accumulation in the liver after SCI increases the

risk of non-alcoholic fatty liver disease, with more than 50% of individuals with SCI having non-alcoholic fatty liver disease from liver adiposity 1-year post-injury. (Rankin *et al.*, 2017) This increased liver adiposity, combined with chronic inflammation resulting from SCI, has the potential to onset tissue fibrosis and non-alcoholic steatohepatitis, a more severe version of fatty liver disease that is linked with increased morbidity (Susuki & Diehl, 2017). Increasing adiposity also causes insulin levels to rise. Since insulin mediates the release of VLDL particles from the liver, hyperinsulinemia arising from SCI-induced adiposity causes VLDL levels in the blood to rise. SCI-induced adiposity also causes a rise in free fatty acid levels in the blood, which blocks glucose usage in the liver and skeletal muscles. This leads to high glucose intolerance and insulin resistance in individuals with SCI (Roy & Tedeschi, 2021).

Overall, SCI deregulates lipids/lipoprotein levels and their usage in structural components and energy metabolism. This creates multiple lipid-linked targets for future treatments, like modulating cholesterol, targeting lipid transporters, and promoting leptin signaling. However, further research needs to be conducted for a more detailed understanding of lipid/lipoprotein dysregulation and dysfunction after SCI and the development of more comprehensive lipid-targeting treatments.

Influence of APOE on SCI

ApoE is a type of apolipoprotein and is a component of plasma lipoproteins. It has a role in transporting lipids, which are important in cell membranes, scaffolding, and signaling. In the CNS, it is produced in glial cells and is abundant in the brain, liver, and cerebral spinal fluid. It can bind both to cell surface receptors and lipids. There are 3 main genotypes of the ApoE gene encoding for 3 isoforms of ApoE protein: ApoE2, ApoE3, and ApoE4. More recently, much attention has been paid to the ApoE4 variant, which differs from the most common ApoE isoform, ApoE3. ApoE4 has a higher affinity for VLDL lipoproteins, while ApoE3 binds more with HDL lipoproteins. ApoE4 has been found to be a risk factor in Alzheimer's, Lewy Body Dementia, cardiovascular disease, and other conditions. It increases cholesterol accumulation, increases triglyceride lipid droplet prevalence, causes inflammation, worsens neuron-glial interactions, inhibits neuron branching, and increases tau protein and amyloid beta protein accumulation (Huang & Mahley, 2014; Yang *et al.*, 2023).

Currently, the precise role of ApoE in SCI is not fully known. In a SCI study in rats, researchers found that ApoE deficiency was linked to worse locomotor recovery, larger lesion areas, less intact motor neurons, higher inflammatory cytokine expression, reduced anti-oxidative stress factor expression, and increased pro-apoptotic factor expression, suggesting that ApoE plays a role in facilitating the SCI recovery process (Yang *et al.*, 2018; Yang *et al.*, 2023). Recently, there has been growing research conducted specifically on the effects of the ApoE4 isoform in SCI. In one mouse model of traumatic SCI, ApoE4 mice exhibited poorer locomotor function, decreased axon regeneration, increased inflammation, and decreased synaptic activity compared to ApoE3 mice (Toro *et al.*, 2021). Another traumatic SCI mouse model found that ApoE isoform and sex factors together influence the outcome of intermittent hypoxia, a potential SCI treatment that enhances plasticity, as a treatment (Strattan *et al.*, 2021). A mouse model of degenerative cervical myelopathy, a non-traumatic form of SCI, found that ApoE4 animals had decreased grey matter area, delayed locomotor recovery, and increased neuroinflammation (Desimone *et al.*, 2021). This research has identified the APOE4 gene and its associated protein as potential targets for future SCI treatments. However, more research is needed to clearly define the role of the ApoE protein and its isoforms in the molecular processes of SCI.

Studies on the relationship between ApoE and SCI are newly emerging, and further research will help uncover the molecular mechanism through which ApoE4 might lead to poorer recovery from SCI. Although such mechanisms are not currently known, current research on the influence of ApoE4 on SCI recovery has revealed the potential for a new avenue of treatment.

Potential Treatments and Further Research Interest for SCI Recovery

Despite extensive research on recovery after SCI, no entirely complete treatments have emerged yet. Various neuroprotective and neuroregenerative therapeutic strategies are being translated, which include pharmacological, nonpharmacological, and cell therapies (Ahuja & Fehlings, 2016; Ahuja *et al.*, 2017; Lima *et al.*, 2023; Sterner & Sterner, 2023). Currently, no mainstream treatments for SCI directly target lipids or lipoproteins, although the potential to target lipids/lipoproteins for SCI treatment has been identified.

Lipin 1 is an enzyme that converts phosphatidic acid into diglycerides, precursor cells for triglycerides and phospholipids. A study conducted in mouse retinal ganglion neurons found that lipin 1 levels increased after axons were severed by promoting the synthesis of triglycerides over phospholipids, inhibiting axon regeneration. That study also found that inhibiting lipin 1 inhibits triglyceride production and promotes phospholipid synthesis, promoting axon regeneration (Yang *et al.*, 2020). Thus, lipin 1 inhibition has potential as a treatment mechanism to promote axon regeneration that could translate to spinal neurons after SCI.

The regulation of cholesterol has also been investigated as a potential SCI treatment mechanism. SCI disrupts cell membranes and myelin, which causes the release of cholesterol. In old mice, high levels of myelin cholesterol were found to cause cholesterol crystal formation and lysosomal rupture, highlighting the need to regulate cholesterol after CNS injury (Cantuti-Castelvetri *et al.*, 2018). One study found that cholesterol depletion increased growth cone size and promoted axonal regeneration *in vitro* after severance in CNS neurons (Roselló-Busquets, 2019). Another study found that myelin lipids, which are mainly cholesterol and sphingomyelin, inhibit axon regeneration and that the administration of 2-hydroxypropyl-beta-cyckidextrin, a lipid-reducing drug, in wild-type mice lead to increased axon regeneration in the dorsal column after SCI (Mar *et al.*, 2016). However, statins, cholesterol-reducing drugs, have been shown to impede remyelination in the CNS and have been linked with impaired motor recovery after SCI (Miron *et al.*, 2009; Tripley & Scarisbrick, 2021). Therefore, future studies will need to carefully modulate myelin levels post-SCI to optimize treatment by enhancing the benefits of cholesterol depletion while mitigating the detriments.

Some studies have identified other particles to target for potential treatment mechanisms. One such particle is CD36, a lipoprotein receptor that contributes to lipid accumulation. One study in CD36-deprived mice showed that CD36 deletion is protective against atherosclerosis, and another study in CD36-deprived mice showed that CD36 deletion was linked with smaller lesion sizes, reduced macrophage lipid-enrichment, and improved locomotor function after SCI (Febbraio *et al.*, 2000; Zhu *et al.*, 2017). Therefore, CD36 depletion is a potential SCI treatment mechanism that warrants further investigation and may have potential for clinical application. Another protein that could be targeted in SCI treatment is ApoE4, an isoform of apolipoprotein E, which is a lipid-transporting protein. In mice models of Alzheimer's disease, depletion of ApoE4 decreased disease-linked gene expression in neurons and glial cells, protected against synaptic loss, reduced neurodegeneration, and inhibited tau pathology where tau accumulation is a hallmark of Alzheimer's disease (Koutsodendris *et al.*, 2023; Wang *et al.*, 2021; Yang *et al.*, 2023). Since the ApoE4 isoform has been linked with poorer outcomes after SCI, just like how it is linked with increased risk for Alzheimer's, ApoE4 depletion could be an effective SCI recovery treatment. However, the effectiveness of such treatment after SCI is unknown, even in experimental models. Therefore, much research will need to be conducted to determine if ApoE4 depletion is a viable treatment mechanism.

The various studies present that lipid-targeting treatment mechanisms have the potential to develop into viable SCI treatments. However, due to a lack of comprehensive knowledge on such mechanisms, there is currently a lack of lipid-targeting SCI treatments. Further research is needed on the viability of lipid-targeting SCI mechanisms to develop new SCI treatments that would complement existing SCI treatments and improve outcomes for SCI patients.

Conclusion

Lipids and lipoproteins have many roles in the complex pathophysiology of SCI. In the CNS, they are structural components in cell membranes and myelin, signaling molecules, and energy sources. SCI causes numerous physiological changes associated with lipids and lipoproteins, including lower HDL-C levels, damaged myelin sheaths, cholesterol release, higher levels of lipid metabolism in the brain, increased lipid accumulation in peripheral tissues, and decreased glucose usage in certain organs. As lipids and lipoproteins have a wide range of roles and implications from their dysregulation after SCI, they may be very useful targets for potential SCI treatments aiming to increase neuroprotection or promote tissue regeneration. However, although multiple potential SCI treatments targeting a wide range of SCI complications have been identified and tested, relatively few have targeted lipids or lipoproteins. Thus, future studies should further elucidate the role of lipids/lipoproteins in the spinal cord and the complexity of their dysregulation after SCI, allowing for more comprehensive SCI treatment.

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