Rethinking neurodegenerative diseases

neurometabolic concept linking lipid oxidation to diseases in the central nervous system

Helgudóttir, Steinunn Sara; Mørkholt, Anne Skøttrup; Lichota, Jacek; Bruun-Nyzell, Preben; Andersen, Mads Christian; Kristensen, Nanna Marie Juhl; Johansen, Amanda Krøger; Zinn, Mikela Reinholdt; Jensdóttir, Hulda Maria; Nieland, John Dirk Vestergaard

Published in:
Neural Regeneration Research

DOI (link to publication from Publisher):
10.4103/1673-5374.387965

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

Rethinking neurodegenerative diseases: neurometabolic concept linking lipid oxidation to diseases in the central nervous system

Steinunn Sara Helgudóttir[1, #], Anne Skøttrup Mørkholt[1, #], Jacek Lichota[2], Preben Bruun-Nyzell[1], Mads Christian Andersen[2], Nanna Marie Juhl Kristensen[2], Amanda Krøger Johansen[2], Mikela Reinholdt Zinn[2], Hulda Maria Jensdóttir[2], John Dirk Vestergaard Nieland[1, 2, *]

https://doi.org/10.4103/1673-5374.387965

Date of submission: May 31, 2023

Date of decision: August 31, 2023

Date of acceptance: September 21, 2023

Date of web publication: November 8, 2023

From the Contents

Abstract

Currently, there is a lack of effective medicines capable of halting or reversing the progression of neurodegenerative disorders, including amyotrophic lateral sclerosis, Parkinson's disease, multiple sclerosis, or Alzheimer's disease. Given the unmet medical need, it is necessary to reevaluate the existing paradigms of how to target these diseases. When considering neurodegenerative diseases from a systemic neurometabolic perspective, it becomes possible to explain the shared pathological features. This innovative approach presented in this paper draws upon extensive research conducted by the authors and researchers worldwide. In this review, we highlight the importance of metabolic mitochondrial dysfunction in the context of neurodegenerative diseases. We provide an overview of the risk factors associated with developing neurodegenerative disorders, including genetic, epigenetic, and environmental factors. Additionally, we examine pathological mechanisms implicated in these diseases such as oxidative stress, accumulation of misfolded proteins, inflammation, demyelination, death of neurons, insulin resistance, dysbiosis, and neurotransmitter disturbances. Finally, we outline a proposal for the restoration of mitochondrial metabolism, a crucial aspect that may hold the key to facilitating curative therapeutic interventions for neurodegenerative disorders in forthcoming advancements.

Key Words: brain disease; carnitine palmitoyl transferase 1; epigenetics; metabolism; gut microbiome; mitochondrial dysfunction; neurodegeneration; oxidative stress

Neurodegenerative Diseases from a Meta Perspective

The prevalence of neurodegenerative diseases affecting the central nervous system (CNS) is on the rise, mostly attributed to the extended lifespan of the general populations (Swenson et al. 2019). The disorders encompassed within this category include amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), multiple sclerosis (MS), Alzheimer's disease (AD), and other related conditions (Li and Le, 2017; Mcdonald et al., 2018). Numerous pharmaceutical interventions have been developed to treat a subset of the symptoms that follow, however, there is currently no efficacious treatment available to halt disease progression, nor is there a cure in sight for any of the aforementioned diseases. Given the increasing incidence of neurodegenerative disorders, it is imperative to advance the development of enhanced therapeutics and explore potential shared characteristics that may serve as viable targets.

It is troubling that while possessing a catalog of known mutations that increase the risk of developing neurodegenerative diseases, we remain unable to forecast the occurrence, timing, and causative factors behind the manifestation of these disorders in certain individuals while others remain unaffected. There appears to be a part of the puzzle that remains elusive or inconspicuous. To achieve significant advancements in the treatment of neurodegeneration, it would seem necessary to adopt a different perspective in our approach. This includes the identification of factors that contribute to or are essential for the development and progression of neurodegenerative disorders.

Over the past two decades, our team and researchers globally have been engaged in the exploration of a novel conceptual framework where we adopt a metaposition in the examination of diseases, wherein the focus shifts from isolated symptoms or the presence of mutated proteins to a systemic understanding of the disease as a whole. Challenging an established framework frequently elicits significant resistance from the collective, although there appears to be growing acceptance of the need to reconsider the etiology of neurodegenerative disorders. This review aims to provide a comprehensive overview of the existing literature on lipid metabolism and its implications in brain diseases. Additionally, it will highlight the advancements that have been achieved in this area of research, with the ultimate goal of enhancing comprehension of this subject matter. Furthermore, this review will explore the potential integration of this novel perspective into future drug development strategies for neurodegenerative disorders such as ALS, PD, MS, and AD.

Search Strategy

Literature cited in this narrative review was published from 1984 to 2023 and was retrieved from the PubMed database. The search was conducted using the following terms: "mitochondria" AND "neurodegenerative disease"; "lipid metabolism" AND "neurodegenerative diseases"; "beta oxidation" AND "neurodegenerative disease"; mitochondria energy metabolism; "PD" AND "mitochondria", "AD" AND "mitochondria"; "ALS" AND "mitochondria"; "glucose metabolism" AND "neurodegenerative diseases"; "therapeutics" AND "neurodegenerative diseases"; "microbiota" AND "neurodegenerative diseases"; "gene mutations" AND "neurodegenerative diseases". The reviewers selected eligible studies by reviewing their titles and abstracts.

Current Status of Treatment of Neurodegenerative Diseases

Presently, there is a lack of medications capable of effecting a cure or complete reversal of ALS, PD, MS, and AD. Furthermore, the available

[1]2N Pharma ApS, NOVI Science Park, Aalborg, Denmark; [2]Molecular Pharmacology Group, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark
*__Correspondence to:__ John Dirk Vestergaard Nieland, PhD, jdn@hst.aau.dk.
https://orcid.org/0000-0001-7423-0122 (John Dirk Vestergaard Nieland)
#Both authors contributed equally to this work.

How to cite this article: *Helgudóttir SS, Mørkholt AS, Lichota J, Bruun-Nyzell P, Andersen MC, Kristensen NMJ, Johansen AK, Zinn MR, Jensdóttir HM, Nieland JDV (2024) Rethinking neurodegenerative diseases: neurometabolic concept linking lipid oxidation to diseases in the central nervous system. Neural Regen Res 19(7):1437-1445.*

therapy modalities aimed at changing the course of these diseases are notably restricted in their scope (van Dyck et al., 2023). When considering the limited advancements in the treatment of neurodegenerative disorders during the past few decades, it is difficult to avoid feelings of discouragement. Fortunately, there have been notable advancements in the treatment of MS, as several therapeutic interventions have demonstrated efficacy in decelerating the progression of the disease. Despite being classified as a neurodegenerative illness, the treatment approach for MS extends beyond the confines of the brain. The effective strategies include immune modification in the periphery through the retention of naive memory T cells in the lymph nodes or lymphatic tissues using fingolimod, the reduction of cytotoxic T cells in the blood with dimethyl fumarate, and the depletion of circulating autoreactive B and T lymphocytes with cladribine (Derfuss et al., 2020; Jacobs et al., 2018). The therapy landscape for ALS is very limited, encompassing only four therapeutic choices, with the European Medicines Agency having approved only one of them (Feldman et al., 2022). Regrettably, the efficacy of these treatments is modest, as they usually only extend the lifespan of those affected by ALS by a maximum of 6 months. The most effective treatment for PD is L-DOPA (Lee and Yankee, 2022), which increases dopamine levels and thus reduces some disease symptoms. Nevertheless, it should be noted that not all patients exhibit a positive response to the medication. The approved drugs for AD primarily target amyloid-β (Aβ) deposition in the brain resulting in a slightly improved clinical outcome (Passeri et al., 2022). Given the absence of efficacious medicines capable of impeding the progression of neurodegenerative illnesses, it is essential to reassess the prevailing perspective on these conditions and formulate novel treatment approaches. The neurodegenerative diseases mentioned in this review ultimately present in different cerebral regions, but they share pathological features that result in cognitive deterioration and locomotor dysfunction (Ruffini et al., 2022; **Table 1**). Rather than fixating on a singular pathogenic mechanism, it is prudent to adopt a more comprehensive approach by considering the wealth of data accumulated over several decades of research.

What Does Energy Production Have to Do with Neurodegenerative Diseases? From Biochemistry to Hypothesis

The significance of metabolic pathways in both health and disease has historically been underestimated. Mitochondria, which are regarded as the powerhouses of cellular activity, are responsible for energy production in nearly all cell types. A mitochondrion that is operating under normal conditions possesses the ability to selectively utilize the substrates that are available to it, hence exhibiting the capacity to shift between different metabolic pathways, primarily those involving lipids and glucose. The mitochondria utilize acetyl-CoA within the tricarboxylic acid cycle (TCA) to generate NADH and FADH2 which are subsequently employed in the electron transport chain for adenosine triphosphate (ATP) synthesis (Houten and Wanders, 2010; Spinelli and Haigis, 2018; **Figure 1**).

One notable distinction between glucose and lipid metabolism is in the quantity of oxygen required to generate each ATP molecule. The utilization of lipids results in elevation of the FADH2/NADH ratio, leading to reduced transfer of electrons to complex I in comparison to complex II within the electron transport chain. Consequently, ATP synthesis is reduced, thereby necessitating an increase in oxygen consumption as a compensatory mechanism. The formation of reactive oxygen species (ROS) may be attributed to the decreased ATP/oxygen ratio, which could elucidate the preference for glucose as a substrate (Hue and Taegtmeyer, 2009; Schönfeld and Reiser, 2013). In this discussion, we shall explore the uptake and utilization of glucose and lipids for ATP generation.

Glucose is transported into the cell by the glucose transporter and metabolized into pyruvate by glycolysis in the cytosol (Brown, 2000; Spinelli and Haigis, 2018). The transportation of pyruvate across the inner mitochondrial membrane is facilitated by the mitochondrial pyruvate carrier

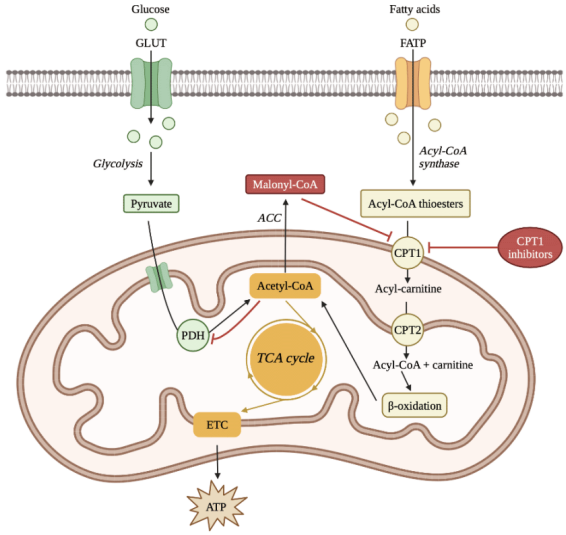

Figure 1 | Simplified illustration of glucose (left) and lipid metabolism (right) in the cell.
The rate-limiting step for glucose and lipid metabolism is PDH and CTP1, respectively. CPT1 can endogenously be inhibited by malonyl-CoA and by exogenous CPT1 inhibitors. Created with BioRender.com. ACC: Acetyl-CoA carboxylase; CPT: carnitine palmitoyl transferase; ETC: electron transport chain; FATP: fatty acid transport protein; GLUT: glucose transporter; PDH: pyruvate dehydrogenase; TCA cycle: tricarboxylic acid cycle.

protein. Inside the mitochondria, the pyruvate is converted to acetyl-CoA by pyruvate dehydrogenase (PDH), thus ready for the TCA cycle (Spinelli and Haigis, 2018). In instances where there is a substantial accumulation of acetyl-CoA, the PDH undergoes phosphorylation by pyruvate dehydrogenase kinase in a negative feedback mechanism. In contrast, elevated concentrations of pyruvate have an inhibitory effect on pyruvate dehydrogenase kinase, resulting in greater synthesis of acetyl-CoA by the PDH (Hue and Taegtmeyer, 2009; Houten and Wanders, 2010).

The mitochondria have the ability to utilize lipid metabolism as an alternate means of energy production in situations such as dietary stress and fasting (Houten and Wanders, 2010; Longo et al., 2016; Spinelli and Haigis, 2018). Within the context of lipid metabolism, cellular uptake of long-chain fatty acids is facilitated by the fatty acid transport protein situated within the cell membrane. In addition to its role as a transporter, fatty acid transport protein facilitates the conversion of fatty acids into acyl-CoA thioesters through its acyl-CoA synthase activity (Houten and Wanders, 2010; Longo et al., 2016). These acyl-CoA products cannot enter the mitochondria without prior conjugation to carnitine to produce acyl-carnitines, a process facilitated by carnitine palmitoyl transferase 1 (CPT1). Subsequently, the acyl-carnitine molecule can be transported across the outer mitochondrial membrane by the carnitine acylcarnitine translocase. Carnitine palmitoyl transferase 2 (CPT2) is located on the inner mitochondrial membrane and functions to catalyze the reconversion of acyl-carnitines into carnitine and acyl-CoA. The carnitine acylcarnitine translocase facilitates the transports of carnitine from the mitochondria back to the cytosol. Conversely, the acyl-CoA transported into the mitochondrial matrix can be utilized in β-oxidation to generate acetyl-CoA, which is then utilized in the TCA cycle (Houten and Wanders, 2010; Longo et al., 2016; Spinelli and Haigis, 2018). The CPT1 enzyme constitutes the rate-limiting step of lipid metabolism and can be endogenously inhibited by malonyl-CoA. CPT1 exists in three distinct isoforms. The liver isoform, known as CPT1a, is ubiquitously expressed in various cell types across

Table 1 | The common pathological mechanisms in amyotrophic lateral sclerosis, Parkinson's disease, multiple sclerosis, and Alzheimer's disease

Mechanism	Amyotrophic lateral sclerosis	Parkinson's disease	Multiple sclerosis	Alzheimer's disease
Mitochondrial dysfunction	Trabjerg et al., 2020	González-Rodríguez et al., 2021; Vos, 2022; Trabjerg et al., 2023	Mao and Reddy, 2010	Chen and Zhong, 2014
Inflammation	McCombe and Henderson, 2011	Pajares et al., 2020	Frischer et al., 2009	Kinney et al., 2018
Oxidative stress	Saso et al., 2022	Henchcliffe and Beal, 2008	Zhang et al., 2020	Ionescu-Tucker and Cotman, 2021
Demyelination	Zhou et al., 2017	Dean et al., 2016	The Lancet Neurology, 2021	Papuć and Rejdak, 2020
Neurotransmitter disturbances	Heath and Shaw, 2002	Barone, 2010	Akyuz et al., 2023	Kaur et al., 2019
Gut dysbiosis	Martin et al., 2022	Huang et al., 2021	Thirion et al., 2023	Liu et al., 2020
Disrupted iron homeostasis	Petillon et al., 2018	Ward et al., 2014	Duarte-Silva et al., 2023	Liu et al., 2018
HPA-axis disruption (stress)	Mentis et al., 2021	Du and Pang, 2015	Melief et al., 2013	Ahmad et al., 2019
Insulin resistance	Reyes et al., 1984	Hogg et al., 2018	Ruiz-Argüelles et al., 2018	Kellar and Craft, 2020
Protein aggregates	Blokhuis et al., 2013	Stott et al., 2020	David and Tayebi, 2014	Serrano-Pozo et al., 2021
Decreased glucose metabolism	Tefera et al., 2021	Dunn et al., 2014	Zahoor et al., 2021	Butterfield and Halliwell, 2019
Increased lipid metabolism	Chaves-Filho et al., 2019	Alecu and Bennett, 2019	Pineda-Torra et al., 2021	Hooijmans and Kiliaan, 2008

HPA: Hypothalamic-pituitary-adrenal.

the body. Conversely, the muscle isoform, referred to as CPT1b, exhibits a more selective distribution, mostly localized in the muscles, testis, and heart (Bonnefont et al., 2004). Finally, CPT1c is found to be brain-specific (Bonnefont et al., 2004; Immordino et al., 2006; Pinto, 2014). It is located in the endoplasmic reticulum, not the mitochondrial membrane, however, its precise role remains largely unexplored (Gratacòs-Batlle et al., 2018).

But what is the relationship between energy generation and neurodegenerative diseases? The role of mitochondria is characterized by its multifaceted and multifunctional nature, as comprehensively elucidated in Monzel et al. (2023). Additionally, it has been observed that mitochondria will undergo reversible physiological recalibrations in order to adapt to changing conditions (Monzel et al., 2023). However, persistent alterations in mitochondrial bioenergetics are of great concern. Deficient glucose metabolism and significantly increased lipid metabolism are frequently observed characteristics of several brain diseases, including ALS, PD, MS, and AD (Pathak et al., 2013; Yin et al., 2017; Wareham et al., 2022). It may be challenging to conceive that a cellular activity of such a fundamental nature might become imbalanced. A cell often possesses compensation mechanisms that can operate temporarily without inflicting significant harm, contingent upon the cell's condition and metabolic resources. Nevertheless, it is possible for cells to become trapped in a self-reinforcing state of imbalance due to the inhibitory effect of enhanced ß-oxidation on the PDH transporter, consequently impeding glucose metabolism (Elnwasany et al., 2023). As a consequence of heightened lipid metabolism, the occurrence of oxidative stress has the potential to trigger mitochondrial dysfunction and resulting mitochondrial fission (Jheng et al., 2012). The process of mitochondrial fission can lead to insensitivity of CPT1 towards Malonyl-CoA (Ngo et al., 2023), which can induce a persistent transition from glucose to lipid metabolism as the predominant source of energy generation.

A Novel Neurometabolic Hypothesis

In this paper, we present a neurometabolic hypothesis that is founded on evidence obtained from animal models. Furthermore, we provide support for this theory by the analysis of human data, which indicate that the pathological brain is characterized by a persistent and self-perpetuating metabolic imbalance (Mørkholt et al., 2019; Trabjerg et al., 2020, 2021, 2023). The neurometabolic hypothesis posits that a sustained shift from glucose to lipids as the primary fuel for energy generation promotes the pathogenesis of neurodegeneration through several complex and interconnected mechanisms including oxidative stress, inflammation, aggregation of misfolded proteins, demyelination, disturbances in neurotransmitter function, and the onset of gut dysbiosis. This section will predominantly examine the influence of established risk factors on the alteration of metabolism in relation to the development of neurodegenerative diseases. Additionally, it will illustrate the interconnectedness of the common pathogenic pathways involved, as depicted in **Figure 2**.

Risk factors for development of neurodegenerative diseases

A healthy brain, being the most metabolically active organ in the body, is reliant on glucose as its primary source of energy production. However, as discussed above, a persistent shift from glucose to lipids as the main substrate is often observed in brain diseases (Yin, 2023). The etiology of the change remains poorly understood, but we hypothesize that potential catalysts include a combination of environmental toxins, physiological or psychological stressors, infectious agents, and genetic susceptibility (**Figure 2**).

Numerous genetic factors, including mutations in SOD1, TDP43, C9ORF, PARK2, PARK7, PINK, LRRK2, and APP, among others, have been found to be correlated with neurodegenerative diseases. However, in our experience with animal models, several of the mutations, for example, LRRK2, C9ORF, APP, PARK2, and PARK7 require additional stressors to ensure the manifestation of the disease. Other researchers have reported similar results. For instance, Dafinca et al. (2021) saw comparable findings in animals with C9ORF mutations, while Holcomb et al. (1998) and Kang et al. (2007) found similar outcomes in mice with APP mutations. Mice with a mutation in the SOD1 gene exhibit accelerated onset of disease when subjected to stress induced by cortisone injection or when placed on a diet high in saturated fat (Trabjerg et al., 2021). Likewise, in the case of PARK2 mice, the disease induction is expedited when animals are exposed to environmental toxins such as rotenone (Trabjerg et al., 2023).

What insights may be gained from these animal models? Laboratory animals with mutations in specific genes are subject to an elevated susceptibility to illness, however, the presence of such mutations does not invariably entail the development of neurodegenerative disease. This can be attributed to the different environmental conditions experienced by these animals in comparison to animals in the wild. In high barrier facilities commonly employed for experiments, animals are typically shielded from exposure to infectious diseases or diverse gut microorganisms (Schlapp et al., 2018). Moreover, laboratory animals are usually not exposed to equivalent levels of stress or sensory stimulation as animals in the wild. The diet provided to experimental animals is uniform and unrestricted, a factor that exerts a significant impact on brain function (Koizumi et al., 2018). Furthermore, the impact of age on disease progression is often disregarded in animal studies. Alteration in metabolism with advancing age, namely a tendency to shift from glucose to lipids (Ravera et al., 2019) has been identified as a potential influential component in the pathogenesis of brain diseases (Johnson and Stolzing, 2019). It is evident that a direct comparison between humans and mice is not feasible. Nevertheless, there is mounting evidence that the environment may have an impact on human disease.

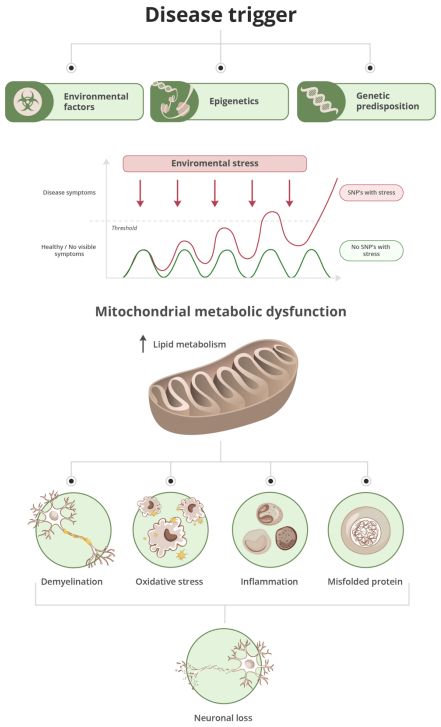

Figure 2 | An overview of identified and suggested factors commonly linked to neurodegenerative pathological etiology.
Stressors can be various environmental factors, inherited genetic mutations, and epigenetic alterations. This can shift the metabolism in the mitochondria from glucose to lipids. This will generate oxidative stress, induce inflammation, cause misfolding of proteins, demyelination, and more. The neurons in the affected area will die, leading to neurodegeneration and ultimately neurodegenerative diseases such as amyotrophic lateral sclerosis, Parkinson's disease, multiple sclerosis, or Alzheimer's disease. Created with graphical designer Maria Rasmussen using Adobe Illustrator®. SNP: Single nucleotide polymorphisms.

The development of a particular disease is influenced by a complex interplay of genetic and environmental factors, rather than being solely determined by genetics (Virolainen et al., 2023). Environmental factors have been shown to play a decisive role in the development of different diseases in humans, with research on both identical and dizygotic twins providing valuable insights into the significance of these factors. Examples of studies include those in PD (Vieregge et al., 1999; Goldman et al., 2019), AD (Koncz et al., 2022), and MS (Ingelfinger et al., 2022). These studies have shown that there is a lack of concordance in disease incidence among identical twins, and in many cases, the incidence is equally frequent in identical twins and dizygotic twins. Multiple environmental factors, including stress, dietary patterns, viral infections, and exposure to toxins, have been identified as potential contributors to increased susceptibility to neurodegenerative diseases. However, it is unclear through which precise mechanism these factors increase or decrease the risk of developing ALS, PD, MS, or AD. One possible answer is epigenetics, the study of the transcriptome rather than the DNA itself. It has been defined as heritable changes in gene expression that are stable between cell divisions and even between generations without involving changes in the DNA sequence (Arrowsmith et al., 2012; Cavalli and Heard, 2019). All cells in a particular organism contain the same genetic material, but the biological characteristics and functionalities of cells and tissues differ as a result of variations in the transcriptome (Arrowsmith et al., 2012; Tough et al., 2016). Epigenetic factors exert a regulatory influence on gene expression, operating in conjunction with transcription factors that govern the transcriptome, in order to regulate how and when genes are expressed depending on the changing environment (Qureshi and Mehler, 2011; Arrowsmith et al., 2012; Szyf, 2015). Epigenetic modifications have the capacity to alter the expression of genes implicated in the pathogenesis of neurological disorders (Allison et al., 2021), e.g., CPT1A (Lai et al., 2020). Furthermore, these modifications can be influenced by various environmental factors such as dietary patterns, stress, infectious agents, and exposure to toxic substances, as evidenced by studies conducted in human populations (Fleming et al., 2018).

Stress is a reaction to external or internal pressures that can be both beneficial and harmful to an individual's well-being, depending on the intensity and duration of the stressor. Epigenetic changes resulting from stress can have a variety of effects on the body. For example, it has been observed that epigenetic modifications can induce alterations in the expression of genes associated with stress response, immunological function,

and inflammation, leading to an increased risk of chronic diseases (Shi et al., 2022). These changes in gene expression, initially transient in nature, might become permanent due to epigenetic modifications. One example is in military personnel where there exists a correlation between epigenetic modifications and the manifestation of diseases such as post-traumatic stress disorder (Raza et al., 2023). Furthermore, it is noteworthy that US military personnel who served in the first gulf war had a remarkable 100% increase in the prevalence of ALS compared to the overall population of the United States (Haley, 2003; Rose, 2003). According to a study by Seals et al. (2016), it was shown that Danish military personnel exhibit a 30% higher incidence of ALS compared to the general Danish population. It is evident that military personal are likely to experience a higher level of stress compared to the general population (Wu et al., 2023), and chronic stress is considered an important risk factor in the development of AD (Peña-Bautista et al., 2020). The presence of multiple stressors at the same time may exacerbate the detrimental impact. By virtue of their profession, military personal may often find themselves in demanding environments, where they are simultaneously exposed to psychological and physical stress, hazardous substances, unusual pathogens, and unfamiliar dietary stressors. Military veterans may be at a higher risk of neurodegenerative illnesses due to various additional factors, including injuries sustained during their service and their socioeconomic condition. Head trauma is a known risk factor for the development of multiple neurodegenerative diseases, and veterans are more likely than the general population to have sustained a head injury (Gardner and Yaffe, 2015). The impact of stressful periods can be intensified by their timing, and research has shown that exposure to stress during childhood can elevate the risk of dementia even further (Peña-Bautista et al., 2020). Chronic stress has been found to induce alternations in DNA methylation, histone modifications, and non-coding RNA expression, which can have enduring effects on an individual's mental and physical well-being (Dion et al., 2022; Dee et al., 2023). The impact of different stressors and chronic periodical stress on an individual is an area of research that has received limited attention. We posit that gaining a comprehensive understanding of the consequences of stress may facilitate the advancement of novel therapeutic approaches, not only for neurodegenerative diseases, but also for human pathology more broadly.

There is evidence to suggest that the dietary choices we make can exert a direct influence on our susceptibility to neurodegenerative diseases. For example, a diet high in saturated and trans fats has been associated with an increased risk of developing AD, while a diet rich in fruits, vegetables, and fish has been found to be connected with a reduced risk of developing the disease (Boeing et al., 2012). Similarly, consumption of a diet high in red meat and processed foods has been linked to an increased risk of developing PD (Agim and Cannon, 2015), while a diet rich in antioxidants and omega-3 fatty acids has been associated with a decreased risk of the disease (Avallone et al., 2019).

A range of infections has been correlated to increased susceptibility to the onset of neurodegenerative disorders (Levine et al., 2023). The Epstein-Barr virus is classified as a member of the herpes virus family and can establish a latent infection within host cells. The virus is best known for causing the illness known as infectious mononucleosis. According to a recent study by Bjornevik et al. (2022), those who have been infected with Epstein-Barr virus were 31 times more likely to develop MS, in comparison to those who have not been infected. Remarkably, recent research shows that 22 virus types are associated with an increased risk of neurodegenerative disease, and that the risk persists years after the initial virus infection (Levine et al., 2023). The findings of Levine et al. (2023) have the potential to facilitate the implementation of prophylactic treatments, such as vaccinations and antiviral therapies, in order to reduce the risk of developing neurodegenerative diseases. Furthermore, these results could help future clinical drug trials stratify patient groups more successfully based on previous viral infections and the likelihood of faster disease progression due to predisposition (Levine et al., 2023).

What is the mechanism by which these stress factors influence disease pathology and how does this align with the neurometabolic hypothesis? The primary emphasis of the concept is that sensitivity to exposures or forms of stress, such as infections, psychological stress, toxins, or dietary stress, is rooted in single nuclear polymorphisms or nucleotide polymorphisms (SNPs). When an organism is subjected to environmental stress, its response may vary depending on genetic predisposition or sensitivities. Hence, in some cases, environmental factors have the potential to disrupt the organism's equilibrium. Certain SNPs are known as mutations such as SOD1 G93A or C9ORF, Park2, and others. However, there exists a multitude of SNPs that elicit minor disturbances when subjected to stressors at specific temporal intervals. These stressors, including some that may be imperceptible, have the potential to elicit a metabolic response that alters the equilibrium between glucose and lipid catabolism, with a shift towards favoring lipids. This transition induces various pathological processes further elucidated in the next section.

The inability to identify a single etiological factor for neurodegeneration can be elucidated by the neurometabolic hypothesis. The effect of stressors on an individual can vary depending on their inherent resilience or predispositions. Furthermore, the hypothesis elucidates the rationale behind the absence of illness in individuals with certain mutations or SNPs, as the onset of disease necessitates a threshold level of stress that is contingent upon the unique characteristics of each individual. Several studies have provided evidence of the association between depression, stress, and disease risk in various contexts. For instance, Justice (2018), Mirza et al. (2016), Shaw et al. (2017), and Sugama et al. (2016) have all presented compelling data in the fields of AD, PD, and MS, where repeated episodes of depression or prolonged exposure to depression or stress have been shown to elevate the likelihood of developing these conditions. The many pathogenic pathways observed in ALS, PD, AD, and MS ultimately lead to neuronal death (**Table 1**) and are associated with alterations in mitochondrial metabolism. To construct a model predicated on these pathologic mechanisms, we hypothesized that all processes leading to disease exhibit interconnections.

How mitochondrial energy generation initiates pathological mechanisms in ALS, PD, MS, and AD

The connection between energy generation, oxygen consumption, oxidative stress, protein misfolding, and neuroinflammation may not be readily apparent. Mitochondrial function is affected by increased lipid oxidation as the process requires almost twice as much oxygen per unit of ATP generated in comparison to glucose oxidation (Leverve et al., 2007). Mitochondria can adapt to mild stress with metabolic reprogramming which enhances their oxidative tolerance to a given stimuli. This response is referred to as mitohormesis (Timblin et al., 2021) and confers advantageous effects on cellular viability. Nonetheless, a sustained shift from glucose to lipids as the predominant source of energy generation can lead to chronic hypoxia followed by excessive synthesis of ROS, a type of free radical molecules, characterized by the presence of an unpaired electron, rendering them inherently unstable and highly reactive (Baev et al., 2022). Over several decades, ROS have been widely recognized as significant contributors to irreparable cell and tissue damage. Antioxidants have been employed in the mitigation of ROS, given their capacity to donate an electron to a free radical to stabilize it, while maintaining their stability. Glutathione and tocopherol are among the various examples of antioxidants. Oxidative stress arises from an imbalance between the production of free radicals and the capacity of antioxidants to neutralize them. Consequently, the excessive presence of highly reactive free radicals leads to damage to DNA, lipids, and proteins (Xiao et al., 2022). Maintaining the equilibrium of oxygen levels within the mitochondria is of the utmost importance since deviations in both excessive and insufficient quantities can significantly impact mitochondrial function. Leigh syndrome, the most common pediatric mitochondrial disorder, has been shown to cause cerebral hyperoxia in murine models, resulting in an increase in partial oxygen pressure. Leigh syndrome currently lacks a viable treatment option, but a team of pioneering researchers have demonstrated that the induction of chronic hypoxic exposure successfully reversed neurological damage in afflicted mice. This reversal may be attributed to the prevention of oxygen toxicity at its fundamental level, rather than utilizing antioxidants that specifically address the downstream pathological consequences (Jain et al., 2019). The presented data provide further evidence about the significance of mitochondrial function in the context of neurodegenerative disorders and underscore the importance of re-evaluating the prevailing hypothesis on the pathogenesis of these diseases, which remain without a cure.

The endoplasmic reticulum is a complex organelle that has many functions, one of which is the intricate process of protein folding. Studies have shown that oxidative stress and endoplasmic reticulum stress are correlated and can lead to protein misfolding (Abramov et al., 2020). Accumulation of misfolded proteins causes cellular damage and mitochondrial dysfunction and is associated with a range of neurodegenerative diseases, including ALS (misfolded SOD1, TDP-43, C9orf72) (McAlary et al., 2020), PD (misfolded α-synuclein) and AD (misfolded Aβ and Tau) (Abramov et al., 2020).

Oxidative stress is known to promote the synthesis of prostaglandin-E2, a proinflammatory mediator that plays a crucial role in attracting and activating the immune system, thereby inducing inflammation at the site of heightened lipid metabolism (Liu et al., 2023). Neuroinflammation is a commonly observed feature in neurodegenerative diseases, characterized by increased levels of proinflammatory cytokines including IL18, IL-1β, and tumor necrosis factor alpha (Leng and Edison, 2021).

The excessive consumption of lipids for energy generation and the subsequent increase of ROS in the brain also affect other mechanisms within the CNS. Myelin is a crucial component consisting of lipids and proteins that envelop nerves, serving as a protective barrier against external electrical interference while greatly increasing the speed of neuronal signal transmission and reducing the energy expenditure required for such transmission (Moore et al., 2020). Myelin sheaths, however, naturally degrade and need constant maintenance and replenishment, which is the role of oligodendrocytes. ROS have the potential to cause damage to the myelin sheaths and facilitate an immune system response through the activation of macrophage cells. When the myelin sheaths suffer significant damage, demyelination occurs, which is associated with a significant reduction of nerve conduction velocity (Chung et al., 2014). The half-life of lipids bound to myelin basic protein is approximately three days (Bizzozero and Good, 1991), indicating that lipids are continuously replenished in the neuronal axon. The heightened lipid metabolism within the CNS results in diminished availability of lipids for replenishing those that have been depleted. Regrettably, oligodendrocytes are sensitive to oxidative stress, possibly due to their limited capacity for antioxidant defense (Giacci et al., 2018) and their high iron content (Reinert et al., 2019). Consequently, the occurrence of oxidative stress may lead to the death of oligodendrocytes, thereby impeding the process of remyelination.

The presence of elevated iron levels in brain regions affected by neuroinflammation has been reported, for example, in substantia nigra in

post-mortem samples from patients with PD (Martin-Bastida et al., 2021), and in substantia nigra, globus pallidum, hippocampus, putamen and caudate nucleus in AD (Ward et al., 2022). Mitochondrial ROS can increase the secretion of pro-inflammatory cytokines (Urrutia et al., 2014), and consequently initiate a cascade of pathological events that eventually leads to the death of neurons in a particular part of the brain.

As the brain is the most energy-demanding organ, consuming approximately 20% of the body's metabolic energy, an imbalance in the CNS will have a systemic effect. The heightened lipid metabolism results in elevated concentrations of glucose in the blood, leading to a gradual decline in glucose tolerance. According to Savage et al., (2007), the development of insulin resistance is likely to occur, providing a potential explanation for the prevalence of type 2 diabetes among individuals with neurodegenerative diseases. Elevated glucose levels subsequently induce the process of protein glycation. The process of glycation of hemoglobin is well-documented (Kuo et al., 2016), however, it has also been observed that other proteins and even DNA can undergo glycation, potentially resulting in the development of pathological conditions (Ng and Freeze, 2018) This is precisely the reason why the PARK7 mutation is considered a risk factor for PD, as PARK7 deglycates these constructs. In the absence of its proper functioning, these constructs remain glycated (König et al., 2018). Molecules can undergo acylation, a process that results in modification of their properties. N-acylated-Dopamine (Zajac et al., 2014) and N-Arachidonoyl-Dopamine (Piscitelli and Bradshaw, 2017) can increase the sensitivity of dopamine receptors and consequently reduce the amount of dopamine required to elicit a response. Increased lipid metabolism will deplete the lipid available for posttranslational modification of dopamine and will therefore have an indirect negative effect on dopamine response, as the production of acylated and arachidonylated dopamine will decrease.

The impact of microbiota alterations on the development of neurodegenerative diseases

The impact of dietary choices on overall well-being is significant. According to Malesza et al. (2021), the western diet is increasingly high in fat and refined sugars, a dietary pattern that has been linked to a decline in the integrity of the gut barrier, leading to the release of harmful bacterial metabolites into the bloodstream. The exposure to this factor has been found to elicit a state of low-grade systemic inflammation (Malesza et al., 2021; Thomas et al., 2022). This inflammatory response has been associated with an elevated susceptibility to various health conditions, including cancer, diabetes, and neurodegenerative diseases (Moyse et al., 2022). The consumption of a high-fat diet has been shown to induce a metabolic shift in the mitochondria towards fatty acid β-oxidation in the small intestines (Guerbette et al., 2022). This observation provides a potential explanation for the direct association between mitochondrial function and factors such as dietary choices, microbiota composition, and inflammatory processes.

There is a growing body of evidence linking microbiota alteration and the pathogenesis of neurogenerative diseases (Kraimi et al., 2022). Elevated blood glucose levels, alongside various other factors, have the potential to induce changes in the composition of the gut microbiota, leading to a state of dysbiosis. The elevated expression of certain microbiota strains has been found to be associated with the onset of brain diseases (Vogt et al., 2017). Notably, opportunistic gram-negative bacteria such as *Escherichia coli*, *Shigella*, *Helicobacter*, and *Odoribacter* have been implicated in this connection, as has a decrease in beneficial microbiota strains like *Bifidobacterium* and *Eubacterium* (Cattaneo et al., 2017; Gentile et al., 2020). Together this underscores the importance of maintaining gut homeostasis in the prevention and potential treatment of neurodegenerative diseases. Dysbiosis is a commonly observed phenomenon in individuals afflicted by neurodegenerative disorders. For instance, a reduction in community diversity has been demonstrated in AD patients (Vogt et al., 2017; Haran et al., 2019). Similarly, multiple studies conducted on individuals with ALS showed variations in bacterial composition, accompanied by reduced levels of microbial diversity (Calvo et al., 2022).

But why is microbiota composition so important? The influence of gut microbiota on the production and translocation of metabolites across the gut membrane is well established. The generation and consumption of metabolites in the gut are contingent upon the species of bacteria, yeasts, and archeobacteria that are present (Zhu et al., 2020). Hence, it becomes evident that a reciprocal relationship exists between metabolites within the human body and microbiota residing in the gastrointestinal tract (Visconti et al., 2019). There is increasing evidence suggesting that microbiota exert a significant influence on brain health. The concept of the microbiota gut-brain axis pertains to the intricate communication network that exists between gut microbiota and the brain, which occurs via multiple pathways including the vagus nerve and metabolites (Cryan et al., 2019). Microbiota can even induce DNA methylation, leading to epigenetic modifications (Woo and Alenghat, 2022). According to Huang et al. (2021), the microbiota play a crucial role in the development of the blood-brain barrier, myelination of neurons, and maturation of microglia (Huang et al., 2021). In addition, the microbiota has the ability to synthesize neurotransmitters and their precursors (Chen et al., 2021). Consequently, dysbiosis in neurodegenerative diseases will result in disruptions of neurotransmitter function and subsequent detrimental effects. There is growing interest in the potential of modulating the gut microbiota-brain axis through dietary adjustments. Gates et al., (2022) found that the consumption of fermented foods that are high in bioactive polyphenols and complex carbohydrates has potential benefits in mitigating neuroinflammation, oxidative stress, and neuronal death in AD and PD (Gates et al., 2022). The efficacy of targeting the microbiota-brain axis in improving cognition in individuals with mild to moderate AD has been established through the use of GV-971, as demonstrated in a Phase 3 trial (Xiao et al., 2021). GV-971 is a seaweed derivative that can restore the balance of microorganisms in the gut and reduce peripheral infiltration of immune cells to the brain. As a result, it effectively inhibits or diminishes neuroinflammation. According to Gates et al. (2022), animal studies have demonstrated that GV-971 is able to effectively cross the blood-brain barrier and mitigate the accumulation of Aβ in the brain.

We propose that restoring mitochondrial metabolism may hold significant potential in the treatment of neurodegenerative diseases, relieving most, if not all, downstream pathological processes. The focal point of this hypothesis revolves around CPT1, the rate-limiting molecule for lipid oxidation. The next section will examine the impact of inhibiting CPT1 and its potential for prophylaxis or disease modification.

Human Genetics Demonstrate the Prophylactic Effect of CPT1 Inhibition

The neurometabolic hypothesis, which posits a connection between alterations in metabolic demands and the pivotal role of CPT1 in the pathogenesis of brain diseases is supported by studies of human genetics. Several human mutations in CPT1A are reported. Certain population groups, such as Inuit, Alaska Natives, and Hutterite, exhibit a high prevalence of genetic mutations that result in reduced activity of CPT1A. Notably, there exists a significant correlation between the presence of these mutations and a decreased occurrence of specific neurodegenerative diseases. Alaska Natives refer to the indigenous population of the state of Alaska, encompassing several distinct groups. Genetic studies have shown this population migrated to Alaska from Asia millennia ago. Alaska is home to a population of approximately 86,000 Alaska Natives, with an estimated 17,000 living outside the state. The Inuit are a group of indigenous peoples of the Arctic regions of Canada, Greenland, and parts of Alaska. Of the approximately 148,000 Inuit, 65,000 live in Canada, 50,000 in Greenland, 15,000 in Alaska, and 15,000 in Denmark. The genetic sequence variant c.1436C→T of CPT1A or SPT1AP479L, commonly referred to as the Artic variant, is prevalent among Alaska Natives and Inuit populations. Studies have reported that 63% of Alaska Natives, 98% of Canadian Inuit, and 92% of Greenland Inuit individuals possess either homozygous or heterozygous mutations (Greenberg et al., 2009; Rajakumar et al., 2009; Gessner et al., 2011). A homozygous mutation reduces the activity of CPT1A to 22% of that of the wild-type molecule. The incidence rate of ALS for Alaska Natives was reported to be 0.63 per 100,000 while it is estimated to be between 2 and 4 in the general US population (Gordon et al., 2013). The disparity is particularly evident in the case of MS with an incidence rate of 2 per 100,000 among Canadian Inuit, compared to the significantly higher rate of 285 per 100,000 in the general Canadian population. Regrettably, we have not been able to estimate the incidence rate of PD and AD in these populations. The Hutterites are an ethnoreligious community originated in 16th century Switzerland but now almost exclusively living in Western Canada and the upper Great Plains of the United States. The population is estimated to number approximately 45,000 individuals. Approximately 30% of the Hutterite Brethren have at least one allele with another CPT1A mutation, the CPT1A G710E that completely knocks out CPT1A activity (Prasad et al. 2001; Mørkholt et al. 2019). The incidence rate of MS among the Hutterite community is 91 per 100,000 compared to 285 per 100,000 in the general Canadian population (Ross et al., 1995).

These observations in humans could be caused by factors beyond genetic influences. However, the prophylactic role of reduced CPT1A activity in brain diseases has been substantiated in several murine models. A mouse line was generated harboring the identical CPT1 P479L artic mutation. These mice were tested in animal models of MS (the experimental autoimmune encephalomyelitis model), ALS (SOD1 G93A model), and PD (rotenone model) (Mørkholt et al., 2019; Trabjerg et al., 2020, 2021, 2023). The findings from these studies collectively demonstrate that the presence of the CPT1A P479L mutation exhibits a prophylactic effect in MS and PD and a disease-modifying effect in ALS models. This underscores the significant role of lipid metabolism, and more specifically CPT1, in the pathogenesis of brain diseases.

Therapeutic Potential of Targeting Lipid Metabolism

In light of the substantial unmet medical need arising from the limited disease-modifying therapeutic options to treat neurodegenerative diseases, we contend that a reassessment of the prevailing treatment regimen is warranted. Given the underlying hypothesis positing that mitochondrial metabolic dysfunction, and in particular aberrant lipid metabolism, is the main trigger of the onset of various neurodegenerative diseases, several potential approaches exist for rectifying this perturbation. Firstly, one strategy involves the promotion of glucose metabolism. Secondly, an alternative approach involves the utilization of small-chain fatty acids (SCFA) and ketone bodies to bypass the metabolic pathway associated with fatty acid metabolism. Lastly, a third option entails the regulation of fatty acid metabolism, particularly the metabolism of long-chain fatty acid (LCFA), by targeting the CPT1 enzyme. As the objective is to return the metabolism to utilizing glucose as the primary substrate for energy generation, treatments that stimulate glucose metabolism or affect the glucose levels in the blood have been utilized. These

treatments included metformin and acarbose, which are typically used to treat type 2 diabetes (Smith et al., 2019; Frohlich et al., 2021). However, the upregulation of lipid oxidation leads to the downregulation of PDH, the molecule that is necessary for the conversion of pyruvate to acetyl-CoA for the TCA cycle. This creates a negative feedback loop that is challenging to disrupt, and as a result, a longer treatment duration is most likely required before any noticeable effects can be observed.

The utilization of ketone bodies or SCFA represents an alternative method. An important advantage of these compounds is their ability to diffuse over the mitochondrial membrane, obviating the need for active transportation by the CPT1 complex (Bitto et al., 2023). The SCFAs and ketone bodies are of particular interest owing to their synthesis by intestinal microbiota, which have been shown to have a protective effect against the development of brain diseases (Smith et al., 2019; Jensen et al., 2020). The precise mechanisms of the positive effect of ketone bodies and SCFA on CNS diseases remain incompletely elucidated. One plausible hypothesis suggests that high levels of cellular stress can lead to an increase in mitochondrial fission, which in turn desensitizes CPT1 to inhibition by malonyl-CoA (Zhu et al., 2023), resulting in unregulated transport of LCFA into the mitochondria. In contrast, SCFA and ketone bodies diffuse across the mitochondrial membrane, requiring less energy compared to the active transportation of LCFA. The molecules are subsequently metabolized in the mitochondria, and therefore, may have an osmotic effect that inhibits the transport of LCFA into the mitochondria. Consequently, over time, these molecules would therefore downregulate the hyper-metabolization of LCFA. In addition, it has also been found that the metabolization of SCFA and ketone bodies induce less ROS than the metabolization of LCFA (Maalouf et al., 2007; Schönfeld and Wojtczak, 2016). We have conducted research with molecules that modulate energy generation from LCFA, resulting in the normalization of mitochondrial metabolism by restoring glucose as the preferred energy substrate. Targeted inhibition of aberrant lipid metabolism holds promise as an effective treatment strategy for brain diseases. In this section, we discuss the concepts surrounding the targeting of CPT1A and its implications for lipid metabolism in both physiological and pathological contexts. In the framework of our neurometabolic model, we hypothesize that neurodegenerative diseases are characterized by a cascade of events resulting from impaired mitochondrial metabolic function. Specifically, oxidative stress, accumulation of misfolded proteins, demyelination, inflammation, and neuronal loss are theorized to manifest as downstream consequences of this dysfunction. From the illustration below (**Figure 3**) it is readily apparent why the current treatment options on the market today lack curative efficacy as they are not targeting the root of the diseases.

But according to our neurometabolic model, how could neurodegenerative diseases be prevented or treated? There are several factors to consider when examining the disease triggers. It may be possible to adopt a preventative approach, which entails minimizing the exposure to known pathological, psychological, and physical stressors. The achievement of improved health outcomes would most likely necessitate considerable personal commitment in terms of lifestyle choices, possibly combined with health enhancing government policies, for example, banning known disease-inducing chemicals and improving the quality of life of vulnerable social groups. While certain environmental factors, such as diet, can be influenced by individuals, there exist numerous stressors in life that are beyond an individual's control. Hence, achieving complete prevention of neurodegenerative diseases poses a formidable challenge. Nevertheless, it is posited that a substantial reduction in their prevalence can be attained through the adoption of lifestyle modifications, including the cultivation of a nutritious diet, engagement in regular physical activity, and effective management of daily stressors (Casanova et al., 2023).

An alternative approach involves the modulation of epigenetic changes. The emergence of drugs targeting epigenetic mechanisms has presented new therapeutic opportunities due to the presence of various alternations in the epigenome associated with cognitive decline and neurodegenerative diseases (De Simone and Milelli, 2019). A great example is valproic acid, an U.S. Food and Drug Administration-approved anti-epileptic drug with a wide range of effects, including increasing the activity of the inhibitory neurotransmitter gamma-aminobutyric acid (Bertelsen et al., 2018) and reducing neuroinflammation in late stages of AD Tg6779 mice (Noh and Seo, 2014). Valproic acid inhibits histone deacetylase and the deacetylation process, which enhances gene transcription (Bhatti et al., 2019) by modulating the expression of multiple genes, representing an interesting approach when targeting multifactorial diseases. The potential to modulate multiple targets implicated in a disease could result in a synergistic positive effect (De Simone and Milelli, 2019). A limitation associated with histone deacetylase inhibitors is the lack of target specificity. Histone deacetylase inhibitors have been used in cancer as they display a broad anti-tumor activity. Conversely, they simultaneously increase the expression of ABC efflux transporters on tumor cells, making them more resistant to chemotherapy (You et al., 2020). There is much knowledge to be gained in the epigenome, and the potential within the epigenetic drug discovery landscape seems promising, however development of novel therapeutics in this domain is likely to require considerable time, possibly several decades.

The third option is to employ gene therapy to directly target mutations and SNP sites related to neurodegenerative diseases. CRISPR-Cas9 is especially promising in that regard. It has already been tested in multiple neurodegenerative animal models displaying reduced Aβ pathology in APP-KI mice (Nagata et al., 2018), reduced Aβ production in Tg2576 mice (Sun et al., 2019), decreased α-synuclein production in rats (Yoon et al., 2022) and restored wild-type phenotype in C9ORF72 mutated mice (Piao et al., 2022). There are, however, multiple challenges associated with CRISPR-Cas9 gene therapy, such as delivery challenges, off-target genome editing effects, and incomplete editing (De Plano et al., 2022). In addition, there are ethical concerns surrounding gene editing that should not be overlooked (Joseph et al., 2022). Gene editing could eliminate mutations and SNP sites that increase the risk of developing neurodegenerative diseases, however, these are not the sole etiological factors responsible for the onset and progression of such diseases.

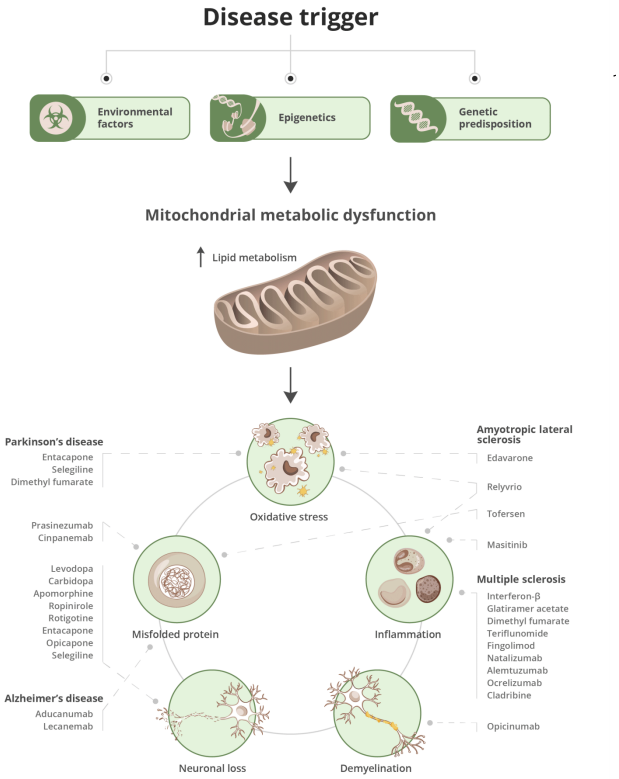

Figure 3 | **How therapeutics on the market target what we believe to be downstream pathological mechanisms following increased lipid metabolism.**
Created with graphical designer Maria Rasmussen using Adobe Illustrator®.

We hypothesize that targeting defective mitochondrial energy production represents a novel and obtainable target. As discussed above, we believe many of the pathological processes of neurodegeneration can be explained by a metabolic imbalance where the dominant metabolism in the brain, glucose oxidation, undergoes a sustained and self-reinforcing shift to lipid oxidation. In this scenario, the two options to re-establish the optimal metabolic homeostasis are to promote glucose metabolism or inhibit lipid metabolism. Both methods are being explored and could in principle have the desired effect. However, we hypothesize that the promotion of glucose metabolism will be hindered by high concentrations of acetyl-CoA produced as a result of highly upregulated lipid oxidation, which downregulates PDH and thereby prevents pyruvate from entering the mitochondria. Any pharmaceutical intervention to stimulate glucose oxidation would therefore have to overcome this obstacle. On the other hand, lipid metabolism can be effectively inhibited by targeting the rate-limiting enzyme for transport of long-chain fatty acids into the mitochondria, CPT1. We have shown in animal models that inhibition of CPT1 reduces fatty acid oxidation to normal levels and restores glucose as the preferred energy substrate, and subsequently reverses pathological processes including oxidative stress, protein aggregation, mitochondrial dysfunction, inflammation, and disturbance of gut microbiota (Mørkholt et al., 2019; Trabjerg et al., 2020, 2021, 2023). The data presented in these studies demonstrate a significant disease-modifying effect, thereby providing compelling evidence to support the adoption of this approach. The neurometabolic approach is a multidimensional perspective that emphasizes the involvement of environmental factors, genetics, and epigenetics in the pathology of brain diseases. This approach represents a cutting-edge method for understanding the etiology and progression of these diseases.

Conclusion

Neurodegenerative diseases are complicated in terms of their multifarious neurodegenerative symptoms as well as their intricate genetic landscape. Most cases are considered sporadic and are characterized by multiple genetic SNPs that confer a predisposition to these disorders. Familial cases characterized by a mutation on a single gene are considerably less common

and although they exhibit a strong causative effect, it is not certain that an individual will develop neurodegenerative disease when carrying the mutated gene. Environmental factors and epigenetic changes can act as disease triggers, initiating a cascade of pathological downstream events. The neurometabolic approach establishes a connection between the many pathological mechanisms of neurodegenerative diseases and impaired mitochondrial energy generation. The theory is substantiated by research conducted on animals as well as investigations into human genetics. Novel therapeutic approaches are currently under development with the objective of restoring the equilibrium between glucose and lipid metabolism. These interventions hold promise as potential truly disease-modifying treatments for neurodegenerative diseases.

Acknowledgments: *We thank Maria Rasmussen (2N Pharma ApS, Denmark) for graphic design.*
Author contributions: *Writing, coordinating and correcting the manuscript: SSH, ASM; writing and correcting the manuscript: PBN; writing the epigenetic part and correcting the manuscript: JL; generating a figure and writing some text of the manuscript: MCA, NMJK, AKJ, MRZ; generating a figure for the manuscript: HMJ; general concept, writing and correcting the manuscript: JDVN. All authors approved the final version of the manuscript.*
Conflicts of interest: *Steinunn Sara Helgudóttir and Anne Skøttrup Mørkholt are employed by 2N Pharma. Preben Bruun Nyzell and John Dirk Vestergaard Nieland are co-founders of 2N Pharma. Other authors declare no conflicts of interest.*
Data availability statement: *The data are available from the corresponding author on reasonable request.*

Open peer reviewer: *Manlio Vinciguerra, Research Institute of the Medical University, Bulgaria.*
Additional file: *Open peer review report 1.*

References

Abramov AY, Potapova EV, Dremin VV, Dunaev AV (2020) Interaction of oxidative stress and misfolded proteins in the mechanism of neurodegeneration. Life (Basel) 10:101.
Agim ZS, Cannon JR (2015) Dietary factors in the etiology of Parkinson's disease. Biomed Res Int 2015:672838.
Ahmad MH, Fatima M, Mondal AC (2019) Role of hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-gonadal axis and insulin signaling in the pathophysiology of Alzheimer's disease. Neuropsychobiology 77:197-205.
Akyuz E, Celik BR, Aslan FS, Sahin H, Angelopoulou E (2023) Exploring the role of neurotransmitters in multiple sclerosis: an expanded review. ACS Chem Neurosci 14:527-553.
Alecu I, Bennett SAL (2019) Dysregulated lipid metabolism and its role in α-synucleinopathy in Parkinson's disease. Front Neurosci 13:328.
Allison J, Kaliszewska A, Uceda S, Reiriz M, Arias N (2021) Targeting DNA methylation in the adult brain through diet. Nutrients 13:3979.
Arrowsmith CH, Bountra C, Fish PV, Lee K, Schapira M (2012) Epigenetic protein families: a new frontier for drug discovery. Nat Rev Drug Discov 11:384-400.
Avallone R, Vitale G, Bertolotti M (2019) Omega-3 fatty acids and neurodegenerative diseases: new evidence in clinical trials. Int J Mol Sci 20:4256.
Baev AY, Vinokurov AY, Novikova IN, Dremin VV, Potapova EV, Abramov AY (2022) Interaction of mitochondrial calcium and ROS in neurodegeneration. Cells 11:706.
Barone P (2010) Neurotransmission in Parkinson's disease: beyond dopamine. Eur J Neurol 17:364-376.
Bertelsen F, Landau AM, Vase KH, Jacobsen J, Scheel-Krüger J, Møller A (2018) Acute in vivo effect of valproic acid on the GABAergic system in rat brain: a [11C]Ro15-4513 microPET study. Brain Res 1680:110-114.
Bhatti UF, Williams AM, Georgoff PE, Alam HB (2019) The 'Omics' of epigenetic modulation by valproic acid treatment in traumatic brain injury—what we know and what the future holds. Proteomics Clin Appl 13:e1900068.
Bitto A, Grillo AS, Ito TK, Stanaway IB, Nguyen BMG, Ying K, Tung H, Smith K, Tran N, Velikanje G, Urfer SR, Snyder JM, Barton J, Sharma A, Kayser EB, Wang L, Smith DL Jr, Thompson JW, DuBois L, DePaolo W, Kaeberlein M (2023) Acarbose suppresses symptoms of mitochondrial disease in a mouse model of Leigh syndrome. Nat Metab 5:955-967.
Bizzozero OA, Good LK (1991) Rapid metabolism of fatty acids covalently bound to myelin proteolipid protein. J Biol Chem 266:17092-17098.
Blokhuis AM, Groen EJ, Koppers M, van den Berg LH, Pasterkamp RJ (2013) Protein aggregation in amyotrophic lateral sclerosis. Acta Neuropathol 125:777-794.
Boeing H, Bechthold A, Bub A, Ellinger S, Haller D, Kroke A, Leschik-Bonnet E, Müller MJ, Oberritter H, Schulze M, Stehle P, Watzl B (2012) Critical review: vegetables and fruit in the prevention of chronic diseases. Eur J Nutr 51:637-663.
Bonnefont JP, Djouadi F, Prip-Buus C, Gobin S, Munnich A, Bastin J (2004) Carnitine palmitoyltransferases 1 and 2: biochemical, molecular and medical aspects. Mol Aspects Med 25:495-520.
Brown GK (2000) Glucose transporters: structure, function and consequences of deficiency. J Inherit Metab Dis 23:237-246.
Butterfield DA, Halliwell B (2019) Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nat Rev Neurosci 20:148-160.
Calvo AC, Valledor-Martín I, Moreno-Martínez L, Toivonen JM, Osta R (2022) Lessons to learn from the gut microbiota: a focus on amyotrophic lateral sclerosis. Genes (Basel) 13:865.
Casanova A, Wevers A, Navarro-Ledesma S, Pruimboom L (2023) Mitochondria: it is all about energy. Front Physiol 14:1114231.
Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, Ferrari C, Guerra UP, Paghera B, Muscio C, Bianchetti A, Volta GD, Turla M, Cotelli MS, Gennuso M, Prelle A, Zanetti O, Lussignoli G, Mirabile D, Bellandi D, et al. (2017) Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging 49:60-68.
Cavalli G, Heard E (2019) Advances in epigenetics link genetics to the environment and disease. Nature 571:489-499.
Chaves-Filho AB, Pinto IFD, Dantas LS, Xavier AM, Inague A, Faria RL, Medeiros MHG, Glezer I, Yoshinaga MY, Miyamoto S (2019) Alterations in lipid metabolism of spinal cord linked to amyotrophic lateral sclerosis. Sci Rep 9:11642.
Chen Y, Xu J, Chen Y (2021) Regulation of neurotransmitters by the gut microbiota and effects on cognition in neurological disorders. Nutrients 13:2099.
Chen Z, Zhong C (2014) Oxidative stress in Alzheimer's disease. Neurosci Bull 30:271-281.
Chung T, Prasad K, Lloyd TE (2014) Peripheral neuropathy: clinical and electrophysiological considerations. Neuroimaging Clin N Am 24:49-65.
Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, Codagnone MG, Cussotto S, Fulling C, Golubeva AV, Guzzetta KE, Jaggar M, Long-Smith CM, Lyte JM, Martin JA, Molinero-Perez A, Moloney G, Morelli E, Morillas E, O'Connor R, et al. (2019) The microbiota-gut-brain axis. Physiol Rev 99:1877-2013.
Dafinca R, Barbagallo P, Talbot K (2021) The role of mitochondrial dysfunction and ER stress in TDP-43 and C9ORF72 ALS. Front Cell Neurosci 15:653688.
David MA, Tayebi M (2014) Detection of protein aggregates in brain and cerebrospinal fluid derived from multiple sclerosis patients. Front Neurol 5:251.
Dean DC 3rd, Sojkova J, Hurley S, Kecskemeti S, Okonkwo O, Bendlin BB, Theisen F, Johnson SC, Alexander AL, Gallagher CL (2016) Alterations of myelin content in Parkinson's disease: a cross-sectional neuroimaging study. PLoS One 11:e0163774.
De Plano LM, Calabrese G, Conoci S, Guglielmino SPP, Oddo S, Caccamo A (2022) Applications of CRISPR-Cas9 in Alzheimer's disease and related disorders. Int J Mol Sci 23:8714.
Dee G, Ryznar R, Dee C (2023) Epigenetic changes associated with different types of stressors and suicide. Cells 12:1258.
Derfuss T, Mehling M, Papadopoulou A, Bar-Or A, Cohen JA, Kappos L (2020) Advances in oral immunomodulating therapies in relapsing multiple sclerosis. Lancet Neurol 19:336-347.
Dion A, Muñoz PT, Franklin TB (2022) Epigenetic mechanisms impacted by chronic stress across the rodent lifespan. Neurobiol Stress 17:100434.
Du X, Pang TY (2015) Is dysregulation of the HPA-axis a core pathophysiology mediating co-morbid depression in neurodegenerative diseases? Front Psychiatry 6:32.
Duarte-Silva E, Meuth SG, Peixoto CA (2023) The role of iron metabolism in the pathogenesis and treatment of multiple sclerosis. Front Immunol 14:1137635.
Dunn L, Allen GF, Mamais A, Ling H, Li A, Duberley KE, Hargreaves IP, Pope S, Holton JL, Lees A, Heales SJ, Bandopadhyay R (2014) Dysregulation of glucose metabolism is an early event in sporadic Parkinson's disease. Neurobiol Aging 35:1111-1115.
Elnwasany A, Ewida HA, Szweda PA, Szweda LI (2023) Inhibition of pyruvate dehydrogenase in the heart as an initiating event in the development of diabetic cardiomyopathy. Antioxidants (Basel) 12:756.
Feldman EL, Goutman SA, Petri S, Mazzini L, Savelieff MG, Shaw PJ, Sobue G (2022) Amyotrophic lateral sclerosis. Lancet 400:1363-1380.
Fleming TP, Watkins AJ, Velazquez MA, Mathers JC, Prentice AM, Stephenson J, Barker M, Saffery R, Yajnik CS, Eckert JJ, Hanson MA, Forrester T, Gluckman PD, Godfrey KM (2018) Origins of lifetime health around the time of conception: causes and consequences. Lancet 391:1842-1852.
Frischer JM, Bramow S, Dal-Bianco A, Lucchinetti CF, Rauschka H, Schmidbauer M, Laursen H, Sorensen PS, Lassmann H (2009) The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain 132:1175-1189.
Frohlich J, Chaldakov GN, Vinciguerra M (2021) Cardio- and neurometabolic adipobiology: consequences and implications for therapy. Int J Mol Sci 22:4137.
Gardner RC, Yaffe K (2015) Epidemiology of mild traumatic brain injury and neurodegenerative disease. Mol Cell Neurosci 66:75-80.
Gates EJ, Bernath AK, Klegeris A (2022) Modifying the diet and gut microbiota to prevent and manage neurodegenerative diseases. Rev Neurosci 33:767-787.
Gentile F, Doneddu PE, Riva N, Nobile-Orazio E, Quattrini A (2020) Diet, microbiota and brain health: unraveling the network intersecting metabolism and neurodegeneration. Int J Mol Sci 21:7471.
Gessner BD, Gillingham MB, Johnson MA, Richards CS, Lambert WE, Sesser D, Rien LC, Hermerath CA, Skeels MR, Birch S, Harding CO, Wood T, Koeller DM (2011) Prevalence and distribution of the c.1436C→T sequence variant of carnitine palmitoyltransferase 1a among alaska native infants. J Pediatr 158:124-129.
Giacci MK, Bartlett CA, Smith NM, Iyer KS, Toomey LM, Jiang H, Guagliardo P, Kilburn MR, Fitzgerald M (2018) Oligodendroglia are particularly vulnerable to oxidative damage after neurotrauma in vivo. J Neurosci 38:6491-6504.
Goldman SM, Marek K, Ottman R, Meng C, Comyns K, Chan P, Ma J, Marras C, Langston JW, Ross GW, Tanner CM (2019) Concordance for Parkinson's disease in twins: a 20-year update. Ann Neurol 85:600-605.
González-Rodríguez P, Zampese E, Stout KA, Guzman JN, Ilijic E, Yang B, Tkatch T, Stavarache MA, Wokosin DL, Gao L, Kaplitt MG, López-Barneo J, Schumacker PT, Surmeier DJ (2021) Disruption of mitochondrial complex I induces progressive Parkinsonism. Nature 599:650-656.

Gordon PH, Mehal JM, Holman RC, Rowland LP, Rowland AS, Cheek JE (2013) Incidence of amyotrophic lateral sclerosis among American Indians and Alaska natives. JAMA Neurol 70(4):476-480.

Gratacòs-Batlle E, Olivella M, Sánchez-Fernández N, Yefimenko N, Miguez-Cabello F, Fadó R, Casals N, Gasull X, Ambrosio S, Soto D (2018) Mechanisms of CPT1C-dependent AMPAR trafficking enhancement. Front Mol Neurosci 11:275.

Greenberg CR, Dilling LA, Thompson GR, Seargeant LE, Haworth JC, Phillips S, Chan A, Vallance HD, Waters PJ, Sinclair G, Lillquist Y, Wanders RJ, Olpin SE (2009) The paradox of the carnitine palmitoyltransferase type Ia P479L variant in Canadian aboriginal populations. Mol Genet Metab 96:201-207.

Guerbette T, Boudry G, Lan A (2022) Mitochondrial function in intestinal epithelium homeostasis and modulation in diet-induced obesity. Mol Metab 63:101546.

Haley RW (2003) Excess incidence of ALS in young gulf war veterans. Neurology 61:750-756.

Haran JP, Bhattarai SK, Foley SE, Dutta P, Ward DV, Bucci V, McCormick BA (2019) Alzheimer's disease microbiome is associated with dysregulation of the anti-inflammatory P-glycoprotein pathway. mBio 10:e00632-19.

Heath PR, Shaw PJ (2002) Update on the glutamatergic neurotransmitter system and the role of excitotoxicity in amyotrophic lateral sclerosis. Muscle Nerve 26:438-458.

Henchcliffe C, Beal MF (2008) Mitochondrial biology and oxidative stress in Parkinson disease pathogenesis. Nat Clin Pract Neurol 4:600-609.

Hogg E, Athreya K, Basile C, Tan EE, Kaminski J, Tagliati M (2018) High prevalence of undiagnosed insulin resistance in non-diabetic subjects with Parkinson's disease. J Parkinsons Dis 8:259-265.

Hooijmans CR, Kiliaan AJ (2008) Fatty acids, lipid metabolism and alzheimer pathology. Eur J Pharmacol 585:176-196.

Houten SM, Wanders RJ (2010) A general introduction to the biochemistry of mitochondrial fatty acid β-oxidation. J Inherit Metab Dis 33:469-477.

Huang Y, Liao J, Liu X, Zhong Y, Cai X, Long L (2021) Review: the role of intestinal dysbiosis in Parkinson's disease. Front Cell Infect Microbiol 11:615075.

Hue L, Taegtmeyer H (2009) The randle cycle revisited: a new head for an old hat. Am J Physiol Endocrinol Metab 297:E578-591.

Immordino ML, Dosio F, Cattel L (2006) Stealth liposomes: review of the basic science, rationale, and clinical applications. Int J Nanomedicine 1:297-315.

Ingelfinger F, Gerdes LA, Kavaka V, Krishnarajah S, Friebel E, Galli E, Zwicky P, Furrer R, Peukert C, Dutertre CA, Eglseer KM, Ginhoux F, Flierl-Hecht A, Kümpfel T, De Feo D, Schreiner B, Mundt S, Kerschensteiner M, Hohlfeld R, Beltrán E, et al. (2022) Twin study reveals non-heritable immune perturbations in multiple sclerosis. Nature 603:152-158.

Ionescu-Tucker A, Cotman CW (2021) Emerging roles of oxidative stress in brain aging and Alzheimer's disease. Neurobiol Aging 107:86-95.

Jacobs BM, Ammoscato F, Giovannoni G, Baker D, Schmierer K (2018) Cladribine: mechanisms and mysteries in multiple sclerosis. J Neurol Neurosurg Psychiatry 89:1266-1271.

Jain IH, Zazzeron L, Goldberger O, Marutani E, Wojtkiewicz GR, Ast T, Wang H, Schleifer G, Stepanova A, Brepoels K, Schoonjans L, Carmeliet P, Galkin A, Ichinose F, Zapol WM, Mootha VK (2019) Leigh syndrome mouse model can be rescued by interventions that normalize brain hyperoxia, but not HIF activation. Cell Metab 30:824-832.

Jensen NJ, Wodschow HZ, Nilsson M, Rungby J (2020) Effects of ketone bodies on brain metabolism and function in neurodegenerative diseases. Int J Mol Sci 21:8767.

Jheng HF, Tsai PJ, Guo SM, Kuo LH, Chang CS, Su IJ, Chang CR, Tsai YS (2012) Mitochondrial fission contributes to mitochondrial dysfunction and insulin resistance in skeletal muscle. Mol Cell Biol 32:309-319.

Johnson AA, Stolzing A (2019) The role of lipid metabolism in aging, lifespan regulation, and age-related disease. Aging Cell 18:e13048.

Joseph AM, Karas M, Ramadan Y, Joubran E, Jacobs RJ (2022) Ethical perspectives of therapeutic human genome editing from multiple and diverse viewpoints: a scoping review. Cureus 14:e31927.

Kaur S, DasGupta G, Singh S (2019) Altered neurochemistry in Alzheimer's disease: targeting neurotransmitter receptor mechanisms and therapeutic strategy. Neurophysiology 51:293-309.

Kellar D, Craft S (2020) Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. Lancet Neurol 19:758-766.

Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT (2018) Inflammation as a central mechanism in Alzheimer's disease. Alzheimers Dement (N Y) 4:575-590.

Koizumi R, Kiyokawa Y, Mikami K, Ishii A, Tanaka KD, Tanikawa T, Takeuchi Y (2018) Structural differences in the brain between wild and laboratory rats (Rattus Norvegicus): potential contribution to wariness. J Vet Med Sci 80:1054-1060.

Koncz R, Thalamuthu A, Wen W, Catts VS, Dore V, Lee T, Mather KA, Slavin MJ, Wegner EA, Jiang J, Trollor JN, Ames D, Villemagne VL, Rowe CC, Sachdev PS; Older Australian Twins Study collaborative team (2022) The heritability of amyloid burden in older adults: the older Australian twins study. J Neurol Neurosurg Psychiatry 93:303-308.

König A, Vicente Miranda H, Outeiro TF (2018) Alpha-synuclein glycation and the action of anti-diabetic agents in Parkinson's disease. J Parkinsons Dis 8:33-43.

Kraimi N, Lormant F, Calandreau L, Kempf F, Zemb O, Lemarchand J, Constantin P, Parias C, Germain K, Rabot S, Philippe C, Foury A, Moisan MP, Carvalho AV, Coustham V, Dardente H, Velge P, Chaumeil T, Leterrier C (2022) Microbiota and stress: a loop that impacts memory. Psychoneuroendocrinology 136:105594.

Kuo IC, Lin HY, Niu SW, Hwang DY, Lee JJ, Tsai JC, Hung CC, Hwang SJ, Chen HC (2016) Glycated hemoglobin and outcomes in patients with advanced diabetic chronic kidney disease. Sci Rep 6:20028.

Lai CQ, Parnell LD, Smith CE, Guo T, Sayols-Baixeras S, Aslibekyan S, Tiwari HK, Irvin MR, Bender C, Fei D, Hidalgo B, Hopkins PN, Absher DM, Province MA, Elosua R, Arnett DK, Ordovas JM (2020) Carbohydrate and fat intake associated with risk of metabolic diseases through epigenetics of CPT1A. Am J Clin Nutr 112:1200-1211.

Lee TK, Yankee EL (2022) A review on Parkinson's disease treatment. Neuroimmunol Neuroinflammation 8:222.

Leng F, Edison P (2021) Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat Rev Neurol 17:157-172.

Leverve X, Batandier C, Fontaine E (2007) Choosing the right substrate. Novartis Found Symp 280:108-121.

Levine KS, Leonard HL, Blauwendraat C, Iwaki H, Johnson N, Bandres-Ciga S, Ferrucci L, Faghri F, Singleton AB, Nalls MA (2023) Virus exposure and neurodegenerative disease risk across national biobanks. Neuron 111:1086-1093.

Li S, Le W (2017) Milestones of Parkinson's disease research: 200 years of history and beyond. Neurosci Bull 33:598-602.

Liu JL, Fan YG, Yang ZS, Wang ZY, Guo C (2018) Iron and Alzheimer's disease: from pathogenesis to therapeutic implications. Front Neurosci 12:632.

Liu S, Gao J, Zhu M, Liu K, Zhang HL (2020) Gut microbiota and dysbiosis in Alzheimer's disease: implications for pathogenesis and treatment. Mol Neurobiol 57:5026-5043.

Liu Y, Zhou L, Lv C, Liu L, Miao S, Xu Y, Li K, Zhao Y, Zhao J (2023) PGE2 pathway mediates oxidative stress-induced ferroptosis in renal tubular epithelial cells. FEBS J 290:533-549.

Longo N, Frigeni M, Pasquali M (2016) Carnitine transport and fatty acid oxidation. Biochim Biophys Acta 1863:2422-2435.

Maalouf M, Sullivan PG, Davis L, Kim DY, Rho JM (2007) Ketones inhibit mitochondrial production of reactive oxygen species production following glutamate excitotoxicity by increasing NADH oxidation. Neuroscience 145:256-264.

Malesza IJ, Malesza M, Walkowiak J, Mussin N, Walkowiak D, Aringazina R, Bartkowiak-Wieczorek J, Mądry E (2021) High-fat, western-style diet, systemic inflammation, and gut microbiota: a narrative review. Cells 10:3164.

Mao P, Reddy PH (2010) Is multiple sclerosis a mitochondrial disease? Biochim Biophys Acta 1802:66-79.

Martin S, Battistini C, Sun J (2022) A gut feeling in amyotrophic lateral sclerosis: microbiome of mice and men. Front Cell Infect Microbiol 12:839526.

Martin-Bastida A, Tilley BS, Bansal S, Gentleman SM, Dexter DT, Ward RJ (2021) Iron and inflammation: in vivo and post-mortem studies in Parkinson's disease. J Neural Transm (Vienna) 128:15-25.

McAlary L, Chew YL, Lum JS, Geraghty NJ, Yerbury JJ, Cashman NR (2020) Amyotrophic lateral sclerosis: proteins, proteostasis, prions, and promises. Front Cell Neurosci 14:581907.

McCombe PA, Henderson RD (2011) The role of immune and inflammatory mechanisms in ALS. Curr Mol Med 11:246-254.

McDonald C, Gordon G, Hand A, Walker RW, Fisher JM (2018) 200 years of Parkinson's disease: what have we learnt from James Parkinson?" Age Ageing 47:209-214.

Melief J, de Wit SJ, van Eden CG, Teunissen C, Hamann J, Uitdehaag BM, Swaab D, Huitinga I (2013) HPA axis activity in multiple sclerosis correlates with disease severity, lesion type and gene expression in normal-appearing white matter. Acta Neuropathol 126:237-249.

Mentis AA, Bougea AM, Chrousos GP (2021) Amyotrophic lateral sclerosis (ALS) and the endocrine system: are there any further ties to be explored? Aging Brain 1:100024.

Monzel AS, Enríquez JA, Picard M (2023) Multifaceted mitochondria: moving mitochondrial science beyond function and dysfunction. Nat Metab 5:546-562.

Moore S, Meschkat M, Ruhwedel T, Trevisiol A, Tzvetanova ID, Battefeld A, Kusch K, Kole MHP, Strenzke N, Möbius W, de Hoz L, Nave KA (2020) A role of oligodendrocytes in information processing. Nat Commun 11:5497.

Mørkholt AS, Trabjerg MS, Oklinski MKE, Bolther L, Kroese LJ, Pritchard CEJ, Huijbers IJ, Nieland JDV (2019) CPT1A plays a key role in the development and treatment of multiple sclerosis and experimental autoimmune encephalomyelitis. Sci Rep 9:13299.

Moyse E, Krantic S, Djellouli N, Roger S, Angoulvant D, Debacq C, Leroy V, Fougere B, Aidoud A (2022) Neuroinflammation: a possible link between chronic vascular disorders and neurodegenerative diseases. Front Aging Neurosci 14:827263.

Nagata K, Takahashi M, Matsuba Y, Okuyama-Uchimura F, Sato K, Hashimoto S, Saito T, Saido TC (2018) Generation of App knock-in mice reveals deletion mutations protective against Alzheimer's disease-like pathology. Nat Commun 9:1800.

Ng BG, Freeze HH (2018) Perspectives on glycosylation and its congenital disorders. Trends Genet 34:466-476.

Ngo J, Choi DW, Stanley IA, Stiles L, Molina AJA, Chen PH, Lako A, Sung ICH, Goswami R, Kim MY, Miller N, Baghdasarian S, Kim-Vasquez D, Jones AE, Roach B, Gutierrez V, Erion K, Divakaruni AS, Liesa M, Danial NN, et al. (2023) Mitochondrial morphology controls fatty acid utilization by changing CPT1 sensitivity to malonyl-CoA. EMBO J 42:e111901.

Noh H, Seo H (2014) Age-dependent effects of valproic acid in Alzheimer's disease (AD) mice are associated with nerve growth factor (NGF) regulation. Neuroscience 266:255-265.

Pajares M, I Rojo A, Manda G, Boscá L, Cuadrado A (2020) Inflammation in Parkinson's disease: mechanisms and therapeutic implications. Cells 9:1687.

Papuć E, Rejdak K (2020) The role of myelin damage in Alzheimer's disease pathology. Arch Med Sci 16:345-351.

Passeri E, Elkhoury K, Morsink M, Broersen K, Linder M, Tamayol A, Malaplate C, Yen FT, Arab-Tehrany E (2022) Alzheimer's disease: treatment strategies and their limitations. Int J Mol Sci 23:13954.

Pathak D, Berthet A, Nakamura K (2013) Energy failure: does it contribute to neurodegeneration? Ann Neurol 74:506-516.

Peña-Bautista C, Casas-Fernández E, Vento M, Baquero M, Cháfer-Pericás C (2020) Stress and neurodegeneration. Clin Chim Acta 503:163-168.

Petillon C, Hergesheimer R, Puy H, Corcia P, Vourc'h P, Andres C, Karim Z, Blasco H (2018) The relevancy of data regarding the metabolism of iron to our understanding of deregulated mechanisms in ALS; hypotheses and pitfalls. Front Neurosci 12:1031.
Piao X, Meng D, Zhang X, Song Q, Lv H, Jia Y (2022) Dual-GRNA approach with limited off-target effect corrects C9ORF72 repeat expansion in vivo. Sci Rep 12:5672.
Pineda-Torra I, Siddique S, Waddington KE, Farrell R, Jury EC (2021) Disrupted lipid metabolism in multiple sclerosis: a role for liver X receptors? Front Endocrinol (Lausanne) 12:639757.
Pinto L (2014) Neuronal carnitine palmitoyl transferase1c in the central nervous system: current visions and perspectives. J Alzheimers Dis Parkinsons doi: 10.4172/2161-0460.1000132.
Piscitelli F, Bradshaw HB (2017) Endocannabinoid analytical methodologies: techniques that drive discoveries that drive techniques. Adv Pharmacol 80:1-30.
Prasad C, Johnson JP, Bonnefont JP, Dilling LA, Innes AM, Haworth JC, Beischel L, Thuillier L, Prip-Buus C, Singal R, Thompson JR, Prasad AN, Buist N, Greenberg CR (2001) Hepatic carnitine palmitoyl transferase 1 (CPT1 A) deficiency in North American Hutterites (Canadian and American): evidence for a founder effect and results of a pilot study on a DNA-based newborn screening program. Mol Genet Metab 73:55-63.
Qureshi IA, Mehler MF (2011) Advances in epigenetics and epigenomics for neurodegenerative diseases. Curr Neurol Neurosci Rep 11:464-473.
Rajakumar C, Ban MR, Cao H, Young TK, Bjerregaard P, Hegele RA (2009) Carnitine palmitoyltransferase IA polymorphism P479L is common in greenland inuit and is associated with elevated plasma apolipoprotein A-I. J Lipid Res 50:1223-1228.
Ravera S, Podestà M, Sabatini F, Dagnino M, Cilloni D, Fiorini S, Barla A, Frassoni F (2019) Discrete changes in glucose metabolism define aging. Sci Rep 9:10347.
Raza Z, Hussain SF, Foster VS, Wall J, Coffey PJ, Martin JF and Gomes RSM (2023) Exposure to war and conflict: the individual and inherited epigenetic effects on health, with a focus on post-traumatic stress disorder. Front Epidemiol 3:1066158.
Reinert A, Morawski M, Seeger J, Arendt T, Reinert T (2019) Iron concentrations in neurons and glial cells with estimates on ferritin concentrations. BMC Neurosci 20:25.
Reyes ET, Perurena OH, Festoff BW, Jorgensen R, Moore WV (1984) Insulin resistance in amyotrophic lateral sclerosis. J Neurol Sci 63:317-324.
Rose MR (2003) Gulf war service is an uncertain trigger for ALS. Neurology 61:730- 731.
Ross RT, Nicolle LE, Cheang M (1995) Varicella zoster virus and multiple sclerosis in a Hutterite population. J Clin Epidemiol 48:1319-1324.
Ruffini N, Klingenberg S, Heese R, Schweiger S, Gerber S (2022) The big picture of neurodegeneration: a meta study to extract the essential evidence on neurodegenerative diseases in a network-based approach. Front Aging Neurosci 14:866886.
Ruiz-Argüelles A, Méndez-Huerta MA, Lozano CD, Ruiz-Argüelles GJ (2018) Metabolomic profile of insulin resistance in patients with multiple sclerosis is associated to the severity of the disease. Mult Scler Relat Disord 25:316-321.
Saso L, Chakrabarti S, Miller E (2022) Pharmaceutical and pharmacological aspects of modulation of oxidative stress 2020. Oxid Med Cell Longev 2022:9842198.
Schlapp G, Fernández-Graña G, Arévalo AP, Crispo M (2018) Establishment of an environmental microbiological monitoring program in a mice barrier facility. An Acad Bras Cienc 90:3155-3164.
Schönfeld P, Reiser G (2013) Why does brain metabolism not favor burning of fatty acids to provide energy? Reflections on disadvantages of the use of free fatty acids as fuel for brain. J Cereb Blood Flow Metab 33:1493-1499.
Schönfeld P, Wojtczak L (2016) Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. J Lipid Res 57:943-954.
Serrano-Pozo A, Das S, Hyman BT (2021) APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. Lancet Neurol 20:68-80.
Shi Y, Zhang H, Huang S, Yin L, Wang F, Luo P, Huang H (2022) Epigenetic regulation in cardiovascular disease: mechanisms and advances in clinical trials. Signal Transduct Target Ther 7:200.
De Simone A, Milelli A (2019) Histone deacetylase inhibitors as multitarget ligands: new players in Alzheimer's disease drug discovery? ChemMedChem 14:1067-1073.
Smith BJ, Miller RA, Ericsson AC, Harrison DC, Strong R, Schmidt TM (2019) Changes in the gut microbiome and fermentation products concurrent with enhanced longevity in acarbose-treated mice. BMC Microbiol 19:130.
Spinelli JB, Haigis MC (2018) The multifaceted contributions of mitochondria to cellular metabolism. Nat Cell Biol 20:745-754.
Stott SRW, Wyse RK, Brundin P (2020) Novel approaches to counter protein aggregation pathology in Parkinson's disease. Prog Brain Res 252:451-492.
Sun J, Carlson-Stevermer J, Das U, Shen M, Delenclos M, Snead AM, Koo SY, Wang L, Qiao D, Loi J, Petersen AJ, Stockton M, Bhattacharyya A, Jones MV, Zhao X, McLean PJ, Sproul AA, Saha K, Roy S (2019) CRISPR/Cas9 editing of APP C-terminus attenuates β-cleavage and promotes α-cleavage. Nat Commun 10:53.
Swenson BL, Meyer CF, Bussian TJ, Baker DJ (2019) Senescence in aging and disorders of the central nervous system. Transl Med Aging 3:17-25.
Szyf M (2015) Prospects for the development of epigenetic drugs for CNS conditions. Nat Rev Drug Discov 14:461-474.
Tefera TW, Steyn FJ, Ngo ST, Borges K (2021) CNS glucose metabolism in amyotrophic lateral sclerosis: a therapeutic target? Cell Biosci 11:14.
The Lancet Neurology (2021) Multiple sclerosis under the spotlight. Lancet Neurol 20:497.
Thirion F, Sellebjerg F, Fan Y, Lyu L, Hansen TH, Pons N, Levenez F, Quinquis B, Stankevic E, Søndergaard HB, Dantoft TM, Poulsen CS, Forslund SK, Vestergaard H, Hansen T, Brix S, Oturai A, Sørensen PS, Ehrlich SD, Pedersen O (2023) The gut microbiota in multiple sclerosis varies with disease activity. Genome Med 15:1.
Thomas MS, Blesso CN, Calle MC, Chun OK, Puglisi M, Fernandez ML (2022) Dietary influences on gut microbiota with a focus on metabolic syndrome. Metab Syndr Relat Disord 20:429-439.
Timblin GA, Tharp KM, Ford B, Winchester JM, Wang J, Zhu S, Khan RI, Louie SK, Iavarone AT, Ten Hoeve J, Nomura DK, Stahl A, Saijo K (2021) Mitohormesis reprogrammes macrophage metabolism to enforce tolerance. Nat Metab 3:618-635.
Tough DF, Tak PP, Tarakhovsky A, Prinjha RK (2016) Epigenetic drug discovery: breaking through the immune barrier. Nat Rev Drug Discov 15:835-853.
Trabjerg MS, Mørkholt AS, Lichota J, Oklinski MKE, Andersen DC, Jønsson K, Mørk K, Skjønnemand MN, Kroese LJ, Pritchard CEJ, Huijbers IJ, Gazerani P, Corthals A, Nieland JDV (2020) Dysregulation of metabolic pathways by carnitine palmitoyl-transferase 1 plays a key role in central nervous system disorders: experimental evidence based on animal models. Sci Rep 10:15583.
Trabjerg MS, Andersen DC, Huntjens P, Oklinski KE, Bolther L, Hald JL, Baisgaard AE, Mørk K, Warming N, Kullab UB, Kroese LJ, Pritchard CEJ, Huijbers IJ, Nieland JDV (2021) Downregulating carnitine palmitoyl transferase 1 affects disease progression in the SOD1 G93A mouse model of ALS. Commun Biol 4:509.
Trabjerg MS, Andersen DC, Huntjens P, Mørk K, Warming N, Kullab UB, Skjønnemand MN, Oklinski MK, Oklinski KE, Bolther L, Kroese LJ, Pritchard CEJ, Huijbers IJ, Corthals A, Søndergaard MT, Kjeldal HB, Pedersen CFM, Nieland JDV (2023) Inhibition of carnitine palmitoyl-transferase 1 is a potential target in a mouse model of Parkinson's disease. NPJ Parkinsons Dis 9:6.
Urrutia PJ, Mena NP, Núñez MT (2014) The interplay between iron accumulation, mitochondrial dysfunction, and inflammation during the execution step of neurodegenerative disorders. Front Pharmacol 5:38.
van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, Kanekiyo M, Li D, Reyderman L, Cohen S, Froelich L, Katayama S, Sabbagh M, Vellas B, Watson D, Dhadda S, Irizarry M, Kramer LD, Iwatsubo T (2023) Lecanemab in early Alzheimer's disease. N Engl J Med 388:9-21.
Vieregge P, Hagenah J, Heberlein I, Klein C, Ludin HP (1999) Parkinson's disease in twins. Neurology 53:566.
Virolainen SJ, VonHandorf A, Viel KCMF, Weirauch MT, Kottyan LC (2023) Gene-environment interactions and their impact on human health. Genes Immun 24:1-11.
Visconti A, Le Roy CI, Rosa F, Rossi N, Martin TC, Mohney RP, Li W, de Rinaldis E, Bell JT, Venter JC, Nelson KE, Spector TD, Falchi M (2019) Interplay between the human gut microbiome and host metabolism. Nat Commun 10:4505.
Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, Johnson SC, Carlsson CM, Asthana S, Zetterberg H, Blennow K, Bendlin BB, Rey FE (2017a) Gut microbiome alterations in Alzheimer's disease. Sci Rep 7:13537.
Vos M (2022) Mitochondrial complex I deficiency: guilty in Parkinson's disease. Signal Transduct Target Ther 7:136.
Ward RJ, Zucca FA, Duyn JH, Crichton RR, Zecca L (2014) The role of iron in brain ageing and neurodegenerative disorders. Lancet Neurol 13:1045-1060.
Ward RJ, Dexter DT, Crichton RR (2022) Iron, neuroinflammation and neurodegeneration. Int J Mol Sci 23:7267.
Wareham LK, Liddelow SA, Temple S, Benowitz LI, Di Polo A, Wellington C, Goldberg JL, He Z, Duan X, Bu G, Davis AA, Shekhar K, Torre A, Chan DC, Canto-Soler MV, Flanagan JG, Subramanian P, Rossi S, Brunner T, Bovenkamp DE, et al. (2022) Solving neurodegeneration: common mechanisms and strategies for new treatments. Mol Neurodegener 17:23.
Woo V, Alenghat T (2022) Epigenetic regulation by gut microbiota. Gut Microbes 14:2022407.
Wu Q, Yang Z, Qiu R, Cheng S, Zhu X, Han Z, Xiao W (2023) The military occupational stress response scale: development, reliability, and validity. Front Psychol 14:1032876.
Xiao B, Kuruvilla J, Tan EK (2022) Mitophagy and reactive oxygen species interplay in Parkinson's disease. NPJ Parkinsons Dis 8:135.
Xiao S, Chan P, Wang T, Hong Z, Wang S, Kuang W, He J, Pan X, Zhou Y, Ji Y, Wang L, Cheng Y, Peng Y, Ye Q, Wang X, Wu Y, Qu Q, Chen S, Li S, Chen W, et al. (2021) A 36-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial of sodium oligomannate for mild-to-moderate Alzheimer's dementia. Alzheimers Res Ther 13:62.
Yin F, Sancheti H, Patil I, Cadenas E. (2017) Energy metabolism and inflammation in brain aging and Alzheimer's disease. Physiol Behav 176:139-148.
Yin F (2023) Lipid metabolism and Alzheimer's disease: clinical evidence, mechanistic link and therapeutic promise. FEBS J 290:1420-1453.
Yoon HH, Ye S, Lim S, Jo A, Lee H, Hong F, Lee SE, Oh SJ, Kim NR, Kim K, Kim BJ, Kim H, Lee CJ, Nam MH, Hur JW, Jeon SR (2022) CRISPR-Cas9 gene editing protects from the A53T-SNCA overexpression-induced pathology of Parkinson's disease in vivo. CRISPR J 5:95-108.
You D, Richardson JR, Aleksunes LM (2020) Epigenetic regulation of multidrug resistance protein 1 and breast cancer resistance protein transporters by histone deacetylase inhibition. Drug Metab Dispos 48:459-480.
Zahoor I, Rui B, Khan J, Datta I, Giri S (2021) An emerging potential of metabolomics in multiple sclerosis: a comprehensive overview. Cell Mol Life Sci 78:3181-3203.
Zajac D, Spolnik G, Roszkowski P, Danikiewicz W, Czarnocki Z, Pokorski M (2014) Metabolism of N-acylated-dopamine. PLoS One 9:e85259.
Zhang SY, Gui LN, Liu YY, Shi S, Cheng Y (2020) Oxidative stress marker aberrations in multiple sclerosis: a meta-analysis study. Front Neurosci 14:823.
Zhou T, Ahmad TK, Gozda K, Truong J, Kong J, Namaka M (2017) Implications of white matter damage in amyotrophic lateral sclerosis (Review). Mol Med Rep 16:4379-4392.
Zhu S, Jiang Y, Xu K, Cui M, Ye W, Zhao G, Jin L, Chen X (2020) The progress of gut microbiome research related to brain disorders. J Neuroinflammation 17:25.
Zhu Y, Wang Y, Li Y, Li Z, Kong W, Zhao X, Chen S, Yan L, Wang L, Tong Y, Shao H (2023) Carnitine palmitoyltransferase 1A promotes mitochondrial fission by enhancing MFF succinylation in ovarian cancer. Commun Biol 6:618.

P-Reviewer: Vinciguerra M; C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y