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CURRENT PERSPECTIVES

# The Promise of Niacin in Neurology

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**Abstract**
Niacin (vitamin B3) is an essential nutrient that treats pellagra, and prior to the advent of statins, niacin was commonly used to counter dyslipidemia. Recent evidence has posited niacin as a promising therapeutic for several neurological disorders. In this review, we discuss the biochemistry of niacin, including its homeostatic roles in $NAD^+$ supplementation and metabolism. Niacin also has roles outside of metabolism, largely through engaging hydroxycarboxylic acid receptor 2 (Hcar2). These receptor-mediated activities of niacin include regulation of immune responses, phagocytosis of myelin debris after demyelination or of amyloid beta in models of Alzheimer's disease, and cholesterol efflux from cells. We describe the neurological disorders in which niacin has been investigated or has been proposed as a candidate medication. These are multiple sclerosis, Alzheimer's disease, Parkinson's disease, glioblastoma and amyotrophic lateral sclerosis. Finally, we explore the proposed mechanisms through which niacin may ameliorate neuropathology. While several questions remain, the prospect of niacin as a therapeutic to alleviate neurological impairment is promising.

**Keywords** Niacin treatment · $NAD^+$/NADP · Hydroxycarboxylic acid receptor (Hcar)2 · Neurological diseases · Phagocytosis · Immunomodulation

## Introduction

Niacin, also known as vitamin $B_3$, is an essential nutrient obtained through dietary intake, where rich food sources include meat, fish, grains, and vegetables [1]. The importance of maintaining proper niacin levels is clearly established, as niacin-deficient individuals develop pellagra, a disease characterized by dementia, dermatitis, diarrhea, and, ultimately, death [2]. Niacin is thus a medication that is used to treat pellagra [3], and it was commonly indicated for dyslipidemia [4] prior to the advent of statins. In humans, the recommended minimum intake of niacin is between 15 and 20 mg/day [5], while pharmacological doses up to 3000 mg/day have been administered for dyslipidemia, demonstrating its tolerability across a broad range of doses [6].

Recent evidence has posited niacin as an exciting therapeutic option for a range of neurological disorders. Ranked as the third most promising repurposed drug candidate for progressive multiple sclerosis (MS) [7], niacin promotes phagocytosis of inhibitory myelin debris following demyelination in an animal model of MS, leading to remyelination [8]. In animal models of Parkinson's [9] and Alzheimer's disease [10], niacin ameliorates neuropathology through mechanisms such as immunomodulation and dopamine supplementation. Furthermore, niacin reduces tumour size and mortality in an animal model of glioblastoma [11] and is currently being investigated in a clinical trial of patients with glioblastoma [12]. Niacin also alleviates motor symptoms in patients with Parkinson's disease [13], and dietary intake of niacin is associated with reduced incidence of Alzheimer's disease and cognitive decline [14].

Despite the promise of niacin in neurological diseases, several unanswered questions remain regarding the actions of niacin in the central nervous system (CNS); these include the mechanisms of neuroprotection by niacin and whether it is a pro- or anti-inflammatory agent. In this review, we discuss the biochemistry and activity of niacin, and its receptor-dependent and -independent activities. We then consider the

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mechanisms of action of niacin within the CNS and explore its potential role as a therapeutic for neurological diseases.

## Biology and Chemistry of Niacin

Niacin exists as the vitamers nicotinic acid and nicotinamide, which can give rise to the niacin derivatives nicotinamide riboside and nicotinamide mononucleotide. Niacin generates nicotinamide adenine dinucleotide ($NAD^+$) through a series of metabolic pathways summarized in Fig. 1. In the Preiss-Handler pathway, nicotinic acid is converted into $NAD^+$ in three steps, utilizing the intermediates nicotinic acid mononucleotide and nicotinic acid adenine dinucleotide [15]. The salvage pathway recycles nicotinamide, the by-product of enzymatic activities of $NAD^+$, and dietary nicotinamide riboside to generate $NAD^+$ [16]. Lastly, de novo biosynthesis of $NAD^+$ is accomplished via the kynurenine pathway (Fig. 1), where dietary tryptophan serves as a precursor and is converted to $NAD^+$ through a series of eight enzymatic steps; notably, this is the only $NAD^+$ synthesis pathway that operates independently of niacin [17]. The de novo pathway is the longest and most energy-intensive; as a result, tryptophan is less efficient at increasing $NAD^+$ levels compared to other precursors, and this pathway plays a modest role in $NAD^+$ production [18, 19]. In contrast, the salvage pathway is the chief producer of $NAD^+$ in mammalian cells and is largely responsible for maintaining homeostatic levels of this metabolite [18].

Once generated, $NAD^+$ serves as a precursor for its phosphorylated form, nicotinamide adenine dinucleotide phosphate (NADP), which is generated via $NAD^+$ kinases [20, 21]. NAD(P) homeostasis involves a balance between biosynthesis and use by $NAD^+$-consuming enzymes. $NAD^+$ and NADP are critical coenzymes for oxidoreductases, and $NAD^+$ also serves as a substrate for redox-independent enzymatic processes in the cell [22]. Thus, NAD(P) homeostasis is essential to the proper metabolic functioning of a cell. In the context of oxidation–reduction reactions such as glycolysis and oxidative phosphorylation, $NAD^+$ serves as a proton

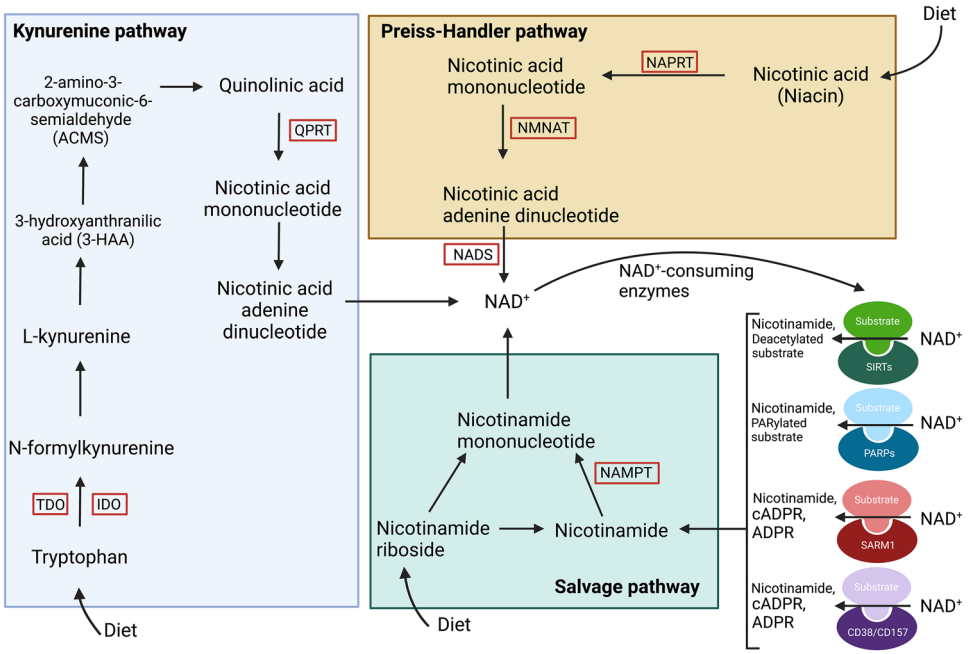


**Fig. 1 $NAD^+$ biosynthesis pathways**. In the kynurenine pathway, dietary tryptophan is first converted to N-formylkynurenine via tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO). Through a series of four enzymatic steps, N-formylkynurenine generates quinolinic acid, which gives rise to nicotinic acid mononucleotide in a reaction catalyzed by quinolinic acid phosphoribosyl transferase (QPRT). In the final steps, nicotinic acid mononucleotide is converted to nicotinic acid adenine dinucleotide, which generates $NAD^+$. In the Preiss-Handler pathway, dietary nicotinic acid (niacin) is converted to nicotinic acid mononucleotide via nicotinate phosphoribosyltransferase (NAPRT). Nicotinic acid mononucleotide is then converted to nicotinic acid adenine dinucleotide in a nicotinamide mononucleotide adenylyl transferase (NMNAT)-catalyzed reaction, and this gives rise to $NAD^+$ via $NAD^+$ synthase (NADS). In the salvage pathway, nicotinamide that has been recycled from the enzymatic activities of $NAD^+$ is used to generate nicotinamide mononucleotide via nicotinamide phosphoribosyltransferase (NAMPT). Dietary nicotinamide riboside can produce either nicotinamide mononucleotide, or nicotinamide. In the final step of this pathway, nicotinamide mononucleotide gives rise to $NAD^+$. Once generated, $NAD^+$ is consumed by several enzymes, including sirtuins (SIRTs), poly(ADP-ribose) polymerases (PARPs), and sterile alpha and TIR motif-containing 1 (SARM1), as well as the cyclic ADP-ribose (cADPR) synthases CD38 and CD157. These enzymes generate nicotinamide as a by-product. Figure created using BioRender

acceptor, generating its reduced form NADH. NADH is then oxidized in the electron transport chain, contributing to the mitochondrial proton gradient and allowing for the generation of ATP via ATP synthase [23].

$NAD^+$ also has redox-independent functions, serving as a cosubstrate for several important enzymes, which catabolize $NAD^+$ and generate nicotinamide as a by-product (Fig. 1) [24]. These enzymes include sirtuins (SIRTs), poly(ADP-ribose) polymerases (PARPs), sterile alpha, and TIR motif-containing 1 (SARM1) and cyclic ADP-ribose (cADPR) synthases such as CD38 and CD157 [25]. Sirtuins are a family of protein deacetylases involved in processes such as cell metabolism, inflammation, and oxidative stress [26]. During a sirtuin-catalyzed deacetylation, $NAD^+$ is cleaved into nicotinamide and ADP-ribose (ADPR). ADPR serves as an acyl acceptor, allowing for the removal of an acyl group from the substrate [27]. PARPs catalyze the transfer of multiple ADP-ribose groups from $NAD^+$ onto target macromolecules in a process termed poly-ADP-ribosylation [28]. PARP activity is upregulated following DNA damage, leading to substantial decreases in total $NAD^+$ levels and initiation of DNA repair signalling [29]. In response to neuronal damage or injury, SARM1 is activated, catalyzing the cleavage of $NAD^+$ to nicotinamide, ADPR, and cADPR via its Tol/interleukin-1 receptor (TIR) motif; this in turn promotes axon degeneration [30–32]. Finally, CD38 and CD157 hydrolyze $NAD^+$ to nicotinamide, ADPR, and cADPR, the latter of which serves as a second messenger in $Ca^{2+}$ signalling [33, 34]. The activity of these enzymes is dependent on $NAD^+$ levels. Thus, a disruption in $NAD^+$ biosynthesis or a lack of $NAD^+$ precursors such as niacin can lead to dysregulated cellular activities.

NADP plays an essential role in the pentose phosphate pathway (Fig. 2). Here, the reduction of NADP to NADPH is coupled to the synthesis of ribose-5-phosphate which serves as a precursor to many biological molecules including DNA and RNA. NADPH is then used as a reducing agent in the generation of molecules such as fatty acids, sterols, and nucleotides [35]. NADPH is also involved in the balance of oxidative stress, serving as a cofactor for glutathione reductase in the production of the antioxidant glutathione [36], and acting as a substrate for NADPH oxidases, donating an electron in the generation of reactive oxygen species [37, 38]. Thus, through supplementation of NAD(P), niacin restores proper metabolic functions (Fig. 2).

At endogenous levels, niacin works through supplementation of $NAD^+$ and NADP in a receptor-independent manner, restoring proper metabolic function. In a rodent model of abdominal aortic aneurysm, nicotinic acid and nicotinamide reduce aneurysm incidence and pathology by increasing $NAD^+$ levels and Sirtuin1 activity, rather than by activating a principal receptor for niacin, the hydroxycarboxylic acid receptor (Hcar2) [39]. In addition, patients with mitochondrial myopathy experience muscle weakness and fatigue, as well as reduced $NAD^+$ levels likely caused by altered mitochondrial activity. Niacin supplementation in these

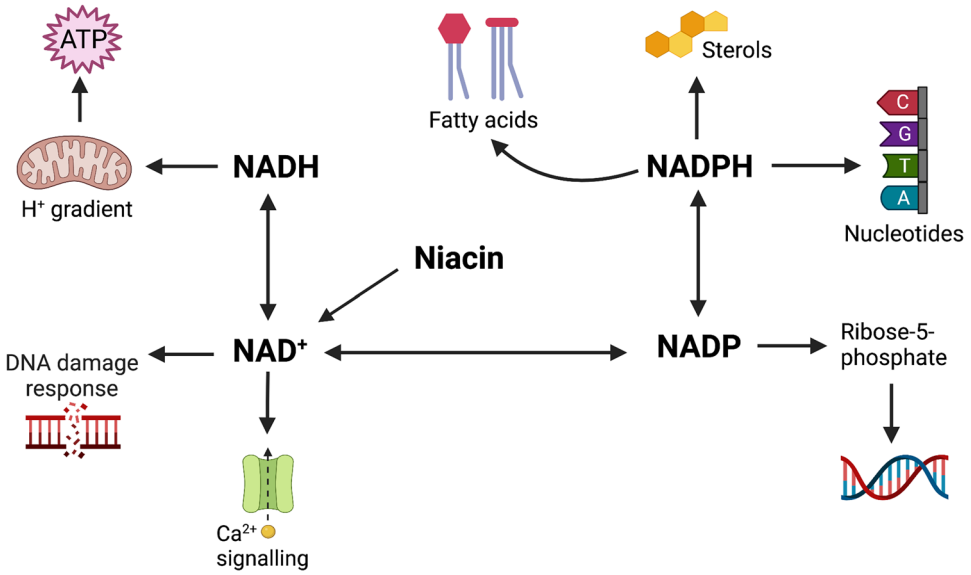


**Fig. 2 Homeostatic roles of niacin as a precursor to $NAD^+$.** Through the activity of $NAD^+$-consuming enzymes, niacin is involved in the maintenance of cellular processes such as the DNA damage response and $Ca^{2+}$ signalling. $NAD^+$ is reduced to form NADH, which serves as a proton donor in the electron transport chain, generating the mitochondrial proton gradient and leading to the production of ATP. $NAD^+$ is also phosphorylated to generate NADP. NADP serves as a precursor for ribose-5-phosphate, which gives rise to nucleic acids such as DNA and RNA. Finally, NADP is reduced to generate NADPH. NADPH is then used as a reducing agent in the generation of biological molecules such as fatty acids, sterols, and nucleotides. Figure created using BioRender

patients increases their systemic and muscle levels of $NAD^+$ and leads to increased muscle strength and improved mitochondrial biogenesis [40]. Further, decreased retinal levels of $NAD^+$ have been observed with age and are associated with retinal pathologies such as glaucoma [41]. In a rodent model of glaucoma, prevention of $NAD^+$ decline by supplementation with nicotinamide prevents retinal ganglion cell neurodegeneration [42] while also protecting against glaucoma-induced metabolic changes and preserving integrity of mitochondrial morphology [43].

Of note, it is unlikely that niacin acts through $NAD^+$ supplementation in the brain, as levels of nicotinamide phosphoribosyltransferase (NAMPT) and nicotinate phosphoribosyltransferase (NAPRT), enzymes required for the synthesis of $NAD^+$ from nicotinic acid, are much lower in the brain compared to other tissues [44, 45]. As a result, $NAD^+$ in the CNS is likely derived from other sources, such as the kynurenine metabolism pathway [44]. Thus, while $NAD^+$ supplementation may be the canonical role of niacin, there are other important pathways that mediate its effects in the body, particularly in the CNS.

Another notable biochemical feature of niacin is its rapid elimination from the body; maximum plasma concentrations are reported 30–60 min after oral intake, and it has an estimated half-life between 28 and 40 min in both humans and mice [46–48].

## Niacin Receptors

### Hydroxycarboxylic Acid Receptor (Hcar)2

The primary receptor for niacin is the inhibitory $G_{i/o}$ protein coupled receptor (GPCR) Hcar2, also known as GPR109A [49, 50]. As a GPCR, Hcar2 is characterized by a seven-transmembrane domain structure with an extracellular N terminus that interacts with ligands and an intracellular C terminus that engages in signal transduction via interaction with heterotrimeric G proteins [51]. Once bound by an extracellular ligand such as niacin, Hcar2 undergoes a conformational change and binds to the $G_{i/o}$ protein alpha subunit. In adipocytes, this stimulates a downstream signalling cascade which inhibits adenylyl cyclase activity, as well as reduces intracellular cyclic AMP levels [52, 53]. In immune cells, ligand binding to Hcar2 leads to a transient increase in intracellular $Ca^{2+}$ (Fig. 3) [54].

The primary endogenous ligands of Hcar2 are the short-chain fatty acid butyrate and the ketone body β-hydroxybutyrate [55–57]. At pharmacological doses, nicotinic acid, but not nicotinamide, serves as a ligand for Hcar2 [58, 59]. Of note, monomethyl fumarate, a metabolite of the MS medication dimethyl fumarate, is also able to stimulate the Hcar2 receptor, and this mediates at least part of its therapeutic response in a model of MS [60–62].

Hcar2 is widely expressed throughout the body, which likely explains the broad range of physiological and pharmacological effects that Hcar2 ligands such as niacin can have. On adipocytes of white and brown adipose tissue, Hcar2 acts as a metabolite sensor, inhibiting lipolysis in times of fasting and contributing to the lipid-modifying effects of niacin [58, 63]. Hcar2 is also expressed on immune cells such as macrophages, dendritic cells, and neutrophils, underlying the immunomodulatory properties of niacin (Fig. 3) [49, 64]. In addition, Hcar2 is expressed on epithelial cells of the retina, colon, and apical intestine, as well as keratinocytes of the skin [55, 65]. Activation of Hcar2 on the latter cell type leads to release of prostaglandins, which partially mediates the flushing response associated with niacin supplementation [66].

While endogenous levels of nicotinic acid (< 0.3 nM) [67] are too low to significantly impact the activity of Hcar2 and likely act through $NAD^+$ supplementation, pharmacological doses are sufficient to activate Hcar2 and mediate a separate range of biological activities [68]. Indeed, humans taking 1 g of niacin for dyslipidemia have an average serum concentration of 120–230 µM of nicotinic acid, 1–2 h after intake [69]. Experimental studies have shown that the $EC_{50}$ for nicotinic acid on Hcar2 in humans is between 0.13 and 1 µM, with a maximal response achieved between 10 and 100 µM [50, 70, 71]. This demonstrates that the plasma levels of niacin obtained following pharmacological niacin supplementation are within the optimal window for Hcar2 activation.

### Hcar2 Agonism

As aforementioned, Hcar2 is widely expressed on adipocytes. During periods of fasting or exercise, Hcar2 on adipocytes is activated by ketone bodies such as β-hydroxybutyrate, one of its primary endogenous ligands [72]. This activation leads to the inhibition of adenylyl cyclase, a concomitant reduction in cyclic AMP levels and protein kinase A activity, and ultimately decreased activity of hormone sensitive lipase, an enzyme responsible for lipolysis [73, 74]. In adipocytes cultured from wild-type mice, administration of β-hydroxybutyrate or nicotinic acid reduces the amount of free fatty acids present in the cell culture medium, indicating reduced lipolysis. Of note, this result is abolished in adipocytes from PUMA-G knockout mice, the rodent ortholog of Hcar2 [75], a finding that has been reported elsewhere [70]. In transgenic rats overexpressing human Hcar2, plasma free fatty acid levels are reduced during fasting, compared to wild-type controls [76]. Furthermore, nicotinic acid administration more strongly decreases free fatty acid levels in these transgenic mice, when compared to wild-type, indicating that niacin works through Hcar2 to decrease lipolysis (Fig. 3) [76]. As such, Hcar2 suppresses lipolysis during periods of fasting, reducing the

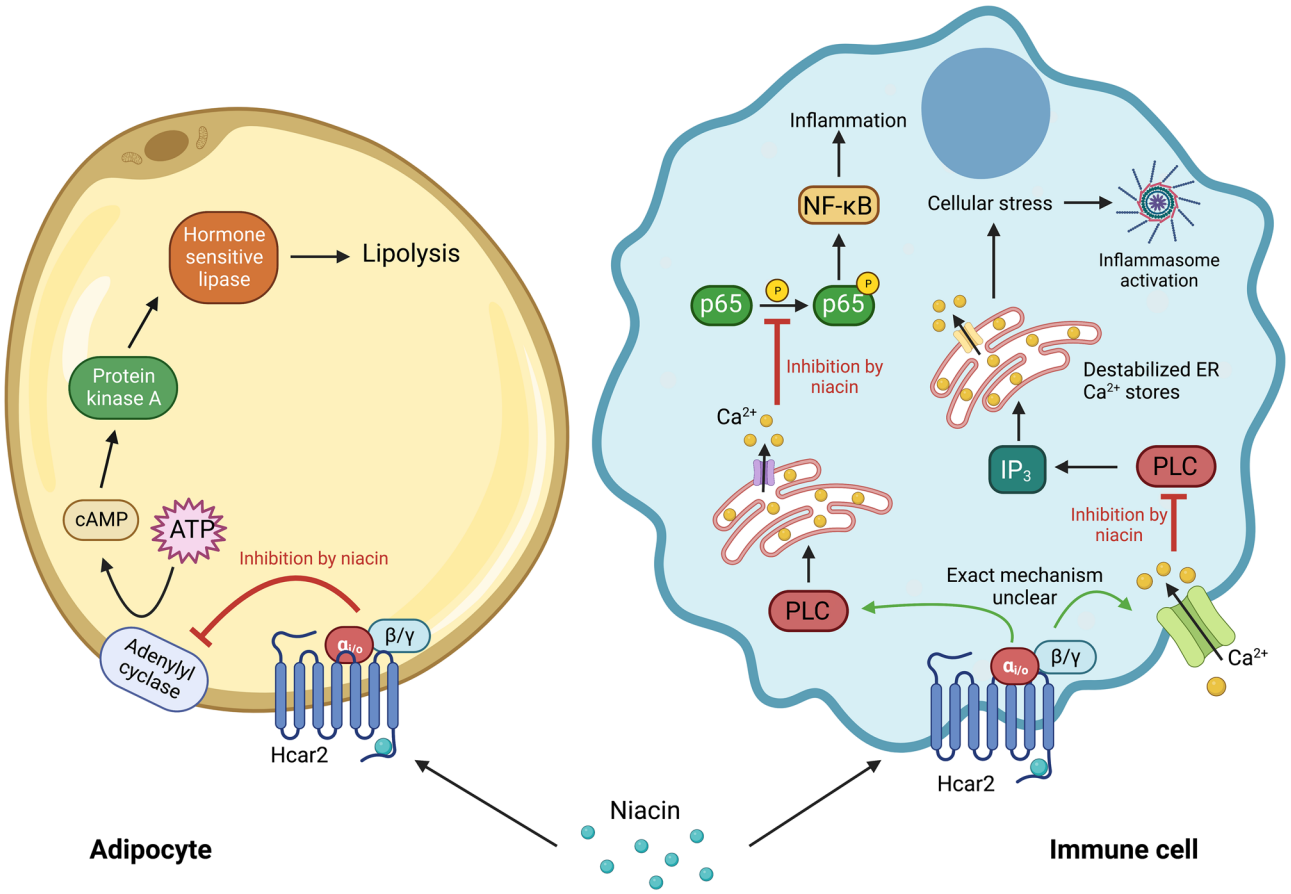


**Fig. 3 Activity of niacin at Hcar2 in adipocytes and immune cells.** In adipocytes, niacin acts through hydroxycarboxylic acid receptor (Hcar2) to inhibit adenylyl cyclase activity. Under normal conditions, adenylyl cyclase generates cAMP, which activates protein kinase A. Protein kinase A phosphorylates and activates hormone-sensitive lipase, which increases lipolysis. By inhibiting adenylyl cyclase, niacin reduces activity of this pathway and leads to suppression of lipolysis. In immune cells, niacin binding to Hcar2 leads to an increase in intracellular $Ca^{2+}$. Although the precise mechanism has yet to be elucidated, one model suggests that Hcar2 agonism activates phospholipase C (PLC), promoting the release of $Ca^{2+}$ from intracellular stores within the endoplasmic reticulum. $Ca^{2+}$ then acts as a second messenger, inhibiting the phosphorylation of p65 which is downstream from inflammatory NF-κB activation. Conversely, it is thought that the transient increase in $Ca^{2+}$ could originate from extracellular sources. This would stabilize the intracellular $Ca^{2+}$ stores found within the endoplasmic reticulum, making the cell more resistant to stress. Cellular stress leads to the activation of the NLRP3 inflammasome, which promotes cholesterol accumulation within macrophages and leads to a proinflammatory, detrimental immune cell phenotype. In the figure, the step of inhibition of inflammatory activity in immune cells subsequent to niacin/Hcar2 interaction is depicted by the red T sign. Figure created using BioRender

levels of free fatty acids mobilized in the blood stream. This activity underlies the lipid-modifying aspects of niacin that have led to its use in the treatment of dyslipidemia.

The other primary cell type known to express Hcar2 is immune cells, including macrophages, microglia, dendritic cells, and neutrophils. While precise mechanisms remain unclear, there are two main hypotheses regarding the effects of Hcar2 agonism in immune cells. In a model of atherosclerosis, activation of Hcar2 on macrophages by nicotinic acid leads to an increase in intracellular $Ca^{2+}$ from extracellular sources, inhibiting the phospholipase C (PLC)/inositol trisphosphate ($IP_3$) pathway that leads to the release of $Ca^{2+}$ from the endoplasmic reticulum [77]. Notably, inhibition of PLC by Hcar2 is $Ca^{2+}$ dependent, as PLC inhibition is lost following the application of an intracellular $Ca^{2+}$ chelator [77]. Thus, it is hypothesized that the stabilization of intracellular $Ca^{2+}$ stores prevents cellular stress and inflammasome activation (Fig. 3).

In contrast to the above hypothesis, work in the EAE model suggests that agonism of Hcar2 leads to a $G_{i/o}$ signalling cascade in which the PLC pathway is *activated*. This leads to an elevation in intracellular $Ca^{2+}$ from intracellular sources, preventing the hyperphosphorylation of p65 and downstream activation of NF-κb, a transcription factor that regulates the expression of many pro-inflammatory cytokines (Fig. 3) [60, 61]. Thus, while it is clear that agonism of Hcar2

by niacin or other compounds leads to an increase in intracellular $Ca^{2+}$ and a reduction in inflammation, the specific pathways remain to be fully elucidated.

Expression of Hcar2 on immune cells contributes to the anti-atherogenic and immune modulatory properties of niacin. Indeed, while it was previously thought that the antiatherogenic properties of niacin were derived from its antilipolytic effects, where reduced plasma levels of free fatty acids would lead to decreased synthesis of VLDL and LDL, with an increase in HDL [78–80], current research shows that the antiatherogenic properties of niacin instead involve Hcar2 activation on immune cells. Indeed, in the apolipoprotein E knockout model of atherogenesis, activation of Hcar2 on macrophages promotes cholesterol efflux and reduces atherosclerotic plaque burden [77].

Agonism of Hcar2 expressed on immune cells also serves to modulate inflammation. In LPS-activated human monocytes and mouse macrophages, niacin treatment reduces the expression of pro-inflammatory cytokines such as TNFα and IL-6, an effect that is lost following knockdown of Hcar2 [81, 82]. This reduction in cytokine release likely occurs due to inhibited NF-κB signalling, as intermediates of the NF-κB pathway such as phosphorylated p-65 and phosphorylated NF-κB are decreased upon Hcar2 agonism [81, 82]. Although activation of Hcar2 by niacin has previously been described as primarily anti-inflammatory, the recent work demonstrates that niacin acts to promote a beneficial phenotype typified by altered cytokine production and enhanced phagocytosis, rather than simply suppressing immune activity. In support of this view, studies in several models of neurological disease have shown that niacin can enhance the activity of microglia/macrophages, promoting a beneficial phenotype characterized by increased phagocytosis of pathological particles and reduced pathology [8, 10, 11]. Furthermore, in a model of stroke, niacin treatment activates a population of Hcar2-expressing neuroprotective macrophages, which infiltrate into the ischemic brain and ameliorate neuropathology [83].

### Hcar3

Another receptor that niacin has been suggested to act through is Hcar3, also known as GPR109B or HM74. Hcar3 is also primarily expressed on adipocytes and immune cells, where it regulates fatty acid metabolism and inflammation through its primary endogenous ligands 3-hydroxyoctanoic acid and kynurenic acid [84]. Similar to Hcar2, Hcar3 is a $G_{i/o}$-coupled GPCR that exerts its effects through downstream pathways involving modulation of adenylyl cyclase, cyclic AMP and intracellular $Ca^{2+}$ levels [73, 85]. Although earlier studies reported Hcar3 as a second niacin receptor [86, 87], more recent work suggests that despite high homology with Hcar2, Hcar3 displays low affinity binding to niacin [88]. Indeed, Hcar3 binds niacin with approximately 1000-fold less affinity as compared to Hcar2 [50, 71]. As a result, the actions of niacin exerted at this receptor are minimal compared to that of Hcar2.

### Transient Receptor Potential Cation Channel Subfamily V Member 1 (Trpv1)

Niacin has also been shown to bind to and activate the capsaicin receptor Trpv1, a nonselective cation channel [89]. Trpv1 is widely expressed throughout the body, and located in neurons, sensory cells of the gastrointestinal tract, immune cells, epithelial cells, and others [90]. As a heat-sensing receptor, the activation of Trpv1 leads to thermoregulatory processes including vasodilation. In mice, treatment with nicotinic acid leads to cutaneous vasodilation, as detected by Doppler perfusion imaging. This vasodilation was ameliorated in Trpv1 knockout mice [91] and following antagonism of the Trpv1 receptor [92]. Together, these results suggest that activation of Trpv1 by niacin is partly responsible for the flushing side effect, commonly reported in individuals taking niacin supplements.

## Mechanisms and Applications of Niacin in Neurological Disease

### Niacin and the Blood Brain Barrier

Before a medication can exert a direct pharmacological effect in the CNS, it must first cross the blood brain barrier, a quality of niacin that has been demonstrated. Indeed, cerebral uptake of nicotinic acid and nicotinamide is detected by positron emission tomography imaging following intravenous administration in both healthy volunteers and patients with neurodegenerative disease [93]. Furthermore, a significant increase in brain nicotinic acid levels is observed in mice following oral administration [10].

### Multiple Sclerosis

MS is a chronic inflammatory disease of the CNS, characterized by demyelination, inflammation, and progressive neurodegeneration. In MS patients, remyelination is associated with reduced score of clinical disability [94], while in a model of MS, remyelination facilitates functional recovery [95]. Current treatments for MS focus on modulating inflammation to prevent relapses, but none of the approved therapeutics target remyelination [96]. Demyelination in MS leads to the generation of myelin debris, which inhibits remyelination by preventing maturation of oligodendrocyte progenitor cells [97]. As a result, increased phagocytic capacity of microglia and infiltrating macrophages, allowing

for enhanced clearance of inhibitory myelin debris, would be a promising therapeutic strategy in MS.

Cholesterol is a major component of myelin and cannot be broken down by most mammalian cells [98]. Following the phagocytosis of lipid-rich myelin debris by microglia or macrophages, cholesterol undergoes reverse cholesterol transport or is esterified which is then stored in lipid droplets or released as lipoproteins [99]; these mechanisms protect the cell from the toxic effects of free cholesterol [100, 101]. In the CNS, cholesterol homeostasis is regulated by liver X receptors (LXRs), which form obligate heterodimers with retinoid X receptors [102]. Cholesterol derivatives such as oxysterols and desmosterol serve as ligands for LXRs, providing an indicator for the level of intracellular cholesterol [103]. Upon oxysterol binding, these receptors act as transcription factors, promoting the expression of apolipoprotein E (ApoE), as well as ATP binding cassette subfamily members ABCA1 and ABCG1 [103, 104]. ABCA1, and to a lesser extent, ABCG1, mediate the transport of cholesterol to the extracellular acceptor ApoE, leading to the generation of HDL-like particles that disperse lipids throughout the CNS [104, 105]. Once effluxed from macrophages, cholesterol may be taken up by oligodendrocytes and recycled for use in the creation of new myelin, thus facilitating remyelination (Fig. 4) [106].

Niacin modulates cholesterol recycling and efflux from macrophages. In vitro, HDL particles collected from healthy, niacin-treated humans promote cholesterol efflux from

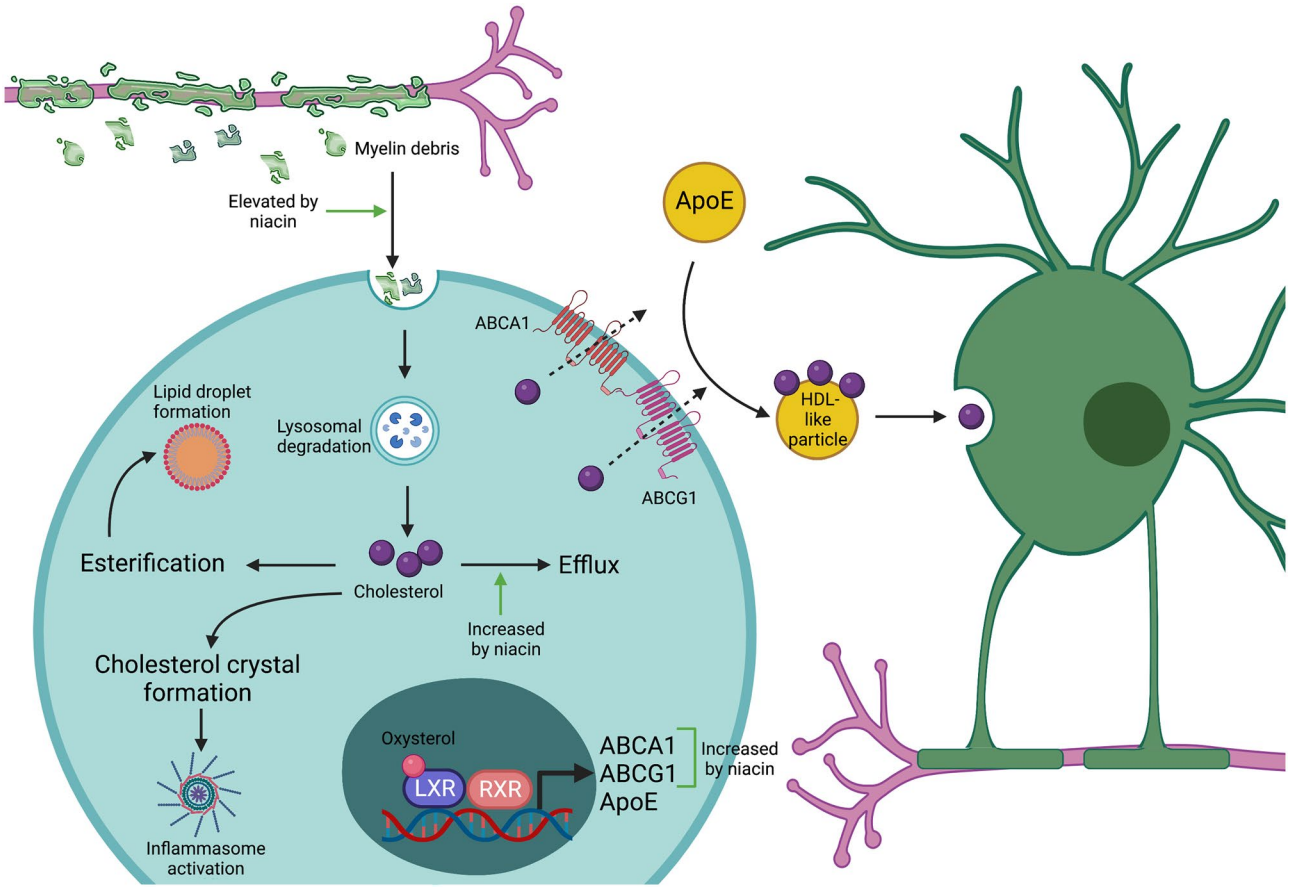


**Fig. 4 Cholesterol recycling in the CNS and impact of niacin.** Demyelination often occurs as a result of CNS insult or injury, producing myelin debris which is phagocytosed by microglia/macrophages in the CNS. This uptake of debris is promoted by niacin [8]. Following phagocytosis, myelin debris is partially degraded in the lysosome. Cholesterol, which cannot be broken down, is either esterified for storage in lipid droplets, or effluxed out of the cell. Impaired cholesterol processing leads to sustained cholesterol accumulation and the formation of cholesterol crystals, which promote an inflammatory macrophage phenotype. Cholesterol efflux is mediated by the ABCA1 and ABCG1 transporters, which transfer free cholesterol onto lipid-poor ApoE particles. There is evidence that niacin promotes the mRNA level of ABCA1 and ABCG1 [107, 108] and cholesterol efflux [106] although whether the latter is due to passive diffusion or through an ABCA1-dependent mechanism is unresolved. Together, cholesterol and ApoE generate an HDL-like particle, which distributes cholesterol throughout the CNS. Oligodendrocytes are one cell type that receives this free cholesterol, using it in the generation of new myelin. In the nucleus, cholesterol derivatives (e.g., oxysterol) bind to LXR. LXR forms a heterodimer with RXR and serves as a transcription factor, promoting transcription of ApoE, ABCA1 and ABCG1. Figure created using BioRender

foamy macrophages in an ABCA1- and ABCG1-dependent manner [107]. Further, niacin treatment in ApoE knockout mice increases mRNA expression of *Abca1*, *Abcg1*, and *LXR-α* [108]. Incubation of human monocytes with niacin increases mRNA expression of *ABCA1* and promotes cholesterol efflux to lipid-poor HDL particles [109]. In humans with a history of cardiovascular disease, a combination therapy of niacin and atorvastatin increases macrophage cholesterol efflux capacity beyond the levels observed in the statin-only group, although there was no observed increase in ABCA1-specific cholesterol efflux in this study [110]. Lastly, an in vitro experiment examining the effect of extended-release niacin found that while it increases passive diffusion-mediated cholesterol efflux capacity, there was no significant effect on ABCA1-mediated efflux [111]. Together, these studies demonstrate that while niacin promotes cholesterol efflux from macrophages, it remains to be determined whether this is done in an ABCA1-dependent or ABCA1-independent manner, or both.

Impaired cholesterol recycling and efflux can have negative consequences for the function and phenotype of macrophages. For instance, impaired cholesterol recycling and the concomitant production of intracellular cholesterol crystals lead to NLRP3 inflammasome activation [112, 113]. In the lysolecithin model of MS, impaired intracellular cholesterol esterification results in decreased lipid droplet formation and defective remyelination [114]. In addition, impaired cholesterol efflux and sustained myelin fragment accumulation within phagocytes produces an inflammatory foamy macrophage phenotype [115] which may lose their ability to effectively phagocytose debris [116]. Of note, dysregulated lipid metabolism has been implicated in the pathology of MS [117]. For example, LXR knockout mice have reduced CNS myelination [118], and serum levels of low-density lipoprotein cholesterol are positively associated with disease activity in MS patients, as indicated by MRI [119].

Cholesterol homeostasis in macrophages is related to their phagocytic capacity, as lipid-laden macrophages are unable to continue effectively phagocytosing debris and may eventually undergo apoptosis [116, 120]. Thus, it is thought that niacin works to promote remyelination in the MS context through increased phagocytosis of inhibitory myelin debris, perhaps linked to niacin's ability to promote cholesterol efflux [107]. By enhancing cholesterol efflux that may in turn be consumed by cholesterol-rich membrane-forming regenerating oligodendrocytes, niacin would prevent prolonged lipid accumulation within macrophages and free up their phagolysosomes for further digestion of engulfed material, while also avoiding a detrimental inflammatory macrophage phenotype (Fig. 4).

Promising data has been obtained from preclinical studies, demonstrating that niacin ameliorates disease in models of MS [121]. In the lysolecithin demyelination model, niacin treatment promotes phagocytosis of inhibitory myelin debris by microglia/macrophages, leading to increased numbers of oligodendrocyte progenitor cells in the lesion site and improved remyelination [8]. Of note, this enhanced phagocytosis is thought to be due in part to increased expression of the scavenger receptor CD36 on microglia/macrophages [8]. EAE mice treated with niacin experience ameliorated neurological deficits, reduced number of inflammatory infiltrates, and enhanced neuroprotection [122]. Furthermore, young rats fed a nicotinic acid-rich diet have enhanced developmental myelination, when compared to controls [123]. As a result of this promising evidence, a recent study aiming to identify licensed drugs with potential to be repurposed for clinical trials involving progressive MS patients put forth niacin as one of three highly recommended candidate drugs [7]. Future studies will allow us to determine whether niacin has therapeutic effects in people with MS, given its potential remyelinating and immunomodulatory responses (Fig. 5).

## Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder primarily caused by a loss of dopaminergic neurons in the substantia nigra pars compactica [124]. This neuropathology leads to dopamine deficiency in the basal ganglia and manifests in patients as bradykinesia, tremor, and/or rigidity, as well as other nonmotor symptoms such as cognitive decline and depression [125]. The first line of treatment for patients with PD is levodopa, a precursor of dopamine. Although levodopa is effective at treating motor symptoms, it does not prevent neurodegeneration and does not impact underlying inflammation; therefore, there is a need for improved therapeutic options [126].

There are several mechanisms through which niacin may act to ameliorate PD pathology, the first of which is through immune modulation. Aberrant neuroinflammation is increasingly being recognized as a key driver of PD pathogenesis. Activated microglia are enriched in the post-mortem brains of people with PD, particularly in affected areas such as the substantia nigra [127, 128]. Furthermore, there is increased signalling of proinflammatory cytokines such as IL-6, IFN-γ, and IL-1β in the CSF and peripheral blood of PD patients compared to healthy controls [129]. As such, it may be beneficial to modulate immune activity in the context of PD, which niacin has been shown to do. Macrophages collected from niacin-treated PD patients show polarization towards a beneficial, rather than detrimental inflammatory phenotype [130]. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD, treatment with the niacin metabolite NADPH leads to reduced gliosis and inflammatory NF-κB activation [131].

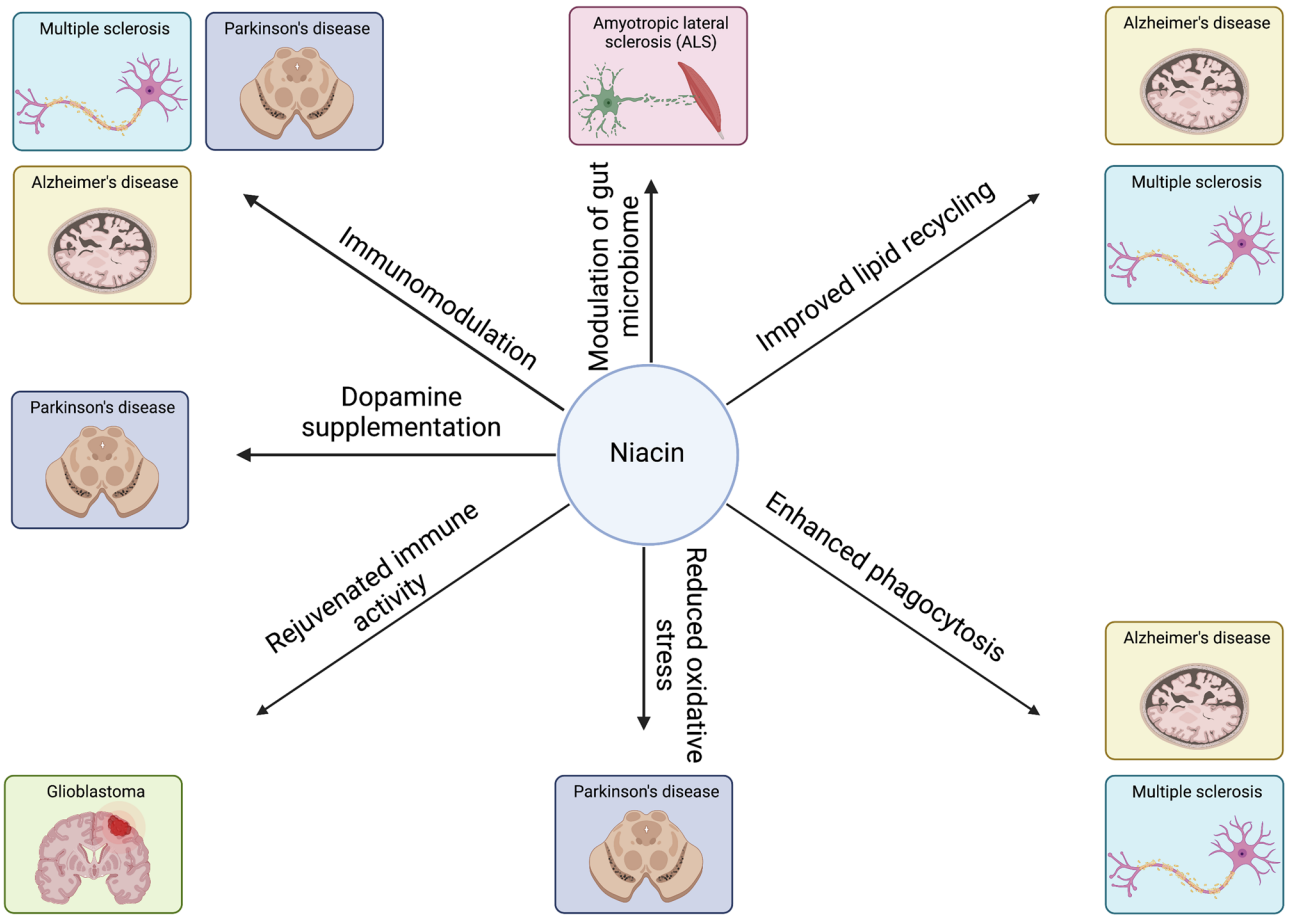


**Fig. 5 Mechanisms of niacin in neurological disease.** Niacin may act through a variety of mechanisms to alleviate pathology in neurological and neurodegenerative diseases. These putative mechanisms based on preclinical studies include enhanced phagocytosis and lipid recycling, immunomodulation, and ameliorated oxidative stress. Figure created using BioRender

Due to the loss of dopaminergic neurons, PD is characterized by decreased dopamine receptor signalling. Another mechanism through which niacin may modulate PD pathology is by supplementing dopamine levels. As mentioned, niacin gives rise to $NAD^+$ and NADH, which are involved in the production of dopamine [132]. Indeed, incubation of rodent cells with NADH leads to increased dopamine biosynthesis via elevated recycling of quinonoid dihydrobiopterin to tetrahydrobiopterin [133]. Tetrahydrobiopterin is a cofactor necessary for the synthesis of tyrosine hydroxylase, a rate-limiting enzyme in dopamine production [134, 135]. Preclinical data has shown support for this mechanism of action, as niacin treatment in the rotenone model of PD increases brain dopamine levels, compared to vehicle controls [9]. In striatal brain slices, application of NADH leads to increased KCl-evoked dopamine release [136].

Oxidative stress is increasingly being recognized as a key driver of neurodegeneration in PD, possibly underlying neuronal loss [137]. Markers of oxidative stress are observed in the blood of PD patients [138], and genetic disruption of mitochondrial complex I in the dopaminergic neurons of rodents leads to progressive, human-like parkinsonism [139]. In models of PD, niacin has been shown to ameliorate PD-related oxidative stress. Indeed, niacin treatment in the rotenone model reduces malondialdehyde level that informs on oxidative stress and increases the levels of antioxidants glutathione and superoxide dismutase [9]. In the MPTP model, intraperitoneal administration of NADPH restores glutathione levels and reduces reactive oxygen species production [131].

In sum, it is likely that niacin acts through several neuroprotective mechanisms to modify the pathology of PD, including altered inflammatory state, dopamine supplementation, and reduced oxidative stress (Fig. 5). Preliminary clinical data shows that niacin is a promising treatment in people with PD, and several clinical trials are ongoing (Table 1). Intake of niacin-rich foods is negatively associated with the risk of developing PD [140, 141], and in people with PD, low-dose niacin supplementation over the course of 12 months improves the Unified Parkinson's Disease Rating

**Table 1** Ongoing and completed trials of niacin in neurological disorders

| Disorder | Trial details and status | Niacin formulation and oral dose | Primary outcome | Some secondary end points | Data |
|---|---|---|---|---|---|
| Glioblastoma | Phase I-II (NCT04677049); recruiting; planned study end date January 2026 | Niacin CRT™.<br>Phase I: Dose escalation study, in steps of 500 mg/d every 4 weeks up to 3 g/d<br>Phase II: Maximally tolerated dose, as recommended from Phase I | Phase I: Maximally tolerated dose<br>Phase II: Progression free survival at 6 months | Change in peripheral monocytes, QOL | Trial in progress, no available data |
| Parkinson's disease | Phase II (NCT03462680); completed April 2020 | Nicotinic acid; 250 mg/d | MDS-UPDRS, REM sleep pattern, sleep percentages, MMSE, Stroop test, fatigue | CSF and plasma cytokine changes, niacin levels in plasma and urine, Hcar2 expression, plasma serotonin levels | No significant difference in motor function [143] |
| Ischemic stroke | Phase II (NCT00796887); completed August 2012 | Niaspan®; 500 or 1000 mg/d | Adverse events | Functional recovery | No significant differences in functional recovery. HDL cholesterol was significantly increased in niacin-treated group [144] |
| Parkinson's disease | Phase II (NCT03808961); active, not recruiting; planned study end date April 2024 | Nicotinic acid or nicotinamide; 100 mg tablets, twice daily | MDS-UPDRS, MMSE, Hcar2 expression, plasma cytokine levels, niacin levels in plasma and urine | VAFS, TMT, arm strength and fatigue | Trial in progress, no available data |
| Alzheimer's disease or Mild cognitive impairment | Phase II (NCT03061474); active, not recruiting; planned study end date August 2022 | Nicotinamide, sustained release tablet; 750 mg tablets, twice daily | Change in CSF p-tau231 | Change in CSF p-tau 181 and total tau | Trial in progress, no available data |
| Alzheimer's disease | Phase II (NCT00580931); completed July 2014 | Endur-amide® (nicotinamide); 1500 mg tablets, twice daily | ADAS-Cog | CIBIC-Plus, ADCS-ADL, CDR | No significant difference in primary or secondary end points [145] |
| Parkinson's disease | Phase I (NCT05589766); not yet recruiting; planned study end date December 2024 | Niagen™ (nicotinamide riboside); dose escalation to a maximum of 3000 mg/d | Cerebral and CSF NAD levels, NRRP expression | Adverse events, QOL, NAD metabolite levels, MDS-NMS, MoCA, GIDS-PD, MDS-UPDRS | Trial in progress, no available data |
| Alzheimer's disease | Phase I (NCT05617508); not yet recruiting; planned study end date December 2024 | Niagen™ (nicotinamide riboside); dose escalation to a maximum of 3000 mg/d | Cerebral and CSF NAD levels, FDG-PET, 31P-MRS | Adverse events, ADAS-Cog, CDR-SB, MoCA, TMT, IADL, PSMS, NPI-Q, MADRS | Trial in progress, no available data |
| Parkinson's disease | Phase II (NCT03568968); recruiting; planned study end date March 2024 | Niagen™ (nicotinamide riboside); 1000 mg/d | MDS-UPDRS | NAD metabolite levels | Trial in progress, no available data |

**Table 1** (continued)

| Disorder | Trial details and status | Niacin formulation and oral dose | Primary outcome | Some secondary end points | Data |
|---|---|---|---|---|---|
| Parkinson's disease | Phase I (NCT05344404); completed July 2022 | Niagen™ (nicotinamide riboside); 1500 mg tablets, twice daily | Severe adverse events | Mild adverse events, NAD metabolome, MDS-UPDRS | Results not yet available |
| Alzheimer's disease or Mild cognitive impairment | Early Phase I (NCT04430517); recruiting; planned study end date April 2025 | Niagen™ (nicotinamide riboside); 250 mg tablets, four times per day | Brain NAD, Brain redox state | Mitochondrial function, GSH levels | Trial in progress, no available data |
| Mild cognitive impairment | Phase I (NCT02942888); completed August 2021 | Niagen™ (nicotinamide riboside); dose escalation to a maximum of 1000 mg/d | MoCA | Cerebral blood flow, plasma NAD level, SPPB, IADL, arterial pressure, GDS, GAS, CLOX, EXIT, TAPS, Grip strength | Results not yet available |
| Mild cognitive impairment | Phase II (NCT04078178); planned study end date September 2022 | Niagen™ (nicotinamide riboside); 1200 mg/d | RBANS | N/A | Trial in progress, no available data |
| Parkinson's disease | Phase II (NCT03816020); completed February 2020 | Nicotinamide riboside; 500 mg tablets, twice daily | PDRP changes | MDS-UPDRS | Significant increase in cerebral NAD levels and altered cerebral metabolism [146] |

*31P-MRS* $^{31}$Phosphorous-magnetic resonance spectroscopy, *ADAS-Cog* Alzheimer's Disease Assessment Scale-Cognitive Subscale, *ADCS-ADL* Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale, *CDR* Clinical Dementia Rating Scale, *CDR-SB* Clinical Dementia Rating Scale Sum of Boxes, *CIBIC-Plus* Clinician's Interview-Based Impression of Change Plus Caregiver Input, *CLOX* Clock Drawing Task Protocol, *CSF* cerebrospinal fluid, *EXIT* Executive Interview, *FDG-PET* fluorodeoxyglucose-positron emission tomography, *GAS* Geriatric Anxiety Scale, *GDS* Geriatric Depression Scale, *GSH* glutathione, *GIDS-PD* Gastrointestinal Dysfunction Scale for Parkinson's Disease, *IADL* Instrumental Activities of Daily Living, *MADRS* Montgomery-Asberg Depression Rating Scale, *MDS-NMS* Movement Disorder Society Non-Motor Rating Scale, *MDS-UPDRS* Movement Disorder Society Unified Parkinson's Disease Rating Scale, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment, *NAD* Nicotinamide adenine dinucleotide, *NPI-Q* Neuropsychiatric Inventory brief questionnaire form, *NRRP* Nicotinamide Riboside Related Pattern, *PDRP* Parkinson's disease related pattern, *PSMS* Physical Self-Maintenance Scale, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status, *SPPB* Short Physical Performance Battery, *TAPS* Test of Auditory Processing Skills, *TMT* Trail making test, *QOL* Quality of life, *VAFS* Visual analogue fatigue scale

Scale, a measure of motor disability [13]. Furthermore, a case study demonstrated reduced rigidity and bradykinesia in a PD patient administered niacin for dyslipidemia [142].

## Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia, and its prevalence and burden on the healthcare system will only increase as our population ages. The pathological hallmarks of AD include amyloid-β plaques and neurofibrillary tangles [147], and people with AD experience reduced cognition including memory, language, and executive functions [148]. Current treatment options for individuals with AD are limited and primarily focus on symptom management without affecting neuropathology [149].

The mechanisms through which niacin may act in AD have similarities to those employed in MS, particularly its regulation of liver X receptor expression and lipid recycling (Fig. 5). Altered lipid dynamics have been implicated in the pathogenesis of AD [150]. For instance, the ApoE gene is strongly implicated in AD pathology; while the ApoE ε4 allele is the strongest genetic risk factor for AD development, individuals carrying the ε2 allele experience protection from the disease [151]. Furthermore, neuronal cholesterol levels control amyloid-β production by regulating the cleavage of amyloid precursor protein [152, 153]. In addition, ABCA1- and ABCG1-mediated cholesterol efflux is impaired in the CSF of AD patients, when compared to healthy and non-AD dementia controls [154]. Thus, the lipid-modifying actions of niacin, where niacin promotes cholesterol efflux and regulates CNS cholesterol and lipid homeostasis (Fig. 4), may allow it to modulate AD pathogenesis.

In addition to its lipid-modifying properties, niacin alters AD pathology by promoting a rejuvenated microglia/macrophage phenotype, enhancing the phagocytosis of pathological amyloid-B plaques. In the 5xFAD transgenic mouse model of AD, treatment with slow-release niacin (niaspan$^{R}$) increases microglia engagement with plaques, reduces plaque number and area, and promotes expression of microglial genes related to phagocytosis [10]. This, in turn, has a positive effect on clinical aspects, reducing cognitive deficits [10].

Gene expression analysis has also been performed to identify novel mechanisms of action for niacin in the context of AD. In the APP/PS1 transgenic model of AD, mice that received niacin supplementation had enhanced cognition. Niacin-supplemented AD mice also had elevated expression of genes including *Ctnnb1*, *Mdm2*, and *Pten*, which are involved in processes such as Wnt signalling, posttranslational modifications, and regulation of mTOR signalling [155].

Longitudinal studies suggest that niacin may have therapeutic potential in the context of people with AD. For example, previous work has established that increased intake of dietary niacin is associated with improved cognition [156] and reduced risk of AD later in life [14]. Whether or not niacin is an effective treatment in patients with AD remains to be investigated but is a promising avenue for future research.

## Glioblastoma

Glioblastomas (GBMs) are the most common primary tumours in the CNS in adults, and they affect approximately 2.3 people per 100,000 [157]. The current treatment involves surgical resection followed by radiation and chemotherapy with temozolomide, yet GBMs are one of the deadliest forms of cancer, with a median survival time of less than 15 months following diagnosis [158]. Treatment advances are in part halted by the self-renewing capacity of brain tumour initiating cells (BTICs), an immunosuppressive tumour microenvironment, and limited CNS access due to the BBB [159, 160]. Indeed, treatment of GBM has not improved since 2005 with the introduction of temozolomide into the therapeutic regimen, despite research efforts [161].

BTICs are a subclass of cancer cells that initiate glioblastoma growth and development due to their capacity for self-renewal and proliferation [162]; engraftment of as few as 100 human BTICs is sufficient to generate an identical tumour in recipient mice [163]. These cells have highly efficient DNA repair machinery, making them resistant to traditional radiation treatment that induces cell death by causing double-stranded DNA breaks [164]. BTICs have also demonstrated resistance to chemotherapy, although the mechanisms involved are not as clear [165]. Effective GBM treatment is further hindered by the presence of an immunosuppressive tumour microenvironment. Tumour-associated macrophages are the most abundant nontransformed cells in the tumour microenvironment, and they demonstrate a clear protumour phenotype, releasing anti-inflammatory cytokines and failing to initiate T cell responses [166]. Furthermore, tumour-infiltrating immune cells display an exhausted phenotype with reduced activity and fail to mount a proper immune response towards tumour cells [167]. Thus, a potential treatment for GBM would ably cross the BBB and stimulate immune activity, counteracting immune suppression and promoting recognition of BTICs by immune cells.

In a rodent model of GBM, treatment with niacin promotes beneficial immune modulation, rejuvenating immunosuppressive myeloid cells and increasing their tumour-fighting abilities (Fig. 5). Indeed, niacin activates myeloid cells derived from GBM patients in vitro, leading to their enhanced release of cytokines such as TNFα and IL-6, and niacin-treated monocytes attenuate the growth of GBM patient-derived BTICs [11]. Furthermore, niacin treatment in BTIC-implanted mice reduces brain tumour

growth and prolongs survival. Following these promising preclinical results, the addition of slow-release niacin (niacin$^{CRT}$) to standard of care entered a Phase I/IIa clinical trial in individuals with GBM (clinicaltrials.gov NCT04677049) (Table 1). Results from this ongoing trial will increase our knowledge on the potential of niacin to promote antitumour immune functions in a clinical setting.

### Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder, characterized by the loss of both upper and lower motor neurons. Current treatments target symptoms such as muscle spasticity, sialorrhea, and pain, but disease-modifying therapies are nonexistent [168]. Recently, the gut microbiome has been implicated in the pathogenesis of many disorders, including ALS [169], with a particular interest being paid to the microbiota-gut-brain axis [170]. In animal models of ALS, impaired tight junction integrity and enhanced gut permeability are observed [171], and microbiome dysbiosis precedes motor deficits [172]. Furthermore, ALS patients have significantly altered gut microbiota composition compared to controls [173], and repeated antibiotic use is associated with increased risk of developing ALS [174]. Notably, the recent work described below suggests that niacin may exert its therapeutic effects in part through modulation of the gut microbiome.

In the Sod1 transgenic mouse model of ALS, supplementation of *Akkermansia muciniphila* increases the serum levels of nicotinamide and leads to improvements in motor and neurological function, suggesting that nicotinamide released from gut microbiota has a beneficial effect on ALS pathogenesis [175]. Further, ALS patients have altered serum levels of molecules involved in nicotinamide synthesis, and increased serum nicotinamide correlates with better functional status [175]. Beyond the ALS literature, in obese humans, low levels of dietary niacin intake are correlated with low alpha-diversity and reduced *Bacteroidetes* abundance [176], a microbe that is largely considered to be beneficial [177]. Administration with delayed-release nicotinic acid leads to a significant increase in *Bacteroidetes* abundance, indicating that niacin administration can modulate composition of the microbiome [176]. In ACE2 knockout mice, which are prone to colitis and experience altered microbiome ecology, nicotinamide administration restores the microbiome composition to control levels and ameliorates gastrointestinal symptoms of colitis [178]. Thus, by modulating the gut microbiome, niacin may serve as a promising therapeutic option for ALS and other CNS disorders (Fig. 5).

## Conclusion and Remaining Questions

In conclusion, niacin is an essential vitamin that has long served as a well-tolerated treatment for a variety of disorders. While its canonical role is as a precursor for $NAD^+$/NADP, niacin has additional mechanisms of action, including agonistic activity at the GPCR Hcar2, and modulation of the microbiome. Due to the expression of Hcar2 on immune cells, niacin is emerging as a potent modulator of the immune system and has been shown to promote a beneficial immune cell phenotype, enhancing phagocytosis of harmful debris and reducing neuropathology in several neurological disorders. Niacin also plays a role in regulating cholesterol recycling, which is critical following the uptake of lipid-rich debris such as myelin by CNS macrophages. The recent work is establishing niacin as a promising therapeutic option in a range of neurological diseases such as MS, Alzheimer's disease, and glioblastoma.

Several questions remain about the mechanisms and utility of niacin. At what doses are its effects due solely to metabolism such as conversion to $NAD^+$? When high pharmacological doses are used where Hcar2 stimulation is thought to be engaged, to what extent is the benefit conferred by metabolic mechanisms? Are there as yet unidentified receptors for niacin? Is niacin anti-inflammatory or pro-inflammatory, and is there a concentration range that separates these potentially divergent activities? Would long-term use in chronic conditions such as MS run into risks of pro-inflammatory responses? Can niacin be combined with other therapeutic agents, such as direct agonists at LXRs, for a more efficacious outcome? Are there additional neurological conditions that may benefit from niacin therapy? Future studies will elucidate the role of niacin as a neuroprotective agent, allowing for its widespread adoption into clinical practice.

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## References

1. Mielgo-Ayuso JA-O, Aparicio-Ugarriza R, Olza JA-O, Aranceta-Bartrina J, Gil Á A-O, Ortega RA-O, et al. Dietary intake and food sources of niacin, riboflavin, thiamin and vitamin $B_6$ in a representative sample of the Spanish population. The anthropometry,

intake, and energy balance in Spain (ANIBES) study †. Nutrients. 2018;10(2072–6643 (Electronic)):846.
2. Hołubiec P, Leończyk M, Staszewski F, Łazarczyk A, Jaworek AK, Rojas-Pelc A. Pathophysiology and clinical management of pellagra - a review. Folia Med Crac. 2021;61(0015–5616 (Print)):125–37.
3. Prabhu D, Dawe RS, Mponda K. Pellagra a review exploring causes and mechanisms, including isoniazid-induced pellagra. Photodermatol Photoimmunol Photomed. 2021;37(2):99–104.
4. Boden WE, Sidhu MS, Toth PP. The therapeutic role of niacin in dyslipidemia management. J Cardiovasc Pharmacol Ther. 2014;19(1940–4034 (Electronic)):141–58.
5. Organization WH. Pellagra and its prevention and control in major emergencies. 2000.
6. Goldberg A, Alagona P Jr, Capuzzi DM, Guyton J, Morgan JM, Rodgers J, et al. Multiple-dose efficacy and safety of an extended-release form of niacin in the management of hyperlipidemia. Am J Cardiol. 2000;85(9):1100–5.
7. Cunniffe N, Vuong KA, Ainslie D, Baker D, Beveridge J, Bickley S, et al. Systematic approach to selecting licensed drugs for repurposing in the treatment of progressive multiple sclerosis. J Neurol Neurosurg Psychiatry. 2020;92(3):295–302.
8. Rawji KS, Young AMH, Ghosh T, Michaels NJ, Mirzaei R, Kappen J, et al. Niacin-mediated rejuvenation of macrophage/microglia enhances remyelination of the aging central nervous system. Acta Neuropathol. 2020;139(5):893–909.
9. Motawi TK, Sadik NAH, Hamed MA-O, Ali SA, Khalil WKB, Ahmed YR. Potential therapeutic effects of antagonizing adenosine A(2A) receptor, curcumin and niacin in rotenone-induced Parkinson's disease mice model. Mol Cell Biochem. 2020;465(1573–4919 (Electronic)):89–102.
10. Moutinho M, Puntambekar SS, Tsai AP, Coronel I, Lin PB, Casali BT, et al. The niacin receptor HCAR2 modulates microglial response and limits disease progression in a mouse model of Alzheimer's disease. Sci Transl Med. 2022;14(637):eabl7634.
11. Sarkar S, Yang R, Mirzaei R, Rawji K, Poon C, Mishra MK, et al. Control of brain tumor growth by reactivating myeloid cells with niacin. Sci Transl Med. 2020;12(537):eaay9924.
12. US National Library of Medicine. ClinicalTrialsgov. 2022:https://clinicaltrials.gov/ct2/show/NCT04677049. Accessed 8 Dec 2022.
13. Chong R, Wakade C, Seamon M, Giri B, Morgan J, Purohit S. Niacin enhancement for Parkinson's disease: an effectiveness trial. Front Aging Neurosci. 2021;13:667032.
14. Morris MC, Evans DA, Bienias JL, Scherr PA, Tangney CC, Hebert LE, et al. Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline. J Neurol Neurosurg Psychiatry. 2004;75(8):1093–9.
15. Katsyuba E, Romani M, Hofer D, Auwerx J. NAD(+) homeostasis in health and disease. Nat Metab. 2020;2(1):9–31.
16. Lundt S, Ding S. NAD(+) metabolism and diseases with motor dysfunction. Genes (Basel). 2021;12(11):1776.
17. Castro-Portuguez R, Sutphin GL. Kynurenine pathway, NAD(+) synthesis, and mitochondrial function: targeting tryptophan metabolism to promote longevity and healthspan. Exp Gerontol. 2020;132:110841.
18. She J, Sheng R, Qin Z-H. Pharmacology and potential complications of nicotinamide adenine dinucleotide precursors. Aging Dis. 2021;12(8):1879–97.
19. Horwitt MK. Niacin-tryptophan relationships in the development of pellagra. Am J Clin Nutr. 1955;3(3):244–5.
20. Hoxhaj G, Ben-Sahra I, Lockwood SE, Timson RC, Byles V, Henning GT, et al. Direct stimulation of NADP(+) synthesis through Akt-mediated phosphorylation of NAD kinase. Science. 2019;363(6431):1088–92.
21. Love NR, Pollak N, Dölle C, Niere M, Chen Y, Oliveri P, et al. NAD kinase controls animal NADP biosynthesis and is modulated via evolutionarily divergent calmodulin-dependent mechanisms. Proc Natl Acad Sci USA. 2015;112(5):1386–91.
22. Covarrubias AJ, Perrone R, Grozio A, Verdin E. NAD(+) metabolism and its roles in cellular processes during ageing. Nat Rev Mol Cell Biol. 2021;22(2):119–41.
23. Xiao W, Wang RS, Handy DE, Loscalzo J. NAD(H) and NADP(H) redox couples and cellular energy metabolism. Antioxid Redox Signal. 2018;28(3):251–72.
24. Lautrup S, Sinclair DA, Mattson MP, Fang EF. NAD(+) in brain aging and neurodegenerative disorders. Cell Metab. 2019;30(4):630–55.
25. Zapata-Pérez R, Wanders RJA, van Karnebeek CDM, Houtkooper RH. NAD(+) homeostasis in human health and disease. EMBO Mol Med. 2021;13(7):e13943.
26. Khan H, Tiwari P, Kaur A, Singh TG. Sirtuin acetylation and deacetylation: a complex paradigm in neurodegenerative disease. Mol Neurobiol. 2021;58(8):3903–17.
27. Verdin E. $NAD^+$ in aging, metabolism, and neurodegeneration. Science. 2015;350(6265):1208–13.
28. Cohen MS. Interplay between compartmentalized NAD(+) synthesis and consumption: a focus on the PARP family. Genes Dev. 2020;34(5–6):254–62.
29. Pandey N, Black BE. Rapid detection and signaling of DNA damage by PARP-1. Trends Biochem Sci. 2021;46(9):744–57.
30. Figley MD, DiAntonio A. The SARM1 axon degeneration pathway: Control of the NAD(+) metabolome regulates axon survival in health and disease. Curr Opin Neurobiol. 2020;63:59–66.
31. Essuman K, Summers DW, Sasaki Y, Mao X, DiAntonio A, Milbrandt J. The SARM1 toll/interleukin-1 receptor domain possesses intrinsic NAD(+) cleavage activity that promotes pathological axonal degeneration. Neuron. 2017;93(6):1334-43.e5.
32. Figley MD, Gu W, Nanson JD, Shi Y, Sasaki Y, Cunnea K, et al. SARM1 is a metabolic sensor activated by an increased NMN/NAD(+) ratio to trigger axon degeneration. Neuron. 2021;109(7):1118-36.e11.
33. Chini CCS, Zeidler JD, Kashyap S, Warner G, Chini EN. Evolving concepts in NAD(+) metabolism. Cell Metab. 2021;33(6):1076–87.
34. Lee HC, Deng QW, Zhao YJ. The calcium signaling enzyme CD38 - a paradigm for membrane topology defining distinct protein functions. Cell Calcium. 2022;101:102514.
35. Ge T, Yang J, Zhou S, Wang Y, Li Y, Tong X. The role of the pentose phosphate pathway in diabetes and cancer. Front Endocrinol (Lausanne). 2020;11:365.
36. Gansemer ER, McCommis KS, Martino M, King-McAlpin AQ, Potthoff MJ, Finck BN, et al. NADPH and glutathione redox link TCA cycle activity to endoplasmic reticulum homeostasis. iScience. 2020;23(5):101116.
37. Ganguly U, Kaur U, Chakrabarti SS, Sharma P, Agrawal BK, Saso L, et al. Oxidative stress, neuroinflammation, and NADPH axidase: implications in the pathogenesis and treatment of Alzheimer's disease. Oxid Med Cell Longev. 2021;2021:7086512.
38. Duan J, Gao S, Tu S, Lenahan C, Shao A, Sheng J. Pathophysiology and therapeutic potential of NADPH oxidases in ischemic stroke-induced oxidative stress. Oxid Med Cell Longev. 2021;2021:6631805.
39. Horimatsu T, Blomkalns AL, Ogbi M, Moses M, Kim D, Patel S, et al. Niacin protects against abdominal aortic aneurysm formation via GPR109A independent mechanisms: role of NAD+/nicotinamide. Cardiovasc Res. 2020;116(14):2226–38.
40. Pirinen E, Auranen M, Khan NA, Brilhante V, Urho N, Pessia A, et al. Niacin cures systemic NAD(+) deficiency and improves muscle performance in adult-onset mitochondrial myopathy. Cell Metab. 2020;31(6):1078-90.e5.
41. Cimaglia G, Votruba M, Morgan JE, André H, Williams PA. Potential therapeutic benefit of NAD(+) supplementation for glaucoma and age-related macular degeneration. Nutrients. 2020;12(9):2871.

42. Williams PA, Harder JM, Foxworth NE, Cochran KE, Philip VM, Porciatti V, et al. Vitamin B(3) modulates mitochondrial vulnerability and prevents glaucoma in aged mice. Science. 2017;355(6326):756–60.
43. Tribble JR, Otmani A, Sun S, Ellis SA, Cimaglia G, Vohra R, et al. Nicotinamide provides neuroprotection in glaucoma by protecting against mitochondrial and metabolic dysfunction. Redox Biol. 2021;43:101988.
44. Duarte-Pereira S, Pereira-Castro I, Silva SS, Correia MG, Neto C, da Costa LT, et al. Extensive regulation of nicotinate phosphoribosyltransferase (NAPRT) expression in human tissues and tumors. Oncotarget. 2016;7(2):1973–83.
45. Zamporlini F, Ruggieri S, Mazzola F, Amici A, Orsomando G, Raffaelli N. Novel assay for simultaneous measurement of pyridine mononucleotides synthesizing activities allows dissection of the NAD(+) biosynthetic machinery in mammalian cells. FEBS J. 2014;281(22):5104–19.
46. Neuvonen PJ, Roivas L, Laine K, Sundholm O. The bioavailability of sustained release nicotinic acid formulations. Br J Clin Pharmacol. 1991;32(4):473–6.
47. Bodor ET, Offermanns S. Nicotinic acid: an old drug with a promising future. Br J Pharmacol. 2008;153(Suppl 1):S68-75.
48. Hepler C, Foy CE, Higgins MR, Renquist BJ. The hypophagic response to heat stress is not mediated by GPR109A or peripheral β-OH butyrate. Am J Physiol Regul Integr Comp Physiol. 2016;310(10):R992–8.
49. Graff EC, Fang H, Wanders D, Judd RL. Anti-inflammatory effects of the hydroxycarboxylic acid receptor 2. Metabolism. 2016;65(2):102–13.
50. Wise A, Foord SM, Fraser NJ, Barnes AA, Elshourbagy N, Eilert M, et al. Molecular identification of high and low affinity receptors for nicotinic acid. J Biol Chem. 2003;278(11):9869–74.
51. Hilger D, Masureel M, Kobilka BK. Structure and dynamics of GPCR signaling complexes. Nat Struct Mol Biol. 2018;25(1):4–12.
52. Cosín-Roger J, Ortiz-Masia D, Barrachina MD, Calatayud S. Metabolite sensing GPCRs: Promising therapeutic targets for cancer treatment? Cells. 2020;9(11):2345.
53. de Oliveira PG, Ramos MLS, Amaro AJ, Dias RA, Vieira SI. Gi/o-protein coupled receptors in the aging brain. Front Aging Neurosci. 2019;11:284–93.
54. Gaidarov I, Chen X, Anthony T, Maciejewski-Lenoir D, Liaw C, Unett DJ. Differential tissue and ligand-dependent signaling of GPR109A receptor: implications for anti-atherosclerotic therapeutic potential. Cell Signal. 2013;25(10):2003–16.
55. Carretta MD, Quiroga J, López R, Hidalgo MA, Burgos RA. Participation of short-chain fatty acids and their receptors in gut inflammation and colon cancer. Front Physiol. 2021;12:662739.
56. Cresci GAM, Mayor PC, Thompson SA. Effect of butyrate and Lactobacillus GG on a butyrate receptor and transporter during Campylobacter jejuni exposure. FEMS Microbiol Lett. 2017;364(6):fnx046.
57. Boccella S, Guida F, De Logu F, De Gregorio D, Mazzitelli M, Belardo C, et al. Ketones and pain: Unexplored role of hydroxyl carboxylic acid receptor type 2 in the pathophysiology of neuropathic pain. FASEB J. 2019;33(1):1062–73.
58. Tuteja S. Activation of HCAR2 by niacin: benefits beyond lipid lowering. Pharmacogenomics. 2019;20(16):1143–50.
59. Tunaru S, Lättig J, Kero J, Krause G, Offermanns S. Characterization of determinants of ligand binding to the nicotinic acid receptor GPR109A (HM74A/PUMA-G). Mol Pharmacol. 2005;68(5):1271–80.
60. Parodi B, Sanna A, Cedola A, Uccelli A, Kerlero de Rosbo N. Hydroxycarboxylic acid receptor 2, a pleiotropically linked receptor for the multiple sclerosis drug, monomethyl fumarate. Possible implications for the inflammatory response. Front Immunol. 2021;12:655212.
61. Parodi B, Rossi S, Morando S, Cordano C, Bragoni A, Motta C, et al. Fumarates modulate microglia activation through a novel HCAR2 signaling pathway and rescue synaptic dysregulation in inflamed CNS. Acta Neuropathol. 2015;130(2):279–95.
62. Chen H, Assmann JC, Krenz A, Rahman M, Grimm M, Karsten CM, et al. Hydroxycarboxylic acid receptor 2 mediates dimethyl fumarate's protective effect in EAE. J Clin Invest. 2014;124(5):2188–92.
63. Ahmed K, Tunaru S, Offermanns S. GPR109A, GPR109B and GPR81, a family of hydroxy-carboxylic acid receptors. Trends Pharmacol Sci. 2009;30(11):557–62.
64. Li M, van Esch B, Wagenaar GTM, Garssen J, Folkerts G, Henricks PAJ. Pro- and anti-inflammatory effects of short chain fatty acids on immune and endothelial cells. Eur J Pharmacol. 2018;831:52–9.
65. Jiang D, Ryals RC, Huang SJ, Weller KK, Titus HE, Robb BM, et al. Monomethyl fumarate protects the retina from light-induced retinopathy. Invest Ophthalmol Vis Sci. 2019;60(4):1275–85.
66. Hanson J, Gille A, Zwykiel S, Lukasova M, Clausen BE, Ahmed K, et al. Nicotinic acid- and monomethyl fumarate-induced flushing involves GPR109A expressed by keratinocytes and COX-2-dependent prostanoid formation in mice. J Clin Invest. 2010;120(8):2910–9.
67. Ganapathy V, Thangaraju M, Prasad PD, Martin PM, Singh N. Transporters and receptors for short-chain fatty acids as the molecular link between colonic bacteria and the host. Curr Opin Pharmacol. 2013;13(6):869–74.
68. Gasperi V, Sibilano M, Savini I, Catani M. Niacin in the central nervous system: an update of biological aspects and clinical applications. IJMS. 2019;20(4):974.
69. Carlson LA, Orö L, Ostman J. Effect of a single dose of nicotinic acid on plasma lipids in patients with hyperlipoproteinemia. Acta Med Scand. 1968;183(5):457–65.
70. Tunaru S, Kero J, Schaub A, Wufka C, Blaukat A, Pfeffer K, et al. PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effect. Nat Med. 2003;9(3):352–5.
71. Soga T, Kamohara M, Takasaki J, Matsumoto S, Saito T, Ohishi T, et al. Molecular identification of nicotinic acid receptor. Biochem Biophys Res Commun. 2003;303(1):364–9.
72. Newman JC, Verdin E. β-hydroxybutyrate: a signaling metabolite. Annu Rev Nutr. 2017;37:51–76.
73. Offermanns S. Hydroxy-carboxylic acid receptor actions in metabolism. Trends Endocrinol Metab. 2017;28(3):227–36.
74. Blad CC, Tang C, Offermanns S. G protein-coupled receptors for energy metabolites as new therapeutic targets. Nat Rev Drug Discov. 2012;11(8):603–19.
75. Taggart AK, Kero J, Gan X, Cai TQ, Cheng K, Ippolito M, et al. (D)-beta-Hydroxybutyrate inhibits adipocyte lipolysis via the nicotinic acid receptor PUMA-G. J Biol Chem. 2005;280(29):26649–52.
76. Masuda Y, Kurikawa N, Nishizawa T. Overexpressing human GPR109A leads to pronounced reduction in plasma triglyceride levels in BAC transgenic rats. Atherosclerosis. 2018;272:182–92.
77. Zhang SJ, Li ZH, Zhang YD, Chen J, Li Y, Wu FQ, et al. Ketone body 3-hydroxybutyrate ameliorates atherosclerosis via receptor Gpr109a-mediated calcium influx. Adv Sci (Weinh). 2021;8(9):2003410.
78. van der Hoorn JW, de Haan W, Berbée JF, Havekes LM, Jukema JW, Rensen PC, et al. Niacin increases HDL by reducing hepatic expression and plasma levels of cholesteryl ester transfer protein in APOE*3Leiden.CETP mice. Arterioscler Thromb Vasc Biol. 2008;28(11):2016–22.
79. Gille A, Bodor ET, Ahmed K, Offermanns S. Nicotinic acid: pharmacological effects and mechanisms of action. Annu Rev Pharmacol Toxicol. 2008;48:79–106.

80. Hernandez M, Wright SD, Cai TQ. Critical role of cholesterol ester transfer protein in nicotinic acid-mediated HDL elevation in mice. Biochem Biophys Res Commun. 2007;355(4):1075–80.
81. Digby JE, Martinez F, Jefferson A, Ruparelia N, Chai J, Wamil M, et al. Anti-inflammatory effects of nicotinic acid in human monocytes are mediated by GPR109A dependent mechanisms. Arterioscler Thromb Vasc Biol. 2012;32(3):669–76.
82. Zandi-Nejad K, Takakura A, Jurewicz M, Chandraker AK, Offermanns S, Mount D, et al. The role of HCA2 (GPR109A) in regulating macrophage function. FASEB J. 2013;27(11):4366–74.
83. Rahman M, Muhammad S, Khan MA, Chen H, Ridder DA, Müller-Fielitz H, et al. The β-hydroxybutyrate receptor HCA2 activates a neuroprotective subset of macrophages. Nat Commun. 2014;5:3944.
84. Kapolka NJ, Isom DG. HCAR3: an underexplored metabolite sensor. Nat Rev Drug Discov. 2020;19(11):745.
85. Ahmed K. Biological roles and therapeutic potential of hydroxycarboxylic acid receptors. Front Endocrinol (Lausanne). 2011;2:51.
86. Kamanna VS, Kashyap ML. Nicotinic acid (niacin) receptor agonists: will they be useful therapeutic agents? Am J Cardiol. 2007;100(11 a):S53-61.
87. Knowles HJ, te Poele RH, Workman P, Harris AL. Niacin induces PPARgamma expression and transcriptional activation in macrophages via HM74 and HM74a-mediated induction of prostaglandin synthesis pathways. Biochem Pharmacol. 2006;71(5):646–56.
88. Adepu KK, Kachhap S, Anishkin A, Chintapalli SV. Structural and energetic insights into the interaction of niacin with the GPR109A receptor. Bioinform Biol Insights. 2021;15:11779322211056122.
89. Kwon DH, Zhang F, Suo Y, Bouvette J, Borgnia MJ, Lee SY. Heat-dependent opening of TRPV1 in the presence of capsaicin. Nat Struct Mol Biol. 2021;28(7):554–63.
90. Storozhuk MV, Moroz OF, Zholos AV. Multifunctional TRPV1 ion channels in physiology and pathology with focus on the brain, vasculature, and some visceral systems. Biomed Res Int. 2019;2019:5806321.
91. Ma L, Lee BH, Mao R, Cai A, Jia Y, Clifton H, et al. Nicotinic acid activates the capsaicin receptor TRPV1: potential mechanism for cutaneous flushing. Arterioscler Thromb Vasc Biol. 2014;34(6):1272–80.
92. Clifton HL, Inceoglu B, Ma L, Zheng J, Schaefer S. TRPV1 channels are involved in niacin-induced cutaneous vasodilation in mice. J Cardiovasc Pharmacol. 2015;65(2):184–91.
93. Hankes LV, Coenen HH, Rota E, Langen KJ, Herzog H, Wutz W, et al. Effect of Huntington's and Alzheimer's diseases on the transport of nicotinic acid or nicotinamide across the human blood-brain barrier. In: Schwarcz R, Young SN, Brown RR, editors. Kynurenine and Serotonin Pathways. 294. Boston, MA: Springer New York; 1991. p. 675–8.
94. Bodini B, Veronese M, García-Lorenzo D, Battaglini M, Poirion E, Chardain A, et al. Dynamic imaging of individual remyelination profiles in multiple sclerosis. Ann Neurol. 2016;79(5):726–38.
95. Duncan ID, Brower A, Kondo Y, Curlee JF, Schultz RD. Extensive remyelination of the CNS leads to functional recovery. Proc Natl Acad Sci USA. 2009;106(16):6832–6.
96. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis: A review. JAMA. 2021;325(8):765–79.
97. Kotter MR, Li WW, Zhao C, Franklin RJ. Myelin impairs CNS remyelination by inhibiting oligodendrocyte precursor cell differentiation. J Neurosci. 2006;26(1):328–32.
98. Dietschy JM. Central nervous system: cholesterol turnover, brain development and neurodegeneration. Biol Chem. 2009;390(4):287–93.
99. Luo J, Yang H, Song BL. Mechanisms and regulation of cholesterol homeostasis. Nat Rev Mol Cell Biol. 2020;21(4):225–45.
100. Lee-Rueckert M, Lappalainen J, Leinonen H, Plihtari R, Nordström T, Åkerman K, et al. Acidic extracellular pH promotes accumulation of free cholesterol in human monocyte-derived macrophages via inhibition of ACAT1 activity. Atherosclerosis. 2020;312:1–7.
101. Ho CM, Ho SL, Jeng YM, Lai YS, Chen YH, Lu SC, et al. Accumulation of free cholesterol and oxidized low-density lipoprotein is associated with portal inflammation and fibrosis in nonalcoholic fatty liver disease. J Inflamm (Lond). 2019;16:7.
102. Wang B, Tontonoz P. Liver X receptors in lipid signalling and membrane homeostasis. Nat Rev Endocrinol. 2018;14(8):452–63.
103. Mouzat K, Chudinova A, Polge A, Kantar J, Camu W, Raoul C, et al. Regulation of brain cholesterol: What role do liver X receptors play in neurodegenerative diseases? IJMS. 2019;20(16):3858.
104. Courtney R, Landreth GE. LXR regulation of brain cholesterol: from development to disease. Trends Endocrinol Metab. 2016;27(6):404–14.
105. Marais AD. Apolipoprotein E in lipoprotein metabolism, health and cardiovascular disease. Pathology. 2019;51(2):165–76.
106. Berghoff SA, Spieth L, Sun T, Hosang L, Schlaphoff L, Depp C, et al. Microglia facilitate repair of demyelinated lesions via post-squalene sterol synthesis. Nat Neurosci. 2021;24(1):47–60.
107. Yvan-Charvet L, Kling J, Pagler T, Li H, Hubbard B, Fisher T, et al. Cholesterol efflux potential and antiinflammatory properties of high-density lipoprotein after treatment with niacin or anacetrapib. ATVB. 2010;30(7):1430–8.
108. Du R, Wang Z. Effects of niacin on ApoE-/- mice' adipose tissue, serum lipid and atherosclerosis. J Am Coll Cardiol. 2015;66(16_Supplement):C43-C.
109. Rubic T, Trottmann M, Lorenz RL. Stimulation of CD36 and the key effector of reverse cholesterol transport ATP-binding cassette A1 in monocytoid cells by niacin. Biochem Pharmacol. 2004;67(3):411–9.
110. Ronsein GE, Hutchins PM, Isquith D, Vaisar T, Zhao XQ, Heinecke JW. Niacin therapy increases high-density lipoprotein particles and total cholesterol efflux capacity but not ABCA1-specific cholesterol efflux in statin-treated subjects. Arterioscler Thromb Vasc Biol. 2016;36(2):404–11.
111. Franceschini G, Favari E, Calabresi L, Simonelli S, Bondioli A, Adorni MP, et al. Differential effects of fenofibrate and extended-release niacin on high-density lipoprotein particle size distribution and cholesterol efflux capacity in dyslipidemic patients. J Clin Lipidol. 2013;7(5):414–22.
112. Cantuti-Castelvetri L, Fitzner D, Bosch-Queralt M, Weil M-T, Su M, Sen P, et al. Defective cholesterol clearance limits remyelination in the aged central nervous system. Science. 2018;359(6376):684–8.
113. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature. 2010;464(7293):1357–61.
114. Gouna G, Klose C, Bosch-Queralt M, Liu L, Gokce O, Schifferer M, et al. TREM2-dependent lipid droplet biogenesis in phagocytes is required for remyelination. J Exp Med. 2021;218(10):e20210227.
115. Bogie JFJ, Grajchen E, Wouters E, Corrales AG, Dierckx T, Vanherle S, et al. Stearoyl-CoA desaturase-1 impairs the reparative properties of macrophages and microglia in the brain. J Exp Med. 2020;217(5):e20191660.
116. Wang X, Cao K, Sun X, Chen Y, Duan Z, Sun L, et al. Macrophages in spinal cord injury: Phenotypic and functional

change from exposure to myelin debris: myelin debris altering macrophage function. Glia. 2015;63(4):635–51.
117. Pineda-Torra I, Siddique S, Waddington KE, Farrell R, Jury EC. Disrupted lipid metabolism in multiple sclerosis: a role for liver X receptors? Front Endocrinol. 2021;12:639757.
118. Meffre D, Shackleford G, Hichor M, Gorgievski V, Tzavara ET, Trousson A, et al. Liver X receptors alpha and beta promote myelination and remyelination in the cerebellum. Proc Natl Acad Sci U S A. 2015;112(24):7587–92.
119. Uher T, Fellows K, Horakova D, Zivadinov R, Vaneckova M, Sobisek L, et al. Serum lipid profile changes predict neurodegeneration in interferon-β1a-treated multiple sclerosis patients. J Lipid Res. 2017;58(2):403–11.
120. Grajchen E, Hendriks JJA, Bogie JFJ. The physiology of foamy phagocytes in multiple sclerosis. Acta Neuropathol Commun. 2018;6(1):124.
121. Oh J, Bar-Or A. Emerging therapies to target CNS pathophysiology in multiple sclerosis. Nat Rev Neurol. 2022;18(8):466–75.
122. Zhang J, Chen J, Li Y, Cui X, Zheng X, Roberts C, et al. Niaspan treatment improves neurological functional recovery in experimental autoimmune encephalomyelitis mice. Neurobiol Dis. 2008;32(2):273–80.
123. Nakashima Y, Suzue R. Effect of nicotinic acid on myelin lipids in brain of developing rat. J Nutr Sci Vitaminol (Tokyo). 1982;28(5):491–500.
124. Simon DK, Tanner CM, Brundin P. Parkinson disease epidemiology, pathology, genetics, and pathophysiology. Clin Geriatr Med. 2020;36(1):1–12.
125. Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet. 2021;397(10291):2284–303.
126. Church FC. Treatment options for motor and non-motor symptoms of Parkinson's disease. Biomolecules. 2021;11(4).
127. Badanjak K, Fixemer S, Smajić S, Skupin A, Grünewald A. The contribution of microglia to neuroinflammation in Parkinson's disease. IJMS. 2021;22(9).
128. Marogianni C, Sokratous M, Dardiotis E, Hadjigeorgiou GM, Bogdanos D, Xiromerisiou G. Neurodegeneration and inflammation-an interesting interplay in Parkinson's disease. IJMS. 2020;21(22):8421.
129. Pajares M, A IR, MG, Boscá L, Cuadrado A. Inflammation in Parkinson's disease: mechanisms and therapeutic implications. Cells. 2020;9(7).
130. Wakade C, Giri B, Malik A, Khodadadi H, Morgan JC, Chong RK, et al. Niacin modulates macrophage polarization in Parkinson's disease. J Neuroimmunol. 2018;320:76–9.
131. Zhou Y, Wu J, Sheng R, Li M, Wang Y, Han R, et al. Reduced nicotinamide adenine dinucleotide phosphate inhibits MPTP-induced neuroinflammation and neurotoxicity. Neuroscience. 2018;391:140–53.
132. Aaseth J, Dusek P, Roos PM. Prevention of progression in Parkinson's disease. Biometals. 2018;31(5):737–47.
133. Vrecko K, Storga D, Birkmayer JG, Möller R, Tafeit E, Horejsi R, et al. NADH stimulates endogenous dopamine biosynthesis by enhancing the recycling of tetrahydrobiopterin in rat phaeochromocytoma cells. Biochim Biophys Acta. 1997;1361(1):59–65.
134. Rai SN, Singh P, Steinbusch HWM, Vamanu E, Ashraf G, Singh MP. The role of vitamins in neurodegenerative disease: an update. Biomedicines. 2021;9(10).
135. Nagatsu T, Nakashima A, Ichinose H, Kobayashi K. Human tyrosine hydroxylase in Parkinson's disease and in related disorders. J Neural Transm (Vienna). 2019;126(4):397–409.
136. Pearl SM, Antion MD, Stanwood GD, Jaumotte JD, Kapatos G, Zigmond MJ. Effects of NADH on dopamine release in rat striatum. Synapse. 2000;36(2):95–101.
137. Dionísio PA, Amaral JD, Rodrigues CMP. Oxidative stress and regulated cell death in Parkinson's disease. Ageing Res Rev. 2021;67:101263.
138. Vida C, Kobayashi H, Garrido A, Martínez de Toda I, Carro E, Molina JA, et al. Lymphoproliferation impairment and oxidative stress in blood cells from early Parkinson's disease patients. IJMS. 2019;20(3).
139. González-Rodríguez P, Zampese E, Stout KA, Guzman JN, Ilijic E, Yang B, et al. Disruption of mitochondrial complex I induces progressive parkinsonism. Nature. 2021;599(7886):650–6.
140. Hellenbrand W, Boeing H, Robra BP, Seidler A, Vieregge P, Nischan P, et al. Diet and Parkinson's disease. II: a possible role for the past intake of specific nutrients. Results from a self-administered food-frequency questionnaire in a case-control study. Neurology. 1996;47(3):644–50.
141. Fall PA, Fredrikson M, Axelson O, Granérus AK. Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. Mov Disord. 1999;14(1):28–37.
142. Alisky JM. Niacin improved rigidity and bradykinesia in a Parkinson's disease patient but also caused unacceptable nightmares and skin rash–a case report. Nutr Neurosci. 2005;8(5–6):327–9.
143. Wakade C, Chong R, Seamon M, Purohit S, Giri B, Morgan JC. LowdDose niacin supplementation improves motor function in US veterans with Parkinson's disease: A single-center, randomized, placebo-controlled trial. Biomedicines. 2021;9(12):1881.
144. Russman AN, Silver B, Katramados A, Chopp M, Burmeister C, Schultz L, et al. Abstract WP156: A phase IIa double-blind, placebo controlled study of extended-release niacin for stroke recovery. Stroke. 2018;49.
145. Phelan MJ, Mulnard RA, Gillen DL, Schreiber SS. Phase II clinical trial of nicotinamide for the treatment of mild to moderate Alzheimer's disease. Gerontol Geriatr Med. 2017;3(1):021.
146. Brakedal B, Dölle C, Riemer F, Ma Y, Nido GS, Skeie GO, et al. The NADPARK study: a randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. Cell Metab. 2022;34(3):396-407.e6.
147. Sengoku R. Aging and Alzheimer's disease pathology. Neuropathology. 2020;40(1):22–9.
148. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and management of dementia: review. JAMA. 2019;322(16):1589–99.
149. Srivastava S, Ahmad R, Khare SK. Alzheimer's disease and its treatment by different approaches: A review. Eur J Med Chem. 2021;216: 113320.
150. Yin F. Lipid metabolism and Alzheimer's disease: clinical evidence, mechanistic link and therapeutic promise. FEBS J. 2022.
151. Serrano-Pozo A, Das S, Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. Lancet Neurol. 2021;20(1):68–80.
152. Wang H, Kulas JA, Wang C, Holtzman DM, Ferris HA, Hansen SB. Regulation of beta-amyloid production in neurons by astrocyte-derived cholesterol. Proc Natl Acad Sci U S A. 2021;118(33).
153. Rudajev V, Novotny J. Cholesterol as a key player in amyloid β-mediated toxicity in Alzheimer's disease. Front Mol Neurosci. 2022.
154. Marchi C, Adorni MP, Caffarra P, Ronda N, Spallazzi M, Barocco F, et al. ABCA1- and ABCG1-mediated cholesterol efflux capacity of cerebrospinal fluid is impaired in Alzheimer's disease. J Lipid Res. 2019;60(8):1449–56.
155. Wang Z, Zou Z, Li Q. Nicotinic acid supplementation contributes to the amelioration of Alzheimer's disease in mouse models. Ann Transl Med. 2022;10(19):1049.
156. Qin B, Xun P, Jacobs DR Jr, Zhu N, Daviglus ML, Reis JP, et al. Intake of niacin, folate, vitamin B-6, and vitamin B-12 through young adulthood and cognitive function in midlife: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Am J Clin Nutr. 2017;106(4):1032–40.

157. Tamimi AF, Juweid M. Epidemiology and outcome of glioblastoma. In: De Vleeschouwer S, editor. Glioblastoma. Brisbane (AU) 2017.
158. Tan AC, Ashley DM, López GY, Malinzak M, Friedman HS, Khasraw M. Management of glioblastoma: state of the art and future directions. CA Cancer J Clin. 2020;70(4):299–312.
159. Ou A, Yung WKA, Majd N. Molecular mechanisms of treatment resistance in glioblastoma. IJMS. 2020;22(1).
160. Wu W, Klockow JL, Zhang M, Lafortune F, Chang E, Jin L, et al. Glioblastoma multiforme (GBM): an overview of current therapies and mechanisms of resistance. Pharmacol Res. 2021;171:105780.
161. Ma R, Taphoorn MJB, Plaha P. Advances in the management of glioblastoma. J Neurol Neurosurg Psychiatry. 2021;92(10):1103–11.
162. Huang T, Song X, Xu D, Tiek D, Goenka A, Wu B, et al. Stem cell programs in cancer initiation, progression, and therapy resistance. Theranostics. 2020;10(19):8721–43.
163. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, et al. Identification of human brain tumour initiating cells. Nature. 2004;432(7015):396–401.
164. Schulz A, Meyer F, Dubrovska A, Borgmann K. Cancer stem cells and radioresistance: DNA repair and beyond. Cancers (Basel). 2019;11(6).
165. Alves ALV, Gomes INF, Carloni AC, Rosa MN, da Silva LS, Evangelista AF, et al. Role of glioblastoma stem cells in cancer therapeutic resistance: a perspective on antineoplastic agents from natural sources and chemical derivatives. Stem Cell Res Ther. 2021;12(1):206.
166. De Leo A, Ugolini A, Veglia F. Myeloid cells in glioblastoma microenvironment. Cells. 2020;10(1).
167. Daubon T, Hemadou A, Romero Garmendia I, Saleh M. Glioblastoma immune landscape and the potential of new immunotherapies. Front Immunol. 2020;11:585616.
168. Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol. 2020;27(10):1918–29.
169. Martin S, Battistini C, Sun J. A gut feeling in amyotrophic lateral sclerosis: microbiome of mice and men. Front Cell Infect Microbiol. 2022;12:839526.
170. Socała K, Doboszewska U, Szopa A, Serefko A, Włodarczyk M, Zielińska A, et al. The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. Pharmacol Res. 2021;172:105840.
171. Wu S, Yi J, Zhang YG, Zhou J, Sun J. Leaky intestine and impaired microbiome in an amyotrophic lateral sclerosis mouse model. Physiol Rep. 2015;3(4).
172. Figueroa-Romero C, Guo K, Murdock BJ, Paez-Colasante X, Bassis CM, Mikhail KA, et al. Temporal evolution of the microbiome, immune system and epigenome with disease progression in ALS mice. Dis Model Mech. 2019;13(2).
173. Di Gioia D, Bozzi Cionci N, Baffoni L, Amoruso A, Pane M, Mogna L, et al. A prospective longitudinal study on the microbiota composition in amyotrophic lateral sclerosis. BMC Med. 2020;18(1):153.
174. Sun J, Zhan Y, Mariosa D, Larsson H, Almqvist C, Ingre C, et al. Antibiotics use and risk of amyotrophic lateral sclerosis in Sweden. Eur J Neurol. 2019;26(11):1355–61.
175. Blacher E, Bashiardes S, Shapiro H, Rothschild D, Mor U, Dori-Bachash M, et al. Potential roles of gut microbiome and metabolites in modulating ALS in mice. Nature. 2019;572(7770):474–80.
176. Fangmann D, Theismann EM, Türk K, Schulte DM, Relling I, Hartmann K, et al. Targeted microbiome intervention by microencapsulated delayed-release niacin beneficially affects insulin sensitivity in humans. Diabetes Care. 2018;41(3):398–405.
177. Zafar H, Saier MH Jr. Gut Bacteroides species in health and disease. Gut Microbes. 2021;13(1):1–20.
178. Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature. 2012;487(7408):477–81.