Pharmacological Insights into Statins' Role in Neurological Disorders

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Abstract

Statins, widely used as lipid-lowering agents, have been shown to exert multiple beneficial effects through mechanisms independent of cholesterol metabolism. These pleiotropic effects are attributed to the inhibition of isoprenoid intermediate synthesis within the mevalonate pathway, leading to the suppression of small GTP-binding protein signaling. Statins enhance endothelial nitric oxide synthase (eNOS) expression and nitric oxide (NO) bioavailability, while reducing reactive oxygen species (ROS) levels. They inhibit NADPH oxidase activity and expression, a primary source of superoxide generation in vascular tissues and the central nervous system. Statins also upregulate eNOS expression and activity, improve its enzymatic coupling, and increase NO bioavailability. Additionally, statins act as matrix metalloproteinase (MMP) inhibitors, reducing MMP production and activity, which is associated with various neurological disorders. Growing evidence suggests potential therapeutic applications for statins in stroke, Alzheimer's disease, Parkinson's disease,

multiple sclerosis, and primary brain tumors. However, the efficacy and safety of statins in these neurological conditions require further confirmation through randomized clinical trials. While statins are generally well-tolerated, potential adverse effects, such as myopathy and liver toxicity, should be monitored. The pleiotropic effects of statins highlight their promise as neuroprotective agents, warranting further research to elucidate their mechanisms of action and therapeutic potential in neurological disorders.

Keywords: Statins, Neurological Disorders

Introduction

Emerging evidence suggests that statins serve functions beyond their conventional role as lipid-lowering agents. A substantial number of experimental studies in recent years have demonstrated that these compounds exert multiple potentially beneficial effects through mechanisms unrelated to cholesterol metabolism. Many of these so-called pleiotropic effects are attributed to the inhibition of isoprenoid intermediate synthesis within the mevalonate pathway, such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). Consequently, these effects are independent of intracellular cholesterol biosynthesis, extending the therapeutic benefits of statins beyond their hypolipidemic activity. Isoprenoid intermediates function as critical lipid moieties for post-translational modifications of various proteins, including heterotrimeric G proteins and small GTP-binding proteins from the Ras, Rho, Rap, and Rab GTPase families. The process of isoprenylation plays a pivotal role in the intracellular trafficking and functionality of these small GTP-binding proteins. Specifically, FPP modification is essential for the appropriate localization of Ras family proteins, while GGPP modification is required for Rho, Rab, and Rap family proteins. Farnesylation and geranylgeranylation are necessary for the proper function and intracellular localization of some Rho GTPases. By inhibiting the isoprenylation of Ras and Rho, statins cause the cytoplasmic accumulation of their inactive forms, thereby suppressing their signaling activities.

Notably, small G-proteins such as Rho and Rac influence the expression of endothelial nitric oxide synthase (eNOS) and the bioavailability of nitric oxide (NO). Rho negatively regulates eNOS expression, while Rac contributes to the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and subsequent superoxide production, which inactivates NO. Statins inhibit geranylgeranylation, thereby suppressing Rho and Rac GTPase activity, resulting in the upregulation of eNOS. Intriguingly, studies have shown that some beneficial effects of statins, such as improved cardiovascular functions, occur earlier than reductions in cholesterol levels. These early effects, likely due to enhanced eNOS expression and activity, lead to reduced platelet activation, decreased adhesion molecule expression, diminished inflammatory cytokine production, and increased reactive oxygen species (ROS) levels. Cholesterol-independent effects of statins include reductions in platelet activation, attenuation of the pro-coagulation cascade, increased fibrinolysis and anticoagulant activity, improved endothelial function, increased NO bioavailability, and antioxidant, immune-modulatory, anti-inflammatory, and atherosclerotic plaque-stabilizing properties.

These findings suggest potential therapeutic applications for the pleiotropic effects of statins in neurological disorders. Supporting this hypothesis, growing clinical and experimental evidence indicates that statins, in addition to their well-documented cardioprotective properties, exhibit neuroprotective effects in various central nervous system (CNS) disorders. This study aims to review the primary mechanisms underlying the neuroprotective properties of statins, including their antioxidant effects, regulation of NO production, modulation of eNOS, and impact on matrix metalloproteinases (MMPs), which play a critical role in the immune-modulatory effects of statins in cerebral ischemic stroke and other neurological disorders.

Statins and ROS

Key cardiovascular risk factors such as hypercholesterolemia, diabetes mellitus, chronic smoking, metabolic syndrome, and hypertension are associated with excessive ROS production

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and neuronal tissue damage. ROS generation is regulated by several oxidase enzymes and mitochondrial electron transport mechanisms. Abnormal ROS production, along with reduced vascular bioavailability of NO, has been implicated as a common pathogenic mechanism in endothelial dysfunction, a condition associated with a wide range of cardiovascular diseases (CVDs). NO plays a crucial role in endothelial function through its regulation of endothelium-dependent vascular relaxation. However, the reaction between superoxide (produced by NADPH oxidase or xanthine oxidase) and NO results in the formation of peroxynitrite, a reactive nitrogen species that exacerbates ROS production and accelerates atherosclerosis by inducing structural damage.

Enhanced ROS production has been linked to early stages of atherosclerosis in animal models, including vascular cell dysfunction, intimal thickening, plaque formation, and destabilization. Consequently, ROS have been identified as contributors to the development of CVD, supporting the exploration of antioxidant treatments as therapeutic strategies. However, studies testing the effects of traditional antioxidants such as vitamin C, vitamin E, or folic acid (in combination with vitamin E) have yielded disappointing results, failing to improve cardiovascular outcomes in prospective trials. Before dismissing the potential of antioxidants, methodological limitations in these studies—such as trial design, treatment duration, target populations, outcome measures, and concomitant therapies—must be carefully addressed. This underscores the need for more rigorous clinical trials to provide a stronger basis for evaluating antioxidant therapies. Additionally, efforts to develop novel antioxidant compounds targeting oxidative stress through alternative mechanisms remain a promising area of research. While specific inhibitors of pro-oxidant enzymes are under investigation, their efficacy in improving cardiovascular outcomes has yet to be established.

Recent evidence suggests that certain phytonutrients, including flavanols, may exert vascular protective effects that are independent of their in vitro antioxidant properties. However, there is insufficient evidence to conclude that antioxidants alone can significantly impact cardiovascular diseases. Instead, substances such as statins, angiotensin-converting enzyme inhibitors, and AT1-receptor blockers—which exhibit indirect antioxidant effects by stimulating NO production and simultaneously inhibiting superoxide production (e.g., from NADPH oxidase)—have demonstrated efficacy in improving vascular function and reducing cardiovascular events in patients with CVD. Statins, in particular, are well-established for their roles in the primary and secondary prevention of CVD, attributed to both their lipid-lowering effects and pleiotropic properties.

Cell culture and animal studies have provided significant insights into the effects of statins on vascular redox homeostasis and NO bioavailability. For instance, atorvastatin has been shown to upregulate catalase expression in human endothelial cells without affecting superoxide dismutase (SOD) isoforms or glutathione peroxidase (GPx) expression. In vascular smooth muscle cells (VSMCs), simvastatin induces the expression of heme oxygenase, an important antioxidant defense enzyme, both in vitro and in vivo. Simvastatin administration has been reported to increase SOD and GPx expression in aortic rings from spontaneously hypertensive rats. In rabbits, pitavastatin has been found to enhance aortic tissue Cu/Zn SOD activity while reducing vascular O_2^- production.

These findings suggest that statins enhance vascular redox balance by improving antioxidant defenses at the cellular level, thereby facilitating ROS elimination. Statins have also been shown to prevent endothelial dysfunction by lowering LDL-cholesterol levels, which enhances NO-dependent vasodilation and reduces oxidative stress in the vessel wall. Furthermore, the pleiotropic effects of statins are known to directly mitigate oxidative stress within blood vessels. Although significant progress has been made in understanding the pleiotropic effects

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of statins through numerous cell culture, animal, and translational studies, the precise mechanisms underlying these effects remain incompletely understood.

Statins and NADPH Oxidase

Emerging evidence highlights NADPH oxidase as a primary source of superoxide generation in vascular tissues and the central nervous system (CNS). The inhibition of NADPH oxidase is recognized in numerous studies as a key mechanism underlying the pleiotropic effects of statins. Specifically, statins downregulate the activity and expression of NADPH oxidase isoforms, such as Nox1 and Nox2. Research on rat aortic vascular smooth muscle cells (VSMCs), conducted both in vitro and in vivo using spontaneously hypertensive rat models, demonstrated that atorvastatin reduced Nox1 mRNA expression and inhibited the translocation of Rac1 to the membrane, thereby suppressing $O2-$ production through a mechanism dependent on mevalonate. In mouse models subjected to angiotensin infusion or deficient in ApoE, chronic atorvastatin treatment reduced the expression of Nox1, Nox2, and Nox4 homologues in vascular tissues. Moreover, statins have been shown to inhibit the activity of NADPH oxidase in THP-1 monocytes, a cell type critical to the pathogenesis of atherosclerosis and vascular inflammation. Statins such as atorvastatin, simvastatin, rosuvastatin, and fluvastatin have all been demonstrated to inhibit NADPH oxidase activity. Additional research indicated that atorvastatin reduced ROS generation induced by homocysteine, which subsequently inhibited NADPH oxidase activation. This reduction was accompanied by a decrease in Nox4 mRNA levels, decreased expression of p-p38MAPK protein, and reduced apoptosis of endothelial progenitor cells (EPCs).

Statins and eNOS

In pathological conditions characterized by endothelial dysfunction associated with increased oxidative stress, endothelial nitric oxide synthase (eNOS) expression is often paradoxically elevated. The neuroprotective effects of statins are likely attributable to the upregulation of eNOS. Studies have shown that statins enhance both the expression and activity of eNOS, improve its enzymatic coupling, and increase nitric oxide (NO) bioavailability, thereby ameliorating endothelial function. In cell culture experiments, statins upregulate eNOS gene expression through the inhibition of Rho GTPase signaling. This effect is reversed by the addition of geranylgeranyl pyrophosphate (GGPP) and l-mevalonate, but not by farnesyl pyrophosphate (FPP) or low-density lipoprotein (LDL). Treatment with simvastatin or rosuvastatin in endothelial cells has been shown to increase eNOS transcripts with long poly(A) tails, conferring greater stability to eNOS mRNA via Rho inhibition. Phosphorylation of eNOS at serine/threonine residues is known to influence its enzymatic activity. Simvastatin has been observed to induce phosphorylation of eNOS at Ser633 in an AMP-activated protein kinase (AMPK)-dependent manner in endothelial cells. In animal models, statins activate AMPK signaling, leading to eNOS phosphorylation at Ser1177 in a l-mevalonate-dependent manner and enhancing acetylcholine-induced vasorelaxation. These findings suggest that statin-mediated eNOS phosphorylation at Ser1177 and Ser633 is a mechanism by which statins enhance eNOS activity and improve NO bioavailability. Furthermore, statins increase the vascular bioavailability of tetrahydrobiopterin (BH4), a critical cofactor for coupled electron transfer and NO production. By upregulating GTP cyclohydrolase I (GTPCH), the primary enzyme responsible for BH4 biosynthesis, statins regulate BH4 availability and maintain eNOS coupling in human atherosclerosis. Additionally, statins indirectly increase BH4 levels by reducing ROS generation from sources such as NADPH oxidase, thus preserving eNOS coupling.

Statins and MMPs

Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteolytic enzymes that play key roles in physiological and pathological processes. In humans, the MMP family consists of 23 members that are involved in central nervous system (CNS) development,

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normal adult function, and responses to injury. Typically, MMP levels are low but increase in response to transcriptional regulation. MMPs share similar structures and are categorized based on their chromosomal pre-synthetic regions and substrate specificity. Elevated MMP levels are associated with various diseases, including multiple sclerosis (MS), ischemic stroke, spinal cord injury, and neurodegenerative disorders. Statins have been identified as MMP inhibitors, as they reduce MMP production and activity. For instance, in a prototypical animal model of MS, experimental autoimmune encephalomyelitis (EAE), statins delayed disease onset, reversed symptoms, or prevented relapses in chronic EAE in rodents. Additionally, in vitro treatment of human peripheral blood mononuclear cells (PBMCs) from MS patients with lovastatin, simvastatin, and mevastatin reduced proliferation and decreased MMP-9 secretion. Following ischemic injury, MMP-9 can be released by neurons, oligodendroglia, reactive astrocytes, and activated microglia. Tissue plasminogen activator (tPA) is a common therapy for stroke but increases the risk of intracerebral hemorrhage, partly due to MMP-9 activation, which compromises the blood-brain barrier (BBB) and causes cerebral edema and hemorrhagic transformation (Inzitari et al., 2013). Studies have demonstrated that combining atorvastatin with tPA reduced hemorrhagic transformation and abolished tPA-induced MMP-9 upregulation in rats with embolic middle cerebral artery occlusion. Similarly, simvastatin mitigated tPA-induced MMP-9 dysregulation by inhibiting the Rho signaling pathway. Moreover, simvastatin demonstrated neuroprotection in vitro and in vivo by modulating MMP-9 and TNF-alpha levels, highlighting its anti-inflammatory properties through the modulation of N-methyl-d-aspartate (NMDA) receptors, which are implicated in Parkinson's disease (PD). In Alzheimer's disease (AD), MMP-9 levels are upregulated in brain tissue, where its induction in microglia and astrocytes by amyloid-beta (Aβ) may contribute to disease progression during chronic inflammation. Pravastatin inhibited MMP-9 activation in Aβ-stimulated glioma cells in vitro, suggesting a potential therapeutic target for statins in AD.

Statins and Main Neurological Diseases

Statins are well-established as first-line agents for preventing cardiovascular disease (CVD) and atherosclerotic complications associated with hypercholesterolemia. Increasing evidence indicates that, beyond their vascular benefits, including plaque stabilization and reduced carotid intimal-medial thickness, statins exhibit pleiotropic effects that are independent of their cholesterol-lowering action. Basic and experimental research has emphasized the critical role of inflammation in all stages of atherosclerosis. Statins are recognized for their endothelial-protective actions, including modulation of nitric oxide synthase, antioxidant properties, anti-inflammatory effects, and anti-platelet activities. These mechanisms suggest potential therapeutic applications for statins in various neurological disorders. Although a definitive link between neurodegenerative diseases, vascular risk factors, and atherosclerosis remains speculative, growing evidence supports this connection. This study highlights current understanding of statin effects in stroke, AD, PD, MS, and primary brain tumors, while also addressing potential adverse effects and limitations in their use.

Stroke

Cerebrovascular disease remains one of the primary causes of morbidity and mortality globally, imposing a significant burden on healthcare systems. While the associated risk factors are well-established and largely modifiable, controlling blood pressure and lowering serum cholesterol levels present considerable promise in reducing the risk of stroke. Statins are widely recognized for their ability to reduce cholesterol levels and prevent coronary heart disease (CHD). However, establishing a clear link between cholesterol and stroke has been challenging, with studies reporting conflicting outcomes. For instance, several epidemiological investigations, including the Framingham Study and the Honolulu Heart Study, did not find a significant

association between blood cholesterol levels and stroke risk. Consequently, a direct connection between hypercholesterolemia and stroke remains inconclusive. Notably, this lack of association was observed in populations where cholesterol levels strongly correlated with CHD.

In contrast, the Prospective Studies Collaboration, which analyzed 13,000 strokes across 450,000 individuals in 45 prospective cohorts, identified a positive association between blood pressure and stroke but not between cholesterol and stroke. Conversely, data from the Multiple Risk Factor Intervention Trial (MRFIT), which examined 350,000 men, suggested a correlation between elevated cholesterol levels and mortality due to ischemic stroke. Additional studies have suggested that statin use during hospitalization for acute first-ever ischemic stroke may improve clinical outcomes, particularly in non-minor stroke cases, by enhancing functional recovery and reducing mortality (Song et al., 2014). Current guidelines recommend statin therapy for secondary prevention following stroke or transient ischemic attacks to mitigate the risk of recurrent stroke or major cardiovascular events, though the potential risk of cerebral hemorrhage remains a topic of debate (Hong et al., 2013; Laloux, 2013; Makihara et al., 2013). Evidence from recent research suggests that statin therapy might improve outcomes following spontaneous intracerebral hemorrhage, and discontinuing statin therapy in such cases may not be advisable (Molina & Selim, 2013). Pre-treatment with statins has been associated with reduced stroke severity across high, moderate, and low doses. However, due to limited reliable evidence from clinical trials, no definitive conclusions can be drawn regarding the efficacy and safety of cholesterol reduction in aneurysmal subarachnoid hemorrhage (SAH) (Liu et al., 2013).

Several explanations may account for these discrepancies. First, stroke is not a uniform entity, as it can be either ischemic or hemorrhagic. Prospective studies have demonstrated that elevated cholesterol levels are associated with an increased risk of ischemic stroke, whereas low cholesterol levels have been linked to a higher risk of hemorrhagic stroke. Ischemic stroke itself comprises different subtypes, including large-vessel atherothrombotic, cardioembolic, and lacunar strokes, each with distinct pathophysiological mechanisms. Thus, a single risk factor or therapeutic intervention may not exert equivalent effects across these subtypes. Additionally, ischemic stroke is more prevalent in older populations compared to CHD. In a five-year trial evaluating simvastatin, one of the most effective statins, a significant reduction in myocardial infarction, coronary deaths, and stroke rates was observed. Simvastatin has also been shown to attenuate serum markers of brain injury, reduce vasospasm following SAH, and delay ischemic deficits in humans. The potential for reduced stroke rates due to statin therapy is considerable, given that hypercholesterolemia is a potent risk factor for precerebral atherosclerosis, which can lead to artery-to-artery embolic stroke.

Mechanisms of Action

The stabilization of atherosclerotic plaques has been proposed as a plausible explanation for the reduced incidence of clinical events in patients undergoing statin therapy. Two critical events in atherogenesis include lipid deposition and the migration and proliferation of vascular smooth muscle cells. Statins have demonstrated the ability to inhibit cholesterol accumulation and matrix metalloproteinases (MMPs) in macrophages in vitro, reduce macrophage foam cell formation and diminish carotid and peripheral arterial intimal lesions induced by vascular injury in animal models. They have also been shown to inhibit cholesterol accumulation in vascular smooth muscle cells. Statins have an impact on carotid intimal-medial thickness (IMT), a surrogate marker for early atherosclerotic cerebrovascular disease. Moreover, statins appear to influence platelet activity. For instance, a 30–40% reduction in LDL cholesterol following simvastatin therapy in hypercholesterolemic patients was associated with decreased platelet aggregation and thromboxane production. This anti-platelet effect is thought to result from reduced platelet membrane cholesterol content.

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There is substantial evidence to suggest that statins possess additional mechanisms of action that may influence brain injury prevention before (Radosevich et al., 2013), during, and after cerebral ischemia. These mechanisms include promoting nitric oxide production, exerting anti-inflammatory effects, providing antioxidant activity, and offering neuroprotection (Posada-Duque et al., 2013).

Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked pathologically by the presence of senile plaques in the brain, which are composed of aggregated β-amyloid. Emerging research suggests a potential link between cholesterol levels and AD. While serum cholesterol levels in individuals with AD do not significantly differ from those of age-matched controls, evidence indicates that cholesterol levels may be elevated before the onset of the disease and subsequently decline as the disease progresses. Elevated intracellular cholesterol levels may influence amyloid precursor protein processing, thereby promoting the production of β-amyloid (Aβ). Elevated cholesterol levels, alongside the presence of atherosclerosis, have also been associated with an increased risk of developing AD (Wood et al., 2014). In animal models, high dietary cholesterol intake has been linked to increased intra-neuronal β-amyloid accumulation and diffuse amyloid plaque formation, with regression observed when cholesterol is removed from the diet. The apoE4 allele of the apolipoprotein E gene, which is linked to elevated cholesterol levels, has also been associated with an increased risk of AD. Additionally, specific genotypes of lipoprotein receptor-related protein (LRP) may modulate this heightened risk of AD (Li et al., 2014).

Observational studies have suggested that cholesterol-lowering treatments with statins may offer therapeutic benefits for AD. Long-term statin use has been associated with reduced hospitalization rates among patients with dementia (Corrao et al., 2013). Simvastatin has been shown to lower plasma levels of apoE, while lovastatin appears to reduce the production of senile plaque components characteristic of AD. Several observational studies have demonstrated a 60–73% lower prevalence of probable AD in patients taking lovastatin or pravastatin, but not simvastatin, compared to those taking other cardiovascular medications. Another study reported a 71% relative reduction in the likelihood of receiving an AD diagnosis among statin users compared to controls. However, due to the retrospective case-control design of these studies, which is prone to selection and information biases, these findings should be interpreted with caution.

The role of inflammation in AD pathogenesis is also significant. Although the initial inflammatory response may offer protection, such as clearing modified low-density lipoproteins (LDL) or Aβ peptides, the failure to resolve the initial stimulus may lead to chronic inflammation, which significantly contributes to the disease's clinical manifestations. In AD, astrocytes and neurons secrete pro-inflammatory molecules and matrix proteins, which localize at sites such as senile plaques and are consistently upregulated at these sites. A novel mechanism of action proposed for atorvastatin involves activation of the heme oxygenase/biliverdin reductase (HO/BVR-A) system, which has neuroprotective effects, suggesting a therapeutic role in AD and potentially explaining the reduced incidence of AD among statin users (Barone et al., 2014).

It remains unclear why certain statins, such as lovastatin and pravastatin, may reduce AD risk while others, like simvastatin, do not. Furthermore, individuals diagnosed with probable AD may have concurrent or predominant vascular dementia, which could respond to the vascular effects of statins. The potential risks of statin use in AD must also be considered, as evidence suggests possible cognitive impairments linked to cholesterol-lowering therapies. A trial involving dietary cholesterol reduction reported negative effects on cognitive performance,

with greater cholesterol reductions associated with more significant impairment. Before recommending cholesterol-lowering treatments for AD, data from randomized clinical trials are needed to confirm the efficacy and rule out any adverse cognitive effects of statins (Swiger et al., 2013).

Parkinson's Disease (PD)

Statins have not been shown to exacerbate Parkinson's disease (PD) but may reduce the prevalence of complications such as wearing-off, dyskinesia, and dementia (Tison et al., 2013). The anti-inflammatory properties of statins are particularly relevant to PD, as inflammation is recognized as a contributing factor to its pathogenesis. Continued use of lipophilic statins has been associated with a lower incidence of PD compared to discontinuation. A recent study demonstrated that simvastatin reversed the loss of striatal dopamine activity and the production of nitrosylated free radicals while inducing neuroprotection. Simvastatin also prevented striatal dopamine depletion by suppressing the release of inflammatory mediators from microglia. These findings suggest that statins may have potential for the prevention and treatment of PD, but definitive conclusions regarding their efficacy should await further evidence from prospective and clinical studies.

Multiple Sclerosis (MS)

Recent animal studies have highlighted the immune-modulatory properties of statins, which may benefit the treatment of neuro-inflammatory disorders such as multiple sclerosis (MS). Statins are particularly appealing for MS therapy, given that currently approved immune-modulatory treatments, such as interferon-β, glatiramer acetate (GA), and mitoxantrone, are administered parenterally, exhibit limited efficacy, and are associated with side effects and toxicities. The immunological impact of statins was first observed in 1995, when cardiac transplant patients treated with pravastatin experienced fewer episodes of hemodynamically significant rejection and reduced mortality, independent of cholesterol reduction. Subsequent studies have confirmed the immune-regulatory and anti-inflammatory effects of statins.

Statins inhibit the expression of major histocompatibility complex (MHC) class II genes and the transcription of the MHC class II transactivator CIITA, a critical transcription factor for MHC II expression. They also exhibit other immune-modulatory effects, such as suppressing human natural killer cell activity, reducing leukocyte-endothelial adhesion, inhibiting CD40 and adhesion molecule expression, and blocking lymphocyte function-associated antigen-mediated co-stimulation. Additionally, simvastatin inhibits the secretion of Th17-polarizing cytokines and antigen presentation by dendritic cells (Zhang et al., 2013). Statins also reduce the release of pro-inflammatory cytokines from astrocytes, microglia, and macrophages in vitro. These effects suggest that the anti-inflammatory and immune-modulatory properties of statins could be exploited for treating inflammatory and immune-related neurological disorders like MS.

In experimental autoimmune encephalomyelitis (EAE), a model for human MS, lovastatin was shown to inhibit the expression of iNOS, TNF-α, and IFN-γ, prevent mononuclear cell infiltration into the CNS, and improve clinical symptoms, suggesting therapeutic potential for MS. Lovastatin also reduces brain endothelial cell Rho-mediated lymphocyte migration across the blood-brain barrier (BBB), mitigating the acute phase of EAE and preventing disease relapse. Similarly, atorvastatin prevents EAE development or reverses the disease while reducing histopathological changes. In a small open-label trial involving relapsing-remitting MS, simvastatin was administered at a high dose (80 mg daily) over six months. Brain MRI analyses showed approximately a 45% reduction in the mean number and volume of gadolinium-enhancing lesions. While these results are encouraging, larger placebo-controlled trials are necessary to confirm these findings.

Ongoing research is exploring the potential of combining statins with existing disease-modifying therapies. Combination therapies should ideally involve agents with distinct

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mechanisms of action and minimal overlapping toxicities, offering additive or synergistic effects. Current clinical trials are examining the combination of IFN-β1a with statins (Kamm et al., 2014). Despite the demonstrated anti-inflammatory and immune-modulatory effects of statins, caution is warranted due to the essential role of cholesterol in myelinogenesis, synaptogenesis, and axonal regeneration. Inhibition of cholesterol synthesis by statins could impede remyelination and neural repair in MS lesions.

Primary Brain Tumors

Statins show potential in the prevention of central nervous system (CNS) malignancies. Their anti-proliferative, anti-tumor, and pro-apoptotic effects have been demonstrated in various experimental systems. Malignant gliomas, the most common type of primary brain tumor, heavily rely on the mevalonate pathway for synthesizing lipid components essential for cell replication. Studies have shown that the addition of lovastatin to human glioblastoma cells can arrest malignant cell growth. Furthermore, combining simvastatin with cytotoxic chemotherapy has exhibited synergistic anti-tumor activity in animal models of neuroblastoma and glioma. Medulloblastoma and neuroblastoma cells also appear to depend on the HMG-CoA reductase pathway, with lovastatin demonstrated to inhibit their growth and induce apoptosis in vitro. However, the specific intermediary product of the HMG-CoA reductase pathway responsible for these effects on cellular proliferation remains unidentified. Evidence also indicates that atorvastatin may reduce the pro-tumorigenic effects of microglia on glioma migration and invasion by downregulating microglial membrane type 1 metalloproteinase (MT1-MMP) expression (Yongjun et al., 2013). Additionally, some studies propose that simvastatin's inhibition of autophagy enhances its anti-glioma effects. Preclinical studies on statins are uncovering new non-selective statin targets, providing a basis for developing targeted anticancer drugs. While preliminary findings suggest that statins may be promising for treating certain CNS malignancies, further research is required to substantiate these results.

Depression

The relationship between statin use and depression is complex, with research yielding mixed and controversial results. Some authors propose that statins may lead to depression by lowering cholesterol, given cholesterol's important role in the serotonin system. Conversely, other studies suggest that statin therapy may lower the risk of post-stroke depression (Kim et al., 2014).

Statins and Carotid Stenting

In cases of acute symptomatic carotid stenosis associated with transient ischemic attacks, pre-treatment with statins has been linked to a reduced risk of stroke, which aligns with findings from randomized trials on acute coronary syndromes. This protective effect may occur via pleiotropic plaque stabilization. Moreover, in patients undergoing carotid stenting, high-dose atorvastatin has been shown to protect against early ischemic cerebral events (Patti et al., 2013).

Potential Negative Effects of Statins

Although numerous experimental studies highlight the beneficial effects of statins, some findings necessitate caution, particularly when these drugs are used in combination with other agents. Statins' inhibition of cholesterol synthesis has been found to induce apoptosis in several models, including neuronal and glial cells in culture. This effect may result from the inhibition of the isoprenoid pathway, which blocks the isoprenylation of proteins involved in regulating cell proliferation and survival. Systemic adverse effects of statins are rare but well-documented, including myopathy and liver toxicity. Statins are metabolized via the cytochrome P450 pathway and may occasionally cause hepatotoxicity in less than 3% of patients, usually manifesting as a reversible increase in transaminase levels. For this reason, monitoring liver function tests is recommended during therapy. Myopathy occurs in fewer than 0.2% of patients

receiving statins. In severe cases (less than 0.05%), skeletal muscle injury can lead to rhabdomyolysis with myoglobinuria, potentially resulting in kidney failure. In 2001, cerivastatin (Lipobay) was voluntarily withdrawn from the U.S. market due to the high rate of fatal rhabdomyolysis associated with its use. Rhabdomyolysis is more likely to occur when statins are combined with other lipid-lowering drugs, such as fibrates, or with compounds also metabolized via the cytochrome P450 pathway. Myopathy typically resolves following the cessation of therapy. Another infrequent side effect is polyneuropathy. A study assessing the relative risk of polyneuropathy among statin users reported an incidence rate of 0.73 per 10,000 person-years, which is slightly higher than the rates observed in the untreated hyperlipidemia cohort (0.40 per 10,000 person-years) and the general population cohort (0.46 per 10,000 person-years).

Conclusion

Statins have revolutionized the management of cardiovascular diseases, primarily due to their lipid-lowering effects. However, the emerging understanding of their pleiotropic properties has extended their potential therapeutic applications beyond cholesterol reduction. Through mechanisms such as antioxidant activity, regulation of nitric oxide bioavailability, inhibition of NADPH oxidase, and immune modulation, statins exhibit profound effects on vascular and neuronal health. These properties make them promising candidates for addressing a variety of conditions, including cerebrovascular diseases, neurodegenerative disorders like Alzheimer's and Parkinson's diseases, and neuroinflammatory diseases such as multiple sclerosis.

While the pharmacological benefits of statins in these conditions are compelling, their application in non-cardiovascular contexts must be approached cautiously. The potential risks, including cognitive effects and the inhibition of critical pathways like cholesterol synthesis essential for neural repair, warrant further investigation. Randomized controlled trials are needed to validate the efficacy and safety of statins in these diverse therapeutic areas. Overall, the pharmacology of statins represents an exciting frontier, offering novel insights and therapeutic avenues in both cardiovascular and neurological health.

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