

# The Therapeutic Potential of Statins in Neurological Disorders

G.K. Rajanikant, D. Zemke, M. Kassab and A. Majid\*

*Department of Neurology and Ophthalmology, Michigan State University, East Lansing, Michigan 48824, USA*

**Abstract:** Statins are currently among the most commonly prescribed agents for the prevention of cardiovascular disease. Statins reduce serum cholesterol levels by reversibly inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme in cholesterol biosynthesis, in the nanomolar range. Mounting evidence suggests that in addition to their vascular effects such as stabilization of atherosclerotic plaques and decreased carotid intimal-medial thickness, statins have additional properties such as endothelial protection via actions on the nitric oxide synthase system as well as antioxidant, anti-inflammatory and anti-platelet effects. These effects of statins might have potential therapeutic implications in various neurological disorders such as stroke, Alzheimer's disease, Parkinson's disease, multiple sclerosis and primary brain tumors. In this review, the major protective mechanisms of statins and their applicability to the treatment of neurological disease are summarized. Although further experiments are required, currently available data would seem to indicate that clinical trials to determine the safety and efficacy of statins in a number of disorders are warranted.

**Keywords:** Statin, cholesterol, inflammation, nitric oxide synthase, stroke, alzheimer's disease, parkinson's disease, multiple sclerosis.

## INTRODUCTION

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) inhibitors, are front-line therapeutic agents for the prevention of cardiovascular disease (CVD) and atherosclerotic disorders related to hypercholesterolemia [1-4]. According to statistics from the U.S. Federal Agency for Healthcare Research and Quality (AHRQ), the proportion of the Medicare population using statins more than doubled between 1997 (12 %) and 2002 (27 %) [5]. Currently, six statins with U.S. Food and Drug Association (FDA) approval are available for lowering cholesterol: rosuvastatin (Crestor), atorvastatin (Lipitor), simvastatin (Zocor, Lipex), pravastatin (Pravachol, Selektine, Lipostat), fluvastatin (Lescol) and lovastatin (Mevacor, Altacor). Statins are administered orally, are well tolerated and have a good overall safety profile to date [6,7].

Statins exert additional pleiotropic activities that are independent of their cholesterol-lowering effect, and hence the benefits of statins may extend beyond their hypolipidemic activity [8-10]. Cholesterol-independent effects of statins include but are not limited to the reduction of hemostasis by reducing platelet activation and the pro-coagulation cascade, increasing fibrinolysis and the anti-coagulation cascade, improvement of endothelial function, enhanced nitric oxide (NO) bioavailability, antioxidant, immunomodulatory and anti-inflammatory activities and stabilization of atherosclerotic plaques [6,8,10]. These findings have led to the speculation that the cholesterol-independent properties of statins may have potential therapeutic implications in various neurological disorders. To support this hypothesis, mounting clinical and experimental evidence suggests that statins, in addition to

their potent cardioprotective effects, are neuroprotective in various disorders of the central nervous system (CNS) [11-14].

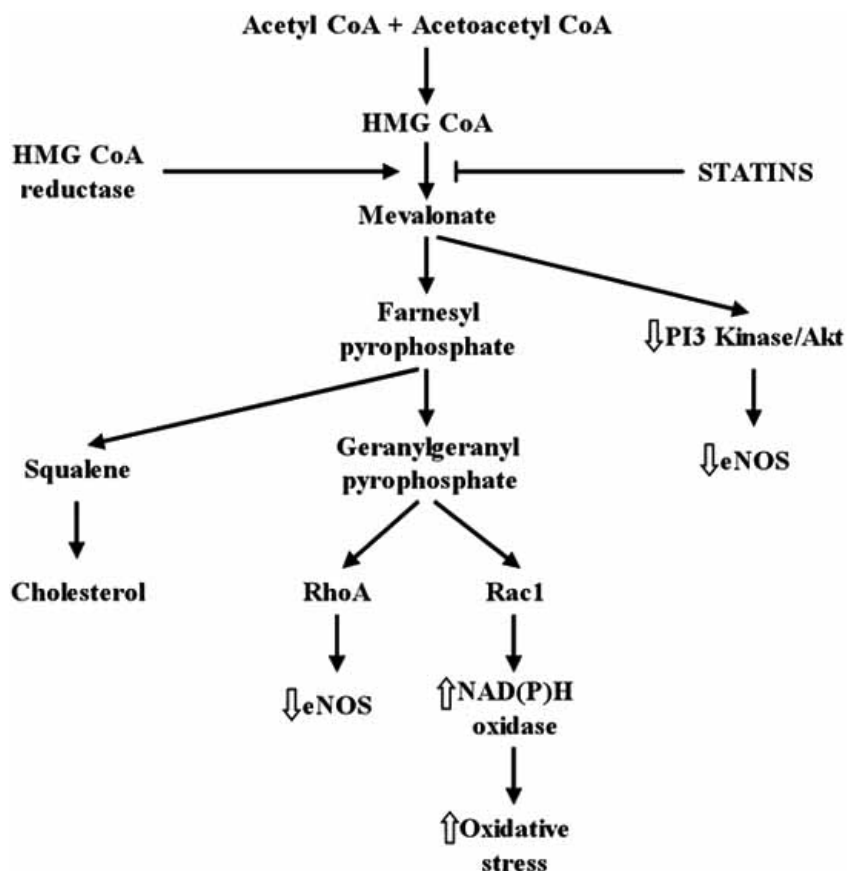
## 1. CHEMICAL, PHARMACOLOGICAL AND PHARMACOKINETIC PROPERTIES OF STATINS

### 1.1. Physico-Chemical Properties

All statins share an HMG-like moiety [15] and inhibit HMGR (the rate-limiting enzyme in cholesterol biosynthesis) at nanomolar range in a competitive, dose-dependent, and reversible fashion (Fig. 1). The chemical structures of the different statins are shown in (Fig. 2). Lovastatin, pravastatin, and simvastatin contain a substituted decalin ring structure. Fluvastatin, atorvastatin, and rosuvastatin are fully synthetic HMGR inhibitors with larger fluorophenyl groups linked to the HMG-like moiety. The bulky hydrophobic group of statins that is covalently linked to the HMG-like moiety occupies the HMG-binding pocket and part of the binding surface for CoA, thus sterically preventing substrate (HMG-CoA) from binding to the enzyme [15]. The substrate-binding pocket of the enzyme also undergoes a rearrangement that enables the rigid, hydrophobic ring structures of the statins to be accommodated. The tight binding is probably due to the large number of van der Waals interactions between the statin and enzyme [15].

The side groups on the rings define the solubility, pharmacological and pharmacokinetic properties of statins and contribute to actions that are independent of HMGR inhibition (i.e., rho kinase inhibition, antioxidant action, and nitric oxide synthase expression). Atorvastatin, fluvastatin, lovastatin and simvastatin are relatively lipophilic compounds, whereas pravastatin and rosuvastatin are more hydrophilic as a result of polar hydroxyl and methane sulphonamide groups [16,17]. The differences in

\*Address correspondence to this author at the Department of Neurology and Ophthalmology, Michigan State University, 138 Service Road, Suite A-217, East Lansing, MI 48824 USA; Tel: +1-517-432-9277; Fax: +1-517-432-9414; E-mail: arshad.majid@ht.msu.edu



**Fig. (1).** Mevalonate pathway for cholesterol biosynthesis. Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, thereby reducing serum cholesterol level.

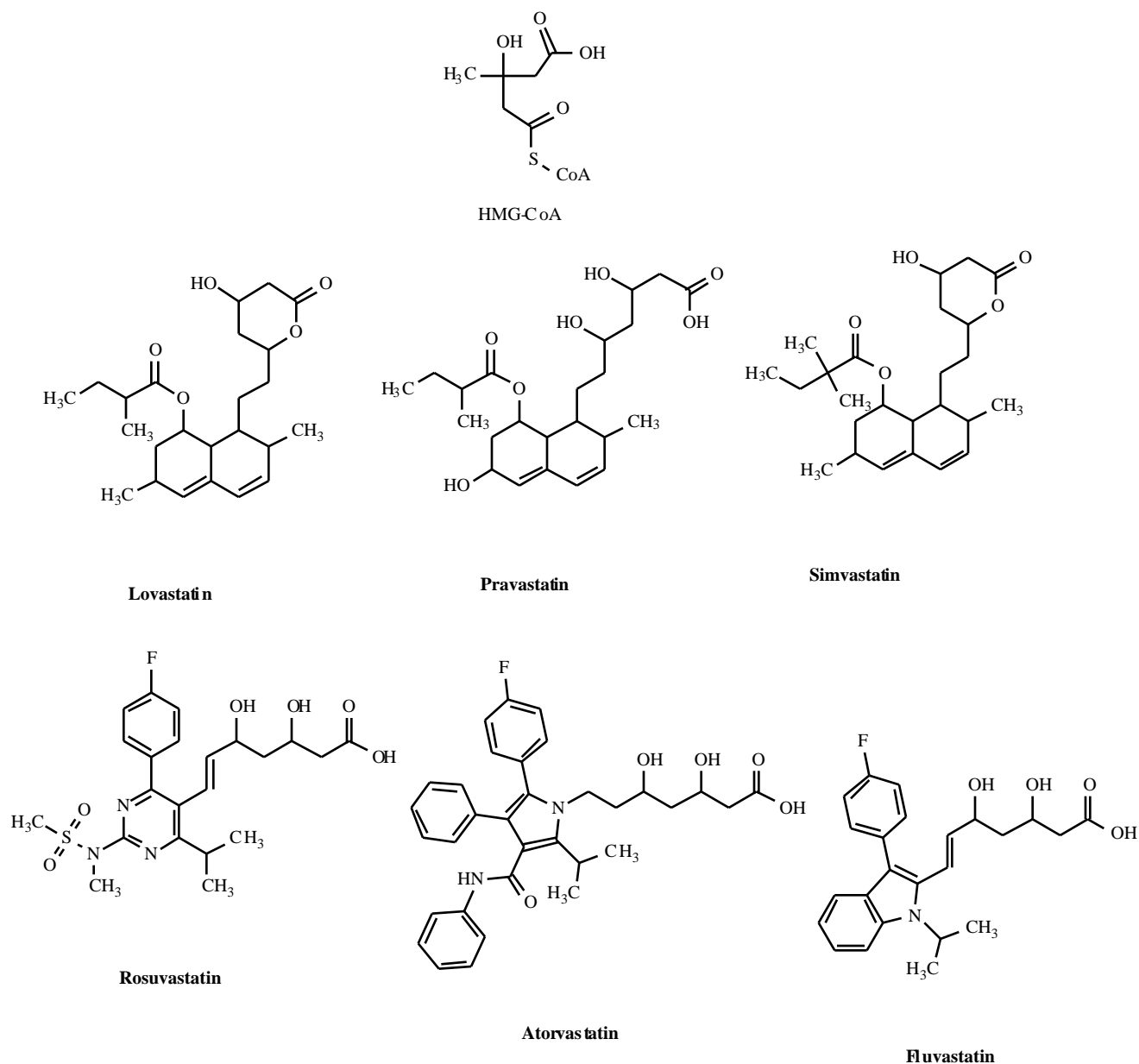
lipophilicity are reflected in the potential of statins to cross cellular membranes non-selectively by passive diffusion, and explain why pravastatin does not easily cross cellular membranes whereas lovastatin and simvastatin do [18]. For example, pravastatin has a polar hydroxyl group that contributes to its greater hydrophilicity and therefore requires an active transport system to enter cells [19]. In contrast, atorvastatin consists of a pyrrole ring covalently linked to multiple aromatic structures that contributes to its high lipophilicity and facilitates hydrophobic interactions with phospholipid acyl chains of various target cellular membranes. Fluvastatin was characterized as a high permeability drug despite its relatively high hydrogen bond number. It was therefore suggested that this molecule, due to its amphiphilic character, might form intra-molecular hydrogen bonds, thereby increasing its apparent lipophilicity and cell membrane permeability [20]. However, fluvastatin, like pravastatin, does not cross the blood-brain barrier to any significant extent in contrast to the more lipophilic lactone compounds, lovastatin and simvastatin [21].

## 1.2. Pharmacology and Pharmacokinetics of Statins

Lovastatin, simvastatin and pravastatin are fungal-derived statins and have elimination half-lives of 1–3 h, whereas fluvastatin, atorvastatin and rosuvastatin are synthetic HMGR inhibitors with elimination half-lives ranging from 1 h for fluvastatin to 19 h for rosuvastatin [22,23]. With the

exception of lovastatin and simvastatin (which are administered as lactone prodrugs and must be hydrolyzed *in vivo* to the corresponding -hydroxy acid to achieve pharmacologic activity) [24], all statins are administered as the active -hydroxy acid form. Although all statins share a common pharmacological target essential to sterol biosynthesis, they differ in terms of their pharmacokinetic profile, and exhibit variable dose-related lipid-modifying efficacy (Table 1) [25–29]. The statins have an affinity for the enzyme HMG-CoA [30]. The rank order of potency of statins for HMGR inhibition is simvastatin > pravastatin > lovastatin > mevastatin [31]. The  $IC_{50}$  values for these statins correspond to their relative potency for lowering serum cholesterol levels *in vivo* (i.e., simvastatin > lovastatin) [32].

Food intake has a variable effect on statin absorption; lovastatin is more effectively absorbed when taken along with food [33], whereas the bioavailability of atorvastatin, fluvastatin and pravastatin is decreased [34–36]. With the exception of pravastatin, all statins are extensively bound to plasma proteins (Table 1), and as a result systemic exposure to unbound, pharmacologically active drug is relatively low [37]. All statins are relatively hepatoselective with respect to inhibition of HMGR, an important property given that the majority of endogenous cholesterol production takes place in the liver. The mechanisms contributing to this



**Fig. (2).** Chemical structures of HMG-CoA and marketed statins for lowering cholesterol.

hepatoselective effect are governed by the solubility profile of the statin. For lipophilic statins, passive diffusion through hepatocyte cell membranes is primarily responsible for efficient first-pass uptake, while for hydrophilic statins extensive carrier-mediated uptake is the major mechanism [38,39]. Statins are predominantly metabolized by the cytochrome P450 (CYP450) family of enzymes, composed of over 30 isoenzymes [40]. The predominant route of elimination for the majority of statins is via the bile after metabolism by the liver [41].

## 2. EFFECT OF STATINS ON STROKE OUTCOME

Although a fundamental relationship between hypercholesterolemia and stroke has not been well defined [42-47], evidence suggests that cholesterol-lowering medications (i.e. statins) reduce the incidence of cerebrovascular events

[26,48,49]. In a 5-year study of treatment with simvastatin, the most effective of the currently known statins, the rate of myocardial infarction and coronary death was significantly reduced [50]. In addition, a significant reduction was also observed in the rate of stroke. Further study confirmed the reduction of stroke rate with simvastatin, even in patients with normal cholesterol levels [51]. Cerebral vasospasm remains a major source of morbidity after aneurysmal subarachnoid hemorrhage (SAH) and recently simvastatin has been demonstrated to reduce serum markers of brain injury, attenuate vasospasm after SAH and delay ischemic deficit in humans [52]. It has been found in a phase II randomized controlled trial that acute treatment with pravastatin after aneurysmal SAH is safe and ameliorates cerebral vasospasm, improves cerebral autoregulation, and reduces vasospasm-related delayed ischemic deficits [53]. Detailed review articles on clinical and preclinical studies of

**Table 1. Comparative Efficacy and Pharmacokinetic Properties for Various Statins<sup>a</sup>**

Drug	Percent cholesterol reduction	Doses (mg)	t <sub>1/2</sub> (h) <sup>b</sup>	IC <sub>50</sub> (nM) <sup>c</sup>	C <sub>max</sub> (ng/mL) <sup>e</sup>	Percent bioavailability	Protein binding (%)	CYP450 metabolism and isoenzyme
Atorvastatin	25–45	10, 20, 40, 80	13–30	0.8	27–66	12	80–90	3A4
Fluvastatin	16–27	20, 40, 80	0.5–3	4.8	448	19–29	>98	2C9
Lovastatin	16–34	10, 20, 40	2–4	NA <sup>d</sup>	10–20	5	>95	3A4
Pravastatin	16–25	10, 20, 40, 80	2–3	5	45–55	18	43–55	NA
Rosuvastatin	33–46	5, 10, 20, 40	19	0.3	37	20	90	Limited
Simvastatin	19–36	5, 10, 20, 40, 80	1–3	5.2	10–34	5	95–98	3A4

<sup>a</sup>See references [16,17, 23]; <sup>b</sup>t<sub>1/2</sub> = half-life; <sup>c</sup>IC<sub>50</sub> = concentration producing 50% inhibition in rat hepatocytes; <sup>d</sup>NA = not available; <sup>e</sup>C<sub>max</sub> = maximum concentration.

statins in stroke prevention can be found elsewhere [26,44,48,54–56].

The possibility of reduced stroke rate as a consequence of statin therapy is strong since hypercholesterolemia is a potent risk factor for precerebral atherosclerosis and thus artery-to-artery embolic stroke. Statins also improve the endothelial dysfunction that accompanies hypercholesterolemia and may reduce the incidence of hemorrhagic stroke [57]. Statin treatment may also ameliorate cerebral vasospasm resulting from subarachnoid hemorrhage [53,58]. Further, statin therapy reduces the incidence of coronary events in patients with previous history of stroke [59]. Recently, atorvastatin has been shown to significantly reduce the risk of secondary stroke or cardiovascular events over a 5 year period after an initial stroke or transient ischemic attack [60]. This evidence suggests that statins may be beneficial in prophylactic therapy for stroke.

### 2.1. Statins and Endothelial Function

Hypercholesterolemia and oxidative stress (superoxide anion) impair endothelial function, and an important characteristic of endothelial dysfunction is the impaired synthesis, release and activity of endothelial-derived NO [61]. Endothelial NO mediates vascular relaxation [62] and inhibits platelet aggregation [63], vascular smooth muscle proliferation [64] and endothelial-leukocyte interactions [65]. However, statins preserve endothelial nitric oxide synthase (eNOS) activity in cerebral vasculature and augment NO bioavailability via several cholesterol-dependent and -independent mechanisms [66–69]. The expression of eNOS is negatively regulated by oxidized low density lipoprotein (LDL) [66], and hence reducing cholesterol by statins indirectly increases eNOS expression. Cholesterol-independent mechanisms include the direct upregulation of eNOS by statins via inhibiting geranylgeranyl pyrophosphate synthesis and increasing the inactive cytosolic state of the small GTPase Rho (Fig. 1) [67]. In addition, statins directly activate eNOS via the protein kinase Akt (Fig. 1), thereby improving endothelium-dependent vasodilation, which is the earliest clinically recognizable effect of statins [70,71].

Another potential mechanism by which statins may improve endothelial function is through their antioxidant effect [26,72]. There are two prominent sources of superoxide radicals within vascular cells, activation of

NAD(P)H-oxidase and activation of angiotensin AT1 receptor by angiotensin II. Statins confer protection to endothelial cells against superoxide radical damage by attenuating angiotensin II-induced free radical production, inhibiting Rac1 (small GTP binding protein) mediated NAD(P)H oxidase activity (Fig. 1) and downregulating angiotensin AT1 receptor expression [73,74].

### 2.2. Statins and Inflammation

Inflammation is the hallmark of atherosclerosis and an initiating pathway in acute ischemic damage to the brain. Mounting evidence suggests that statins possess anti-inflammatory properties owing to their ability to attenuate leukocyte adhesion and inhibit the induction of various inflammatory mediators such as C-reactive protein, intercellular adhesion molecule-1, interleukin-6, iNOS and P-selectin [75–79]. Thus, statin therapy may represent a novel means of attenuating inflammatory responses that occur during ischemia and reperfusion.

### 2.3. Statins and Platelet Function

Circulating platelets are associated with thrombus formation at the site of atherosclerosis (atherothrombosis) and play an important role during brain infarction. Hypercholesterolemia correlates with an increase in platelet activity [80]. Statins have been shown to influence platelet function and thrombus formation, which at least in part might be mediated by eNOS and the platelet inhibitory effects of NO [81]. Potential additional mechanisms include regulation of fibrinolytic balance by upregulating tissue plasminogen activator (tPA) and inhibiting plasminogen activator inhibitor, reduction in the production of thromboxane A2 and modification of the cholesterol content of platelet membranes [82–84]. Both lovastatin and fluvastatin have been shown to reduce platelet aggregation via two distinct mechanisms: indirectly by lowering platelet cholesterol content, and directly via a primary inhibitory effect on platelet function [85].

### 2.4. Statins and Excitotoxicity

Excitotoxicity mediated by overstimulation of glutamate receptors is a well-documented cause of neuronal death after an ischemic brain insult [86,87]. Reducing neuronal

membrane cholesterol could have profound effects on NMDA receptor-mediated excitotoxicity and ischemic neurodegeneration because they are mediated, in part, by a tri-partite protein complex [88] that resides in sterol-rich neuronal membrane microdomains known as lipid rafts [89]. Furthermore, treatment with statins alters the function of lipid raft-associated protein complexes in cultured neurons [90]. These observations lead to the hypothesis that reducing neuronal cholesterol by inhibiting brain HMGR protects neurons from NMDA receptor-mediated excitotoxicity. To test this hypothesis, Zacco *et al.* [91] conducted experiments to explore whether statins protect cultured neurons from excitotoxic death caused by the glutamate receptor agonist NMDA. Results suggest that statins render cortical neurons more resistant to NMDA-induced excitotoxic death as a result of changes in cell cholesterol homeostasis, a potential neuroprotective action of statins distinct from their beneficial effects on cerebrovascular function.

### 2.5. Statins and Progenitor Cells

Circulating endothelial progenitor cells (EPCs) contribute to ischemia-induced neovascularization [92,93]. Statins have been found to modulate stem cell regulation and increase the number of circulating EPCs via activation of PI3 kinase/Akt and eNOS [70,94-96]. Hence, statins may promote both angio- and vasculogenesis in the postischemic brain by inducing the proliferation, migration, and survival of circulating EPCs. In addition, proliferation of neuronal progenitor cells in the brain by statins may contribute to neurogenesis and synaptogenesis after stroke [97].

### 3. ALZHEIMER'S DISEASE (AD)

Alzheimer's disease is a chronic neurodegenerative disorder characterized pathologically by the appearance of brain senile plaques composed of aggregated forms of  $\beta$ -amyloid (A $\beta$ ) [98]. Experimental, clinical and epidemiologic studies suggest that hypercholesterolemia is involved in the development of AD [99-101]. Elevated intracellular cholesterol levels might affect the processing of amyloid precursor protein, promoting the production of A $\beta$ . Several observations demonstrate that lowering cholesterol with statins may have potential therapeutic benefit in AD [102]. Experimental studies have revealed that lowering cholesterol levels with statins decreases the production of A $\beta$  [90,103-105].

Moreover, the putative anti-inflammatory and antioxidant properties of statins may confer additional neuroprotection since oxidative stress and inflammation are two common pathological events closely associated with the onset of disease [106]. Retrospective clinical studies indicate that individuals chronically treated with statins are at lower risk of developing Alzheimer's disease [14,107]. Consistent with these results, several observational and epidemiological studies suggest that statin treatment lowers the incidence of AD [108-111]. Pilot proof-of-concept trials support the hypothesis that excess brain cholesterol promotes A $\beta$  production and that statin therapy may be an effective treatment to delay the progression of AD among mild-to-moderately affected patients [14,112].

However, a substantial number of clinical studies have found no association between statin use and subsequent onset of dementia or AD [113-121]. Another experimental study revealed that statin treatment enhanced A $\beta$  production and senile plaque deposition in the brains of female mice [122]. AD patients may be extra-susceptible to the anti-proliferative and proapoptotic effects of the statins due to preexisting aberrations in signal transduction and perturbed cholesterol and energy metabolism in the brain [123]. Therefore, conducting clinical studies with extended treatment periods to evaluate the effect of statin treatment on cognitive and AD biomarker outcomes should be a high priority [124-126]. The pleiotropic effects of statins should be investigated further in order to elucidate the connection between Alzheimer's disease and statin treatment. Further, it would be beneficial to test essentially two different types of statins (hydrophilic and lipophilic) to compare the effects on the cognitive decline in AD.

### 4. PARKINSON'S DISEASE (PD)

An inevitable consequence of statin therapy is reduced levels of coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) [127,128]. CoQ<sub>10</sub>, a key component of the mitochondrial electron transport chain (ETC) not only serves as the electron acceptor for complexes I and II of the ETC but is also an antioxidant. Levels of CoQ<sub>10</sub> have been reported to be decreased in blood and platelet mitochondria from PD patients [129]. As CoQ<sub>10</sub> may play a role in PD [130-131], it is possible that statins may also have detrimental effects. However, it has been demonstrated that statins do not worsen PD, at least as assessed by stage and the prevalence of wearing-off, dyskinesia, and dementia [132]. The anti-inflammatory potential of the statins may be extended to the treatment of PD since inflammation is accepted as a contributor to the etiology of PD. In support of this notion, a recent study has demonstrated that simvastatin was able to completely reverse the loss of striatal dopamine activity and that this effect paralleled a reduction of TNF- $\alpha$  levels in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease [133]. Furthermore, the production of nitrosylated free radicals, an effect thought to contribute directly to neuronal cell death, was also reversed by simvastatin. Simvastatin prevented striatal dopamine depletion by decreasing the release of inflammatory mediators from microglia. While statins have appeal for the prevention or treatment of PD, any conclusions about their efficacy should await more definitive evidence from prospective preclinical and clinical studies.

### 5. STATINS, IMMUNOMODULATION AND MULTIPLE SCLEROSIS (MS)

Statins inhibit expression of the major histocompatibility complex (MHC) class II gene and transcription of the MHC class II transactivator CIITA, a transcription factor essential for the expression of MHC II genes [134,135], providing for the first time a scientific rationale for advocating statins as immunomodulators. Lately, additional immunomodulatory effects of statins, such as inhibition of human natural killer cell activity [136],

reduction of leukocyte endothelial adhesion [137], inhibition of CD40 and adhesion molecule expression [138,139] and blockage of lymphocyte function-associated antigen-1 mediated co-stimulation [140] have been reported. Further, statins have been demonstrated to inhibit lipopolysaccharide and cytokine-mediated expression of iNOS and the release of proinflammatory cytokines in astrocytes, microglia, and macrophages *in vitro* [77]. These findings have led to the speculation that the putative anti-inflammatory and immunomodulatory properties of statins might be exploited for the treatment of inflammatory and immune-related neurological disorders such as multiple sclerosis [141-144].

Multiple sclerosis is a multiphasic, auto-immune and inflammatory demyelinating disease of the CNS, hallmarked by multiple demyelinated lesions throughout the brain and spinal cord. Activation of microglia, the resident macrophages of the CNS, is also thought to be a key element in the development of the disease [145-147]. Administration of lovastatin inhibited the expression of iNOS, TNF- and IFN- in the brains of rats with experimental allergic encephalomyelitis (EAE), a model for human MS [142]. Lovastatin improved the clinical signs of EAE, suggesting that it may have therapeutic potential in the treatment of neuroinflammatory diseases like MS [142]. Lovastatin treatment also prevented infiltration by mononuclear cells into the CNS and induction of inflammatory cytokines and iNOS in the spinal cords of EAE rats, thereby improving clinical signs of the disease [148]. Further, a novel effect of lovastatin in modulating the immune response has been demonstrated in the relapsing-remitting EAE disease model in mice, where it inhibited brain endothelial cell Rho-mediated lymphocyte migration across the blood-brain barrier, attenuated the acute phase of EAE and prevented the onset of disease relapse [149].

In preclinical studies, atorvastatin prevented the development of EAE or reversed the process, as well as reduced the histopathological changes [143,144]. In these experiments, statin treatment reduced CNS infiltration by Th1 lymphocytes, reduced MHC class II expression, inhibited the activity of CD40, CD80, CD86 and secretion of TNF, interferon-, interleukin-12, and even induced the production of anti-inflammatory cytokines tumor growth factor- $\beta$  (TGF- $\beta$ ) and IL-10. In addition, statin treatment of either antigen-presenting cells or T lymphocytes from EAE-susceptible mice suppressed antigen-specific T-cell activation. These findings were largely confirmed in another recent report [150]. Simvastatin is currently being tested in a small open-label trial in relapsing-remitting MS [151].

These studies demonstrate the anti-inflammatory and immunomodulatory effects of statins in improving the disease condition and may provide an additional rationale for their use in the treatment of chronic MS. Nevertheless, caution is recommended since cholesterol is essential for myelinogenesis [152], synaptogenesis [153] and axonal regeneration [154], and inhibition of cholesterol synthesis by statins could impede remyelination and neural repair in the MS lesion. Statins differ in their pharmacodynamic characteristics [29] and also in their immunomodulatory potency [140,150]. Moreover, individual immunologic profile, lipophilicity of candidate statin, accumulation in the normal and affected areas of brain, short elimination half-life

and side effects at high steady state levels could be relevant for the therapeutic efficacy of statins in chronic neuroinflammatory disorders. These issues need to be addressed in order to draw any conclusion about their efficacy in treating MS.

## 6. PRIMARY BRAIN TUMORS

Statins have an established record of human safety and efficacy in the prevention of cardiovascular disease and show promise for the prevention of CNS malignancies. The antiproliferative, anti-tumor and apoptotic effects of statins have been observed in several experimental systems [155-157]. In one study, addition of lovastatin to human glioblastoma cells arrested malignant cell growth by decreasing the synthesis of intermediary products of cholesterol biosynthesis required for tumor growth [155]. Combining simvastatin with cytotoxic chemotherapy resulted in synergistic anti-tumor activity in animal models of neuroblastoma and glioma [158,159]. The pleiotropic effects of statins are related to their interactions with diverse signaling pathways and targets [8]. Medulloblastoma and neuroblastoma cells appear to be highly dependent on the HMG-CoA reductase pathway, and lovastatin has been shown to inhibit growth and promote apoptosis of these cells *in vitro* [160,161]. The specific intermediate products of the HMGR pathway responsible for cellular proliferation and tumorigenic processes are unknown [160]. Preclinical studies on statins are identifying new non-selective statin targets that provide a basis for the development of new targeted anticancer drugs [155-157,162]. Nevertheless, preliminary data suggest that treatment of some CNS malignancies with statins holds promise, and further research into this area appears warranted.

## 7. POTENTIAL ADVERSE EFFECTS OF STATINS

The safety and tolerability of pharmaceutical agents is perhaps the most important consideration in their clinical use. Although rare, numerous adverse effects of statin treatment have been reported and commonly affect the muscle, liver, kidney, and nervous system [163]. Adverse effects on muscle include myalgia, myopathy (defined as elevated creatine kinase levels), and rhabdomyolysis. In addition, the development of myasthenia gravis has been reported in isolated cases after treatment with a number of statins [164]. Cerivastatin appears to present a greater risk for adverse muscle effects at marketed doses than the other statins, and was withdrawn from use in 2001 after several fatalities due to rhabdomyolysis [165]. Fluvastatin, on the other hand, appears to have the least myotoxicity [166]. Increased risk of adverse muscle effects of statins is associated with higher doses and combined treatment of statins with various drugs such as bile acid sequestrants, fibrates, niacin, gemfibrozil, and ezetimibe [163]. The mechanism by which statins lead to myotoxicity is not completely understood. Adverse effects of statins on other tissues are quite rare. The primary effect of statins in hepatic tissue is an elevation in liver enzymes, and the majority of cases appear to be associated with drug interactions or other complicating factors [163]. In addition to rhabdomyolysis,

the renal effects of statins include proteinuria and hematuria. Reported effects of statins on the nervous system are controversial. A decrease in cognition and memory has been associated with statin treatment in some studies, whereas others have shown no link. Similarly, statins have alternately been shown to worsen or improve both dementia and Alzheimer disease in different studies. Inhibition of cholesterol synthesis by statins has been shown to induce apoptosis in neuronal and glial cell lines, and it has been suggested that this effect may partially be due to inhibition of the isoprenoid pathway and the isoprenylation of proteins involved in regulating cell proliferation and survival [167]. In rare instances, statin treatment has also been reported to have adverse effects on other systems. Pravastatin and simvastatin have been linked to lichenoid drug eruptions in isolated cases [168,169]. Lovastatin and simvastatin have been reported to cause lupus-like syndromes [170,171]. Overall, however, the incidence of adverse effects due to statin treatment is very low and the benefits are considered to significantly outweigh the risks.

## CONCLUSIONS

In addition to their potent anti-atherosclerotic and cardioprotective effects, compelling clinical and preclinical studies delineate the neuroprotective efficacy of statins in various neurological disorders. It is apparent from these studies that most patients with CNS disorders probably benefit to some extent from lipid-lowering therapy. However, in the coming years ongoing experimental and clinical trials should be able to indisputably determine if statin therapy should be recommended for neurological disorders. If these promising cholesterol-independent neuroprotective effects of statins are proven to be clinically effective, this class of drugs will find wide-ranging utility in the management of a variety of neurological disorders in patients with or without hypercholesterolemia.

## LIST OF ABBREVIATIONS

Abeta	=	-amyloid
AD	=	Alzheimer's disease
AHRQ	=	Agency for Healthcare Research and Quality
AT	=	Angiotensin
CIITA	=	Class II, major histocompatibility complex, transactivator
C <sub>max</sub>	=	Maximum concentration
CNS	=	Central nervous system
CoA	=	Coenzyme A
CoQ <sub>10</sub>	=	Coenzyme Q <sub>10</sub>
CVD	=	Cardiovascular disease
CYP450	=	Cytochrome P450
EAE	=	Experimental allergic encephalomyelitis
eNOS	=	Endothelial NO synthase

EPCs	=	Endothelial progenitor cells
ETC	=	Electron transport chain
FDA	=	Food and Drug Association
HMGR	=	3-hydroxy-3-methylglutaryl coenzyme A reductase
IC <sub>50</sub>	=	Inhibition constant
iNOS	=	Inducible NO synthase
LDL	=	Low-density lipoprotein
MHC	=	Major histocompatibility complex
MPTP	=	1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine
MS	=	Multiple sclerosis
NA	=	Not available
NADP(H)	=	Nicotinamide adenine dinucleotide phosphate
NMDA	=	N-methyl-D-aspartic acid
NO	=	Nitric oxide
NOS	=	Nitric oxide synthase
PD	=	Parkinson's disease
PI3 kinase	=	Phosphoinositide-3-kinase
Rac1	=	Rho family of GTPases
RhoA	=	Ras homolog gene family, member A
SAH	=	Subarachnoid hemorrhage
T <sub>1/2</sub>	=	Half-life
TNF-	=	Tumor necrosis factor alpha
tPA	=	Tissue plasminogen activator

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