ISSN 0974-3618 (Print)
0974-360X (Online)

www.rjptonline.org

REVIEW ARTICLE

Neuroprotective Properties of Statins

Sree Lekshmi. R. S[1], P. Shanmugasundaram[2]*

[1]School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies [VISTAS], Chennai, India.

[2] Director, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies [VISTAS], Vels University, Chennai, India.

*Corresponding Author E-mail: **samsimahe@gmail.com**

ABSTRACT:

The risk of ischemic stroke between patients with increased risk of vascular disease is decreased by treatment with statins. Neuroprotective properties of statins in acute cerebral ischemia is pointed out in current experimental abstracts. There is an established fact in between bioavailability of nitric oxide and the activity of statins and ischemic stroke. Statins have been contemplated in the therapy of a number of the central nervous system disorders, including cerebral ischemia, Alzheimer's disease, Parkinson's disease, tumors, and trauma on account of their capability to up-regulate nitric oxide synthase. It has been asserted that they restrain inflammatory response and secondary injury after acute ischemia.

KEYWORDS: Statins, neuroprotection, Alzheimer's disease, multiple sclerosis, Parkinsons Disease.

INTRODUCTION:

Statins are having a promising ability to accommodate a new therapeutic goal for multitudinal neurological disorders at present. It is well full-fledged that statins decrease levels of cholesterol and anticipate CHD. In addition to that, attestations proposed that in addition to antioxidant, anti-inflammatory and anti-platelet effects, statins have supplementary possessions suchlike endothelial protection through action on the nitric oxide synthase system. Not only in stroke but also these possessions might have potential therapeutic association in neurological disorders such as Alzheimer disease, Parkinson's disease, multiple sclerosis and primary brain tumors. The inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and thus the restriction of the enzyme in the biosynthesis of cholesterol is the principal mechanism of action of statins. That results in the growth in a number and activity of LDL receptors, and decrease in this cholesterol fraction in the plasma as a consequence [1]

Received on 19.04.2018 Modified on 12.05.2018
Accepted on 19.06.2018
Research J. Pharm. and Tech 2018; 11(8): 3581-3584.
DOI: 10.5958/0974-360X.2018.00659.5

Statins also precisely regulate endothelial nitric oxide synthase expression, autonomous of cholesterol levels, exclusively from cholesterol-dependent mechanisms of action. [2, 3].

2. STATINS AND STROKE:

By modulation of pre-cerebral atherothrombosis in the carotid artery and the aorta and therefore anticipating artery-to artery thromboembolism and plaque division by restricting coagulation at its various levels, degenerating tissue factor, innovation of prothrombin to thrombin activity etc statins through an array of mechanisms can decrease strokes of various etiology. [4].

Vaughan et al. [5] in experimental models of ischemic stroke have shown that size of brain infarct is reduced by statin therapy and by direct up-regulation of brain endothelial NO synthase, the ameliorate neurologic effect is decresed. Additional to that he showed the anti-inflammatory actions of statins that probably will contribute to neuroprotection and stroke prevention.

The Pravastatin Lipids and Atherosclerosis in the Carotids II (PLACII) study also established a cognent decline in carotid intimal-medial thickness in pravastatin-treated patients. The impact of statin treatment on aortic atherosclerosis has not been broadly

analysed [5]. Decrease in stroke incidence by statins like pravastatin, simvastatin [6] and lovastatin were also accustomed in short-term clinical studies [7].

In the experiment conducted by The Large Prospective Studies Collaboration Group, there was no correlation between cholesterol and stroke. However, they did not categorize between ischemic and hemorrhagic stroke [8]. Cucchiara et al. [8] have shown that the opposing effects of cholesterol on ischemic versus hemorrhagic stroke risk may confuse efforts to compare cholesterol levels with stroke except stroke type (i.e. hemorrhagic *vs*. ischemic) is taken into account.

In the Cholesterol and Recurrent Events (CARE) Trial, the pravastatin group had a 31% lower incidenceof all strokes, even though again the incidence of lethal strokes was about the same. Summarizing, there was no increase in the rate of hemorrhagic stroke [9].

On Comparisons of statins, Laufs et al. [10] have showed the results that eshtablish that rosuvastatin is at least as effective as simvastatin and atorvastatin and provided better protection than lovastatin and mevastatin in the mouse middle cerebral artery (MCA) stroke model.

2.2 STATINS AND AZD:

In 2013, as many as 5 million Americans were living with Alzheimer's disease [11]. By 2050, this number is calculated to reach to 14 million, a almost three-fold increase [11]. Increased levels of β-amyloid and apolipoprotein E have been found to be affliated with AD [12-14]. Inclusion to that, atherosclerosis and elevated levels of plasma total cholesterol or triglyceride and low-density lipoprotein cholesterol (LDL-C) exasperated the symptoms of AD.

According to a current study, Alzheimer's is evoked by a lower intake in omega-3 fatty acids, found in fish [15]. The study farther explicated that cholesterol esters are a common pool for fatty acids in plasma. Inpoint of fact, it is found that there are considerably lower numbers of fatty acids, phospholipids and esterified cholesterol in the CSF of accustomed Alzheimer's subjects [16].

Dr. Seneff also asserted that lower levels of fatty acids are found in the CSF in patients with Alzheimer's. In point of fact, it was bring into being that about Alzheimer's patients have less that 20% of the concentration of fatty acids in CSF compared to non-Alzheimer's patients [17]. Taling into account that statins can additionally reduce this number by lowering the carry capacity of fats by cholesterol, it should be made alert that statins can possibly pose a threat to provoking Alzheimer's rather than preventing it.

Follow-up studies in humans have currently suggested that patients getting statin therapy have a reduced incidence of dementia. Cholesterol lowering with statins may have potential therapeutic benefit in AD. Simvastatin has been shown to decrease plasma levels of apoE in patients with senile AD, though cerebrospinal fluid levels of apoE were not significantly replaced[18,19].

2.3 STATINS AND PARKINSONS DISEASE:

Many studies have shown that statins can decrease the incidence of PD, although cholesterol level may be associated with a higher incidence of this illness. Some clinical studies have reported that statin use is irrelevant to the progression of PD and dementia [20-22].

In a meta-analysis of observational studies, statin use significantly reduced the risk of PD by 23% [21]

One study showed the statins can reduce the elevation of the levodopa equivalent daily dose over 2 years in PD patients, which suggested that statin use may be involved in the onset and development of PD [23].

A 12-year follow-up of 644 incident PD cases found that regular use of statins was associated with a modest decrease in PD risk [24].

Koob found that lovastatin could reduce alpha-synuclein aggregation, the neuropathologic hallmark of PD, in a transgenic model [25].

2.4 STATINS AND MULTIPLE SCLEROSIS:

In a review done, eight trials were included [26] five of statin add-on to interferon (IFN)-β treatment in RRMS, one of statin monotherapy in CIS, one of statin monotherapy in optic neuritis (ON)/CIS, and one of statin monotherapy in secondary progressive MS (SPMS)]. Three trials with eligible characteristics had not been published in peer-reviewed journals and were therefore excluded. In CIS and SPMS due to the less number of trials, meta-analysis of primary outcomes was only performed for RRMS studies. Meta-analysis showed no significant effect of statin add-on to IFNβ therapy. Actually, a trend towards a rise in disease activity was exhibited in the statin group with commendations to new T2 lesions, relative amount of patients with relapse, and whole brain atrophy but not for EDSS progression.

An open label clinical trial of simvastatin and atorvastatin for SM disclosed a significant diminishing in the number and volume of new MRI lesions and a agreeable safety profile [27].

In vitro studies with human peripheral blood lymphocytes disclosed that the anti-inflammatory effects of simvastatin, lovastatin, and mevastatin are strong and eivalent with those of interferon -1b. Some proinflammatory effects caused by heavy secretion of interferon and interleukin 12 were also noticed. The blending of statins and interferon -1b had hooking anti-inflammatory effects [28, 29].

In addition, statins abridge T-cell proliferation, under expression of activation surface markers and induce production of the cytokine IL-4. At present, simvastatin is being tested in a phase II clinical trial in SM [30].

2.5 STATINS AND VASCULAR DEMENTIA:

Statins can have neuroprotective effects in patients with vascular dementia (VaD) [31]; these effects have been well recorded, the mechanisms of which may be connected with modulation of nitric oxide (NO).

Nitric oxide can anticipate the advancement of VaD by harmonising the cerebral blood flow. Lower NO levels can lead to cognitive drop in serum of VaD patients [32], whereas statins can increase NO generation [33].

Different mechanisms have been contemplated to annotate the protective role of statins in eNOS [34,35].

In an Sprague Dawley (SD) rat model of transient middle cerebral artery occlusion (tMCAO), rosuvastatin inhibited the upregulation of glycoprotein 91 (phox) and p22phox, the phosphorylation of nuclear factor-kappa B, and the induction of cyclooxygenase 2 and inducible nitric oxide synthase [36].

Hypercholesterolemia and atherosclerosis can actuate eNOS dysfunction and decrease the expression of eNOS and NO [37], when it fact, statins can prevent cognitive impairment by their anti-atherosclerotic effects [38]. Statins can also prevent the advncement of vascular-related cognitive impairment by an antiplatelet mechanism [39]. Treatment with statins can decrease the incidence of VaD [40].

The confederation between blood pressure and dementia appears to be complex. The impairment of cognitive function has been associated with both high and low blood pressure levels in older subjects [41].

Age-related changes in both blood pressure level and cognitive function, as well as vascular brain damage and systemic arterial aging, may have a confusing role. Hypertension is an freewheeling risk factor for mild cognitive impairment [42].

A previous systematic review showed that antihypertensive medication could decrease the risk of vascular dementia, by a mechanism that may be associated with reducing the risk of stroke through improved blood pressure control [43]. One study found that higher ambulatory pulse pressure is associated with poor cognitive outcomes [44].

3. CONCLUSION:

This review has confabulated current experimental attestations suggesting that some mechanisms of action of statins can protect from ischemic stroke. To survey the initial observations suggesting the neuroprotective properties of statins, additional investigation using neuroimaging studies and serial cognitive evaluation studies are authorised. Statins may show distinctive neuroprotective effects in neurodegenerative diseases,when taken together.

4. ABBREVIATIONS:

CHD : Coronary Heart Disease
LDL : Low Density Lipoproteins
AZD : Alzheimer's Disease
CSF : Cerebro Spinal Fluid

5. REFERENCE:

1. Yoshida M: Potential role of statins in inflammation and atherosclerosis. J Atheroscler Thromb, 2003, 10, 140–144.
2. Hernandez-Perera O, Perez-Sala D, Navarro-Antolin J, Sanchez-Pascuala R, Hernandez G, Diaz C, Lamas S: Effects of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, atorvastatin and simvastatin, on the expression of endothelin-1 and endothelial nitric oxide synthase in vascular endothelial cells. J Clin Invest, 1998, 101, 2711–2719.
3. Laufs U, Liao JK: Post-transcriptional regulation of endothelial nitric oxide synthase mRNA stability by Rho GTPase. J Biol Chem,1998, 273, 24266–24271.
4. Okopieñ B, Krysiak R, Madej A, Belowski D, Zieliñski M, Kowalski J, Herman ZS: Effect of simvastatin and fluvastatin on plasma fibrinogen levels in patients with primary hypercholesterolemia. Pol J Pharmacol, 2004, 56, 781–787.
5. Vaughan CJ: Prevention of stroke and dementia with statins. Effects beyond lipid lowering. Am J Cardiol, 2003, 91, Suppl, 23B–29B.
6. Heeschen C, Hamm CW, Laufs U, Snapinn S, Bohm M, White HD: Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Investigators: withdrawal of statins increases event rates in patients with acute coronary syndromes. Circulation, 2002, 105, 1446–1452.
7. Di Napoli P, Taccardi AA, Oliver M, De Caterina R: Statins and stroke: evidence for cholesterol-independent effects. Eur Heart J, 2002, 23**,** 1908–1921.
8. Cucchiara B, Kasner SE: Use of statins in CNS disorders. J Neurol Sci, 2001,187, 81–89.
9. Plehn JF, Davis BR, Sacks FM, Rouleau JL, Pfeffer MA, Berstein V, Cuddy TE et al.: Reduction of stroke incidence after myocardial infarction with pravastatin. The cholesterol and recurrent event (CARE) study. Circulation, 1999, 99, 216–223.
10. Laufs U, Gertz K, Dirnagl U, Bohm M, Nickenig G, Endres M: Rosuvastatin, a new HMG-CoA reductase inhibitor,upregulates endothelial nitric oxide synthase and protects from ischemic stroke in mice. Brain Res, 2002, 942, 23–30.
11. Hebert LE, Weuve J, Scherr PA and Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology 2013; 80: 1778-1783.
12. Wood H. Alzheimer disease: Scanning ultrasound elicits amyloid-beta clearance in mice. Nat Rev Neurol 2015; 11: 247.

13. Wang L, Benzinger TL, Hassenstab J, Blazey T, Owen C, Liu J, Fagan AM, Morris JC and Ances BM. Spatially distinct atrophy is linked to beta-amyloid and tau in preclinical Alzheimer disease. Neurology 2015; 84: 1254-1260.
14. Nordberg A. Dementia in 2014. Towards early diagnosis in Alzheimer disease. Nat Rev Neurol 2015; 11: 69-70.
15. Cunnane, S.C., Schneider, J.A., Tangney, C., Tremblay-Mercier, J., Fortier, M., Bennett, D.A. and Morris, M.C. (2012) Plasma and Brain Fatty Acid Profiles in Mild Cognitive Impairment and Alzheimer's Disease. *Journal of Alzheimer's Disease*, **29**, 691-697.
16. Mulder, M., Ravid, R., Swaab, D.F., de Kloet, E.R., Haasdijk, E.D., Julk, J., van der Boom, J.J. and Havekes, L.M. (1998) Reduced Levels of Cholesterol, Phospholipids, and Fatty Acids in Cerebrospinal Fluid of Alzheimer Disease Patients Are Not Related to Apolipoprotein E4. *Alzheimer Disease and Associated Disorders*, **12**, 198-203.
17. Seneff, S. (2009) APOE-4: The Clue to Why Low Fat Diet and Statins May Cause Alzheimer's. http://people.csail.mit.edu/seneff/alzheimers_statins.html
18. Mitchel YB, Kramer MS, Matzura-Wolfe DM, Strittmatter W, Peskind E, Ferris S: The effect of simvastatin on cerebrospinal fluid levels of apolipoprotein E in patients with Alzheimer's disease. Abstract: Atherosclerosis, 1995, 115**,** Suppl, S113.
19. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary artery disease. The Scandinavian Simvastatin Survival Study (4S). Lancet, 1994, 344, 1383–1389
20. Huang X, Alonso A, Guo X, Umbach DM, Lichtenstein ML, Ballantyne CM, Mailman RB, Mosley TH and Chen H. Statins, plasma cholesterol, and risk of Parkinson's disease: a prospective study. Mov Disord 2015; 30: 552-559.
21. Undela K, Gudala K, Malla S and Bansal D. Statin use and risk of Parkinson's disease: a meta-analysis of observational studies. J Neurol 2013; 260: 158-165.
22. Tison F, Negre-Pages L, Meissner WG, Dupouy S, Li Q, Thiolat ML, Thiollier T, Galitzky M, Ory-Magne F, Milhet A, Marquine L, Spampinato U, Rascol O and Bezard E. Simvastatin decreases levodopa-induced dyskinesia in monkeys, but not in a randomized, placebo-controlled, multiple cross-over ("n-of-1") exploratory trial of simvastatin against levodopa-induced dyskinesia in Parkinson's disease patients. Parkin-sonism Relat Disord 2013; 19: 416-421.
23. Mutez E, Duhamel A, Defebvre L, Bordet R, Destee A and Kreisler A. Lipid-lowering drugs are associated with delayed onset and slower course of Parkinson's disease. Pharmacol Res 2009; 60: 41-45.
24. Gao X, Simon KC, Schwarzschild MA and Ascherio A. Prospective study of statin use and risk of Parkinson disease. Arch Neurol 2012; 69: 380-384
25. Koob AO, Ubhi K, Paulsson JF, Kelly J, Rock-enstein E, Mante M, Adame A and Masliah E. Lovastatin ameliorates alpha-synuclein accumulation and oxidation in transgenic mouse models of alpha-synucleinopathies. Exp Neurol 2010; 221: 267-274.
26. Pihl-Jensen, G., Tsakiri, A. & Frederiksen, J.L. CNS Drugs (2015) 29: 277. https://doi.org/10.1007/s40263-015-0239-x
27. Neuhaus O, Stüve O, Zamvil SS, Hartung HP**:** Are statins a treatment option for multiple sclerosis? Lancet Neurol, 2004, 3**,** 369–371.
28. Aktas O, Waiczies S, Smorodchenko A, Dorr J, Seeger B, Prozorovski T, Sallach S et al.: Treatment of relapsing paralysis in experimental encephalomyelitis by targeting Th1 cells through atorvastatin. J Exp Med, 2003, 197**,** 725–733.
29. Youssef S, Stüve O, Patarroyo JC, Ruiz PJ, Radosevich JL, Hur EM, Bravo M et al.: The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. Nature, 2002, 420, 78–84.
30. Neuhaus O, Archelos JJ, Hartung HP: Immunomodulation in multiple sclerosis: from immunosupression to neuroprotection. Trends Pharmacol Sci, 2003, 23, 131–138.
31. Sakurai H and Hanyu H. [Lipid abnormality]. Nihon Rinsho 2014; 72: 697-701.
32. Corzo L, Zas R, Rodriguez S, Fernandez-Novoa L and Cacabelos R. Decreased levels of serum nitric oxide in different forms of dementia. Neurosci Lett 2007; 420: 263-267.
33. Tong XK and Hamel E. Simvastatin restored vascular reactivity, endothelial function and reduced string vessel pathology in a mouse model of cerebrovascular disease. J Cereb Blood Flow Metab 2015; 35: 512-520.
34. Giannopoulos S, Katsanos AH, Tsivgoulis G and Marshall RS. Statins and cerebral hemodynamics. J Cereb Blood Flow Metab 2012; 32: 1973-1976.
35. Nakata S, Tsutsui M, Shimokawa H, Yamashita T, Tanimoto A, Tasaki H, Ozumi K, Sabanai K, Morishita T, Suda O, Hirano H, Sasaguri Y, Nakashima Y and Yanagihara N. Statin treatment upregulates vascular neuronal nitric oxide synthase through Akt/NF-kappaB pathway. Arterioscler Thromb Vasc Biol 2007; 27: 92-98.
36. Ma M, Uekawa K, Hasegawa Y, Nakagawa T, Katayama T, Sueta D, Toyama K, Kataoka K, Koibuchi N, Kuratsu J and Kim-Mitsuyama S. Pretreatment with rosuvastatin protects aga-inst focal cerebral ischemia/reperfusion injury in rats through attenuation of oxidative stress and inflammation. Brain Res 2013; 1519: 87-94
37. Heeba G, Moselhy ME, Hassan M, Khalifa M, Gryglewski R and Malinski T. Anti-atherogenic effect of statins: role of nitric oxide, peroxynitrite and haem oxygenase-1. Br J Pharmacol 2009; 156: 1256-1266.
38. Fukuda K, Matsumura T, Senokuchi T, Ishii N, Kinoshita H, Yamada S, Murakami S, Nakao S, Motoshima H, Kondo T, Kukidome D, Kawasaki S, Kawada T, Nishikawa T and Araki E. Statins meditate anti-atherosclerotic action in smooth muscle cells by peroxisome proliferator-activated receptor-gamma activation. Biochem Biophys Res Commun 2015; 457: 23-30.
39. Suribhatla S, Dennis MS and Potter JF. A study of statin use in the prevention of cognitive impairment of vascular origin in the UK. J Neurol Sci 2005; 229-230: 147-150.
40. Giannopoulos S, Katsanos AH, Kosmidou M and Tsivgoulis G. Statins and vascular dementia: a review. J Alzheimers Dis 2014; 42 Suppl 3: S315-320.
41. Viscogliosi G. [Disentangling the differential contribution of hypertension and aging on dementia risk]. Recenti Prog Med 2015; 106: 92-96.
42. Zou Y, Zhu Q, Deng Y, Duan J, Pan L, Tu Q, Dai R, Zhang X, Chu LW and Lu Y. Vascular risk factors and mild cognitive impairment in the elderly population in Southwest China. Am J Alzheimers Dis Other Demen 2014; 29: 242-247.
43. Rouch L, Cestac P, Hanon O, Cool C, Helmer C, Bouhanick B, Chamontin B, Dartigues JF, Vellas B and Andrieu S. Antihypertensive drugs, prevention of cognitive decline and dementia: a systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms. CNS Drugs 2015; 29: 113-130.
44. Riba-Llena I, Nafria C, Filomena J, Tovar JL, Vinyoles E, Mundet X, Jarca CI, Vilar-Bergua A, Montaner J and Delgado P. High daytime and nighttime ambulatory pulse pressure predict poor cognitive function and mild cognitive impairment in hypertensive individuals. J Cereb Blood Flow Metab 2016; 36: 253-63.