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Review Article

CURRENT APPROACH FOR THE TREATMENT OF PARKINSON'S DISEASE BY SIMVASTATIN: A REVIEW

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ABSTRACT

Parkinson disease has become one of the common life-threatening health problem in the world. But the pathogenesis and related mechanisms are still unclear. Current therapy of Parkinson's disease (PD) is not satisfactory, which is the use of combinations of levodopa with other dopaminergic agonist but it is symptomatic in nature and does not slow down the disease course. Many studies have revealed that statins which are used as an antihyperlipidemic drug and have the ability to protect the dopaminergic cells from neurodegeneration. They have anti-inflammatory, suppression of oxidative stress, anticoagulation, angiogenesis actions. So in this review, we are trying to find out the actions of statins on Parkinson disease.

Keywords: Parkinson disease, neuro-inflammation, inflammatory cytokines, Statins, Glial cell

INTRODUCTION

Parkinson disease is a neurodegenerative disease leading to motor deficits mainly in the form of tremor, rigidity and akinesia and gait impairment. Adult-onset Parkinson disease, Young-onset Parkinson's disease and Juvenile Parkinson's disease are some of the different types of PD. Substantia nigra (SN) and pars compacta are the two important regions involved in the PD. Substantia nigra plays a key role in the movement and reward located in the mid brain. The SN is a Latin word which means "Black substance" pointing the fact that it is having high levels of neuromelanin in dopaminergic neurons which is responsible for the black color compared to the neighboring cells. Pars compacta is a part of SN situated in the midbrain. These areas will be affected by the loss of dopaminergic neurons as well as the presence of the Lewy body proteins. During the normal aging process, some amount of dopaminergic neurons would be lost from our brain, but this rate will increase in Parkinson patients. Also, these patients will be having alpha synuclein proteinaceous inclusions either in the form of Lewy bodies or Lewy neuritis in their remaining dopaminergic neurons that indicate the presence of Parkinson disease. Ubiquitin- proteasome system (UPS) plays a major role in the Parkinson disease. The inability of the UPS to clear the excess or misfolded protein from the brain, mutation in the components of UPS such as parkin and ubiquitin c are some reasons for PD. Interaction of Environmental toxins and alpha-synuclein can inhibit the UPS from its action of protein clearance. The major disease mechanisms include Dysfunction of the UPS, Oxidative stress response abnormalities, Defects in mitochondrial functions, Glial cell activation.[1] Even though now it is identified as alpha- synuclein has a key role in the disease progression and useful for the therapeutic targets. None of the current therapeutic protocols for PD have proved to obtain a convincing effect on the motor symptoms, but progressing investigations of new therapeutic strategies are performed to stop or to slow the development rate of the disease. Several dopaminergic drugs are able to reduce the loss of dopaminergic neurons but they are unable to suppress the disease progression in Parkinson patients. Statins,[2] 3- Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors coming under the class of lipid-lowering drugs used for the treatment of dyslipidemia. Several studies have shown that Statins has a clear effect on dementia, cognition and progressive Parkinson disease.[3] Other than cholesterol-lowering action it has been found that Statins have neuroprotection, immunomodulation, and anti-inflammation. This review mainly focuses on the therapeutic actions of Statins that would be helpful for the treatment of PD.

PARKINSON'S DISEASE PATHOGENESIS[4-6]

Parkinson's disease is related to the corresponding death of different types of neurons. The Substantia nigra and Pars compacta located in the mesencephalon or midbrain will be affected by the loss of dopaminergic neurons, as a result, the amount of dopamine will get reduced in the putamen and corpus striatum. Followed by the reduction of dopamine level, neuronal cell death happens in the Substantia nigra that is responsible for the motor symptoms.

Lewy bodies are the proteins that will aggregates inside the nerve cells during PD. Lewy bodies and Lewy neuritis both are made up of proteins and they are not only having neuroprotective action in diseases like multiple systemic atrophy, Alzheimer's[7] etc. but also having neurodegenerative

action by the aggregation of Lewy bodies in the substantia nigra located in the midbrain. Underlying mechanisms[8] involved in the PD is still unclear. Several disease mechanisms include mitochondrial defects, misfolding of proteins, cell death, mutated inflammatory cytokines[9] consists of TNF alpha (Tumor necrosis factor), IL-1 alpha (Interleukin), IL- 1 beta, activated microglia and excitotoxicity.

Glial cell activation

Glial cells positioned all through the brain and spinal cord which is responsible for the immune competent actions. Glial cells are the cells having performance in controlling the brain for infections caused by pathogens as well as immune insults.[4] The microglial activation is because of winding up the inhibitory action exerted by the neurons on the microglial cells. CD200 is a cell surface transmembrane glycoprotein secreted by the neurons can bind to the microglia expressing receptor CD200R present on the microglial cells, this binding maintains the glial cells in a deactivated state in healthy brains. During the time of immune insults the expression of CD200 got down-regulated as a result they fail to bind on the CD200R, the receptor present on the microglial cells that in turn activate the microglia.

Activated microglia has shown many protective characters in the brain. In developing brain they engulf excessively produced neurons and cell debris. They are able to protect the brain structures and functions via remodeling from resting ramified shape to activated amoeboid shape. Activated microglia can secrete many immune- modulatory molecules include chemokine, cytokines, neutrophins, reactive oxygen species and nitric oxide species are able to exchange the signals to the nearby cells. Cytokines have many actions on brain cells including the effect on astrocytes and oligodendrocytes, the release of neurotransmitters, growth hormones. Chemokines are the chemoattractants, they will attract more microglia to the place of injury. The reactive oxygen species and nitric oxide species produced by the microglia are able to kill the nearby pathogens at the same time these free radicals are able to destroy the surrounding neurons and resulting neuronal cell death. So activated microglia is one of the reasons for neurodegenerative diseases.

Defective mitochondrial functions[3]

Many studies have shown that the main reason for the mitochondrial degeneration is the loss of Parkin and PINK1 (PTEN- induced putative kinase 1). Mitochondrial dysfunction will lead to the dopamine neuron cell death and reduced dopamine level is responsible for the PD.

Neuroinflammation

The production of inflammatory cytokines like TNF- alpha (Tumor necrosis factor), IL 1(Interleukin), IL-6 from lipid polysaccharide (LPS) induced PD patients will be less as compared to the healthy patients, and it is inversely proportional to the disease progression. However, some other cytokines like TNF alpha and some interleukins are seemed to be increased in postmortem substantia nigra.[1]

Reactive molecular species and oxidative stress[9]

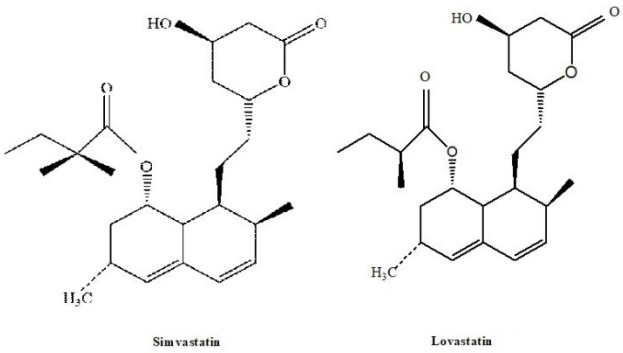
Statins are able to protect the tissues from oxidative damage by activating NADPH (nicotinamide adenine dinucleotide phosphate) complex. The oxygen radical NO (Nitric oxide) is a potent vasodilator has the main role in the signaling molecule in the vascular area. Endothelial nitric oxide, immune nitric oxide and neuronal nitric oxide, are the three enzymes responsible for the activation of the signaling molecule. Statins can control the production of inflammatory nitric oxide and protect the tissues from oxidative damage.

SIMVASTATIN

Statins are the reversible inhibitor of the enzyme HMG CoA which inhibit the conversion of HMG CoA to mevalonate which is one of the rate-limiting step in the cholesterol synthesis.[10] Inhibition of the enzyme HMG CoA (3-hydroxyl-3-methylglutaryl coenzyme A) reductase enzyme will lead to the reduction in cholesterol and up-regulation of LDL (Low-density lipoprotein) receptors. Statins will take 4-6 weeks to show a reduction in the plasma cholesterol level. It can reduce cholesterol by 20%-30% as well as 35% reduce the chances of cardiovascular diseases. The liver is the target organ for statins which is the major site of cholesterol synthesis, as LDL synthesis lipoprotein production. There are two types of statins such as type 1 statin include statins having same hydro naphthalene rings such as simvastatin, pravastatin, and type 2 statins are synthetic statins like atorvastatin, cerivastatin and rosuvastatin.

Pharmaceutical properties

Simvastatin is originated from fungi. 2, 2 dimethyl butyrate analogue[11] of Pravastatin chemically modified to form Simvastatin. Simvastatin, pravastatin, and fluvastatin are structurally related molecules having hydro naphthalene ring in their structure only difference in some of their molecular sites. Pravastatin and Simvastatin are orally administered prodrugs which will get activated after conversion into the reactive substance. The solubility of statins are quite different according to their partition coefficient, Simvastatin and Lovastatin are lipophilic in nature as they are more readily dissolve in octanol as compared to water. Statins such as simvastatin and lovastatin are lipophilic in nature and able to cross the blood- brain barrier. Statins are hepato selective in nature, most of the statins are undertake from intestinal tract to the liver, which is the major location for the cholesterol production in our body. The rest of the drug will bind to the plasma protein, therefore, total amount of free drug intended for systemic exposure will be less. Statins are considered to be a safe and effective drug, even though it is having some noxious effects such as muscle ache, intestinal discomfort, hepatotoxicity, sleep disturbances etc.



Simvastatin Lovastatin

Fig 1: Structure of simvastatin and lovastatin

Cellular levels of mechanism of action

Effect on cholesterol level: One of the major effects of statins is the reduction of cholesterol level. Cholesterol synthesis is the process consists of 28 steps, starting from acetoacetyl coenzyme A. Up- regulation of LDL receptor is the after effect of reduced cholesterol level.[12] As a result LDL cholesterol, good cholesterol level will increase in the body.[13] Statins are seen to be more effective and able to reduce the risk of MI(Myocardial infarction). Many reports revealed that short-term use of statins only reduce the CSF(Cerebrospinal fluid) cholesterol level but long-term use of statins will reduce the brain cholesterol.[14] Statins will inhibit the rate-limiting step in the cholesterol synthesis and thus reducing the cholesterol level. Statins bind to the HMG CoA reductase enzyme and inhibit the conversion of HMG CoA to mevalonate. Statins have higher affinity to HMG receptor as compared to the HMG CoA reductase enzyme so activity is desirable.[15]

Exhaustion of isoprenoid products[16]

The other mechanism of statin is executed by the blockade of nonsterol isoprenoid products involved in the cholesterol synthesis. The seventh step of cholesterol synthesis is the formation of farnesyl pyrophosphate (FPP) which is transformed to squalene in the next step and then the final product cholesterol. FPP not only used for the cholesterol formation but also used for the geranyl geranyl pyrophosphate (GGPP). [15] These both FPP and GGPP are important for the modification of the protein. Hemet A, ubiquinone and dolichol are formed with the help of FPP as a substrate. Ubiquinone and heme A having the antioxidant action and dolichol is a free radical scavenger. In these three statins have action on ubiquinone level, an antioxidant, which is suppressed by the statins and hence the side effect.[17]

Several in vitro studies shown that statins executed neuroprotection towards excitotoxicity in neurodegenerative disease by reducing the cholesterol level, higher cholesterol level can reverse the condition. So statin depends more on cholesterol level rather than isoprenoid units.

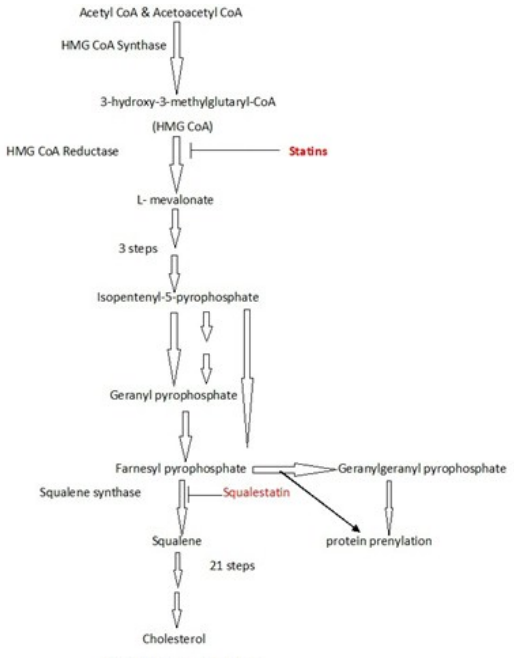


Fig 2: Mevalonate pathway

Activation of neuroprotective signaling pathways by statin

Statin has the ability to activate many neuroprotective signaling pathways. The neuroprotective actions executed by statins are correlated with the efficiency of blocking the cholesterol synthesis.

In vivo experiments done by the group of Chopp explained that statins are capable of initiating or enhancing the neurogenesis and synaptogenesis after brain damage. Statins gaining this neuroprotective action by the release of neurotrophic factors. Simvastatin has released brain-derived neurotrophic factors (BDNF) in the treatment of traumatic brain injury.

Several in vitro and in vivo studies explained that statins stimulate neuroprotective protein kinase B (PKB)[18] and render the neuroprotection. Lovastatin pretreatment protects the excitotoxic damage of the neurons in labs. Lovastatin is able to enhance the expression of TNF receptor 2 via activating the PKB hence neuroprotection.[15] How statins can activate the neuroprotection is still unknown. In the case of simvastatin, showed less Rho- associated kinase (ROCK)[19] activity as compared to placebo. Small GTP ases (Guanosine triphosphate), Rho[20] needs non- sterol isoprenoid unit for their action, since simvastatin is inhibiting this isoprenoid units they deactivate the action of Rho. It is found that the inactivation of Rho result in the activation of PKB and hence the neuroprotective actions.[15]

Statins: systemic action

Since all statins are not lipophilic in nature, they cannot cross blood-brain barrier. So they have some peripheral actions like reduction of oxidative stress, enhanced vascular function and peripheral anti-inflammatory actions.[15]

Reduction of oxidative stress

Clinical studies and in vivo studies revealed that statins can protect the tissue from oxidative damage. They are able to reduce lipid peroxidation by activating NADPH complex. Statins can reduce the concentration of reactive oxygen species.[9]

Enhanced vascular function

Signaling molecule in the vascular function is known as nitric oxide (NO).[21] It is a potent vasodilator. The enzymes which produce nitric oxide are an endothelial nitric oxide (eNOS), neuronal nitric oxide synthase (nNOS) and inflammatory nitric oxide synthase (iNOS). The overproduction of these enzymes of nitric oxide after an ischemic insult will result in the oxidative damage[22]
Statins will increase the production[23]of starting endothelial nitric oxide species and reduce the overproduction by controlling the expression of inflammatory nitric oxide species.[24]

Coagulation is the process involving a number of proteases. Coagulation[25] involves both intrinsic pathway and extrinsic pathway. In both prothrombin is converted into thrombin is responsible for the conversion of fibrinogen to fibrin leading to the formation of the clot. Statins increase the amount of plasmin by increase the conversion of plasminogen to plasmin which breaks the clot.

Anti-inflammatory reactions

Statins have action on immune response system[26] Studies have shown that statins reduce the immune response and tissue infiltration.[7] The first mechanism is expressed by the hindrance of antigen presentation. Statins decrease the amount of cytokine-induced inflammatory mediators and later the expression of MHC (Major histocompatibility complex) class 2 molecules.[27] T cell is also reduced by statins. It can change T cell phenotype into Th2 phenotype which is an anti-inflammatory phenotype.[28]

Pharmacokinetics

Simvastatin is an inactive prodrug which is converted into an active acid metabolite by the cytochrome p450 system through hydroxylation. Bioavailability[29] is less than 5% is because the HMG CoA reductase inhibition and the activation of the drug is done by presysytemically. Compared to other statin drug simvastatin has a highest hepatic extraction. The half-life of simvastatin is found to be 1.9 hr. is dosed once daily in the evening.[30]

ROLE OF STATINS IN PD

Current therapeutic strategies for PD are symptomatic in nature and are not capable to slow or reverse the natural course of the disease. But new therapeutic protocols are carried out to slow down the disease progression. Many studies have revealed that statins have neuroprotective action on neurodegenerative diseases[31,32] via decreasing the alpha-synuclein aggregation, neuroprotective actions through reducing cholesterol level, inhibition of inflammatory responses, suppression of thrombotic effect, inhibition of intracellular adherence molecule 1(ICAM-1), devaluation of serum levels of Apo lipoprotein E.[1]

Many animal studies have shown that statins inhibit aggregation of alpha- synuclein, one of the major reason for PD. As per epidemiological studies, long-term statin users supposed to have a low incidence of Parkinson disease.[2,29] The other major mechanism of statins is by inhibiting the inflammatory responses. In experimental studies, simvastatin has shown that the activation of brain-derived neutrotrophic factors (BDNF) and suppression of proinflammatory cytokines, IL-1beta, TNF alpha, iNOS, and PKB. Also plays a role in delaying the dopaminergic neurodeganaration. Some other experiments explained the neuroprotective action of statin through the suppression of oxidative stress.[33]

Statin has been known to be a protector of neurons with anti-inflammatory response, anti-oxidant and anti excitotoxicity. The different ways of statins to exhibit neuroprotection are an inflection of inflammatory response, suppression of oxidative stress, regulation of oxygen radical, anti-coagulation, angiogenesis. Moreover, statins are able to activate the signaling pathways such as protein kinase B, TNF receptor 2 expressions and Rho-associated kinase.

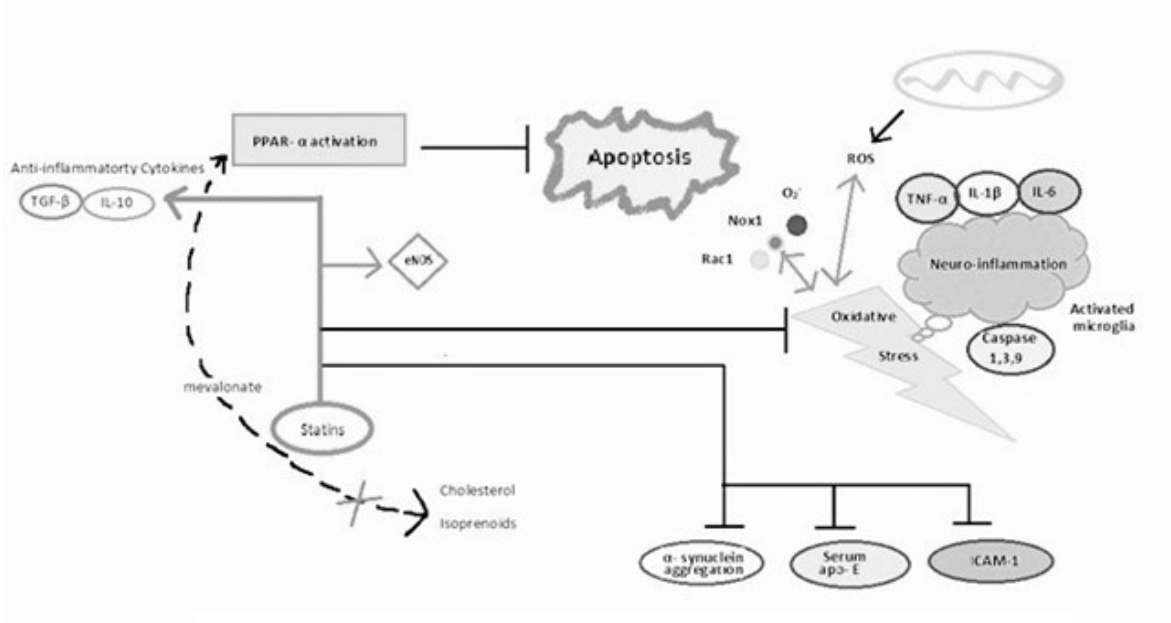


Fig 3: Schematic representation of statin inhibiting Parkinson's disease

CONCLUSION

Parkinson disease has become the second most common life-threatening disease in the world. Nearly all the available treatments for PD are symptomatic in nature and do not appear to slow or reverse the natural course of the disease. But reports have shown that statins have neuroprotective action and they are able to suppress the progression of disease using different mechanisms. None of the studies explained clearly about the dependence of blockade of mevalonate pathway and Parkinson disease. Anyways Statins neuroprotective action can be useful in the treatment of PD. However further investigations are necessary to explain the main course mechanism underlying around Statins.

REFERENCES

1. Saravi SS, Saravi SS, Khoshbin K, Dehpour AR. Current insights into pathogenesis of Parkinson's disease: Approach to mevalonate pathway and protective role of statins. Biomed Pharmacother 2017; Jun 1;90:724-30.
2. Yan JQ, Sun JC, Zhai MM, Cheng LN, Bai XL, Feng CL. Lovastatin induces neuroprotection by inhibiting inflammatory cytokines in 6-hydroxydopamine treated microglia cells.Int J Clin Exp Med. 2015;8(6):9030.

3. Büeler H. Impaired mitochondrial dynamics and function in the pathogenesis of Parkinson's disease. Exp Neurol 2009 Aug 1; 218(2):235-46.
4. Long-Smith CM, Sullivan AM, Nolan YM. The influence of microglia on the pathogenesis of Parkinson's disease. Prog Neurobiol 2009 Nov 1; 89(3):277-87.
5. Shadrina MI, Slominsky PA, Limborska SA. Molecular mechanisms of pathogenesis of Parkinson's disease. Int Rev Cell Mol Biol. 2010 Dec 31; 281:229-66.
6. AlDakheel A, Kalia LV, Lang AE. Pathogenesis-targeted, disease-modifying therapies in Parkinson disease. Neurotherapeutics. 2014 Jan 1;11(1):6-23
7. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM et al. Inflammation and Alzheimer's disease. Neurobiol Aging 2000 Jun 30; 21(3):383-421.
8. McFarland AJ, Anoopkumar-Dukie S, Arora DS, Grant GD, McDermott CM, Perkins AV et al. Molecular mechanisms underlying the effects of statins in the central nervous system. Int J Mol Sci 2014 Nov 10;15(11):20607-37.
9. Mosley RL, Benner EJ, Kadiu I, Thomas M, Boska MD, Hasan K et al. Neuroinflammation, oxidative stress, and the pathogenesis of Parkinson's disease. J Clin Neurosci 2006 Dec 31;6(5):261-81.
10. Tiwari V, Khokhar M. Mechanism of action of anti-hypercholesterolemia drugs and their resistance. Eur. J. Pharmacol 2014 Oct 15;741:156-70.
11. Lennernäs H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors. Clin Pharmacokinet 1997 May 1;32(5):403-25.
12. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature 1990 Feb; 343(6257):425-430.
13. Gouni-Berthold I, Berthold HK, Gylling H, Hallikainen M, Giannakidou E, Stier S et al. Effects of ezetimibe and/or simvastatin on LDL receptor protein expression and on LDL receptor and HMG-CoA reductase gene expression: a randomized trial in healthy men. Atherosclerosis 2008 May 31; 198(1):198-207.
14. Fassbender K, Stroick M, Bertsch T, Ragoschke A, Kuehl S, Walter S et al. Effects of statins on human cerebral cholesterol metabolism and secretion of Alzheimer amyloid peptide. Neurology 2002 Oct 22; 59(8):1257-8.
15. Van der Most PJ, Dolga AM, Nijholt IM, Luiten PG, Eisel UL. Statins: mechanisms of neuroprotection. Prog. Neurobiol 2009 May 31; 88(1):64-75.
16. Corsini A, Bellosta S, Baetta R, Fumagalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. Pharmacol. Ther 1999 Dec 31; 84(3):413-28.
17. Paoletti R, Bolego C, Cignarella A. Lipid and non-lipid effects of statins. In Atherosclerosis: Diet and Drugs.HEP.2005;170:365-388
18. Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J. Exp. Med 2005 Jan 17;201(2):233-40.
19. Liu A, Tegmark M, Bowman J, Hewitt J, Zaldarriaga M. An improved method for 21-cm foreground removal Mon. Notices Royal Astron. Soc.2009 Aug 19;398(1):401-6.
20. Calandra T, Echtenacher B, Le Roy D, Pugin J, Metz CN, Hültner L et al. Protection from septic shock by neutralization of macrophage migration inhibitory factor. Nat. Med. 2000 Feb 1;6(2):164-70.
21. van Horssen R, ten Hagen TL, Eggermont AM. TNF-α in cancer treatment: molecular insights, antitumor effects, and clinical utility. Oncologist 2006 Apr 1;11(4):397-408.
22. Abdolmaleky HM, Smith CL, Faraone SV, Shafa R, Stone W, Glatt SJ et al. Methylomics in psychiatry: modulation of gene–environment interactions may be through DNA methylation. Am. J. Med. Genet. B Neuropsychiatr. Genet. 2004 May 15;127(1):51-9.
23. Arnaud C, Braunersreuther V, Mach F. Toward immunomodulatory and anti-inflammatory properties of statins. Trends Cardiovasc. Med. 2005 Aug 31;15(6):202-6.
24. Kureishi Y, Luo Z, Shiojima I, Bialik A, Fulton D, Lefer DJ et al. The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals Nat. Med. 2000 Sep 1;6(9):1004-10.
25. Asahi M, Huang Z, Thomas S, Yoshimura SI, Sumii T, Mori T et al. Protective effects of statins involving both eNOS and tPA in focal cerebral ischemia. J. Cereb. Blood Flow Metab. 2005 Jun;25(6):722-9.
26. Malfitano AM, Marasco G, Proto MC, Laezza C, Gazzerro P, Bifulco M. Statins in neurological disorders: an overview and update. Pharmacol. Res. 2014 Oct 31;88:74-83.
27. Littarru GP, Langsjoen P. Coenzyme Q 10 and statins: biochemical and clinical implications. Mitochondrion. 2007 Jun 30;7:S168-74.
28. Kuipers HF, van den Elsen PJ. Immunomodulation by statins: inhibition of cholesterol vs. isoprenoid biosynthesis. Biomed. Pharmacother. 2007 Aug 31;61(7):400-7.
29. Wang Q, Yan J, Chen X, Li J, Yang Y, Weng J et al. Statins: multiple neuroprotective mechanisms in neurodegenerative diseases. Exp. Neurol. 2011 Jul 31;230(1):27-34.
30. Lennernäs H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors. Clin Pharmacokinet. 1997 May 1;32(5):403-25.
31. Ciurleo R, Bramanti P, Marino S. Role of statins in the treatment of multiple sclerosis. Pharmacol. Res. 2014 Sep 30;87:133-43.
32. Yan J, Xu Y, Zhu C, Zhang L, Wu A, Yang Y et al. Simvastatin prevents dopaminergic neurodegeneration in experimental parkinsonian models: the association with anti-inflammatory responses. PLoS One. 2011 Jun 22;6(6):e20945.
33. Wahner AD, Bronstein JM, Bordelon YM, Ritz B. Statin use and the risk of Parkinson disease. Neurology. 2008 Apr 15;70(16 Part 2):1418-22

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