Review Article

Statins as Potentially Neuroprotective Agents: A Review

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Abstract

The aim of this literature review is to assess the experimental and clinical evidence regarding potential neuroprotective effects of statins and their possible perioperative benefit. Statins are drugs used to control cholesterol disorders and prevent cardiovascular diseases by four mechanisms: improvement of endothelial function, modulation of inflammatory responses, maintenance of plaque stability, and prevention of thrombus formation. It is possible that these various effects may also be neuroprotective. The anti-inflammatory effects of statins on endothelial cell mechanisms are better understood than their role in neuroprotection or tumoral apoptosis and evidence is only just emerging that statins may be beneficial. Data regarding perioperative use of statins in neurosurgery is scarce, controversial and inconclusive since there is a lack of convincing randomized, prospective clinical trials. More trials in humans are needed to determine whether statins could contribute to the current management of neurosurgical diseases. Not much is known about utilizing statins as a prophylactic treatment and some would probably advocate that we should be treating 'at risk' patients with statins perioperatively or at least it is important to try to put this into a clinical perspective.

Keywords: Statins; Anti-inflammatory; Statins in neurosurgery; Perioperative; Neuroprotection

Introduction

The aim of this literature review is to assess the experimental and clinical evidence regarding potential neuroprotective effects of statins and their possible perioperative benefit. Statins are drugs primarily used to control cholesterol disorders and prevent cardiovascular disease. They inhibit hydroxymethylglutaryl–coenzyme A (HMG-CoA) reductase, an enzyme that plays a central role in the production of cholesterol in the liver (Figure 1). Since elevated serum cholesterol levels have been associated with cardiovascular diseases [1], statins are known to be effective in decreasing mortality and morbidity in patients with cardiovascular disease. Statins are currently recommended for patients at high risk of developing heart disease and they are known to lower cholesterol, decrease the number of cardiac events, and reduce the risk of stroke [2]. Improvement of endothelial function, modulation of inflammatory responses, maintenance of plaque stability, and

prevention of thrombus formation are other actions of statins beyond their lipid-lowering activity in the prevention of atherosclerosis [3]. The anti-inflammatory effects of statins on endothelial cell mechanisms are better understood than their role in neuroprotection or tumoral apoptosis and evidence is only just emerging that statins may be beneficial in the neurosurgical patient.

Statins as anti-inflammatory agents

A brief review of the anti-inflammatory properties of statins is necessary to understand their possible role in neuroprotection. The anti-inflammatory properties of statins are exemplified by reduced plasma concentrations of the inflammatory cytokines like Tissue Necrosis Factor (TNF) and InterLeukin (IL)-6 in patients receiving pravastatin [4]. Inflammatory processes play a pivotal role in the pathogenesis of atherosclerosis, and elevated plasma levels of markers of inflammation such as high sensitivity C- Reactive Protein (hs-CRP), serum amyloid A, IL-6 and soluble intercellular adhesion molecule-1 have been shown to predict cardiovascular events. Mechanism by which statins may reduce vascular event rates is related to potential anti-inflammatory effects of these agents [5-8]. There is data that preoperative statin therapy attenuates the release of pro-inflammatory
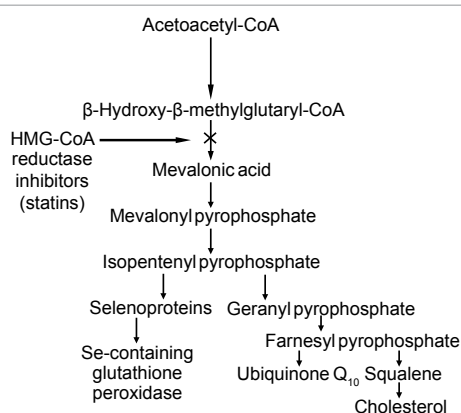

Figure 1: The mevalonate pathway. Statins inhibit production of HMG-CoA reductase, which is responsible for the conversion of HMG-CoA to mevalonate and thus prevent downstream cholesterol, ubiquinone-, and dolichol - dependent effects. (Adopted from: Hothersall E, Mc Sharry C, Thomson NC (2006) Potential therapeutic role for statins in respiratory disease. Thorax 61: 729-734).

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IL-6 and up-regulates anti-inflammatory IL-10 after cardiac surgery with cardioplegia [9].

Cell-contact-dependent interactions between T cells and macrophages are now recognized to be of fundamental importance in promoting chronic inflammation in several autoimmune diseases [10]. There is evidence that statins affect macrophage function. Macrophages are capable of degrading the extracellular matrix and, by secreting Matrix MetalloProteinase (MMP), may weaken the fibrous cap and thus predispose an atheromatous plaque to rupture. Statins as Fluvastatin and Simvastatin have recently been shown to inhibit MMP-9 (gelatinase B) activity and secretion by macrophages [11]. Statins cause decreased macrophage expression of soluble intercellular adhesion molecule-1 and lipopolysaccharide-induced secretion of IL-6 and TNF by monocytes and macrophages [12-14]. Simvastatin therapy for 8 weeks reduces monocyte expression of TNF and IL-1 [15]. Statins are known to inhibit T-cell activation [16,17]. This effect is reversed by mevalonic acid, directly implicating HydroxyMethylGlutaryl-Coenzyme A (HMG-CoA) reductase in this activity. Lovastatin and simvastatin suppress critical T-cell co stimulatory events [18]. Overall, clinical data regarding the anti-inflammatory role of statins has until recently been limited and it is difficult to say if all statins have clinically relevant anti-inflammatory effects or whether any one agent is more powerful than another in this regard.

Statins in the perioperative care of patients

What is the role of statins in perioperative care? The use of statins in the general population is widespread. Many patients presenting for surgery are regularly taking them but the evidence for the prophylactic use of statins perioperatively is weak and lacks prospective controlled studies. Statins have beneficial effects beyond those of lipid lowering, including reducing the perioperative risk of cardiac complications and sepsis [19]. It was shown that patients hospitalized with an acute coronary syndrome, ischemic stroke, or revascularization and prescribed a statin demonstrated a lower incidence of sepsis compared with controls [20]. One retrospective cohort analysis determined that statin used before hospital admission, and continued after sepsis, correlated with decreased mortality rates from septicemia [21]. Some studies have been performed in animals with death as the endpoint. For example, in mice, pretreatment with simvastatin before induction of sepsis using the cecal ligation puncture model increased survival rate four-fold [22]. In a subsequent study of treatment with a number of different statins given after the onset of sepsis, statins also improved survival [23].

The 2007 American Heart Association guidelines [24] indicate that there is evidence that supports the use of statins perioperatively to prevent cardiac complications during non-cardiac surgery. The guidelines state that it is unclear how we would identify those patients in whom to initiate statin therapy and for what duration. Abrupt stopping of statins is associated with an increased morbidity and mortality [25] as measured by an increase in troponins and cardiac events. Some authors suggest that statins are effective in lipid-independent conditions like sepsis [20], nephropathy, decreasing the rate of renal damage in diabetics [26], Alzheimer's disease and dementia, decreasing incidence and progression of autoimmune disease [27,28], rheumatoid arthritis [29], organ transplantation, decreasing rejection rates [30], gastrointestinal disease, possibly decreasing the incidence of colon cancer [31], inflammatory bowel disease [32], osteoporosis and macular degeneration [33]. Although the proposed benefits of statin therapy seem to be as widespread as their use, their use is associated with significant adverse effects. Most common are hepatic

dysfunction and muscle problems like myalgia and rhabdomyolysis [12,34]. Myalgia is possibly related to mitochondrial dysfunction. Statins inhibit synthesis of mevalonate, a precursor of ubiquinone that is a central compound of the mitochondrial respiratory chain. Statin therapy can be associated with high blood lactate/pyruvate ratio. All this is suggestive of mitochondrial dysfunction [35].

Trials of statin therapy have had conflicting findings on the risk of development of diabetes mellitus in patients given statins. Statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events [36]. The mechanism underlying the increase in type II Diabetes in patients undergoing statin therapy has not been fully identified. It is possible that statins may influence muscle or liver insulin sensitivity directly, but there is no specific experimental evidence to support any feasible hypothesis [37,38]. Other possible adverse effects include cognitive loss, neuropathy, pancreatic and sexual dysfunction [39]. The question remains, should we use statins perioperatively for neurosurgical patient? To elucidate this it would be important to know if statins provide neuroprotection.

Neuroprotective effects of statins

Modern concept of providing cerebral protection focuses on blocking the cascade of events that occur during ischemia. Cytokines are prominent mediators of inflammatory and immunologic responses in the brain and are produced by neurons, glial cells, and endothelium. Although, the precise mechanism of cerebral ischemic damage by cytokines needs to be further elucidated, their importance has been shown by studies demonstrating a reduction in cerebral infarct size in animals treated with cytokine receptor antagonists. Surgical stress triggers an inflammatory response and releases mediators into human plasma such as interleukins. Craniotomy performed under general anesthesia may be associated with different levels of stress and plasma IL-6 level is significantly increased [40]. Aspirin has shown laboratory evidence of neuronal protection due to its anti-inflammatory action [41]. Possibly statins as agents with anti-inflammatory properties could do same. Cytokines have a major role in ischemic neuronal damage primarily during reperfusion which is followed by leukocyte infiltration, primarily neutrophils. Cytokines are necessary for the optimal function of leukocytes, and they are considered the key mediators of acute phase responses to tissue injury. The adhesion of leukocytes to the walls of
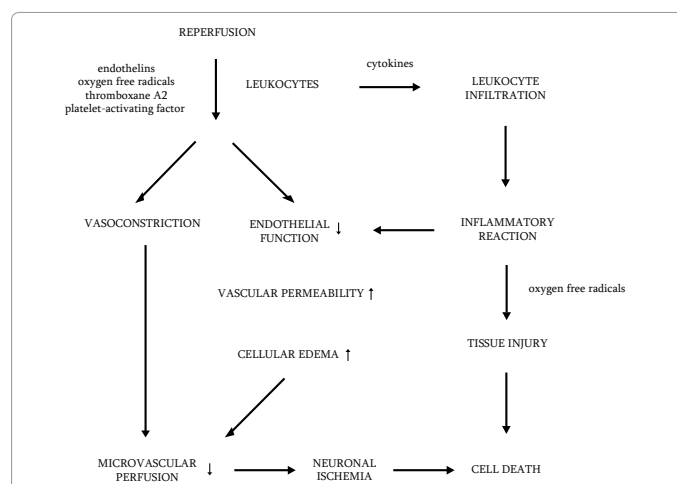

Figure 2: Cytokines and their role in ischemic neuronal damage during reperfusion. (Based on adaptation from Barone FC, Feuerstein GZ (1999) Feuerstein Journal of Cerebral Blood Flow and Metabolism 19: 819-834).

cerebral blood vessels is induced by cytokines. Tumor necrosis factor alpha and interleukin 1-beta seem to play a significant role in ischemic brain injury. This cytokine-induced leukocyte infiltration into ischemic brain tissue activates an inflammatory reaction, which results in the release of oxygen free radicals (Figure 2). Statins are known to attenuate the inflammatory cytokine response to ischemia [42].

Endothelial glycocalyx plays one of the pivotal roles in ischemic damage. Drugs that can specifically increase the synthesis of glycocalyx components, refurbish it, or selectively prevent its enzymatic degradation could be very beneficial but do not seem to be available. Pharmacological blockers of radical production may be useful to diminish the oxygen radical stress on the glycocalyx; statins inhibitory effect on the cytokine tumor necrosis factor and inflammatory mediators release can be one of the tenable therapeutic options to improve glycocalyx layer [43].

The effect of simvastatin on the development of cerebral aneurysms and vasospasm was studied in rats. Treatment with simvastatin decreased induced aneurysm development [44]. If statins decrease the progression of cerebral aneurysms then the incidence of SAH may be lower in patients treated with statins. There are no long enough follow-up studies to answer this question now. Initiating simvastatin at the time of SAH also decreased vasospasm and improved neurobehavioral outcomes [45]. Retrospective clinical studies are conflicting with some reporting decreased vasospasm, improved short-term clinical outcome and decreased mortality with statins, and others finding no effect or an increased risk of vasospasm in patients on statins [46].

Three randomized clinical trials revealed controversial results [47-49]. In those studies statins had no effect on mortality and did not significantly decrease symptomatic vasospasm, but the numbers of patients treated were small. In other studies statins have exhibited some promise in the setting of SubArachnoid Hemorrhage (SAH): significantly reduced incidence of vasospasm and rebleeds, delayed ischemic deficits and mortality [49,50] and worse outcome if statins were discontinued [51]. This means statins may provide cerebrovascular protection which is lost if therapy is discontinued.

As the major regulator of homeostasis, the vascular endothelium exerts a number of vasoprotective effects, such as vasodilatation, suppression of smooth muscle cell growth, and inhibition of inflammatory responses. These effects are largely mediated by nitric oxide. Nitric oxide opposes the effects of endothelium-derived vasoconstrictors and inhibits oxidation of low-density lipoprotein. Poor production or activity of nitric oxide leads to impaired endothelium-dependent vasodilatation. A number of clinical trials have shown that statins improve endothelial dysfunction in patients with coronary risk factors beyond what could be attributed to their impact on plasma lipids. Several possible mechanisms by which statin therapy may improve endothelial dysfunction may include upregulation of nitric oxide production or activity and reduction of oxidative stress. One important pathway appears to be the effects of statins on NO production via increased availability of nitric oxide synthase [52]. This means statins possess beneficial effects during ischemic stroke and reperfusion. Statins can ameliorate ischemic damage by improving blood flow to the ischemic brain and by making the brain parenchyma intrinsically more resistant to the effects of ischemia. The proposed mechanisms includes upregulation of endothelial nitric oxide synthase (which promotes vasodilation) while inhibiting inducible nitric oxide synthase (which increases ischemic damage) [42].

Statins can be beneficial in Traumatic Brain Injury (TBI) [53].

After the initial insult to the brain, the delayed secondary effects of TBI often cause long-term severe injury. The secondary events are neurochemically mediated resulting in brain ischemia and hypoxia. The various effects of statins, especially anti-inflammatory and vasoactive effects, have been found to counter some of the secondary damage from traumatic brain injury and restore neural function. Therefore, statins may offer a potential novel therapeutic strategy for TBI [54,55].

Statins showed significant benefit in models of TBI [56]. Simvastatin promotes functional recovery after Traumatic Brain Injury (TBI) in rat; however, the underlying mechanisms remain poorly understood. TBI causes inflammatory reaction, including increased levels of IL-1β, IL-6 and TNF-α, as well as activated microglia. Simvastatin selectively reduces IL-1β expression and inhibits the activation of microglia and astrocytes after TBI, which may be one of the mechanisms underlying the therapeutic benefits of simvastatin treatment of TBI [57]. Simvastatin decreases post-TBI polymorphonuclear neutrophil infiltration and prevents release of proinflammatory mediators leading to blood-brain barrier disruption. Simvastatin does not stop the full insult of brain edema and restore BBB permeability but, it is able to limit the extravasation of large molecules in the pericontusional areas of TBI [58]. Animal TBI models showed functional and histological improvement after administration of statins [59,60]. Mice that were pretreated with atorvastatin and simvastatin, and then subjected to controlled head injury displayed recovery in vestibulomotor function, decreased degeneration of neurons within the hippocampus, and a decreased reduction in cerebral blood flow following the trauma. These results of neurocognitive improvements were reproduced in animals that were given atorvastatin post-injury as well. The mechanism by which atorvastatin attenuates this neuroinflammatory cytokine-mediated response seems to be by diminishing microglial activation which contributes to the development of cerebral edema and neuronal injury. Atorvastatin significantly lowered post-injury TNFα and IL-6 levels as compared to control mice [59]. Simvastatin, similarly attenuated inflammatory mediator, IL-1β, and decreased reactive astrogliosis, thereby rescuing neuronal cells and increasing survival in the hippocampus and dentate gyrus post-injury [57,61]. Lovastatin also showed anti-inflammatory protective mechanisms in pretreated rats by reducing TNFα and IL-1β mRNA levels and enhancing motor and somatosensory function [62]. Statins promote angiogenesis and neurogenesis which are keys to recovery from traumatic brain injury [63]. Lu et al. administered atorvastatin to rats on day 1 and for 14 consecutive days after TBI and found a significant improvement in motor and spatial function [64]. Lu et al. found comparable outcomes with simvastatin [53]. Animal models had significant improvement in functional recovery after administration of atorvastatin which was quantitatively identified by an increase of angiogenesis [65].

Conclusions

Statins are drugs known to improve endothelial function, modulate inflammatory responses, and maintain plaque stability and prevention of thrombus formation. Based on laboratory evidence statins could offer substantial benefit in the perioperative management of neurosurgical diseases. The origin of neuroprotective effects of statins has not been well explained and the available data regarding perioperative use of statins in neurosurgery is inconclusive. There is certainly a lack of convincing randomized double-blind prospective clinical trials. Further studies in humans are needed to determine whether statins could contribute to the current management of neurosurgical diseases. An important question remains about utilizing statins as a prophylactic treatment as opposed to perioperative use.

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