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CHEST Commentary

Statins and Brain Dysfunction

A Hypothesis to Reduce the Burden of Cognitive Impairment in Patients Who Are Critically Ill

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Delirium is a frequent form of acute brain dysfunction in patients who are critically ill and is associated with poor clinical outcomes, including a critical illness brain injury that may last for months to years. Despite widespread recognition of significant adverse outcomes, pharmacologic approaches to prevent or treat delirium during critical illness remain unproven. We hypothesize that commonly prescribed statin medications may prevent and treat delirium by targeting molecular pathways of inflammation (peripheral and central) and microglial activation that are central to the pathogenesis of delirium. Systemic inflammation, a principal mechanism of injury, for example, in sepsis, acute respiratory distress syndrome, and other critical illnesses, can cause neuronal apoptosis, blood-brain barrier injury, brain ischemia, and microglial activation. We hypothesize that the known pleiotropic effects of statins, which attenuate such neuroinflammation, may redirect microglial activation and promote an antiinflammatory phenotype, thereby offering the potential to reduce the public health burden of delirium and its associated long-term cognitive injury.

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Abbreviations: BBB = blood-brain barrier; eNOS = endothelial nitric oxide synthase; iNOS = inducible nitric oxide synthase; LPS = lipopolysaccharide; LTCI = long-term cognitive impairment; MCP = monocytic chemoattractant protein; TBI = traumatic brain injury; TNF = tumor necrosis factor

Delirium is a manifestation of acute brain dysfunction that occurs in up to 80% of patients who are critically ill and is associated with higher mortality and long-term cognitive impairment (LTCI), which is akin to a dementia-like cognitive disability.[1-7] This acquired cognitive impairment—critical illness brain injury—has important public health implications for both younger and older patients (the latter an increasingly larger proportion of the population), threatening the functional independence and quality of life of millions of ICU survivors in the coming decades. Given that delirium in the ICU represents early brain dysfunction during critical illness and can be easily assessed using validated bedside instruments,[1,8] novel therapies that prevent or treat delirium may prevent its associated immediate and long-term sequelae.

Findings from animal and human studies suggest a neuroinflammatory pathogenesis of delirium and long-term brain dysfunction associated with critical illness. We propose a testable hypothesis, based on existing data, that the pleiotropic effects of statin medications can mitigate the mechanisms of delirium and LTCI associated with critical illness. Specifically, that statins may modify two processes leading to brain injury: neuroinflammation and activation of proinflammatory microglia.

Effects on Neuroinflammation During Critical Illness

An intense systemic inflammatory response to illness or injury is a key mediator of organ dysfunction during critical illness. Several conditions that often lead to an ICU admission are examples of the deleterious effects of systemic inflammation (eg, severe sepsis, trauma, acute respiratory distress syndrome). Proinflammatory cytokines (eg, tumor necrosis factor [TNF]-α and IL-1β) and chemokines (eg, monocytic chemoattractant protein [MCP]-1) activate leukocytes and endothelial cells (which express leukocyte

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adhesion molecules), resulting in endothelial damage and tissue factor expression that initiate a procoagulant cascade, ultimately leading to microvascular thrombosis, impaired blood flow, and end-organ damage (Fig 1). In addition, cytokines trigger production of inducible nitric oxide synthase (iNOS), which causes nitric oxide-mediated hypotension, further inflammation, and apoptosis. Ultimately, the characteristic inflammatory state of critical illness causes multiple mechanisms of injury in the brain, including vascular damage, ischemia, breakdown of the blood-brain barrier (BBB), local neuroinflammation, and apoptosis, all of which are observed, for example, in animal models of sepsis and in humans with sepsis-associated delirium.[9,10] In addition to directly injuring neurons, this neuroinflammation activates quiescent microglia, the resident macrophages in the brain (Fig 1),[10-12] a process that van Gool and colleagues[13] proposed as pivotal to CNS damage from systemic inflammation. Microglia are usually activated to clear apoptotic cells resulting from an injury.[14] Their overactivation, however, can be responsible for an exaggerated inflammatory response.[14] Van Gool and colleagues,[13] in fact, postulated that impaired cholinergic inhibition of microglia is responsible for overactivation of microglia that can persist for months following critical illness, contributing to ongoing neuroinflammation, with resultant neurodegeneration manifesting as severe prolonged delirium and LTCI.

In vitro and human studies have shown that, in addition to their effect on cholesterol synthesis, statins have complex pleiotropic effects, including antiinflammatory, immunomodulatory, endothelial function-enhancing, and anticoagulant effects.[15] These pleiotropic effects may prevent or attenuate delirium during critical illness by acting on causative mechanisms, including neuroinflammation, BBB injury, neuronal apoptosis, ischemia and hemorrhage, and microglial activation (Fig 1).[9,10] Specifically, in vitro and animal studies have shown that statins suppress upregulation of toll-like receptors (which trigger inflammation in response to infection) and reduce the release of TNF-α, IL-1β, and MCP-1 as well as leukocyte adhesion molecules involved in the development of endothelial damage and BBB alterations.[15,16] Statins also reduce iNOS expression, thereby reducing neuronal apoptosis and increasing BP and cerebral blood flow, and they increase endothelial nitric oxide synthase (eNOS) expression, preserving microcirculatory blood flow via local vasodilation.[17] Lastly, statins counteract the procoagulant cascade promoted by inflammation through the following mechanisms: blunting monocytic expression of tissue factor, increasing thrombomodulin availability (important in the activation of protein C), and reducing levels of plasminogen activator inhibitor-1, which impairs the fibrinolytic system.[15]

Though no studies to date have evaluated the effect of statins on delirium in patients in the ICU, this drug class has been examined in models of traumatic brain injury (TBI),[18] which involves pathophysiologic changes (eg, neuronal damage and apoptosis, neuroinflammation, and BBB injury) similar to those observed in other types of critical illness, including sepsis and acute respiratory distress syndrome. The benefits of statins observed in animal studies of TBI include increased hippocampal neuron survival and improved neurologic function.[18-22] In humans, one clinical trial reported a reduction in amnesia and increased orientation in patients with TBI who were treated with rosuvastatin.[23] Studies investigating the effect of statins on patients with postoperative delirium, a population with different clinical profiles than patients in the ICU, have yielded inconsistent results.[24,25] One retrospective study[25] reported an increased risk of postoperative delirium for patients who had elective surgery and were taking statins, whereas a prospective study[24] found a significant reduction in postoperative delirium for patients who had cardiac surgery and were taking statins. Well-designed, randomized, placebo-controlled trials are required to determine the true effect of statins on delirium during critical illness.

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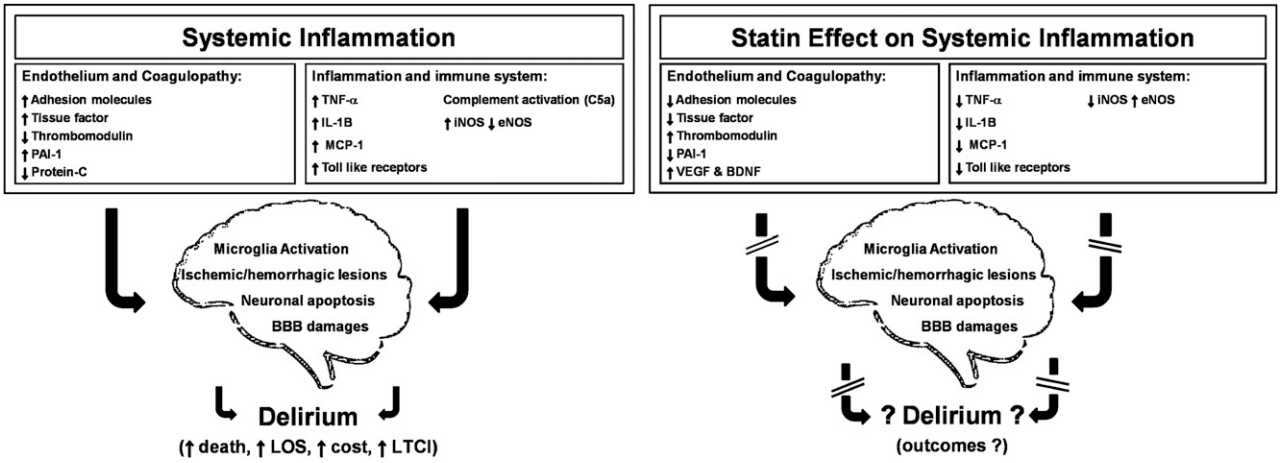

FIGURE 1. The systemic inflammatory cascade, effects of delirium, and sites of action for statins in critical illness. The systemic inflammatory cascade in critical illness is one of the main drivers of delirium. Different clinical conditions that often lead to an ICU admission could be used as examples of systemic inflammation (eg, severe sepsis, acute respiratory distress syndrome). This figure describes the principal mechanisms responsible for brain injury in critical illness. Consequently, we show the proven pleiotropic effect of statins on the systemic inflammatory cascade, representing the basis by which statins may reduce delirium and its long-term neurologic sequelae in ICU survivors. BBB = blood-brain barrier; BDNF = brain-derived neurotrophic factor; eNOS = endothelial nitric oxide synthase; iNOS = inducible nitric oxide synthase; LOS = length of stay; LTCI = long-term cognitive impairment; MCP = monocytic chemoattractant protein; PAI = plasminogen activator inhibitor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

Effects on Microglial Activation and Phenotype Switching

The effects of acute systemic inflammation on delirium might be explained through the activation of primed microglia.[13,26,27] Perry and colleagues[28] described how microglia in the brain can already be activated as a result of an ongoing brain pathology (eg, Alzheimer disease, Parkinson disease, or prion disease) or aging. These microglia are named primed microglia, and their stimulation by central or systemic challenges (eg, an infection) can lead to exaggerated and long-lasting inflammatory responses compared with those of subjects who have unprimed microglia. In fact, van Gool et al[13] hypothesized that a cholinergic impairment from systemic inflammation may cause uncontrolled activation of brain microglia that can last for months, especially in patients with primed microglia, and can eventually lead to or worsen neurodegeneration. In a model of prion disease, lipopolysaccharide (LPS) exposure led to activation of microglia, with expression of IL-1β, IL-6, TNF-α, and iNOS, and eventual neuronal death.[26]

While the hypothesis of impaired cholinergic inhibitory control of the brain microglia still needs to be proven, the cholinergic effects on peripheral macrophages have been well described in animal models using the term "inflammatory reflex."[29,30] It has been reported that the release of acetylcholine through vagal nerve stimulation in response to endotoxin exposure suppresses proinflammatory cytokine release (eg, IL-6, TNF-a, IL-1, IL-18) without affecting the production of the antiinflammatory cytokine IL-10.[29] Additionally, in vitro studies have shown that microglia express acetylcholine receptors, in particular the nicotinic receptor α7, supporting the hypothesis that a central antiinflammatory cholinergic pathway may limit the response of microglia in the periphery via release of acetylcholine by neurons.[31,32]

Systemic inflammation can influence acute and chronic microglial activation, promoting the proinflammatory rather than the antiinflammatory phenotype.[26,27] In fact, exposure to LPS has been shown in a rat model of Parkinson disease to shift the primed microglia to a proinflammatory phenotype with increased secretion of IL-1β.[27] Additionally, a peripheral infection in animal models of prion disease with primed microglia led to a switching to a proinflammatory phenotype.[33] Hughes and colleagues,[34] however, raised the question of whether microglia activated by LPS actually led to an enhanced inflammatory state. In this study[34] conducted on microglia in animals with prion disease, it was found that microglia engaged in phagocytosis of apoptotic cells remain in an antiinflammatory state, at least with regard to the lack of production of the proinflammatory IL-1B, when exposed to LPS. These data suggest that a phagocytic state does not necessarily imply the production of inflammatory mediators by microglia.

Statins may counteract the inflammation-induced action of proinflammatory-phenotype microglial activation during critical illness. Their actions favor a switch toward antiinflammatory phenotypes that may contribute to neuronal healing rather than damage (Fig 2), a process observed in studies of animal models and cultured mouse microglial cells. Li et al[35] reported that mice treated with simvastatin had significantly

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fewer activated microglia after TBI than mice treated with placebo. Famer and colleagues[36] reported a significant reduction in microglia activation in animal models treated with rosuvastatin. Similarly, Townsend et al[37] found that lovastatin significantly reduced CD40 expression (a marker of microglial activation) in primary culture microglial cells by indirectly blocking the expression of proinflammatory mediators. In addition, lovastatin significantly increased microglial phagocytic function, an indicator of the antiinflammatory phenotype and a process inhibited by CD40 activation.

Microglial activation leads to the induction of iNOS, a deleterious component of the inflammatory cascade involved in neuronal damage.[38] Statins have been shown to reduce the production of iNOS from activated microglial cells and macrophages.[39,40] Additionally, lovastatin was also shown to significantly reduce prostaglandin E2 release from microglia, either under basal conditions or after stimulation by IL-1B, in primary cultures of rat cortical microglia.[41] Statins have also been shown in rats and human microglia to reduce the production of the proinflammatory cytokine IL-6.[36,42]

Circulating cytokines released as the result of an inflammatory response can cross the BBB and activate quiescent microglia or cause an exaggerated inflammatory response in primed microglia. Statins can also counteract the deleterious effects associated with microglial activation through their effects on the peripheral

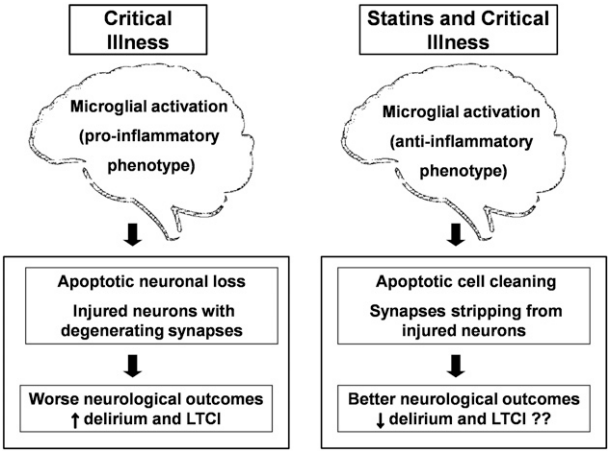

FIGURE 2. The microglia phenotypes, effects of delirium, and hypothesized mechanism of action of statins in critical illness. A systemic inflammatory cascade caused by infection (eg, sepsis) or by other critical illnesses (eg, acute respiratory distress syndrome) may result in a microglial proinflammatory phenotype potentially leading to worse neurologic outcomes as manifested by delirium and LTCI. The pleiotropic effect of statins might redirect the microglia to an antiinflammatory phenotype, activating mechanisms responsible for brain protection and therefore possibly leading to better immediate and long-term neurologic outcomes for survivors of critical illness. See Figure 1 legend for expansion of the abbreviation.

inflammatory status, as described in the first section of this article.

Thus, statins might redirect the pathophysiologic response of the CNS to inflammation during critical illness, promoting an antiinflammatory response, enhancing apoptotic cell cleaning and synapse stripping, and leading to a reduction in delirium and LTCI. Additionally, statins can reduce the immediate increase in neuroinflammation secondary to activation of quiescent and primed microglia. This hypothesis could be tested in animal models of sepsis, correlating the biologic findings of microglial switching with behavioral assessments indicative of delirium.

Effects of Statins and Clinical Outcomes

In clinical trials, statins given late in life have not prevented or delayed the onset of dementia,[43] but these results do not preclude a beneficial effect of statins on delirium or LTCI due to critical illness. The use of statins during an immediate inflammatory response, as witnessed in patients who were critically ill, might have different consequences than the use of statins on the low-grade chronic inflammation related to dementia.

Importantly, animal and human studies have also shown that abrupt discontinuation of statins can lead to an acute rebound inflammation and worsening of clinical outcomes.[44-48] Animal studies have demonstrated that short-term withdrawal of statin therapy leads to suppressed eNOS production, elevated oxygen free-radical production, and increased endothelial dysfunction as soon as 2 days after discontinuation.[49,50] These changes supersede the beneficial effects of statin therapy on platelet function and neuronal cell protection.[46,51]

A proinflammatory rebound is reported within 5 days of statins interruption in patients with myocardial infarction.[44] The observed proinflammatory state was found to be threefold higher in those patients than in patients not receiving statin therapy before or during hospitalization.[44] Demonstrating its importance, inflammation after myocardial infarction has been associated with ventricular dysfunction and sudden death up to 2 years after the initial event.[52,53] Heeschen et al[47] found an increased cardiac risk in patients who were long-term statin users and who were admitted for acute coronary syndromes in which statins were withdrawn, abrogating the beneficial effect of these drugs on the clinical outcomes. A large case-control study reported that statin withdrawal (within 30 days) led to a twofold increase in the risk of subarachnoid hemorrhage.[48] Finally, a randomized clinical trial tested the effects of statin withdrawal during the first 3 days of admission on clinical outcomes

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in patients admitted for acute stroke.[45] Patients for whom statins were withdrawn had a significant 8.67-fold increase in the risk of neurologic deterioration and a 4.66-fold increase in the combined risk of functional dependency and death.[45]

Observational studies are, therefore, warranted to examine whether the continuation vs discontinuation of statins during critical illness alters inflammatory biomarkers and the course of delirium and, subsequently, the development of LTCI. Additionally, if the results of observational studies are promising, randomized, placebo-controlled trials could investigate the efficacy of statins initiated early during an ICU stay for the prevention or treatment of delirium and the related neurocognitive sequelae coupled with standard clinical outcomes. Because differential effects on neuroinflammation during critical illness might result from treatment with lipophilic vs hydrophilic statins, both types of drugs should be tested in clinical trials. The safety profile of drugs administered during critical illness is always a concern because of alterations in kidney and liver function and other factors predisposing patients to adverse reactions; statins, fortunately, are generally safe, resulting in a very low incidence of myopathy (0.01%) and liver enzyme abnormalities (0.1%) at standard doses.[54] Also, an intervention intended to prevent or treat delirium in patients in the ICU needs to work quickly (over hours rather than days or weeks). Animal models of TBI have shown that statins produce pleiotropic effects within a few hours of administration, making them attractive agents for study during critical illness.[20] Finally, the effects of statins on the mechanisms of neuronal injury during critical illness can be studied using anatomic and functional neuroimaging to examine brain volumes and functional activation to help understand whether statins promote switching from microglia activation to an antiinflammatory phenotype with reduction in brain atrophy and preservation of brain function.[37,55] In conclusion, statins are ideal candidates to investigate in the hope of mitigating the rapidly growing public health problem of ICU delirium and the acquisition of long-term critical illness brain injury affecting thousands of survivors of critical illness annually.

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