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Original Article

The Effect of Statins in Epilepsy: A Systematic Review

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Abstract

Background and Objectives: Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, used for the management of hypercholesterolemia and related atherosclerotic diseases. Several studies have indicated the neuroprotective effects of statins on several neuropathological conditions. However, the role of these medications in epilepsy is still unclear. The purpose is to evaluate and summarize the level of evidence on the efficacy of statins in neuronal hyperexcitability and the neuroinflammatory processes of epilepsy. **Methods:** A systematic review was performed. Eligibility Criteria: This review involved studies conducted in humans and nonhuman experimental models, covering the use of an inhibitor of HMG-CoA reductase, alone or accompanied by another medication, in epilepsy. Information Sources: A systematic literature search was performed in PubMed, Embase, Ebsco Host, Scopus, Science Direct, Medline, and LILACS. Risk of Bias: It was evaluated with the Newcastle–Ottawa Scale and the experimental studies were evaluated using the GRADE tool. **Results:** Twenty articles of the 183 evaluated were included. Sixteen studies were conducted in animal models and four studies in humans. Most studies in mice reported a reduction in epileptiform activity and reduction in systemic inflammation with the treatment of statins, potentially influencing epilepsy control. Few studies in humans were performed in the geriatric population with variable results (neuroinflammation, seizure prevention, cell death, prevention of kindling, increase in convulsive threshold, increase in latency, decrease in frequency of crisis, and reduction in mortality) related to reduction in the rate of hospitalizations, mortality, and prevention of epilepsy. Studies in mice found a decrease in interleukin-1β (IL-1β), IL-6, and tumor necrosis factor alpha and an increase in IL-10 and endothelial nitric oxide synthase. **Conclusions:** The possible antiepileptic mechanism of statins may be related to the reduction in neuroinflammation mediated by a decrease in pro-inflammatory cytokines and action in the nitrergic system. Further studies evaluating the impact of statins on seizure control are necessary.

Keywords: *Brain, epilepsy, seizure, statins*

Introduction

Epilepsy is a neurological disease generated by an abnormal brain electrical activity in certain regions of the brain that predisposes to recurrent unprovoked attacks. Worldwide, a prevalence of 1%–2% is estimated, affecting between 50 and 65 million people, with 50,000–100,000 new cases per year. In addition, it is estimated that 30%–40% are refractory to seizure treatment.[1-3] Epilepsy is considered a public health problem worldwide and is one of the most frequent neurological disorders.[3]

Statins are inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, used for the management of hypercholesterolemia and related atherosclerotic diseases, such as coronary artery

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disease.[1,4,5] The enzyme HMG-CoA reductase catalyzes the conversion of HMG-CoA to L-mevalonate; statins prevent the biological activities of L-mevalonate due to the aforementioned inhibitory effect.[5] Statins perform pleiotropic actions on the endothelium, the inflammatory response, or the production of free radicals. The inhibition of obtaining endogenous cholesterol induces a positive regulation of low-density lipoprotein (LDL) receptors on the cell surface. Obtaining a higher absorption of LDL from the blood and therefore a decrease in its concentration. In addition, high-density lipoprotein levels increase and triglyceride levels decrease.[6]

Several studies have indicated the neuroprotective effects of statins on several neuropathological conditions. The anticonvulsive activity has been explained by suppressing reactive astrogliosis with neuroinflammation in the crises; by stimulating GABAergic activity and inhibiting glutamatergic; by modulating the glycogen synthase kinase-3β pathway; and by decreasing the infiltration of monocytes in the neuronal death of the hippocampus and pro-inflammatory gene expression.[1,4]

The lipophilic statins (atorvastatin [ATV], lovastatin, fluvastatin, pitavastatin, and simvastatin) can passively pass through the blood–brain barrier (BBB); in addition, the hydrophilic statins can also enter the neuroparenchyma.[6,7] All statins are substrates for organic anion transporter polypeptides (OATPs), of which OATP1A2 and OATP1C1 are expressed in the brain. Despite this, the selectivity of hydrophilic statins for these subtypes has not been explored to determine their mechanism of entry to the central nervous system (CNS). In addition, the existence of monocarboxylic acid transporters in the BBB can constitute an alternate route of entry to the CNS although there are no specific studies for the CNS either. Independently of the specific transporters, it is feasible that statins are deposited at different speeds and concentrations within the CNS according to their different lipid solubility alone.[7]

Methods

Objectives

The objective of this review is to answer the following question: What is the level of evidence on the efficacy of statins to decrease neuronal hyperexcitability and neuroinflammatory processes of epilepsy?

To develop the review, the steps of the patients, intervention, comparison, outcomes, and study design strategy were followed.

Inclusion criteria

Types of participants

This review involved studies conducted in humans and nonhuman experimental models.

Type of intervention

It covered the use of inhibitors of HMG-CoA reductase, alone or accompanied by another medication.

Types of studies

The qualitative component of the review included studies that described the molecular mechanisms of statins in the CNS, the pharmacokinetic aspects, and the changes derived from the use of these drugs in neurotransmitters and cerebral cholesterol. The quantitative component included randomized and nonrandomized controlled trials, quasi-experimental designs, prospective or retrospective cohort studies, and nested case–control studies.

Types of results

The benefit of the therapy was defined as the decrease in neuroinflammation derived from seizures, decrease in neuronal death after the seizure, prevention of seizures, decrease in mortality after a seizure episode, increase in seizure threshold, reduction in the frequency, and increase in the latency of the crises.

Search and selection of studies strategy

This systematic review followed the recommendations of the Cochrane Collaboration (PRISMA). A bibliographic search was carried out in the databases: PubMed, Embase, Ebsco Host, Scopus, ScienceDirect, Medline, and LILACS, considering all the publications made up to February 2, 2018. The search was carried out in five steps: First, the keywords using the Medical Subject Headings and DeCs (Health Descriptors), then proceeded to use the descriptors of the subject (hydroxymethyl glutaryl-CoA reductase inhibitors, statins, epilepsy, epileptogenesis) in the databases mentioned. Subsequently, the duplicate records were eliminated (Step 2) and an analysis of the titles and abstracts thrown by the search was continued (Step 3), then the full-text review of the selected articles was proceeded (Step 4), and finally, the references were reviewed of the included articles to identify those studies that also met the eligibility criteria (Step 5). Letters to the editor and studies with a language other than English or Spanish were excluded.

Method of revision

The search strategy and selected studies were evaluated by two independent reviewers (LM and ZC). The discrepancies were discussed with a third reviewer (RM).

Data collection

The following data were extracted from the studies that met the eligibility criteria: authors, year of publication, number of participants, type of study, study objective, statin used, statin dose, epilepsy inducer used, route of administration of the statin, duration of treatment, and results of the study. These data were compiled in Microsoft Excel and were divided into two: collection of human studies and collection of non-human studies.

Assessment of quality and risk of study sessions

The assessment of the risk of bias in human studies was performed using the Newcastle–Ottawa Scale [Figures 1 and 2], while experimental studies in animal models were evaluated using the GRADE tool [Figure 3].

Data synthesis and additional analysis

An analysis of the studies was carried out in nonhuman experimental models that only involved the use of statins, excluding from this analysis those studies that applied a drug or substantial addition to the statin and the studies that did not specify the duration of the treatment. With the Epi-info 7.2 programs, (CDC, Atlanta, Georgia, USA) the median duration of treatment, absolute and relative frequency of the variables were determined: statin used, statin dose, epilepsy inducer used, and route of administration.

Results

Selection of studies

The selection process of the studies was based on the PRISMA foundations as shown in Figure 4. Twenty articles of the 183 included in the bibliographic search were considered.

Characteristics of the studies

Studies in animal models

We identified 16 studies in animal models (mice), of this total only 10 studies (n = 626 mice) met the criteria for descriptive analysis [Table 1]. We excluded three studies that used an additional substance to the statin; one study that did not clearly specify the duration of the treatment and two studies that did not clarify the number of participants. The median duration of treatment with statins was 14 days (IQR = 7–15), the inducers of epilepsy used were pilocarpine, kainic acid, quinolinic acid, pentylenetetrazole (PTZ), and electroshock test, as shown in Figure 5. Sehar *et al*.'s study was performed in two phases: acute and chronic, for statistical analysis were taken as two studies. On the other hand, as can be seen Figure 6, the most used route of administration was

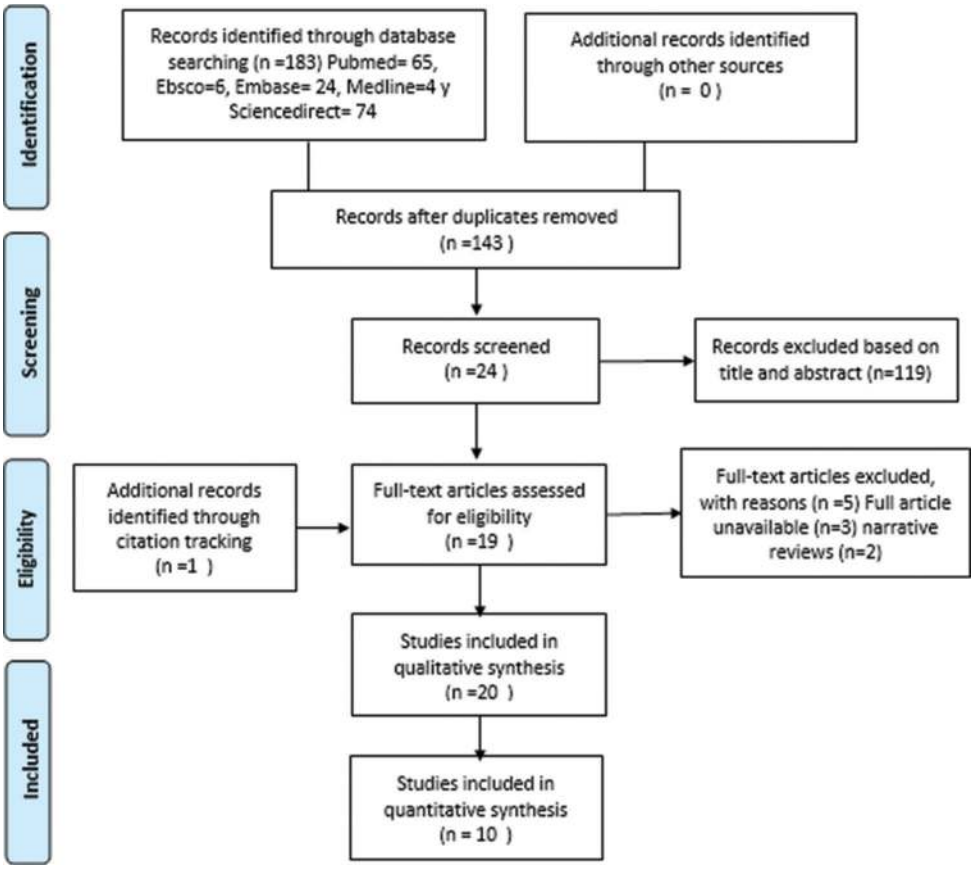

Figure 1: PRISMA flow diagram of our search mechanism

oral. In addition, the most commonly used statin dose was 10 mg of ATV [Figure 7]. In Table 2, it is observed that most of the studies reported a positive change of statin treatment.

Human studies

We identified four studies in humans (n = 1,071,422): 3 (75%) of retrospective cohort and 1 (25%) of nested cases and controls. The results are shown in Table 3.

Evaluation of the risk of bias

The results of the evaluation of the bias are shown in Figures 2-4.

Statins and brain cholesterol

One study quantified sterol levels in the hippocampus of an animal model with unilateral hippocampal lesion induced by kainic acid. The lovastatin treatment was performed 3 days before and 3 days after the induction of status epilepticus (SE). There were no significant changes in the levels of sterols (lanosterol and desmosterol) at 24 h after the SE, but it did detect a bilateral reduction in the hippocampus of the metabolite 24-OHC and cholesterol levels at 48 h and 14 days ($P < 0.001$ and $P < 0.01$, respectively). These periods in which changes were identified corresponded to the preepileptogenic and to the appearance of daily seizures. On the other hand, lovastatin was not associated with alteration of seizures during status.[8]

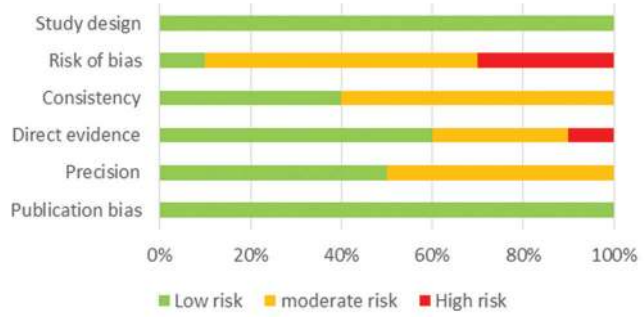

Figure 2: Risk of bias for experimental studies in animal models using GRADE

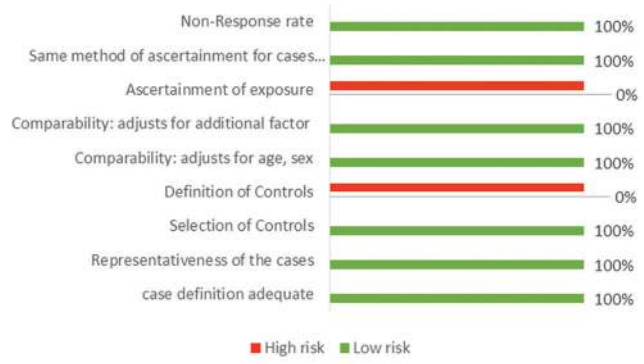

Figure 4: Risk of bias using Newcastle–Ottawa Scale for case–control studies

Statins and neuroinflammation

We identified three studies related to the role of statins in neuroinflammation mediated by cytokines. Two studies used lovastatin and one study used ATV. All three studies administered postinduction statin with pilocarpine. The study by Oliveira *et al*. found a reduction of the pro-inflammatory cytokines: interleukin-1β (IL-1β), IL-6, tumor necrosis factor alpha (TNF-α), and interferon-γ in cortex and hippocampus, 14 days after induction ($P < 0.05$) together with an increase in the levels of the anti-inflammatory cytokine IL-10. These results were better with the dose of ATV 100 mg/kg compared to the dose of 10 mg/kg. In addition, the control group of ATV without induction with pilocarpine also showed a reduction in pro-inflammatory cytokines. In this same study, it was found that mice needed higher doses of the statin to achieve an increase in IL-10, unlike rats, which in turn had higher levels of pro-inflammatory cytokines.[3] Gouveia *et al*.found similar results in both 2011 and 2014.[5,9] The two

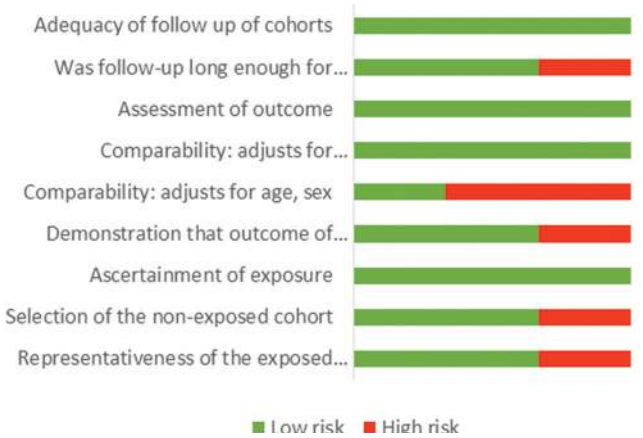

Figure 3: Risk of bias using Newcastle–Ottawa Scale for cohort studies

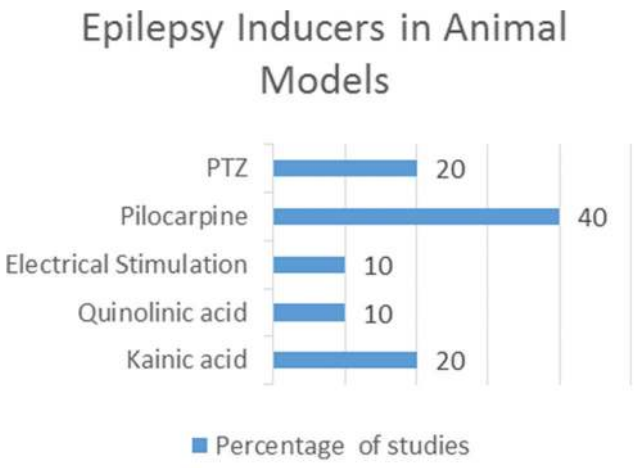

Figure 5: Epilepsy inducers

Table 1: Statin studies in animals

Authors	Year	Number of animals	Statin	Number of times per day	Inductor	Start of statin	Duration of treatment	Evaluations	Results
Sehar *et al.*[1]	2015	24	Controls=6 ATV 20 mg, 40 mg and 80 mg=6 for group	Once a day	PTZ (60 mg/kg)	1 h before PTZ administration	7 days	ICES test, elevated plus maze and forced swim test	ATV 80 mg/kg increased seizure threshold current significantly compared with the control group (22±0.00); did not significantly increase the latency of seizures
		60	Controls=12 Only PTZ=12 ATV 20 mg + PTZ, 40 mg + PTZ y 80 mg + PTZ=12 for group		PTZ (25 mg/kg)	1 h before PTZ administration	7 weeks	Racine scale and assessment of dopamine, glutamate, and GABA levels	ATV 20, 40, and 80 mg/kg suppressed the development of PTZ kindling significantly in a dose-dependent manner (P<0.05, P<0.01, and P<0.001, respectively)
Van Vliet *et al.*[18]	2011	13+	Control with ATV=5, ATV 10 mg/kg + ES=8, vehicle+ ES=8	Once a day	ES	7 before the induction of epilepsy and 7 days after	14 days	Video-EEG monitoring-Racine scale, blood-brain barrier permeability, and fluorescent immunocytochemistry	ATV did not affect the duration of SE or the development of epilepsy, had not reduced inflammation, neuronal death, or synaptic reorganization
Heverin *et al.*[8]	2012	96	4 mg/kg	Once a day	KA (0.3 μg)	1 h before and 1 h after the KA	7 days	EEG telemetry units, sterol analysis, and histopathology	LVT did not alter seizures during SE or seizure-induced neuronal death. Changes in hippocampal cholesterol homeostasis occur bi-laterally
Oliveira *et al.*[3]	2018	108	Saline=22, ATV 10=17, ATV 100=13	Once a day	Pilocarpine (100 mg/kg) after methylscopolamine 1 mg/kg	3 h after diazepam injection	14 days	Cytokine analysis and Behavioral tests	ATV dose-dependently decreased basal and SE-induced levels of (IL-1β), (IL-6), (TNF-α), (INF-γ) and increased (IL-10) levels in the hippocampus and cerebral cortex
Gouveia *et al.*[5]	2014	26	Control=5; LVT (20 mg/kg)=5; Pilocarpine=8 and Pilocarpine plus LVT=8	Twice daily	Pilocarpine (350 mg/kg)	After 2 h of SE onset	15 days	Real-time PCR analysis for cytokines and Immunohistochemistry	LVT induced an increased expression of the IL-10 and the pilocarpine plus lovastatin group showed a significant decrease in the levels of IL-1β and TNF-α during the latent and chronic phase
Piermartiri *et al.*[10]	2009	71	Saline + QA=22 ATV 1 mg/kg + QA=15 ATV 10 mg/kg + QA=34	Once a day	Quinolinic Acid (36.8 nmol)	Before QA administration	7 days	L-[3H] glutamate Uptake, Cell death (Propidium Iodide Staining)	ATV 10 mg/kg prevented seizures induced by QA in 29.41% of the mice. (P=0.004), ATV prevented QA induced cell death in the hippocampus and prevented the reduction in glutamate uptake into the hippocampus

Contd...

Table 1: Contd...

Authors	Year	Number of animals	Statin	Number of times per day	Inductor	Start of statin	Duration of treatment	Evaluations	Results
Lee *et al.*[11]	2008	28	Control=9 ATV 10 mg/kg pre-SE=11 ATV 10 mg/kg Post-SE=8	Once a day	KA (10 mg/kg)	Before KA injection- ATV pre-SE group; 0.5 h after KA in ATV Post-SE group	7 days	Racine scale	Treatment with ATV efficiently decreased convulsive events induced by KA, the neuronal death of the hippocampus, infiltration of monocytes and proinflammatory gene expression
Gouveia *et al.*[9]	2011	20	Control=5, Solo LVT 20 mg=5, Solo pilocarpine=5, pilocarpine plus LVT=5	2 h after the onset of SE and 12 h after the first dose	Pilocarpine (350 mg/kg)- 1 mg/kg before scopolamine methyl nitrate	After pilocarpine injection	0,5 days	Quantitative real-time PCR (for cytokines and kinin B1 and B2 receptors) and corporal temperature	LVT significant decrease in mRNA expression of IL-1β, IL-6, TNF-α, and kinin B1 receptor, also reduced SE-induced hyperthermia
Campos *et al.*[19]	2017	152	Control=14, ATV 10 mg/kg=10, ATV 100 mg/kg=10, Solo SE=13, ATV 10 + SE=18, ATV 100 mg/kg + SE=15	Once a day	Pilocarpine 100 mg/kg and Pilocarpine (30 mg/kg)	After pilocarpine injection	14 days	Giemsa staining	The ATV regarded against tonic-clonic seizures caused by PTZ on the 14th post-SE. The protective effects were similar in female and male mice, requiring a higher amount of ATV in females (100 mg/kg versus 10 mg/kg in males)

PTZ: Pentylenetetrazole, ICES: Increasing current electroshock, ATV: Atorvastatin, ES: Electrical stimulation, EEG: Electroencephalography, SE: Status epilepticus, LVT: Levetiracetam, PCR: Polymerase chain reaction, TNF-α: Tumor necrosis factor alpha, IL-1β: Interleukin-1β, INF γ: Interferon gamma, GABA: gamma-Aminobutyric acid, KA: Kainic acid, QA: Quinolinic acid

Table 2: Positive results reported in experimental studies

Study	Neuro-inflammation	Seizure prevention	Cell death	Prevention of kindling	Increase in convulsive threshold	Increase in latency and decrease in frequency of crisis	Reduction in mortality
Sehar *et al*.[1]				•	•		
Oliveira *et al*.[3]	•						
Akgün *et al*.[2]	•			•		•	•
Gouveia *et al*.[9]	•						
Piermartiri *et al*.[10]		•	•				
Lee *et al*.[11]	•		•				
Gouveia *et al*.[5]	•						
Shafaroodi *et al*.[12]					•		•
Seker *et al*.[13]	•						
Moezi *et al*.[21]					•		•

•The study evaluated the respective parameter, finding positives results after the statin administration

Table 3: Statin studies in humans

Authors	Year	Type of study	Period evaluated	Number of patients	Age	Statin	Objective	Results
Pugh *et al*.[14]	2009	Retrospective cohort study	October 1999-September 2000	Cohort of epilepsy (*n*=1847) cohort without epilepsy (*n*=1,023,376)	≥65	Unspecified	Identify risk factors for new-onset geriatric epilepsy	The prescription of statins showed an OR=0.64, 95% CI=0.56-0.73 for the prevention of epilepsy
Etminan *et al*.[15]	2010	Nested case-control study	1995-2004	217 cases and 2117 controls	69.4±12.3 (cases) 70.0±9.6 (controls)	Atorvastatin, lovastatin, cerivastatin, fluvastatin, pravastatin, simvastatin, and rosuvastatin	To assess the potential efficacy of statins in the prevention of epilepsy	The ARR in patients with current use of statins was 0.65 with 95% CI 0.46-0.92, The ARR for previous users of statins was 0.72 (95% CI 0.39-1.30)
Sierra-Marcos *et al*.[16]	2014	Retrospective cohort study	April 2006-September 2012	427 patients	60.9±17.8	Simvastatin, atorvastatin, and pravastatin	To evaluate the possible role modulator of statins in status epilepticus	Statins were associated with lower mortality (relative risk ratio 0.38, *P*=0.046)
Trivedi *et al*.[17]	2018	Retrospective cohort study	October 2003-March 2012	43,438 patients	56.0±12.0 statin users 55.7±12.4 No statin users	Simvastatin, atorvastatin, pravastatin, and rosuvastatin	To examine the association between the use of statins and the risk of epilepsy	The OR of epilepsy in the general cohort was 0.91 (95% CI=0.67-1.23) and in the healthy cohort, it was 1.08 (95% CI=0.64-1, 83). No significant beneficial or detrimental effect of the use of statins on the risk of epilepsy was demonstrated

ARR: Adjusted rate ratio, OR: Odds ratio, CI: Confidence interval

studies used ATV with a difference in the duration of treatment. However, both studies found a reduction in IL-1β and TNF-α.[5,9]

Statins and nitric oxide

Four studies evaluated the effect of statins on nitric oxide. Three studies used PTZ as an inducer and one used penicillin G ATV.[13,16,17,20] Akgün Dar *et al*, administered ATV 30 min before induction found that pretreatment with this statin reduced the inducible nitric oxide synthetase and matrix metalloproteinase 2 that have been related to a proconvulsant activity ($P < 0.001$) and also found a reduction in frequency and an increase in latency of seizures ($P < 0.001$).[2] These findings agree with the results of the study by Shafaroodi *et al*., who used PTZ and electrical stimulation as inductors and

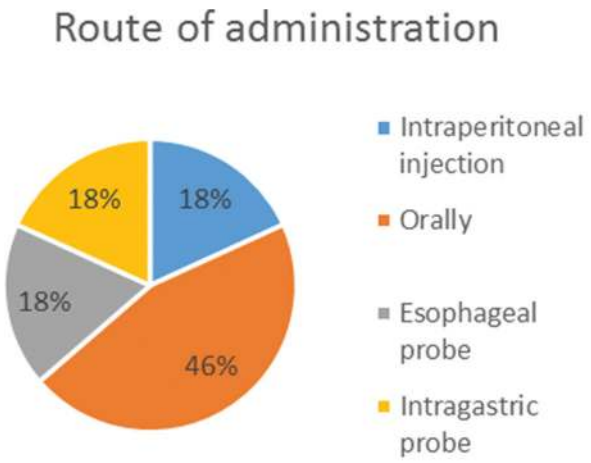

Figure 6: Statin route of administration

administered ATV of 10 and 20 mg/kg; this treatment increased the threshold for tonic seizures caused by PTZ and decreased the appearance of tonic seizures and death in the induction model with electric current.[12] Similarly, the study by Moezi *et al*. found an increase in the seizure threshold for both intravenous and intraperitoneal PTZ models and a decrease in the appearance of tonic seizures and death in the chronically treated group with ATV and induction with intraperitoneal PTZ.[21] In the study by Seker *et al*., ATV, simvastatin, and rosuvastatin were used at a dose of 20 mg/kg; in this case, the group with rosuvastatin presented the best antiepileptic effect with a decrease in the expression of p53, Bax, and caspase 3 that are associated with cellular apoptosis, together with an increase in endothelial nitric oxide synthetase.[13] Three studies (Seker *et al*., Shafaroodi *et al*., and Moezi *et al*.) showed that inhibitors of nitric oxide synthetase (L-NAME and aminoguanidine) decreased the anticonvulsant effect of ATV.[12,13,21]

Statins and specific syndromes associated with epilepsy

We identified two studies that evaluated the use of statins in genetic syndromes with epileptogenic characteristics. In 2013, Osterweil *et al*. found that the administration of 100 mg/kg of lovastatin to genetically modified mice (fragile X syndrome) was able to correct the excessive synthesis of proteins and prevent the outbreak of epileptiform activity in the hippocampus *in vitro*, in addition to protecting the mice *in vivo*.[1,22] On the other hand, in 2018, it was postulated that lovastatin is capable of modulating upregulated protein functions in animal models with Angelman syndrome by a mechanism other than the inhibition of protein synthesis.[23] However, more research is needed to clarify this relationship.

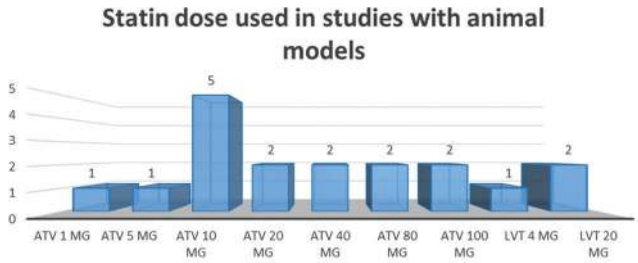

Figure 7: Number of studies and dose of statin used in the experimental studies

Discussion

The neuroprotective effects of statins have been observed in various neurological diseases. However, its protective effect on epilepsy continues to be debated and most studies have been conducted in rats. An association has been found between the use of statins and the reduction of the risk of epilepsy in older adults. Sierra-Marcos *et al*. demonstrated an antiepileptic role of statins in older adults, for which they used the registry of 427 patients with an epileptic episode in a period of 6 years and took into account different predictive items of prognosis, among which if they had used or they use statins. The use of statins was statistically significant, which correlated with a decrease in morbidity and mortality in these patients.[16]

Etminan *et al*. found that statins reduce the risk of hospitalization in patients with epilepsy focused on senile patients and stipulated that the result is directly related to the dose and the possible anti-inflammatory properties that statins confer.[15] The few studies conducted in humans focused on observing the properties of statins in terms of epilepsy have had an effect in elderly people who have been shown to have a certain risk of developing epilepsy associated with cerebrovascular diseases and dementia. Pugh *et al*., in their study on the risk factors of epilepsy of onset in old age, observed that in patients with prescription of statins, the development of epilepsies was lower.[14]

There is research in humans that suggests the neuroprotective benefit of statins that is generalized to the entire population. Trivedi *et al*. could not determine the benefit of statins in their study where they included healthy individuals or those with few comorbidities and who used statins or not; however, it is emphasized that they were not associated with an increase in the risk of statins. Development of epilepsies which allows establishing that the use of statins is safe in patients who have epilepsy.[17] All studies reviewed in humans agree on the need for more research on the subject to be able to define the beneficial effect of statins and be able to explain it.

Summary of evidence

This systematic review gives an overview of the available literature on the role of statins and its possible effect on epilepsy. This study only provides evidence 3b.

Limitations

Our study has some limitations. Most studies focused largely on an experimental level. All articles included in this review are peer-reviewed. There is a possibility of publication bias. Finally, the inclusion of only articles in English and Spanish could affect the generalization of our findings.

Conclusions

The role as anticonvulsant agents of statins is not completely known. Still, there is missing evidence to know how this type of mechanism works modulating the immune system. The participation of statins as reducing agents of neuroinflammation requires more studies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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