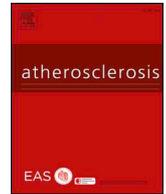




ELSEVIER

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Correspondence

An update on statins: Pleiotropic effect performed in intracerebral hemorrhage



ARTICLE INFO

Keywords:

Intracerebral hemorrhage
 Statin
 Neutrophil apoptosis
 Microglia polarization
 Hematoma absorption

To the Editor,

We read with interest the recent article by Chung et al. [1] published in this issue of *Atherosclerosis*, in which the authors demonstrated that patients with intracerebral hemorrhage (ICH), who continued statin therapy, had better all-cause mortality outcomes compared with those who did not continue statin therapy. Although the authors have some possible explanations for the mechanism via the pleiotropic effect of statins, such as anti-oxidative, BBB protection and anti-inflammation, experimental evidence of continue statin therapy is still lacking. Therefore, we employed an animal model to explore the potential neuroprotective mechanism of continuing statin for ICH.

In our study, the ICH model was induced in adult male Sprague–Dawley rats by an injection of autologous blood [2]. To simulate continuous statin administration, animals randomly received simvastatin or vehicle daily from 5 days before ICH until sacrifice. The results showed that continuing simvastatin effectively decreased the peripheral neutrophil count, neutrophil to lymphocyte ratio (NLR) and brain neutrophil-invading, as well as attenuated ICH-induced brain edema and neurological deficits. Further research shed light on the underlying mechanisms. On the one hand, simvastatin inhibited the transcription of chemokines and vascular cell adhesion molecule in perihematomal issue, such as TNF- α , IL-6, CCL2 and ICAM-1, which subsequently suppressed neutrophil mobilization from bone marrow and chemotaxis to injured tissues following ICH. On the other hand, through disorganizing the expression of apoptotic proteins in neutrophil, simvastatin accelerated the apoptosis of neutrophil and lowered the circulating neutrophil count. Recently, increasing evidence supports that higher neutrophil count and NLR at early stage of ICH contributes to the poorer outcome [3–6]. Thus, in view of these results, we could speculate that peripheral neutrophil modulation may also be involved in the neuroprotective effect of continuing statin for ICH, in addition to the anti-oxidative and BBB protection. Since all included ICH patients have a history of dyslipidemia in this cohort study, animal models with dyslipidemia will be ideal for statin research in the future.

Additionally, findings from our team also proposed that statins have a potential to promote intracranial hematoma resolution. In an experimental IVH model, we observed that simvastatin significantly enhanced brain hematoma absorption, alleviated iron deposition and hydrocephalus, and promoted neurological recovery after IVH, which may in part be due to the increased expression of CD36 scavenger receptor (facilitating phagocytosis) in the perihematomal and periventricular area [7]. Furthermore, by using the rat model of ICH, we found that animals treated with simvastatin presented smaller hematoma volume than the control group ($9.75 \pm 4.92 \text{ mm}^3$ vs. $17.65 \pm 6.43 \text{ mm}^3$, $p < 0.05$) at 4 weeks based on the comparable baseline in each group [8]. According to previous literature, microglia are the major phagocytes of the brain. *In vitro*, activated microglia develop into either classically activated (M1, proinflammatory) or alternatively activated (M2, anti-inflammatory) phenotypes, a process termed polarization [9]. Thus, to formulate the possible mechanism of hematoma clearance, we further explored the relationship between simvastatin and microglia polarization following ICH. Notably, in our study, simvastatin effectively upregulated the expression of CD206 (a marker of M2) and CD36 while significantly reduced the expression of CD86 (a marker of M1) on perihematomal microglia, by promoting M2 phenotype polarization. Moreover, simvastatin increased PPAR γ activation and enhanced microglia-induced erythrocyte phagocytosis *in vivo* and *in vitro*. All the above effects of simvastatin were abolished by PPAR γ inhibitor GW9662 [8]. Therefore, we could speculate that simvastatin accelerates hematoma cleanup post-ICH via facilitating erythrocyte endogenous phagocytosis by microglia/macrophages through activation of PPAR γ and microglia M2 polarization.

Taken together, clinical evidence is still required to approve these potential pleiotropic effects of statins in animal models, which could be beneficial to neurological recovery and better outcome for patients with ICH in the future.

DOI of original article: <https://doi.org/10.1016/j.atherosclerosis.2018.08.049>

<https://doi.org/10.1016/j.atherosclerosis.2019.01.020>

Received 26 December 2018; Accepted 22 January 2019

Available online 25 January 2019

0021-9150/© 2019 Elsevier B.V. All rights reserved.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

References

- [1] C.M. Chung, M.S. Lin, C.H. Liu, et al., Discontinuing or continuing statin following intracerebral hemorrhage from the view of a national cohort study, *Atherosclerosis* 278 (2018) 15–22.
- [2] J. Zhang, X. Shi, N. Hao, et al., Simvastatin reduces neutrophils infiltration into brain parenchyma after intracerebral hemorrhage via regulating peripheral neutrophils apoptosis, *Frontiers in Neurosciences* 12 (2018) 977.
- [3] S. Lattanzi, C. Cagnetti, L. Provinciali, et al., Neutrophil-to-Lymphocyte ratio predicts the outcome of acute intracerebral hemorrhage, *Stroke* 47 (2016) 1654–1657.
- [4] A.M. Gusdon, G. Gialdini, G. Kone, et al., Neutrophil-lymphocyte ratio and perihematomal edema growth in intracerebral hemorrhage, *Stroke* 48 (2017) 2589–2592.
- [5] C. Tao, X. Hu, J. Wang, et al., Admission neutrophil count and neutrophil to lymphocyte ratio predict 90-day outcome in intracerebral hemorrhage, *Biomark. Med.* 11 (2017) 33–42.
- [6] F. Wang, S. Hu, Y. Ding, et al., Neutrophil-to-Lymphocyte ratio and 30-day mortality in patients with acute intracerebral hemorrhage, *J. Stroke Cerebrovasc. Dis. : the official journal of National Stroke Association* 25 (2016) 182–187.
- [7] Q. Chen, X. Shi, Q. Tan, et al., Simvastatin promotes hematoma absorption and reduces hydrocephalus following intraventricular hemorrhage in part by upregulating CD36, *Translational stroke research* 8 (2017) 362–373.
- [8] Y. Wang, Q. Chen, Q. Tan, et al., Simvastatin accelerates hematoma resolution after intracerebral hemorrhage in a PPARgamma-dependent manner, *Neuropharmacology* 128 (2018) 244–254.
- [9] X. Lan, X. Han, Q. Li, et al., Modulators of microglial activation and polarization after intracerebral haemorrhage, *Nature reviews, Neurology* 13 (2017) 420–433.

Qianwei Chen

Department of Neurosurgery, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, 400038, China
 Department of Neurosurgery, Air Force Hospital of Western Theater, Chengdu, Sichuan, 610021, China

Jianbo Zhang

Department of Neurosurgery, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, 400038, China

Hua Feng

Department of Neurosurgery, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, 400038, China

Zhi Chen*

Department of Neurosurgery, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, 400038, China
 E-mail address: zhichen@tmmu.edu.cn.

* Corresponding author. Department of Neurosurgery, Southwest Hospital, Third Military Medical University (Army Medical University), No. 30, Gaotanyan Street, Chongqing, 400038, China.