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Response to Letter to the Editor from Dr. Dale Ding: Abrogation of cerebral edema and vascular inflammation following subarachnoid hemorrhage by cannabinoid receptor activation

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We would like to thank Dr. Ding for his interest in our paper. Dr. Ding provides constructive comments for the potential clinical translation of cannabinoid receptor agonists in SAH patients. We agree with Dr. Ding that immunohistochemical staining to visualize leukocyte infiltration in cerebral vessels may strengthen the findings in our study. Although not after subarachnoid hemorrhage (SAH) but in LPS induced encephalitis, Ramirez et al. reported that vascular leukocyte adhesion was attenuated by the administration of cannabinoid type 2 receptor (CB2R) agonists which was visualized by intravital microscope [1]. Dr. Ding also suggests evaluating pro-inflammatory cytokines during brain inflammation after SAH. We agree with the author that inflammation plays an important role in the progression of SAH, since the disruption of the blood-brain barrier facilitates the infiltration of peripheral inflammatory cells, leading to further parenchymal damage that is related to cell death after SAH [2,3]. CB2R agonist was reported to reduce tumor necrosis factor- α (TNF) expression [4,5]; therefore, it is possible that CB2R stimulation may also attenuate cytokine and chemokine release after SAH.

Dr. Ding brings up a very interesting point that the effect of CB2R activation on the cerebrovascular smooth muscle cells (SMC) during cerebral vasospasm needs to be evaluated, which can alter post-SAH neurological outcomes. It is still unknown whether CB2R stimulation ameliorates acute vasoconstriction in the SMC; however, Rajesh et al. reported that CB2R agonist decreased TNF- α -induced RhoA activation in human coronary artery endothelial cells (HCAECs) [5]. Since RhoA activates Rho kinase (ROCK), which contributes to BBB disruption and abnormal SMC contractions after SAH [6], it is possible that CB2R stimulation may ameliorate ROCK-derived cerebral vasospasm.

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Conflict of interest

The authors do not have any conflict of interest.

We agree with Dr. Ding's suggestion that the modulation of cannabinoid-mediated pathways could be a promising therapeutic avenue to alter post-SAH neurological outcomes and that further investigation is needed to evaluate the safety of cannabinoid derivatives in SAH patients. Our study showed that the selective CB2R agonist attenuated neurological outcome, brain edema, and inflammation after SAH. Since, cannabinoid receptor type 1 (CB1R) signaling has a psychoactive potency and may have neurotoxic effects [7], we speculate that the weak CB1R and CB2R agonist, dronabinol, may not be a suitable candidate for preclinical studies as Dr. Ding suggested. Additionally, it is also important to decide on a proper timing and dosage of CB2R agonist administration for clinical trials. Higher dose of selective CB2R agonist may activate CB1R in the target tissues and result in unwarranted pharmacological effects. Likewise, CB2R agonists appear to be most effective if given before the initiation of the insult, and may lose their efficacy or even promote inflammation when given at later time points [8]. We agree with the author that further work is required to gain additional insight into physiological and pathophysiological consequences of SAH including the inflammatory response, and that the safety of selective CB2R agonists require further exploration.

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