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The authors reply: P2X7 receptor and apoptosis

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We would like to thank Li et al. (1) for their comments on our previously published study (2), which demonstrated that brilliant blue G, a selective P2X7 receptor antagonist, ameliorated neuronal apoptosis via inhibiting P38 mitogen-activated protein kinase (MAPK) after subarachnoid hemorrhage (SAH). In the letter by Li et al., two interesting concerns were raised: first, the effect of P38 MAPK on apoptosis should be detected by its inhibitor and double immunofluorescence staining of P38 MAPK and terminal deoxynucleotidyl transferase-mediated uridine 5'-triphosphate-biotin nick end-labeling (TUNEL); and second, P2X7 receptor-induced proinflammatory cytokines may trigger neuronal apoptosis.

In our published study, we focused on P2X7 receptor and the potential therapeutic effect of its antagonist brilliant blue G (2). Apoptosis was one of the outcome measurements but not the focus of the study. Furthermore, the role of P38 MAPK in apoptosis after SAH has been explored in previous studies (3, 4). The phosphorylation of P38 MAPK was observed in the cerebral arteries and cortex after SAH (5). Inhibition of P38 MAPK prevented apoptosis both in cortex and in basal artery after SAH (3, 4). Due to the abovementioned reasons, we did not repeat P38 MAPK-related experiments such as P38 MAPK inhibitor and double immunofluorescence staining of P38 MAPK and TUNEL. In our published study, we found that inhibition of P2X7 receptor reduced the activation of P38 MAPK and caspase-3, which indicated that P38 MAPK may be one of downstream molecules of P2X7 receptor. It has been established that P38 MAPK plays an important role in caspase-3-dependant apoptosis (6). Therefore, we draw the conclusion that inhibition of P2X7 receptor ameliorated apoptosis possibly via inhibiting P38 MAPK. However, we cannot exclude other possibilities such as reactive oxygen species and Ca²⁺ overload that may be involved in P2X7 receptor-activation induced apoptosis, as Li et al. proposed.

Regarding the second concern that P2X7 receptor activation resulted in the production of proinflammatory cytokines via cryopyrin inflammsome after SAH in rats (7), we had discussed this limitation in the published study (1). We agree with Li et al that

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proinflammatory cytokines, such as IL-1 β and TNF α , may lead to neuronal apoptosis which in turn may aggravate the inflammatory response. On the contrary, there are cytokines that are neuroprotective and beneficial to brain tissues. For instance, IL-10 may facilitate brain repair processes in most form of brain damage (8). The relationship between inflammation and apoptosis after SAH is complex and so far, the underlying mechanisms are poorly understood. Further researches are needed to explore the link between inflammation and apoptosis, which may provide a novel strategy to attenuate inflammation and apoptosis simultaneously.

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