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Response to Deficiency of Bradykinin Receptor B2 Is not Detrimental in Experimental Stroke

Our response was solicited by the editor based on the article by Kleinschnitz et al.1 We stand by our results that deficiency in the kinin B2 receptor exacerbates ischemic stroke deficits.2 Kleinschnitz et al1 doubt the possibility of dissecting 8 coronal sections from the mouse brain. In fact, it is easy to dissect each mouse brain into 8 serial sections using a 1-mm mouse brain matrix (RBM-2000C, ASI Instruments). We incorrectly identified the thickness as ~2 mm instead of 1 mm per section (page 753), and cubic millimeters per rat instead of cubic millimeters per mouse (page 754).2 The sections were stained with 2% 2,3,5-triphenyltetrazolium chloride and individually photographed by James Nicholson in the Laboratory Medicine Imaging Core Facility at the Medical University of South Carolina. During image assembly, we misplaced 1 of the 8 sections on the bottom of the right panel (first row) in the bradykinin B2 receptor knockout group 3 days after middle cerebral artery occlusion (MCAO; Figure 3; shown here). The correct image of the 2,3,5-triphenyltetrazolium chloride–stained serial section of the bradykinin B2 receptor knockout mouse is indicated by an arrow.

Kleinschnitz et al1 indicated that the infarct size was small in our study.2 All of the images from the series of 2,3,5-triphenyltetrazolium chloride–stained sections of wild-type and B2R-KO mice were sent to Dr Cesar V. Borlongan (Department of Neurology and Institute of Molecular Medicine and Genetics, Medical College of Georgia) to calculate the infarct volume in a blinded fashion. The reason for the discrepancy is that we measured infarct size and volume corresponding with striatum only, which is the most consistent brain area damaged by MCAO. Our calculated infarct volume in wild-type mice 1 day after MCAO is quite close to the published data.3 The infarct size usually reaches a maximum at day 2 or 3 after MCAO and reduces gradually.4 Moreover, the infarct size is not significantly increased when the occlusion time changes from 60 minutes to 180 minutes.5

We chose to use only mice with neurologic deficit scores ≥5 after fully recovering from anesthesia to assure that MCAO was successful.2 Our results showed that the mortality rate and neurologic deficit scores of bradykinin B2 receptor knockout mice (n=48) after MCAO were significantly increased compared with wild-type mice (n=40). The protective role of the kinin B2 receptor in ischemic brain injury was supported by our previous study using a rat MCAO model.6 Delayed systemic kallikrein gene delivery after MCAO was effective in reducing neurologic dysfunction, infarct size, apoptosis, and inflammation and promoting angiogenesis and neurogenesis. Neuropeptidergic effects of kallikrein were mediated by the kinin B2 receptor, because icatibant blocked the effects of kallikrein.6 Most importantly, a recent clinical report has demonstrated that human tissue (urinary) kallikrein is effective in the treatment of patients with acute brain infarction when intravenously infused within 48 hours of stroke onset.7 Given the current evidence, we are convinced that kallikrein/kinin through kinin B2 receptor activation plays a neuroprotective role in ischemic brain injury.

Disclosures

None.

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