Response to Letter Regarding Article, “Delayed Administration of Tat-HA-NR2B9c Promotes Recovery After Stroke in Rats”

We thank Drs Zuo and Xu for their interesting letter pertaining to our recently published article, “Delayed administration of Tat-HA-NR2B9c promotes recovery after stroke in rats.” We would like to take this opportunity to formally address Drs Zuo and Xu’s letter.

Cyclin-dependent kinase 5 (Cdk5) is a multifaceted serine/threonine kinase protein. The 35-kDa regulatory activator (p35) of cdk5 is a brain-specific calpain-substrate. Under physiological conditions, Cdk5/p35 is involved in many neuronal processes. However, p35 is a short-lived protein with a half-life ($t_{1/2}$) of 20 to 30 minutes. Stimulation of the N-methyl-D-aspartate receptor in primary cortical neurons by glutamate triggers calcium-dependent calpain–mediated proteolytic cleavage of p35 into a smaller 25-kDa form (p25) that possesses a longer half-life. Enhanced Cdk5/p25 activity has been implicated in many neurodegenerative diseases, including ischemic stroke. In our article, we found that ischemia caused a significant increase in Cdk5 activity but not p35 expression at 1, 4, 7, and 10 days after stroke. Although we did not measure p25 level, it has been reported that increased levels of p25 are found in the brains of mice subjected to focal ischemic stroke and global cerebral ischemia and in brain specimens from patients with ischemic stroke. Thus, we could not exclude the possibility that the rapid conversion of p35 into p25 in the ischemic brain leads to the normal p35 level and that increased p25 contributes to ischemia-induced increase in Cdk5 activity.

Stimulation of the GluN2B-containing N-methyl-D-aspartate receptor in the extrasynaptic sites by ischemic glutamate release triggers excitotoxic neuronal death. Extrasynaptic N-methyl-D-aspartate receptors–mediated increase in nitric oxide can produce S-nitrosylation of Cdk5, and the S-nitrosylation of Cdk5 results in excessive activation of Cdk5, contributing to mitochondrial dysfunction, synaptic damage, and neuronal cell death. Our study showed that ischemia induced the formation of S-nitrosylated Cdk5. Therefore, S-nitrosylated Cdk5, at least in part, contributes to ischemia-induced increase in Cdk5 activity in our study.

Finally, we wish to address the concern about sample size. We know that it is important that the sample size chosen to ensure adequate power to detect a prespecified effect size. For Western blots, we estimated the sample size by analyzing pre-experimental data with power analysis and sample size software. Based on the estimation, we measured Cdk5 activity and expression, and p35 level with 4 samples in our study.

Disclosures

None.

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Stroke. 2015;46:e193; originally published online June 25, 2015;
doi: 10.1161/STROKEAHA.115.010073

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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