Response to Letter by Tsuda

Response:
With interest we read an insightful letter written by Dr Tsuda on account of our article. Dr Tsuda has pointed out that glutamate excitotoxicity is a major component of neural cell damage and the inhibition of NMDA receptors as well as sympatholytic action may both be important for isoflurane-induced neuroprotection. Furthermore, he suggests that the readers may want to know the effect of isoflurane on the contents and release of catecholamines in the injured regions and whether isoflurane acts synergistically with MK-801 against the hypoxic-ischemic brain injury.

We want to acknowledge the importance of excitotoxic events and NA release in neonatal brain injury. In fact, we named excitotoxicity as one of the major pathophysiological perpetrators for neonatal hypoxia-ischemia in the introductory section of our article.

Studies have shown, however, that nearly all general anesthetic agents including isoflurane can block NMDA receptors or enhance GABA<sub>A</sub> receptors. Therefore, it is important to further dissect other and perhaps more specific pathways of neuroprotection triggered by each and every anesthetic agent. Moreover, clinical trials with NMDA antagonists failed, which inarguably calls for exploring alternative pathways when studying putative neuroprotective agents.

Interestingly, the role of glutamate excitotoxicity has been thoroughly established in adult models of brain injury while less so in the immature brain. It has been postulated that the effectiveness of glutamate receptor antagonists in reducing neonatal brain injury depends on the treatment regimen and is age specific. Recent studies have demonstrated that NMDA receptor antagonist MK801 may even induce caspase-3 activation and brain injury in postnatal brain, which is consistent with the notion of earlier authors stating that “moderate NMDA receptor activation is probably involved in the survival signal of the neuron.”

Clearly, NMDA inhibition may not fully account for soundly beneficial effects of acute isoflurane exposure in the setting of neonatal hypoxia-ischemia. In face of the aforementioned as well as our findings, brain protective effects of isoflurane in hypoxia-ischemia may rely on other molecular events.

In the present study we focused on sphingosine-1-phosphate/PI3K pathway. Besides combating apoptosis, S1P receptor activation may be involved in modulation of immune and inflammatory response to cerebral hypoxia-ischemia. S1P receptor agonism suppresses leukocyte adhesion to activated endothelium and inhibits inflammatory neutrophil recruitment through a nitric oxide–dependent mechanism. Therefore, modifying S1P pathway may offer an additional protection extended way beyond the excitotoxicity phase.

In the current study we have demonstrated that isoflurane post-treatment reduced brain injury after neonatal hypoxia-ischemia. Isoflurane-induced neuroprotection was abrogated with VCP23019 and wortmannin, implicating S1P and PI3K for causation of isoflurane neuroprotection. We agree that the effect of isoflurane on NMDA in neonatal hypoxia-ischemia deserves study. Likewise, other candidate mechanisms of neuroprotection should be investigated in order to strengthen translational potential of isoflurane post-treatment in neonatal hypoxia-ischemia.

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Stroke. 2010;41:e579; originally published online September 2, 2010; doi: 10.1161/STRKEAHA.110.595991

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