Neuroprotective Effects of MK-801 and Catecholamine Release in the Central Nervous System

To the Editor:

We read with great interest the recent article by Gerriets and colleagues dealing with the neuroprotective effects of MK-801, the N-methyl-D-aspartate (NMDA) receptor antagonist, in the different rat stroke models for the permanent middle cerebral artery occlusion (MCAO). The results of their presented study demonstrated that, because hypothalamic damage and subsequent hyperthermia can confound the results, the macrosphere MCAO models without hypothalamic damage may be more appropriate to study the neuroprotective effects of MK-801 than the suture MCAO and the macrosphere MCAO models with hypothalamic infarction.

Several studies have reported the mechanisms for the neuroprotective effects of MK-801 in the central nervous system. In a study we presented earlier, changes in norepinephrine (NE) release evoked by L-glutamate was investigated in rat central nervous system. In an in vitro study, we showed that L-glutamate increased the release of NE from rat medulla oblongata, and further observed that the facilitative effect of L-glutamate on NE release was more pronounced in spontaneously hypertensive rats than in normotensive rats. In addition, it was demonstrated that MK-801 significantly reversed the increase in NE release evoked by L-glutamate. It would be possible that the sympatholytic action might partially explain the neuroprotective effects of MK-801 against hypertension and other neurotoxic disorders.

In the ischemic neuronal models, Nakai et al showed that ischemia significantly increased NE release in rat spinal cord. They also demonstrated that MK-801 suppressed the release of NE and glutamate produced by ischemia. The finding suggests that glutamate release and NMDA receptors may be involved in the acute effect of oxygen and glucose deprivation on the excessive release of NE in the ischemic regions. It was also reported that in the unilateral brain ischemia model induced by injecting microspheres into the left internal artery of the rat, the embolization caused significant depletion of catecholamine levels in the injured hemisphere. Therefore, we would like to know the magnitude of the changes in the content or release of catecholamines and glutamate in the injured regions of the macrosphere MCAO models without hypothalamic damage. Further studies should be performed to assess more thoroughly the relationships between brain ischemia and neuroprotective effects of MK-801.

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Response: Neuroprotective Effects of MK-801 and Catecholamine Release in the Central Nervous System

Dr. Tsuda reported interesting observations from in vitro and in vivo experiments, suggesting a 2nd neuroprotective effect of MK-801 (besides NMDA antagonism) that is based on sympatholytic effects of this drug. Our recent paper indicates that MK-801 is significantly less (or not) effective if animal models for permanent middle cerebral artery occlusion (MCAO) are applied that do not avoid hypothalamic damage with subsequent hyperthermia. However, the release of norepinephrine or glutamate within the affected hemisphere has not been analyzed in our experiments. We agree that further studies of catecholamine and glutamate release in different models would be highly interesting in this context. One can speculate whether hypothalamic damage and artificial hyperthermia (which are typical complications of the suture-MCAO model) might affect the release of glutamate or noradrenaline (or both) in the injured hemisphere, and thus contribute to the confounding effects of hypothalamic infarction on neuroprotective drug studies. We have no good explanation for the depletion of dopamine and noradrenaline levels in the hemisphere affected by microsphere injection into the carotid artery as performed in the experiments of Bralet and coworkers in 1980. However, the microsphere model that was used in this study typically consists of the injection of hundreds or thousands of very small particles blocking the cerebral microcirculation. Our new macrosphere model, in contrast, consists of the embolization of only 6 large spheres leading to an occlusion of the MCA mainstem, similar to the suture technique. We would like to place particular emphasis on this important difference between the microsphere and the macrosphere model.

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