Editorial

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Pharmacological neuroprotection: that long, long road from idea to practice

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Pharmacological treatment of ischemic brain injury has been under investigation for more than a quarter of century [1]. Despite this, we still have little solid evidence that such therapy is effective.

In an article published in this issue of Korean Journal of Anesthesiology, Kim et al. [2] provide a fascinating preclinical study examining neuroprotective effect of gabapentin on ischemic brain. In this issue, Kim et al. make two important contributions to our understanding of the effects of gabapentin on ischemic brain. First, they show conclusively that gabapentin is neuroprotective against focal cerebral ischemia. Second, they provide evidence that the neuroprotective effect of gabapentin is likely related to expression of Hsp70.

The ischemic pathway overlaps greatly with seizure processes and therefore anticonvulsants have been proposed as possible neuroprotective agents [3]. High-dose gabapentin decreases acute seizure frequency and reduce brain atrophy [4]. Gabapentin shows no neuroprotective effects in the treatment of cultured neurons exposed to neurotoxic or ischemic insults, suggesting that in vivo neuroprotection can be attributed to antiseizure effects [5]. The findings of Kim et al. suggests that low-dose gabapentin also have neuroprotective effect apart from anti-seizure activity.

The data of Kim et al. can be interpreted in a different way. Gabapentin directly inhibits necrotic responses to focal ischemia but fails to inhibit apoptosis that is concurrently stimulated, with the net result being neuroprotective in 24 hours. Although gabapentin may abate necrotic responses to ischemia, anti-apoptotic drug is still required. This holds experimental promise, but there are no clinically available anti-apoptotic drugs.

The current study raises several questions. One of the more interesting is whether neuroprotection is dependent on some particular quality of gabapentin distinct from its capacity to prevent seizures. Although Kim et al. shows increase of heat shock protein 70, experiment on the neuronal cell death was not performed. Further studies with mechanism based on examinations of neuroprotective actions should be able to reveal the answer to this question.

Durability is still questioned. Almost all purported neuroprotective compounds have failed to provide protection against severe ischemic insults when outcome was assessed after long postischemic intervals [6,7]. Of note, there have been no long-term outcome studies in animals or humans that have demonstrated sustained benefit from barbiturates, etomidate, or propofol, regardless of duration of the ischemic insult. Long-term outcome study on the neuroprotective effect of gabapentin is required.

An important question is whether the findings of Kim et al. will renew interest in testing neuroprotectants in human neuroprotection trials, an effort that had clearly waned after the failure of countless clinical studies of stroke neuroprotection. If an intervention that has shown effective neuroprotection in preclinical studies fails in clinical trials, what then are the prospects for demonstrating the neuroprotective efficacy in preclinical investigations? Clearly, much more work is needed

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before gabapentin can be evaluated as a neuroprotectant, especially considering the large and expensive clinical trial that necessarily lies ahead. In today's environment of outcomes research driving evidence-based clinical practice, whether it is even possible to obtain good evidence for neuroprotection in humans is a matter for debate. Although the contribution of Kim et al. is a major step in neuroprotection in the laboratory, history teaches us that much more remain to be written in the clinic.

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