New Paradigm for Brain Protection After Stroke

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Poor cognitive performance significantly impairs social interaction and the quality of life of patients after a stroke. However, once there is a cognitive decline, little can be done therapeutically to reverse the symptoms. In this issue of *Hypertension*, Shimamura et al. reported that gene therapy with hepatocyte growth factor (HGF) into the brain using hemagglutinating virus of Japan (HVJ)-envelope vector based on their previous report prevented the impairment of learning and memory in the chronic stage of cerebral infarction. Shimamura et al. reported that the mechanisms of HGF-mediated inhibition of cognitive loss are as follows: (1) HGF enhances neuron extension and synaptogenesis through one of the Rho family GTPases, Cdc42; (2) it prevents glial scar formation with an influence on astrocytes demonstrated by GFAP immunoreactivity; and (3) it increases microvessels in the penumbra. HGF is a polypeptide growth factor that acts by binding to the Met tyrosine kinase receptor. The HGF/Met system plays significant roles in central nervous system development as a chemoattractant and survival factor for embryonic motor neurons. HGF is reported to have greater efficacy as a short-term survival factor compared with other neurotrophic factors, such as brain-derived neurotrophic factor and ciliary neurotrophic factor. Therefore, this new finding provides a potential powerful tool for a therapeutic option to prevent cognitive decline after stroke.

Recently, a phase I trial of ex vivo nerve growth factor gene delivery, implanting autologous fibroblasts genetically modified to express human nerve growth factor into the forebrain, in patients with mild Alzheimer disease has been performed with the expectation of reducing cholinergic neuron loss; however, cerebrovascular gene therapy especially focused on neuroprotection after brain damage has been limited because of problems such as transfection efficiency and the safety of vectors. For example, carcinogenic side effects resulting from gene transfer of growth factors are a frequent concern. Indeed, HGF is reported to be expressed and related to malignant pathways in central nervous system tumors. However, the HVJ-liposome gene transfer system used in the article by Shimamura et al. achieved temporary nonviral gene expression with some advantages to overcome these problems, because a temporary increase in HGF secretion inhibits overgrowth signaling by HGF in brain tissue, and a nonviral gene transfer system avoids viral infection-associated toxicity, immunologic compromise, and deleterious side effects. However, careful monitoring for side effects after gene transfer is necessary in the preparation for clinical use.

Vascular endothelial growth factor (VEGF), which is mostly known as an angiogenic factor, also mediates the effect of the environment on neurogenesis and cognition, acting through VEGF receptor type 2. However, Shimamura et al. previously demonstrated the possibility of greater efficacy of HGF gene transfer into the brain for neuroprotection compared with VEGF. They showed that overexpression of HGF in the brain does not exacerbate cerebral edema in contrast to VEGF, which has been reported to increase blood–brain barrier leakage and cerebral edema in spite of reducing neurological deficit during stroke recovery. Shimamura et al. have already developed HVJ-based VEGF gene transfer. Therefore, the differences in the effects of overexpression between HGF and VEGF using HVJ-based gene transfer for the effect on cognitive decline need to be clarified in the future.

The molecular mechanisms of the effects of HGF on different tissues, such as neurons, glia, and blood vessels, are under consideration. It is still unclear whether HGF-mediated brain protection is because of a different independent effect on each component, a similar intracellular signaling effect, or an effect dependent on increased blood supply through angiogenesis. Moreover, caution is needed in relation to the experimental limitation of evaluating cognitive function using rodents, because their locomotor activities are closely associated with learning and memory. Therefore, the detailed mechanisms of HGF-induced neuroprotective effects and the inhibitory effects on cognitive decline should be clarified before clinical trials.

HGF treatment could not reduce the ischemic area, indicating that the repair of brain damage after stroke is limited. Management of hypertension is very effective to prevent not only stroke onset but also cognitive impairment. Therefore, the most effective way to prevent cognitive impairment in hypertensive patients is control of blood pressure with appropriate antihypertensive drugs for cerebral and cerebrovascular protection before the onset of stroke. A major clinical study (Study on Cognition and Prognosis in the Elderly and a clinical double-blind study have proved that angiotensin II type 1 receptor blocker (ARB) have an additional therapeutic effect on impaired cognitive function beyond their antihypertensive effects compared with other antihypertensive drugs. Iwai et al. reported that angiotensin II type 2 receptor–deficient mice exhibit a larger ischemic area and worse neurological deficit, whereas an ARB, valsartan, reduced the

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ischemic area and improved the neurological score. Furthermore, our unpublished experimental findings indicate that angiotensin II type 2 receptor signaling also may improve cognitive impairment after stroke. Therefore, we speculate that the challenges relating to the poor cognitive performance after stroke involve prevention of expansion of the ischemic area and protection against neural damage, in addition to preventing the onset of stroke. The article by Shimamura et al in this issue raises the possibility of prevention of impairment of learning and memory after stroke by HGF-induced brain protection and offers hope to patients experiencing stroke-induced dementia.

References


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