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Journal of Neurological Disorders & Stroke

Editorial

Proposed Treatment of Cerebral Infarction with HSP27 Protein

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Submitted: 23 July 2013

Accepted: 23 July 2013

Published: 25 July 2013

EDITORIAL

Heat shock protein 27 (HSP27) belongs to the small heat shock protein (HSP) subfamily and provides robust cellular protection against various neurological insults and diseases, including cerebral ischemia [1]. The functions of HSP27 include adenosine triphosphate-independent chaperoning, free radical scavenging, and apoptosis control [2]. HSP27-transgenic mice exhibit numerous cytoprotective effects in *in vivo* models of various diseases, including a reduced infarct size after transient cerebral ischemia [3]. Furthermore, viral delivery of HSP27 and intraperitoneal injection of PEP1-HSP27 recombinant protein into ischemic mice are protective [4,5]. Therefore, HSP27 has emerged as a particularly potent neuroprotective agent.

We recently published a paper demonstrating that intravenous injections of human-derived, phosphorylated HSP27 protein (hHSP27) protected the brain against ischemic brain injury [6]. We examined the neuroprotective effect of hHSP27 in mice subjected to transient (1 h) middle cerebral artery occlusion, by injecting either hHSP27 (5 or 50μg ip) or BSA (50 μg, as control) 0, 1, 3, or 6h after reperfusion. Mice were then examined 24h after reperfusion. Infarct volume was reduced by 61% in mice treated at 1h with 50μg of hHSP27 (infarct volume 12.39±0.73 mm^3, $P<0.001$) vs. controls (infarct volume 31.55±1.28 mm^3) administered BSA immediately after reperfusion. Delayed intravenous injections of hHSP27 1h after reperfusion reduced neurological deficits and apoptotic cell death, as indicated by decreased TUNEL staining and decreased levels of cytochrome c, cleaved caspase-9, and cleaved caspase-3. Using 8-OHdG and HHE as markers of oxidative stress and Iba-1 and GFAP as markers of inflammatory responses, we also showed that hHSP27 decreased oxidative DNA damage and lipid peroxidation, and inhibited glial activation. Thus, hHSP27 protected the brains of transiently ischemic mice by inhibiting apoptosis, oxidative stress, and inflammation following ischemia/reperfusion. We also confirmed that HSP27 was the active molecule, as the HSP27 antibody inhibited this protection function.

By contrast, recombinant HSP27 (rHSP27) did not protect against ischemic brain damage. HSP27 exists as dimers, tetramers, multimers, and large oligomers that are phosphorylated or dephosphorylated. Compared with rHSP27, hHSP27 was comprised of more dimers, tetramers, and multimers and less large oligomers. Dephosphorylation of hHSP27 increased the number of large oligomers, decreased the numbers of dimers, tetramers, and multimers, and resulted in a loss of its protective functions. In addition to being phosphorylated, isolated hHSP27 also contained small amounts of ab-crystalline and HSP20 as part of the high molecular weight HSP27 oligomers. The necessary modifications of rHSP27, including phosphorylation and interaction with ab-crystalline and HSP20, required to mimic hHSP27 in ischemic brain treatment should be identified. We are currently investigating the neuroprotective effects of active rHSP27 generated via posttranslational modifications. Because hHSP27 is purified from human tissues, its effects in humans should not be influenced by interspecies differences. Hence, hHSP27 has potential as a medical intervention to suppress cell death in ischemic stroke patients. In the future, we hope that HSP27 therapy will be useful for patients suffering from transient cerebral ischemia.

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