Neuroprotective Effects of Leptin and Nitric Oxide Against Cerebral Ischemia

To the Editor:

We read with great interest the article by Dr Valerio and colleagues1 dealing with the neuroprotective effect of leptin against ischemic stroke in mice. The results of their study demonstrated that leptin counteracted oxygen-glucose deprivation–induced neuronal apoptosis through signals converting on glycogen synthase kinase-3β (GSK3β) inhibition. The authors also indicated that nuclear factor κB (NF-κB) subunit c-Rel was necessary to leptin-mediated Bcl-xL induction and neuroprotection. In addition, it was shown that leptin mRNA and protein were upregulated after ischemic stroke, and that leptin administration reversed cerebral infarct damage in a c-Rel–dependent manner. The authors proposed that neuroprotective effect of leptin was dependent on the phosphatidylinositol 3-kinase, MEK, and protein kinase C signaling pathways that might mediate c-Rel–activation and GSK3β-inactivation, suggesting that leptin would act as an endogenous mediator of neuroprotection during cerebral ischemia.

Evidence indicates that nitric oxide (NO) may actively participate in neuroprotection in cerebral ischemia. Khan et al2 showed the cerebrovascular protective efficacy of various NO donors in rats after experimental stroke. Recently, it has been proposed that leptin has an important role in the regulation of NO production. It was shown that plasma leptin concentration was significantly correlated with plasma NO-metabolite levels in human subjects.3 In a study we presented earlier, a relationship between membrane fluidity (a reciprocal value of membrane microviscosity) of red blood cells (RBCs) and leptin was investigated in humans by means of an electron paramagnetic resonance method.4 The reduced membrane fluidity of RBCs might cause a disturbance in the blood rheological behavior and the microcirculation, which could contribute, at least in part, to the pathophysiology of circulatory disorders. We demonstrated that leptin increased the membrane fluidity of RBCs and improved the rigidity of cell membranes in humans via the NO-dependent mechanism.4 One hypothesis is that leptin may actively participate in the improvement of the rheological behavior of RBCs and the microcirculation by increasing NO production, which would be a defense against vascular complications in circulatory disorders. In the separate series of the experiments, we showed that the relaxing effect of leptin on rat blood vessels was partially mediated by the NO-dependent pathway.5 We strongly speculate that leptin-induced NO production might have a crucial role in the neuroprotective effect against cerebral ischemia. Therefore, we would like to know whether NO signaling might be related to the leptin-effect in the study of Dr Valerio and colleagues. Further studies should be performed to assess more precisely the mechanisms of leptin-effect against cerebral ischemia.

Disclosures

None.

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Stroke. 2009;40:e406; originally published online March 26, 2009;
doi: 10.1161/STRKKEAH.109.549402
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/40/5/e406

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