Neuroglobin: Endogenous Neuroprotectant or Maintenance of Homeostasis?

To the Editor:

We would like to comment on the latest experimental stroke study in a neuroglobin (Ngb) knock-in mouse by Wang et al.\(^1\) The intriguing idea that Ngb could act as a reservoir of oxygen, facilitate oxygen transportation or act as a scavenger of reactive oxygen species in the brain has been the main research hypotheses since its discovery.\(^2\) Notably, the investigation of the role of Ngb in pathophysiological conditions like hypoxia and ischemia has promoted the idea of an endogenous neuroprotectant.\(^3\) However, we would like to challenge the ruling theory of a possible neuroprotective function of Ngb. Instead, we propose a homeostatic role based on the distinct expression pattern (Figure),\(^4\) the old evolutionary history and highly conserved structure of Ngb.\(^5\)

Wang et al.\(^1\) thoroughly characterized the differences in infarct volume, malondialdehyde (MDA) formation and sensorimotor function in Ngb-overexpressing transgenic (Ngb-Tg) mice and wild-type littermates. Forced Ngb expression significantly reduced the cortical infarct volumes 22 hours after 2-hour intraluminal transient middle cerebral artery occlusion whereas no difference was seen in the subcortical structures at that time point. Surprisingly, subcortical structures were significantly spared in Ngb-Tg 14 days after 60-minute focal transient ischemia. Unfortunately, this phenomenon is not discussed by the authors. The less MDA formation after 8 and 22 hours in Ngb-Tg is interpreted as a possible antioxidative action of Ngb. We think MDA production reflects the significant difference in stroke volumes after 22 hours. MDA is not only a surrogate biomarker of reactive oxygen species but probably also of infarct size.

Previously published differences in Ngb expression are attributable to the use of different antibodies and ribonucleotide probes. In our hands the cortical and striatal Ngb expression was always very scarce despite ischemic challenge.\(^6\) Mice even expressed less Ngb in the mentioned areas compared to rats. In addition we only found colocalization of Ngb and nNOS in very few neuronal populations residing outside the cortex and striatum.\(^7\) In our opinion Ngb does not have a pathophysiological action as oxygen buffer or sensor. We do not dispute that Ngb can act as an endogenous neuroprotectant in the brain, but we do dispute the notion that Ngb primarily offers protection against ischemia in cortical and subcortical areas. Finally, the possible mechanism of neuroprotective action remains to be elucidated and has not been further characterized by Wang et al.\(^1\)

Sources of Funding

C.A.H. is supported by The Danish Medical Research Council, NOVO Nordisk Foundation and The Lundbeck Foundation.

Disclosures

None.

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Figure. Ngb expression is restricted to a few neuron populations in the evolutionary oldest parts of the brain. This suggests Ngb involvement in the sleep-wake cycle, circadian rhythm or food regulation. A, Ngb in situ hybridization (Ngb ISH) staining and (B) Ngb immunohistochemistry (Ngb IHC) of a coronal section in a C57:black mouse at bregma level 2.00. Bed nuclei of the stria terminalis (BST), lateral septal nucleus (LS), medial preoptic area (MPA).

(Stroke. 2008;39:e177-e178.)
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Stroke is available at http://stroke.ahajournals.org
DOI: 10.1161/STROKEAHA.108.526533


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Stroke. 2008;39:e177-e178; originally published online September 18, 2008;
doi: 10.1161/STROKEAHA.108.526533
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:
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