Nitric oxide (NO) plays a major role in both vascular and neural biology in health and disease. This concept is exemplified when one examines the role of NO in the brain and the cerebral circulation. NO is a potent vasodilator, and blood vessels in the brain are normally exposed to NO from 2 major sources—endothelium and neurons. Acting as a messenger molecule, NO mediates the majority of endothelium-dependent responses in the brain. The source of this NO is the endothelial isoform of NO synthase (eNOS). This prominent role for NO has been observed in a variety of blood vessels from multiple species including humans. Through this signaling mechanism, NO influences resting vascular tone and mediates responses to varied stimuli, including endothelium-dependent agonists and increases in blood flow (Figure). In addition, eNOS inhibits vasoconstrictor responses and cerebral vasospasm and can affect permeability of cerebral endothelium, the blood-brain barrier (Figure). eNOS normally inhibits cerebral vascular growth or hypertrophy (Figure), a structural change that can have functional consequences by impairing of maximal vasodilator capacity. Impairment of NO-mediated signaling is a key underlying mechanism of vascular dysfunction in diverse forms of disease and aging. Impairment of these eNOS-dependent mechanisms in the presence of cardiovascular risk factors may contribute to reductions in cerebral blood flow, vascular cognitive impairment, and stroke.

Among the more interesting recent findings with regard to eNOS are those related to the impact of the enzyme on neuronal function. For example, basal NO produced by eNOS in endothelium affects local neuronal transmission via its effects on axons (Figure). Neuronal stem cells are present in portions of the brain and the activation of these cells by injury (ie, ischemia) can result in neurogenesis that promotes functional recovery. Endothelial cells promote neurogenesis. eNOS-deficient mice have impaired angiogenesis as well as impaired neurogenesis and recovery of neuronal functional following experimental stroke. Thus, endothelial dysfunction and loss of eNOS-mediated signaling produces deleterious vascular effects, but may also impair neuronal signaling and neurogenesis following stroke (Figure).

Previous studies have demonstrated that eNOS protects against brain injury following focal ischemia, in part by contributing to the maintenance of greater levels of blood flow. Exercise increases vascular expression of eNOS, improves endothelium-dependent relaxation, and increases cerebral blood flow. The study by Gertz et al in this issue of Circulation Research sought to extend those findings, provide additional mechanistic insight into how eNOS and exercise produce such beneficial effects, and to examine the impact of eNOS on long-term recovery from ischemia. The approach that was used was the study of mice which exercised voluntarily (by running on a wheel) compared with sedentary mice. Using this design, mice that exercised had reduced infarct size following transient occlusion of one middle cerebral artery compared with controls. This effect was dependent on NO and eNOS, as the protection was prevented by pharmacological inhibition of NO and was absent in eNOS-deficient animals. Exercise also increased long-term cognitive function following stroke.

Endothelial progenitor cells (EPCs) are known to increase endothelial function and angiogenesis, and exercise increases EPC numbers in blood and bone marrow as well as stimulate the formation of new blood vessels. In this new study, exercise increased the circulating levels of vascular endothelial growth factor, which activates eNOS and promotes angiogenesis, along with eNOS expression in the vasculature and in EPCs. Recruitment of EPCs occurred in the ischemic region and exercise augmented this effect. Exercise increased vascular density and cerebral blood flow in ischemic and nonischemic brain regions. Thus, exercise produced both short and long-term effects that increased cerebral perfusion and cognitive function through its effects on eNOS and EPCs (Figure).

Many questions arise from this work. What is the relative role of increased expression of eNOS within endothelial cells versus within EPCs? Would exercise produce similar protective effects in aged animals or in models with cardiovascular risk factors such as hypertension? Such risk factors produce endothelial dysfunction in the brain which is thought to contribute to an increased likelihood of stroke and/or cognitive decline. How does exercise produce these effects, including increasing the expression of eNOS? Clearly one potential mechanism relates to effects of increased shear stress on expression of the eNOS gene in endothelium. However, although cerebral blood flow may increase in regions involved with locomotion, global cerebral blood flow changes little during exercise. Are only the regions which exhibit increased cerebral blood flow during exercise the sites that exhibit increased eNOS expression and neuroprotection following ischemia? Are other regions protected? Do mechanisms other than increases in shear stress increase expression of eNOS?

A concept that is sometimes put forward is that the functional importance of eNOS and NO-mediated signaling decreases with progression from aorta and large arteries down the vascular tree into the microcirculation. This simple view is not accurate for the brain. There are many examples in which endothelium-derived NO and
eNOS have a major impact at the level of the cerebral microcirculation—including in arterioles within the brain parenchyma—now often referred to as the neurovascular unit.1,3,4,10,15,18 Many of the eNOS dependent effects described in the study by Gertz et al21 occurred in the microcirculation within the brain parenchyma. The findings described above provide yet another example of the potential translational benefits from targeting eNOS with therapeutic approaches. Previous studies suggest that such targeting may be achieved using pharmacological approaches with agents such as statins, corticosteroids, or thyroid hormone.25–27 Increases in cerebral blood flow in response to diverse stimuli (both acute and chronic), affects permeability of the blood-brain barrier, inhibits vascular growth (hypertrophy of vascular muscle), alters neuronal signaling and promotes angiogenesis and neurogenesis. See text for details.

**Sources of Funding**

Work reviewed in this manuscript from this laboratory was supported by National Institutes of Health grants HL-38901, NS-24621, and HL-62984; and by a Bugher Foundation Award in Stroke from the American Heart Association (0575092N).

**Disclosures**

None.

**References**


Protecting the Brain With eNOS: Run for Your Life
Frank M. Faraci

_Circ Res._ 2006;99:1029-1030
doi: 10.1161/01.RES.0000250961.47984.80

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/99/10/1029

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/