What is the cause of Alzheimer’s disease? What is the treatment? Currently, there is no (clear) answer. But wait, perhaps NO (nitric oxide) is part of the answer.

It is known that amyloid-β peptides (Aβ), the major components of amyloid plaque in Alzheimer’s disease, produce endothelial dysfunction in aorta and cerebral blood vessels (Figure). In addition, cardiovascular risk factors and cerebrovascular dysfunction are associated with vascular dementia, as one might expect, but also with Alzheimer’s disease. Thus, the current state of knowledge is that Aβ produces endothelial dysfunction, and endothelial dysfunction is associated with Alzheimer’s disease.

In this issue of Circulation Research, Austin et al. look at the association of endothelial dysfunction and Alzheimer’s disease in a novel way. They tested the hypothesis that NO from endothelial nitric oxide synthase (eNOS) inhibits expression of amyloid precursor protein (APP) and processing of APP to Aβ in microvessels and brain parenchyma. They suggest that NO may directly modulate levels of Aβ, APP, and the rate-limiting protease β-site APP cleaving enzyme (BACE1), which, together with secretase-γ, cleaves APP to generate Aβ. The findings suggest that NO derived from normal endothelium protects against increases in Aβ. An implication of the study is that decreased bioavailability of NO from endothelial dysfunction may contribute to increases in Aβ and possibly to Alzheimer’s disease.

First, the authors measured effects of changes in NO and cGMP on the pathway that produces amyloid plaques. They used 2 approaches to alter NO: enzymatic inhibition of NOS with Nω-nitro-L-arginine methyl ester (L-NAME) and deleterious NO with L-NAME and deleterious NO with Nω-nitro-L-arginine methyl ester (L-NAME) and deletion of eNOS in mice. They also inhibited soluble guanylyl cyclase (sGC) with 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ) and increased cGMP with sildenafil. The major finding of the study is that inhibition of NO/sGC increased APP and Aβ, whereas increases of cGMP reduced APP. The implication is that endothelial NO/sGC, and normal endothelial function, may suppress development of Alzheimer’s disease.

Second, Austin et al. measured expression and activity of secretase enzymes that cleave APP to generate the amyloidogenic Aβ. They found that NO/cGMP modulates expression and activity of BACE1, but not other secretase enzymes. They also demonstrated that NO does not affect enzymes that degrade Aβ. The findings localize effects of NO to synthesis, not degradation, of Aβ. If the findings can be extrapolated to Alzheimer’s disease, NO/sGC may be useful in prevention but not reversal of Alzheimer’s disease.

Third, the authors demonstrated (by studying eNOS−/− mice) that NO derived from eNOS, not from neuronal NOS or inducible (i)NOS, accounts for effects that they observed. This approach was important because deletion of neuronal NOS may produce behavioral changes in mice and because iNOS may modulate Alzheimer’s disease–like changes.

In this study, immunofluorescence indicated widespread expression of APP but restricted expression of BACE1. The findings support the rationale for current studies that target BACE1 for treatment of Alzheimer’s disease.

No severe neurological changes, let alone Alzheimer’s disease, have been identified in eNOS-deficient mice. Furthermore, the mice used in this study were young, before the age at which amyloid plaques and amyloid angiopathy would appear even in murine models of Alzheimer’s disease. It would be of interest to determine whether eNOS modifies development of Alzheimer’s disease, by crossing eNOS-deficient mice with Alzheimer’s disease mice. Expression of eNOS has been examined in Alzheimer’s disease with variable results. One might expect that eNOS deficiency would enhance the phenotype of Alzheimer’s disease mice, because of increased APP, BACE1, and Aβ in both neurons and microvessels. Such studies have been reported with iNOS-deficient mice with conflicting results.

This study demonstrates a negative regulation of APP and BACE1 by eNOS/sGC at the protein level. Is regulation transcriptional, posttranscriptional, translational, or posttranslational? The promoter of BACE1 contains cAMP response element-binding (CREB) sites, and phosphorylation (activation) of CREB protein is associated with downregulation of BACE1 expression in a mouse model of Alzheimer’s disease. Because NO increases cGMP and activates cGMP protein kinase, which may then phosphorylate CREB, NO may reduce BACE1 expression. The promoter of APP also contains AP-1 and Sp1 sites, which increase transcription of APP, but decreases Sp1 binding. We speculate that these effects of NO may modulate expression of BACE1 and perhaps APP at the transcription level and contribute to the findings by Austin et al.

Finally, this study points to the eNOS/NO/sGC/cGMP pathway as a possible therapeutic target for Alzheimer’s disease. This potential target is consistent with the concept of Alzheimer’s disease as being part of the syndrome of cerebrovascular, cardiac, and peripheral vascular diseases associated with end-organ dysfunction.

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Editorial

See related article, pages 1498–1502

NO Answer to Alzheimer’s Disease?

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that cerebrovascular dysfunction may be an early event in development of Alzheimer’s disease, as proposed by Iadecola.21 Indeed, a recent study demonstrated that inhibition of phosphodiesterase 5 (which increases cGMP) improves synapti-
function, memory, and reduces Aβ load in a mouse model of Alzheimer’s disease.22 Sildenafil produced a rapid and long-lasting reduction in levels of Aβ1-40 and Aβ1-42. The rationale was that both NO donors and cGMP analogs counteract CREB phosphorylation and Aβ-induced impairment in long-term potentiation.23 As pointed out above, CREB phosphorylation may account, at least in part, for downregulation of BACE1 by eNOS/sGC in this study. Thus, beneficial effects of sildenafil in a previous study22 may also be attributable, in part, to reduction of BACE1 (and perhaps APP) in both neurons and microvessels.

Familial Alzheimer’s disease, with identified gene mutations in APP and PSEN1/2, is rare, and sporadic Alzhei-
mer’s disease accounts for more than 90% of cases of Alzheimer’s disease.14 The road to understanding the pathophysiology of sporadic Alzheimer’s disease will be long and to effective treatment even longer. Nevertheless, this study may help provide a novel direction, because it implies a link between NO deficiency and Alzheimer’s disease.

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