Untangling Neurons With Endothelial Nitric Oxide

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Editorial

Alzheimer’s disease (AD) is the most prevalent cause of age-related dementia, which, because of demographic shifts and increasing life expectancy, afflicts a growing segment of the world population and is anticipated to reach epidemic proportions in the decades to come. Central to the pathogenesis of AD is the cerebral accumulation of amyloid-β peptides (Aβ) and the microtubule-associated protein tau leading to the formation of extracellular amyloid plaques and intracellular neurofibrillary tangles, respectively. Much of the attention in this field has focused on neurons and on neuronal mechanisms responsible for Aβ cleavage from the amyloid precursor protein (APP) and for tau phosphorylation, misfolding, and aggregation. In this issue of the journal, however, Austin et al1 shift the focus from neurons to cerebral blood vessels and provide evidence that the endothelial isoform of nitric oxide (NO) synthase (eNOS) protects neurons from tau phosphorylation, thought to be a key step in tau pathogenicity. Although the findings implicate for the first time the endothelium in the molecular pathology of tau, they also provide further evidence of the importance of vascular factors in the expression of AD pathology.

eNOS Regulates Tau Phosphorylation: Aβ Required?

Tau phosphorylation is finely controlled by a network of kinases and phosphatases, the balance of which is needed to maintain tau homeostasis and prevent misfolding and neurotoxicity. Austin et al1 discovered that eNOS is critical for the maintenance of this delicate balance. By crossing mice lacking eNOS with mice overexpressing mutated APP and presenilin 1 in neurons (APP/PS1), a model of amyloid pathology, they observed an increase in phosphorylated tau (ptau) compared with APP/PS1 mice or eNOS−/− mice.

Then, they sought to define the molecular mechanisms of the effect and found that eNOS−/− mice have increased levels of p25, an activator of the tau-phosphorylating enzyme cyclin–dependent kinase 5 (Figure), whereas glycogen synthase kinase 3β and Akt, enzymes also involved in tau phosphorylation, were not affected. Furthermore, p25 levels and cyclin-dependent kinase 5 activity were also increased in neurons of APP/PS1/eNOS−/− mice, suggesting a link between eNOS deficiency, cyclin-dependent kinase 5 hyperactivation, and tau phosphorylation. These results are surprising because NO has been reported to have the opposite effect, that is to enhance the tau phosphorylation via the activation of glycogen synthase kinase 3β. Nevertheless, Austin et al1 broaden our thinking about the biology of tau and raise the novel prospect that diffusible mediators arising from vascular cells protect neurons from tau phosphorylation and, potentially, pathogenicity.

Lack of eNOS is not sufficient to induce ptau because eNOS-null mice did not exhibit evidence of tau hyperphosphorylation despite the p25 increase, whereas lack of eNOS was able to increase ptau in APP/PS1 mice. This observation is consistent with the notion that Aβ fosters tau phosphorylation and, presumably, neurotoxicity. Furthermore, the fact that Aβ may be required for eNOS deficiency to induce ptau would place Aβ upstream of tau phosphorylation and provide further evidence that Aβ is likely to be the initiating pathogenic factor in AD. On the other hand, tau is needed for Aβ neurotoxicity, the full expression of which may require postsynaptic targeting of the kinase Fyn, a tau-dependent process.
Irrespective of the underlying molecular mechanisms, these findings suggest a synergistic interaction between Aβ and ptau with implications for the synaptic dysfunction and neurotoxicity in AD. It would be of interest to determine whether eNOS also protects from phosphorylation of mutant tau, which has a greater propensity to phosphorylation and aggregation. If so, eNOS could play a role also in inherited tauopathies unrelated to AD.

Endothelium and ptau: Further Evidence for a Role of Vascular Factors in AD

Increasing evidence indicates that AD, a condition traditionally considered a disease of neurons, has also cerebrovascular components. Although epidemiological studies have shown that vascular risk factors increase the risk of AD, clinical-pathological studies have revealed that AD pathology most often coexists with ischemic brain lesions, which markedly amplify the expression of the cognitive dysfunction. On the other hand, cerebrovascular function is altered in mouse models of AD, an effect mediated by Aβ vasotoxicity through innate immunity receptors and oxidative stress. How cerebrovascular dysfunction contributes to AD remains to be firmly established, but hypoperfusion caused by endothelial dysfunction, altered coupling between neural activity of cerebral blood flow, blood–brain barrier dysfunction, and reduced vascular clearance of Aβ and tau by faltering blood vessels are potential contributors. The finding that suppressing the source of endothelial NO promotes tau phosphorylation provides a new mechanism by which a dysfunctional endothelium could contribute to AD pathology. Therefore, in AD, endothelial dysfunction induced by vascular risk factors, in concert with Aβ, could promote tau phosphorylation and, presumably, misfolding, aggregation, and neurotoxicity.

Unanswered Questions and Next Steps

The provocative findings of Austin et al raise new questions concerning the role of eNOS and cerebral endothelium in tau pathobiology. For example, how does eNOS increase cyclin-dependent kinase 5 activity? The authors suggest that NO may nitrosylate and inhibit calpain, the enzyme responsible for cleavage of p35 to p25 (Figure). This hypothesis is supported by relevant literature but needs experimental validation.

Another question concerns why eNOS-derived NO suppresses, while NO derived from other sources promotes tau phosphorylation. Although differences in the models used may contribute, NO levels and the spatiotemporal pattern of NO production are likely to have a role. Unlike neuronal NOS, which produces bursts of NO during glutamatergic synaptic activity, and the immunologic isoform of NOS, which synthesizes toxic amounts of NO during inflammation, eNOS is thought to produce low levels of NO continuously, which, because of the proximity between brain vessels and neurons, may be able to influence neuronal function. Thus, eNOS-derived NO has been implicated in hippocampal long-term potentiation, the neurophysiological bases of learning and memory, in neuroendocrine regulation, and neurohumoral activation in hypertension and heart failure. Consequently, the basal tone of NO provided by eNOS throughout the brain could be responsible for keeping tau phosphorylation in check.

In this regard, studies in mice lacking other NOS isoforms in AD and other tauopathies models would be informative.

Does eNOS protect the brain from the synaptic dysfunction induced by tau and the associated cognitive decline? As the authors point out, this is a fundamental question that cannot be answered at this time. Tau phosphorylation has been linked to misfolding and aggregation, but its role in neurotoxicity is complex and depends on specific phosphorylation sites. The observation by Austin et al that eNOS deletion does not lead to neurofibrillary tangles in APP/PS1 mice does not rule out a potential effect of NO deficiency on tau-induced cognitive dysfunction. This is because in animal models as in humans neurofibrillary tangles are not required for the cognitive dysfunction associated with tau. This and other observations have led to the hypothesis that tau in monomeric form or in low-order aggregates (oligomers, protofibrils, fibrils, etc.), not larger complexes (ie, tangles), is responsible for the neuronal dysfunction and toxicity underlying cognitive impairment. Exploring the role of eNOS in the downstream processes leading to tau misfolding and aggregation, as well as synaptic dysfunction, would help define the role of this novel pathway in the mechanisms of tau pathogenicity and cognitive impairment (Figure).

eNOS Therapy for AD?

A final question concerns the potential therapeutic value of boosting eNOS-derived NO in AD and other tauopathies. Enhancing eNOS has been proposed as a therapy for cerebrovascular diseases, and statins, physical exercise, steroids, and diets rich in flavonoids and polyphenols have been shown to upregulate eNOS and protect from experimental ischemic brain injury. These interventions have also been reported to attenuate tau pathology in different models. Although other effects of these pleiotropic treatments cannot be excluded, it is...
conceivable that restoring or upregulating eNOS-derived NO may be beneficial. Considering that eNOS deficiency is also associated with increased Aβ production,21 preserving or restoring endothelial function would be highly effective in staying off AD pathology. Support for this hypothesis has recently been provided by a growing number of studies demonstrating that a better control of vascular risk factors has led to a decline in the incidence of all dementias by ≈20% per decade.1 The compelling findings of Austin et al3 provide a new mechanism in the incidence of all dementias by the β2-adrenergic receptor.17 The proposes p25 generation and tau phosphorylation in a murine model of Alzheimer’s disease. Circ Res. 2016;119:1128–1134. doi: 10.1161/CIRCRESAHA.116.309686. 

References

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