Does peripheral inflammation contribute to Alzheimer disease?

Evidence from animal models

M. Kerry O'Banion, MD, PhD

Correspondence to Dr. O'Banion: kerry_obanion@urmc.rochester.edu

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There is long-standing interest in the association between inflammation and Alzheimer disease (AD), driven by overwhelming evidence that brain inflammation (e.g., neuroinflammation) is a prominent feature of AD pathology, that nonsteroidal anti-inflammatory drugs may lower AD risk, and that some inflammatory gene loci are linked to AD.[1] Yet the mechanisms by which inflammation contributes to disease pathogenesis are complex and how inflammation might be manipulated for therapeutic benefit remains elusive. One key is to recognize that inflammation may have different roles depending on whether it arises within the brain or from processes occurring in the periphery.

In this issue of *Neurology*®, Singh-Manoux et al.[2] report that elevated interleukin-6 protein levels in middle-aged British civil service staff are associated with decreased reasoning and greater decline in reasoning and Mini-Mental State Examination scores over a 10-year period. As reviewed in their article, others have reported similar associations between systemic inflammatory markers and cognitive performance, although not all studies are consistent. If systemic inflammation is a component of age-associated reduction in cognitive performance, does it also contribute to age-associated neurodegeneration and dementia? As described below, results from preclinical animal models provide compelling evidence for this possibility.

Peripheral administration of lipopolysaccharide (LPS), a Gram-negative bacterial cell wall component, is a well-characterized model for induction of systemic inflammation in rodent models. Repeated LPS exposure led to increased glial activation and neuronal accumulation of the amyloid precursor protein (APP) and its product, amyloid-β, in a transgenic mouse expressing the human Swedish APP mutation.[3] In a study using a mouse expressing mutant human APP, presenilin, and tau, repeated LPS administration caused increased tau phosphorylation without clear evidence of amyloid-β changes.[4] More recently, respiratory infection of mice carrying mutant human APP and presenilin transgenes with *Bordetella pertussis* resulted in T-cell infiltration, glial activation, and increased deposition of amyloid-β.[5] Together, these studies indicate that systemic inflammation associated with bacterial infection might exacerbate AD pathology.

Using a transgenic mouse model of osteoarthritis with inducible expression of interleukin-1β in the joints that leads to joint pathology, pain, and dysfunction, we explored whether joint inflammation could influence AD pathogenesis.[6] This was accomplished by crossing these mice with an AD mouse model overexpressing mutant human transgenes for APP and presenilin. In animals induced to have joint inflammation at 2 months of age, we found evidence for accelerated amyloid-β deposition, with mice showing glial activation and amyloid plaques just 2 months later, a pattern not seen in AD mice without interleukin-1β induction in the joints. Moreover, amyloid-β deposition was substantially greater in 8-month-old AD mice with inflamed joints than in noninflamed AD mice. Importantly, there was clear evidence of systemic inflammation in these mice based on increased liver Kupffer cell major histocompatibility complex II staining and elevated serum interleukin-6 levels.[6]

In addition to our model of osteoarthritis, other models of age-associated diseases associated with systemic inflammation have been evaluated for effects on AD pathogenesis. For example, 12 weeks after mice overexpressing 2 mutant human APP transgenes were treated with streptozotocin to induce insulin-deficient diabetes, there were increased levels of amyloid-β peptide, plaque deposition, and tau phosphorylation relative to untreated APP controls.[7] These mice also showed decreased brain synaptophysin levels, suggesting loss of functional synapses. In a separate study, another AD mouse model expressing a different mutant human APP transgene was crossed with leptin-deficient *ob/ob* mice, a model of insulin-resistant diabetes. The resulting diabetic AD mice showed dramatic exacerbation of cognitive deficits in the Morris Water maze and significantly increased amyloid angiopathy, although total amyloid-β levels remained unchanged.[8] Finally, AD transgenic mice fed high-fat diets showed increased brain levels of insoluble amyloid-β peptide and tau pathology,[9] suggesting that other metabolic conditions can alter AD pathology.

Although systemic inflammation is a well-known component of diabetes and obesity, the studies exploring

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From the Department of Neurobiology & Anatomy, University of Rochester School of Medicine & Dentistry, Rochester, NY.

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effects of diabetes or fat intake on AD pathology mentioned above did not directly measure systemic inflammation and are complicated by metabolic changes in the brain such as insulin resistance. Nevertheless, a likely common feature to these models and those described earlier is cerebrovascular inflammation secondary to systemic changes. Cerebrovascular inflammation is in turn linked to increased glial activation, which may contribute to enhanced AD pathology. Alternatively, cerebrovascular inflammation modulates the transport of amyloid-β at the blood–brain barrier. Indeed, impaired brain efflux of amyloid-β has been observed following LPS administration.[10] This may represent an important mechanism linking systemic inflammatory changes to AD pathology.

One caveat to all of the preclinical studies described here is the use of transgenic mouse models engineered to show accumulation of amyloid-β or phosphorylated tau protein. Thus these studies provide little insight into whether inflammation leads de novo to AD pathology. However, with the proportion of individuals susceptible to AD in old age approaching 40%,[11] that systemic inflammation may play a role in accelerating cognitive decline and disease onset cannot be ignored.

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