

 NEURODEGENERATIVE DISEASES

## Microglia's little helper

The locus coeruleus is the major source of noradrenaline in the brain, and its degeneration in Alzheimer's disease is closely associated with the progression of symptoms. It has recently been shown that noradrenergic transmission can decrease amyloid- $\beta$  ( $A\beta$ ) deposition, but how it achieves this effect was unclear. Heneka *et al.* now show that noradrenaline acts by preventing neuroinflammation and stimulating microglial recruitment and phagocytosis of  $A\beta$ .

The authors found that the  $A\beta$ -induced expression of pro-inflammatory genes in microglia was abolished in the presence of noradrenaline. Moreover, noradrenaline increased microglial migration and phagocytosis of fluorescence-labelled  $A\beta$ . These effects seemed to be mediated by activation of  $\beta$ -adrenoceptors, as treatment with the specific agonist isoproterenol yielded similar results.

To test their observations *in vivo*, the authors treated mice that overexpressed amyloid precursor protein (*APP*) with DSP4, a neurotoxin that specifically targets axons arising from the locus coeruleus. Treated mice exhibited a 70–80% reduction in forebrain noradrenaline levels and a concomitant increase in

$A\beta$  deposition in the hippocampus and the frontal cortex. The number of activated microglia surrounding the plaques and the amount of  $A\beta$  inclusions in microglial cells was reduced after treatment. This suggests that lack of noradrenergic innervation from the locus coeruleus impairs the recruitment of microglia to the plaques and subsequent phagocytosis of  $A\beta$ , thereby enhancing plaque formation. Finally, treatment with the noradrenaline precursor L-3,4-dihydroxyphenylserine reversed the effects of noradrenaline depletion on microglial migration and phagocytosis in *APP*-transgenic mice.

These findings emphasize the role of noradrenaline as a regulator of microglial function, in addition to its more well-known function in neurotransmission. Moreover, the data explain the association between locus coeruleus degeneration and Alzheimer's disease progression, suggesting that noradrenergic innervation from this nucleus provides an important defence mechanism against chronic  $A\beta$  deposition.

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**ORIGINAL RESEARCH PAPER** Heneka, M. T. *et al.* Locus coeruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine. *Proc. Natl Acad. Sci. USA* **107**, 6058–6063 (2010)

