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What astrocytes need to do

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“Bad men need nothing more to compass their ends, than that good men should look on and do nothing,” said the British philosopher John Stuart Mill in his 1876 address to St Andrews University. Not in the moral remit, but in the physiological context, astrocytes certainly do more than “look on and do nothing”. They are responsible for metabolic coupling with neurons, which ensures ionic, neurotransmitter, pH, redox, and bioenergetic homeostasis, and actively meets neuronal demands to achieve homeostatic regulation.^{1,2} Astrocytes are also in intimate contact with brain capillaries (a connection observed by Santiago Ramón y Cajal), strengthening the blood-brain barrier, and mediate neurovascular coupling—the process that translates neuronal activity into local vasodilation (appendix).

In people with Alzheimer’s disease, their role is less clear. Alzheimer’s disease causes changes in astrocytes that reduce their neuroprotective homeostatic support.¹ However, evidence points to a role beyond a mere loss of a supportive function. Astrocytes from animal models of Alzheimer’s disease exhibit aberrant Ca²⁺ signals, which contribute to cognitive dysfunction.³ Moreover, the risk of developing Alzheimer’s disease is influenced by their genotype. For instance, dementia susceptibility genes, such as *CLU* and *APOE*, are strongly expressed in astrocytes. The *APOE4* allele exacerbates amyloid β deposition, promotes neuroinflammation, impairs neurovascular coupling, and weakens the blood-brain barrier.^{4,5}

To prevent Alzheimer’s disease from compassing its ends, astrocyte-focused therapies must address their tendency to lose their neurosupportive roles,¹ and stop their conversion into the “bad men” doing nothing to protect the brain.

Supplementary Material

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