Microglia are brain macrophages and, as such, key immune-competent cells that can respond to environmental changes. Understanding the mechanisms of microglia-specific responses during pathologies is hence vital for reducing disease burden. The definition of microglial functions has so far been hampered by the lack of genetic in vivo approaches that allow discrimination of microglia from closely related peripheral macrophage populations in the body. Here we introduce a mouse experimental system that specifically targets microglia to examine the role of a mitogen-associated protein kinase kinase (MAP3K), transforming growth factor (TGF)-β-activated kinase 1 (TAK1), during autoimmune inflammation. Conditional depletion of TAK1 in microglia only, not in neuroectodermal cells, suppressed disease, significantly reduced CNS inflammation and diminished axonal and myelin damage by cell-autonomous inhibition of the NF-κB, JNK and ERK1/2 pathways. Thus, we found TAK1 to be pivotal in CNS autoimmunity, and we present a tool for future investigations of microglial function in the CNS.