

REVERSE OF THE RHEUMATOID ARTHRITIS-INDUCED ACCELERATION OF BRAIN AGING IN THE MIDDLE AGE BY MINOCYCLINE

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We have previously found age-dependent differential cytokine responses through activation of glial cells, microglia and astrocytes, in the brain of adjuvant arthritic (AA) rats, an animal model of rheumatoid arthritis [1-5]. Both microglia and astrocytes in the proximity of the leptomeninges/choroidal plexus produce anti-inflammatory cytokines including interleukin (IL)-10 and transforming growth factor (TGF)-beta1 in the young adult AA rats. In contrast, microglia in the proximity to the leptomeninges in the middle-aged AA rats produce pro-inflammatory cytokines, including IL-1beta, but less IL-10 and TGF-beta1. To further elucidate the outcome of age-dependent differential cytokine responses, we measured the hippocampal long-term potentiation (LTP), which is postulated to be a cellular substrate for learning and memory. LTP was significantly impaired in the middle-aged AA rats, but not in the young adult AA rats, indicating that systemic inflammation accelerates the brain aging. Systemic administration of minocycline significantly suppressed the microglial expression of IL-1beta and improved hippocampal LTP in the middle-aged AA rats without a significant effect on paw edema. Therefore these observations strongly suggest that minocycline can reverse the rheumatoid arthritis-induced acceleration of brain aging through suppression of microglial activation. References (1) Nakanishi H, Wu Z., *Behav. Brain Res.* 201, 1-7, 2009. (2) Wu Z. et al., *J. Immunol.* 184, 3191-3201, 2010. (3) Wu Z. et al., *Neurobiol. Disease* 32, 543-551, 2008. (4) Wu Z. et al., *J. Neurosci. Res.* 85, 184-192, 2007. (5) Wu Z. et al., *J. Neuroimmunol.* 167, 90-98, 2005