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Microglia and Neuronal Degeneration

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Multiple sclerosis (MS) has been considered as an inflammatory demyelinating disease. However, recent evidences suggest that neuronal degeneration occurs in the early stage of MS, and continues throughout the disease course. Thus, we need a new strategy to suppress neuronal degeneration to treat MS. Accumulation of activated microglia is observed not only in the MS lesions, but also in a variety of neurological disorders. There, microglia are activated and produce both neurotoxic and neuroprotective factors. We have examined the functions of microglia-derived cytokines on neuronal degeneration. Supernatant of LPS-stimulated microglia induced neuronal cell death in several hours. However, all the recombinant cytokines, included in the supernatant from activated microglia, did not induce neuronal cell death, while IFNγ and TNFα induced neuritic beading, an early feature of neuronal degeneration. This suggests that cytokines derived from microglia may synergistically function in neuronal degeneration, and/or that some of them may also function in regeneration by inducing neurotrophic factors. Then, we searched the factor(s) toxic to neurons in the supernatant of activated microglia, and found that glutamate is the most potent neurotoxic factor. Interestingly, microglia produce glutamate with glutaminase using extracellular glutamine as a substrate and release it through gap-junction, but not through glutamate transporters. This suggests that inhibitors to glutaminase or gap-junction may effectively suppress glutamate production by activated microglia without perturbing physiological functions of glutamate in the central nervous system. Gap-junction inhibitor, carbenoxolone, effectively suppressed glutamate release and subsequent neuronal damage by microglia, both in vitro and in vivo models. We then synthesized new compounds using carbenoxolone as a lead compound. A new compound, named INI0602, significantly suppressed clinical signs of experimental autoimmune encephalomyelitis (EAE), an animal model of MS. The drug also suppressed neuronal damages in the animal models of amyotrophic lateral sclerosis (ALS) and Alzheimer's disease. Thus, to suppress glutamate release from activated microglia may be useful strategy against neuronal degeneration in both neuroinflammatory and neurodegenerative disorders.

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