Astrocyte-microglia-neuron interaction in Parkinson's disease animal model

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Background: Astrocytes have been acknowledged as neuronal supporters, synapse assistants, microglial partners in neuroinflammation but also as a potentially dangerous cell death executors. They are strategically positioned in the interplay between microglia and neurons. Microglia activation can be induced by different effectors which determine their specific profile of inflammatory process. Strongly activated microglia can be dangerous even for healthy cells, while in mild activation is regenerative. Routinely the interaction direction is described as from microglia to astrocyte, where microglia senses the danger signals using their receptors and informs astrocytes to induce their, secondary activation. The other way round interaction is described mostly as astrocytes calming microglia and promoting homeostasis.

The aim of this study was to analyze microglia activation in response to astrocyte death vs neuronal death.

Methods: Selective dopaminergic neuron death was induced by 6-OHDA injection into the medial forebrain bundle of rat brain. Astrocyte degeneration was caused by 7-day infusion of fluorocitrate into substantia nigra. Behavioral, immunohistological staining, densitometric and cell morphology, stereological cell counting and Western blot, HPLC dopamine and metabolite levels and energy metabolism markers analyses were performed.

Results: Both treatments caused similar, progressive cell loss of approx. 30%, neurons or astrocytes. Neuronal lesion verified by temporarily reduced locomotor activity, reduced TH+/CV+ neuron density, dopamine decrease and its turnover increase, caused minor change visible only in less ramified microglia morphology. Astrocyte degeneration verified by reduced S100beta+ cell density, ALDH1L1, glutamate synthetase, GFAP amounts caused massive microglia activation proven by Iba1+ cell density and protein amount, energy metabolism markers and simplified cell morphology.

Conclusions: Microglia is highly reactive to astrocyte dysfunction while reaction to neuronal death is very subtle. This difference could be due to the proliferation of astrocytes, that could be replaced, while neurons cannot. Neurons probably carry memory functions that has to be kept during many years of life and instead of replaced should be repaired. Therefore, much more subtle activation of potentially dangerous microglia is triggered by neurodegeneration than by astrocyte death. Such hypothesis should be further verified.

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