

Mechanisms of microglial responses to injury related focal ATP events

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Microglia, the main immunocompetent cells in the central nervous system, rapidly respond to disturbances in their microenvironment, largely relying on purinergic (ATP, ADP) signaling through P2Y12 receptors. However, while the effects of exogenous ATP on microglial activity have been extensively tested in previous studies, the mechanisms involved in microglial response to endogenous, focal ATP events in the brain tissue are unclear. To visualize changes in the extracellular ATP levels, we introduced a sensitive fluorescent ATP sensor (GRAB-ATP) to cultured neurons and astrocytes and prepared acute brain slices from mice expressing the sensor in VGlut1+ neurons. We observed both spontaneous and injury-related ATP events in astrocytes and neurons *in vitro*, and detected significant extracellular ATP increase after slice preparation or secondary injury, even hours after slice cutting. ATP accumulation due to blockade of ecto-ATPase activity indicated an ongoing ATP release from the damaged tissue. Interestingly, we also observed a highly dynamic, focal, flashing ATP activity, persisting for hours *ex vivo*. Importantly, microglia processes were recruited to complex, nano- and micromolar ATP events in a P2Y12R and CX3CR1 dependent way, leading to marked morphological transformation of the cells. Microglial response to spontaneous- and injury-related ATP signals also occurs *in vivo* as revealed by *in vivo* two-photon microscopy. We suggest that focal, submillimolar ATP events represent a major modulator of microglial states and are likely to alter inflammatory responses in different CNS disorders.

Keywords:

ATP, microglia, acute brain slice

Reference:

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