S30-2 The Role of Brain Zinc in Microglial Activation

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Microglia, resident immune cells in the CNS, have branched processes in the resting state and play roles in the maintenance of brain functions and surveying invaded microorganisms. When activated by brain damage, microglia tract the branched processes to form an activated, amoeboid morphology, and engage in the clearing unwanted debris and releasing pro-inflammatory mediators. These microglial responses provide defense system against insults, but contribute to neurodegeneration. However, underlying signal transduction pathways for microglial activation are not well established. A part of brain zinc, concentrated in the presynaptic vesicles of a subset of glutamatergic axon terminals, is massively released into extracellular space in pathological conditions, which are thought to cause neuronal death. Here, we show zinc triggers morphological microglial activation through poly(ADP-ribose) polymerase (PARP)-1 activation, which are blocked by inhibiting NADPH oxidase activity or P2X7 receptor (P2X7R) antagonist. Furthermore, zinc induced release of ATP, endogenous P2X7R agonist, from microglia via hemichannels. These results suggest zinc triggers microglial activation through the release of ATP via hemichannels and the autocrine/ paracrine sequential activation of P2X7R, NADPH oxidase and PARP-1, which may give a new insight into role of zinc in neurological disorders.