Activation of Neuroglia in the CNS Diseases

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Activation of neuroglia, including astroglia and microglia, play important roles in the pathogenesis of numerous CNS diseases, such as ischemic stroke, Alzheimer's disease, and Parkinsonian disease. Under these neuropathological conditions, neuroglia are activated by proteases and cytokines and then produce neurotoxic molecules that eventually induce neuronal death. Especially, among neurotoxic molecules, reactive nitrogen species (RNS), reactive oxygen species (ROS), proinflammatory cytokines, and matrix metalloproteinases (MMPs) are known to contribute to the pathogenesis of CNS diseases. Thus, the advances in understanding the mechanisms of neuroglial activation can be a major challenge for the development of medicinal therapeutics. This presentation falls into three categories:

Theme one: The activated astroglia-induced death of neurons or astroglia.

The fatality of the patients with recurrent stroke is much greater than that with first stroke due to more severe damage in the brain. Under the recurrent stroke condition, neurons as well as astroglia can be severely damaged. The purpose of this study is to elucidate the mechanism for the death of those cells under the recurrent stroke condition.

Astroglia were activated by the treatment with LPS+IFN-γ (immunostimulation, IS). Neurons were highly vulnerable to glucose deprivation (GD) in the presence of immunostimulated astroglia, which was due to the NO produced from immunostimulated astroglia. Interestingly, immunostimulated astroglia were also highly vulnerable to glucose deprivation, which was due to the peroxynitrite and hydrogen peroxide (H_2O_2) produced from those cells. The production of those toxic molecules by IS/GD were more than that by IS or GD alone, which was the main factor for the astroglial death. In IS/GD-treated astroglia, the decrease in ATP occurred well ahead of cell death. Glutathione (GSH) content, a main intracellular antioxidant, was also decreased, and mitochondrial function was disrupted. Loss of ATP, GSH, and mitochondrial potential were induced by peroxynitrite and H_2O_2. MAPKs were involved in the production of peroxynitrite and H_2O_2 from immunostimulated astroglia. It was tested whether the supply of cellular ATP level could block the cell death in our conditions. Adenosine, a purine nucleoside, has been reported to supply energy substrates through cellular metabolism. In IS/GD-treated astroglia, adenosine treatment completely attenuated cell death and ATP loss. But this protection was not dependent on adenosine receptor.

Uridine, a pyrimidine nucleoside, can also supply energy substrates like adenosine. In IS/GD-treated astroglia, uridine treatment completely attenuated cell death and ATP loss, which was due to the uridine phosphorylase-mediated phosphorolysis of uridine. Under glucose-deprived condition, the potentiation of neuronal death by immunostimulated astroglia or potentiated death of immunostimulated astroglia themselves may be clinically implicated in the tendency of recurrent ischemic insults to be more severe and fatal than an initial ischemic insult.

Theme two: The induction of MMP-9 in activated astroglia.

In spite of pathological importance, little is known about the signal transduction pathways leading to the induction of MMPs in the CNS. The purpose of this part was to elucidate the signaling mechanisms for the induction of MMP-9 in LPS-stimulated astroglia. LPS treatment induced the phosphorylation of MAPKs, including ERK1/2, p38 MAPK, and JNK/SAPKs and increased the expression of MMP-9. The induction of MMP-9 by LPS is mediated by the sequential activation of PKC and ERK1/2. In contrast to ERK1/2, the activation of p38 MAPK was related with the downregulation of MMP-9 expression. However, the activation of JNK/SAPKs was not involved in the LPS-stimulated MMP-9 induction. The elaborate interplay between Erk1/2 and p38 MAPK pathway would provide more sophisticated mechanism for the regulation of MMP-9 activity in neuroinflammatory diseases.

Theme three: The PAR-2-mediated activation of neuroglia.

Protease-activated receptors (PARs) are G protein-coupled receptors that initiate cell signaling by the proteolytic activity of extracellular serine protease. A second member of the PAR family, PAR-2 is activated by trypsin and some reports suggest that PAR-2 activation may be involved in the inflammation processes, contributing to neurodegenerative diseases. The purpose of this part is to elucidate the mechanism for the trypsin-induced activation of astroglia and microglia via PAR-2. By RT-PCR, western blot, calcium imaging, it was found that PAR-2 was functionally expressed in rat primary astrocytes and microglia. The trypsin-mediated PAR-2 activation caused the iNOS-derived NO/peroxynitrite production in both cells via NF-κB activation. In this process, several signaling molecules, such as PKC and MAPKs, were involved. It was tested if activated microglial by trypsin would play a role in the process of neuronal death. Conditioned medium from activated microglia by trypsin caused the apoptotic death of neurons, which was due to the toxic molecules, including RNS and ROS. These results suggest that trypsin can trigger the production of neurotoxic molecules from neuroglia via PAR-2 and thereby induce neuronal death.

Keywords:

Astroglia, Microglia, Neuronal death, Immunostimulation, Reactive nitrogen species, Reactive oxygen species, Matrix metalloproteinase, Protease-activated receptor-2