[16:50~17:30]

Role of Activated Microglial/Macrophageal Cells in Cerebral Ischemic Injury

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During cerebral ischemic insult, neuronal cells undergo apoptotic or necrotic death due to various neurotoxic mediators. Although the central nervous system has been recognized as an immune privileged region, immune cells are implicated in various neuropathological conditions (Table 1). As shown in Fig. 1, in cerebral ischemic insults, activated inflammatory cells such as microglia and macrophages may be implicated in the pattern and degree of ischemic injury via production of various bioactive mediators such as inflammatory cytokines and nitric oxide (NO). In my presentation, I will show (LPS) into rat corpus callosum markedly induces macropha-

Table 1. Immune cells implicated in different biological entities

Biological entity	Neutrophils	Monocytes	T lymphocytes
Infection	+	+	+
Trauma	+	+	+
Hemorrhage	+	+	+
Ischemia	+	+	+
Cerebral palsy	chemokines	chemokines	chemokines

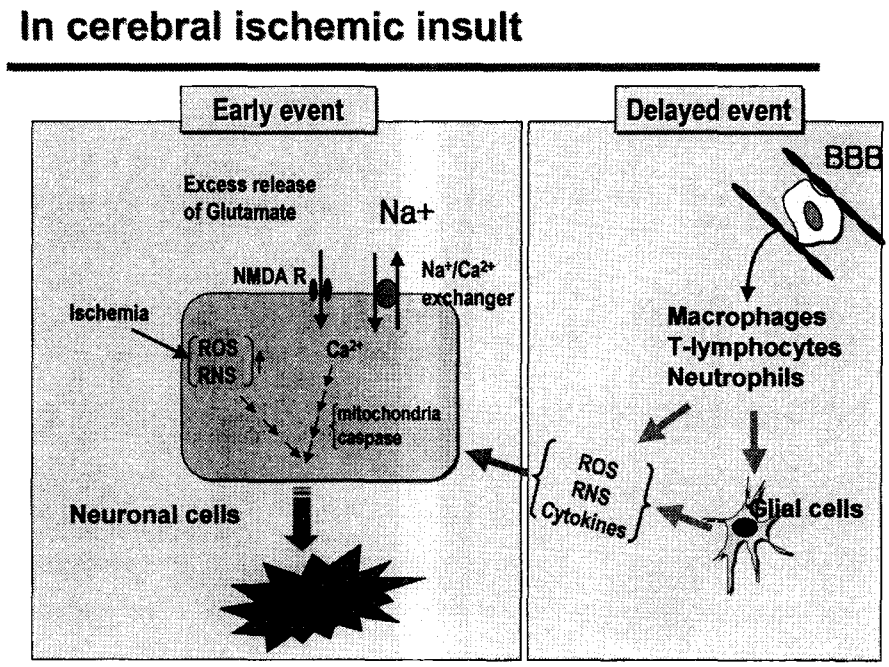

Fig. 1. Early and delayed events in cerebral ischemic insult.

geal/microglial activation and subsequently accelerates ischemic injury by middle cerebral artery occlusion. In control rats, expectedly, ischemic injury was little evoked by 2-h middle cerebral artery occlusion (MCAO) followed by 3-h reperfusion. However, cerebral ischemic injury was markedly increased in rats pre-injected with LPS 1 day before MCAO (Fig. 2). Interestingly, however, no significant difference between control and LPS-pretreated groups was observed after 24-h reperfusion. Furthermore, the ischemic injury was ameliorated 7 day after LPS microinjection into corpus callosum (Fig. 2). To address the peripheral or parenchymal origin of the activated inflammatory cells, LPS (5 μg/5 ml) was microinjected into rat corpus callosum. LPS induced many of the features characterizing pro-inflammatory macrophageal and microglial activation.

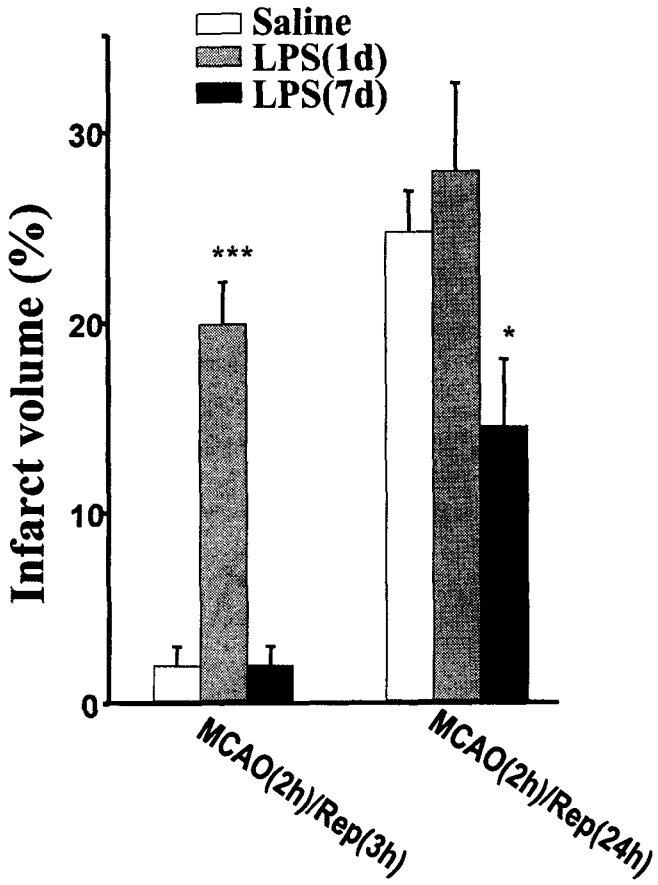

Fig. 2. Infarct volumes by MCAO 1 or 7 d after LPS microinjection

Isolectin B4-, myeloperoxidase- and ED1-positive cells with round shape were abundantly observed in ipsilateral side at 1 day in LPS-injected rats. The increased ischemic injury in LPS-treated rats was well correlated with iNOS level expressed over 3 orders of magnitude than in LPS-untreated rats. Immunohistochemical studies showed that iNOS- and nitrotyrosine (a peroxynitrite marker)-positive cells were prominent throughout the infarct area. NOS inhibitors aminoguanidine or N^G-nitro-L-arginine,

simultaneously injected with LPS, reduced the iNOS immunoreactivity and infarct volume, especially in penumbra regions. Total glutathione levels in ischemic regions were decreased more in LPS pre-injected rats than in control ones. RNA protection assay, RT-PCR and ELISA also showed that LPS microinjection rapidly increased mRNA and proteins expression for pro-inflammatory cytokines including IL-1β and TNF-α. To further investigate what the origin of inflammatory cells was, we eliminated immune cells by gamma irradiation: thus, the number of those immune cells was found markedly decreased in rats whose body, not head, was exposed to gamma irradiation. Consistently, the level of a pro-inflammatory cytokine IL-1β was significantly reduced in LPS-treated brain. Gamma irradiation prior to LPS injection significantly reduced the infarct volume (Fig. 3).

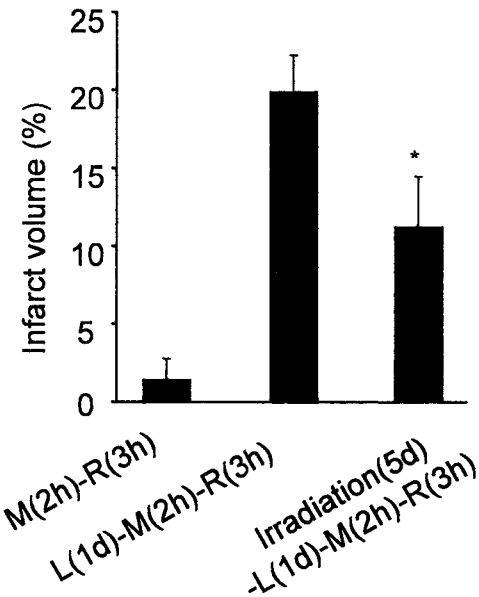

Fig. 3. Gamma-irradiation 5 days before LPS microinjection ameliorates the LPS-accelrated ischemic injury.

M(2h): MCAO for 2 h; R(3h): Reperfusion for 3 h

The present results indicate that activated macrophages/microglia enhances the extent of ischemic brain injury through expression of pro-inflammatory molecules (Fig. 4).

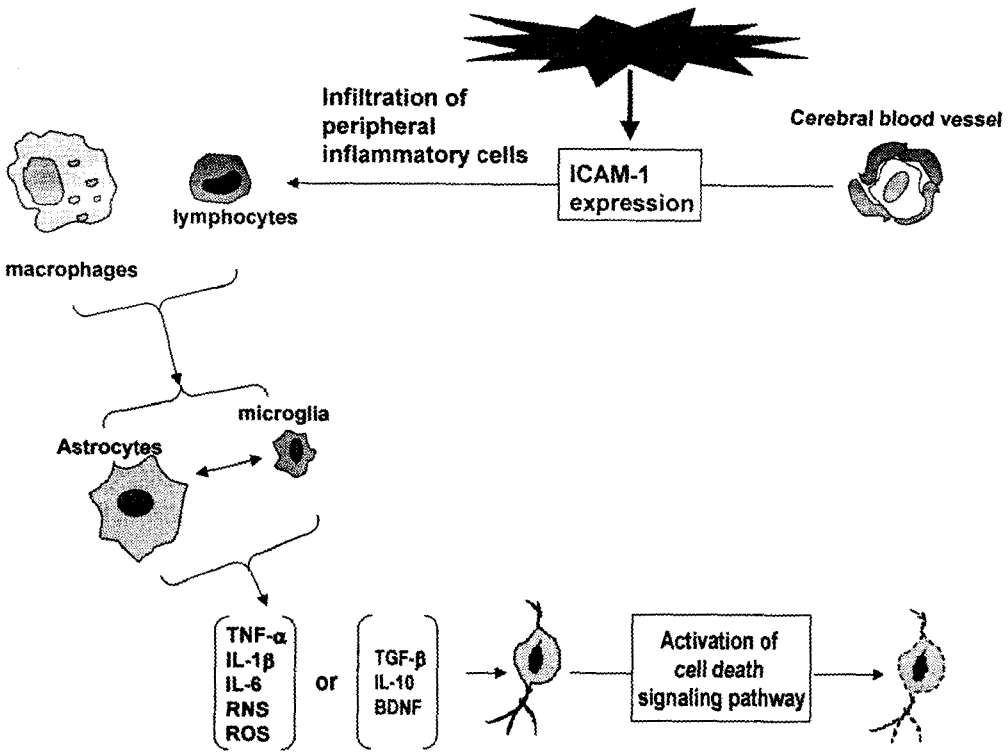

Fig. 4. Role of leucocytes and glial cells in the cerebral ischemic insult

S9 10:00~10:40 November 12, 2004 (Fri)

Applying Lessons from Development to Neuronal Stem Cell Biology

Samuel L. Pfaff (The Salk Institute, USA)

S10 10:40~11:20 November 12, 2004 (Fri)

Potential Role of Onconeural Antigen, cdr2 in Dopaminergic Neuronal Cell Death: Involvement of Calpain and Proteasome System

Young Jun Oh (Yonsei University)

S11 11:20~12:00 November 12, 2004 (Fri)

Neuropharmacology of the Histaminergic System in the Brain

Kenji Onodera (Okayama University, Japan)

S12 12:00~12:40 November 12, 2004 (Fri)

Inflammatory Signals to TRPV1, the Capsaicin Channel

Uhtaek Oh (Seoul National University)