**O3G4-3** Intracerebroventricular administration of an endothelin ET<sub>B</sub> receptor agonist increases expression of tissue inhibitor of matrix metalloproteinase-1 and -3 in rat brain

Yutaka Koamal', Akemichi Baba<sup>2</sup>, Toshio Matsuda<sup>3,4</sup>

1 Lab. of Pharmacol., Faculty of Pharmacy, Osaka Ohilani Univ.,
Tonda-Bayashi 584-8540, Japan, 2 Lab. of Mol. Neuropharmacol.,
Grad. Sch. of Pharmaceutical Sci., Osaka Univ., Suita, 565-
0871, Japan, 3 Lab. of Medicinal Pharmacol., Grad. Sch. of
Pharmaceutical Sci., Osaka Univ., Suita, 565-0871, Japan, 4
The Osaka-Hamamatsu Joint Research, Center for Mental
Development, Osaka Univ., Suita, 565-0871, Japan

Production of tissue inhibitor of matrix metalloproteinases (TIMPs), secreted protein family having inhibitory actions on matrix metalloproteinases (MMPs), are up-regulated in nerve injuries and suggested to be neuroprotective. To clarify extracellular signals involving in the injury-induced TIMP production, effects of endothelins (ETs), which promote several pathophysiological responses of nerve system, were examined. Intracerebroventricular administration of 500 pmole/day Ala<sup>3,13,15</sup>-ET-1, an ET<sub>B</sub> receptor agonist, increased TIMP-1 mRNA in rat hippocampus, caudate putamen and cerebrum. TIMP-3 mRNA in cerebrum was increased by Ala<sup>3,13,15</sup>-ET-1, while TIMP-2 mRNA was not affected in these brain regions. Ala<sup>3,13,15</sup>-ET-1 stimulated production of TIMP-1 and TIMP-3 proteins in cerebrum. Immunohistochemical observations on Ala<sup>3,13,15</sup>-ET-1-infused rats showed that GFAP-positive astrocytes had immunoreactivity TIMP-1 and TIMP-3. These findings indicated that activation of brain ET<sub>B</sub> receptors caused production of TIMP-1 and TIMP-3, and suggest an involvement of astrocytes in the ET-induced TIMP production.

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**O3G4-4** Effect of edaravone on MPTP-induced neurotoxicity and behavioral impairment in mice.

Toshiyuki Kawasaki<sup>1</sup>, Kotarou Ishihara<sup>1</sup>, Tetsuaki
Nashida<sup>1</sup>, Yukio Ago<sup>1</sup>, Akemichi Baba<sup>2</sup>, Toshio Matsuda<sup>3,4</sup>

Univ., 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan, 2 Lab.
1-6 Yamada-oka, Suita, Osaka 565-0871, Japan, 3 Center for
Child Mental Dev., Grad. Sch. Med., Osaka Univ., 2-2 Yamada-
oka, Suita, Osaka 565-0871, Japan

Methyl-4-phenyl-1,2,3,6-tetrahydropyrindine (MPTP) causes
dopaminergic neurotoxicity and behavioral impairment in rodents as seen in Parkinson's disease. Previously, we reported that edaravone, a radical scavenger, prevents methamphetamine induced dopaminergic neurotoxicity in mouse striatum (Eur J Pharmaco 542, 92, 2006). In this study, we studied the effect of edaravone on MPTP-induced neurotoxicity and behavioral impairment in mice. MPTP treatment (10mg/kg X 4 with 2 h intervals) showed dopaminergic neurotoxicity and microglial activation in the striatum and substantia nigra pars compacta (SNpc). Pretreatment with edaravone (3mg/kg) significantly reduced the neurotoxicity and microglial activation in the SNpc but not in the striatum. Furthermore, MPTP treatment induced a marked increase in lipid peroxidation product in the midbrain, but not in the striatum, and this effect was inhibited by pretreatment with edaravone. Behavioral analyses showed that edaravone attenuated MPTP-induced hypolocomotion and loss of motor coordination. These results suggest that edaravone protects against MPTP-induced neurotoxicity in the SNpc by scavenging radicals, and imply that dopaminergic neuron in the SNpc may play an important role in motor function of mice.