ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of late life characterized by progressive muscle weakness, atrophy and spasticity, which ultimately leads to paralysis and death within 3 to 5 years. Recently, several studies show that, aside from the dramatic loss of motor neurons, gliosis is, as in human ALS, a striking neuropathological feature of the spinal cord of transgenic mSOD1 mice. In the previous study, we reported increased NOS expression in the astrocytes in the spinal cord of the mutant transgenic mice that are used as ALS animal model. In the present study, we performed immunocytochemical studies to investigate the changes of p53-, bcl-2- and bax-immunoreactivity in the brains of the transgenic mice expressing a human Cu/Zn SOD mutation. We also performed immunocytochemical studies to investigate the changes of nitrotyrosine-immunoreactivity in the brains of the transgenic mice, and demonstrated in vivo evidence of peroxynitrite-mediated oxidative damage in the pathogenesis of ALS.

Immunocytochemistry showed intensely stained p53-, bcl-2-, and nitrotyrosine-immunoreactive (IR) astrocytes in all levels of the spinal cord of the mutant transgenic mice, but no p53-, bcl-2-, and nitrotyrosine-IR astrocytes were observed in the spinal cord of the control mice. P53- bcl-2-, and nitrotyrosine-IR astrocytes were also detected in the brainstem of transgenic mice. Immunostaining for bax was identified only in neurons and not in glial cells. Bax-IR neurons were detected in the spinal cord and brainstem of transgenic mice. In the cerebellum, bax-IR neurons were observed in the Purkinje cell layer and cerebellar nuclei. Bax-IR neurons in the hippocampus and motor cortex showed intense staining. In contrast to the transgenic mice, no bax-IR neurons were detected in the spinal cord and...
brainstem of the control mice. Interestingly, nitrotyrosine-IR neurons were observed in the hippocampal formation and septal area of the transgenic mice. Overall, the results of our previous study combined with the present findings suggest that NO- and p53-mediated cellular damage may play a role in the pathogenesis and progress of ALS. The results also suggest that bcl-2 and bax-associated apoptosis may be an important mechanism of cell loss in the pathogenesis of ALS. Further multidisciplinary investigations involving apoptosis, apoptosis-related genes and nitric oxide are needed to clarify the pathogenesis of ALS.

Keywords: Amyotrophic Lateral Sclerosis; Transgenic mice; p53; bcl-2; bax; Nitrotyrosine; Astrocyte; Immunocytochemistry

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