学位論文内容の要旨

Amyotrophic lateral sclerosis (ALS) is a fatal neurological disorder characterized by selective degeneration of upper and lower motor neurons. Although mutations in the Cu/Zn superoxide dismutase (SOD1) gene have been reported in about 20% of familial ALS, the exact mechanism of selective motor neuron death has not yet been elucidated. A balance of cell survival signals (such as activated phosphatidylinositol 3-kinase (PI3-K), its key downstream serine/threonine kinase AKT, mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK)) and death signals (such as Bad, Apaf-1 and activated caspases) is important to determine the cell fate into survival or death, both under normal and pathological conditions.

Expression of survival p-AKT and p-ERK signals was examined by immunohistochemistry and Western blotting in the lumbar spinal cord of 12-week-old pre-symptomatic mice with human mutant G93A SOD1 gene (transgenic, Tg) and their wild-type (Wt) littermates during normoxia, and 0 and 6 h after 2 h of 9% hypoxia. During normoxia, a stronger p-AKT signal was detected in the nucleus of the motor neurons of Tg animals. At 0 h of recovery from 2 h of hypoxia, both p-AKT and p-ERK signals were induced at a slightly lower level in Tg (1.1–1.2-fold) compared to those of Wt (1.2–1.5-fold) animals. At 6 h of recovery, both p-AKT and p-ERK signals were sustained in the lumbar spinal motor neurons of Tg animals, while those in Wt animals quickly returned to baseline level. As a control, at 6 h of recovery, the hippocampus of Tg animals showed significantly sustained p-AKT levels, but not p-ERK levels, compared to Wt.

The current results suggest that the presence of mutant SOD1 alters survival p-AKT and p-ERK signals, possibly to compensate for the acquired gain-of-function of the mutant protein.