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授与した学位	博　　士
専攻分野の名称	医　　学
学位授与番号	博甲第　2866　号
学位授与の日付	平成１７年３月２５日
学位授与の要件	医歯学総合研究科生体制御科学専攻 （学位規則第４条第１項該当）
学位論文題目	Sustained induction of survival p-AKT and p-ERK signals after transient hypoxia in mice spinal cord with G93A mutant human SOD1 protein (G93A変異型ヒトSOD1トランスジェニックマウス脊髄における一過性低酸素刺激後の生存因子p-Akt, p-ERKの持続的誘導)
論文審査委員	教授　小川紀雄　教授　伊達　勲　助教授　淺沼幹人

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 immunohisto chemistry 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.

論文審査結果の要旨

家族性ALSのおよそ20%にSOD1遺伝子の変異が存在すると報告されているが、SOD1遺伝子の変異が選択的運動ニューロン死をもたらす機序の詳細については今なお十分に明らかにされていない。本研究は、変異型ヒトSOD1トランスジェニック(Tg)マウスを用いてsurvival signalとdeath signalの変化を免疫組織化学ならびにWestern blotを用いて検討したもので、一過性低酸素負荷後のTgマウス脊髄においてはp-AKTとp-ERKの誘導が長時間にわたって持続することを明らかにした価値ある業績である。

よって、本研究者は博士（医学）の学位を得る資格があると認める。