(nNOS) is increased in astrocytes surrounding motor neurons in the spinal cord and brainstem (Cha et al., 1998). Also increased nitrotyrosine labeling in motor neurons and in the ventral horn has been reported in ALS and mutant SOD1-expressing mouse models (Abe et al., 1995; Beal et al., 1997; Ferrante et al., 1997; Cha et al., 2000). In the present study we did not find any nitrotyrosine immuno-positive cells in the brain and spinal cord of 9-month old $SOD2^{lox/lox}$;$Cre^{slow/-}$ mice. Furthermore, neither signs of reactive gliosis (GFAP-IR) nor peroxinitrite-mediated oxidative damage (nitrotyrosine-IR) in astrocytes surrounding SOD2-deficient motor neurons were evident. We speculate that elevated levels of $O_2^{\cdot -}$ in motor neurons is not by itself enough to trigger chronic cell injury, but NO produced from neighboring astrocytes resulting in peroxinitrite production may be a further requirement to trigger ROS-induced toxicity.

Axonal disorganization and reduced slow axonal transport are well-known hallmarks of ALS. Although our present results indicate that loss of SOD2 function is not by itself sufficient to kill motor neurons in vivo, it does modify axonal susceptibility to nerve injury. Recently Vande Velde et al. (2004) reported that Wld^s protein, the dominant neuroprotective factor that markedly delays Wallerian axonal degeneration after nerve injury, does not prevent SOD1-mediated motor neuron loss when introduced the Wld^s mutation into the $SOD1^{G37R}$ or $SOD1^{G85R}$ ALS mouse models. These results show that inhibiting axonal degeneration is not effective to ameliorate ALS pathogenesis induced by the mutant SOD1 protein.

Although the precise pathologic role of $O_2^{\cdot -}$ in motor neuron degeneration remains to be fully clarified, the present study is consistent with the possible involvement of nonneuronal cells in mitochondrial-derived, superoxide-induced injury in motor neurons. Thus a rational

therapeutic strategy that delivers antioxidants to surrounding astrocytes or microglia may significantly help motor neurons survive oxidative stress.

Acknowledgements

The authors thank Drs. K. Amano and K. Yamakawa (RIKEN Brain Science Institute) for FISH analysis of VAChT-Cre.Slow mice; Drs. K. Endo and M. Ichikawa (Tokyo Metropolitan Institute for Neuroscience; TMIN) for valuable advice on electron microscopy; Drs. K. Kohyama, Y. Matsumoto, and T. Uchihara (TMIN) for muscle biopsy; and Dr. S. E. Craven for critical reading of the manuscript. This work was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and from the Japanese Ministry of Health, Labor and Welfare, Research on Psychiatric and Neurological Diseases and Mental Health.

References

Abe, K., Pan, L.-H., Watanabe, M., Kato, T., Itoyama, Y., 1995. Induction of nitrotyrosine-like immunoreactivity in the lower motor neuron of amyotrophic lateral sclerosis. Neurosci. Lett. 199, 152-154.

Andersen, J.K., 2004. Oxidative stress in neurodegeneration: cause or consequence? Nat. Med. 10 (Suppl), S18-25.

Andreassen, O.A., Ferrante, R.J., Klivenyi, P., Klein, A.M., Shinobu, L.A., Epstein, C.J., Beal, M.F., 2000. Partial deficiency of manganese superoxide dismutase exacerbates a transgenic mouse model of amyotrophic lateral sclerosis. Ann. Neurol. 47, 447-55.

Beal, M.F., 1996. Mitochondria, free radicals, and neurodegeneration. Curr. Opin. Neurobiol. 6, 661-666.

Beal, M.F., Ferrante, R.J., Browne, S.E., Matthews, R.T., Kowall, N.W., Brown, R.H.Jr., 1997. Increased 3-nitrotyrosine in both sporadic and familial amyotrophic lateral sclerosis. Ann. Neurol. 42, 644-654.

Beckman, J.S., Carson, M., Smith, C,D., Koppenol, W.H., 1993. ALS, SOD and peroxynitrite. Nature 364, 584.

Bendotti, C., Carri, MT., 2004. Lessons from models of SOD1-linked familial ALS. Trends Mol. Med. 10, 393-340.

Bindokas, V.P., Jordan, J., Lee, C.C., Miller, R.J., 1996. Superoxide production in rat hippocampal neurons: selective imaging with hydroethidine. J. Neurosci. 16, 1324-1336.

Bruijn, L.I., Becher, M.W., Lee, M.K., Anderson, K.L., Jenkins, N.A., Copeland, N.G.,

Sisodia, S.S., Rothstein, J.D., Borchelt, D.R., Price, D.L., Cleveland, D.W., 1997. ALS-linked SOD1 mutant G85R mediates damage to astrocytes and promotes rapidly progressive disease with SOD1-containing inclusions. Neuron 18, 327-338.

Bruijn, L.I., Miller, T.M., Cleveland D.W., 2004. Unraveling the mechanisms involved in motor neuron degeneration in ALS. Ann. Rev. Neurosci. 27, 723-749.

Cha, C.I., Chung, Y.H., Shin, C-M., Shin, D.H., Kim, Y.S., Gurney, M.E., Lee, K.W., 2000. Immunocytochemical study on the distribution of nitrotyrosine in the brain of the transgenic mice expressing a human Cu/Zn SOD mutation. Brain Res. 853, 156-161.

Cha, C.I., Kim, J-M., Shin, D.H., Kim, Y.S., Kim, J., Gurney, M.E., Lee, K.W., 1998. Reactive astrocytes express nitric oxide synthase in the spinal cord of transgenic mice expressing a human Cu/Zn SOD mutation. NeuroReport 9, 1503-1506.

Clement, A.M., Nguyen, M.D., Roberts, E.A., Garcia, M.L., Boillee, S., Rule, M., McMahon, A.P., Doucette, W., Siwek, D., Ferrante, R.J., Brown, R.H.Jr., Julien, J-P., Goldstein, L.S.B., Cleveland, D.W., 2003. Wild-type nonneuronal cells extend survival of SOD1 mutant motor neurons in ALS mice. Science 302, 113-117.

Dal Canto, MC., Gurney, M.E., 1994. Development of central nervous system pathology in a murine transgenic model of human amyotrophic lateral sclerosis. Am. J. Pathol. 145,

1271-1279.

Ferrante, R.J., Shinobu, L.A., Schulz, R.T., Matthews, R.T., Thomas, C.E., Kowall, N.W., Gurney, M.E., Beal, M.F., 1997. Increased 3-nitrotyrosine and oxidative damage in mice with a human copper/zinc superoxide dismutase mutation. Ann. Neurol. 42, 326-334.

Gong, Y.H., Parsadanian, A.S., Andreeva, A., Snider, W.D., Elliott, J.L., 2000. Restricted expression of G86R Cu/Zn superoxide dismutase in astrocytes results in astrocytosis but does not cause motoneuron degeneration. J. Neurosci. 20, 660-665.

Han, D., Williams, E., Cadenas, E., 2001. Mitochondrial respiratory chain-dependent generation of superoxide anion and its release into the intermembrane space. Biochem. J. 353, 411-416.

Hjalmarsson, K., Marklund, S.L., Engstrom, A., Edlund, T., 1987. Isolation and sequence of complementary DNA encoding human extracellular superoxide dismutase. Proc. Natl. Acad. Sci. U.S.A. 84, 6340-6344.

Howland, D.S., Liu, J., She, Y., Goad, B., Maragakis, N.J., Kim, B., Erickson, J., Kulik, J., DeVito, L., Psaltis, G., DeGennaro, L.J., Cleveland, D.W., Rothstein, J.D., 2002. Focal loss of the glutamate transporter EAAT2 in a transgenic rat model of SOD1 mutant-mediated amyotrophic lateral sclerosis (ALS). Proc. Natl. Acad. Sci. U.S.A. 99, 1604-1609.

Huang, T.T., Carlson, E.J., Kozy, H.M., Mantha, S., Goodman, S.I., Ursell, P.C., Epstein, C.J., 2001. Genetic modification of prenatal lethality and dilated cardiomyopathy in Mn superoxide dismutase mutant mice. Free Radic. Biol. Med. 31, 1101-1110.

Ichikawa, T., Ajiki, K., Matsuura, J., Misawa, H., 1997. Localization of two cholinergic markers, choline acetyltransferase and vesicular acetylcholine transporter in the central nervous system of the rat: in situ hybridization histochemistry and immunohistochemistry. J. Chem. Neuroanat. 13, 23-39.

Ikegami, T., Suzuki, Y., Shimizu, T., Isono, K., Koseki, H., Shirasawa, T., 2002. Model mice for tissue-specific deletion of the manganese superoxide dismutase (MnSOD) gene. Biochem. Biophys. Res. Commun. 296, 729-736.

Jaarsma, D., Rognoni, F., van Duijn, W., Verspaget, H.W., Haasdijk, E.D., Holstege, J.C., 2001. CuZn superoxide dismutase (SOD1) accumulates in vacuolated mitochondria in transgenic mice expressing amyotrophic lateral sclerosis-linked SOD1 mutations. Acta Neuropathol. (Berlin) 102, 239-305.

Lebovitz, R.M., Zhang, H., Vogel, H., Cartwright, J.Jr., Dionne, L., Lu, N., Huang, S., Matzuk, M.M., 1996. Neurodegeneration, myocardial injury, and perinatal death in mitochondrial superoxide dismutase-deficient mice. Proc. Natl. Acad. Sci. U.S.A. 93,

9782-9787.

Li, Y., Huang, T-T., Carlson, E.J., Melov, S., Ursell, P.C., Olson, J.L., Noble, L.J., Yoshimura, M.P., Berger, C., Chan, P.H., Wallace, D.C., Epstein C.J., 1995. Dilated cardiomyopathy and neonatal lethality in mutant mice lacking manganese superoxide dismutase. Nature Genet. 11, 376-381.

Lino, M.M., Schneider, C., Caroni, P., 2002. Accumulation of SOD1 mutants in postnatal motoneurons does not cause motoneuron pathology or motoneuron disease. J. Neurosci. 22, 4825-4832.

Lynn, S., Huang, E.J., Elchuri, S., Naeemuddin, M., Nishinaka, Y., Yodoi, J., Ferriero, D. M., Epstein, C.J., Huang, T-T., 2005. Selective neuronal vulnerability and inadequate stress response in superoxide dismutase mutant mice. Free Radic. Biol. Med. 38, 817-828.

Mack, T.G. A., Reiner, M., Beirowski, B., Mi, W., Emanuelli, M., Wagner, D., Thomson, D., Gillingwater, T., Court, F., Conforti, L., Fernando, F.S., Tarlton, A., Andressen, C., Addicks, K., Magni, G., Ribchester, R.R., Perry, V.H., Coleman, M.P., 2001. Wallerian degeneration of injured axons and synapses is delayed by a Ube4b/Nmnat chimeric gene. Nature Neurosci. 4, 1199-1206.

Marklund S.L., 1982. Human copper-containing superoxide dismutase of high molecular

weight. Proc. Natl. Acad. Sci. U.S.A. 79, 7634-7638.

Mattiazzi, M., D'Aurelio, M., Gajewski, C.D., Martushova, K., Kiaei, M., Beal, M.F., Manfredi, G., 2002. Mutated human SOD1 causes dysfunction of oxidative phosphorylation in mitochondria of transgenic mice. J. Biol. Chem. 277, 29626-29633.

McCord, J.M., Fridovich, I., 1969. The utility of superoxide dismutase in studying free radical reaction I: Radicals generated by the interaction of sulfite, dimetyl sulfoxide, and oxygen. J. Biol. Chem. 244, 6056-6063.

Melov, S., Schneider, J.A., Day, B.J., Hinerfeld, D., Coskun, P., Mirra, S.S., Crapo, J.D., Wallace, D.C., 1998. A novel neurological phenotype in mice lacking mitochondrial manganese superoxide dismutase. Nature Genet. 18, 159-163.

Misawa, H., Nakata, K., Matsuura, J., Nagao, M., Okuda, T., Haga, T., 2001. Distribution of the high-affinity choline transporter in the central nervous system of the rat. Neuroscience 105, 87-98.

Misawa, H., Nakata, K., Toda, K., Matsuura, J., Oda, Y., Inoue, H., Taneno, M., Takahashi, R., 2003. VAChT-Cre.Fast and VAChT-Cre.Slow: postnatal expression of Cre recombinase in somatomotor neurons with different onset. genesis 37, 44-50.

Murakami, K., Kondo, T., Kawase, M., Li, Y., Sato, S., Chen, S.F., Chan, P.H., 1998. Mitochondrial susceptibility to oxidative stress exacerbates cerebral infarction that follows permanent focal cerebral ischemia in mutant mice with manganese superoxide dismutase deficiency. J. Neurosci. 18, 205-213.

Nagai, M., Aoki, M., Miyoshi, I., Kato, M., Pasinelli, P., Kasai, N., Brown, R.H.Jr., Itoyama, Y., 2001. Rats expressing human cytosolic copper-zinc superoxide dismutase transgenes with amyotrophic lateral sclerosis: associated mutations develop motor neuron disease. J. Neurosci. 21, 9246-9254.

Okado-Matsumoto, A., Fridovich, I., 2001. Subcellular distribution of superoxide dismutases (SOD) in rat liver. J. Biol. Chem. 276, 38388-38393.

Okado-Matsumoto, A., Fridovich, I., 2002. Amyotrophic lateral sclerosis: A proposed mechanism. Proc. Natl. Acad. Sci. U.S.A. 99, 9010-9014.

Pramatarova, A., Laganiere, J., Roussel, J., Brisbois, K., Rouleau, G.A., 2001. Neuron-specific expression of mutant superoxide dismutase 1 in transgenic mice does not lead to motor impairment. J. Neurosci. 21, 3369-3374.

Reaume, A.G., Elliott, J.L., Hoffman, E.K., Kowall, N.W., Ferrante, R.J., Siwek, D.F., Wilcox, H.M., Flood, D.G., Beal, M.F., Brown, R.H.Jr., Scott, R.W., Snider, W.D., 1996.

Motor neurons in Cu/Zn superoxide dismutase-deficient mice develop normally but exhibit enhanced cell death after axonal injury. Nature Genet. 13, 43-47.

Schmued, L.C., Albertson, C., Slikker, W.Jr., 1997. Fluoro-Jade: a novel fluorochrome for the sensitive and reliable histochemical localization of neuronal degeneration. Brain Res. 751, 37-46.

Vande Velde, C., Garcia, M.L., Yin, X., Trapp, B.D., Cleveland, D.W., 2004. The neuroprotective factor Wld^s does not attenuate mutant SOD1-mediated motor neuron disease. NeuroMolecular Med. 5, 193-203.

Weisiger, R.A., Fridovich, I., 1973. Mitochondrial superoxide dismutase: Site of synthesis and intramitochondrial localization. J. Biol. Chem. 248, 4793-4796.

Wong, P.C., Pardo, C.A., Borchelt, D.R., Lee, M.K., Copeland, N.G., Jenkins, N.A., Sisodia, S.S., Cleveland, D.W., Price, D.L., 1995. An adverse property of a familial ALS-linked SOD1 mutation causes motor neuron disease characterized by vacuolar degeneration of mitochondria. Neuron 14, 1105-1116.

Xu, Z., Jung, C., Higgins, C., Levine, J., Kong, J., 2004. Mitochondrial degeneration in amyotrophic lateral sclerosis. J. Bioenerg. Biomembr. 36, 395-399.

Figure legends

Fig. 1. Loss of SOD2 immunoreactivity in motor neurons from $SOD2^{lox/lox}$;$Cre^{slow/-}$ mice. (A-G) Paraffin-embedded sections of brain and spinal cord from $SOD2^{lox/lox}$;$Cre^{slow/-}$ mice at 5-months old stained with anti-ChAT antibody (A) or anti-SOD2 antibody (B-G). SOD2-immunoreactivity was lost in a subset of ChAT-positive somatomotor neurons as revealed by serial section through the hypoglossal nuclei (A, B and C) as well as sections through the oculomotor (D), abducens (E), facial (F) nuclei, and the ventral horn of the spinal cord (G). Note that SOD2 immunoreactivity was preserved in visceromotor neurons in the dorsal motor nucleus of the vagus (B). X, dorsal motor nucleus of the vagus; XII, hypoglossal nucleus. The boxed area in B is enlarged in C. (H-J) Paraffin-embedded sections from the ventral horn of the spinal cord were double-stained by immunofluorescence with anti-SOD2 (H) and anti-SMI-32 (I) antibodies. The merged image is shown in J. SOD2 immunoreactivity was lost in a subset of SMI-32-positive large motor neurons (denoted by asterisks) but not in SMI-32-negative small-diameter interneurons. (K-N) Mitochondrial production of $O_2^{\cdot -}$ was increased in $SOD2^{lox/lox}$;$Cre^{slow/-}$ (C-KO) mice compared with $SOD2^{lox/lox}$;$Cre^{-/-}$ (Control) mice in motor neurons in the hypoglossal nucleus (K and L) and ventral horn of the spinal cord (M and N) as revealed by HEt oxidation. HEt signals were detected in motor neurons as small granular particles in the cytosol, indicating mitochondrial production of $O_2^{\cdot -}$ under normal physiological conditions. Scale bars = 100 μm (A; also applies to B); 20 μm (C); 20 μm (D; also applies to E-G); 20 μm (H; also applies to I, J); 20 μm (K; also applies to L, M, N).

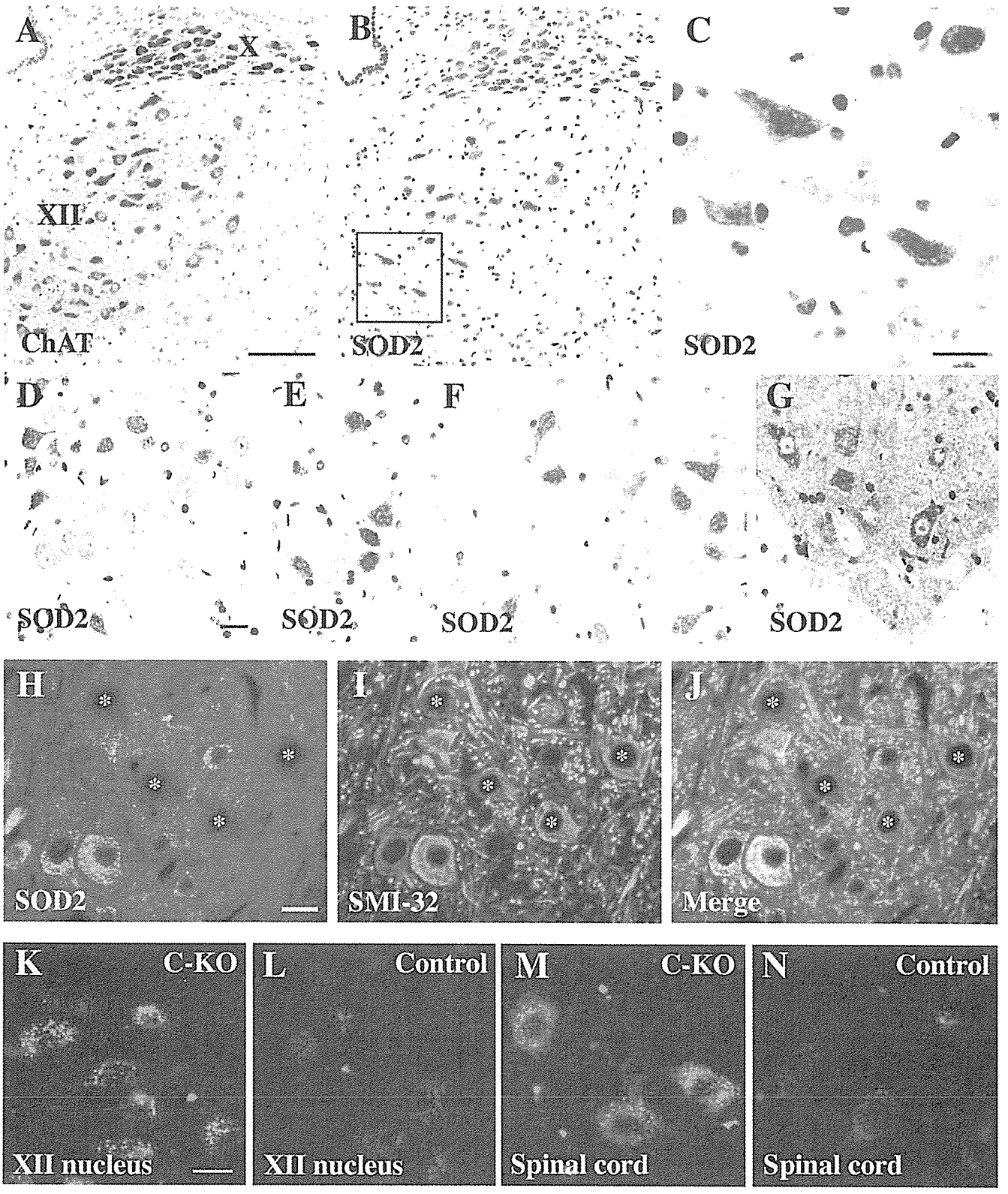
Fig. 2. Detection of SOD2-deficient and ChAT-positive motor neurons in the spinal cord of $SOD2^{lox/lox}$;$Cre^{slow/-}$ mice. Serial paraffin-embedded 5 μm sections of the lumber spinal cord from $SOD2^{lox/lox}$;$Cre^{slow/-}$ mice at 1 month (A, B), 3 months (C, D) or 6 months (E, F) of age were stained with anti-SOD2 (A, C, E) or anti-ChAT (B, D, F) antibodies. Arrows indicate SOD2-negative and ChAT-positive motor neurons. Scale bar = 50 μm. (G) Numbers of spinal cord ChAT-positive motor neurons in $SOD2^{lox/lox}$;$Cre^{slow/-}$ and $SOD2^{lox/lox}$;$Cre^{-/-}$ mice. Numbers were determined from every 5th section for a total of 15 sections. Shown are the means from three mice +/- standard deviation (n = 3).

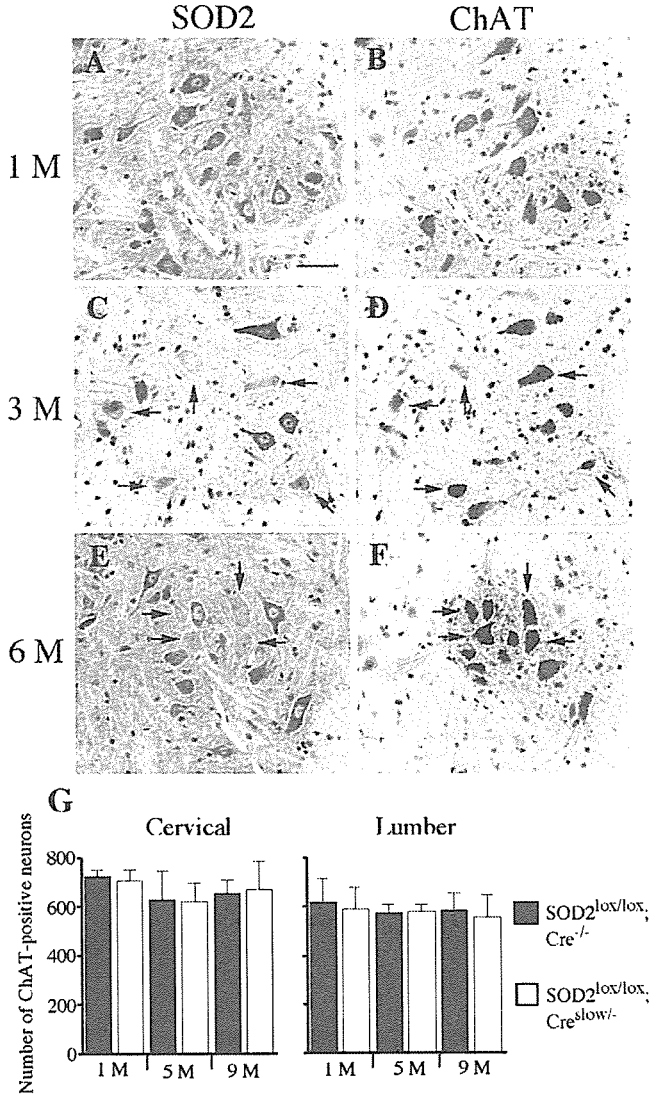
Fig. 3. Morphology of SOD2-deficient motor neurons in 9-month old $SOD2^{lox/lox}$;$Cre^{slow/-}$ mice. Serial sections from the facial nucleus (A, B) or spinal cord ventral horn (C, D) stained with an anti-SOD2 antibody (A, C) or cresyl violet (Nissl; B, D). No overt morphological changes were seen in the SOD2-defiecent motor neurons (arrows). Serial sections from the hypoglossal nucleus stained with anti-SOD2 (E) or anti-SOD1 (F) antibodies. No difference in the staining pattern or intensity was evident between SOD2-negative (arrows) and SOD2-positive motor neurons. Scale bars = 20 μm. (G) Ventral portions of the spinal cord were micro-dissected from $SOD2^{lox/lox}$;$Cre^{slow/-}$ (C-KO) and $SOD2^{lox/lox}$;$Cre^{-/-}$ (Control) mice. Total homogenates (10 μg) were subjected to immunoblot analysis with polyclonal anti-SOD2 or anti-SOD1 antibodies. Actin content is shown as a loading control.

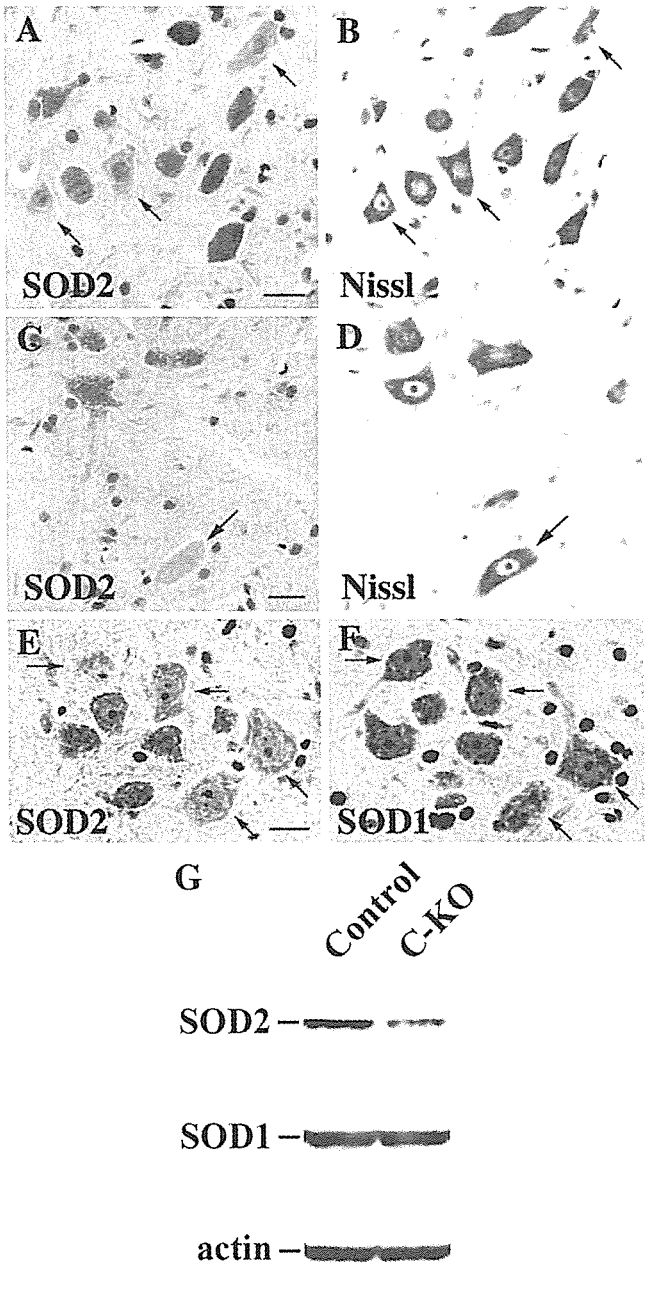
Fig. 4. Absence of muscle atrophy and denervation/remodeling of endplates in $SOD2^{lox/lox}$;$Cre^{slow/-}$ mice. Serial cryo-sections of gastrocnemius muscle from a 9-month old $SOD2^{lox/lox}$;$Cre^{slow/-}$ mouse stained with hematoxylin and eosin (A) or Gomori-trichrome (B). Paraffin-embedded sections (5 μm) of diaphragm muscle containing neuromuscular junction from 9-month old $SOD2^{lox/lox}$;$Cre^{slow/-}$ mice stained with an anti-CHT antibody followed by counter-staining with hematoxilin (C). Scale bar = 20 μm.

Fig. 5. Nissl-staining of hypoglossal motor neurons 5 weeks after axotomy in $SOD2^{lox/lox}$;$Cre^{slow/-}$ (A) and $SOD2^{lox/lox}$;$Cre^{-/-}$ (B) mice. Arrows indicate the operated side. CC, Central canal; X, dorsal motor nucleus of the vagus; XII, hypoglossal nucleus. Scale bar = 100 μm. (C) Number of neurons in hypoglossal nuclei (uncut control or axotomized operated side) from both $SOD2^{lox/lox}$;$Cre^{slow/-}$ and $SOD2^{lox/lox}$;$Cre^{-/-}$ mice (n = 4 for each genotype).

Fig. 6. Accelerated axonal disorganization in $SOD2^{lox/lox}$;$Cre^{slow/-}$ mice after motor nerve injury. (A) Western blot of 200-kDa neurofilament protein (NF-200) demonstrating the extent of degeneration 2 days after nerve transection in the distal transected hypoglossal nerve (Axotomy) or corresponding contralateral uncut nerve (Uncut). The blot was re-probed with control monoclonal antibody (β-tub 2.1) against β-tubulin. Samples from three $SOD2^{lox/lox}$;$Cre^{slow/-}$and two $SOD2^{lox/lox}$;$Cre^{-/-}$ control mice are shown. (B) Representative toluidine blue-stained sections of hypoglossal nerves 2-4 mm distal to the lesion site 2 days after transection or corresponding contralateral uninjured nerve. Scale bar = 20 μm.

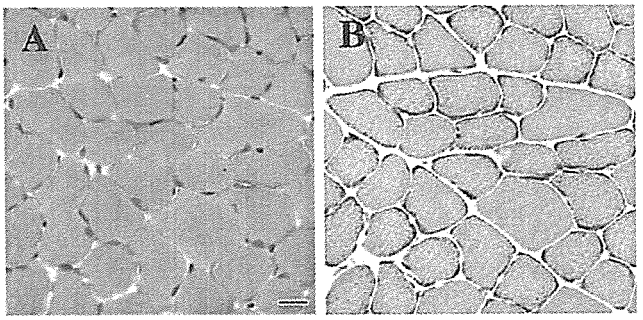

A
X
XII
ChAT
B
SOD2
C
SOD2
D
SOD2
E
SOD2
F
SOD2
G
SOD2
H
SOD2
I
SMI-32
J
Merge
K
C-KO
XII nucleus
L
Control
XII nucleus
M
C-KO
Spinal cord
N
Control
Spinal cord


SOD2
ChAT
A
B
1 M
C
D
3 M
E
F
6 M
G
Cervical
Lumber
Number of ChAT-positive neurons
800
600
400
200
0
1 M
5 M
9 M
1 M
5 M
9 M
SOD2lox/lox, Cre-/-
SOD2lox/lox, Creslow/-

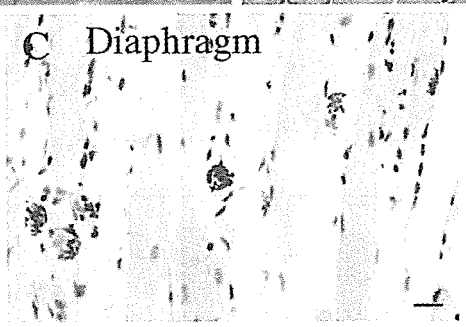

A
SOD2
B
Nissl
C
SOD2
D
Nissl
E
SOD2
F
SOD1
G
Control
C-KO
SOD2
SOD1
actin

Gastrocnemius muscle

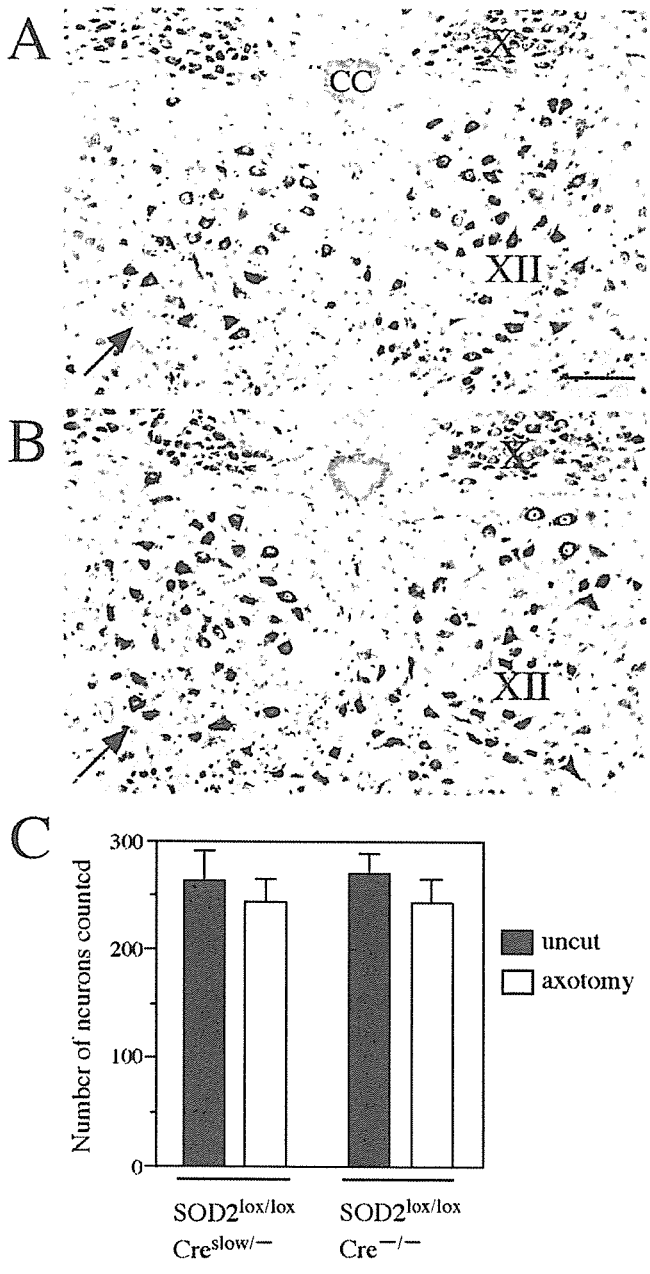
H & E Gomori-trichrome



C Diaphragm



Anti-CHT and Hematoxilin


A
CC
X
XII
B
X
XII
C
Number of neurons counted
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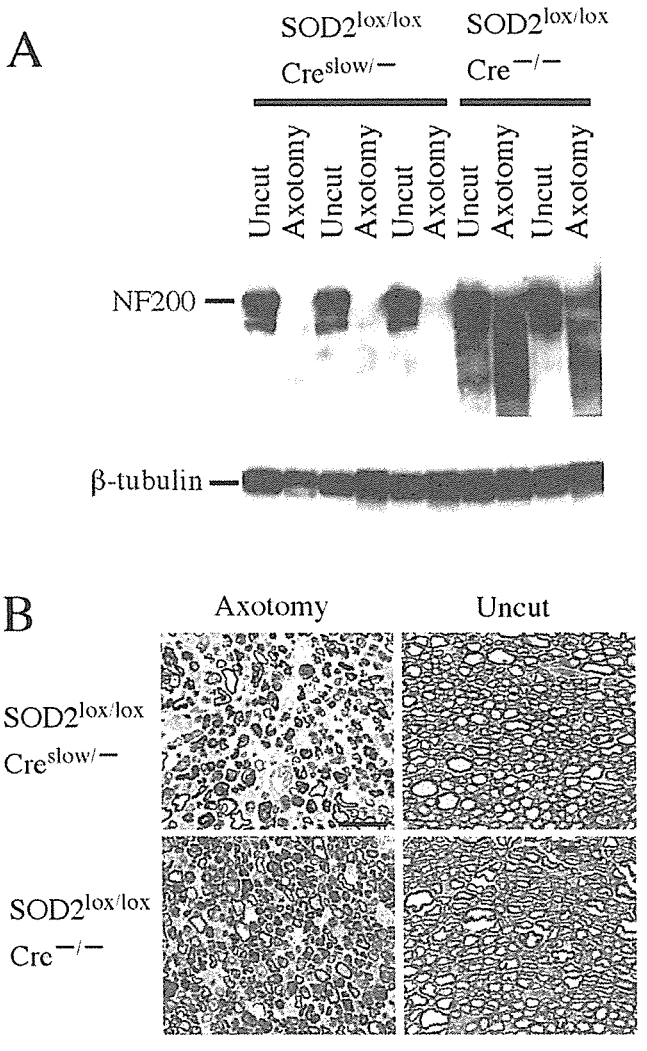
200
100
0
uncut
axotomy
SOD2lox/lox
Creslow/—
SOD2lox/lox
Cre−/−


A
SOD2lox/lox
Creslow/−
SOD2lox/lox
Cre−/−
Uncut
Axotomy
Uncut
Axotomy
Uncut
Axotomy
Uncut
Axotomy
Uncut
Axotomy
NF200
β-tubulin
B
Axotomy
Uncut
SOD2lox/lox
Creslow/−
SOD2lox/lox
Cre−/−

コンフォメーション病のしくみ

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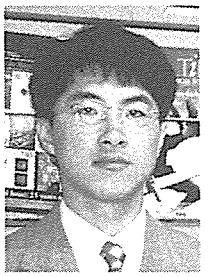

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Key words：コンフォメーション病，神経変性疾患，凝集，封入体，タンパク質品質管理システム

Abstract

病変組織における異常タンパク質の凝集及び蓄積は神経変性疾患の共通の病理所見である。凝集の主な原因は遺伝子の変異によるタンパク質の構造異変であるが、細胞内には分子シャペロンとユビキチン・プロテアソームなどのタンパク質の品質管理システムがあり、タンパク質の機能を安定に保つための働きをしている。老化に伴う細胞ストレスはタンパク質の凝集を促進させる原因の一つであり、神経変性疾患のしくみは原因タンパク質の凝集し易い構造とそれを制御するタンパク質品質管理システムの駆け引きであろう。

はじめに

1997年，Carrell と Lomas により提唱されたコンフォメーション病（フォールディング病）とは，病変組織に異常タンパク質が凝集し，封入体を形成する疾患の総称である。コンフォメーション病は神経系，免疫系，内分泌系，循環系，心筋・骨格筋系などに幅広く存在する。特に神経系においては，日本でも発症が報告され話題となった狂牛病（プリオン病）を始め，パーキンソン病やアルツハイマー病，ハンチントン病，筋萎縮性側索硬化症（ALS）などのいわゆる神経変性疾患で，神経細胞内外のさまざまな封入体の存在が共通の病理所見として知られている。神経変性疾患の原因は長年不明であったが，近年の研究結果から，原因タンパク質が構造異常により不溶化し凝集物を形成していく過程で，細胞死を引き起こすのではないかと考えられている。本稿ではタンパク質の立体構造，分解，凝集のプロセスに注目し，コンフォメーション病としての神経変性疾患の病理形成機序について論じたい。

1. タンパク質のフォールディングと凝集

蛋白質はアミノ酸が直線状につながった高分子の“ひも”である。1950年代のアンフィンセン，C.（1972年ノーベル化学賞受賞）に

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