

for stab wound injury and its regeneration [57]. ‘Why do MT isoforms exist?’ There is no answer yet; however, MT-I/II is thought to be an acutely reactive (anti-inflammatory) protein, while the reaction of MT-III is slower than that of MT-I/II and MT-III continues to work longer, based on the observation of the stab wounds in the rat brain [58].

Similarly there are two types of fiber (type I and type II) in the muscle. The type I muscle fibers react slower and more continuous than the type II muscle fibers. The ratio of type I muscle fibers to type II fibers differs among muscles according to the function. The existence of two types of fibers in the muscle is similar to that of isoforms of MT.

MT-III is abundant in the CNS. It is sure that MT-III plays important roles in the brain and in the progression of neurodegenerative diseases such as ALS, AD, PD, FD, as well as prion disease [59], brain trauma [58], brain ischemia [60], and psychiatric disorders [61]. A combination of MT-I/II and MT-III will be good tools for the treatment of neurodegenerative diseases.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

This work was supported by the grants-in-aids from the Community for Communication of Technology of Gifu University, the Ministry of Education, Culture, Sports, Science and Technology of Japan (Basic Research (B) 19390151), and the Ministry of Health, Labour and Welfare of Japan (Control and Prevention of Intractable Diseases, H22-Intractable-General-202), Japan. The author is grateful for the continuous support and encouraging advice from all members of Tokai Metallothionein Research Group: Professor T. Inuzuka and all his colleagues in Department of Neurology and Geriatrics, Gifu University, Graduate School of Medicine, Gifu, Japan; Professor H. Hara and his colleagues in Department of Biofunctional Evaluation, Molecular Pharmacology, Gifu Pharmaceutical University, Gifu, Japan; Professor H. Nagase of Laboratory of Hygienic Chemistry and Molecular Toxicology, Gifu Pharmaceutical University, Gifu, Japan; Chief Investigator Y. Uchida of Gene Expression Research Group, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan; and Professor M. Sato and his colleagues in Laboratory of Pharmaceutical Health Sciences, School of Pharmacy, Aichi Gakuin University, Nagoya, Japan.

ABBREVIATIONS

AD	=	Alzheimer’s disease
ALS	=	Amyotrophic lateral sclerosis
Cd	=	Cadmium
Cu	=	Copper
FD	=	Fahr’s disease
GSH	=	Glutathione
Hg	=	Mercury
MT	=	Metallothionein

PD	=	Parkinson’s disease
ROS	=	Reactive oxygen species
Zn	=	Zinc

REFERENCES

- [1] Hozumi, I.; Asanuma, M.; Yamada, M.; Uchida, Y. Metallothioneins and neurodegenerative diseases. *J. Health Sci.*, **2004**, *50*(4), 323-331.
- [2] Uchida, Y.; Takio, K.; Titani, K.; Ihara, Y.; Tomonaga, M. The growth inhibitory factor that is deficient in the Alzheimer’s disease brain is a 68 amino acid metallothionein-like protein. *Neuron*, **1991**, *7*(2), 337-347.
- [3] Quaife, C.J.; Findley, S.D.; Erickson, J.C.; Froelick, J.G.; Kelly, E.J.; Zambrowics, B.P.; Palmiter, R.D. Induction of a new metallothionein isoform (MT-IV) occurs during differentiation of stratified squamous epithelia. *Biochemistry*, **1994**, *33*(23), 7250-7259.
- [4] Choudhuri, S.; Kramer, K. K.; Berman, N. E. J.; Dalton, T. P.; Andrews, G. K.; Klaassen, C. D. Constitutive expression of metallothionein genes in mouse brain. *Toxicol. Appl. Pharmacol.*, **1995**, *131*(1), 144-154.
- [5] Hozumi, I.; Suzuki, J.S.; Kanazawa, H.; Hara, A.; Saio, M.; Inuzuka, T.; Miyairi, S.; Naganuma, A.; Tohyama, C. Metallothionein-3 is expressed in the brain and various peripheral organs of the rat. *Neurosci. Lett.*, **2008**, *438*(1), 54-58.
- [6] Uchida, Y.; Gomi, F.; Masumizu, T.; Miura, Y. Growth inhibitory factor prevents neurite extension and the death of cortical neurons caused by high oxygen exposure through hydroxyl radical scavenging. *J. Biol. Chem.*, **2002**, *277*(35), 32353-32359.
- [7] Hozumi, I.; Koumura, A.; Kimura, A.; Hasegawa, T.; Honda, A.; Hayashi, Y.; Hashimoto, K.; Yamada, M.; Sakurai, T.; Tanaka, Y.; Satoh, M.; Inuzuka T. High levels of copper, zinc, iron, and magnesium, but not calcium in the cerebrospinal fluid of patients with Fahr’s disease. *Case Rept. Neurol.*, **2010**, *2*, 46-51.
- [8] Rosen, D.R.; Siddique, T.; Patterson, D.; Figlewicz, D. A.; Sapp, P.; Hentati, A.; Donaldson, D.; Goto, J.; O’Regan, J. P.; Deng, H. X.; Rahmani, Z.; Krizus, A.; McKenna-Yasek, D.; Cayabyab, A.; Gaston, S. M.; Berger, R.; Tanzi, R. E.; Halperin, J. J.; Herzfeldt, B.; Bergh, R. V D.; Hung, W. Y.; Bird, T.; Deng, G.; Mulder, D. W.; Smyth, C.; Laing, N. G.; Soriano, E.; Pericak-Vance, M. A.; Haines, J.; Rouleau, G. A.; Gusella, J. S.; Horvitz, H. R.; Brown R. H. Jr. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature*, **1993**, *362*, 59-62.
- [9] Greenway, M.J.; Andersen, P. M.; Russ, C.; Ennis, S.; Cashman, S.; Donaghay, C.; Patterson, V.; Swingle, R.; Kieran, D.; Prehn, J.; Morrison, K. E.; Green, A.; Acharya, K. R.; Brown, R. H. Jr.; Hardiman, O. ANG mutations segregate with familial and ‘sporadic’ amyotrophic lateral sclerosis. *Nat. Genet.*, **2006**, *38*(4), 411-413.
- [10] Sreedharan, J.; Blair, I. P.; Tripathi, V. B.; Hu, X.; Vance, C.; Rogejl, B.; Ackery, S.; Durnall, J.C.; Williams, K. L.; Buratti, E.; Baralle, F.; de Belleruche, J.; Mitchell, J. D.; Leigh, P. N.; Al-Chalabi, A.; Miller, C. C.; Nicholson, G.; Shaw, C. E. TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. *Science*, **2008**, *319*(5870), 1668-1672.
- [11] Kwiatkowski, T. J. Jr.; Bosco, D. A.; Leclerc, A. L.; Tamrazian, E.; Vanderburg, C. R.; Russ, C.; Davis, A.; Gilchrist, J.; Kasarskis, E. J.; Munsat, T.; Valdmanis, P.; Rouleau, G. A.; Hosler, B. A.; Cortelli, P.; de Jong, P. J.; Yoshinaga, Y.; Haines, J. L.; Pericak-Vance, M. A.; Yan, J.; Ticozzi, N.; Siddique, T.; McKenna-Yasek, D.; Sapp, P. C.; Horvitz, H. R.; Landers, J. E.; Brown, R. H. Jr. Mutations in the FUS/TLS gene on chromosome 16 cause familial amyotrophic lateral sclerosis. *Science*, **2009**, *323*, 1205-1208.
- [12] Vance, C.; Rogejl, B.; Hortobagyi, T.; De Vos, K. J.; Nishimura, A. L.; Sreedharan, J.; Hu, X.; Smith, B.; Ruddy, D.; Wright, P.; Ganeshalingam, J.; Williams, K. L.; Tripathi, V.; Al-Saraj, S.; Al-Chalabi, A.; Leigh, P. N.; Blair, I. P.; Nicholson, G.; de Belleruche, J.; Gallo, J. M.; Miller, C. C.; Shaw, C. E. Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. *Science*, **2009**, *323*(5918), 1208-1211.
- [13] Maruyama, H.; Morino, H.; Ito, H.; Izumi, Y.; Kato, H.; Watanabe, Y.; Kinoshita, Y.; Kamada, M.; Nodera, H.; Suzuki, H.; Komure, O.; Matsuura, S.; Kobatake, K.; Morimoto, N.; Abe, K.; Suzuki, N.; Aoki, M.; Kawata, A.; Hirai, T.; Kato, T.; Ogasawara, K.; Hi-

- rano, A.; Takumi, T.; Kusaka, H.; Hagiwara, K.; Kaji, R.; Kawakami, H. Mutation of optineurin in amyotrophic lateral sclerosis. *Nature*, **2010**, *465*(7295), 223-226.
- [14] Cleveland, D. W.; Rothstein, J. D. From Charcot to Lou Gehrig: deciphering selective motor neuron death in ALS. *Nat. Rev. Neurosci.*, **2001**, *2*, 806-819.
- [15] Boillée, S.; Velde, C.V.; Cleveland, D. W. ALS: a disease of motor neurons and their nonneuronal neighbors. *Neuron*, **2006**, *52*(1), 39-59.
- [16] Ito, Y.; Yamada, M.; Tanaka, H.; Aida, K.; Tsuruma, K.; Shimazawa, M.; Hozumi, I.; Inuzuka, T.; Takahashi, H.; Hara, H. Involvement of CHOP, an ER-stress apoptotic mediator, in both human sporadic ALS and ALS model mice. *Neurobiol. Dis.*, **2009**, *36*(3) 470-476.
- [17] Nagano, S.; Satoh, M.; Sumi, H.; Fujimura, H.; Tohyama, C.; Yanagihara, T.; Sakoda, S. Reduction of metallothioneins promotes the disease expression of familial amyotrophic lateral sclerosis mice in a dose-dependent manner. *Eur. J. Neurosci.*, **2001**, *13*(7), 1363-1370.
- [18] Puttaparthi, K.; Gitomer, W. L.; Krishnan, U.; Son, M.; Rajendran, B.; Elliott, J. L. Disease progression in a transgenic model of familial amyotrophic lateral sclerosis is dependent on both neuronal and non-neuronal zinc binding proteins. *J. Neurosci.*, **2002**, *22*(20), 8790-8796.
- [19] Ishigaki, S.; Niwa, J.; Ando, Y.; Yoshihara, T.; Sawada, K.; Doyu, M.; Yamamoto, M.; Kato, K.; Yotsuji, Y.; Sobue, G. Differentially expressed genes in sporadic amyotrophic lateral sclerosis spinal cords—screening by molecular indexing and subsequent cDNA microarray analysis. *FEBS Lett.*, **2002**, *531*(2), 354-358.
- [20] Hozumi, I.; Yamada, M.; Uchida, Y.; Ozawa, K.; Takahashi, H.; Inuzuka, T. The expression of metallothioneins is diminished in the spinal cords of patients with sporadic ALS. *Amyotroph. Lateral. Scler.*, **2008b**, *9*, 294-298.
- [21] McCrate, M. E.; Kaspar, B. K. Physical activity and neuroprotection in amyotrophic lateral sclerosis. *Neuromolecular Med.*, **2008**, *10*(2), 108-117.
- [22] Kirkinezos, I. G.; Hernandez, D.; Bradley, W. G.; Moraes, C. T. Regular exercise is beneficial to a mouse model of amyotrophic lateral sclerosis. *Ann. Neurol.*, **2003**, *53*(6), 804-807.
- [23] Hashimoto, K.; Hayashi, Y.; Inuzuka, T.; Hozumi, I. Exercise induces metallothioneins in mouse spinal cord. *Neuroscience*, **2009**, *163*(1), 244-251.
- [24] Sakamoto, T.; Kawazoe, Y.; Uchida, Y.; Hozumi, I.; Inuzuka, T.; Watabe, K. Growth inhibitory factor prevents degeneration of injured adult rat motoneurons. *Neuroreport*, **2003**, *14*(17), 2147-2151.
- [25] Hozumi, I.; Uchida, Y.; Watabe, K.; Sakamoto, T.; Inuzuka, T. Growth inhibitory factor (GIF) can protect from brain damage due to stab wounds in rat brain. *Neurosci. Lett.*, **2006**, *395*(3), 220-223.
- [26] Hashimoto, K.; Hayashi, Y.; Inuzuka, T.; Hozumi, I. Growth inhibitory factor inhibits the progression of amyotrophic lateral sclerosis model mice. *Neurology*, **2010**, *74*(Suppl 2), A436.
- [27] Kanias, D.; Kapaki, E. Trace elements, age, and sex in amyotrophic lateral sclerosis disease. *Biol. Trace Element Res.*, **1997**, *56*(2), 187-201.
- [28] Tokuda, E.; Ono, S.; Ishige, K.; Naganuma, A.; Ito, Y.; Suzuki, T. Metallothionein protein expression, copper and zinc concentrations, and lipid peroxidation level in a rodent model for amyotrophic lateral sclerosis. *Toxicology*, **2007**, *229*, 33-41.
- [29] Kim, J.; Kim, T. Y.; Hwang, J. J.; Lee, Y. Y.; Shin, J. H.; Gwag, B. J.; Koh, J. Y. Accumulation of labile zinc in neurons and astrocytes in the spinal cords of G93A SOD-1 transgenic mice. *Neurobiol. Dis.*, **2009**, *34*, 221-229.
- [30] Tokuda, E.; Ono, S.; Ishige, K.; Naganuma, A.; Ito, Y.; Suzuki, T. Ammonium tetrathiomolybdate delays onset, prolongs survivals, and slows progression of disease in a mouse model for amyotrophic lateral sclerosis. *Exper. Neurol.*, **2008**, *214*, 122-128.
- [31] Squitti, R.; Bressi, F.; Pasqualetti, P.; Bonomini, C.; Ghidoni, R.; Binetti, G.; Gassetta, F.; Moffa, F.; Ventriglia, M.; Vernieri, F.; Rossini, P. M. Longitudinal prognostic value of serum “free” copper in patients with Alzheimer disease. *Neurology*, **2009**, *72*(1), 50-55.
- [32] Religa, D.; Strozyk, D.; Cherny, R. A.; Volitakis, I.; Haroutunian, V.; Winblad, B.; Naslund, J.; Bush, A. I. Elevated cortical zinc in Alzheimer disease. *Neurology*, **2006**, *67*(1), 69-75.
- [33] Zarzanz, J. J.; Alegre, J.; Gómez-Esteban, J. C.; Lezcano, E.; Ros, R.; Ampuero, I.; Vidal, L.; Hoenicka, J.; Rodriguez, O.; Atarés, B.; Llorens, V.; Tortosa, E. G.; de Ser, T.; Muñoz, D. J. The new mutation, E46K, of α -synuclein causes parkinson and Lewy body dementia. *Ann. Neurol.*, **2003**, *55*(2), 164-173.
- [34] Kitada, T.; Asakawa, S.; Hattori, N.; Matsumine, H.; Yamamura, Y.; Minoshima, S.; Yokochi, M.; Mizuno, Y.; Shimizu, N. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature*, **1998**, *392*, 605-608.
- [35] Maraganore, D. M.; Lesnick, T. G.; Elbaz, A.; Chartier-Harlin, M. C.; Gasser, T.; Krüger, R.; Hattori, N.; Mellick, G. D.; Quattrone, A.; Satoh, J.; Toda, T.; Wang, J.; Ioannidis, J. P.; de Andrade, M.; Rocca, W. A.; UCHL1 Global Genetics Consortium. UCHL1 is a Parkinson's disease susceptibility gene. *Ann. Neurol.*, **2004**, *55*(4): 512-21.
- [36] Canet-Avilés, R. M.; Wilson, M. A.; Miller, D. W.; Ahmad, R.; McLendon, C.; Bandyopadhyay, S.; Baptista, M. J.; Ringe, D.; Petsko, G. A.; Cookson, M. R. The Parkinson's disease protein DJ-1 is neuroprotective due to cysteine-sulfenic acid-driven mitochondrial localization. *Proc. Natl. Acad. Sci. U.S.A.*, **2004**, *101*(24), 9103-9108.
- [37] Valent, E. M.; Sergio Salvi, S.; Ialongo, T.; Marongiu, R.; Elia, A. E.; Caputo, V.; Romito, L.; Albanese, A.; Dallapiccola, B.; Bentivoglio, A. R. PINK1 mutations are associated with sporadic early-onset parkinsonism. *Ann. Neurol.*, **2004**, *56*(3), 336-341.
- [38] Smith, W. W.; Pei, Z.; Jiang, H.; Moore, D. J.; Liang, Y.; West, A. B.; Dawson, V. L.; Dawson, T. M.; Ross, C. A. (2005) Leucine-rich repeat kinase 2 (LRRK2) interacts with parkin, and mutant LRRK2 induces neuronal degeneration. *Proc. Natl. Acad. Sci. U.S.A.*, **102**(51), 18676-18681.
- [39] DeLong, M. R.; Juncos, J. L. Parkinson's disease and other movement disorders. In Harrison's principles of internal medicine, 16th edition; McGraw-Hill, Ed.; Kasper, D.L.; Braunwald, E.; Fauci, A.S.; Hauser, S. L.; Longo, D. L.; Jameson, J. L.: New York, **2005**; pp. 2406-2418.
- [40] Asanuma, M.; Miyazaki, I.; Higashi, Y.; Tanaka, K.; Haque, M. E.; Fujita, N.; Ogawa, N. Aggravation of 6-hydroxydopamine-induced dopaminergic lesions in metallothionein-I and -II knockout mouse brain. *Neurosci. Lett.*, **2002**, *327*, 61-67.
- [41] Miyazaki, I.; Sogawab, A. C.; Asanuma, M.; Higashi, Y.; Tanaka, K.; Nakanishi, T.; Ogawa, N. Expression of metallothionein-III mRNA and its regulation by levodopa in the basal ganglia of hemiparkinsonian rats. *Neurosci. Lett.*, **2000**, *293*, 65-68.
- [42] Gorell, J. M.; Johnson, C. C.; Rybicki, B. A.; Peterson, E. L.; Kortsha, G. X.; Brown, G. G.; Richardson, R. J. Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. *Neurotoxicol.*, **1999**, *20*(2-3), 239-247.
- [43] Oyanagi, K.; Kawakami, E.; Kikuchi-Horie, K.; Ohara, K.; Ogata, K.; Takahama, S.; Wada, M.; Kihira, T.; Yasui, M. Magnesium deficiency over generations in rats with special references to the pathogenesis of the parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam. *Neuropathol.*, **2006**, *26*(2), 115-128.
- [44] Manyam, B. V. What is and what is not ‘Fahr’s disease’. *Parkinson relat. disord.*, **2005**, *11*(2), 73-80.
- [45] Shibayama, H.; Kobayashi, H.; Nakagawa, M.; Yamada, K.; Iwata, H.; Iwai, K.; Takeuchi, T.; Mu-Qune, X.; Ishihara, R.; Iwase, S.; Kitoh, J. Non-Alzheimer non-Pick dementia with Fahr’s syndrome. *Clinical Neuropathol.*, **1992**, *11*(5), 237-50.
- [46] Kosaka, K. Diffuse neurofibrillary tangles with calcification: a new presenile dementia. *J. Neurol. Neurosurg. Psychiatr.*, **1994**, *57*(5), 594-6.
- [47] Margoshes, M.; Vallee, B. L. A cadmium protein from equine kidney cortex. *J. Am. Chem. Soc.*, **1957**, *79*(19), 4813-4814.
- [48] Miyayama, T.; Suzuki, K. T.; Ogra, Y. Copper accumulation and compartmentalization in mouse fibroblast lacking metallothionein and copper chaperone. *Atox1. Toxicol. Appl. Pharm.*, **2009**, *237*, 205-213.
- [49] Sato, M.; and Bremner, I. Oxygen free radicals and metallothionein. *Free Rad. Biol. Med.*, **1993**, *14* (3), 325-337.
- [50] Kim, C. H.; Kim, K. J.; Lee, J. and Ahn, Y. S. Zinc-induced NF-K. J.; Lee, can be modulated by changes in the intracellular metallothionein level. *Toxicol. Appl. Pharm.*, **2003**, *190*, 186-196.
- [51] Hozumi, I.; Inuzuka, T.; Ishiguro, H.; Hiraiwa, M.; Uchida, Y.; Tsuji, S. Immunoreactivity of growth inhibitory factor in normal rat brain and after stab wounds—an immunocytochemical study using confocal laser scan microscope. *Brain Res.*, **1996**, *741*, 197-204.
- [52] Anezaki, T.; Ishiguro, H.; Hozumi, I.; Inuzuka, T.; Hiraiwa, M.; Kobayashi, H.; Yuguchi, T.; Wanaka, A.; Uda, Y.; Miyatake, T.;

- [53] Tohyama, M. () Expression of growth inhibitory factor (GIF) in normal and injured rat brains. *Neurochem. Int.*, **1995**, *27*, 89-94.
- [54] Yamada, M.; Hayashi, S.; Hozumi, I.; Tsuji, S.; Takahashi, H. () Subcellular localization of growth inhibitory factor in rat brain: light and electron microscopic immunohistochemical studies. *Brain Res.*, **1996**, *735*(2), 257-264.
- [55] Moffatt, P.; Seguin, C. () Expression of the gene encoding metallothionein-3 in organs of the reproductive system. *DNA Cell Biol.*, **1998**, *17*, 501-510.
- [56] Montoliu, C.; Monfort, P.; Carrasco, J.; Palacios, O.; Capdevila, M.; Hidalgo, J.; Felipo, V. () Metallothionein-III prevents glutamate and nitric oxide neutotoxicity in primary cultures of cerebellar neurons. *J. Neurochem.*, **2000**, *75*, 266-273.
- [57] Uchida, Y.; Gomi, F.; Masumizu, T.; Miura, Y. () Growth inhibitory factor prevents neurite extension and the death of cortical neurons caused by high oxygen exposure through hydroxyl radical scavenging. *J. Biol. Chem.*, **2002**, *277*, 32353-32359.
- [58] Hozumi, I.; Uchida, Y.; Watabe, K.; Sakamoto, T.; Inuzuka, T. () Growth inhibitory factor (GIF) can protect from brain damage due to stab wounds in rat brain. *Neurosci. Lett.*, **2006**, *395*: 220-223.
- [59] Hozumi, I.; Inuzuka, T., H.; Hiraiwa, M.; Uchida, Y.; Anezaki, T.; Ishiguro, H.; Kobayashi, H.; Uda, Y.; Miyatake, T.; Tsuji, S. () Changes of growth inhibitory factor after stab wounds in rat brain. *Brain Res.*, **1995**, *688*, 143-248.
- [60] Kawashima, T.; Doh-uraa, K.; Torisu, M.; Uchida, Y.; Furuta, A.; Iwaki, T. () Differential expression of metallothioneins in human prion diseases. *Dement. Geriatr. Cogn. Disord.*, **2000**, *11* (5), 251-262.
- [61] Koumura, A.; Hamanaka, J.; Shimazawa, M.; Honda, M.; Tsurumaa, K.; Uchida, Y.; Hozumi, I.; Satoh, M.; Inuzuka, T.; Hara, H. () Metallothionein-III knockout mice aggravates the neuronal damage after transient focal cerebral ischemia. *Brain Res.*, **2009**, *1292*(25), 148-154.
- Koumura, A.; Kakefuda, K.; Honda, A.; Ito, Y.; Tsuruma, K.; Shimazawa, M.; Uchida, Y.; Hozumi, I.; Satoh, M.; Inuzuka, T.; Hara, H. () Metallothionein-3 deficient mice exhibit abnormalities of psychiatric behaviors. *Neurosci. Lett.*, **2009**, *467*(1), 11-14.

Received: ??????????

Revised: ????????????

Accepted: ????????????

