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Diagnosis of Neurosarcoidosis and Muscular Sarcoidosis

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Sarcoidosis is multisystem granulomatous disease of etiology unknown, and is associated with bilateral hilar lymphadenopathy, pulmonary, skin, eyes, nervous system and muscles. Clinically recognizable nervous system and muscles involved in 5～16% and 1.4～2.3%, respectively, of patients with sarcoidosis. The incidence of subclinical neurosarcoidosis and muscular sarcoidosis, however, may be higher. Neuroradiological studies such as gallium scanning, fluorodeoxyglucose-PET scanning, MRI and CT scans are useful, and especially MRI is the most sensitive diagnostic tools for the detection and localization of neurological lesions. MRI before and after administration of gadolinium-DTPA can detect frequently subclinical or isolated sarcoidosis in the nerve system and muscles. However, MRI findings as well as serum and cerebrospinal fluid findings including angiotensin converting enzyme (ACE) level and neurophysiological findings are not specific for neurosarcoidosis and muscular sarcoidosis. Therefore, isolated sarcoidosis in the nerve sytem and muscles remain a very difficult diagnosis, particularly in the absence of systemic signs of sarcoidosis. Biopsy of nerve or muscle tissue is required to make a definite diagnosis of neurosarcoidosis or muscular sarcoidosis. Histopathological findings show characteristically reveals noncaseating granulomatous lesions, consisting of epithelioid cells, macrophages, Langhans-type giant cells, and lymphocytes, which show phenotypic cellular distribution : $CD68^+$ and $CD4^+$ cell in the center and to some extent, $CD8^+$ cells at the periphery. Ad hoc committee of Japanese Society of Neurology have collaborated with Japanese Sarcoidosis Society and Japanese Society of Respiratory disease to make a new diagnostic criteria of neurosarcoidosis including muscular sarcoidosis.

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L-3,4-Dihydroxyphenylalanine-induced c-Fos expression in the CNS under inhibition of central aromatic L-amino acid decarboxylase

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Abstract

L-3,4-Dihydroxyphenylalanine (DOPA) is a neurotransmitter candidate. To map the DOPAergic system functionally, DOPA-induced c-Fos expression was detected under inhibition of central aromatic L-amino acid decarboxylase (AADC). In rats treated with a central AADC inhibitor, DOPA significantly increased the number of c-Fos-positive nuclei in the paraventricular nuclei (PVN) and the nucleus tractus solitarii (NTS), and showed a tendency to increase in the supraoptic nuclei (SON), but not in the striatum. On the other hand, DOPA with a peripheral AADC inhibitor elevated the level of c-Fos-positive nuclei in the four regions, suggesting that DOPA itself induces c-Fos expression in the SON, PVN and NTS. In rats treated with 6-hydroxydopamine (6-OHDA) to lesion the nigrostriatal dopamine (DA) pathway, DOPA significantly induced c-Fos expression in the four regions under the inhibition of peripheral AADC. However, under the inhibition of central AADC, DOPA did not significantly increase the number of c-Fos-positive nuclei in the four regions, suggesting that DOPA at least in part induces c-Fos expression through its conversion to DA. It was likely that the 6-OHDA lesion enhanced the response to DA, but attenuated that to DOPA itself. In conclusion, we proposed that the SON, PVN and NTS include target sites for DOPA itself.

Keywords: Dopamine; 3,4-Dihydroxyphenylalaine; Neurotransmitter; c-Fos; Autonomic functions; 6-OHDA lesioned rats; Parkinson's disease

1. Introduction

L-3,4-Dihydroxyphenylalanine (DOPA) is one of the most effective drugs for Parkinson's disease (PD). DOPA has been believed to only be a precursor to be converted to dopamine (DA) by aromatic L-amino acid decarboxylase (AADC). Since 1986, we have proposed that DOPA is a neurotransmitter and/or neuromodulator in the central nervous system (CNS). Under in vitro and in vivo experimental conditions, DOPA is released in a transmitter-like manner (Misu and Goshima, 1993) and most responses are antagonized by DOPA methyl ester (DOPA ME), a competitive antagonist for DOPA (Goshima et al., 1991). DOPA appears to be a neuromodulator in the striatum and the hypothalamus (Misu and Goshima, 1993; Goshima et al., 1986). DOPA is highly likely to be a neurotransmitter of the primary baroreceptor afferents in the nucleus tractus solitarii (NTS) (Yue et al., 1994). Although the molecular mechanisms of the DOPA actions are still unknown, it is known that neuronal nitric oxide synthase is involved in depressor responses to DOPA in the NTS (Yamanashi et al., 2002). As shown in Fig. 1, DOPAergic relay from the NTS to the caudal ventrolateral medulla (CVLM) also exists (Miyamae et al., 1999). DOPAergic relays project from the posterior hypothalamic nucleus (PHN) to the pressor sites of the rostral ventrolateral medulla (RVLM) (Nishihama et al., 1999). Concomitant with our functional approach, several groups have developed immunohistochemical methods to demonstrate the existence of neurons that may contain DOPA as an end product in some nuclei in the lower brain stem and the hypothalamic nuclei (Mons and Geffard, 1987; Kitahama et al., 1988; Okamura et al., 1988; Karasawa et al., 1992).

The whole picture of physiological functions of the DOPAergic system, however, remains obscure, because specific receptors and target areas for DOPA itself have not yet been determined. c-Fos is a product of an immediate early gene, and is suggested to act as a "third messenger" molecule in signal transducer systems. To explore the potential target areas for DOPA and to try to perform functional mapping of the DOPAergic system, we comparatively surveyed the number and extent of c-Fos-positive nuclei expressed upon the treatment with DOPA combined with central or peripheral AADC inhibitors. c-Fos would couple short-term intracellular stimuli to long-term responses by altering gene expression (Sagar et al., 1988; Sheng and Greenberg, 1990); it is a biochemical marker for postsynaptic neuronal activation (Sagar et al., 1988; Robertson et al., 1989a,b; Sheng and Greenberg, 1990; Krukoff et al., 1992a,b; Cole et al., 1993; Saka et al., 1999; Svenningsson et al., 2000). Thus, c-Fos is expressed in neurons in response to direct stimulation by growth factors and neurotransmitters.

In rat lesioned with unilateral injection of 6-hydroxydopamine (6-OHDA) into the substantia nigra, DA receptor agonists induce c-Fos expression in the striatum ipsilateral to a 6-OHDA lesion (Robertson et al., 1989a,b). 6-OHDA causes denervation and hypersensitization in the target area, strintum, of nigrostriatal dopaminergic pathways. However, it has not yet been defined sufficiently how the DOPAergic system is affected by 6-OHDA. Here, we found that there were some brain areas, in which c-Fos expressions were potentiated under inhibition of central AADC, suggesting that DOPA itself could

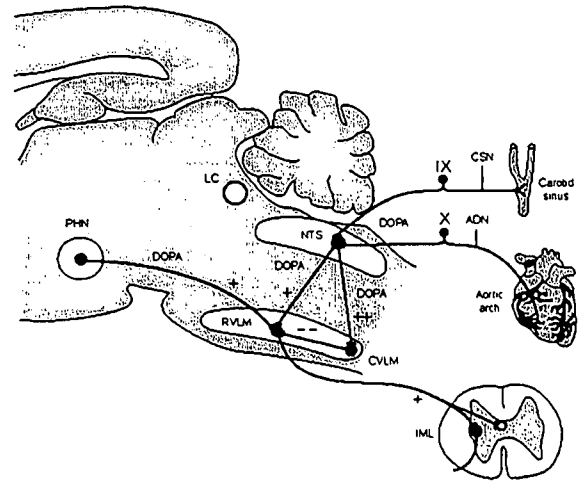

Fig. 1. Baroreflex pathways, central regulation of arterial blood pressure, and probable DOPA-mediated relays in the lower brainstem. Baroreflex is the principal neuronal mechanism by which the cardiovascular system is regulated under negative feedback control. Baroreceptors are located in the aortic arch and the carotid sinus. The primary baroreceptor afferents [the aortic depressor nerve (ADN) and the carotid sinus nerve (CSN)] terminate in depressor sites of the NTS (Aicher et al., 2000). The NTS neurons send excitatory projections to the CVLM and the RVLM. The neurotransmitter of these pathways is believed to be glutamate, from among many candidates. The tonicity of the excitatory NTS–RVLM pathway, shown as '+', appears to be less than the tonicity of the predominant excitatory NTS-CVLM pathway, shown as '++'. Vasomotor tone is reduced by the neuronal activity of the CVLM, the integration of which constitutes the central pathway for baroreflex. GABA-containing neurons in the CVLM project directly to the RVLM to inhibit excitatory activity. The tonicity of GABA-containing neurons is shown as '- -'. The RVLM receives excitatory inputs from various regions including the NTS and the PHN. The excitatory neurons of the RVLM project directly to the intermediolateral cell column (IML) of the thoraco-lumbar spinal cord, the main origin of the sympathetic outflow. The RVLM plays an important role in controlling resting and reflex integration of arterial blood pressure. DOPA is probably a neurotransmitter of the primary baroreceptor afferents. A DOPA-mediated baroreceptor-ADN-NTS-CVLM depressor relay and a DOPA-mediated PHN–RVLM pressor relay appear to exist. LC, locus coeruleus. Modified, with permission, from Misu et al. (1996).

Abbreviations: AADC, aromatic L-amino acid decarboxylase; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate; CNS, central nervous system; CVLM, caudal ventrolateral medullar; DA, dopamine; DMV, dorsal motor vagal nucleus; DOPA, L-3,4-dihydroxyphenylalanine; DOPA ME, DOPA methyl ester; GSA, goat serum albumin; MFB, medial forebrain bundle; NMDA, *N*-methyl-D-aspartate; NTS, nucleus tractus solitarii; 6-OHDA, 6-hydroxydopamine; PBS, phosphate-buffered saline; PD, Parkinson's disease; PHN, posterior hypothalamic nucleus; PVN, paraventricular nucleus; RVLM, rostral ventrolateral medullar; SON, supraoptic nucleus; TH, tyrosine hydroxylase.

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induce c-Fos expression in the CNS. Furthermore, the DOPAergic system was modified by the denervation with 6-OHDA in a different fashion from the DAergic system. Our finding suggests that several target sites for DOPA itself exist in the CNS, and have some relevance to untoward actions during the course of levodopa therapy in PD.

2. Materials and methods

2.1. Animals

All procedures were conducted in accordance with NIH guidelines concerning the Care and Use of Laboratory Animals and with the approval of the Animal Care Committee of the Yokohama City University. Adult male Sprague–Dawley rats (250–300 g, Charles River Laboratories) were individually housed, maintained on a 12-h light, 12-h dark cycle (lights on at 06:00 h) with ad libitum access to food and water for 1 week prior to each experiment. Animals were received daily handling procedure for the 5–6 days preceding the experiment. Throughout the experimental procedures, all efforts were made to minimize the number of animals used and their suffering.

2.2. Immunohistochemical detection of c-Fos expression

Immunostaining was performed on free-floating sections using a standard avidin–biotin peroxidase protocol (Vectastain Elite ABC kit, Vector Laboratories, Burlingame, CA, USA). Sections were first immersed in 5 ml of 0.1 M phosphate-buffered saline (PBS) (pH 7.4) containing anti c-Fos antibody (Calbiochem, San Diego, CA, USA), 1.5% goat serum albumin (GSA) and for 48 h at 4 °C. Sections were then rinsed with PBS, incubated with secondary biotinylated antibody, biotinylated anti-rabbit IgG (H + L) (dilution of 1:500) in 0.2% Triton X-100/1.5% GSA/PBS for 1 h at room temperature, rinsed with PBS, incubated for 2 h in ABC reagent, and rinsed again with PBS. Specific labeling was visualized using 3,3′-diaminobenzidine (DAB; Sigma, St. Louis, MO, USA). Tissue sections were immersed for 5 min in 0.05% DAB 50 mM Tris–HCl buffer containing 0.03% H_2O_2, 5 mM NaOH and 0.01% $NiCl_2$ for 5 min. After rinsing in PBS, sections were mounted on glass slides, air dried, rinsed in ethanol, cleaned in xylene, and cover-slipped with Permount (Fisher Scientific, Pittsburgh, PA, USA). c-Fos-positive neurons were counted manually at adequate magnifications. The number of c-Fos positive nuclei was counted in every third section through the evaluated areas. Using a light microscope, approximately six to ten sections in each area were counted. The counting was independently performed by two investigators blind to the experimental conditions and expectations. Nuclei were defined as c-Fos positive when a brown-black nucleus was clear at 10 × 10 magnification. In intact rats, the number of c-Fos positive nuclei on the right side area was counted. After the sum of c-Fos-positive nuclei per area was obtained for each rat, the average number of c-Fos positive nuclei per area was calculated by dividing the sum of c-Fos-positive nuclei by the number of sections counted.

2.3. 6-OHDA lesions, behavioral testing and drug treatments

Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and placed in a stereotaxic apparatus (Narishige, SR-6). A unilateral 6-OHDA lesion of the right medial forebrain bundle (MFB) was targeted according to the stereotaxic atlas (Paxinos and Watson, 1997) at the following coordinates (in mm) (A 4.0, L 1.3, V 2.0 from the center of interaural). Four microliters of 6-OHDA hydrobromide (2.93 mg/ml in 0.1% ascorbate–saline) infused at a rate of 1.0 μl/min over 4 min through an infusion pump in order to lesion the dopaminergic nigrostriatal pathway. All rats were pretreated with desipramine (25 mg/kg, i.p.) in order to prevent damage to the noradrenergic neurons. Two weeks after the treatment with 6-OHDA, apomorphine hydrochloride (1 mg/kg, s.c., Sigma, St. Louis, MO, USA) was administered to the rats for the assessment of successful lesion. Only rats showing average more than 6 and maximum 8 contralateral rotations/min over first 30 min following administration of apomorphine were used for subsequent studies. During 7 days after the evaluation, rats were housed individually in plastic cages. The 6-OHDA lesioned and intact rats were received intraperitoneal injection of 1 ml of saline, benserazide (50 mg/kg, Sigma), DOPA (50 mg/kg, Nakarai Tesque, Kyoto, Japan) plus benserazide, NSD-1015 (100 mg/kg, Aldrich Inc., WI, USA) or DOPA (50 mg/kg) plus NSD-1015. One hour after these treatments, animals were killed for immunohistochemical analysis, being anesthetized with sodium pentobarbital (70 mg/kg, i.p.) and quickly perfused transcardially with 100 ml of ice-cold PBS (pH 7.4), followed by 400 ml of 0.05 M phosphate buffer containing 4% paraformaldehyde. The brains were removed immediately after perfusion and post-fixed in perfusion buffer for 24 h, and in 20% sucrose/PBS for 24 h. Post-fixed brains were stored at −80 °C until use. According to the stereotaxic atlas (Paxinos and Watson, 1997), serial sections of the supraoptic nucleus (SON) (from bregma −0.92 mm to bregma −1.8 mm), paraventricular nucleus (PVN) (from bregma −1.80 mm to bregma −1.9 mm) and NTS/dorsal motor vagal nucleus (DMV) (from obex +0.62 mm to obex −0.32 mm) were cut transversely at 30 μm on a Cryostat and collected in PBS.

2.4. Data analysis

Data are given as mean ± S.E.M. (n = number of observations). The mean in the each group was compared by two-way ANOVA followed by Dunnett's test for comparison with the DOPA-treated rats in the presence or absence of NSD-1015 or benserazide. P values of less than 0.05 were considered statistically significant.

3. Results

3.1. c-Fos expression in the intact rats

To confirm the effect of DOPA in the CNS, we first estimated the number of c-Fos-positive nuclei in the brain regions in intact rats. DOPA with benserazide, a peripheral AADC inhibitor, induced c-Fos expression in the striatum, SON [$F(4,25) = 3.6060$], PVN [$F(4,11) = 8.3237$] and NTS/DMV [$F(4,16) = 6.2555$] (Fig. 2), results which were consistent result with previous findings (Robertson et al., 1989a; Saka et al., 1999). On the other hand, DOPA with NSD-1015, a central AADC inhibitor, scarcely induced any c-Fos expression in

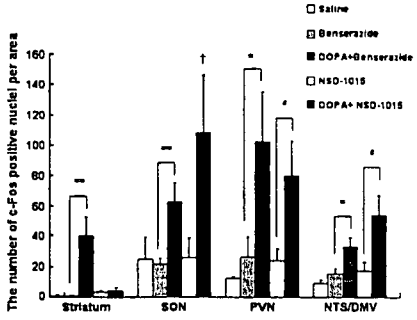

Fig. 2. The number of c-Fos-positive nuclei in the striatum SON, PVN and NTS/DMV of intact rats after administration of DOPA plus benserazide or NSD-1015. Data represent mean ± S.E.M. $n = 5–7$. $^*P < 0.05$, $^{**}P < 0.01$, compared with benserazide alone, $^{\#}P < 0.05$ compared with NSD-1015 alone, $^{\dagger}P = 0.06$ compared with NSD-1015 alone by two-way ANOVA followed by Dunnett's test.

the striatum (Fig. 2). DOPA with NSD-1015 showed a tendency to increase c-Fos expression in the SON, when compared to NSD-1015 alone (Figs. 2 and 3A) [$F(4,25) = 3.6060$]. Furthermore, under inhibition of central AADC, DOPA significantly enhanced c-Fos expression in the PVN (Figs. 2 and 3B) [$F(4,11) = 8.3237$]. The expression level was comparable to that obtained with the peripheral AADC inhibition (Fig. 2). In addition, even under the inhibition of central AADC by NSD-1015, DOPA significantly elevated the level of c-Fos-positive nuclei in the NTS/DMV, when compared to NSD-1015 alone (Figs. 2 and 3C) [$F(4,25) = 7.0083$].

3.2. c-Fos expression in the 6-OHDA-treated rats

Administration of DOPA plus benserazide, a peripheral AADC inhibitor, markedly increased the number of c-Fos-positive nuclei in the striatum ipsilateral to the 6-OHDA lesion of the nigrostriatal pathway (Fig. 4A) [$F(4,20) = 29.219$]. On the other hand, this treatment induced a small, but significant c-Fos expression in the striatum contralateral to the 6-OHDA lesion (Fig. 4A) [$F(4,20) = 17.861$]. The number of c-Fos-positive nuclei observed in the lesioned-side of the striatum of rats treated with NSD-1015 was approximately 10% of that with benserazide in the lesioned striatum. Few c-Fos-positive nuclei were detected in the bilateral side of the striatum of the rats treated with saline, benserazide and NSD-1015 alone (Fig. 4B) [$F(4,20) = 29.219$].

DOPA, when applied with benserazide, induced c-Fos expression in the SON ipsilateral to the 6-OHDA lesion (Fig. 5A) [$F(4,16) = 4.7926$]. NSD-1015 appeared to suppress DOPA-induced c-Fos expression in the SON ipsilateral [$F(4,16) = 4.7926$] and contralateral [$F(4,16) = 2.5937$] to the 6-OHDA lesion, when compared to the level with benserazide (Fig. 5B) [$F(4,16) = 4.7926$]. In the SON ipsilateral [$F(4,16) = 4.7926$] and contralateral [$F(4,16) = 2.5937$] to the 6-OHDA lesion, NSD-1015 alone increased the number of c-Fos-positive nuclei, which was comparable to that in the rats treated with DOPA and benserazide (Fig. 5B) [$F(4,16) = 4.7926$]. In the PVN ipsilateral [$F(4,11) = 7.3054$] and contralateral [$F(4,11) = 8.3237$] to the 6-OHDA lesion, DOPA enhanced c-Fos expression under the treatment with benserazide, when compared to saline or benserazide alone (Fig. 6A). On the other hand, DOPA, when applied with NSD-1015, did not affect the c-Fos expression in the PVN ipsilateral [$F(4,11) = 7.3054$] and contralateral [$F(4,11) = 8.3237$] to the 6-OHDA lesion in comparison with saline or NSD-1015 alone (Fig. 6A). DOPA increased c-Fos expression in the NTS/DMV ipsilateral [$F(4,16) = 4.3617$] and contralateral [$F(4,16) = 6.2555$] to the 6-OHDA lesion under the treatment with benserazide (Fig. 6B). Significant increase in DOPA-induced c-Fos

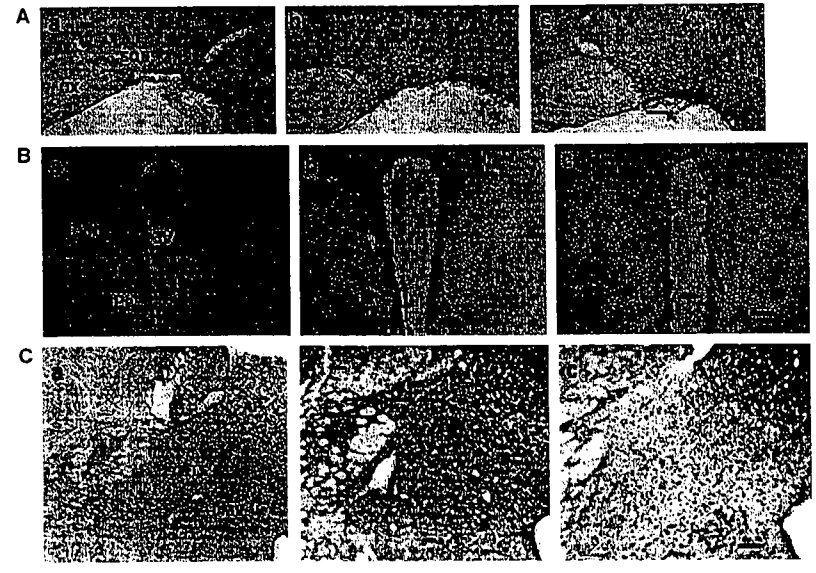

Fig. 3. Photomicrographs showing the distribution of c-Fos expression in the SON (A), PVN (B) and NTS/DMV (C) of intact rats after administration of saline (a), DOPA plus benserazide (b) and DOPA plus NSD-1015 (c). OX, optic chiasm; 3V, 3rd ventricle; Pe, periventricular hypothalamic nucleus; AP, area postrema. Scale bar = 100 μm.

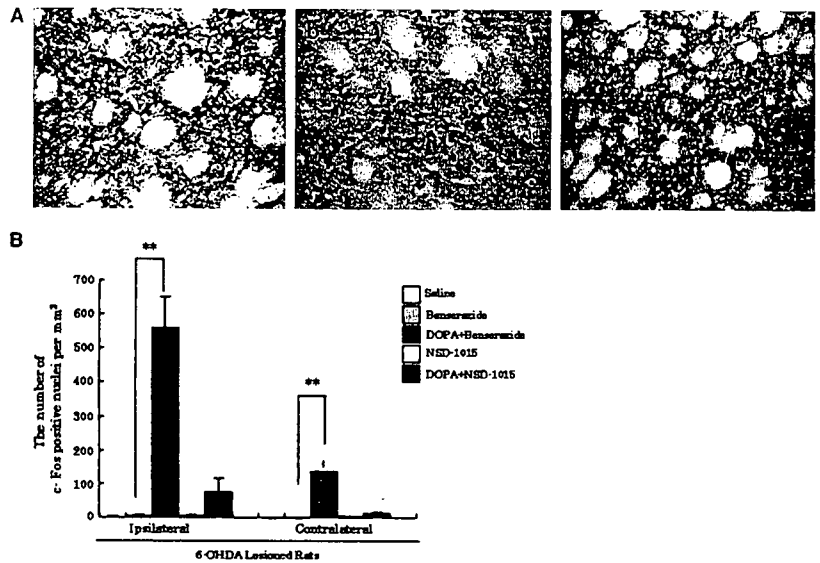

Fig. 4. (A) Photomicrographs showing the distribution of c-Fos-positive nuclei in the striatum ipsilateral to the 6-OHDA lesion of the MFB after administration of saline (a), DOPA plus benserazide (b) and DOPA plus NSD-1015(c). Scale bar = 100 μm. (B) The number of c-Fos-positive nuclei in the striatum ipsilateral and contralateral to the 6-OHDA lesion after combined application of DOPA with benserazide or NSD-1015. Data represent mean ± S.E.M. $n = 5–7$. $^{**}P < 0.01$, compared with benserazide alone by two-way ANOVA followed by Dunnett's test.

expression under the treatment with NSD-1015 was not detected in the NTS/DMV ipsilateral [$F(4,16) = 4.3617$] and contralateral [$F(4,16) = 6.2555$] to the 6-OHDA lesion. The patterns of c-Fos expression in the hypothalamic nuclei and the NTS/DMV were almost symmetrical, whereas c-Fos expressions in the lesioned-side of the striatum, piriform cortex and amygdala were asymmetrical.

3.3. Locomotor activities in the rats

We tried to establish 6-OHDA-lesioned Parkinson's model rats, since c-Fos expression induced by DOPA administration in the striatum has been well documented (Robertson et al., 1989a,b). Treatment with saline or NSD-1015 alone did not show any significant effects on locomotor activities of intact and lesioned rats (data not shown). Treatment with DOPA plus benserazide, a peripherally acting AADC inhibitor, induced the contralateral turning behavior in the 6-OHDA-lesioned rats. On the other hand, DOPA, when applied simultaneously with NSD-1015, induced no apparent behavioral effect on the lesioned rats. This result was consistent with previous reports (Melamed et al., 1984). Saline, benserazide, NSD-1015 and these agents combined with DOPA exhibited no behavioral actions in intact rats (data not shown).

4. Discussion

In this study, we first describe how the four categorized expression patterns of c-Fos in the CNS under inhibition of peripheral or central AADC fall into Table 1. In addition to the striatum, SON, PVN and NTS/DMV, c-Fos expression by DOPA was examined in the olfactory bulb, islands of Calleja, arcuate nucleus, cerebral cortex, piriform cortex, basilar pontine nuclei, hippocampus and substantia nigra (Table 1). The first category involves the hippocampus and the substantia nigra, in which no detectable c-Fos expression was seen under treatment with either benserazide or NSD-1015 (Group I).

The second involves the c-Fos expression under the inhibition of peripheral AADC. This expression was almost completely suppressed by central AADC inhibition by NSD-1015. Furthermore, DOPA markedly enhanced c-Fos expression by combined application with benserazide, for example, in rat lesioned nigrostriatal DA neurons with unilateral 6-OHDA (Group II). In the lesioned rat, DOPA elicited a circling behavior, and this was almost completely prevented by combined application with NSD-1015. DOPA, when applied with benserazide, expressed c-Fos markedly in the striatum ipsilateral to a 6-OHDA lesion. The c-Fos expression induced by DOPA in the lesioned striatum was negligible under the

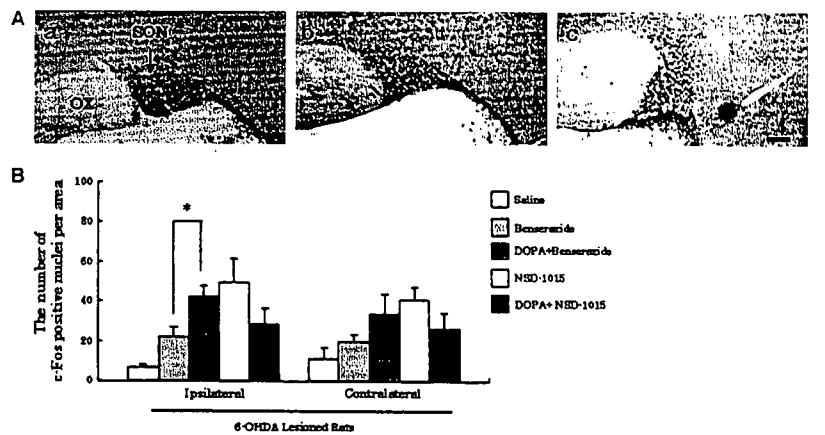

Fig. 5. (A) Photomicrographs showing the distribution of c-Fos-positive nuclei in the SON ipsilateral and contralateral to the 6-OHDA lesion of the MFB after administration of saline (a), benserazide plus DOPA (b), and DOPA plus NSD-1015 (c). Scale bar = 100 μm. (B) The number of c-Fos-positive nuclei in the SON ipsilateral to the 6-OHDA lesion after administration of DOPA plus benserazide or NSD-1015. Data represent mean ± S.E.M. $n = 5–7$. $^{*}P < 0.05$, compared with benserazide alone by two-way ANOVA followed by Dunnett's test.

treatment with NSD-1015. This result indicates that NSD-1015 employed in this study effectively inhibited the conversion of DOPA to DA in the CNS. This is also consistent with previous findings indicating that DOPA activates c-Fos in the striatum ipsilateral to a 6-OHDA lesion in the substantia nigra (Robertson et al., 1989a,b). The expression was observed only in the striatum ipsilateral to the 6-OHDA lesion. This suggests that the striatal c-Fos expression requires denervation and hypersensitization in the target area of nigro-striatal dopaminergic pathways. This idea is consistent with the previous finding that DAergic receptors are highly expressed in these areas (Neve and Neve, 1997). These findings together argue for the idea that the c-Fos expression induced by DOPA in the striatum ipsilateral to the 6-OHDA lesion was due to DA converted from DOPA. These results suggest that DOPA, at least in part, induces c-Fos expression through its conversion to DA in the striatum of the lesioned rats. Although DOPA did not have a significant effect on c-Fos expression, we could not rule out the possibility that DOPA is a neurotransmitter in the striatum based on the following reason. Norepinephrine and glutamate have been identified as important neurotransmitters governing neuroendocrine mechanisms represented in the paraventricular nucleus of the hypothalamus. In the periventricular part of the region, norepinephrine provokes a robust induction of c-Fos, but glutamate does not significantly induce c-Fos (Cole and Sawchenko, 2002). Therefore, the lack of detection of c-Fos-inducing ability does not always indicate that the stimulant is not a transmitter.

The third category also involves the c-Fos expression under the inhibition of central AADC (Group III). The c-Fos expression under treatment with benserazide, but not NSD-1015, was observed in the olfactory bulb, islands of Calleja, arcuate nuclei, cerebral cortex, piriform cortex and basilar pontine nucleus in both the intact and the 6-OHDA-lesioned rats. In these brain areas as well as the striatum, DOPA appeared to induce c-Fos expression via DA. The 6-OHDA-elevated levels of c-Fos expression in these regions were lower than that in the striatum, however.

The fourth category involves the c-Fos expression under the inhibition of central AADC (Group IV). DOPA with benserazide induced c-Fos expression in the SON, PVN and NTS/DMV. In these brain areas, transmitter-like release, uptake and actions of DOPA itself, and neurons containing DOPA as an end product have been shown (Mons and Geffard, 1987; Kitahama et al., 1988; Kubo et al., 1992; Yue et al., 1994; Sugaya et al., 2001; Misu et al., 2003). In these regions, c-Fos expression levels under benserazide treatment in the intact rats appeared to be higher than those in the 6-OHDA-lesioned rats. On the contrary, in the striatum, the c-Fos expression level under the inhibition of peripheral AADC in the 6-OHDA-lesioned rats was much higher than that in the intact rats. It should be noted that DOPA with NSD-1015 did not increase significantly in the SON, PVN and NTS/DMV, indicating that central AADC inhibition augments the effect of DOPA to induce c-Fos expression in the intact rats, but not it in the 6-OHDA-lesioned ones. This suggests that DOPA itself, but not DA, can induce c-Fos expression in these brain areas. The c-Fos expression in the lower brain stem nuclei is consistent with our previous findings that microinjection of DOPA, but not DA, into NTS/DMV elicits depressor or pressor response in anesthetized rat under inhibition of central AADC (Kubo et al., 1992). Electrical stimulation of aortic nerves or

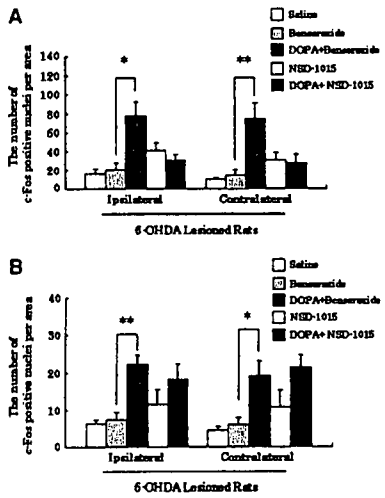

Fig. 6. (A) The number of c-Fos-positive nuclei in the PVN ipsilateral and contralateral to the 6-OHDA lesion after administration of DOPA plus benserazide or NSD-1015. (B) The number of c-Fos-positive nuclei in the NTS/DMV ipsilateral and contralateral to the 6-OHDA lesion after administration of DOPA plus benserazide or NSD-1015. Data represent mean ± S.E.M. $n = 5$–7. $^{*}P < 0.05$, $^{**}P < 0.01$, compared with benserazide alone by two-way ANOVA followed by Dunnett's test.

Table 1
Distribution of DOPA-induced c-Fos expression

Brain region	c-Fos expression levels in the intact rat		c-Fos expression levels in the 6-OHDA lesioned rat	
	DOPA plus NSD-1015	DOPA plus benserazide	DOPA plus NSD-1015	DOPA plus benserazide
Group I				
Hippocampus	→	→	→	→
Substantia nigra	→	→	→	→
Group II				
Striatum	→	↑	→	↑↑
Group III				
Olfactory bulb	→	↑	→	↑
Islands of Calleja	→	↑	→	↑
Arcuate nucleus	→	↑	→	↑
Cerebral cortex	→	↑	→	↑
Piriform cortex	→	↑	→	↑
Basilar pontine nuclei	→	↑	→	↑
Group IV				
SON	↑	↑	→	↑
PVN	↑	↑	→	↑
NTS/DMV	↑	↑	→	↑

pressor response induced by peripheral administration of phenylephrine induces release of DOPA in dialysates perfused through the NTS area. Furthermore, bilateral microinjection of DOPA ME, a competitive DOPA antagonist (Goshima et al., 1991) induces pressor response (Yue et al., 1994). Thus, DOPA is stored and released as an end product in neurons in the SON, PVN and NTS/DMV. We postulated that an unidentified receptor for DOPA existed in these areas. In addition to dopamine, it was likely that DOPA also induced c-Fos expression via its unidentified receptor.

Contrary to the DAergic system, the DOPAergic system appeared to be suppressed by the denervation with 6-OHDA. Can dopamine-denervation affect systems of other neurotransmitters? The gene expression of *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) glutamate receptors have been reported to be modulated in the striatum of the 6-OHDA-lesioned rat (Lai et al., 2003). After 2 weeks of lesion, GluR1 mRNA expression is significantly reduced, whereas NR1 mRNA expression is significantly enhanced in the lesioned side. This suggests that the expression of target sites for DOPA also might be downregulated by the DA denervation with 6-OHDA. In spite of the mechanism being unknown, these c-Fos expressions in the cardiovascular centers are consistent with symptoms of abnormal autonomic-nervous-system function including orthostatic hypotension observed in the PD on levodopa therapy (Goldstein, 2003).

In conclusion, we demonstrated that DOPA could induce c-Fos expression in several brain areas under the inhibition of central AADC. These are the potential target regions for DOPA itself in the CNS. Some of the c-Fos expressions may have relevance to the untoward actions of levodopa observed in the patients with PD.

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Figure 1 (a–d): MR axial images of the brain at the onset of neurological symptoms. (a) FSE T2-weighted image showing extensive signal abnormalities in the midbrain with no evident mass effect. (b, c) FLAIR images show hyperintense signal in the midbrain and right hippocampus, and bilateral involvement of caudate nucleus head and internal capsule with mild mass effect on frontal horns. (d) Post-contrast T1-weighted image displaying multiple enhancing areas of blood–brain barrier breakdown within the lesions. (e–h): MR axial images of the brain obtained 10 months after the onset. (e) T2-weighted image shows only residual gliosis associated with mild atrophy through the midbrain. (f) Axial FLAIR image displays resolution of signal abnormalities in the right hippocampus. (g) Axial T2 image shows evident reduction of the extensive signal abnormalities in the caudate head and internal capsules; no mass effect is seen. (h) Post-contrast T1-weighted image displays some residual punctuate and linear areas of contrast enhancement.

Infections were excluded serologically. There were decreased serum folates, positive anti-nucleus, anti-endomysium and anti-transglutaminase antibodies, while no anti-gliadin IgA were detected. Duodenal biopsy documented absence of villi, crypt hypertrophy and lymphocytic infiltration. Brain MRI showed a multifocal leukoencephalopathy with gadolinium-enhancing lesions, gray matter involvement and a confluent pattern through the midbrain (Fig. 1a–d). The patient was placed on a strict gluten-free diet and high-dose i.v. methylprednisolone was administered twice without significant changes of neurological status. Two weeks later, the patient received i.v. infusion of immunoglobulin with clinical benefit. Seventy-five days after the onset, the patient was dismissed with low-dose oral prednisone. After 24 months, the patient is asymptomatic and neurological examination is normal except for residual right hemianopsia. Brain MRI shows midbrain gliosis and few residual enhancing foci (Fig. 1e–h). Duodenal biopsy reveals resolution of villous atrophy, anti-endomysium and anti-transglutaminase antibodies are negative.

Gluten sensitivity is considered a state of heightened immunologic responsiveness in genetically susceptible people [3] and can be primarily, at times exclusively, a neurological disease [4]. Numerous neurological syndromes have been associated with CD and prevalence of circulating anti-gliadin antibodies and histological evidence of CD in duodenal biopsies is significantly higher in patients with neurological dysfunction of unknown aetiology as compared with controls [5,6]. Nutritional, toxic, metabolic, and immunologic factors have been hypothesized as cause of neurological complication in CD. Although we cannot completely rule out the concomitant occurrence by chance of ADEM and CD in the same patient, we attribute ADEM to the patient's CD. In fact, there was no other apparent cause of leukoencephalopathy, CD was histologically active and gastrointestinal manifestations were reported only 3 months before onset of neurological symptoms. Autoreactive T cells in ADEM, alone or synergycally with antibodies, may attack CNS by recognizing sequences shared with myelin antigens. In CD, other stimuli, alike viral or bacterial superantigens, can activate autoreactive T cells. Activated HLA-restricted gliadin-specific T cells found systemically [7] can cause CNS inflammation. Gluten sensitivity may represent, similarly to infections and vaccinations, a putative novel factor preceding and triggering ADEM. This expands the spectrum of neurological syndromes associated with CD and reinforces the indication to test for serological markers of CD in patients with neurological dysfunctions of unknown cause.

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Rhinolalia after diarrhea: a sole motor symptom occurring in post-infectious neuropathy associated with anti-ganglioside antibodies

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Sir,

Nasal voice is a common complaint occurring in non-neurological diseases, such as rhinitis, nasal polyp, and tonsillar hypertrophy. When nasal voice is caused by palatal palsy, we should consider neurologic causes of rhinolalia, such as peripheral neuropathy, polymyositis, myasthenia gravis, and brainstem stroke. We now report an acute isolated palatal palsy in a patient with post-infectious neuropathy after *Campylobacter jejuni* enteritis, associated with anti-ganglioside antibodies.

A 46-year-old man complained of nasal voice (day 1), 2 weeks after the onset of febrile diarrhea. On admission (day 5), he had a markedly nasal voice without hoarseness. Soft palate movement was bilaterally decreased. Palatal reflex was absent, whereas pharyngeal reflex was normal. He could swallow water easily, although he had a slight amount of liquid reflux to his nose on swallowing. He could normally swallow solid foods without reflux. Deep tendon reflexes were decreased in the upper limbs. Mild paresthesia was found in the palms and soles. Truncal and limb ataxia, ophthalmoplegia, and ptosis were not seen. The neck, face, tongue, and four extremities showed no motor weakness.

Brain magnetic resonance imaging was normal. His rhinolalia was not improved by intravenous edrophonium chloride. Nerve conduction studies and his cerebrospinal fluid on day 5 were normal. Stool culture was positive for *C. jejuni*, Penner O: 4 complex. The serum on admission showed elevated IgG antibody titres to GQ1b (1:256 000), GT1a (1:128 000), GD1a (1:64 000), GD1b (1:1000), and GM1b (1:4000); normal ranges were set at < 500. Anti-GQ1b IgG antibody was absorbed by GT1a at rate of 38%, while anti-GT1a IgG was absorbed by GQ1b at rate of 56%. This indicated cross-reactivity of these antibodies. The patient received intravenous immunoglobulin (0.4 g/kg/day) from day 6 to 10. On day 9, his rhinolalia totally disappeared. Three month after onset, these IgG antibody titres decreased; anti-GQ1b (1:32000), anti-GT1a (1:8000), anti-GD1a (1:8000), anti-GD1b (< 1:500), and anti-GM1b (< 1:500).

Among 220 consecutive patients with Guillain–Barré syndrome (GBS), 20 patients with elevated anti-GT1a IgG antibody often showed oropharyngeal weakness, neck weakness, ophthalmoplegia, and ataxia [1]. An elevated anti-GT1a IgG antibody cross-reacted with anti-GQ1b in 15 patients, and lacked cross reactivity with anti-GQ1b in five patients. Recent study reported 140 patients with anti-GT1a IgG antibodies in a variety of clinical feature; Fisher syndrome (FS) 46%, GBS 16%, Bickerstaff's brainstem encephalitis (BBE) 10%, and pharyngeal-cervical-brachial variant (PCB) of GBS 4% [2]. The presence of a common autoantibody (anti-GT1a IgG) and overlapping illnesses among FS, GBS, BBE, and PCB suggested the view of a condition continuous with each other. Bulbar palsy was relatively frequent and sometimes developed as an initial neurological symptom, in FS, BBE or PCB with an elevated anti-GT1a IgG antibody. Our patient was characterized by acute isolated palatal palsy lacking dysphagia, a preceding *C. jejuni* infection, and elevated anti-GT1a IgG antibody which cross-reacted with GQ1b. Antecedent enteritis in the medical history and high anti-ganglioside antibody titers helped us to make a diagnosis of acute post-infectious neuropathy with anti-GT1a IgG antibody.

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Threshold for perception of vibration is lower at glabrous skin than at subcutaneous bone sites

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It is advocated that perception of vibration, which indicates the integrity of large fibres of peripheral nerves and of dorsal column pathways [1], should be tested at subcutaneous bone sites where vibration stimuli are amplified [2]. The threshold of perception of vibration was, however, lower in ventral great toe, which is glabrous, than in the dorsum [3]. This study was carried out to compare the threshold of perception of vibration in subcutaneous bone sites with that of glabrous skin.

Thresholds for perception of vibration were determined at sites over thenar eminence, instep of the sole, ulnar styloid process, and medial maleolus of subjects without neurological diseases. The glabrous skin sites tested were chosen to avoid proximity to bone as much as possible. A mono-frequency Vibrometer (Biomedical Instrument Co., Newbury, OH, USA), which has a scale of 0–25 vibration units was used. The Vibrometer shaft was placed perpendicularly and firmly against the sites tested [4]. Thresholds for perception of vibration were determined when the amplitude of vibration was increasing and decreasing, and the scores for each site were averaged. Mean thresholds of all glabrous and all subcutaneous sites in the upper and lower limbs of each subject were determined, and differences were compared using *t*-test.

Sixty-four subjects (24 males and 40 females), mean age 25 years (SD 5, range 14–33), mean height 169 cm (SD 8, range 151–185), and mean weight 60 kg (SD 11, range 44–100) were tested. Thresholds of perception of vibration and coefficients of variation are shown in the Table 1. Mean thresholds of perception of vibration were: 2.1 (range 1.0–5.0, 95% CI 1.9–2.3) in glabrous skin and 3.5 (range 1.8–8.8, 95% CI 3.2–3.9) in subcutaneous bone sites of the upper limbs ($P < 0.0001$), but 2.5 (range 0.6–9.4, 95% CI 2.2–2.9) in glabrous skin and 5.5 (range 2.5–16.4, 95% CI 4.9–6.1) in subcutaneous bone sites of the lower limbs ($P < 0.0001$).

This study shows that the threshold of perception of vibration is lower in glabrous skin than in subcutaneous bone sites. Although transmission of vibration over wider tissue area by bone is expected

疫学的データ

英国と世界のCJDの実態

岸田日帯　黒岩義之

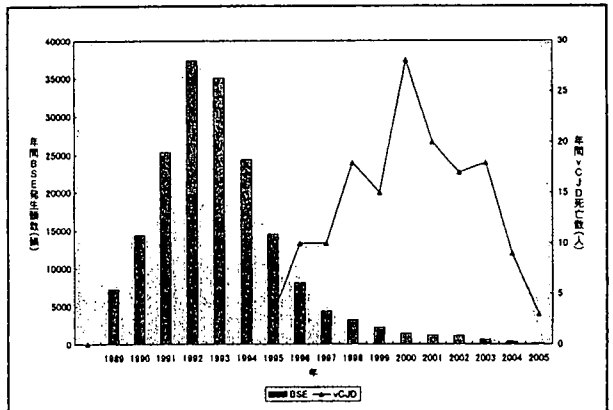
はじめに

2005年9月末日現在，全世界で変異型Creutzfeldt-Jakob病(variant CJD：vCJD)と確認された(definite)のは182症例，そのうち英国以外では23症例が報告され，生存しているほぼ確実例(probable)は英国に6例である．2005年に入ってから英国においてvCJDで死亡した症例は4例であり，ピークだった2000年に28例の報告があってから年々減少傾向にある(図)．しかし一方，英国以外で2005年に入って9月までに9症例のvCJD罹患者が出ている(フランス4人，日本，オランダ，アイルランド，ポルトガル，スペイン各1人)．今年は新たな発生国に日本，オランダ，ポルトガル，スペインの4ヵ国が加わった．BSEの流行が英国に遅れてその他の国々でおこったように，英国以外にもvCJDキャリアーは多数存在し，発症に至る感染者が増える時期に近づいているのだろうか．不気味な予感を抱かせる傾向である．

本稿では，英国を中心にvCJDを含む最近の世界のCJDの疫学的知見を簡単に紹介したい．

英国のCJD

英国では1986年牛海綿状脳症(BSE)が確認された後，「ナショナルCJDサーベイランスユニット(CJDSU)」が1990年に設立された．その目的は，英国における全CJD症例を網羅し，疫学的データを収集して，それぞれの臨床検査，遺伝子分析，分子生物学的データをまとめ，症例対照研究を行うことだった．その結果，科学コミュニティ，政策決定者，一般国民に対してCJDの疫学的変化，潜在的なリスクファクターに関する情報を提供し，この疾患への罹患の可能性に対する対策を講じ，罹患を減らすことが期待された．その期待通り，1996年にvCJDがCJDの新しいタイプとして確認され，BSEとvCJDの関連性が明らかにされて，現在のような「食の安全」が確保される体制が作られたのである．現在もサーベイランスが継続されCJDのデータが蓄積されている．



英国におけるBSEとvCJDの年次推移

英国では1990年から2005年9月末までにCJDSUによって1075例のCJD患者が確認されており，うち805例(75%)は孤発型sporadic，49例(4.6%)は医原性iatrogenic，70例(6.5%)は遺伝性genetic，151例(14%)は変異型variantである．英国ではBSEの減少に連動して2000年を境に国内でのvCJDの年間発生数も減少傾向であり，当初予想された数万人が発病するという最悪のシナリオは回避されたという見方が強い．肉骨粉の禁止によるBSE発生の予防，BSE牛の検査体制が確立し，一次予防の効果が現れていることはいうまでもない．しかし，医原性にヒトからヒトへ感染することが新たな問題として浮き彫りになってきた．

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表1　世界各国の孤発性CJD患者の死亡数と100万人あたりの死亡率：definite and probable cases

	Australia	Austria	Canada	France	Germany	Italy	Netherlands	Slovakia	Spain	Switzerland	UK	Belgium	Denmark	Finland	Greece	Iceland	Ireland	Israel	Norway	Portugal	Sweden	USA
1993	17	6	—	35	21+	27	12	2	21	10	37											
1994	11	9	2	46	70	33	18	2	16	10	53											
1995	19	9	3	59	80	28	8	2	19	9	35											
1996	25	9	13	68	76	51	14	2	27	10	40											
1997	20	6	16	80	107	47	19	3	31	10	60	10	11	9	6	1	1	5	7	5	11	54
1998	25	8	22	81	115	63	18	3	61	9	63	14	5	5	4	0	6	5	2	6	13	44
1999	25	6	26	92	103	77	18	1	50	8	62	13	5	7	7	0	1	1	2	5	11	65
2000	28	8	32	86	112	59	11	2	44	10	50	9	4	4	9	0	3	2	3	5	14	97
2001	20	10	27	110	124	81	14	2	62	18	58	15	4	9	8	0	5	4	5	16	11	138
2002	16	7	31	108	94	80	15	5	52	19	72	21	7	9	11	0	6	3	3	6	10	127
2003	21	15	27	109	100	75	13	2	56	17	77	19	7	5	6	0	3	4	5	10	11	142
2004	15	8	34	93	101	73	16	6	45	16	52	18	4	5	6	0	7	6	7	3	14	167
2005 (～9月)	4	10	2	22	28	35	6	2	4	4	21	1	0	3	2	0	3	1	0	—	5	59
総計	246	111	235	989	1131	729	182	34	488	150	680	120	47	56	59	1	35	31	34	56	100	893
死亡率	1.02	1.13	0.92	1.29	1.1	1.04	0.96	0.56	1.03	1.62	0.94	1.44	1.16	1.27	0.65	0.45	1.05	0.63	0.94	0.73	1.33	—

Canada：1998年4月までにはretrospectiveに検索した患者数
Germany：1993年6月以降

vCJDではリンパ系組織にも病原性プリオン蛋白(PrP^{Sc})が検出されるため，生前診断として扁桃生検の有効性が示されている[1]．摘出された虫垂・扁桃12674検体を免疫組織化学的に検査したところ，3例でPrP^{Sc}が陽性であり，そのうち2例はこれまでに報告されたvCJDとは異なるパターンを示した[2]．この結果からは，英国人100万人当たり237人がsub-clinicalなvCJDキャリアーであるという試算もなされる．英国人のプリオン蛋白遺伝子コドン129の遺伝子型はメチオニン/メチオニン(129 MM)42%，メチオニン/バリン(129 MV)47%，バリン/バリン(129 VV)11%であり[3]，プリオン病抵抗性といわれる129 MVや129 VVの占める割合が多い．これまでにvCJDを発症した患者は全例129 MMであり，129 MVや129 VVを有する人ではPrP^{Sc}をリンパ系組織に有していてもvCJDを早期に発症しない可能性もありうる．ガイドライン[4]にも示されているとおり，孤発型CJD(sCJD)では病原・感染性のあるPrP^{Sc}は中枢神経系に限局する．しかしvCJDではPrP^{Sc}がリンパ組織にも蓄積するために，輸血などの血液製剤やあらゆる外科手術器具，移植された臓器などを介してヒトからヒトへ伝播される可能性がある．

数々の動物実験の結果からプリオン病が輸血を介して感染する可能性は十分に証明されている[5,6]．CJDSUの通達によって英国では，「probable」以上のCJDと診断されると，患者の献血・輸血歴，手術歴に関する情報の届け出がなされ，追跡調査が行われる．すでに2004年2月，輸血によって感染した可能性のある患者が報告された．それは15名のvCJD患者の発病前に献血した血液を輸血された48名のうち，1名が赤血球輸血を受けてから6.5年後にvCVDを発症していた[7]．供血されたのは発病3年半前に献血されたものであり，輸血によって感染したと断定することはできないが，CJDの新しい感染ルートとして懸念さ

表 2：欧州での遺伝性 CJD の性差や遺伝子多型(Ladogana ら[9]より改変)

	n	性別 女性(人)	男性(人)	Codon 129 polymorphism MM(%)	発症年齢(歳)	MV(%)	発症年齢(歳)	VV(%)	発症年齢(歳)
E 200 K gCJD	175	107	68	78.3	60.4±10.8	19.9	60.7± 8.6	1.8	55.7± 9.0
V 210 I gCJD	69	39	30	73.1	59.3± 9.7	26.9	57.9± 9.8	—	—
other gCJD	51	28	23	36.8	70.9± 7.5	34.2	56.2±14.2	29	48.1±12.6
FFI	66	29	37	71.4	50.8±13.4	28.6	52.5±10.0	—	—
GSS	52	29	23	51.7	54.0±11.1	34.5	49.0±12.1	13.8	66.2±17.9
Insert gCJD	42	21	21	48.5	60.9±14.0	30.3	56.2±15.2	21.2	62.7±11.3
total gCJD	455	253	202	67.9	—	25.8	—	6.3	—
normal	—			39	—	50	—	11	—

れた．血液中の vCJD 感染力価の測定は不可能であり，輸血製剤についての安全性が確保できないため，英国では 1980 年 1 月以来輸血を受けた人については，献血を禁止する措置をとった．

さらに同年 7 月，輸血を介した可能性がある 2 例目の症例が報告された．この患者は，供血後に vCJD を発症したドナーからの輸血を 1999 年に受け，生前いかなる vCJD の徴候・症状も呈さずに別の原因により死亡したが，剖検で脾臓に PrP^{Sc} の存在が確認された[6]．さらに重要なことは，本症例が 129 MV の遺伝子型を有していたことである．このことは，vCJD 抵抗性の MV 多型でも PrP^{Sc} が体内に蓄積することを示す初めての報告である．ただし 129 MV や 129 VV でも vCJD を発症するのかはいまだに不明である．このような無症候の vCJD キャリアーを臨床的に診断することは不可能であり，キャリアー由来の血液の感染力価を測定することも不可能である．英国ではこのようなキャリアーが多数潜在している可能性もあり，保健省は輸血を受けたかどうか不明なドナーおよび輸血を受けた既往のある成分献血ドナー全員からの供血の禁止を勧告した．英国では凍結保存されている 10 万個の扁桃についての Western blot による解析が計画されているほか，今後も詳細な CJD モニターの継続が重要である．

欧州の CJD

1993 年に欧州では The European and Allied Countries Collaborative Study Group of CJD(EUROCJD) を設立し，オーストラリア，カナダを含む国々の CJD の発生をモニターしている．1998 年以降，この組織は全ての EU の国が参加して NEUROCJD というプロジェクトになっている．

これらの国々からの報告では，sCJD による死亡数はどの国でも 100 万人あたりにほぼ 1 人程度である[9](表 1)．遺伝性 CJD (genetic CJD；gCJD) や医原性 CJD(iCJD)，vCJD についてはいくつかの特徴がある(表 2，3)．

gCJD に関する欧州の集計では，最も多い遺伝子異常は E 200 K である．家族性致死性不眠症 familial fetal insomnia (FFI) は男性の頻度が高いが，その他は女性の比率が高かった．また gCJD 患者の遺伝子多型は，健常人に比して 129 MM の割合が多いが，発症年齢にはあまり相関がないことが示された[9](表 2)．

スロバキア，イスラエル，イタリアでは gCJD の占める割合が高い[10]．スロバキア北部には gCJD の 3 家系が同じ地域に見つかっており，E 200 K の変異を有する gCJD が多い[8]．イスラエルでも特にリビア系ユダヤ人に E 200 K で多いことが知られており，gCJD における輸血の危険性についてエビデンスはないが，遺伝子異常が判明した人から供血された血液については廃棄処分になっている．イタリアでは V 210 I が集積している[10]．

医原性 CJD の発生は表 3 の通り，乾燥硬膜例の他，成長ホルモンや角膜移植に由来する例も報告されている．「ライオデュラ」の製造元のあったドイツで乾燥硬膜例が報告されていないことは興味深い．

vCJD については 2005 年 11 月 1 日現在，英国以外ではフランスで 15 例，アイルランドで 3 例，アメリカ，カナダ，イタリア，日本，オランダ，ポルトガル，サウジアラビア，スペインでそれぞれ 1 例ずつ報告されている．2000 年秋にフランスで狂牛病危機が発生するまで，「未発生国」だったスペイン，ドイツ，イタリア，ギリシャ，オーストリア，フィンランド，スウェーデンは，輸入品以外の特定危険部位 (SRM) の人間食料・飼料からの排除を一切拒んできた．同年 10 月に EU レベルで SRM 除去をルールとした途端，スペイン，ドイツ，イタリアは BSE が確認され，サーベイランスが不十分だったことが露見した．欧州でも 2000 年以前の BSE 汚染のリスクは高く，vCJD の推移を見守る必要がある．

表 3：各国の遺伝性 CJD，医原性 CJD，変異型 CJD の発生数(Ladogana ら[9]より改変)

	Australia	Austria	Canada	France	Germany	Italy	Netherlands	Slovakia	Spain	Switzerland	UK
CJD(人)	282	130	261	1229	1251	927	205	95	551	154	958
100 万人当たりの死亡数(人)	1.15	1.3	1.04	1.58	1.2	1.26	1	1.4	1.09	1.65	1.28
遺伝性 CJD(人)	29	16	18	108	109	156	4	56	26	3	63
gCJD/CJD(%)	10.3	12.3	6.9	8.8	8.7	16.8	2.0	58.9	4.7	1.9	6.6
医原性 CJD(人)	4	1	4	103	12	3	5	0	5	1	41
(乾燥硬膜/成長ホルモン/角膜移植)	(0/4/0)	(0/1/0)	(0/4/0)	(92/11/0)	(0/10/2)	(0/3/0)	(1/4/0)	(0/0/0)	(0/5/0)	(0/1/0)	(38/3/0)
vCJD(人)	0	0	1	15	0	1	1	0	1	0	151
	Belgium	Denmark	Finland	Greece	Iceland	Ireland	Israel	Norway	Portugal	Sweden	USA
CJD(人)	125	49	59	59	1	39	106	36	58	100	1133
100 万人当たりの死亡数(人)	1.5	1.16	1.32	0.65	0.45	1.15	2.15	1	0.73	1.33	—
遺伝性 CJD(人)	4	0	3	0	0	1	75	2	2	0	163
gCJD/CJD(%)	3.2	0.0	5.1	0.0	0.0	2.6	70.8	5.6	3.4	0.0	14.4
医原性 CJD(人)	0	0	0	0	0	1	0	0	0	0	5
vCJD(人)	0	0	0	0	0	2	0	0	1	0	1

北米の CJD

2003 年 12 月に米国で初めての BSE 感染牛が見つかり，これを受けて日本は米国産牛の輸入停止を行った．

米国は BSE 発生国であるほか，シカのプリオン病が問題となっている．1967 年コロラド州でミュールジカに海綿状脳症が発生し，その後，オオジカやヘラジカなどにも感染することが明らかになり，慢性消耗病 chronic wasting disease (CWD) と呼ばれるようになった．シカのプリオン病では，感染の原因となった経路はよく分かっていない．脳乳剤を仔ジカに経口摂取させると咽頭のリンパ節，扁桃，小腸のパイエル板，回盲部リンパ節に PrP^{Sc} の蓄積が認められた[12]．この結果からは，病原体が唾液や糞便に排出されて，ほかのシカへの感染をおこしている可能性も示唆される．これまでに 11 の州とカナダで発生が確認され，野生ジカにも感染が拡がっていることから母子感染や水平感染の可能性も否定できず，正確な感染状況も把握できていない．それに加えて CWD 発生地域で 3 人のシカ肉を食すことの多い若年のハンターやその家族(28，28，30 歳)が CJD を発症した．各剖検所見は病理学的に sCJD と区別できなかったが，これらの CJD が CWD と関連がないと結論づけることはできない[13]．また CWD の流行によるウシへの影響も懸念される．北米大陸では BSE だけでなく，第二の BSE となりうる CWD のモニターも非常に重要である．米国産牛肉の輸入再開に際し，米国だけでなく全世界の人々の「食の安全」が守られるよう，誠意ある対応を切に希望したい．

その他の国の CJD

1920 年代に，ニューギニア高地で流行した kuru は，Gajdusek らによって，病原性を有する脳を経口摂取したことによる感染性プリオン病であることが判明した．食人習慣の廃止によって年々発症者は減少して，1982 年以降に発生したという報告はない[14]．

BSE によって汚染された肉骨粉が輸出された地域では，今後 vCJD が発生する可能性があり十分な疫学調査が必要

であろう．しかし，アジア，アフリカなどの発展途上国ではCJDの報告も少ないのが現状である[15,16]．

▣ むすび

英国における疫学的研究によってvCJDが発見され，BSE対策がなされたことは，治療方法のない本疾患の一次予防のために非常に重要だった．また今後も感染の拡大を防ぐために食肉検査や輸血といった国家的な取り組みがどうしても必要である．CJDは稀少な疾患であり，一つの国家のみならず世界的なサーベイランスが重要である．わが国でもCJDと診断された患者のうち，病理解剖でdefinite CJDと確認されたのは18%にすぎない．今後も継続的にCJD症例を検討しデータを蓄積していく必要がある．

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Ⅴ．研究報告会等プログラム

難病の Cybernics 研究に関する臨床研究の倫理審査の研究に関する打ち合わせ（Cybernics の倫理的検討など委員会）会議　要旨

場所：ホテル八重洲龍名館

日時：2006 年 6 月 24 日(土)　午後 13 時半から 17 時 30 分

委員および参加者（代理者・同伴者）

中島孝	（独立行政法人国立病院機構新潟病院）
山海嘉之	（筑波大学大学院システム情報工学研究科）
川井充	（独立行政法人国立病院機構東埼玉病院）
伊藤道哉	（東北大学大学院医学系研究科）
志澤聡一郎	（独立行政法人国立病院機構宮城病院）今井尚志代理出席
牛込三和子	（群馬パース大学看護学科）
大生定義	（立教大学社会学部社会学科）
水島洋	（国立がんセンター研究所疾病ゲノムセンター）
宮坂道夫	（新潟大学医歯学系保健学科）
武藤香織	（信州大学医学部保健学科社会学研究室）
吉野英	（山形徳洲会病院神経内科）
川口有美子	（ＮＰＯ法人ＡＬＳ／ＭＮＤサポートセンターさくら会）
杉田俊介	（ＮＰＯ法人ＡＬＳ／ＭＮＤサポートセンターさくら会）
松原洋子	（立命館大学先端総合学術研究科）
居村茂幸	（茨城県立医療大学　保健医療学部）
坂本光広	（Cyberdyne 株式会社）
鈴木千科子	（筑波大学大学院システム情報工学研究科　山海教授秘書）

議事など

1.　主任研究者の趣旨説明

この会合の目的

山海嘉之教授（筑波大学）のサイバニクス研究における、（難病）患者での応用研究の進捗を支援するために、この分野の倫理審査の枠組みと内容を検討し、中央の倫理委員会としての機能をめざすことや、病院や大学、研究所での倫理審査の参考になる内容を目指す。さらに、この分野の研究と関連研究が盛んに行われることを支援する端緒となる。

審議検討すべき内容の概要（アウトライン）

難病は incurable（根治不能）, intractable な特徴があるが、根治不能であっても QOL（生活の質）の向上を目指したケアが必要である。そのために、対症療法（palliation）、リハビリテーション技術、社会心理的アプローチにとどまらず、生体機能を工学的に補完する技術までが研究対象となる。具体的には疾

患によって生じる特定の臓器障害や機能障害に対してその機能を補完・増強する目的でつくられた工学的装置を個体の医学生物学的特性に合わせて装着または接合し、生体情報と工学的装置の制御を人間の意志のもとで統合するシステムについての総合的な学問（Cybernics）が行われている http://sanlab.kz.tsukuba.ac.jp/top.html 難病患者に対する Cybernics 研究は QOL を向上する目的で行われるが、研究開発と臨床応用の過程で機能と、安全性と倫理性の確保が必要である。装着・接合によって生命予後と生体機能が変容する場合、患者が得られる利益と不利益などを整理しておくのみならず、心理・社会的影響や派生する各種の問題ｗ整理しておく必要がある。

難病患者に対する Cybernics 研究は難病患者が抱える困難な状況を鑑み至急推進すべきと考えられるが、過去の経験に乏しいため、臨床研究・開発を円滑にし、推進して、現時点での問題点についての助言をおこなう目的で、倫理審査に関する研究を「特定疾患患者の生活の質（QOL）の向上に関する研究」班などの枠組みで行う。必要に応じて関連した病院、大学、研究所など関連部門が参照できるようにする。

すでに、厚生労働省によって定められた医学研究に関する指針
http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/
の中の臨床研究に関する倫理指針
http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/rinri/0504sisin.html
に従い難病患者のためになる円滑な臨床研究および装置の開発がおこなえるようにする。さらに、医療用具としての申請
http://www.info.pmda.go.jp/nmdevices/nmd-index.html
や開発
http://www.jaame.or.jp/
などに向けての臨床研究になる観点についても配慮する。倫理審査の過程で新たな問題点についても検討する。

進行役（中島）と副進行役（川井）

2. 自己紹介と関連研究の紹介

3. 人を対象とした臨床研究の内容など（山海教授）司会：川井

4. 議論の要旨

(1) この委員会の対象とする範囲と業務は『cybernics によって作られた装置が有効に、安全に患者が利用できるようにするための体制を構築したり必要な申請書類などの作成を支援したり、今後、何らかの問題が生じたとき直ちに対応できるようにするために、想定される問題点を事前に指摘したり検討する』ことを中心とし、それ以外の必要なことも検討する。

(2) 今後、必要な体制の構築について

(ア) 患者は Vulnerable であり、病態は不安定である。希望や願望は先鋭化され無理難題もいわれることがあるし、新しい装置をつかってみたいという気持ちがつよい方もいる。その願望を整理し適切な使用を検討するために専門職種として臨床チームの参加が必要である。さらに臨床評価システムの確立が必要である。倫理性をふくめて総合評価する IRB または類似機能が必要。

(イ) 臨床チームには、組み入れ評価、臨床評価、安全性評価のための体制作りが必要。

(ウ) 臨床評価には通常の QOL 評価のみならず、心理的な評価が必要だろう。

(エ) 安全性評価には通常の枠をこえる問題についても検討すべきだろう。

(3) 今まで補装具に対しては厳密な臨床評価や治験が行われた例はなく、必要性はないとされているようだ。今回、新規の装置の申請や正式の臨床利用として法的・医療的に

扱う際に、Cybernicsによって作成されたHALをbrace（補装具）と考えるなら単なるbraceとして扱えるかどうかも検討する。簡便な手続きで利用可能になる利点がある。厳密な臨床評価や問題点の抽出はbracedであってもその後も継続しておこなう。

(4) 実際には、患者に適応する際には、新規薬剤と同じような既存の治験システムは参考になる。さらに、人工臓器、ペースメーカーなどの臨床評価の方法も検討すべきである、新規の技術であるので、さらに今までの既存の枠組みでは対応できない必要な事項について検討する必要がある。

(5) 病院の倫理委員会や当局への各種申請過程においては患者の利用が後れることや、阻害されないようにも配慮する。

(6) 薬剤やbraceとの相違点としてあがったもの

(ア) 薬剤との相違点：装着により主体側も何らかの運動学習や心理的な変容がおきるだろう。それが現時点では不明なので同時に評価、検討していく。

(イ) 単なるBraceとの相違点：情報化、インテリジェント化されており情報テクノロジーの抱える問題点が包含されている。

(7) 関連行政機関への問い合わせは可能

(ア) 医薬品医療機器総合機構 http://www.pmda.go.jp/

(8) 当面の対象疾患など

(ア) 個別の患者としてALS（プロジェクトリーダーは中島？？）11月下旬

(イ) 疾患として筋ジストロフィー（20歳以上のBecker型）に対するADL改善支援プロジェクトをスタートさせる。8月中に筋ジストロフィーの関連医師のみがあつまり医療部分での体制を話し合う。（プロジェクトリーダーは川井＋中島）

① エントリー基準

② 臨床評価方法

③ アウトカム、エンドポイントなど

(ウ) 各種の患者からの依頼が来た際の受付手順、受付、書式などの統一や評価運営委員会などの体制作りが必要。

(9) 体制やワークフローの構築が必要（別紙素案）

(10) 国内外の動向

(ア) 国内：http://matsuda.c.u-tokyo.ac.jp/sci/project/cyborg/

サイボーグ技術が人類を変える。（東京大学立花隆ゼミのホームページ）

などに技術予測や紹介、倫理・社会的な問題提起が書かれている。

(イ) 国外：http://www.neuroethics.upenn.edu/overview.html

Neuroethics: Overview of the issues

Neuroethics encompasses the myriad ways in which developments in basic and clinical neuroscience intersect with social and ethical issues. The field is so young that any attempt to define its scope and limits now will undoubtedly be proved wrong in the future, as neuroscience develops and its implications continue to be revealed. At present, however, we can discern two general categories of neuroethical issue: those emerging from what we can do and those emerging from what we know.

(1) The "what we can do" problems
In the first category are the ethical problems raised by advances in functional neuroimaging, psychopharmacology, brain implants and brain-machine interfaces.

Brain imaging

- Pharmaceutical enhancement of cognition
- Pharmaceutical enhancement of mood and related functions
- Brain-machine interfaces and nonpharmacologic enhancement

(2) The "what we know" problems

In the second category are the ethical problems raised by our growing understanding of the neural bases of behavior, personality, consciousness, and states of spiritual transcendence.

- Responsibility
- Science and the soul
- The consciousness Continuum

Brain-Machine Interfaces and Non-pharmacological Enhancement

The man on the street is more likely to use pharmaceutical enhancement at some point in his life than any of the methods discussed in this section. Nevertheless, nonpharmaceutical methods for altering brain function have evolved rapidly over the past decade. It seems likely that they will become more widely used for the treatment of neurological and psychiatric disorders and, eventually, for the enhancement of normal healthy brains. Three lines of research are paving the way for nonpharmacologic brain enhancement. The first is The man on the street is more likely to use pharmaceutical enhancement at some point in his life than any of the methods discussed in this section. Nevertheless, nonpharmaceutical methods for altering brain function have evolved rapidly over the past decade. It seems likely that they will become more widely used for the treatment of neurological and psychiatric disorders and, eventually, for the enhancement of normal healthy brains. Three lines of research are paving the way for nonpharmacologic brain enhancement. The first is brain stimulation, either by implanted devices or transcranial magnetic stimulators.

Transcranial magnetic stimulation (TMS) involves stimulation of small areas of the brain by magnetic fields generated outside the head. In recent years it has moved from lab to clinic as a means of treating depression. It is also being explored with healthy subjects as a means to alter mood and or boost creativity, although its efficacy for these purposes has not been well established. More invasive methods of brain stimulation with implanted electrodes are currently last-resort treatments for Parkinson's disease, epilepsy, depression and obsessive-compulsive disorder. Because they are capable of improving mood and cognitive function in at least some cases, they may eventually gain wider use for those purposes.

The second line of research on nonpharmacologic brain enhancement involves surgery to remove or disconnect specific structures within the brain. The history of "frontal lobotomy" was rife with bad science (the functions of prefrontal cortex and its connections to other brain areas were poorly understood) and bad clinical ethics (inadequate or nonexistent informed consent). Modern psychosurgery operates in the shadow of this tragic history, and is currently practiced as a last resort. However, with more precisely targeted lesions and more thorough evaluations of outcome, the state of the art can be expected to improve and may become an option for more patients.

The third line of research is on brain-machine interfaces (BMIs). Here the goals are primarily to enable information from the world to be transduced into neural activity and to enable neural activity to be transduced into information that is externally useful for communication or robotic control. Some BMIs are already in clinical use. The most common BMI is the cochlear implant, which transduces sound waves into electrical patterns that can be sensed by auditory neurons in order to restore hearing in some deaf individuals. Systems that take information in the opposite direction, from brain to world, have been used clinically with paralyzed patients. These systems typically use features of the patient's EEG, recorded noninvasively from electrodes on the scalp, to convey simple commands.

The full potential of BMIs has only begun to be explored, primarily in research with nonhuman subjects. Memory augmentation, as well as perceptual and motor prostheses, is under study. In addition to the formidable technical challenges of interfacing silicon with sufficient numbers of neurons with sufficient precision and reliability, fundamental scientific problems remain. For example, to "converse" with the brain we must speak its "language." One of the goals of BMI research is to better understand the neural coding of information.

Research on electronic brain enhancement conjures up frightening scenarios involving mind control and new breeds of cyborg. The dominant role of the American military in funding the most cutting edge research in this area does little to allay these worries. In the short term, however, the ethical concerns here are similar to those raised by the pharmacological enhancements discussed elsewhere on this site: safety, social effects, and philosophical conundrums involving personhood. Of course, the irreversible nature of some of the non-pharmacological interventions exacerbates these problems.

In the long term, humanity may indeed find itself transformed by the incorporation of new technology into our nervous systems. An intriguing (and reassuring) perspective on this transformation is offered by Andy Clark, who suggests that we are already cyborgs of a kind, and no worse for it.

Martha J. Farah

(11) 今後の体制なども含め、具体的な案を数人で作成して9月以降再度同じメンバーで検討する。

議論に引用された参考文献など

1. サイボーグ・フェミニズム、ダナ ハラウェイ (著) (2001/08) 水声社
2. 猿と女とサイボーグ—自然の再発明、ダナ ハラウェイ (著) (2000/07) 青土社
3. The practice of medicine is an art, based on science は以下からの引用。「平静の心—オスラー博士講演集 (単行本)」医学書院、新訂増補版 (2003/09)、ウイリアム・オスラー著
4. Ars Longa Vita Brevis (ラテン語の格言)
5. Vita brevis, ars vero longa; sed occasio momentosa, empirica periclitatio periculosa, indicium difficile.ヒポクラテス「金言集」から。人生は短く、技芸は永い、に始まるこの句はしばしば、芸術作品は人生を超えて残るという意味で引用される。本来は、人生は短いのに医学技能の修得は果てしがないことを表現した (http://www.md.tsukuba.ac.jp/md-school/guide/hip.html)。
6. 弁才天：ヒンドゥー教の女神であるサラスヴァティー(Sarasvatī) が仏教あるいは神道に取り込まれた呼び名。音楽神とされ、福徳神、学芸神など幅広い性格をもつ。「弁財天」は当て字で、財宝神としては日本で新たに付け加えられた。
7. リハビリテーションは以下の様な時に使われる。 ラテン語が語源で「本来あるべき状態への回復。権利の回復、復権。教会からの破門の取り消し。」『ウィキペディア (Wikipedia)』

第3回　神経難病における音楽療法を考える会　プログラム

日　時：平成18年7月14日（金）　　場　所：神奈川県民ホール・小ホール
〈大会長〉東海大学医学部神経内科　吉井文均
〈主　催〉「神経難病における音楽療法を考える会」代表世話人　近藤清彦
〈共　催〉厚生労働省「特定疾患患者の生活の質（Quality of life,QOL）の向上に関する研究」班　班長　中島　孝
〈後　援〉日本神経治療学会

16:50～17:10	演奏（ヴィオラ・ダ・ガンバ二重奏）
開会および主催者あいさつ	
17:10～17:20	開会あいさつ　東海大学医学部神経内科　吉井　文均 公立八鹿病院神経内科　近藤　清彦
演題　座長　脳血管研究所附属美原記念病院院長　美原　盤 東海大学教養学部芸術学科教授　志水　哲雄	
17:20～17:40	1）パーキンソン病に対する音楽療法 順天堂大学医学部脳神経内科・リハビリテーション医学　林　明人
17:40～18:00	2）日本のブローカ失語に対するNeurologic Music Therapyの適用 -Melodic Intonation Therapyの有用性- 美原記念病院、コロラド州立大学　江尾　睦美
18:00～18:20	3）認知症の進行予防 -ヘルスリズムスを取り入れた脳活性化プログラムの効果- 東海大学医学部神経内科　吉井　文均
特別講演　座長　国立長寿医療センター研究所所長　田平　武	
18:25～19:45	「神経学的音楽療法の紹介～Introduction of Neurologic Music Therapy」 マイアミ大学，音楽療法プログラム・ディレクター　Shannon K. ドゥ・レトワール氏 （通訳：江尾睦美）
パネルディスカッション　司会　独立行政法人国立病院機構新潟病院副院長　中島　孝 東海大学医学部神経内科教授　吉井　文均	
19:50～20:30	テーマ「音楽療法の普及に向けて」 パネリスト：　医療法人矢津内科消化器科クリニック　院長　矢津　剛 昭和音楽大学　助教授　羽石　英里 患者代表　塩沢　功 コメンテーター　Shannon K. ドゥ・レトワール氏 （通訳：江尾睦美）
20:30～20:40	閉会のあいさつ

第2回 神経難病の非侵襲呼吸ケア・ワークショップ

難病診療に関係する医療者にとって、呼吸障害への対処法は診療上必須の知識であり、患者・家族からもより良い方法の応用と周知が待たれております。昨年から始まりました「神経難病の非侵襲呼吸ケア・ワークショップ」は、お陰様で多くの方々の御参加をいただき、ハンズオンを含めて知識を新たにしていただけたものと思います。そこで、本年も引き続き第2回のワークショップを開催いたします。

今回のワークショップは、NPPVや喀痰排出に関する実施上の問題点に焦点をあて、さらに呼吸器内科医からみた神経難病へのNPPVの応用についての講演を企画しました。また、昨年好評だった機器の使用法や排痰・呼吸理学療法についてのハンズオンもございます。

今年も多数の皆様の御参加をお待ちしております。

代表世話人 埼玉医科大学 神経内科 小森 哲夫

開催日 平成18年9月30日(土) 13:30～18:15 (受付13:00～)

開催場所 TIME24(有明) 2F セミナールーム1・2 (裏面地図参照)

〒135-8073 江東区青海2丁目45番 TEL.03-5531-0024

- 参加費：1,000円(ハンズオン参加者は2,000円)当日、会場受付にてお支払いください
- 定　員：200名(ハンズオン参加は120名まで：FAXにて申込順)
- 参加者：医師、看護師、保健師、理学療法士、臨床工学技士、その他

13:30～13:35 開会の挨拶 小森 哲夫 先生 (埼玉医科大学 神経内科 助教授)

特別講演

13:35～14:20 司会：中島 孝 先生 (国立病院機構 新潟病院 副院長)

『NPPV実施におけるリスクとチーム医療(呼吸器内科から見た導入と管理)』

演者：蝶名林 直彦 先生 (聖路加国際病院 呼吸器内科 医長)

教育講演

14:20～15:50 司会：小森 哲夫 先生 (埼玉医科大学 神経内科 助教授)

『リスクマネージメント(安全管理)』

演者：富加見 美智子 先生 (大久野病院 総師長)

『器械的咳介助(MAC)による排痰の導入手順』

演者：三浦 利彦 先生 (国立病院機構 八雲病院 理学療法室長)

『NPPV導入後の問題点(開業医の立場から)』

演者：難波 玲子 先生 (神経内科クリニックなんば 院長)

休憩 10分

ハンズオン

16:00～18:00
① NPPV機器と在宅酸素濃縮器の使用法
② NPPVに使用するマスクの選択と装着法
③ カフアシスト(カフマシーン)の使用法と適用
④ 呼吸理学療法の手技と実際

18:00～18:15 閉会の挨拶 小倉 朗子 先生 (東京都神経科学総合研究所 難病ケア看護 研究員)

主催：神経難病の非侵襲呼吸ケア研究会
共催：特定疾患患者の生活の質(QOL)の向上に関する研究班／ラジ・レスピロニクス株式会社／テルモ株式会社

難病の Cybernics 研究に関する臨床研究の倫理審査の研究に関する打ち合わせ
（Cybernics の倫理的検討など委員会）における

筋ジストロフィー領域打ち合わせ会開催

合同開催

厚生労働省難治性疾患克服研究事業「特定疾患患者の生活の質（QOL）の向上に関する研究」班（主任研究者　中島孝）

厚生労働省　精神・神経疾患研究委託費「筋ジストロフィー治療のエビデンス構築に関する研究」班（主任研究者　川井充）

開催日時：2006 年 9 月 30 日　19 時から 21 時

開催場所：ホテル八重洲龍名館「菊の間」　東京都中央区八重洲 1-3-22　TEL:03-3271-0971

議事次第

- 挨拶　（中島、川井）
  - 打ち合わせメンバーの自己紹介
- 山海教授の現在の Pilot 研究の紹介
  - 討論
- 筋ジストロフィー患者での今後の進め方
- その他（今後の予定）
- 終了の挨拶

特別セミナーご案内

神経疾患の緩和医療とQOL（第４回緩和ケアセミナー）

「神経疾患の緩和医療（Palliative Care in Neurology)」
講師：デイヴィッド オリバー（David Oliver）医師

今回，横浜で開催される国際 ALS/MND シンポジウムのために来日されるデイヴィッド オリバー（David Oliver）先生をお迎えし，神経難病関連の二つの研究班が，共催で，神経疾患の緩和医療を考えるセミナーを企画しました．オリバー先生は，「ALS の緩和ケア」(Palliative Care of Amyotrophic Lateral Sclerosis) はじめ多くの神経難病と緩和医療に関する著書のある臨床医です．横浜での国際シンポジウムに関連したセミナーとして，「神経疾患の緩和医療（Palliative Care in Neurology)」についてご講演していただきます．講演は英語ですが，スライドとハンドアウトは英語/日本語併記とする予定です．

神経変性疾患など難病の診療，保健，福祉，行政，研究に携わる多専門職種の方や患者を支援されている方のご参加を期待致します．

なお，参加費は無料ですが，準備の都合上，ご参加予定を下記の研究班事務局（岩崎あるいは大橋/神垣）まで e-mail 等でお知らせ下さい．

共催：厚生労働省難治性疾患克服研究事業
「特定疾患の生活の質（QOL） の向上に関する研究班」（主任研究者 中島 孝）
「神経変性疾患に関する調査研究班」（主任研究者 葛原 茂樹）

記

日時：平成１８年１２月３日（日曜日）14:00 ～15:30
場所：東京大学本郷キャンパス山上会館
http://www.u-tokyo.ac.jp/campusmap/cam01_00_02_j.html
http://www.u-tokyo.ac.jp/campusmap/index_j.html
本郷キャンパス施設案内図を参照下さい．
交通：地下鉄丸の内線，本郷三丁目駅下車，または地下鉄南北線東大前駅下車
対象者：難病医療の携わる保健・医療・福祉従事者，関係する行政担当者，教育者，研究者，難治性疾患克服研究事業の研究班員、学生，ボランティア、患者を支援している団体、個人など
連絡先：

- 独立行政法人 国立病院機構新潟病院 神経内科「特定疾患患者の生活の質（Quality of life,QOL）の向上に関する研究班」事務局 岩崎まで

TEL／FAX：0257-22-2130（直通），TEL：0257-22-2126（内線 1259）
e-mail: hiwasaki@niigata-nh.go.jp
または

- 三重大学医学部神経内科「神経変性疾患に関する調査研究班」事務局 大橋/神垣まで

Fax 059-231-5082, Phone 059-231-5107
e-mail: s-hensei@clin.medic.mie-u.ac.jp

特別セミナー：神経疾患の緩和医療とQOL（第４回緩和ケアセミナー）プログラムと講師ご紹介

「神経疾患の緩和医療（Palliative Care in Neurology）」
（12月3日（日曜日）14:00～15:30 東京大学本郷キャンパス，山上会館）

プログラム

開会挨拶（14:00）：葛原茂樹（三重大学）

14：05～15：30 座長：中島 孝（新潟病院）
「神経疾患の緩和医療（Palliative Care in Neurology）」
講師：デイヴィッド オリバー（ロチェスターホスピス，英国ケント州）

閉会挨拶（15:30）：成田有吾（三重大学）

講師紹介：

デイヴィッド オリバー先生（Dr. David Oliver）

現在，デイヴィッド オリバー先生は，英国，ケント州，ロチェスターのウィズダム ホスピスの医療責任者兼，緩和医療学の上級指導医で，また，カンタベリーにあるケント大学のケント医療・健康科学研究所の緩和医療学名誉上級講師である．

オリバー先生は，1975 年，大学で科学を修めた後，1978 年ロンドンの University College Hospital で MB BS を得て，総合診療医としての研修を積み，ロンドンの聖クリストファーホスピスに進み，1982～1984 まで同ホスピスにて前期および後期専門研修の後，1984 年に現職．

彼は，1999 年にケント医療・健康科学研究所の緩和医療学名誉上級講師となり，また，フランス，リール大学とケント大学間の共同研究である大学間連携研究で，緩和と支援ケアの修士学位および慢性疾患の緩和ケアの修士学位の研究指導責任者に任ぜられている（現在まで継続）．また，彼は，クロアチアのザグレブ大学医学部の客員教授でもある．

彼は，英国のみならず，クロアチア，ポーランド，米国，オーストラリア，南アフリカ，イタリアおよびニュージーランドなど，広く世界各地で運動ニューロン疾患と緩和医療に関する講演を行ってきた．この功績により，2003 年国際 ALS/MND 協会から人道的活動賞（the Humanitarian Award）を贈られている．

彼には，運動ニューロン疾患患者の緩和ケアと症状コントロールについての広範な著作がある．Oxford University Press から 2000 年に出版され第２版が本年刊行される「ALS の緩和ケア」（Palliative Care of Amyotrophic Lateral Sclerosis）では編集責任者であり，2004 年刊行の「原発および転移性脳腫瘍」（Primary and Metastatic Brain Tumours, Oxford University Press 刊）では顧問編集者，同じく 2004 年刊行の「神経学の緩和ケア」（Palliative Care in Neurology, Oxford University Press 刊）では共同編集者６名のうちの一人である．