of not 10 mg/kg but 20 mg/kg demonstrated a significant increase in Fos-like immunoreactivity in the unlesioned striatum (LaHoste et al., 1993; Pollack and Yates, 1999). Therefore, the dose (20 mg/kg) used in this study is required for SKF38393 to induce gene expression of c-*fos* as well as Homer 1a in normal rats. A larger dose (more than 1 mg/kg) of quinpirole might produce a considerable increase in Homer 1a mRNAs. However, it is unlikely because D_2 receptor antagonism by haloperidol is reported to induce Homer 1a expression in the striatum and nucleus accumbens (de Bartolomeis et al., 2002; Polese et al., 2002).

It has been proposed that Homer 1a modulates neuronal mechanism involving activation of group I mGluRs since it competes with the binding of Homer 1b and 1c to group I mGluRs and uncouples mGluRs from IP_3 receptors for calcium signaling (Brakeman et al., 1997; Kato et al., 1997). Moreover, Homer 1a expression induces constitutive activity in $mGluR_{1a}$ and $mGluR_5$ by direct binding to carboxy-terminal intracellular domains of these receptors (Ango et al., 2001). Homer 1a may therefore play a critical role in synaptic plasticity and other neuronal responses induced by glutamate receptor activation (Kato et al., 1998; Morioka et al., 2001; Bottai et al., 2002; Nielsen et al., 2002). In the striatum, group I mGluRs are primarily expressed postsynaptically in striatal projection and subpopulations of interneurons but also mediate inputs from corticostriatal glutamatergic afferents and nigrostriatal dopaminergic afferents (Testa et al., 1994). Medium spiny neurons in the striosome (patch), projecting directly to dopamine neurons of the substantia nigra pars compacta, contain D_1 receptors that are colocalized with muscarinic M_4 and adenosine A_1 receptors (Silkis, 2001). Taken together, the present results imply regulation of basal ganglia function by Homer 1a expression via D_1 receptor-mediated mechanism. Interestingly, Tappe and Kuner (2006) recently demonstrated that striosomal Homer 1a-expressing mice displayed deficits in motor performance and enhanced behavioral response to amphetamine, which effects might be attributed to alteration of dopaminergic activities.

At present, details of the underlying mechanism for D_1-like receptor-mediated induction of Homer 1a expression are not fully understood. It is most likely that activation of NMDA receptor by D_1 receptor stimulation contributes to Homer 1a expression because of a functional interaction between D_1 receptors and NMDA receptors for calcium signaling in the basal ganglia (for a review, see Cepeda and Levine, 1998). In line with this assumption, SKF38393 potentiated NMDA-induced currents in medium-sized neostriatal neurons possibly though activation of D_1 receptors (Cepeda and Levine, 1998). Furthermore, Ca^{2+} influx induced by stimulation of NMDA receptors led to an increase in Homer 1a mRNA levels (Sato et al., 2001). On the other hand, most of the G-protein coupled receptors including dopamine receptors and mGluRs may share direct or indirect bindings with each other (Agnati et al., 2003). D_1 receptors and mGluRs are demonstrated to form heteromeric receptor complex with adenosine A_1 and A_2 receptors, respectively, via intramembrane protein–protein binding sites (Gines et al., 2000; Ferré et al., 2002). Such a molecular interaction between D_1 receptors and mGluRs may also enhance Homer 1a induction to disrupt multimeric Homer 1b and 1c protein complexes with mGluRs.

Co-administration of SKF38393 and quinpirole increased Homer 1a expression in the striatum and nucleus accumbens, while this effect was not significantly greater than that of SKF38393 alone. In contrast, the same treatment enhanced c-*fos* expression to a greater extent than SKF38393 did alone in these regions. In line with the present results, a number of studies using unilaterally 6-hydroxydopamine-lesioned or reserpine-induced dopamine depleted animals have demonstrated a synergic interaction between D_1 and D_2 receptors on expression of the IEGs including c-*fos* (Keefe and Gerfen, 1995; LaHoste et al., 1993; Paul et al., 1992; Robertson et al., 1992). Gerfen et al. (1995) propose that, in addition to stimulation of D_1-containing neurons, D_2 receptor-mediated inhibition of D_2-containing neurons may contribute to potentiation of D_1 receptor-induced neural response, resulting in the synergic effect on gene expression in the striatum. It is not true of Homer 1a expression in the striatum and nucleus accumbens, as demonstrated by this study. Alternatively, D_1 and D_2 receptors may exert an opposite effect on Homer 1a expression because not only D_1-like receptor stimulation (Berke et al., 1998; Yano et al., 2006) but also D_2-like receptor blockade (de Bartolomeis et al., 2002; Polese et al., 2002) is reported to increase Homer 1a mRNA levels. However, the possibility that SKF38393 and quinpirole at the doses used in this study might be insufficient for synergism of D_1-like and D_2-like receptors is not fully excluded. A role of D_2 receptors in mechanism for action of Homer 1a has yet to be known. Recently, Olson et al. (2005) have demonstrated that the Shank scaffold protein interacting with Homers (1b–d and 2) via the CC-domain is key to modulation of striatal L-type Ca^{2+} channels by D_2 receptors. It is likely that signal transduction cascade of D_2 receptors as well as D_1 receptors can affect the Shank–Homer–IP_3 receptor complex linked with ion channel receptors. Further investigation still remains to elucidate a possible role of D_2 receptors and also its interaction with D_1 receptors for Homer-mediated neuronal response in the striatum.

It should also be noted that, despite a lack of a significant effect of single treatment with either dopamine agonist, combination of SKF38393 and quinpirole significantly increased Homer 1a mRNA levels in the hippocampus. This finding implies a synergic action of simultaneous stimulation of both D_1 and D_2 receptors on Homer 1a expression in this region. Both dopamine receptors and Group I mGluRs have been reported to play an important role in hippocampal synaptic plasticity (Huang and Kandel, 1995; Otmakhova and Lisman, 1996; Camodeca et al., 1999; Fitzjohn et al., 1999). Homer 1a is reported to potentiate synaptic AMPA receptor function in CA1 pyramidal cells, suggesting an involvement of Homer 1a in hippocampal synaptic plasticity (Hennou et al., 2003). It is therefore possible that Homer 1a expression modulates dopamine–glutamate interactions to regulate the hippocampal function such as memory cognition. Clearly, further studies employing immunohistochemical quantification need to elucidate Homer 1a expression within the hippocampus following dopamine agonist treatment because, in this study, the effect of co-treatment with SKF38393 and quinpirole on Homer 1a mRNA levels was modest (only +24% of saline control).

Dopamine agonist treatment in this study had no significant effect on Homer 1a mRNA levels in the medial

prefrontal cortex or substantia nigra. This is consistent with our previous study that dopaminergic activation by methamphetamine did not affect Homer 1a expression in either region (Hashimoto et al., 2004). In the prefrontal cortex, stimulation of serotonin receptor subtypes rather than dopamine receptor subtypes may induce Homer 1a expression because lysergic acid diethylamide (LSD), a hallucinogen displaying potent agonistic activity at serotonin-5-HT_{2A} and/or 5-HT_{2C} receptors, is reported to increase mRNAs of the IEG Ania3, a splicing isoform of Homer 1a (Nichols and Sanders-Bush, 2002). The lack of the ability of dopamine agonists to induce Homer 1a expression in the substantia nigra was strikingly contrast to enhanced gene expression of c-*fos* following the dopamine agonist treatment (Figs. 2E and 3E). It is likely that Homer 1a expression following D_1-like receptor activation occurs region-specifically in the striatum and nucleus accumbens that receive the dopaminergic projection from the substantia nigra pars compacta and ventral tegmental area, respectively, suggesting an implication for dendrite spine morphogenesis (Brakeman et al., 1997; Kato et al., 1997).

In conclusion, this study demonstrates that the dopamine D_1-like agonist SKF38393, but not the D_2-like agonist quinpirole, increased Homer 1a mRNA levels in the striatum and nucleus accumbens. Stimulation of D_1-like receptors, but not D_2-like receptors, may thus induce gene expression of Homer 1a in the basal ganglia. However, unlike c-*fos* expression, simultaneous stimulation of both D_1-like and D_2-like receptors may not exert a synergic action on Homer 1a expression in these regions. The present results provide further evidence for an important role of Homer 1a in the molecular mechanism of dopamine–glutamate interactions in regard to regulation of the basal ganglia function.

4. Experimental procedures

4.1. Animals

Male Wistar rats (Kyudo Animal Laboratory, Kumamoto, Japan) weighing 220–240 g were housed four per cage, maintained on a 12 h light/12 h dark cycle and given access to food and water ad libitum. All procedures were done in accordance with Principles of Laboratory Animal Care (NIH publication no. 86-23, revised 1985).

4.2. Drugs

The D_1-like receptor agonist SKF38393 (SIGMA, St. Louis, MO, USA) and the D_2-like receptor agonist quinpirole (SIGMA) were dissolved in a physiological saline immediately before treatment.

4.3. Drug treatment

Rats were divided into four groups ($n=10$ per group) and injected subcutaneously (s.c.) with saline (2 ml/kg), SKF38393 (20 mg/kg), quinpirole (1 mg/kg) or combination of SKF38393 and quinpirole, respectively. The doses of SKF38393 and quinpirole were chosen on the basis of previous studies showing them to produce a significant increase in Fos-like immunoreactivity in rat striatum, as discussed earlier (LaHoste et al., 1993; Pollack and Yates, 1999).

4.4. Tissue preparation

All rats were decapitated 1 h or 2 h after drug injection according to the previous study showing that methamphetamine-induced Homer 1a expression reached the maximal level 2 h after injection (Hashimoto et al., 2004). The brain was quickly removed and stored at −80 °C. Serial slices of 300 μm were made from the removed brain in a cryostat at −12 °C, and five brain regions were dissected freehand with a microknife, as described previously (Nakahara et al., 1990). Total RNA was prepared from the brain tissue by the method of Chomczynski and Sacchi (1987).

4.5. Reverse transcription-polymerase chain reaction (RT-PCR)

The levels of mRNAs in the discrete brain regions were quantified by reverse transcription-polymerase chain reaction (RT-PCR) with an endogenous internal standard, β-actin, as previously described (Nakahara et al., 1999). RT was performed on 1 μg RNA for 90 min at 42 °C in a 5 μl reaction mixture containing 25 mM Tris–HCl (pH 8.3), 50 mM KCl, 5 mM $MgCl_2$, 2 mM dithiothreitol, 1 mM each deoxynucleotide, 10 U AMV reverse transcriptase (Roche Molecular Biochemicals, Mannheim, Germany), 10 U ribonuclease inhibitor (Roche Molecular Biochemicals) and 0.8 μg oligo (dT) 15 primer (Roche Molecular Biochemicals). The RT was terminated by heating the sample at 95 °C for 2 min. The multiplexed PCR was carried out in a 20 μl reaction mixture containing 10 mM Tris–HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 2% dimethyl sulfoxide, 0.2 mM each deoxynucleotide, 0.1 μM each of 5′ and 3′ β-actin-specific primers, 1 μM each of 5′ and 3′ specific primers, 30 ng of reverse-transcribed total RNA and 0.5 U Taq DNA polymerase (Roche Molecular Biochemicals). The PCR primers used for amplification of β-actin and Homer mRNAs were as follows (GenBank accession number): β-actin (V01217), 5′-TCATGCCATCCTGCGTCTGGACCT-3′(forward); 5′-CCGGACTCATCGTACTCCTGCTTG-3′(reverse); target sequence=582 bp; Homer 1a (AJ276327), 5′-TGGACTGGGATTCTCCTCTG-3′ (forward); 5′-CCATCTCATTTAATCATGATTGC-3′ (reverse); target sequence=309 bp; Homer 1b (AF093267), 5′-CCAGTACCCCTTCACAGGAA-3′ (forward); 5′-TGCTTCACGTTGGCAGTG-3′ (reverse); target sequence=259 bp; Homer 1c (AF093268), 5′-CCAGTACCCCTTCACAGGAA-3′ (forward); 5′-TGCTTCACGTTGGCAGTG-3′ (reverse); target sequence=295 bp; c-*fos* (X06769), 5′-AGTGGTGAAGACCATGTCAGG-3′ (forward); 5′-CATTGGGGATCTTGCAGG-3′ (reverse); target sequence=296 bp. The PCR amplification was performed for 28 (c-*fos*) or 32 (Homer 1a) cycles, consisting of denaturation (95 °C, 45 s), annealing (60 °C, 45 s) and extension (72 °C, 75 s). After 6 (c-*fos*) or 10 (Homer 1a) cycles, 0.1 μM each of β-actin primer pair was added to the reaction mixture and PCR cycles were further continued.

The PCR products were analyzed on a 10% polyacrylamide gel electrophoresis. Gels were stained with ethidium bromide, visualized with UV trans-illumination, photographed and submitted to image analysis. Quantitative image analysis of

the PCR fragments was performed using the NIH image program. The levels of mRNAs were calculated as the ratios of optical density of each PCR product to that of the β-actin PCR product.

4.6. *Statistical analysis*

All data were statistically evaluated with StatView Ver. 4.50 (Abacus Concepts Inc., Berkeley, CA). The mRNA levels relative to β-actin mRNA levels in the various treatment groups were subjects to one-way analyses of variance (ANOVA) followed by post hoc analysis using Fisher PLSD. A probability (P) of less than 0.05 was considered significant in this study.

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Attitude of Patients With Mood Disorder Toward Clinical Trials in Japan

To the Editors:

Some attitude surveys regarding clinical trials have been conducted for the general population, outpatients, and participants in clinical trials. However, in most such surveys, the target subjects tended to be patients with some physical diseases. To our knowledge, despite a very high prevalence of depressive disorders in the general population, few attitude surveys have so far been reported for patients with such a condition. Although a placebo-controlled trial (PCT) has been generally considered desirable for the development of new antidepressants,[1] in Japan, PCTs are rarely conducted at the present time. It is also known that the subject group may not represent a standard patient population. Therefore, to promote and conduct better PCT, it is necessary to investigate the attitudes of patients with mood disorders toward clinical trials.

Patients between the age of 20 and 75 years were recruited from Kyushu University Hospital, Keio University Hospital, or University Hospital of Occupational and Environmental Health. All were outpatients diagnosed to have mood disorders—including depressive disorders, bipolar disorders, and other mood disorders—based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)*. After a complete description of the study, the attitudes of patients toward clinical trials were thus investigated. The patients were asked to complete a multiple choice–type questionnaire developed to survey the patients' attitudes concerning participation in PCT. This questionnaire was developed by the committee for clinical trials of the Japanese Society of Biological Psychiatry.

Seventy-seven patients (31 men and 46 women) with mood disorders were anonymously investigated. The mean ± SD age was 42.9 ± 14.3 years. Thirty-one (40.3%) of the patients knew that clinical trials had previously been conducted for the development of new drugs, 17 (22.1%) knew the word *placebo*, and 14 (18.2%) knew that PCT had previously been conducted for a strict assessment of the efficacy of various drugs. Most of the patients (16 of 17) with any knowledge of the word *placebo*, however, knew the word *placebo effect*. For 42 patients with some knowledge of clinical trials, the most frequent opinions about clinical trials were as follows: (1) clinical trials were necessary for the development of new drugs, (2) they were afraid of possible adverse effects, and (3) it was good that participants were able to contribute to the development of new drugs. After the explanation of PCT to all patients, the most frequent opinions about PCT were as follows: (1) clinical trials were necessary for the development of new drugs, (2) they were afraid of possible adverse effects, and (3) they felt unpleasant because it seemed like an experiment.

Fifteen (19.5%) of the patients stated that they would participate in PCT, whereas 27 (35.1%) stated that they might participate a little and 30 (39.0%) stated that they did not want to participate at all. There were no significant associations between the attitude for participation in PCT and knowledge about clinical trials (Fisher exact test, $\chi^2 = 3.44$, $df = 6$, $P = 0.75$) or *placebo* (Fisher exact test, $\chi^2 = 3.89$, $df = 6$, $P = 0.69$) or PCT (Fisher exact test, $\chi^2 = 0.71$, $df = 6$, $P = 0.99$).

The most frequent reasons why patients did not want to participate in PCT were as follows: (1) they were afraid that their disease status might worsen, (2) the uncertain effect of drug, (3) they were satisfied with existing drugs, and (4) they were afraid of taking a placebo. For 29 patients unwilling to participate in PCT because of fears that their disease status might worsen, 11 of the patients said they would participate in PCT if they were checked and nursed intensively. Second, for 20 patients unwilling to participate in PCT with uncertain effects of the drug as the reason, 10 of the patients said they would participate in PCT if the effect of a trial drug was clearly superior to existing drugs. Third, for 14 patients unwilling to participate in PCT with the reason that they were satisfied with existing drugs, 4 of the patients said they would participate in PCT if existing drugs were not effective enough against severe diseases. Last, for 13 patients unwilling to participate because of fears related to taking a placebo, 2 of the patients said they would participate in PCT if the probability of taking a placebo was lower.

In our survey, the most frequent opinion about clinical trials and PCT was that they were necessary for the development of new drugs, and the most frequent reason why patients did not want to participate in such studies was that they were afraid that their disease status might worsen. In other psychiatric diseases, answers about PCT were similar to the results of our study. For example, in a study of 100 patients with schizophrenia or schizophreniform disorder,[2] the most frequent motivation to participate in PCT was that PCT was needed to develop new drugs, and the most frequent reason for their unwillingness was that patients were afraid of not receiving medication, thus resulting in a worsening in their disease status or a slowing down in their recovery. In terms of patients with physical diseases or healthy general people, however, the attitudes to PCT were somewhat different in comparison with those with psychiatric diseases. For example, in

hypertensive patients,[3] the most frequent motivation for PCT was personal health benefits. In a survey by Cassileth et al,[4] most of the subjects (71%) responded that patients should serve as research subjects for clinical trials because of the potential benefit to others and the opportunity to increase their scientific knowledge. When they were supposed to actually participate in clinical trails, many subjects stated that they could receive highly advanced medical care as their reason for participation. However, differences in the contents of the questionnaire may also account for such reported attitudes, and it will be necessary to use the same questionnaire on PCT to accurately compare the subjects with psychiatric and physical diseases.

In general, clinical trials include problems related to selection bias for the subjects evaluated. In psychiatric disease, Hummer et al[2] reported that more than 50% of the patients were not willing to give their consent to a potential PCT, thus raising doubts about the generalization of data obtained by PCT. Amori and Lenox[5] reported that symptomatic volunteers for drug research tended to be sadder, more discouraged, and less interested in others than were patients drawn from normal clinical practice. In addition, depressive disorder patients have been reported to prefer psychotherapy to antidepressant treatment.[6] In a randomized trial on antimanic treatment, Licht et al[7] reported a significant difference in the symptoms between randomized patients and excluded patients.

Currently, PCTs are difficult to conduct in Japan, and the Japanese public requires more education about such clinical research before it will be feasible to conduct PCT. Our finding regarding the attitude of the patients with mood disorders toward clinical trials may help researchers to perform better PCTs in the future by including more generalized and less biased subjects.

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A neurotoxic dose of methamphetamine induces gene expression of Homer 1a, but not Homer 1b or 1c, in the striatum and nucleus accumbens

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Abstract

Homer proteins, which regulate the signaling pathway of metabotropic glutamate receptors, may contribute to the glutamatergic modulation of dopamine neurons in the basal ganglia. This study examined whether the induction of Homer 1 genes is or not associated with the methamphetamine-induced dopaminergic neurotoxicity in the discrete brain regions of rats. Basal levels of Homer 1a and 1c mRNAs in the forebrain regions were higher than those in the substantia nigra, whereas Homer 1b mRNA levels were higher in the substantia nigra than those in the forebrain regions examined. A neurotoxic dose (40 mg/kg, i.p.) of methamphetamine increased the mRNA and protein levels of Homer 1a in the striatum and nucleus accumbens, but not in the medial prefrontal cortex or the substantia nigra. Both Homer 1b and 1c mRNAs were not affected in any brain regions examined. These results suggest that the induction of Homer 1a gene may be involved at least in part in the methamphetamine-induced dopaminergic neurotoxicity, possibly through the glutamate-dopaminergic interaction.

Keywords: Homer; Methamphetamine; Neurotoxicity; Striatum; Nucleus accumbens

1. Introduction

The interactions between dopamine and glutamate within the various brain regions including the basal ganglia have significant implications for the pathophysiology of schizophrenia and Parkinson's disease (Carlsson and Carlsson, 1990). Many lines of evidence (Morari et al., 1998; Vandershuren and Kalivas, 2000) suggest the glutamatergic control of dopamine transmission and vice versa in the striatum, nucleus accumbens and prefrontal cortex.

Homer proteins have found to be involved in the molecular mechanism for the signaling pathway of metabotropic glutamate receptors (mGluRs) (Brakeman et al., 1997; Kato et al., 1997). The Homer family consists of three independent genes such as Homer 1, 2 and 3. Moreover, Homer 1 comprises three splicing variants; Homer 1a, 1b, and 1c (Xiao et al., 1998). Homer 1a is an immediate early gene (IEG) product that is rapidly responsive to neuronal activity (Brakeman et al., 1997; Kato et al., 1997; Berke et al., 1998), while other members of the Homer family are constitutively expressed. Seizure is reported to induce Homer 1a dramatically in the hippocampus (Brakeman et al., 1997; Xiao et al., 1998; Kato et al., 1998; Morioka et al., 2001; Bottai et al., 2002), striatum and cortex (Kato et al., 1998), and light stimuli also induced it in the suprachiasmatic nuclei (Brakeman et al., 1997; Park et al., 1997; Nielsen et al., 2002). Recently, dopaminergic modulation has been demonstrated to affect gene expression of Homer 1a. Cocaine, a dopamine transporter inhibitor (Brakeman et al., 1997; Swanson et al., 2001), SKF38393, a D_1 receptor agonist (Berke et al., 1998; Yamada et al., 2007), and haloperidol, a D_2 receptor antagonist (de Bartolomeis et al., 2002; Polese et al., 2002), induced the Homer 1a gene expression in the striatum. In

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contrast, SCH23390, a D_1 receptor antagonist, attenuated methylphenidate-induced expression of striatal Homer 1a (Yano et al., 2006). Moreover, Homer 1b- and 1c-knockout mice displayed enhanced methamphetamine-induced motor behavior (Szumlinski et al., 2005), while behavioral response to amphetamine increased in transgenic mice overexpressing Homer 1a in striatal medium spiny neurons localized predominantly in the striosome (patch) (Tappe and Kuner, 2006). These findings suggest that Homer 1a could play a key role on dopamine–glutamate interactions in the striatum.

Administration of high doses (more than 20 mg/kg) of methamphetamine is known to cause the neurotoxic effect on dopamine terminals in the striatum and nucleus accumbens of rodent brain (Fukumura et al., 1998), as indicated by degenerative changes in microscopic morphology, depletion of tissue dopamine contents, decreases in enzymatic activity of dopamine synthesis and number of dopamine transporters (Seiden and Ricaurte, 1987). Methamphetamine-induced increases in extracellular levels of dopamine as well as glutamate may contribute to oxidative stress and/or excitoxicity that damage dopamine neurons (Nash and Yamamoto, 1993; Xue et al., 1996). Because of a possible involvement of Homer 1a in the dopamine-glutamate interaction, the induction of this protein may be associated with methamphetamine-induced dopaminergic neurotoxicity.

To test this hypothesis, we examined the effect of a neurotoxic dose of methamphetamine on gene expression of Homer 1 in the discrete brain regions of rats.

2. Methods

2.1. Animals

Male Wistar rats (Kyudo Animal Laboratory, Kumamoto, Japan) weighing 220–240 g were housed four per cage, maintained on a 12 h light/12 h dark cycle and given access to food and water *ad libitum*. All procedures were done in accordance with Principles of Laboratory Animal Care (NIH publication no. 86-23, revised 1985).

2.2. Drug treatment

Methamphetamine (Dainippon Pharmaceutical Co., Osaka, Japan) was dissolved in 0.9% NaCl and injected intraperitoneally (i.p.) in a volume of 1 ml/kg body weight. For analysis of Homer mRNAs, rats were given methamphetamine (40 mg/kg, i.p.) 1, 2 and 4 h prior to sacrifice ($n = 9$ for each time point). Control group of rats received saline 1 h prior to sacrifice ($n = 9$). For Western blot assays of Homer 1a, the animals were injected with methamphetamine (40 mg/kg) ($n = 10$) or saline ($n = 10$), and then killed 4 h after the injections. The dose of methamphetamine (40 mg/kg) was chosen on the basis of the methamphetamine-induced neurotoxicity to produce long-lasting depletion of contents, synthesis rate and transporter numbers of dopamine (Fukumura et al., 1998; Seiden and Ricaurte, 1987). This dose of methamphetamine was also employed in the previous study (Nakahara et al., 2003; Thiriet et al., 2001) demonstrating the time-dependent profile of the IEG c-fos mRNA levels, together with that of tissue contents of dopamine, serotonin and their metabolites following methamphetamine administration.

2.3. Tissue preparation

The brain was quickly removed and stored at −80 °C. Serial slices of 300 μm were made from the removed brain in a cryostat at −12 °C, and four brain regions were dissected freehand with a microknife, as described previously (Nakahara et al., 1990). Total RNA was prepared from the brain tissue by the method of Chomczynski and Sacchi (1987).

2.4. Reverse transcription-polymerase chain reaction (RT-PCR)

The levels of mRNAs in the discrete brain regions were quantified by reverse transcription-polymerase chain reaction (RT-PCR) with an endogenous internal standard, β-actin, as previously described (Gotoh et al., 2002; Nakahara et al., 2005; Yamada et al., 2007). RT was performed on 1 μg total RNA for 90 min at 42 °C in a 5 μl reaction mixture containing 25 mM Tris-HCl (pH 8.3), 50 mM KCl, 5 mM $MgCl_2$, 2 mM dithiothreitol, 1 mM each deoxynucleotide, 10 U AMV reverse transcriptase (Roche Molecular Biochemicals, Mannheim, Germany), 10 U rebonuclease inhibitor (Roche Molecular Biochemicals) and 0.8 μg oligo $(dT)_{15}$ primer (Roche Molecular Biochemicals). The RT was terminated by heating the sample at 95 °C for 2 min. The multiplexed PCR was carried out in a 20 μl reaction mixture containing 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 2% dimethyl sulfoxide, 0.2 mM each deoxynucleotide, 0.1 μM each of 5′ and 3′ β-actin-specific primers, 1 μM each of 5′ and 3′ specific primers, 25 ng of reverse-transcribed total RNA, and 0.5 U Taq DNA polymerase (Roche Molecular Biochemicals). The PCR primers used for amplification of β-actin and Homer mRNAs were as follows (GenBank accession number): β-actin (V01217), 5′-TCATGCCATCCTGCGTCTGGACCT-3′ (forward); 5′-CCGGACTCATCGTACTCCTGCTTG-3′ (reverse); target sequence = 582 bp; Homer 1a (AJ276327), 5′-TGGACTGGGATTCTCCTCTG-3′ (forward); 5′-CCATCTCATTTAATCATGATTGC-3′ (reverse); target sequence = 309 bp; Homer 1b (AF093267), 5′-CCAGTACCCCTTCACAGGAA-3′ (forward); 5′-TGCTTCACGTTGGCAGTG-3′(reverse); target sequence = 259 bp; Homer 1c (AF093268), 5′-CCAGTACCCCTTCACAGGAA-3′ (forward); 5′-TGCTTCACGTTGGCAGTG-3′ (reverse); target sequence = 295 bp. The PCR amplification was performed for 28 cycles, consisting of denaturation (94 °C, 45 s), annealing (60 °C, 45 s), and extension (72 °C, 75 s). After six cycles, 0.1 μM each of β-actin primer pair was added to the reaction mixture and PCR cycles were further continued.

The PCR products were analyzed on a 10% polyacrylamide gel electrophoresis. Gels were stained with ethidium bromide, visualized with UV transillumination, photographed, and submitted to image analysis. Quantitative image analysis of the PCR fragments was performed using the NIH image program. The levels of mRNAs were calculated as the ratios of optical density of each PCR product to that of the β-actin PCR product.

2.5. Western blot of Homer 1a

The striatal tissues were lysed by sonication (10%, 15 s; Ultrasonic Cell Disruptor, Heat System-Ultorasonics, Farmingdale, NY) in 10 volumes of the lysis buffer (20 mM Tris–HCl, pH 7.4, 1 mM EDTA and 1% Triton X-100) and centrifuged at 13,000 × *g* for 30 min at 4 °C, and then the supernatant was collected. The protein concentration of supernatant was determined using the Bradford colorimetric assay (Wako, Pure Chemical Industries Ltd., Osaka, Japan) following manufacturer's instructions. The supernatants were mixed with an equal volume of 2× SDS gel-loading buffer (125 mM Tris–HCl, pH 6.8, 100 mM dithiothreitol, 4% SDS, 0.2% bromophenol blue and 20% glycerol) and then boiled for 5 min. Aliquots of protein (100 μg/lane) were separated by sodium dodecyl sulfate-polyacrylammide gel electrophoresis (SDS-PAGE) containing 12% polyacrylamide. Separated proteins were transferred to PVDF (polyvinylidenedifluoride) membranes (Roche, Mannheim, Germany) using an electrophoretic transfer kit (LKB, Uppsala, Sweden). Nonspecific sites on the PVDF membrane were blocked by incubating in 5% nonfat dried milk (Amersham, Buckinghamshire, UK) in TBST (20 mM Tris–HCl, pH 7.6, 137 mM NaCl, 0.1% Tween-20) for 1 h. The membranes were incubated with a goat anti-Homer 1a polyclonal antibody (1:1000; Santa Cruz Biotechnology, Santa Cruz, CA) for 1 h at room temperature. After washing in TBST, the membranes were incubated in the anti-goat secondary antibody conjugated to horseradish peroxidase (1:3000; R&D System, Minneapolis, MN) for 1 h at room temperature. Immunoblots were washed with TBST, incubated in ECL solution (Amersham) and apposed to film (Hyperfilm, Amersham). The intensity of the visualized immunoreactive protein was quantified using NIH Image software.

2.6. Statistical analysis

All data were statistically evaluated with StatView Ver. 4.50 (Abacus Concepts Inc., Berkeley, CA). The mRNA levels relative to β-actin mRNA levels in the various treatment groups were subject to one-way analyses of variance (ANOVA) followed by Scheffe's *F*-test. The optical density of immunoreactive bands was analyzed using Student's *t*-test. A probability (*P*) of less than 0.05 was considered significant in this study.

3. Results

Ethidium bromide staining of a polyacrylamide gel revealed a single band at the expected size of amplification product for each of the β-actin and the Homer cDNAs. Since no amplified products were observed when the reverse transcriptase step was omitted, the contamination by genomic DNA did not interfere with the signals of PCR products of Homer 1a, 1b and 1c cDNAs. The contamination by genomic DNA did not interfere with the signals of PCR products of β-actin, Homer 1b and Homer 1c, because these cDNAs were amplified using the pair of primers derived from different exons of the genes.

To determine the optimal amplifications, PCR was performed using different amount of reverse-transcribed total RNA and different numbers of cycles. The results indicated that amplification was exponential between 18 and 24 cycles for β-actin mRNA. Amplification was also exponential between 24 and 30 cycles for Homer 1a and 1c mRNAs. The PCR products were proportional to RNA input over a range of 5–50 ng total RNA for β-actin and Homer mRNAs. Twenty-five nanograms of reverse-transcribed RNA were amplified for 28 cycles for the quantitation of relative amount of the Homer mRNAs in the rat brain.

Acute administration of methamphetamine (40 mg/kg, i.p.) significantly increased Homer 1a mRNA levels in the striatum at 1 h (+66% of the pre-drug basal levels, $F_{3,30} = 6.48$, $P < 0.01$), 2 h (+155%, $F_{3,30} = 35.3$, $P < 0.001$) and 4 h (+84%, $F_{3,30} = 35.3$, $P < 0.001$) after methamphetamine (Fig. 1). Homer 1a mRNA levels were also increased significantly in the nucleus accumbens at 1 h (+60%, $F_{3,32} = 3.26$, $P < 0.05$) and 2 h (+94%, $F_{3,32} = 8.01$, $P < 0.01$) after methamphetamine. Methamphetamine did not affect Homer 1a mRNA levels in the medial prefrontal cortex and substantia nigra. The rank order of the density of Homer 1a mRNA was as follows: the striatum > medial prefrontal cortex > nucleus accumbens > substantia nigra (Fig. 1). The level of Homer 1a mRNA in the striatum was a fivefold higher than that in the substantia nigra.

Homer 1b mRNA levels could be detected in the substantia nigra, but not in other regions examined, under the standard experimental condition, while Homer 1c mRNA were detected with homogeneous distribution in all brain regions examined. Acute administration of methamphetamine (40 mg/kg, i.p.) did not affect gene expression of Homer 1b or 1c in any brain regions (Table 1).

As shown in Fig. 2, Homer 1a protein in the striatum migrated with a band of the molecular weight of 30 kDa estimated using prestained molecular weight marker. Quanti-

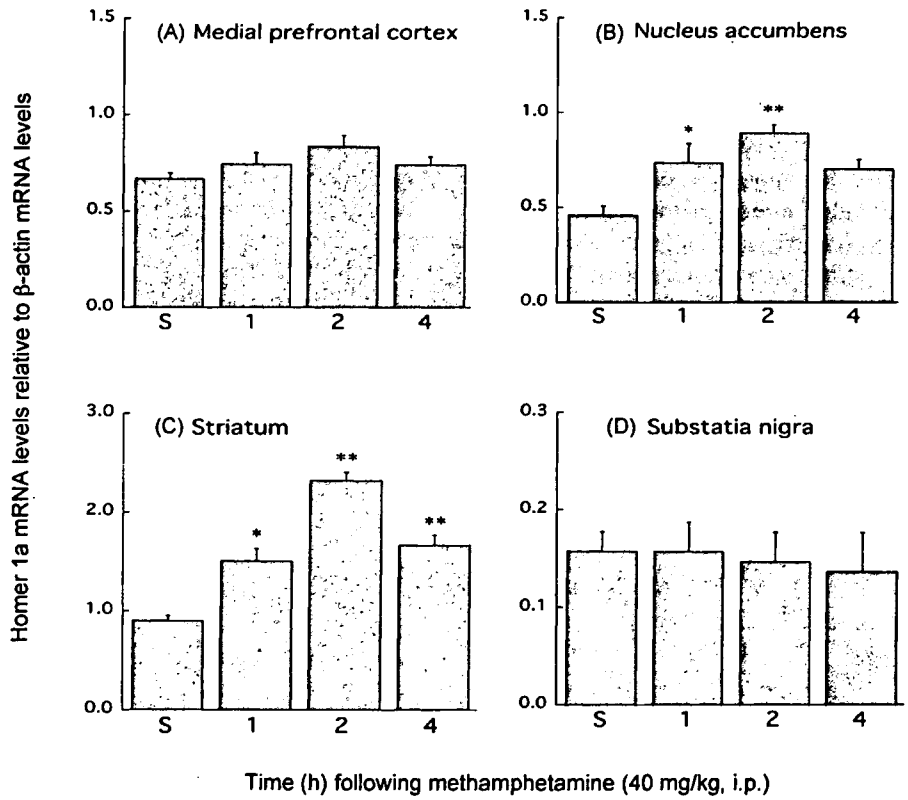

Fig. 1. Time-dependent effects of a neurotoxic dose of methamphetamine on Homer 1a mRNA levels in the rat brain. Rats were killed 1, 2 or 4 h after a single injection of methamphetamine (40 mg/kg, i.p.). The values represent mean ± S.E.M. of nine animals. $^{*}P < 0.05$ and $^{**}P < 0.01$ compared with saline-treated groups (S) using Scheffe's *F*-test.

Table 1
Time-dependent effects of a neurotoxic dose of methamphetamine on the mRNA levels of Homer 1b and 1c in the discrete regions of rat brain

Gene and brain region	Homer mRNA levels relative to β-actin mRNA			
	Saline	Time (h) following methamphetamine (40 mg/kg, i.p.)		
		1	2	4
Homer 1b				
Substantia nigra	0.36 ± 0.07	0.35 ± 0.07	0.29 ± 0.03	0.33 ± 0.03
Homer 1c				
Medial prefrontal cortex	0.99 ± 0.05	0.85 ± 0.07	0.85 ± 0.10	0.81 ± 0.05
Nucleus accumbens	0.96 ± 0.13	0.95 ± 0.08	1.01 ± 0.06	0.97 ± 0.04
Striatum	1.17 ± 0.06	0.90 ± 0.09	0.88 ± 0.07	1.07 ± 0.04
Substantia nigra	0.92 ± 0.10	0.99 ± 0.15	0.88 ± 0.06	1.03 ± 0.14

Data are presented as mean ± S.E.M. of eight animals.

tative analysis of Western blot showed a small but significant increase in Homer 1a protein (+18%, d.f. = 18, $t = 2.61$, $P < 0.05$, Student's t-test, two-tailed) 4 h after administration of methamphetamine (40 mg/kg, i.p.). We replicated the same experiment independently and then also found a significant increase in the striatal Homer 1a protein (+23%, d.f. = 12, $t = 2.44$, $P < 0.05$, Student's t-test, two-tailed) (data not shown).

4. Discussion

The most striking finding of the present study was that methamphetamine induced gene expression of Homer 1a, but nor 1b or 1c, in the striatum and nucleus accumbens. These results further support the hypothesis that the induction of Homer 1a may play an important role in the dopamine–glutamate interaction in the basal ganglia.

Homer 1a selectively blocks binding of Homer 1b and 1c to the group 1 mGluRs (Xiao et al., 1998; Kato et al., 1998). Homer 1b and 1c are constitutively expressed and form a physical linking mGluRs with the inositol triphosphate (IP_3) receptors (Tu et al., 1998). Activation of the group 1 mGluRs, $mGluR_{1a}$ and $mGluR_5$, stimulates phospholipase C and generates IP_3, resulting in the release of Ca^{2+} from intracellular Ca^{2+} stores (Nakanishi, 1994). Therefore, Homer 1a may disrupt the coupling between mGluRs and IP_3 receptors and then inhibit glutamate-induced release of intracellular Ca^{2+}. Moreover, the expression of Homer 1a is reported to induce activation of $mGluR_{1a}$ and $mGluR_5$ (Ango et al., 2001). Our results suggest the methamphetamine-induced modification of excitatory synapse in the striatum and nucleus accumbens.

The dose employed in this study of methamphetamine (40 mg/kg) is sufficient to produce the methamphetamine-induced neurotoxicity to produce long-lasting depletion of contents, synthesis rate and transporter numbers of dopamine (Fukumura et al., 1998; Seiden and Ricaurte, 1987). Such a dose of methamphetamine induces hyperthermia and an excessive increase in extracellular dopamine levels reflected by a decrease in tissue dopamine levels in mice or rats at 1 to 4 h post-treatment of methamphetamine, all of which effects lead to dopaminergic deficits that is evident 24 h after and long persisted (Binienda et al., 2006; Fukumura et al., 1998; Thiriet et al., 2001). Simultaneously, methamphetamine induces expression of several genes in association with the dopaminergic neurotoxicity, as revealed by microarray studies (Xie et al., 2002). The IEG c-fos is also induced in relation to the methamphetamine-induced dopaminergic neurotoxicity (Nakahara et al., 2003; Thiriet et al., 2001) because null mutation of c-fos is reported to exacerbate the methamphetamine-induced dopaminergic deficits (Deng et al., 1999). Moreover, multiple

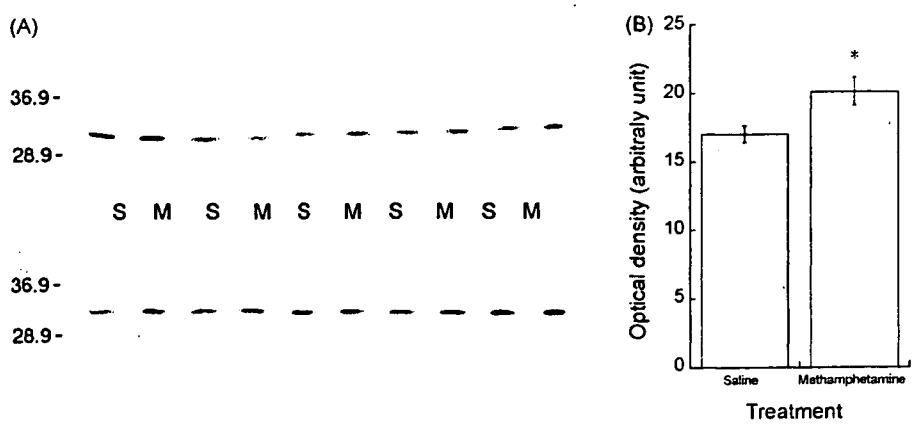

Fig. 2. Effect of a neurotoxic dose of methamphetamine on the protein expression of Homer 1a in rat striatum. (A) Photograph of Western blot of rat striatum obtained from saline (S) or methamphtamine (M) treatment group; (B) quantitative Western blot analysis. The values represent mean ± S.E.M. of 10 animals. $^*P < 0.05$ compared with saline-treated group using Student's t-test.

factors including hyperthermia, mitochondrial disruption, generation of reactive species, alterations of dopamine transporter and vesicular monoamine transporter-2 activities, and changes in glutamate signaling, have been thought to contribute to the methamphetamine-induced dopaminergic neurotoxicity (Riddle et al., 2006). Methamphetamine increases extracellular levels of not only dopamine but also glutamate in the striatum and nucleus accumbens, which may cause exicitoxicity that damages nerve terminals (Nash and Yamamoto, 1993; Xue et al., 1996), while the $mGluR_5$ antagonist prevents the methamphetamine-induced neurotoxicity in a temperature-independent manner (Battaglia et al., 2002). Taken into account with an interaction between Homer 1a and $mGluR_5$ as discussed earlier, the present results imply that the induction of Homer 1a expression may be involved at least in part in the methamphetamine-induced neurotoxicity. In this regard, Tappe and Kuner (2006) recently demonstrated that striosomal Homer 1a-expressing mice enhanced the amphetamine-induced stereotyped behavior as well as c-fos expression, suggesting a critical role of striosomal Homer 1a in dopaminergic responses to amphetamines. While c-fos expression in response to neurotoxic methamphetamine is observed widely throughout the various brain regions including prefrontal cortex and hippocampus (Thiriet et al., 2001), the present results demonstrate the region-specific induction of Homer 1a in the striatum and nucleus accumbens, of which dopamine terminals are most vulnerable to the neurotoxic effect of methamphetamine (Seiden and Ricaurte, 1987).

A high dose of methamphetamine is also known to exert a neurotoxic effect on serotonergic terminals in the cortical areas (Seiden and Ricaurte, 1987), while methamphetamine at the dose used in this study did not induce Homer 1a expression in the medial prefrontal cortex. In the prefrontal cortex, lysergic acid diethylamide (LSD), a hallucinogen displaying potent agonistic activity at serotonin–5-HT_{2A} and/or 5-HT_{2C} receptors, is reported to increase mRNAs of the IEG Ania3, a splicing isoform of Homer 1a (Nichols and Sanders-Bush, 2002). The psychotomimetic phencyclidine that blocks NMDA receptor channels also induces Homer 1a in the same region (Cochran et al., 2002). Taken together with our previous data (Yamada et al., 2007), gene expression of Homer 1a in response to methamphetamine is likely to occur region-specifically in the striatum and nucleus accumbens that abundantly receive the dopaminergic projection from the substantia nigra pars compacta and ventral tegmental area, respectively.

Details of the mechanism by which methamphetamine induces gene expression of Homer 1a has yet to be known. Excessive increases in extracelluar levels of both dopamine and glutamate may be involved (Nash and Yamamoto, 1993; Xue et al., 1996). The striatal Homer 1a was induced to the maximal level 2 h after methamphetamine, which time-dependent profile is similar to that of Homer 1a induction with the dopamine D_1 receptor agonist SKF38393 (Berke et al., 1998; Yamada et al., 2007). Glutamate is reported to induce Homer 1a much slower (the maximal level at 4 h) in cerebellar granule cell culture (Sato et al., 2001). Moreover, activation of D_1 receptors may affect the methamphetamine-induced dopaminergic neurotoxicity due to induction of neuronal nitric oxide synthase mRNA expression in the striatum, which increases reactive species levels (Riddle et al., 2006). Therefore, the methamphetamine-induced D_1 receptor stimulation, as occurs following administration of methamphetamine, may induce Homer 1a mRNA in the striatum. It is most likely that activation of NMDA receptor by D_1 receptor stimulation contributes to Homer 1a expression because of a functional interaction between D_1 receptors and NMDA receptors for calcium signaling in the basal ganglia (Cepeda and Levine, 1998). Most of the G-protein coupled receptors including dopamine receptors and mGluRs may also share direct or indirect bindings with each other. However, it remains unclear whether a non-toxic dose (not more than 5 mg/kg) of methamphetamine induces or not Homer 1a expression. Further studies need to elucidate the molecular mechanism of Homer 1a induction under stimulated conditions.

Basal levels of Homer 1a mRNAs were higher in the forebrain regions than those in the midbrain. In contrast, Homer 1b mRNA levels were higher in the substantia nigra than those in other regions examined. Homer 1b allows translocation and clustering of $mGluR_5$ at dendritic synaptic sites, while the induction of Homer 1a expression triggers translocation of $mGluR_5$ from soma to dendrites (Ango et al., 2000; Tadokoro et al., 1999; Roche et al., 1999). Taken together with the present findings, the mGluRs may exist at axon and/or dendrites in the forebrain and at soma in the substantia nigra, respectively. The large amounts of Homer 1a induced in the striatum and nucleus accumbens may translocate the mGluRs at synaptic sites and enhance the excitability of the synapses after methamphetamine.

In conclusion, a neurotoxic dose of methamphetamine induced Homer 1a gene in the striatum and nucleus accumbens, but not in the medial prefrontal cortex, suggesting that the induction of Homer 1a gene may be associated at least in part with the methamphetamine-induced dopaminergic neurotoxicity. This finding may imply a possible involvement of Homer 1a in the pathophysiology of neurodegenerative diseases in the basal ganglia such as Parkinson disease.

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調査

包括的・全体論的認知リハビリテーションの効果に関する調査*

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Key Words：脳損傷，高次脳機能障害，包括的・全体論的認知リハビリテーション，認知障害，神経心理学

要　旨：〔目的〕包括的・全体論的認知リハビリテーションを2年間実施した効果と各評価指標間の関連について調査した．〔対象〕高次脳機能障害支援モデル事業による福岡市立心身障がい福祉センターのプログラムに参加した男女19名であった．〔方法〕プログラム前後に神経心理学的評価を行い結果を比較した．また，神経心理学的指標と人口統計学的変数・障害尺度との関連について，相関係数，カテゴリカル回帰分析を用いて調べた．〔結果〕カテゴリカル回帰分析から，障害尺度にはWCSTの保続が強い影響を与えている傾向が見いだされた．プログラム前後の比較からは，障害尺度，BI，TMT-B，全IQ，言語性IQ，動作性IQに有意な改善がみられた．またWAIS-Rの下位項目では，数唱，絵画完成，積木，符号が有意に改善していた．〔結語〕包括的・全体論的認知リハビリテーションは，本邦でも実施可能であり，認知機能を改善することのできるプログラムの一つであると思われる．

はじめに

頭部外傷による高次脳機能障害をもつ人に対する認知リハビリテーションは，認知障害，障害認識の欠如，あるいは障害の否認，傷ついた自己概念の相互作用[1)]によって，困難を呈することがしばしばみられる．障害認識の欠如，あるいは低下した自尊心は，訓練不参加の原因となり，同様に障害認識の欠如は，補償手段の使用への抵抗あるいは拒否をもたらす[2)]．そのため認知リハビリテーションにおいては，認知障害へのアプローチのみならず，障害認識の不足と自尊心の低下に対する取り組みも重要となる[1)]．

これらを網羅した取り組みとして最も有名なプログラムが，包括的・全体論的リハビリテーション[2,3)]である．これは，①神経心理学的方向づけ，②統合的治療，③グループによる介入，④専用の資源，⑤チームの一員に神経心理学者が存在，⑥近親者の正規な参加，⑦試験的な雇用・自立生活を含む，⑧多面的な結果の評価，を特徴としており[4)]，『根拠にもとづく認知リハビリテーション』[5)]のなかでも，「クラスⅡ・実施を勧められるプログラム」として推奨されている．

当福岡市立心身障がい福祉センター（以下，心障センター）では，厚生労働省の高次脳機能障害支援モデル事業に参画し，2002年度から，この包括的・全体論的プログラムを目指した取り組みを試行錯誤しながら行い，対象者8名についての1

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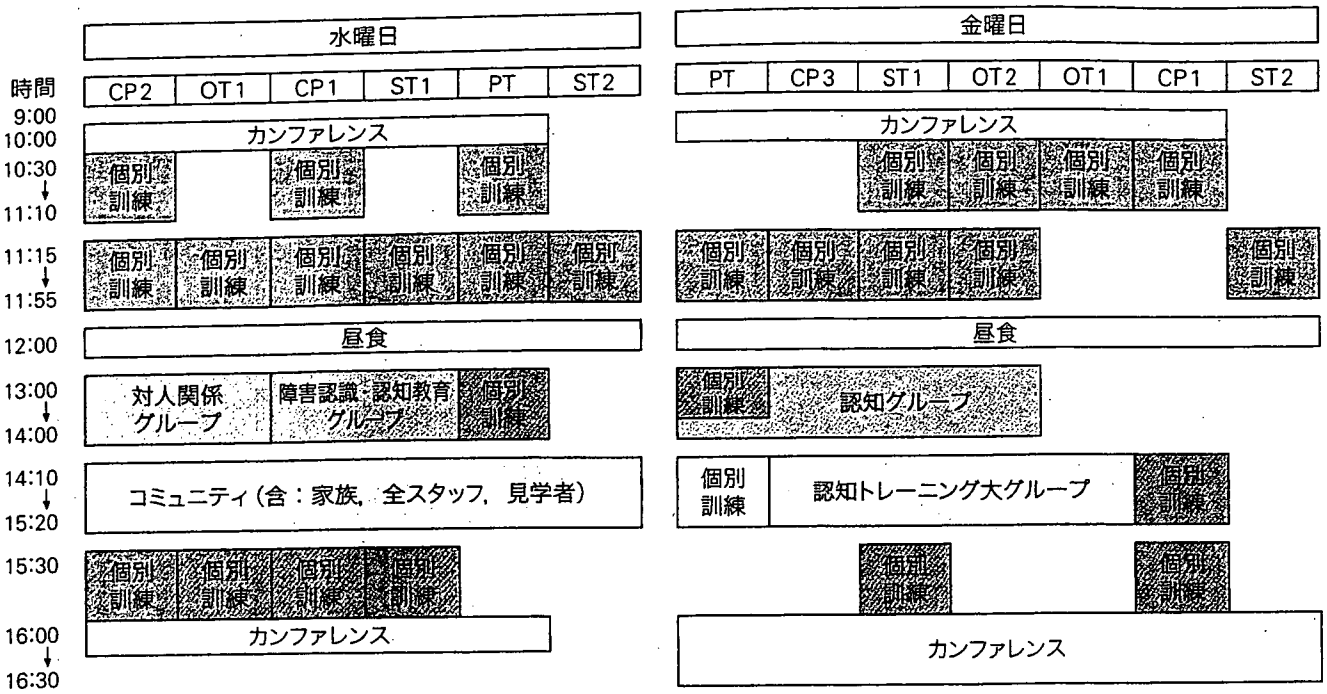

図 1　スタッフとプログラムの配置

年間の効果を第 1 報として報告した[6]．その後対象者も増え，プログラム内容も確立したので，本稿においては，プログラム内容，2 年間の効果，その評価に使用した各指標間の関連について報告する．

対象・方法

1．対　象

対象は，2002～2004 年に心障センターのプログラムに参加した高次脳機能障害をもつ 19 名（男性 17 名，女性 2 名）で，年齢は 17～59 歳（平均 34.2 歳），受診までの期間は 3 か月～14 年 8 か月（平均 4 年 1 か月）であった．効果測定は，個別の訓練担当者によって，訓練開始時から 1 年毎に行われた．ただし，2 年間を経過しない間に修学や就労のために訓練終了となったケースは，終了の時点で測定が行われた．プログラム参加期間は 1～2 年（平均 1 年 5 か月）であった．神経心理学的検査以外の所見としては，失語 2 名（10%），片麻痺 5 名（26%），失調 5 名（26%），半側空間無視 2 名（10%）であった．

2．心障センターにおける全体論的認知リハビリテーションプログラム

スタッフは 9 名で，内訳は臨床心理士（CP）3 名，言語聴覚士（ST）2 名，作業療法士（OT）2 名，理学療法士（PT）1 名，リハビリテーション医 1 名であった．スタッフとプログラム配置を**図 1** に示す．

このプログラムの特徴は，職種に関係なく，全スタッフが共通の内容を行うことである．これは従来の OT は作業療法で，PT は理学療法で，ST は言語療法で，CP はカウンセリングと心理テストで関わっていく多職種チームモデル（multidisciplinary team model）[7]とは異なっている．プログラムは，週 2 回，水曜と金曜の午前 10 時 30 分から午後 4 時に行った．内容は，1 対 1 の個別訓練（40 分，週 1 回），5～6 人の小グループ訓練（60 分，週 2 回），10～13 人の大グループ訓練（60～90 分，週 2 回）から成り立っている．

1）個別訓練

対象者 1 名に対して 1 名の個別担当者がつき，注意力・情報処理速度の向上をねらう認知トレーニングとカウンセリングを行った．カウンセリングでは，神経疲労や感情コントロールに対してリラクセーションや認知行動療法を行ったり，家庭，職場，学校での問題への対処法の検討を行ったりした．また，グループ訓練の目的を意識化させること，来所中に起こる対人関係問題にすぐに介入

することも怠らないようにした.

2）グループ訓練

小グループ訓練としては,「障害認識・認知教育グループ」で,注意障害,神経疲労,脱抑制等についての心理教育を行った.「認知グループ」で,81マス計算と文章要約の訓練を行った.さらに「対人関係グループ」で,ソーシャルスキルトレーニング(SST)を行った.

大グループ訓練としては,「認知大グループ」と「コミュニティ」とがあり,どちらもグループダイナミックスを活用し,集団のなかで,自分の能力を発揮していくことを目的に行った.

「認知大グループ」では,参加者(以下,メンバー)が関心のある新聞記事を持参し,要約して発表することを行った.これは情報をまとめるという認知機能の訓練だけではなく,社会への関心を拡げる,また記事を忘れずに持参するために,メモや手帳の利用を定着させることを目的とした.

「コミュニティ」では,全メンバー,全スタッフ,家族,見学者が参加するなかで,スタッフから出されたテーマについて,各メンバーは自分の考えをまとめ,発表した.その後,メンバーの発表に対する肯定的なコメントが,スタッフ,家族,見学者から述べられた.テーマは,障害・リハビリテーション・家族・仲間・仕事・人生のなかから選ばれた.例としては,「障害によって失った最も大きなものは何か? その理由は何か?」,「リハビリテーションに取り組む時に,勇気づけるものと,やる気を失わせるものは何か?」等である.これは考えを的確な言葉で表現するという認知訓練,コミュニケーション訓練であると同時に,障害を他者の前で話し,他者が障害について話すのを聞くことによって,孤立感が減少し,改善の希望がもたらされ,リハビリテーションに対する主体性が高まることを目的としている.

3）家族の参加

家族の参加の機会は,個別カウンセリングと,「障害認識・認知教育グループ」,「コミュニティ」であった.

個別カウンセリングは,本人の個別訓練の後に10～15分行い,家庭での問題への対処法,家族自身のストレス対処法,センターでの訓練を家庭内へ般化させるための方法等について話し合った.

また,「障害認識・認知教育グループ」へ本人と一緒に参加することで,高次脳機能障害についての正しい知識を得て,本人と障害についてより客観的に話し合えるようになることを目的とした.

「コミュニティ」への参加は,社会からの孤立を防ぎ,本人の障害をより客観的に捉える機会とした.とくに,家族の接し方によって,本人が家族に対してのみ退行した態度をとっている場合があるため,「コミュニティ」への参加は,本人が家族以外の他者にどのような態度をとっているのかを知り,本人に対する接し方を変える機会となることがある.

3．効果測定に使用した変数

人口統計学的変数として,年齢,障害発症年齢,昏睡期間,リハビリテーション受診までの期間を用いた.障害の重症度としては,高次脳機能障害支援モデル事業で使用された障害尺度(範囲1～8:高いほど障害は軽い)[8]を用いた.

認知機能の測定には,ウェクスラー成人知能検査(WAIS-R),かなひろいテスト,トレイル・メイキング・テストA・B(TMT-A・B),ウィスコンシン・カードソーティング・テスト慶應版(WCST),リバーミード行動記憶検査(RBMT)を用いた.感情状態の測定には,気分プロフィール検査(POMS),自尊感情尺度[9],主観的日常生活満足度(SDL)[10]を使用した.全般的な行動・能力の測定には,能力評価表(本人・家族)[11],バーセル・インデックス(BI)を用い,障害認識の程度としては,能力評価における本人評価と家族評価の差を用いた.

4．統計的手法

変数には間隔尺度ではないもの,また正規分布を示さないものが多数含まれているため,ノンパラメトリック検定を使用した.各変数間の関連を調べるために,スピアマンの相関係数とカテゴリカル回帰分析を,プログラム効果としてのプログラム前後の中央値の差の検定には,ウィルコクスンの符号付順位和検定を用いた.

5．倫理的配慮

プログラム参加者全員と家族に対して,リハビリテーションの効果測定のために評価を行うこと

を事前に説明し，了承を得ており，実施後には評価結果を説明した．

結　果

1．相関係数

プログラム開始前の人口統計学的変数，認知機能，感情状態，行動・能力，障害認識の程度の各変数間の相関係数を**表1**に示す．昏睡期間はWCSTの保続と正の相関があり，WCSTの達成カテゴリー，WAIS-Rの言語性IQ，知識，単語，理解と負の相関があった．しかし，障害尺度との間には有意な相関はみられなかった．

障害尺度は，BI，RBMTと正の相関があり，TMT-A・B，WCSTの保続と負の相関があった．

かなひろいテストの正答数は，TMT-A・Bと負の相関，RBMT，WAIS-Rの符号，POMSの活力と正の相関があった．

POMSの不安・緊張はWAIS-Rの知識と負の相関があり，抑うつは，TMT-A，WAIS-Rの積木，POMSの怒り，疲労，混乱と正の相関，知識と負の相関があった．しかし，抑うつと自尊感情尺度との間に有意な相関はみられなかった．活力は，かなひろいテストの正当数と正の相関，TMT-A・Bと負の相関があった．さらに，自尊感情尺度，SDLとも正の相関があった．

本人の能力評価は，WAIS-Rの言語性IQ，理解，類似と負の相関があり，家族の能力評価は，WAIS-Rの積木，自尊感情尺度と正の相関があった．

本人と家族の能力評価の差は，WAIS-Rの言語性IQ，理解，類似，POMSの混乱との間に負の相関がみられた．

表1　人口統計学的変数，認知機能，感情状態，行動・能力，

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1	発症年齢	—																
2	受診までの期間	−0.62**	—															
3	昏睡期間	−0.04	0.17	—														
4	障害尺度	−0.19	−0.20	−0.21	—													
5	BI	−0.21	−0.28	−0.23	0.80**	—												
6	能力評価　本人	0.13	0.05	0.31	−0.07	0.04	—											
7	家族	−0.04	−0.22	0.23	0.51	0.57*	0.16	—										
8	差	0.13	0.09	0.43	−0.15	−0.05	0.83**	−0.39	—									
9	かなひろい　正	−0.26	0.27	−0.22	0.26	0.18	0.25	0.26	0.03	—								
10	誤	0.35	−0.15	−0.25	−0.07	−0.03	0.35	0.09	0.33	0.31	—							
11	TMT　A	0.27	−0.06	0.32	−0.54*	−0.54*	0.09	−0.31	−0.02	−0.65**	−0.31	—						
12	B	0.29	−0.08	0.52	−0.58*	−0.63*	0.03	−0.38	−0.22	−0.74**	−0.80**	0.96**	—					
13	WCST　達成カテゴリー	−0.48	0.13	−0.53*	0.48	0.33	−0.16	0.20	−0.11	0.05	−0.25	−0.15	−0.02	—				
14	保続	0.47	−0.04	0.52*	−0.53*	−0.53	0.23	−0.08	0.09	−0.12	0.19	0.36	0.31	−0.87**	—			
15	セット維持困難	0.10	−0.35	0.28	0.18	0.41	−0.45	0.50	−0.49	−0.16	−0.02	−0.23	−0.13	0.18	−0.41	—		
16	RBMT　SPS	−0.29	0.33	−0.29	0.74**	0.64*	−0.21	0.24	−0.18	0.67*	0.05	0.87**	−0.87**	0.31	−0.53	0.24	—	
17	SS	−0.32	0.25	−0.28	0.73**	0.66*	−0.20	0.11	−0.15	0.64*	0.18	−0.88**	−0.87**	0.24	−0.50	0.21	0.98**	—
18	WAIS-R　全IQ	0.05	−0.03	−0.35	0.39	0.27	−0.32	0.33	−0.39	0.40	0.31	−0.60**	−0.45	0.18	−0.27	0.18	0.63*	0.69**
19	言語性IQ	0.01	−0.13	−0.53*	0.24	0.15	−0.64**	0.27	−0.74**	0.22	0.06	−0.43	−0.29	0.46	−0.51*	0.39	0.57*	0.58*
20	動作性IQ	−0.06	0.21	0.09	0.34	0.19	−0.14	0.20	−0.12	0.44	0.30	−0.56*	−0.45	−0.10	−0.09	0.10	0.69**	0.74**
21	知識	0.21	−0.21	−0.57*	0.25	0.00	−0.42	0.08	−0.33	0.24	0.44	−0.37	−0.40	0.30	−0.28	0.28	0.42	0.44
22	数唱	−0.26	0.17	0.21	−0.22	−0.14	−0.09	−0.21	−0.08	0.44	0.00	−0.26	−0.10	−0.02	−0.19	−0.13	0.24	0.31
23	単語	0.30	−0.18	−0.53*	0.36	0.16	−0.32	0.30	−0.39	0.26	0.34	−0.39	−0.32	0.38	−0.41	0.26	0.64*	0.68**
24	算数	0.19	−0.39	−0.44	0.21	0.08	−0.29	0.18	−0.25	0.16	0.17	−0.37	−0.20	0.23	−0.12	0.10	0.26	0.28
25	理解	−0.02	−0.12	−0.48*	0.15	0.23	−0.57*	0.15	−0.65*	0.07	−0.01	−0.29	−0.21	0.39	−0.47	0.31	0.44	0.49
26	類似	−0.06	−0.00	−0.36	0.17	0.16	−0.61**	0.16	−0.76**	−0.03	−0.24	−0.22	0.06	0.45	−0.44	0.40	0.46	0.42
27	完成	−0.15	0.31	−0.11	0.24	0.17	−0.26	0.15	−0.20	0.41	0.19	−0.55*	−0.35	−0.02	−0.12	0.18	0.64*	0.61*
28	配列	−0.03	0.07	0.22	0.24	0.08	−0.22	−0.13	−0.08	0.31	0.06	−0.37	−0.17	−0.12	−0.03	0.16	0.40	0.48
29	積木	−0.32	0.20	0.00	0.45	0.37	−0.37	0.56*	−0.54	0.29	−0.15	−0.45	−0.40	0.21	−0.42	0.64**	0.59*	0.55*
30	組み合わせ	−0.05	0.11	0.14	0.40	0.36	−0.11	0.27	−0.08	0.30	0.30	−0.53*	−0.47	−0.21	0.02	0.14	0.58*	0.62*
31	符号	14	−0.38	−0.24	0.33	0.30	0.02	0.13	0.20	0.53*	0.49*	−0.72**	−0.68**	−0.08	−0.04	−0.08	0.41	0.49
32	POMS　不安・緊張	−0.16	0.34	0.02	−0.16	0.00	0.02	0.22	−0.36	−0.05	−0.00	0.25	0.08	−0.17	0.25	−0.19	−0.20	−0.17
33	抑うつ	−0.07	0.16	0.06	−0.27	−0.04	0.02	0.12	−0.27	−0.24	−0.17	0.46*	0.47	−0.03	0.09	−0.18	−0.39	−0.34
34	怒り	−0.32	0.27	0.09	0.12	0.19	−0.31	0.22	−0.54	−0.09	0.09	−0.01	−0.13	−0.00	−0.09	0.08	0.12	0.22
35	活力	−0.41	0.26	−0.33	0.35	0.38	0.26	0.29	0.09	0.55*	0.46	−0.53*	−0.82**	0.00	−0.08	−0.07	0.46	0.46
36	疲労	−0.36	0.25	−0.25	0.15	0.09	−0.25	0.08	−0.49	−0.07	−0.14	0.16	−0.01	0.41	−0.39	−0.02	−0.02	0.04
37	混乱	−0.17	0.19	−0.21	0.09	0.14	−0.26	0.28	−0.62*	−0.08	−0.08	0.16	0.02	0.05	0.01	0.10	0.04	0.05
38	TMD	−0.09	0.11	−0.02	−0.07	0.00	−0.20	0.18	−0.50	−0.31	−0.15	0.42	0.32	0.16	−0.04	−0.06	−0.37	−0.31
39	自尊感情尺度	−0.21	0.14	−0.10	0.07	−0.03	0.33	0.66*	−0.18	0.31	0.22	−0.04	−0.16	0.02	0.13	0.18	0.00	−0.15
40	SDL	−0.40	0.22	−0.25	0.24	0.11	0.42	0.16	0.08	0.54	0.16	0.12	−0.33	0.24	−0.07	−0.15	0.15	0.05

注）**p<0.01，*p<0.05

2．カテゴリカル回帰分析

障害の重症度を表す障害尺度に最も関連のある認知機能・感情・行動の変数を調べるために，障害尺度と有意な相関をもつ変数を独立変数，障害尺度を従属変数としてカテゴリカル回帰分析を行ったところ（$R=0.99$，$R^2=0.97$，$R^{*2}=0.90$，$F=13.80$，$p=0.069$），WCST の保続が，障害尺度に強い影響を与えている傾向がある（$p=0.057$，β 値 -0.757）ことが見いだされた．

3．プログラムの効果

プログラム前後の各指標の中央値は**表 2** のとおりである．障害尺度，BI，TMT-B，全 IQ，言語性 IQ，動作性 IQ に有意な改善がみられた．

記憶に関しては，RBMT の SPS と SS には有意差はみられなかったが，下位項目である「見当識」に有意差がみられた．

さらに WAIS-R の下位項目（**図 2**）では，数唱（$Z=-3.05$，$p<0.01$），絵画完成（$Z=-2.13$，$p<0.01$），積木（$Z=-2.41$，$p<0.05$），符号（$Z=-2.50$，$p<0.05$）が有意に改善していた．

4．全 IQ の改善と他の指標の相関

次にプログラムによる全 IQ の改善と関連のある指標を見いだすために，全 IQ のプログラム前後の差と，人口統計学的変数，障害尺度，神経心理学的テストの初期値，訓練期間との相関を調べた．その結果，全 IQ のプログラム前後の差と有意な相関をもつ指標は，開始前の障害尺度（相関係数 0.62，$p<0.01$）と BI の初期値（相関係数 0.65，$p<0.01$）であった．昏睡期間，受診までの期間，訓練期間との間には有意な相関はみられなかった．

障害認識の程度における各変数間の相関係数

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
—																						
0.80**	—																					
0.81**	0.39	—																				
0.62**	0.76**	0.31	—																			
0.23	0.26	0.25	0.05	—																		
0.85**	0.84**	0.54*	0.74**	0.04	—																	
0.56*	0.73**	0.19	0.69**	−0.08	0.66**	—																
0.68**	0.90**	0.26	0.52*	0.20	0.73**	0.66**	—															
0.61**	0.86**	0.23	0.54*	0.20	0.62**	0.53*	0.82**	—														
0.79**	0.53*	0.82**	0.43	0.21	0.52*	0.25	0.35	0.49*	—													
0.66**	0.29	0.84**	0.13	0.47*	0.37	0.10	0.18	0.20	0.70**	—												
0.43	0.29	0.58**	0.12	0.06	0.25	−0.09	0.15	0.23	0.45	0.29	—											
0.64**	0.14	0.87**	0.11	0.09	0.26	−0.04	0.00	0.06	0.75**	0.75**	0.59**	—										
0.57*	0.35	0.49*	0.40	0.21	0.41	0.60**	0.25	0.05	0.35	0.49*	0.03	0.45	—									
−0.16	−0.28	−0.07	−0.47*	−0.24	−0.28	−0.37	−0.08	−0.14	−0.14	−0.19	0.01	0.11	−0.31	—								
−0.12	−0.22	−0.09	−0.55*	−0.11	−0.22	−0.39	0.02	−0.07	−0.16	−0.04	0.02	0.05	−0.36	0.85**	—							
0.14	−0.04	0.27	−0.18	0.10	−0.10	−0.40	0.04	−0.00	0.07	−15	0.47*	0.43	−0.17	0.68**	0.59**	—						
0.17	0.06	0.10	0.21	0.11	0.01	−0.03	0.02	0.03	0.23	−0.09	0.11	0.17	0.18	−0.02	−0.32	0.15	—					
0.01	−0.03	0.09	−0.20	−0.11	−0.00	−0.26	0.04	−0.06	−0.09	0.02	0.32	0.13	−0.22	0.69**	0.69**	0.72**	−0.10	—				
0.05	0.01	0.08	−0.14	−0.30	−0.03	−0.15	0.10	0.13	0.04	−0.09	0.36	0.21	−0.24	0.85**	0.70	0.68**	−0.03	0.79**	—			
−0.06	−0.12	−0.03	−0.34	−0.22	−0.12	−0.29	0.03	−0.02	−0.17	−0.06	0.18	0.11	−0.34	0.85**	0.91**	0.76**	−0.30	0.85**	0.85**	—		
−0.15	−0.01	−0.16	0.20	−0.02	−0.19	−0.03	−0.23	0.12	−0.05	−0.40	0.10	−0.06	−0.18	0.03	−0.24	−0.04	0.66*	−0.16	0.15	−0.11	—	
−0.21	−0.14	−0.16	0.12	−0.25	−0.23	−0.10	−0.13	0.16	−0.18	−0.45	−0.00	−0.13	−0.21	0.23	0.01	0.11	0.66*	0.18	0.42	0.22	0.73	—

表 2　プログラム前後の神経心理学的評価の変化

	n	前 中央値	後 中央値	z 値	有意確率
障害尺度	19	4	5	−3.00	0.003**
BI	18	100 (89)	100 (94)	−2.07	0.038*
能力評価　本人	17	105	103	−0.28	0.977
家族	14	74.5	72.5	−0.25	0.807
差	13	32	15	−0.63	0.529
かなひろい　正	17	15	21	−1.71	0.087
誤	17	5	5	−0.29	0.776
TMT　A	19	201	148	−1.65	0.099
B	15	251	197	−2.37	0.006**
WCST　達成カテゴリー	16	4	4	−0.05	0.959
保続	16	7	4	−0.76	0.450
セット維持困難	16	1	1	−1.22	0.222
RBMT　SPS	14	17.5	13.5	−0.70	0.944
SS	14	6.5	4.5	0.00	1.000
絵	14	9.5	10.0	−1.93	0.054
見当識	14	8 (7.0)	8 (7.8)	−2.04	0.041*
WAIS-R　全 IQ	19	79	94	−3.79	0.000***
言語性 IQ	19	82	92	−3.36	0.001**
動作性 IQ	19	82	84	−2.77	0.006**
POMS　不安・緊張	19	56	50	−0.31	0.760
抑うつ	19	61	56	−0.20	0.840
怒り	19	51	53	−0.31	0.760
活力	19	48	46	−0.14	0.888
疲労	19	53	48	−0.74	0.459
混乱	19	59	53	−0.81	0.420
TMD	19	242	213	−0.61	0.542
自尊感情尺度	13	33	30	−0.27	0.789
SDL	12	37	38	−1.16	0.248

註）BI と見当識は中央値では変化が分からないために括弧内に平均値を示している．
***p<0.001，**p<0.01，*p<0.05

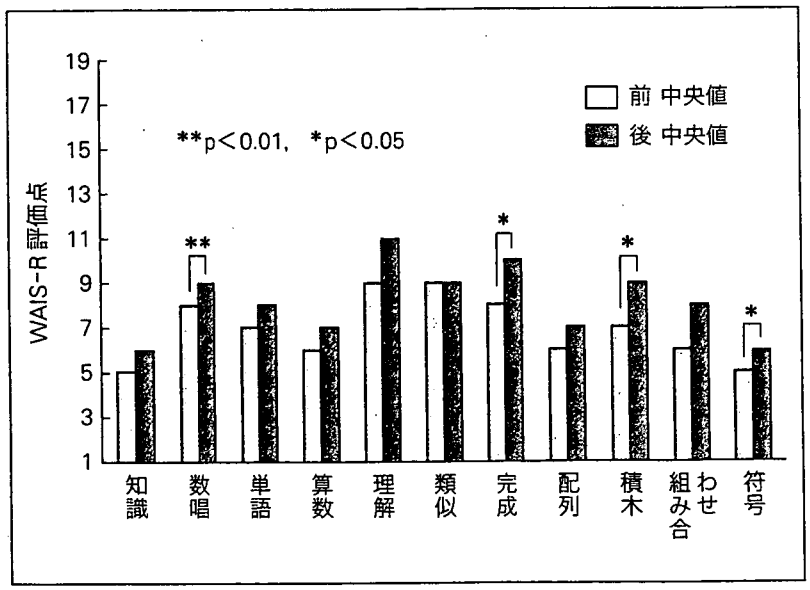

図 2　WAIS-R 下位項目の変化
符号は中央値（前 4.0，後 4.0）では変化が分かりずらいため，平均値で示してある

考　察

1．神経心理学的変数と他の変数の関連

かなひろいテスト，TMT-A・B，RBMT，WAIS-R の符号，POMS の活力の間に有意な相関がみられたことは，注意力，情報処理スピード，記憶，そして活力との間に関連があることを示していると思われる．さらに活力は，SDL，自尊感情尺度とも有意な相関を示していることから，この活力の回復が，高次脳リハビリテーションにおいて重要であることが示唆される．

障害認識の程度と言語性 IQ との相関は，本人の言語的知的能力が高いほど障害をより正確に認識できることを示していると思われる．しかし，POMS の混乱とは負の相関がみられることから，障害認識の程度が高いほど，つまり，より障害が自覚されているほど情緒的混乱が生じやすいと考えられる．また，能力評価の差は WAIS-R の類似と負の相関を示している．この類似は遂行機能を表す指標の一つと言われる[13,14]ことから，障害を正しく認識できるためには，認知機能の改善，とくに遂行機能の改善が必要であると考えられる．

カテゴリカル回帰分析の結果は，障害尺度には，他の指標のなかでもとくに WCST の保続が強く影響している傾向があることを示していた．このことから，Lezak[12]も，この保続を前頭葉損傷を有する患者の特徴と指摘しているように，この保続は高次脳機能障害の重症度を特徴的に表わす指標の一つであると思われる．

2．プログラムの効果

プログラム前後の中央値の比較から，当センターのプログラムを 1～2 年経過することによって，言語性 IQ，動作性 IQ を含む全般的知的機能，日常生活動作の改善がみられる．また，障害尺度は 1 ランク改善する．さらに，WAIS-R の下位項目の改善は，認知機能のなかでも，とくに注意力，注意の切りかえ，集中力・覚醒，情報処理スピード，遂行機能の改善を意味している[13,14]．これらの認知機能の改善は，全体論的認知リハビリテーションプログラムを実践した Prigatano ら[11]による，プログラム参加者 18 人の動作性 IQ，積木，符号，ウェクスラー記憶検査の記憶指数が，17 人の統制群に比べて有意に改善した，という報告と共通している．ただし，Prigatano らのプログラムは 1 日 6 時間，週 4 日を 6 か月間行っており，当センターのプログラムとは集中度，期間の点で違いがある．

全 IQ の改善と各指標の相関からは，当センターのプログラムでは開始時に障害が軽い者ほど，また日常生活動作が良好である者ほど，全 IQ の改善が大きいことが示唆された．しかし，受傷から訓練開始までの期間や，訓練期間の長さは，全 IQ の改善とは相関がみられないことから，訓練を早期に開始することや長期間行うことが，必ずしもより大きな改善を生み出すとは，今回の調査からは言えない．

3．本調査の限界と今後の課題

今回の調査には統制群がないために，自然回復の側面を区別して比較検討できていない．訓練効果としても，記憶の改善や感情面の改善は，評価検査上，十分に現れておらず，また障害認識と自尊心を重視しているプログラムであるにもかかわらず，これらの改善も，評価検査上はみられていない．本邦でも阿部ら[15]の報告では，包括的・全体論的プログラムとは異なる内容の訓練を行い，WAIS-R の全項目，RBMT，かなひろいテスト等に改善がみられていることから，今回示された認知機能の改善が，包括的・全体論的プログラムの独自性からもたらされたかどうかについては，今後検討の余地がある．

包括的・全体論的プログラムは，医療環境と社会の価値観の違いから，本邦では実施が困難であるとの見方もあるが[16]，今回の調査からは，上記のような限界をもつものの，条件によっては本邦でも実施可能であり，認知機能を改善することができるプログラムの一つであると思われる．今後，高次脳機能障害をもつ者の認知機能だけでなく，感情状態，障害認識，そして自尊心も含めて改善することができるプログラムを，さらに発展させることが必要であろう．そのためには，プログラム内容の徹底的な検討と，実施後の効果測定を繰り返すことが不可欠である．

本プログラムは，多くの方々のご協力により実施することができました．プログラムに関わっていただいた福岡市立心身障がい福祉センターの中島大輔氏，福岡リハビリテーション専門学校の沖　雄二氏，村田奈保子氏に心より感謝いたします．また，本論文作成にあたりご指導いただきました久留米大学大学院心理学研究科 津田　彰教授に心より感謝申し上げます．

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