Methamphetamine (METH) is a CNS stimulant that induces increased locomotor activity and stereotyped behavior by inhibiting the reuptake and facilitating the release of dopamine (DA). It is known that repeated administration of METH causes a progressive and long-lasting augmentation of locomotion and stereotyped behaviors, called behavioral sensitization, which is one of the animal models of METH dependence and psychosis.[3,4]

With respect to the relationship between the METH and HA neuron system, there were several reports that HA or its precursor inhibited METH-induced locomotor hyperactivity or stereotyped behaviors in mice.[5,6] Ito *et al.* reported that the effects of HA agents on METH-induced stereotyped behavior and behavioral sensitization were examined in rats, suggesting, by pharmacological studies, that the brain HA has an inhibitory role in acute and chronic behavioral effects of METH[7] and that the effects of HA in the inhibition of behavioral effects of METH were mediated through both the H1 and H2 receptors.[8]

However, these data were mainly obtained by the classical pharmacological experiments using enzyme inhibitors and HA receptor ligands. These agents are specific, but the possibility that they affect the systems other than the HA system cannot be excluded. Studies using more than two drugs may present difficulties in data interpretation because of drug interactions in the metabolic pathways, side effects, difference in duration of drug action, and so on. It has not yet been clarified as to which neurotransmitter systems interact with the HA neuron system in manifesting the inhibitory effects on the behavioral sensitization. Therefore, the data obtained by pharmacological experiments should be reevaluated from a specific point of view. As an alternative approach to this matter, we used genetically altered animals.

LOCOMOTOR ACTIVITIES OF THE HA-RELATED GENE KNOCKOUT MICE AFTER ADMINISTRATION OF METH

Kubota *et al.* reported the effects of METH in the HDC-KO mice[9] in which HA was almost absent and is generated by homologous recombination using a gene-targeting technique.[10] Repeated administration of METH developed behavioral sensitization both in the HDC-KO and the wild type (WT) mice. But the locomotor activity of the HDC-KO mice was significantly more exaggerated than in the WT mice after numerous METH injections.

To further investigate the role of the HA neuron system in chronic behavioral effects of METH, we administrated METH repeatedly on HA receptor gene KO mice. Locomotor activities were measured in the mutant mice lacking the H1 or H2 gene using a gene-targeting technique,[11,12] H1/H2 receptor gene–double KO mice made by crossbreeding of H1-KO mice and H2-KO mice, and WT mice corresponding to each of them. In the treatment with METH, they were injected with METH (1 mg/kg i.p.) once daily in the light period for seven consecutive days. Locomotor activity of mice was monitored under an infrared-ray passive sensor system (SUPERMEX®, Muromachi kikai Co., Tokyo, Japan) for 2 h after the administration of METH in seven consecutive days.

Repeated administration of METH increased the locomotor activity gradually and developed behavioral sensitization both in the H1-KO and the WT mice (FIG. 1a). However, there were no significant differences between the two genotypes

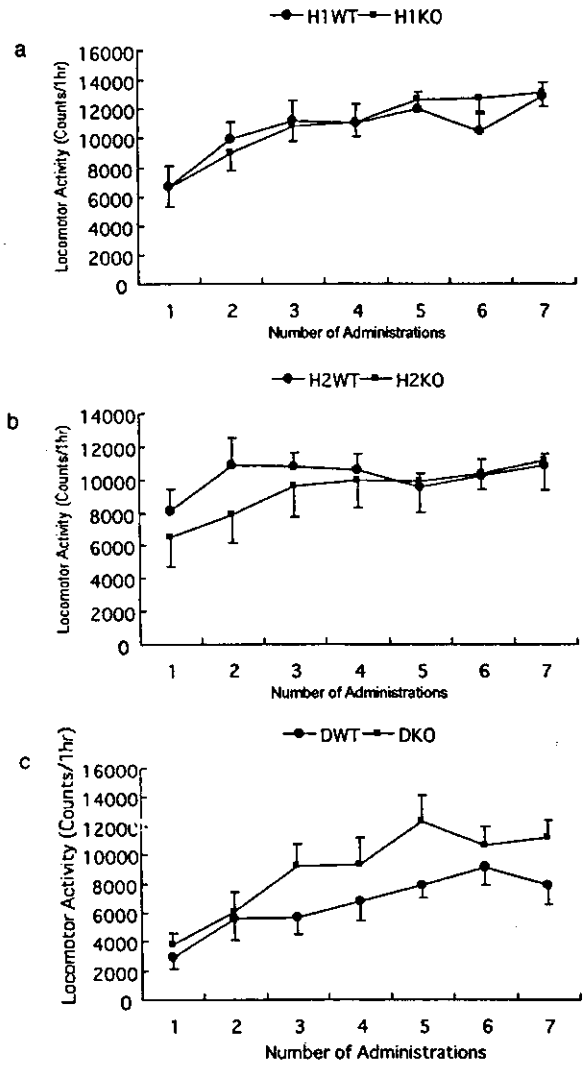

FIGURE 1. Effects of repeated administration of METH in histamine H1 (**A**), H2 (**B**), H1/H2 (**C**) receptor gene knockout mice (*solid square*) and their respective wild type (*solid circle*) mice. Locomotor activity of mice was measured and total counts evaluated per 1 h after the administration of METH (1 mg/kg i.p.) for seven consecutive days. The statistical analyses of data were carried out using two-way ANOVA followed by Bonferoni's test. In all cases, *P* values of less than .05 were considered significant. *P* values of knockout versus the wild type in the H1-, H2-, and H1/H2-gene KO mice were .695, .320, and .001, respectively.

(FIG. 1b). Similarly, any significant difference was not observed between the H2 gene KO and their WT mice. However, the increases of locomotor activity were significantly more exaggerated in the H1/H2 gene double KO mice than in the WT mice (FIG. 1c). In the our studies, we demonstrated that the behavioral sensitization induced by chronic treatment of METH was more pronounced in HDC gene-KO mice and H1/H2 receptor gene–double KO mice compared with those of WT mice. On the other hand, we did not see any significant differences in the chronic effects of METH between the H1 or H2 receptor gene–KO mice and those of WT mice. The lack of either H1 or H2 receptor may be compensated by the remaining counterpart in H1 or H2 receptor–KO mice; in the case of H1/H2 receptor–double KO mice, such a compensational mechanism may not function. Therefore, similar effects of METH on the HDC gene–KO mice and H1/H2 receptor gene–double KO mice could be observed in our studies. In other words, the potencies of the inhibitory effects on the METH-induced behavioral sensitization through H1 and H2 receptors might be equivalent, suggesting that these two receptors are synergetically functioning in the inhibitory effects.

RELATION OF THE HA, DA, GABA NEURONS IN METH ADMINISTRATION

In a previous study, Kubota *et al.* measured the contents of monoamines and amino acids in the brain of HDC gene–KO and their WT mice after the single administration of METH.[9] As a result of disrupting of the HDC gene, the HA contents in the brain regions became almost null in the HDC-KO mice. The single injection of METH significantly increased DA content in the forebrain and decreased it in the

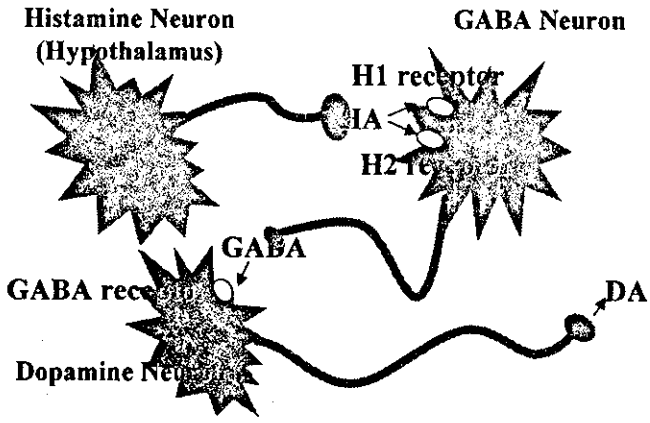

FIGURE 2. Schematic representation of possible mechanisms for histamine receptor-mediated enhancement of GABAergic neurotransmission.

midbrain of the HDC-KO when compared to that in the WT mice. The injection of METH to HDC-KO mice increases the DA content in the forebrain where the terminals of DA neurons exist, while it decreases it in the midbrain where the cell body of DA neurons exist. Therefore, these data suggest that the activity of the dopaminergic neuron system was facilitated more in the HDC KO mice by a single administration of METH. In accordance with our hypothesis, the GABA level in the midbrain of WT mice showed a tendency to decrease by METH treatment, but not in the HDC-KO mice. After the METH treatment, the GABA contents in the midbrain of HDC-KO mice were significantly higher than those of WT mice. It is suggested that deficiency of HA reduces the GABA neurotransmission in the addiction of METH, although further neurochemical studies are needed.

As shown in FIGURE 2, HA released from the histamine neuron may act on the H1 and H2 receptors at the GABA neurons and may enhance GABA release in the brain. Then, enhanced GABA release may inhibit the hyperexcitation of dopamine neurons and suppress the excessive dopamine release. The decreased GABA release may be attributed to the more exaggerated METH-induced behavioral sensitization observed HDC-KO and double H1 and H2 KO. A similar mechanism for histamine-mediated enhanced GABAnergic neurotransmission is postulated in the susceptibility to epilepsy in HA-related gene KO mice.[13]

CONCLUSION

METH-induced locomotor hyperactivity and the development of behavioral sensitization were more facilitated in the HDC-gene KO mice and H1/H2 genes double KO mice than their respective WT mice, suggesting brain HA has an inhibitory effect on the METH-induced behavioral sensitization through both H1 and H2 receptors. In HDC-KO mice, we demonstrated that lack of HA may contribute to increased DA neurotransmission and the decrease of GABA neurotransmission leading to the exaggerated locomotor hyperactivity and behavioral sensitization induced by the METH. Brain HA has an inhibitory role on the METH-induced locomotor hyperactivity and the development of behavioral sensitization.

ACKNOWLEDGMENT

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Histamine H_1 receptors in schizophrenic patients measured by positron emission tomography

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Abstract

Increasing evidence has shown that the histaminergic neuron system is implicated in the pathophysiology of schizophrenia. The aim of this study was to compare the distribution of histamine H_1 receptors between schizophrenics and normal human subjects in vivo using positron emission tomography (PET). H_1 receptor binding was measured in 10 normal subjects and 10 medicated schizophrenic patients by PET and [^{11}C] doxepin, a radioligand for the H_1 receptor. The binding potential (BP=Bmax/K_D) of [^{11}C] doxepin for available brain H_1 receptors was calculated by a graphical analysis on voxel-by-voxel basis and compared between schizophrenics and normal subjects using the regions of interest (ROIs) and the statistical parametrical mapping (SPM99). BP values for H_1 receptors in the frontal and prefrontal cortices and the cingulate gyrus were significantly lower among the schizophrenic patients than among the control subjects. On the contrary, there were no areas of the brain where H_1 receptors were significantly higher among the schizophrenic patients than the control subjects. The results of our study suggest that the central histaminergic neuron system could be involved in the pathophysiology of schizophrenia, although further studies are needed to confirm this hypothesis.

Keywords: Schizophrenia; Histamine; H_1 receptors; [^{11}C] doxepin; Receptor imaging; Histamine neurons; Positron emission tomography

1. Introduction

The central histaminergic neuron system originates from the tuberomamillary nucleus of the posterior hypothalamus and modulates a variety of brain functions such as sleep–awake cycle, appetite control, seizures, learning, memory, aggressive behavior, and emotions (Schwartz et al., 1991; Wada et al., 1991; Brown et al., 2001; Watanabe and Yanai, 2001; Haas and Panula, 2003). It has also been reported that fibers of histamine neurons are extensively projected within the limbic system and neocortex where the highest density of terminals is encountered. The histaminergic neuron system has at least four different receptor subtypes: H_1, H_2, H_3, and H_4 receptors. Presynaptic histamine H_3 autoreceptors have been originally found to regulate histamine synthesis and release (Schwartz et al., 1991; Brown et al., 2001). Histamine H_3 receptors have also been reported to be located in the nerve terminals of other neurons and to regulate the release of other neurotransmitters as heteroreceptors (Hill et al., 1997). Although the clinical importance of histaminergic drugs in the treatment of neuronal and mental disorders has been proposed (Prell and Green, 1986; Schwartz et al., 1991; Watanabe and Yanai, 2001), their possible involvement in psychiatric disorders has not been well clarified.

To date, various radiotracers have been used with positron emission tomography (PET) to visualize specific neurotransmission in the living human brain. We previously visualized the distribution of histamine H_1 receptors in the living human brain using PET and [^{11}C] doxepin, a

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radioligand for the H_1 receptor. Using this technique, we revealed the age-related decline of histamine H_1 receptor binding and its correlation with the cognitive deficits observed in Alzheimer's disease patients (Higuchi et al., 2000). We also reported the interaction between histamine H_1 receptor occupancy and cognitive impairment induced by sedative antihistamines (Yanai et al., 1995; Okamura et al., 2000; Tagawa et al., 2001; Tashiro et al., 2004).

There is some evidence that the histaminergic neuron system is implicated in the pathophysiology of schizophrenia (Rauscher et al., 1980). Indeed, a significant increase in the level of N^{τ}-methylhistamine was found in the cerebrospinal fluid of schizophrenics when compared to controls (Prell et al., 1995). In addition, in postmortem binding studies using ^{3}H-mepyramine as a ligand, Nakai et al. found that the number of histamine H_1 receptors in the frontal cortex of schizophrenics was reduced (Nakai et al., 1991). Although previous findings have suggested that the high activity of brain histamine synthesis or release could be related to schizophrenia, no report has investigated the measurement of brain H_1 receptors in schizophrenic patients in vivo.

In this study, the distribution of histamine H_1 receptors in schizophrenics was compared to that in normal subjects. We measured cerebral H_1 receptor binding by PET and [^{11}C] doxepin in 10 patients with schizophrenia and in age-matched 10 normal subjects using the same methods used in the studies of H_1 receptor occupancy.

2. Methods and materials

2.1. Subjects

Ten male patients with schizophrenia and ten normal male volunteers with no neurological abnormalities were enrolled in this study. The schizophrenic subjects were diagnosed according to the diagnostic and statistical manual of mental disorders (DSM)-IV criteria from the clinical services affiliated with Tohoku University Hospital. Psychopathology was assessed by means of brief psychiatric rating scale (BPRS) as shown in Table 1. Patients with psychiatric disorders other than schizophrenia were excluded based on conventional unstructured interviews and each patient medical history. All patients had physical, neurologic, blood, urine, and radiological examinations to exclude other diseases. Healthy control subjects were recruited through advertisement. Based on unstructured psychiatric screening interviews, the control subjects were free of and never had any psychiatric or major medical diseases, had no relatives with neuropsychiatric disorders, and showed no anatomical abnormalities according to MRI images. All schizophrenic patients were treated with haloperidol. Nine patients were treated for akathisia with biperiden, and five patients were treated for insomnia or anxiety with benzodiazepines [flunitrazepam (two patients), brotizolam, cloxazolam, and quazepam (one patient each)]. The average age of the patients and controls (means±S.D.) was 29.4±6.1 (20–38) and 29.9±7.9 (21–43), respectively. The subjects were given a description of the study, and a written informed consent was obtained from each subject. This study was approved by the Ethics Committee of Tohoku University School of Medicine and was performed in accordance with the policy of the Declaration of Helsinki.

2.2. PET measurement

PET measurements were performed at Tohoku University Cyclotron Radioisotope Center using SET2400W (Shimadzu Inc., Kyoto, Japan) scanner in three-dimensional mode. The SET2400W scanner collected 63 simultaneous transverse slices with a spatial resolution of 4 (transaxial) and 4.5 mm (axial) full width at half maximum (FWHM) in the center of the field of view (FOV) (Fujiwara et al., 1997) and sensitivity for a 20-cm cylindrical phantom of 48.6 k.c.p.s.kBq^{-1} ml^{-1} in the 3D-mode. Following Ge/Ga transmission scan, dynamic PET images were obtained for 90 min (sequential 22 frames; 90 s×6 frames, 180 s×7 frames, 5 min×6 frames, and 10 min×3 frames) after intravenous injection of [^{11}C] doxepin. [^{11}C]-doxepin-injected dose and its specific activity at the time of injection were approximately 180 MBq and 74 (mean of n=20; range, 20–210) TBq/mmol, respectively.

Table 1
Clinical features of the 10 schizophrenic patients

Patient no.	Age	Morbidity period (years)	Antipsychotics (haloperidol/day) (mg)	Anticholinergics (biperidenl/day) (mg)	Benzodiazepines (mg)	BPRS score
1	38	16	1.5	1	Brotizolam (0.25)	10
2	21	2	3	2		15
3	29	3.5	1.5	1		20
4	30	3	6	2	Cloxazolam (2)	24
5	36	10	5	8		11
6	26	9	15	4		26
7	31	1	9	3	Quazepam (15)	27
8	29	12	4.5	3	Flunitrazepam (2)	14
9	36	19	2.5			29
10	20	2.5	9	6	Flunitrazepam (1)	17

Age at PET scan, morbidity periods, daily dose of antipsychotics / anticholinergics / benzodiazepines, BPRS scores for each patient are listed.

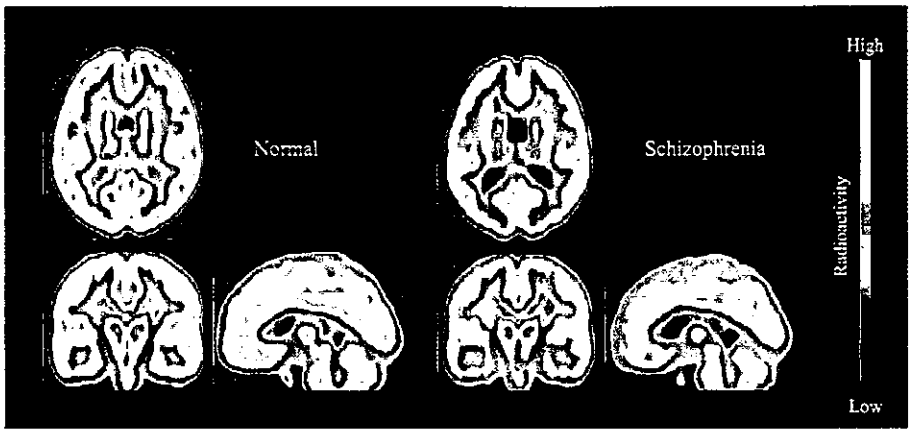

Fig. 1. Brain distribution of [^{11}C]-doxepin radioactivity in schizophrenic patients and healthy control subjects. Averaged PET images are shown at the corresponding levels. The images were obtained 45–90 min after intravenous injection of [^{11}C] doxepin.

[^{11}C] doxepin radiochemical purity was more than 99%. The specificity of doxepin binding was previously confirmed using the histamine H_1 receptor gene knockout (H_1KO) mice (Inoue et al., 1996). In that study, more than 95% of specific binding of doxepin in the brain was lost in H_1KO mice at lower ranges of doxepin concentration, suggesting that [^{11}C] doxepin binding in the human brain almost reflects the binding to histamine H_1 receptors.

2.3. Image analysis for measurement of histamine H_1 receptor in schizophrenic patients

Binding potential (BP=Bmax /K_D) values of [^{11}C] doxepin for available brain histamine H_1-receptors in the schizophrenics and control subjects were calculated using a previously reported method of H_1 receptor occupancy (Yanai et al., 1995; Okamura et al., 2000; Tagawa et al., 2001; Tashiro et al., 2004). Parametric neuroimages that present the distribution volume (DV=K1/k2) for [^{11}C] doxepin were generated by Logan's graphical analysis (Logan et al., 1990). Regions of interest (ROIs) were placed on the cerebellum as a reference region for the neuroimages of DV, and the neuroimages of BP were constructed by subtracting 1.0 from the value in each voxel divided by the cerebellar ROI value according to the method described previously (Carson et al., 1998; Higuchi et al., 2000). To compare BP values of [^{11}C] doxepin for available brain histamine H_1 receptors between the schizophrenic patients and the controls, the parametric neuroimages of BP obtained by SET2400W scanner were analyzed statistically on a voxel-by-voxel basis using a statistical parametrical mapping software (SPM99; Wellcome department of Cognitive Neurology, London, UK) according to the method of Friston (Friston, 1995). Images of the distributed radioactivity after injection of [^{11}C] doxepin were matched to the regional cerebral blood flow template, which conformed to the standard anatomical space (Talairach and Tournoux, 1988), and estimated parameters for spatial normalization were applied to each neuroimage of BP. The images were then smoothed by an isotropic Gaussian kernel with FWHM of 16 mm. Differences in parameter values between the schizophrenic patients and the controls were statistically analyzed by the paired t test without any corrections for the global value.

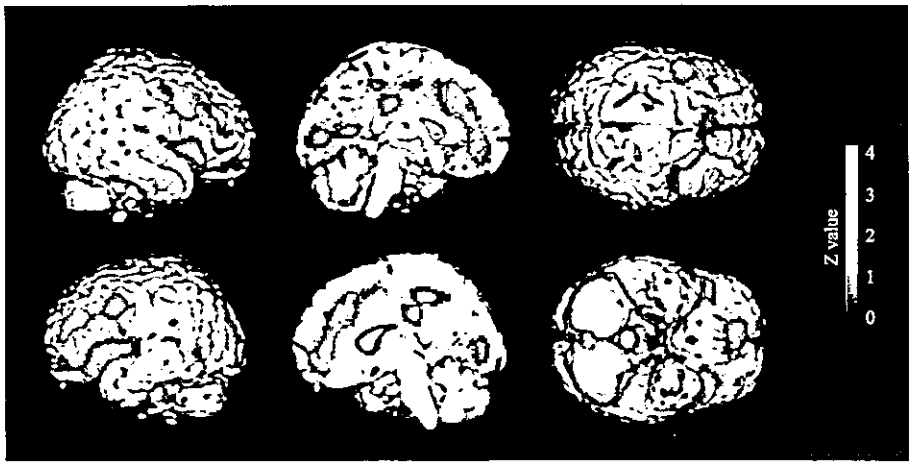

Fig. 2. Brain distribution of [^{11}C]-doxepin radioactivity in schizophrenic patients and healthy control subjects using SPM99. The colored areas show areas where BP values of [^{11}C]-doxepin in schizophrenic patients were significantly lower than those in the control subjects (p<0.001, uncorrected).

In addition to the analysis of parametric neuroimages of BP, ROI-based analyses were conducted to evaluate brain histamine H_1 receptor binding capacity. Values of BP were obtained from ROIs placed on the frontal cortex, the anterior/posterior cingulate cortex, and the thalamus in the images. Each ROI was set using an initial PET image (0–45 min after [^{11}C] doxepin injection), which reflected an image of cerebral blood flow. The values in each ROI were then compared between the schizophrenic patients and the controls using ANOVA with Bonferroni correction.

3. Results

3.1. Distribution of [^{11}C] doxepin in the brain of schizophrenic patients

Averaged PET images obtained 45–90 min after intravenous injection of [^{11}C] doxepin are shown in Fig. 1. High radioactivity was observed in the frontal, temporal, and occipital cortices, the cingulate gyrus, striatum, and thalamus in the normal subjects. On the other hand, the distribution patterns of radioactivity in the cortical areas of schizophrenic patients were apparently lower than those of the control subjects.

3.2. Comparison of parametric neuroimages of BP values between schizophrenic patients and control subjects

Parametric neuroimages of BP of [^{11}C] doxepin in the schizophrenic patients and in the control subjects were constructed by graphical analysis and statistically compared using SPM99 on a voxel-by-voxel basis (Fig. 2; Table 2).

Table 2
Regional maxima showing significant differences in BP values estimated by SPM99 between schizophrenic patients and the controls ($p<0.001$, uncorrected)

Area	(Brodmann area)	Side	Z -score	Talairach coordinates		
				x	y	z
Gyrus frontalis medialis	(8)	L	4.37	−10	32	44
Gyrus frontalis inferior	(47)	L	4.33	−28	30	−12
Gyrus frontalis medius	(9)	L	4.05	−28	42	36
Gyrus frontalis medius	(6)	L	3.95	−46	4	46
Gyrus frontalis inferior	(47)	R	3.87	46	26	−2
Gyrus occipitalis medius	(19)	L	3.69	−50	−60	−4
Gyrus lingualis	(18)	R	3.54	16	−82	0
Precuneus	(7)	R	3.53	16	−34	50
Gyrus frontalis medialis	(6)	L	3.46	−12	−8	48
Precuneus	(7)	L	3.43	−14	−36	48

The colored areas show areas where BP values in the schizophrenic patients were significantly lower than those in the control subjects. In addition, histamine H_1 receptors density was significantly low in the cortices, especially the frontal and prefrontal, and the cingulate gyrus, which are known to be H_1-receptor-rich regions. In contrast, SPM99 analysis could not detect any area where BP values were significantly higher in the schizophrenic patients than in the control subjects. In the schizophrenic patients, there was no brain region, estimated by either SPM99 or ROIs, in which binding potential values significantly correlated with the score of BPRS total or positive/negative symptom subscale (data not shown). Moreover, there was no brain region in which binding potential values significantly correlated with the dose of the treatment drug—haloperidol, biperiden, or benzodiazepines (data not shown).

3.3. ROI-based comparison of BP values

BP values in the prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex, and thalamus were evaluated using ROI-based analysis (Fig. 3). BP values in the schizophrenic patients were significantly lower than those in the controls in the prefrontal cortex and cingulated cortex. These results are essentially consistent with the results of SPM analysis.

4. Discussion

H_1 receptors estimated on a voxel-by-voxel basis using SPM99 were significantly lower in several brain areas of the schizophrenic patients than in the normal subjects. Similarly, H_1 receptor bindings evaluated using ROIs placed on the prefrontal cortex and the anterior and posterior cingulate gyrus were significantly lower in the schizophrenic patients than in the normal subjects. Although two different approaches for imaging analyses, SPM99 and ROI-based analyses, were used, the results are quite similar. These results are generally consistent with those of histamine H_1 receptor binding assays in post-mortem schizophrenic brains (Nakai et al., 1991). The present study demonstrates for the first time the decrease of histamine H_1 receptor density in the brain of schizophrenic patients in vivo by PET, although a careful interpretation of our results is needed.

Our PET studies confirm the results of a previous autopsy study on histamine H_1 receptor binding. Mancama et al. (2002) reported a weak independent association between variants at the histamine H_1 receptor gene-1536-G/C locus and schizophrenia, with an excess of the H_1-1536-C allele observed among schizophrenics. However, this association was no longer statistically significant upon correction for multiple testing, and the authors concluded that this H_1 polymorphism promoter is unlikely to have effect on the histamine H_1 receptor, particularly in view of

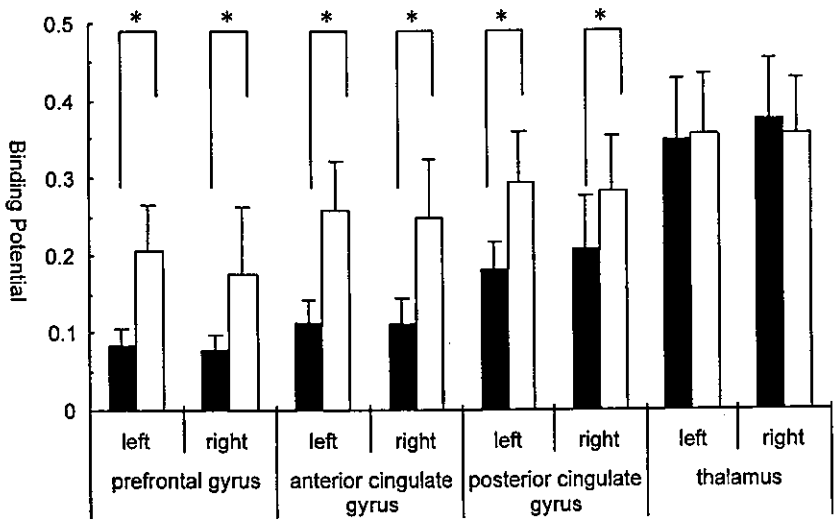

Fig. 3. ROI-based analysis of histamine H_1 receptors in the prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex, and thalamus. BP values (means±S.D.) for the schizophrenic patients (■) and the controls (□) are shown. *$p<0.05$ statistical significance.

its apparent lack of function and influence on receptors expression (Mancama et al., 2002). These findings on the histamine H_1 receptor in the brain of schizophrenics indicate that histamine H_1 receptors are decreased in schizophrenics and that this decrease might not be caused by the H_1 polymorphism promoter.

In other studies on the metabolites of histamine in schizophrenics, a significant increase in the level of N^{τ}-methylhistamine, the primary metabolite of histamine and an index of brain histaminergic activity, was found in the cerebrospinal fluid of schizophrenics when compared to controls (Prell et al., 1995). In addition, the level of N^{τ}-methylhistamine was significantly related to the severities of schizophrenics symptoms (Prell et al., 1995). In contrast, no significant differences in C314T and CA-repeated polymorphisms of the histamine *N*-methyltransferase gene, which affects histamine *N*-methyltransferase activity, were found between schizophrenics and controls (Yan et al., 2000). These findings suggest that there is increased histamine release from the presynaptic sites of histamine neurons in schizophrenics. From the findings of decreased histamine H_1 receptors in schizophrenics, we hypothesize that a down-regulation of histamine H_1 receptor expression could be caused by increased presynaptic histamine release from central histamine neurons. Although we did not confirm the correlation between BP values and BPRS scores, it might be probably due to a small number of subjects.

It cannot be ruled out that the observed decrease in histamine H_1 receptors binding might be attributed to the effects of patient's medication such as antipsychotics, benzodiazepines, and anticholinergics as these drugs might bring about changes in the histamine H_1 receptor bindings. Indeed, it has been reported that haloperidol has very low affinity for the histamine H_1 receptor in the human brain. In addition, Richelson and Souder reported that the equilibrium dissociation constant (K_D) for haloperidol at H_1 receptor is 260±20 nM (Richelson and Souder, 2000). Moreover, in competition experiments for the high-affinity binding site of [^{3}H] doxepin (0.1 nM), the K_D values obtained for haloperidol was considerably high (1.7±0.5 μM) (Kanba and Richelson, 1984). It has also been reported in the same study that the K_D values obtained for benzodiazepines, such as alplazolam or nitrazepam, and anticholinergics, such as atropine or benztropine, in competition experiments for the [^{3}H] doxepin were much higher than the K_D value for haloperidol. Therefore, the concomitant use of these drugs might not change the results of PET study using [^{11}C] doxepin as a ligand because, in our study, there was no brain region where binding potential values significantly correlated with the dose of concomitant drugs.

The PET findings of this study are preliminary and require replication because of the relatively small number of subjects and the problem of patients medication. However, the present study clearly demonstrates a decrease of histamine H_1 receptors in chronic schizophrenics by PET. It is speculated that neuronal histamine functions as a bioprotective system against various noxious and unfavorable stimuli such as convulsion, nociception, drug sensitization, ischemic lesions, and stress (Watanabe and Yanai, 2001). There is evidence that implicates brain histamine in animal models of psychosis and schizophrenia (Ito et al., 1997; Morisset et al., 2002). We have also previously reported that the histaminergic neurotransmission was changed in social isolation stress (Dai et al., 2004) and food-deprived activity stress (Endou et al., 2001). The decrease of H_1 receptors observed in the schizophrenic patients in this study would be a consequence of down-regulation caused by excessive histamine release from histamine neurons. Here, we propose that histamine neurons have an inhibitory role on the development of stress vulnerability or schizophrenic symptoms. To confirm this, further studies, particularly studies of drug-naïve patients, are needed.

Recently, Pillot et al. reported that acute administration of ciproxifan, a histamine H_3 receptor antagonist/inverse agonist, potentiates the neurochemical and behavioral effects of haloperidol in the rat (Pillot et al., 2002). These results suggest that histaminergic neurotransmission may be involved in the pathophysiology of schizophrenia and that dysfunction of the histaminergic neuron system might be important as one of the extradopaminergic functional abnormalities in the schizophrenic brain. Therefore, activation of the histaminergic neuron system might be useful for the treatment of schizophrenia.

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特集：この14年間の生物学的精神医学の進歩

285-291

統合失調症の異種性
——オーダーメード医療を目指して——

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抄録：薬物療法や心理社会療法などの治療方法の発展とともに，精神医療でのオーダーメード医療が求められるようになってきた。そのためには，最初に患者個人の特徴と直接関連する疾患の異種性を明らかにする必要がある。そこで，統合失調症を取り上げて異種性の病態構造を検討した。その結果，統合失調症を複数の異なる疾患の集合体とみるのではなく，複数の異なる病態生理過程の複合体（"病態複合体"）とみることが妥当と考察した。病態複合体を反映する複数の有力な臨床指標を用いて病態を定性化，定量化することで，個人ごとに病初期から長期経過を予測し適切な治療法を選択できるようにすることが今後求められる。

脳と精神の医学 14(4)：285-291，2003

Key words：heterogeneity, order-made medicine, schizophrenia, cognitive dysfunction

1．はじめに

これからの先進医療では，再生医療と遺伝子治療を組み合わせて行う個別医療 personalized medicine（オーダーメード医療またはテーラーメード医療）が期待されている。精神医療ではどうであろうか？　もちろん再生医療も遺伝子治療も今のところ非現実的で，当分は薬物療法と心理社会療法が中心となる。精神医療は経過を見ながら考える医療で，何らかの治療行為を行いその結果をみて軌道修正をして理想的な治療に近づけていくというのが現実であろう。確かに，最近では治療アルゴリズムやEBMが精神医学に浸透してきたが，初めて精神科を受診してきた患者の特徴からその後の経過を正確に予測して，最善の治療を選択するということまではできない。しかし，内因性精神疾患では異種性が推定されており，本来，精神医療はオーダーメード医療を積極的にめざさなければならない。

ここでは，生物学的精神医学の立場から統合失調症を取り上げて，精神医療におけるオーダーメード医療の可能性について異種性の観点から考察したい。

Heterogeneity of schizophrenia：towards an order-made medicine

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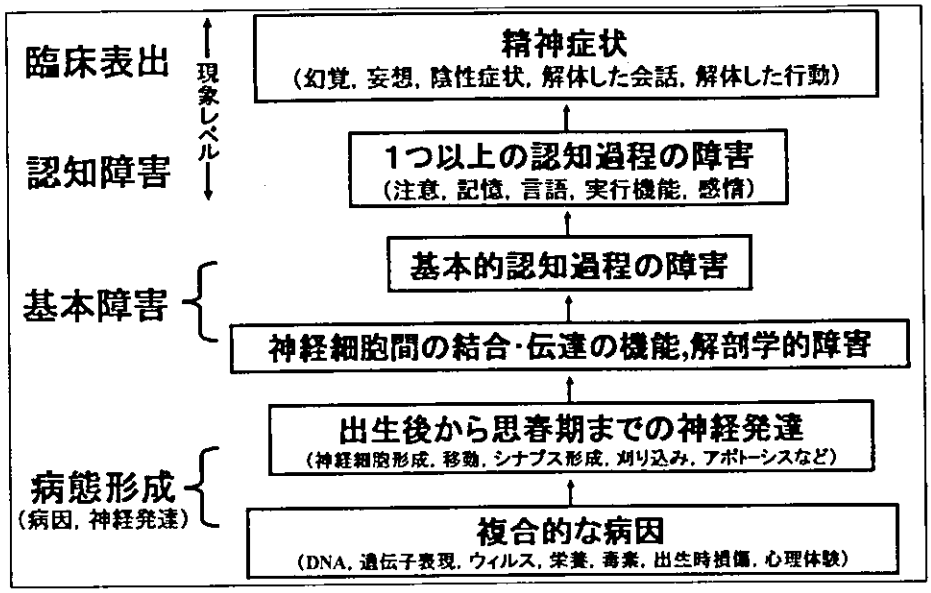

図1 統合失調症の病態モデル
Andreasen[1]によって提唱された統合失調症の病態を，病態形成，基本障害，認知障害，臨床表出のレベルごとに示している。ここでは認知障害を，基本的な認知障害と可視的な認知障害とに分けている。異種性は各レベルでの多様性に内在する。

2．異種性の認識

統合失調症の発病年齢，発症様式，臨床症状，経過，予後，治療反応性などの臨床特徴は極めて多様である。縦断的特徴をとってみても，M. Bleuler の長期経過研究[2]でよく知られているように，発症様式，途中経過，予後などの特徴によって多くの経過型に分類される。横断的特徴に関しても，かつては基本症状として「思考障害」，「感情・意欲の障害」または「知覚・注意障害」が提唱されたこともあったが，全例に共通する症状は存在しない。さらに，病因，神経画像，神経病理などに関する研究成果を見てもすべての患者に共通するものは見つかっていない。したがって，病因から臨床像そして神経病理までのすべてが合致するような単一の疾患単位として統合失調症をとらえることには困難があり，統合失調症は異種的な疾患であることが推測されてきた。

一方で，従来の妄想型，緊張型，破瓜型，単純型などの亜型分類は縦断的にみると相互に移行がありうるため[5,15]，疾病分類として用いるには限界があった。1980 年代には，Andreasen による病態の連続体としての陽性統合失調症，陰性統合失調症，Crow による脳の構造変化の有無によるタイプⅠ，タイプⅡなどの分類が登場したが，陰性症状と陽性症状の単純な二分法には限界があり[10]，統合失調症をいくつかの疾患に分類する試みは十分な成果をあげることができなかった。

以上のように，臨床的には異種性が支持されるにもかかわらず，統合失調症“群”において疾患単位を見つけだせないできたところに，統合失調症の異種性の難しさがある。

3．異種性を決定するレベル

図1は，Andreasen[1]によって提唱された病態モデルを簡略に示したものである。病因には遺伝要因と環境要因が関係し，思春期まで続く神経発達に影響を与える。これは，特定の神経ネットワークにおける神経細胞間の解剖学的・機能的な結合異常という病態に帰結し，認知機能の障害を

引き起こして基本障害が形成される。そして，最終的には可視的な認知障害や臨床症状が出現するというものである。彼女は基本障害として認知的ジスメトリア cognitive dysmetria という概念を提唱しており，統合失調症を統一的にとらえようとしている。しかし，これは必ずしも単一の疾患単位を意味するものではない。異種性は，以下に述べるように病態形成，基本障害，認知障害，臨床表出のあらゆるレベルにおける多様性に内在すると考えることができるからである。以下にそれら各レベルでの知見を簡単にまとめる。

統合失調症の病因は，多くが遺伝要因と環境要因（生物学的なものから心理社会的なものを含む）との相互作用で形成される“多因子病”と考えられている。さらに，遺伝的要因に関しては大半が孤発例で複数の遺伝子異常により規定されるとみなされ[7]，本疾患は多因子・多遺伝子疾患といえる。ただし，例外的に家族内集積をみるような単一遺伝子によるメンデル遺伝を示す稀な一群の存在が知られており，また一方で，臨床的には遺伝要因が関係しない“二次性統合失調症”[9]も含まれる可能性がある。次に，環境要因には，胎生期のウィルス感染症や栄養状態，出生時脳損傷，出生後の心理体験（親との別離，幼少期の被虐待，ストレスの強い環境）などさまざまな要因が発病に関わることがわかってきた。いずれにせよ，病因としての遺伝要因も環境要因もそれぞれ多様であるため，統合失調症の病因は単一とは言い難い。

疾患の基本障害（脆弱性）は，特定の神経ネットワークに関連する上述の遺伝要因が，環境要因の影響下で神経発達過程を通してその神経ネットワークの機能的・解剖学的異常を引き起こし形成される（図1）。しかし，神経画像や神経病理の知見をみてもさまざまな部位の異常が報告されており，少なくとも統合失調症をある限られた脳部位の異常によって説明することには無理がある。こうした知見を統合するために，背外側前頭前野・内側側頭葉結合障害[20]，前頭葉・線条体・視床ネットワーク障害[16]，皮質・視床・小脳ネットワーク障害[1]などの神経ネットワークの異常が提唱されている。この場合，臨床特徴などの多様性は，神経ネットワークにおける異常の程度や広がりで決定されることになるだろうが，今のところそれが統合失調症全例に共通したものかどうかは明らかになっていない。

基本障害の現象レベルとして，最近では精神症状の基盤に認知障害の存在が想定されている（図1）。それは，知覚・注意，言語，記憶，実行機能，感情など広範な認知機能領域に及ぶが[13]，ここにおいても全例が均一な認知障害を示すわけではない。ただし，神経心理の研究から，広範な障害の中でも記憶，学習の障害[18]あるいは記憶，注意，実行機能の障害[6]が，主要な障害として挙げられている。しかし，方法論や検査感度に関する神経心理検査固有の問題もあり，神経画像や精神生理学の手法を組み合わせて認知機能の時空間的データも解析することが今後重要となるだろう[8]。

精神症状に関しては，最近の多くの統計学的研究から，統合失調症状は幻覚・妄想，解体症状（形式的思考障害，不適切感情），陰性症状など少なくとも三つ以上の症状群に区別されることが指摘されている[17]。局所脳血流研究においても，三症状群はそれぞれ異なる血流パターンを示すことが示されている[11]。経過の多様性については前項で述べた。

4．異種性に関する試案

図2は，前項でのまとめをもとに各レベルでの異種性の組み合わせを示している。精神症状と病態形成については異種的と仮定して，認知障害と基本障害のレベルを検討した。認知障害のレベルでも異種性が存在する可能性があり図2のAは否定的で，一方，異種性という言葉によって単純にイメージされる図2のDについては，疾患単位としての亜型の存在が今のところ明らかになっておらずこれも否定的である。したがって，図2のB，Cのように，異種性は複数の異なる病態生理過程によって形成される病態複合体[3,4]とみなすことが理解しやすい。

同様に，Carpenter らのグループ[3,4]は統合失調症の病態生理過程について三つのモデルを挙げて

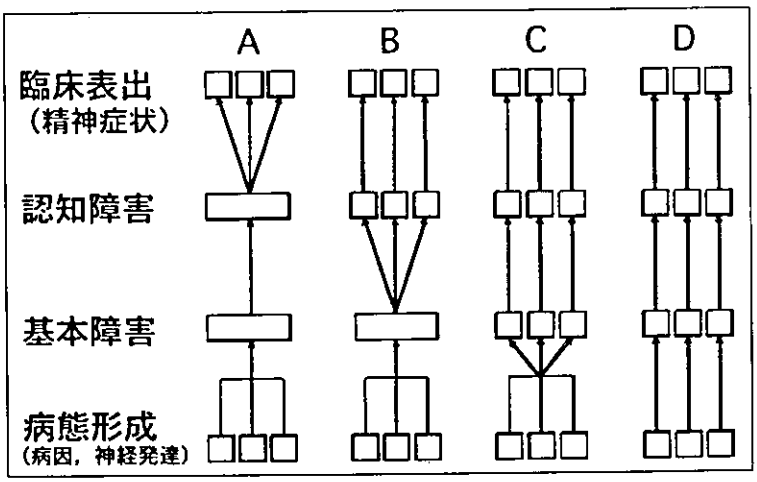

図2　異種性の構造
臨床表出と病態形成を異種性と仮定して，認知障害と基本障害の異種性の組み合わせを示している。BとCが有力。

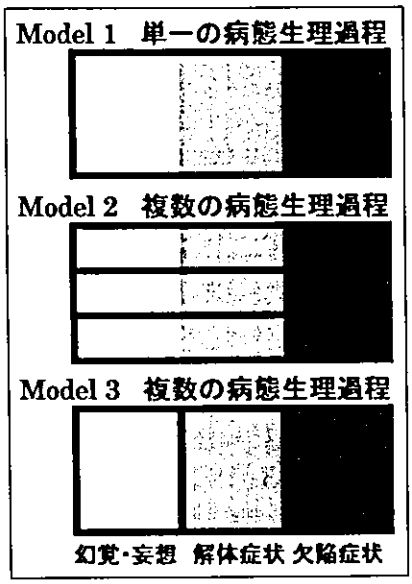

図3　統合失調症の病態生理モデル
Carpenter ら[9]によって提唱された病態生理モデル。モデル3が有力。

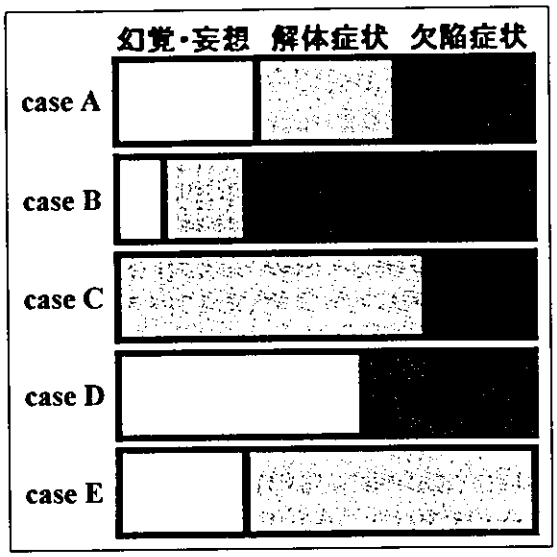

図4　症例ごとの症状異種性
図3のモデル3をもとに，症状の多様性を示している。症状群が単一の場合は省略。

考察している（図3）。モデル1は単一の病理過程がすべてを決定するという考えで，例えば，進行麻痺がこれに該当する（図2には相当するものはない）。この場合の異種性は障害部位，重症度，発病環境，発症年齢などに依存する。統合失調症の病態仮説の中では，狭義の神経発達障害仮説がこれに該当する。モデル2は複数の異なる疾患過程が類似の症状群を形成するという考えで，例えば，精神遅滞がこれに該当する。この場合の異種性は各疾患過程の差異に依存し，疾患分類を想定した従来の亜型分類やE. Bleulerの統合失調症概念に近い（図2のD）。モデル3は複数の異な

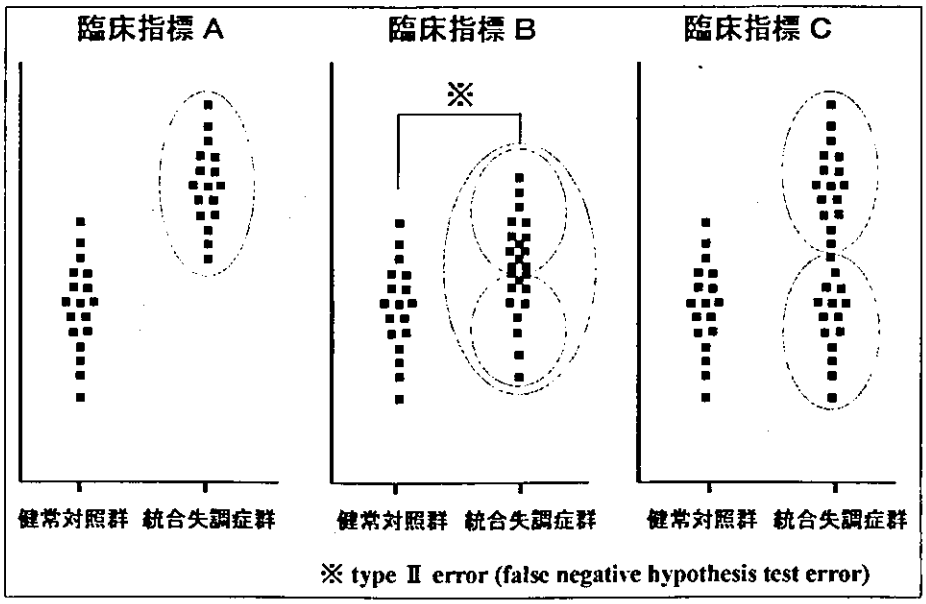

図5　ある臨床指標でみた健常者と統合失調症患者のデータ分布
Aの場合は単一の病態が推定され，Cの場合は複数の病態が推定される。実際は，Bの分布が多く，偽陰性のエラーを避けるためには統合失調症群を二群に分けて検討するのがよい（松岡，松本[14]より引用）。

る病態生理過程が異なる症状群を規定するという考えで，この場合の異種性は各病態生理過程の組合せによって決定される（図2のB，C）。モデル1やモデル2を支持する根拠は乏しく，モデル3が実用的である。

図4は症状プロフィールのいくつかの具体例を示している（一つの症状群だけの場合は省略）。各症状群に対応する病態の臨床指標が確立されれば，個人ごとに病態を評価して適切な治療方法を選択することができる。図5[14]は，ある臨床指標で統合失調症群と健常対照群とを比較したときの，個人データの分布を示している。臨床指標Aは統合失調症が単一の病態の場合に見られる分布だが，現在知られている臨床指標はこうした分布を示すことはない。一方，臨床指標Cは統合失調症が複数の病態から構成されている場合に見られる分布であるが，多くはAとCの中間である臨床指標Bのような分布を示す。この場合に統合失調症群を単一の群と仮定すると統計学的に偽陰性エラーが生じやすいので，これを避けるためには，統合失調症群を仮に二つの群に分けて検討することが有用である[4]。したがって，何らかの臨床指標が見つかった場合に，それが患者全体の特徴なのか，あるいはある一群の患者の特徴なのかを検証する必要がある。逆にネガティブデータが得られたとしても，それが統合失調症のある一群の特徴である可能性を検討するべきである。

5．異種性を考慮したオーダーメード医療

各病態を規定する臨床指標とそれらに対応する治療方法が確立されれば，病初期の横断像の特徴からオーダーメード医療が可能になる。最近では複数の非定型抗精神病薬が認知障害に対して異なる改善作用を示すことが明らかになりつつあり，認知障害のプロフィールに応じた治療薬の選択が今後可能になるかもしれない。基本障害の直接的表現型でありしかも定性性および定量性に優れた認知障害の臨床指標が確立されれば，異種的な“病態複合体”を個人ごとに評価することが可能になるだろう。

縦断像に関しては，再発や陰性症状を規定する

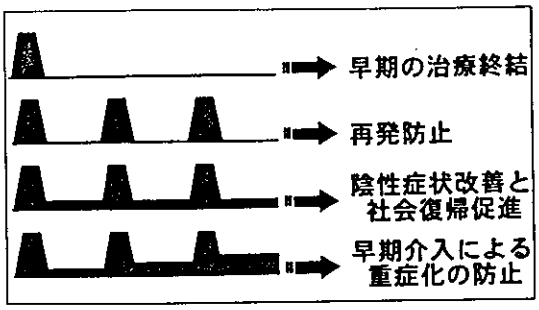

図6　統合失調症の縦断的特徴と治療
Shepherd[19]によって提示された経過特徴を参考にして作成。上から，単一エピソードで寛解する群，再発を繰り返すが寛解する群，再発と再発の間に残遺症状を認める群，再発を繰り返しながら陰性症状などが増悪する群，を示している。

要因，進行性の経過を規定する要因などが明らかになれば，図6のように患者の経過特徴に応じて治療を決めることが可能になる。1のパターンが予想できる症例であれば早期の治療終結の方法について，2であれば再発防止の方法について，3であれば陰性症状の改善と社会復帰促進の方法について，4であれば早期介入による進行性悪化の防止の方法について，とより焦点的な検討が必要となる。具体的な臨床指標（例えば，再発の予測指標）については，他の論文を参照されたい[12,14]。

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特集：生物学的精神医学研究の現状と展望

1-7

統合失調症における認知障害
——東北大学における取り組みを中心に——

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Key words：automatic processing，controlled processing，cognitive dysfunction，event-related potential，schizophrenia

1．はじめに

近年，統合失調症において認知機能の重要性が指摘されている[40]。それは一つには，陽性症状や陰性症状以上に認知障害が患者の社会的・職業的機能の決定要因になることが認識されるようになってきたためである[6][7]。これによって，創薬も含めて認知障害を標的とした治療方法の開発が求められるようになってきた。もう一つは，統合失調症の基本障害が認知障害としてとらえうることが指摘されるようになり[1]，認知障害が精神症状の基盤にあると考えられるため，遺伝子研究などにおける特異性と感受性に優れた表現型マーカーとして有力視されてきたためである。ここでは，東北大学の研究成果を基にして，統合失調症の病態構造における認知障害の位置付けに関する私論を述べたい。

2．認知機能の重要性

統合失調症における臨床症状は，感覚，知覚，思考，記憶，自我意識，感情，意欲，行動など多様な脳機能領域においてある特徴をもって出現する。それらの基本症状あるいは基本障害として，歴史的には注意障害，思考障害，知覚障害あるいは感情障害などのいずれかを重視する考えがあったが，一つの脳機能領域の障害をもってして全てを説明することは困難であった[28][29]。近年の神経心理学を中心とした研究において，様々な認知機能が検討されてきており，統合失調症では知覚・注意，思考，記憶，実行機能など広範囲にわたる多様な認知機能に障害のあることが明らかにされてきた[2][21][26][28][29]。広範な障害の中でも，記憶，

Cognitive dysfunction in schizophrenia with special reference to the research in Tohoku University

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