inhibition of inhibitory GABAergic inputs onto VTA dopaminergic neurons [31] and resultant dopaminergic disinhibition. In both of these cases, modulation of dopaminergic tone by peptides interacting with μ-opioid receptors could well modulate the rewarding influences of blockade of dopamine and other monoamine transporters.

Reduced cocaine reward in OPRM1 knockout mice contrasts strongly with increased locomotor activation after the within-subjects dose–response experiments, which appeared to result from increased sensitization to the locomotor stimulant effects of cocaine. Since OPRM1 knockout did not influence the locomotion elicited by a single high cocaine dose in naïve mice, and since the knockouts did influence the results of the sensitization experiment, the increased locomotor activity observed in within-subjects experiments seems likely to be due to genotype-dependent differences in locomotor sensitization. These increased cocaine-sensitized locomotor responses stand in contrast to the reduced rewarding effects of cocaine in the conditioned place preference paradigm. This increased sensitization also contrasts with literature that equates locomotor sensitization with reward system sensitization described in terms of "craving", relapse of drug-seeking and increased incentive motivation [28,58]. Nonetheless, the present data are consistent with the idea that μ-opioid receptor-dependent processes interact with monoaminergic systems differently in producing reward and locomotor sensitization. We have previously identified striking μ-opioid receptor dependence of morphine-stimulated locomotion and reward using the present mouse strains [66]. The current observations also add to prior data from other knockout and transgenic mice that reveal dissociations between acute psychostimulant effects, conditioned place preference, and locomotor sensitization (Refs. [59,64,67]; Randall, Hall and Uhl, unpublished findings, and see Ref. [70] for an overall discussion).

The mechanisms that might underlie such dissociations between different behavioral actions of cocaine in these knockout mice are unknown, but might very well involve effects on other neurotransmitter systems from either chronic changes in opioidergic function or developmental consequences of such changes. Heterozygous OPRM1 knockout mice display 50% of wild-type μ-opioid receptor expression levels, while homozygous OPRM1 knockout mice have no detectable expression [63]. No changes in other opioid receptors are observed [30]. With regard to potential changes in other systems, initial microarray studies suggest that about 1% of the genes studied changed expression more than twofold in the brains of OPRM1 knockout mice (Liu, Uhl and Hall, unpublished findings). Initial observations also suggested that compensatory changes in dopaminergic systems were not prominent in OPRM1 knockout mice [63], although regional analyses have indicated increases in both dopamine D1 receptor and dopamine D2 receptor mRNAs [53].

These data may have implications for the role of μ-opioid receptors in influencing the sensitivity to different effects of cocaine in humans. Several studies of human individual differences in μ-opioid receptor expression in humans suggest the possibility that trait and/or state differences can produce common ranges of individual differences in expression up to the 50% levels found in the heterozygous knockout mice [17,19]. If these changes are largely mediated through haplotypes in the μ-opioid receptor gene or in genes that act to regulate it, such variants could contribute to the polygenic influences on human differences in various aspects of drug reward, and, conceivably, to human individual differences in addiction vulnerability.

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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.

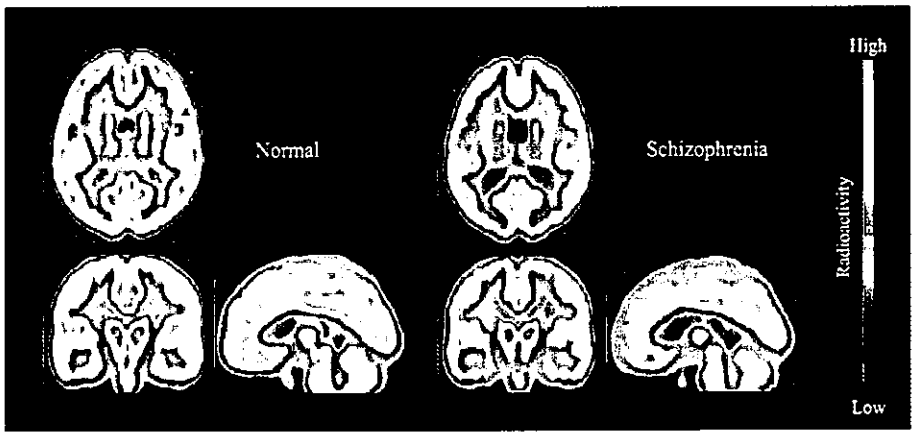

Fig. 1. Brain distribution of [^{11}C]-doxepin radioactivity in schizophrenic patients and healthy control subjects. Averaged PET images are shown at the corresponding levels. The images were obtained 45–90 min after intravenous injection of [^{11}C] doxepin.

[^{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.

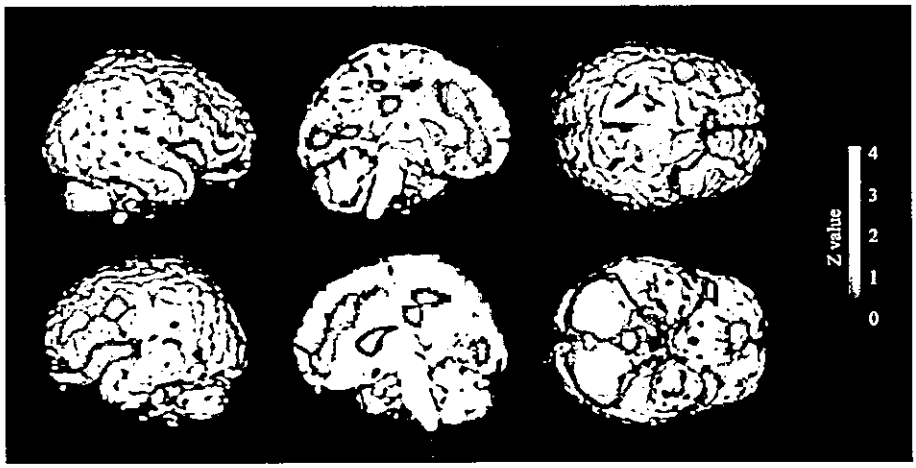

Fig. 2. Brain distribution of [^{11}C]-doxepin radioactivity in schizophrenic patients and healthy control subjects using SPM99. The colored areas show areas where BP values of [^{11}C]-doxepin in schizophrenic patients were significantly lower than those in the control subjects (p<0.001, uncorrected).

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 postmortem 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

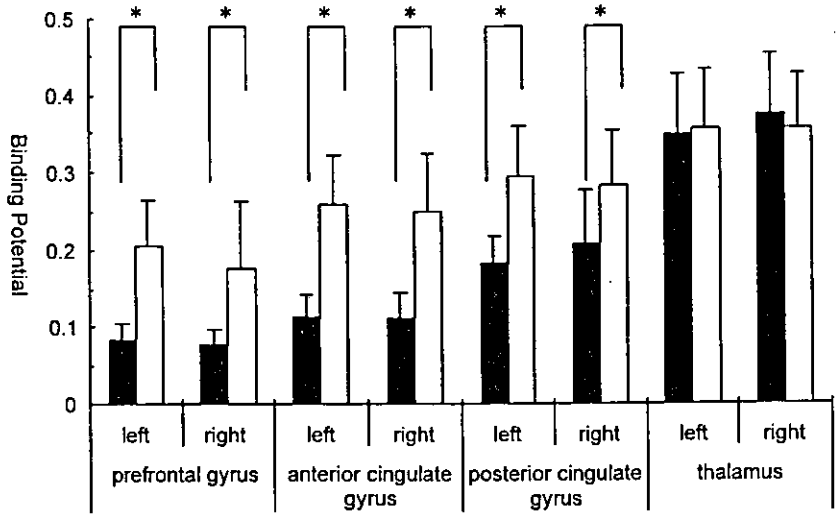

Fig. 3. ROI-based analysis of histamine H_1 receptors in the prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex, and thalamus. BP values (means±S.D.) for the schizophrenic patients (■) and the controls (□) are shown. *$p<0.05$ statistical significance.

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：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[4-10]。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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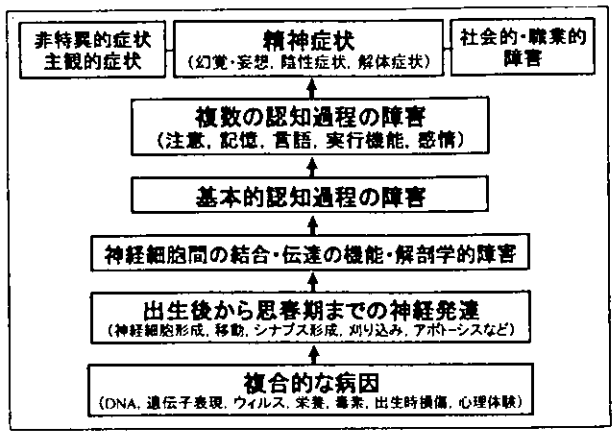

図1 統合失調症の病態モデル.
統合失調症の病態を，病態形成（病因，神経発達），基本障害（機能・解剖学的障害，基本的認知過程の障害），複数の認知過程の障害，臨床表出（最上段）として示している（Andreasen[1]の図を改変）。

学習の障害[39]あるいは記憶，注意，実行機能の障害[5]を中核的な障害として重視する立場もあるが，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まだ確立されていない。統合失調症患者では，包括的な神経心理検査を用いると高頻度にしかもかなりの程度で異常が認められ，それは発病時点で既に存在し寛解しても長期間にわたり持続するものである[26][29][40]。

最近では，上述のような比較的要素的な認知機能を神経認知 neurocognition と呼ぶのに対比させて，社会認知 social cognition という概念が確立されてきた[37]。その根拠の一つは，精神症状の構造を陽性症状評価尺度と陰性症状評価尺度を用いて統計学的に検討した研究により，精神症状が四つあるいはそれ以上の比較的独立した群に分けられる可能性が示されたことである。Peralta ら[36]は，幻覚・妄想，陰性症状（感情と意欲の障害），解体症状（思考形式の障害，不適切な感情）に加えて，従来は陰性症状に含まれていた親密さを感じる能力，対人関係の能力における障害を四番目の症状群（"rational syndrome"）として取り出した。陰性症状と対人関係の障害を分ける試みは以前よりあったが[41]，最近になり"社会認知"という立場から新たな脳科学の研究領域が提唱されている。具体的には，こころの理論 Theory of Mind，帰属スタイル attributional style，社会知覚 social perception（顔の感情認識や社会的手がかりの知覚など）の研究がそれに該当する[37]。

実際，統合失調症患者では，こうした神経認知や社会認知に関係すると推定される主観的な訴えがよく聞かれる。例えば，「集中できない」，「考えがまとまらない」，「他人の気持ちが理解できない」，「仲間を作れない」，「忘れっぽい」，「あたりまえにできた家事や仕事の段取りがわからない」などは，陽性症状や陰性症状以上に患者にとっては深刻なことが多い。患者の主観的症状を評価した研究では，他の疾患と比較しても統合失調症では思考，知覚，体感に関する訴えが多く，それらは思考，言語，記憶，注意の領域の障害によるものと推定される[35]。また，発病や再発の前駆期においても，感情，知覚・注意，記憶，思考，身体や行動の変化など非特異的徴候が頻繁に認められる[2]。こうした，主観的症状や非特異的徴候は，認知障害と臨床表出の関連を検討する上で今後重要となるだろう。

図1は，Andreasen[1]によって提唱された病態モデルを一部改変（最上段を改変）したもので，ここではこれに基づいて認知障害の位置づけをまとめる。病因には遺伝要因と環境要因が関係し，

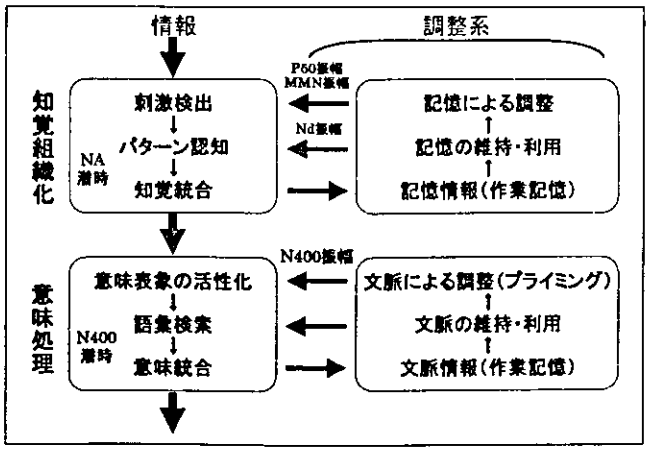

図2　認知障害の病態構造と事象関連電位の関係
単語の意味処理の例で，左列は統御処理過程（知覚組織化と意味処理），右列は統御処理を効率的に行うための自動処理過程（調整系）を示している（松岡，松本[26]の図を改変）。

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。彼女は共通の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いる。詳細は別稿を参照されたい[26)27)29)]。最上段の臨床表出レベルに，非特異的症状・主観的症状および社会的・職業的障害を筆者が加えた。

認知障害は，臨床表出と病態・基本障害のあいだを結ぶ架け橋として位置づけられる。それは社会的・職業的機能も含めた各種の臨床表出を規定する一方で，病態や基本障害と直接的に結びつく表現型でもあり，遺伝子研究のさいの定量性・定性性の優れた表現型マーカーとして有力視されている。さらに，最近では非定型抗精神病薬が認知障害を改善する作用をもつことが指摘され[29)30)31)]，治療標的としても認知障害が重要視されるようになってきた。これに伴いいずれは統合失調症の創薬において認知改善薬あるいは認知増強薬という領域が発展するだろう[4)]。

3．統合失調症における認知機能の評価

欧米における神経心理学研究の隆盛によって，統合失調症の認知機能が包括的，網羅的に検討されており，その結果，知覚・注意，思考，記憶，実行機能にわたる広範な認知障害が明らかにされてきた[21)28)]。さらに冒頭で述べたように，最近では社会認知という観点からの検討もすすんでいる。ここでは，事象関連電位を用いた精神生理学の研究による統合失調症の認知障害について，当教室のデータを中心に紹介したい[25)]。

図2は筆者らの作業仮説である[26)]。外界からの情報を知覚しその意味を処理する一連の過程を示した。情報処理の中心は左列の流れであり，随意的で努力を要する統御処理 controlled processing を意味する。一方，情報処理を効率的に行うために，右列のように様々なレベルで記憶情報を利用して統御処理を調節しているが（調整系），これらは非随意的で無意識的に行われる自動処理 automatic processing である。この図をもとにして事象関連電位の研究を紹介する。

1．統御処理：NA 電位

外界からの情報は，刺激検出，パターン認知，

知覚統合といった一連の知覚組織化過程で処理される。この処理過程は，事象関連電位の一つである処理陰性電位 processing negativity という脳波活動として観察することができる[19]。筆者らは処理陰性電位の一種である NA 電位を用いて，統合失調症での知覚組織化過程を検討した。NA 電位は，標的弁別課題のさいの非標的刺激に対する反応から単純反応課題での反応を差し引きすることで得られる電位である[38]。これは，両反応に共通する刺激の物理的特徴によって誘発される外因性成分と刺激探知までの電位を引算操作で相殺し，刺激探知後の刺激弁別に関連する電位だけを抽出しようというものである。統合失調症では，文字，図形，単語刺激のいずれでも，NA 電位の頂点潜時が遅延している[16][17][32]。この異常は，精神症状と直接関連するものではなく，2 年間の追跡期間における再発の有無と強く関連していることがわかり，知覚・注意の障害が易再発性の臨床指標となる可能性が示唆される[18][20][23]。再発に関する生物学的な脆弱性指標に関する報告は非常に少ないが，Nuechterlein ら[34]も筆者らと類似した課題である持続遂行課題や標的弁別課題を用いそれらの遂行成績が再発の脆弱性指標となることを報告しており，筆者らの結果も併せて考えると再発脆弱性は感覚情報の統合障害と関連していることが推測される。

2．統御処理：N 400 電位

知覚組織化の後にさらに高次の処理を要する場合についてであるが，ここでは単語の意味範疇の処理と関連する N 400 電位を取り上げる。N 400 は，文章の文末語に対する事象関連電位を記録したさいに，その語が期待に一致する場合は P 300 が出現するが，期待に反する意味的逸脱語が提示されると刺激後約 200 msec に起始し 400 msec に頂点をもつ陰性電位として発見された[12]。その後，N 400 は期待と一致する語でも多少なりとも出現し，意味的逸脱語のように意味処理をより必要とするような状況で大きな振幅を示すことがわかった。N 400 は文章のみならず単語を単独で提示することでも出現し，さらに言葉を用いない手話，絵，顔写真でも意味的処理を必要とする場合にも類似の電位が出現し，N 400 は意味処理の指標として確立された。また，同一の単語の繰り返しで N 400 振幅にプライミング効果の生じることが知られており（後述の自動処理を参照），N 400 は記憶処理の指標としても用いられている。詳細は別稿[13][22][25]を参照されたい。

統合失調症では，N 400 頂点潜時の遅延ないし N 400 の延長が認められ，NA 電位も含めて統御処理全体が遅延していることがわかる。しかも，これらの課題では反応時間の延長と誤反応率の増加も見られ，これは，健常者でみられる速度と精度の trade-off 現象（速度が遅いと精度が高くなる）を考慮すると，統合失調症では情報処理内容の質的な異常も伴っていることを推測させる。さらに，NA 電位と N 400 電位の潜時と振幅に関する変数を相互に比較したところ，両者間では関連を認めず，知覚組織化の異常と意味処理の異常は相互に独立的なものと考えられた。

3．自動処理：P 50，ミスマッチ陰性電位

知覚組織化や意味処理に対する調整系（図 2 の右列）を見ると，情報の最初の入力段階における検討では，聴覚刺激を用いた研究がすすんでいる。その一つは，対刺激を行ったさいの第二刺激に対する聴覚 P 50 振幅抑制に関するものである。P 50 は一次感覚野付近で発生する反応と考えられ，視床など皮質下での感覚ゲーティングの影響をうける。P 50 振幅抑制は一種の慣れの現象であり，統合失調症ではこの P 50 振幅抑制に障害があるため，外界の情報が過剰に流入していると解釈される[11]。

もう一つは，ミスマッチ陰性電位を用いた研究である。これは一定の聴覚刺激が提示されている中に物理特性（例　刺激強度，周波数など）の異なる刺激に対して発生する電位で，先行刺激に対する記憶痕跡（感覚記憶）を利用して行われる脳の自動的な刺激偏倚の検出機構と考えられる[19]。統合失調症ではこの電位の振幅が減弱しており，これは，感覚記憶の容量の減少ないし急速な減衰によるもので，最終的には知覚組織化や作業記憶に影響すると推定されている[10]。

以上のように，統合失調症では，外界からの情

報の入力レベルですでに不要な情報を抑制することあるいは必要な情報を獲得することに障害が生じており，情報処理が効率的に行われていないと思われる。

4．自動処理：N 400 反復プライミング

神経心理学の記憶研究では，統合失調症では顕在記憶の障害が強く，一方，潜在記憶の障害はほとんどないとされてきた[21][28]。しかし，神経心理学と比べて検出感度の優れた事象関連電位を用いた研究で，潜在記憶の障害が明らかになってきた[9][24]。筆者ら[14][24]は統合失調症においてN 400振幅に対する反復プライミング効果を検討したが，N 400振幅抑制が出現せず反復プライミング効果が顕著に減弱していた。これは，先行刺激による記憶情報や文脈情報を利用して意味処理を効率的に行うことを可能にするような脳の調整系（作業記憶など）の障害を意味するものである。さらに，このN 400反復プライミング効果は，思考障害評価尺度[42]で客観化した思考障害と関連することが見出されている[15]。

Bosch[3]は精神症状の発現機序に関して，調整的役割をもつ自動的な情報処理の破綻が，統御処理へ過剰な負荷をかけるために症状が発現するという仮説を提唱しており興味深い。筆者らは，脆弱性の病態自体に既に統御処理系と調整系の障害が内在していて，おそらく調整系の破綻とそれによる統御処理へのさらなる負荷が症状発現を導くものと考えている[26]。

4．今後の認知障害研究

統合失調症の病態はある特定の神経ネットワークの障害として理解されるようになってきたが[33]，図2のような情報処理過程を想定しながら障害されている神経ネットワークの機能全体を評価することが今後重要となるだろう。神経心理学の研究は，統合失調症における認知障害の重要性を認識させてくれた。しかし，潜在記憶の例でもわかるように，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，今後は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必要となるだろう[8]。さらに，認知障害を治療標的とするためにも，研究だけではなく実際の臨床に役立てることを目指して，外来や病棟で反復して治療経過を観察できるような簡便な認知機能評価方法を確立することが急務である。

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統合失調症の認知障害と脳波

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Cognitive dysfunction and electroencephalogram in schizophrenia

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要約

神経科学の発展に伴い神経心理学と神経画像研究から統合失調症における認知障害の重要性が認識されるようになってきた。それは、病態論においては臨床症状の基盤となり、一方で、遺伝子研究におけるエンドフェノタイプをはじめとした脆弱性指標ともなりうる。認知機能の中でも、特に患者の社会的・職業的機能を規定する可能性のある"社会認知"は新たな研究領域として注目されている。さらに治療論においては、第二世代の抗精神病薬が認知機能を改善させる可能性があり、これによって患者の長期予後やQOLをも改善させるかを解明する必要がある。認知機能の評価には神経心理検査が多用されているが、時間解像度に優れた脳波、特に事象関連電位検査も有用であり、それと空間解像度の優れた神経画像検査とを相補的に用いることが今後望まれる。ここでは、P50、MMN、Nd、NA、P300、N400などの事象関連電位を用いた研究を紹介し、こうした情報処理から見た統合失調症の病態モデルを提示した。そのモデルには、知覚統合や意味処理などに関わる統御処理システムと、その効率化に関わる主に自動処理としての調整システムとが含まれる。統合失調症では元来その両システムが脆弱で、何らかの原因による調整システムの破綻が、統御システムへの過剰負荷を招き発病するものと仮定される。今後は、こうした情報処理システム全体をより精緻に評価する方法を用いて統合失調症を研究する必要がある。

＜索引用語：統合失調症、認知障害、脳波、事象関連電位＞

1．はじめに

統合失調症に関する最近の臨床研究においては、神経科学の発展を背景にして神経心理学と神経画像における領域の精力的な研究成果によって認知機能の重要性が指摘されてきた[24,54]。それは、認知障害が臨床表現の決定因となる可能性があるだけでなく、一方で基本障害や遺伝子異常の表現型ともなりうる点で、病態論の中核的あるいは架け橋的存在となることがわかってきたためである[33,34,35,36,37]。認知機能の中でも新たな研究領域として"社会認知"という領域が発展し、症候論的にも新たな展開を見せ始めている[10,51]。さらに、治療論においても次のような点で認知機能は重要な位置を占めるようになってきた[36]。それは第一に、先の社会認知とも関連するが、患者の社会復帰に関わる社会的・職業的機能の決定因の中で認知機能が最も大きな影響力をもつことがわかってきたこと、第二に新規抗精神病薬が認知機能に対する改善効果をもつことが示されるようになり、認知機能が治療あるいは創薬の標的となる可能性が指摘されるようになっている。

本稿では統合失調症における認知機能の病態論、症候論、治療論における意義を概説し、それらとの関わりで認知機能の評価方法としての電気生理学（事象関連電位）の現状と将来性について述べたい。統合失調症の神経生理および精神生理の現状に関してはKellyとNuechterleinの優れた総説[23]がある。なお、認知cognitionあるいは認知機能cognitive functionという用語は、精神科診断学、認知心理学、精神病理学、神経科学など様々な領域で異なる意味に用いられている．ここでは、神経科学の趨勢にしたがって、感覚システム，運動の方略と計画，注意，記憶，言語，思考と心像，情動，意識などを広く包含する意味で用いる[13,37]。

2．認知障害と病態論

図1は統合失調症に関するAndreasenの病態仮説[3]を基に筆者が改変したものである[36]。病因としての遺伝要因と環境要因によって思春期まで続く神経発達に影響を与え病態が形成される。そ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

結合異常に帰結し、それが認知障害を引き起こして基本障害が形成される。そして、最終的には現象レベルでの認知障害や臨床症状が出現するというものである。

精神症状に関しては、症状構造の統計学的解析より、陽性症状、陰性症状、解体症状に加えて、これまで陰性症状に含まれていた親密さを感じる能力、対人関係の能力における障害を比較的独立した症状群（"関係症状群 relational syndrome"）とする考えから[50]、関係症状群を図に加えた。さらに、患者の主観的症状を評価した研究では、他の疾患と比較しても統合失調症では思考，知覚，体感に関する訴えが多く[46]、また、発病や再発の前駆期において感情，知覚・注意，記憶，思考，身体や行動の変化など非特異的徴候が頻繁に認められる[4]。こうした主観的症状や非特異的徴候は、認知障害と臨床表出の関連を検討する上で重要と思われ図に主観的症状を加えた。関係症状群と主観的症状は後述する社会認知とも関係する。さらに、社会的・職業的機能を病態論的にも検討する必要があるため図に加えたが、これは認知障害それ自体および精神症状によって影響を受ける[36]。

図１のように，認知障害は統合失調症の病態の中核をなすもので、臨床表出と基本障害のあいだを結ぶ架け橋としての役割をもつ。特に、最近の遺伝子機能研究（ゲノム機能学 functional genomics）では、図２のような方法論が急速に展開している[14,25]。ここでは、統合失調症の候補として挙げられているいくつかの感受性遺伝子を中心とした病態の概念を図１の病態構造に照らして描いた。最下段のカッコ内が候補遺伝子の染色体上の位置で、その上にその遺伝子が関与する生成物を示している。１つの遺伝子異常は統合失調症の全例ではなく一部で認められるもので、ある個人で見ると複数の遺伝子異常の相加的作用が発病に関係してくるが（多遺伝子仮説）、最上段のように同じ複数の遺伝子異常があっても発病しない場合もある（遺伝要因と環境要因による多因子病仮説）。遺伝子と認知機能との対応が明確になると、それは創薬への有力な手がかりとなる。

図２のエンドフェノタイプ endophenotype[14]とはある疾患に関連する遺伝子型によって規定さる認知特性で、通常は脳機能・構造画像、神経心理、精神生理などの手法によって明らかにされるものを示す。障害に先行して一定して見られ、さらに同じ遺伝子をもち発病しない血縁者にも出現する。つまり、エンドフェノタイプは遺伝子異常の直接的な表現型であり、遺伝子の臨床相関を研究するさいに最も注目されている臨床指標である。したがって、実際の臨床表出や行動表現は、遺伝子異常の特徴（つまり、感受性遺伝子群の中のどこに異常があるのか？）と環境要因とによって規定されることになる。なお、環境要因は、図１の最下段にもあるように、胎生期、周生期、出生後にわたる脳に対する直接的侵襲から心理社会的要因まで様々なものが知られている。エンドフェノタイプの有力な指標には、感覚ゲイティング（P50 抑制）、感覚・運動ゲイティング（プレパルス・インヒビション）、眼球運動、記憶を用いた操作機能である作業記憶などがよく知られている[14]。この中でも、これまでの研究からは空間的作業記憶が最有力候補ともいわれている[25]。繰り返しになるが、エンドフェノタイプは発病していない血縁者にも見られる素因脆弱性であり、発病の直接的指標ではないことが重要な点である。つまり素因脆弱性に獲得脆弱性が加わり統合失調症としての病態が出来上がる[38]。

３．認知障害と症候論、治療論

従来、認知障害は知覚、注意、思考、記憶、作業記憶・実行機能といった観点から検討されてきた。認知障害と症候論との関連に関して多くの研究が行われているが、十分に解明