that circulating levels of BDNF are negligible. In addition, Karege et al. [26] also reported that an alteration of serum or plasma BDNF is not due to the change in blood BDNF but rather is probably related to the mechanisms of BDNF release, and that depression results from lowered platelet BDNF release. Moreover, Lommatzsch et al. [30] demonstrated that age, weight, gender, and the menstrual cycle have a specific impact on platelet and plasma BDNF levels in healthy adults. In the present study, however, no association was found between age, weight, and the gender and plasma BDNF levels in depressed patients. In addition, we have demonstrated that no significant correlation was observed between serum levels of BDNF and age, weight, and the gender in 103 healthy volunteer (manuscript in preparation). Taking these findings together, although It still remains controversial whether the plasma levels of MHPG and BDNF reflect those of the brain, we speculate that rTMS influences noradrenergic neurons and BDNF, which might be related to the improvement of depressive symptoms, especially agitation/anxiety. Actually, several reports have demonstrated that exposure to stress induced an increase in the MHPG levels, suggesting hyperactivity of noradrenergic systems [43,47,49] and decreased BDNF mRNA levels [45]. The results in the present study are in accordance with these findings.

We are aware of the limitations of the present study; i.e., our sample size was very small and heterogeneous, and the duration of treatment was not adequate. The most serious problem in the present study is that there was no control group without rTMS (the sham-controlled group), which makes it difficult to attribute the improvements of Ham-D to rTMS rather to a placebo response. In addition, the patients were taking antidepressants. Moreover, neurochemical changes are also not incompatible with a placebo effect, as imaging findings in depressed patients showed that the clinical improvement following placebo treatment was substantiated by regional metabolic changes in the cortical and subcortical regions [33]. Thus, definitively attributing the behavioral or neurochemical changes to rTMS is not possible until these results are replicated in a controlled fashion. In addition, we used antidepressant drugs combined with rTMS treatment, which could not rule out the effects of ongoing drugs on plasma levels of catecholamine metabolites and BDNF. Therefore, further study will be needed to confirm these preliminary findings.

In conclusion, we have found that rTMS results in some improvement and is well tolerated for treatment-refractory depression, especially in those for whom the symptom of agitation is dominant. In addition, the efficacy of rTMS for treatment-refractory depression might be related to its effect on noradrenergic neurons and BDNF.

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Two Cases of Bipolar Disorder Successfully Stabilized for Five Years with a Low Dose of Risperidone and Lithium

R. Yoshimura, N. Ueda, K. Shinkai, J. Nakamura

Two patients with bipolar I disorder were successfully treated with a combination of risperidone and lithium in their acute manic states and maintenance periods. Although lithium monotherapy alone could not prevent relapse in these patients, the addition of a low dose of risperidone was well tolerated and effective for preventing recurrence over the long term. Plasma levels of HVA and MHPG were found to be elevated during the manic episodes and gradually decreased after the risperidone treatment. These results indicate that a low dose of risperidone to the lithium regimen was an effective and well tolerated means for treatment in the acute manic state and the later maintenance period in parallel with decreasing plasma levels of HVA and MHPG.

Introduction

Lithium and valproic acid are the recommended first-line treatments for bipolar disorder [1, 3], but may take up to 2 weeks to take effect. In clinical practice, therefore, a combination treatment with a mood stabilizer and an antipsychotic drug is often used with as many as 90% of subjects with acute mania receiving mood stabilizer and antipsychotic combinations [5]. Recently, augmentation therapy with atypical antipsychotics has been investigated in both acute and long-term treatment of bipolar disorder with or without psychosis [2, 6, 7]. However, observation periods are relatively short in most studies with atypical antipsychotics.

In the present study, we report the cases of two patients with bipolar disorder whose acute manic episodes were successfully treated with a combination of lithium and risperidone. Since we hypothesized that plasma levels of catecholamine metabolites might change during risperidone treatment for bipolar disorder patients as well as schizophrenic patients [11], we also longitudinally investigated the plasma levels of catecholamine metabolites. We discuss the efficacy of this combination therapy for acute or maintenance treatment of bipolar disorder from a pharmacological point of view.

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Measurement of plasma levels of catecholamine metabolites

The plasma levels of homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) were analyzed by high-performance liquid chromatography with electrochemical detection (HPLC-ECD) according to the method of described previously [11].

Case report

Case 1

The patient was a 33-year-old male with a diagnosis of bipolar I disorder without psychotic features according to the DSM-IV. His family history had no remarkable findings. He had his first manic episode at the age of 28. He visited our university hospital and was diagnosed with manic episode with elevated mood, talkativeness, hyperactivity, excitement, aggression, hypersexuality, and insomnia. His score in Young Mania Rating Scale (YMRS) was 30. He was started on lithium carbonate (400 mg/day), which was gradually titrated up to 800 mg/day, and his plasma level of lithium carbonate was 0.8 mEq/l. In order to control his manic symptoms rapidly, risperidone (4 mg/day) was added to the ongoing lithium carbonate therapy. His manic state gradually decreased within 8 weeks (his score in YMRS was 4). His plasma levels of homovanillic acid (HVA) were 11.8, 10.8, 8.4, 8.8, and 8.0 ng/ml at before and 2, 4, 6, and 8 weeks after administration of risperidone, respectively. His plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) were 12.2, 11.8, 10.5, 7.8, and 7.9 ng/ml at before and 2, 4, 6, and 8 weeks after administration of risperidone, respectively. After his manic state had subsided, the risperidone was tapered off, and he was maintained with lithium carbonate (800 mg/day) alone. Two months later, his manic state recurred (his plasma levels of HVA and MHPG were 10.9 and 12.8 ng/ml, respectively; his score in YMRS was 25). Risperidone (2 mg/day) was again added to the ongoing lithium carbonate monotherapy (800 mg/day), and he again recovered from the manic episode (his plasma levels of HVA and MHPG were 8.2 and 9.0 ng/ml, respectively; his score in YMRS was 5). Because he became slightly depressive a month later, and his score in Hamilton Rating Scale for Depression (HAM-D) was 18, risperidone was stopped and only lithium carbonate was continued. His plasma levels of lithium carbonate were stable (0.6–0.9 mEq/l). After one year, he again had a manic episode (his plasma levels of HVA and MHPG were 10.9 and 12.1 ng/ml, respectively; his score in YMRS was 26). Risperidone (2 mg/day) was added to his lithium carbonate treatment (lithium carbonate was increased to 1000 mg/day, and his plasma levels of lithium carbonate were 0.9–1.1 mEq/L). His manic state was remitted within 4 weeks (his plasma levels of HVA and MHPG were 8.1 and 9.1 ng/ml, respectively; his score in YMRS was 5). Thereafter, he was treated with a combination of risperidone (1 mg/day) and lithium carbonate (800 mg/day), and has had no recurrence for a period of more than 5 years. At last measurement, his plasma levels of HVA and MHPG were 8.3 and 8.8 ng/ml, respectively. His body weight and plasma glucose level were constant and no extrapyramidal symptoms were seen during the risperidone and lithium carbonate treatment.

Case 2

The patient was a 34-year-old female with a diagnosis of bipolar I disorder without psychotic feature according to DSM-IV. She had no family history of neuropsychiatric disease. After her divorce at

the age of 28 years, she was in a moderately depressive state for one month (her score in HAM-D was 17), and received no antidepressant treatment. Gradually, she developed into a manic state with elevated mood, talkativeness, agitation, hyperactivity, excitement, high self-esteem, and insomnia (her score in YMRS was 28), and she visited our university hospital at the age of 29. She was commenced on lithium carbonate (400 mg/day), which was gradually titrated up to 1000 mg/day in two weeks later, and her plasma level of lithium carbonate was 0.8 mEq/l. Then, risperidone (4 mg/day) was added to the ongoing lithium carbonate therapy in order to rapidly control her manic symptoms. Her manic state gradually decreased over a period of 8 weeks (her score in YMRS was 4). Her plasma levels of HVA were 8.2, 8.3, 7.8, 7.1, and 6.5 ng/ml at before and 2, 4, 6, and 8 weeks after administration of risperidone, respectively. Her plasma levels of MHPG were 11.8, 10.9, 8.9, 8.7, and 8.5 ng/ml at before and 2, 4, 6, and 8 weeks after administration of risperidone, respectively. After her manic state subsided, the risperidone was tapered off, and she was maintained with lithium carbonate monotherapy (800 mg/day). Ten months later, she became manic again (her plasma levels of HVA and MHPG were 8.4 and 10.9 ng/ml, respectively; her score in YMRS was 25). Risperidone (4 mg/day) was added to her lithium carbonate regimen (lithium carbonate was increased to 1200 mg/day, and her plasma levels of lithium carbonate were 0.9–1.2 mEq/L) and her manic state subsided within 6 weeks (her plasma levels of HVA and MHPG were 6.9 and 8.1 ng/ml, respectively; her score in YMRS was 3). Thereafter, she was treated with risperidone (1 mg/day) and lithium carbonate (800 mg/day), and she has been stable for more than 5 years. At last measurement, her plasma levels of HVA and MHPG were 6.1 and 8.6 ng/ml, respectively. Her body weight and plasma glucose level were constant and no extrapyramidal symptoms were seen during the risperidone and lithium carbonate treatment.

Discussion

In the two present cases, combination treatment with risperidone and lithium was well tolerated and effective for treatment of acute mania and prevention of its relapse over the long term. The plasma levels of HVA and MHPG were elevated during the manic episode and were gradually decreased after risperidone administration for the treatment of acute mania. In addition, the decreases of the plasma HVA and MHPG levels paralleled the improvement of manic symptoms. The plasma levels of MHPG and HVA were raised during the manic state and were maintained at low levels during the remissional state. In both cases, we reconfirmed that lithium monotherapy could not prevent the relapse of the manic episodes of bipolar disorder, even though the plasma levels of lithium were adequate. Furthermore, side effects such as extrapyramidal symptoms, glucose metabolism, and weight gain were not observed during the long-term risperidone treatment. A number of studies have demonstrated that the combination of risperidone and a mood stabilizer was efficacious and well tolerated for the continued treatment of patients who had been initially hospitalized for the management of an acute episode [8] and the results of the present cases are in agreement with these studies. However, we cannot rule out the possibility that risperidone alone would have been effective for preventing the relapse of mania in the present cases. The main strengths of this study were that the follow-up periods were much longer (more than 5 years) than those of earlier studies, and the plasma levels of MHPG and HVA were longitudinally monitored. We also found that addition of the risperidone does not significantly influence the plasma levels of lithium (case 1: the median plasma levels of lithium before and after risperidone administration were 0.7 and 0.7, respectively; case 2: 0.8 and 0.7, respectively). Several reports have demonstrated that pretreatment cerebrospinal fluid (CSF) HVA is elevated in certain groups of manic episodes [9,10]. Mazure and Bowers [4] reported that there is a significant relationship between elevated pretreatment plasma HVA and antipsychotic drug response in mania, and that plasma MHPG has not been as consistent a marker for successful treatment with antipsychotic drugs. Our data are consistent with the results of Mazure and Bowers [4] regarding plasma HVA levels but not MHPG levels. On the other hand, the plasma MHPG levels in these two cases were also elevated during the manic episodes and gradually declined along with the improvement of manic symptoms by risperidone treatment.

In conclusion, we have presented here two cases of bipolar I disorder patients who were successfully treated with a combination of risperidone and lithium in the acute manic state and the later maintenance period. Since the dosage of lithium was increased in both cases (case 1; third manic episode, case 2; second manic episode), the possibility that lithium monotherapy would be effective for these acute manic episodes could not be completely ruled out.

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Case report

Plasma levels of brain derived-neurotrophic factor and catecholamine metabolites are increased during active phase of psychotic symptoms in CNS lupus: A case report

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Abstract

In the present study, the authors reported a case of systemic lupus erythematosus (SLE) with central nervous system involvement (CNS lupus). The authors also longitudinally investigated plasma levels of brain-derived neurotrophic factor (BDNF) and catecholamine metabolites in the patient, and found that plasma levels of BDNF, 3-methoxy-4-hydroxyphenylglycol (MHPG), and homovanillic acid (HVA) were raised in accordance with the severity of psychotic symptoms in this case of CNS lupus. These results suggest that it is useful to measure plasma levels of BDNF and the catecholamine metabolites in order to predict the severity of psychotic symptoms in CNS lupus and to provide a differential diagnosis from that of steroid-induced psychosis.

Keywords: Brain-derived neurotrophic factor; Delirium; Homovanillic acid; Systemic lupus erythematosus; 3-Methoxy-4-hydroxyphenylglycol

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a critical mediator of neuronal development, survival, and function (Lewin and Barde, 1996). In addition, BDNF is currently considered to modulate and regulate immune functions (Vega et al., 2003; Nockher and Renz, 2003). Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by several abnormalities of the cellular immune system, including a loss of B cell tolerance and the production of pathogenic autoantibodies (Shlomchik et al., 1994). Between 18% and 67% of patients with SLE exhibit central nervous system (CNS) involvement (CNS lupus), which is associated with inflammatory features in the brain. Patients with CNS lupus often reveal various psychiatric features such as delirium, cognitive blunting, psychosis, and affective disorder (Warnatz et al., 2003). Since patients with SLE are occasionally treated with corticosteroids, it is difficult to differentiate between CNS lupus psychosis and steroid-induced psychosis (Hall et al., 1979; Lewis and Smith, 1983) in this population. The IgG index and IL-6 levels are used as biological markers of the cerebral activity in patients with CNS lupus (The American College of Rheumatology, 1999). In the present study, we report a case of CNS lupus, in which we longitudinally investigated the plasma levels of BDNF and catecholamine metabolites during active psychotic phases and inactive phases in a patient with CNS lupus. We found that plasma levels of BDNF, free 3-methoxy-4-hydroxyphenylglycol (MHPG), and homovanillic acid (HVA) were elevated in correlation with the activity of psychotic symptoms in this case of CNS lupus.

2. Case report

A 20-year-old woman in a delirious state was admitted to the psychiatric ward at our university hospital. Three months prior to her admission, the patient had been diagnosed with SLE, as based on the presence of antinuclear antibodies, increased DNA binding, photosensitivity, aphthosis, Jaccoud's arthritis, anaemia,

Abbreviations: BDNF, brain-derived neurotrophic factor; SLE, systemic lupus erythematosus; HVA, homovanillic acid; MHPG1, 3-methoxy-4-hydroxyphenylglycol.

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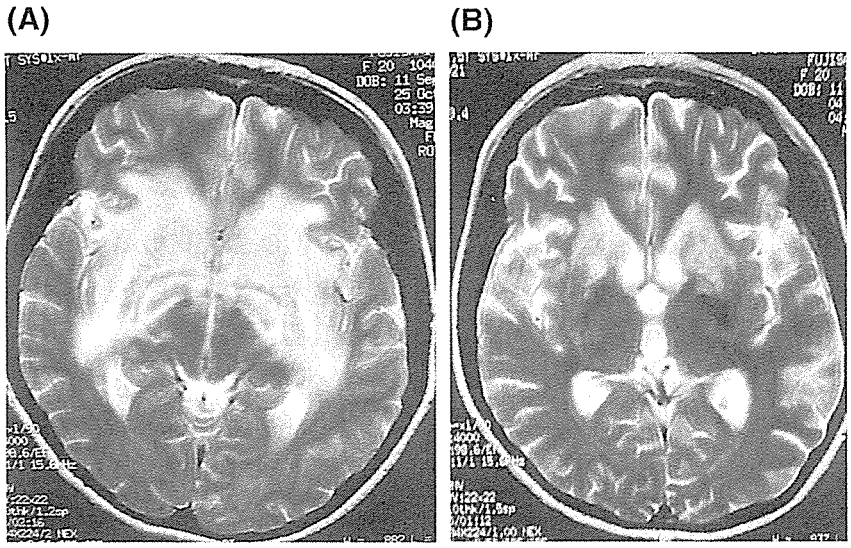

Fig. 1. Sagittal T2-weighted MRI. (A) Day 0, (B) Day 130.

and leucopenia. In addition, a MRI scan showed a large high signal intensity area on T2-weighted imaging in the bilateral basal ganglia and white matter regions (Fig. 1A); moreover the patient's SPECT images showed an area of hypoperfusion area in the same regions (Fig. 2A) (Day 0). The patient's IgG index and the level of IL-6 in her level of cerebrospinal fluid (CSF) were 1.06 and 4.7 pg/mL, respectively. Based on the results of these clinical examinations and imaging studies, the patient was diagnosed with CNS lupus. After the patient had been treated with predonisolone and cyclophosphamide pulse therapy, the clinical course of illness was stabilized. The patient's IgG index and the CSF level of IL-6 were improved to 0.79 and 1.1 pg/mL, respectively (Fig. 3). After stabilization, the cyclophosphamide therapy was discontinued, and the dosage of predonisolone gradually reduced. As the patient experienced a delirious episode; her scores of the Delirium Rating Scale Revised 98 (DRS-R-98) (Trzepacz et al., 2001) and the Mini-mental state examination (Folstein et al., 1975) were 18 and 6, respectively in spite of the discontinuance of cyclophosphamide and the tapering off the prednisolone. Her clinical diagnosis evaluated in DSM-IV-TR (American Psychiatric Association, 2000) was Mental Disorders (Delirium) Due to a General Mental Condition. Treatment with an oral solution of risperidone was initiated, and the dosage was increased to 2 mg/day to treat the episode of delirium. After the latter treatment had been administered, the patient's state of delirium gradually subsided; her scores of the DRS-R-98 were 12, 8, and 6 at 1, 2, and 4 weeks after risperidone administration, and her score of the MMSE was 26. The MRI findings revealed the disappearance of the large high signal intensity area (Fig. 1B), and the SPECT results showed a recovery from hypoperfusion in the same region (Fig. 2B) (Day 130). Furthermore, since the patient occasionally exhibited mood fluctuations; her score of the Young Mania Rating Scale (YMRS) (Young et al., 1978) was 20, lithium carbonate was administered, and the dosage was increased to 1000 mg/day (plasma lithium level: 0.7 mEq/L). The patient's mood was

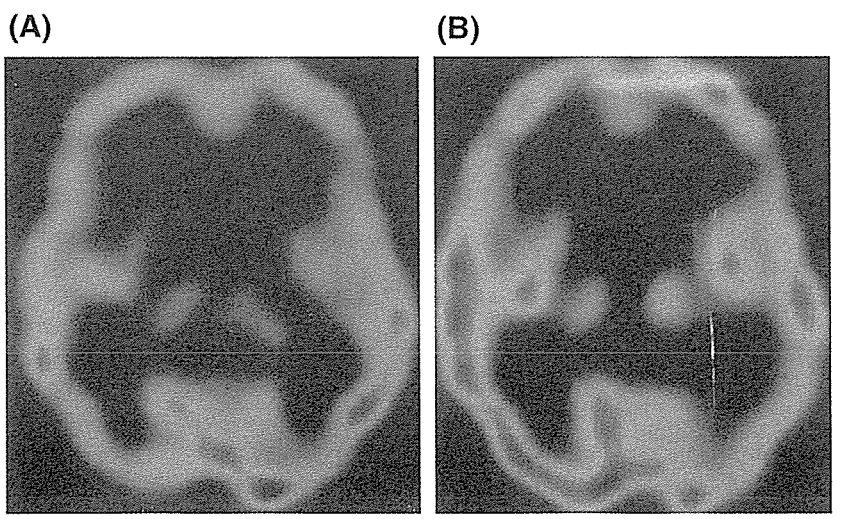

Fig. 2. SPECT images. (A) Day 0, (B) Day 130.

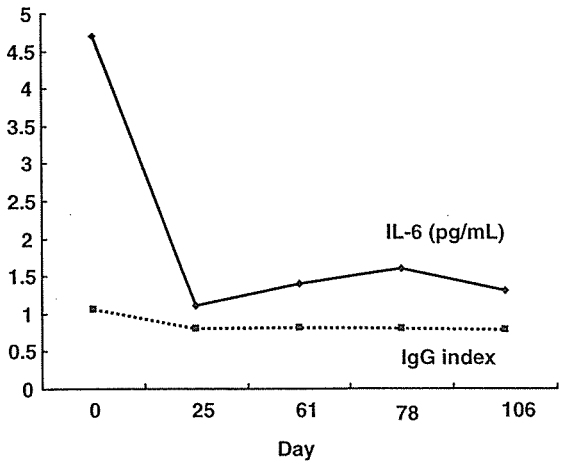

Fig. 3. Changes in IgG index and CSF levels of IL-6.

stabilized 2 weeks after the administration of lithium; her score of the YMRS was 4.

3. Measurement of plasma levels of BDNF and catecholamine metabolites

In the present case, we analyzed the patient's plasma levels of BDNF and those of the catecholamine metabolites 3-methoxy-4-hydroxyphenylglycol (MHPG) and homovanillic acid (HVA). All blood samples were drawn to plastic tubes with ethylenediaminetetraacetic acid at 7:00 a.m. before breakfast. The plasma samples were quickly separated in a centrifuge (2000×*g*, 10 min, 4 °C) and plasma fractions were stored at − 80 until use for the assay. Plasma levels of MHPG and HVA were analyzed by previously described high-performance liquid chromatography methods (Yoshimura et al., 2000; Kakihara et al., 2005). Plasma BDNF levels were measured using the BDNF Emax Immunoassay System Kit (Promega, Madison, WI, USA) according to the manufacturer's instructions.

4. Changes in plasma levels of BDNF and catecholamine metabolites in the present case

The patient's plasma level of BDNF was 620–660 pg/mL when her mental status was stable (Days 0, 7, 130, 148, and 167). However, her BDNF levels increased up to 1220–1370 pg/mL during active psychotic episodes (Days 61, 70, 78, and 106). Similarly, the patient's plasma level of MHPG increased from 8.4–8.8 ng/mL to 11.9–14.4 ng/mL, and her plasma level of HVA increased from 7.9–8.9 ng/mL to 13.1–15.1 ng/mL (Fig. 4).

5. Discussion

The most interesting finding of the present study was that in this CNS lupus patient, the plasma levels of BDNF and catecholamine metabolites (MHPG and HVA) were increased in parallel with the activity of her psychotic symptoms, and not as might have been expected with the dosage of prednisolone or cyclophoaphamide. In contrast, the IgG index and the CSF level of IL-6 reflected the physical activity of SLE, however, those were not in accordance with the severity of her psychotic symptoms. Although BDNF is highly concentrated in the brain, it is also present in the plasma and serum; however the source of circulating BDNF remains unknown. Platelets, brain neurons, and vascular endothelial cells have been considered as candidate sources of circulating BDNF (Hashimoto et al., 2004). It has been reported that BDNF is able to cross the blood–brain barrier (Pan et al., 1998), and that BDNF levels in the brain and serum undergo similar changes during maturation and aging in rats (Karege et al., 2002), thus indicating that plasma BDNF levels might, at least in part, reflect the BDNF levels in the brain. In addition, it has been hypothesized that one-third of the plasma MHPG and 30–50% of the plasma HVA are derived from the brain (Yoshimura et al., 2004). The reasons for which the levels of plasma BDNF and catecholamine metabolites (MHPG and HVA) were increased during the active

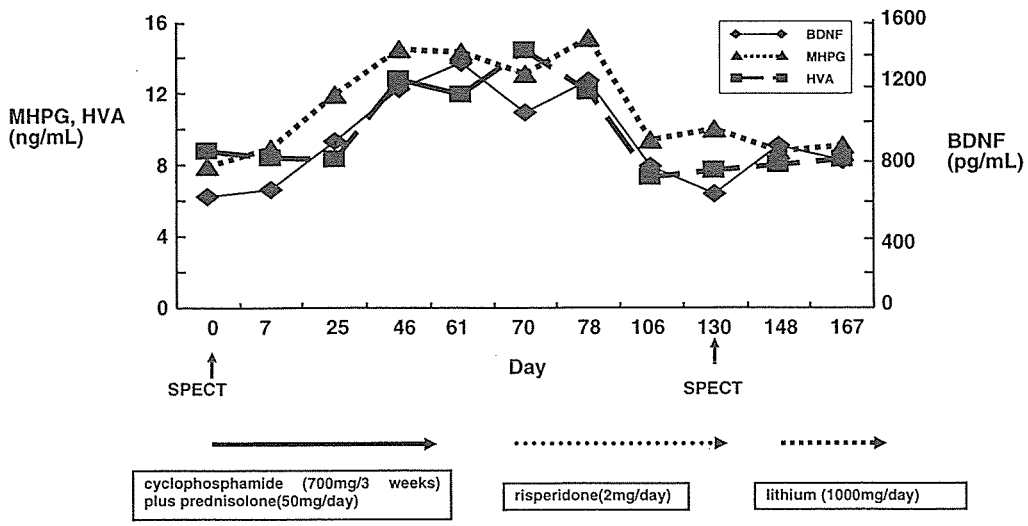

Fig. 4. Changes in plasma levels of BDNF and catecholamine metabolites.

phase of CNS lupus in this patient remain unknown. It has been reported that BDNF is upregulated by inflammatory mediators such as TNFα and IL-6, and BDNF is known to play a critical role in B cell development; all of these factors are in some manner related to the pathophysiology of SLE (Schuhmann et al., 2005; Schulte-Herbrüggen et al., 2005). Taken together, the results of this study and those of previous reports suggest that increased plasma BDNF is reflective of hyperactivity of the immune system in both the brain and peripheral organs. Not only BDNF, but also the two catecholamine metabolites (MHPG and HVA) were found to be increased during the active phase of disease in this patients with CNS lupus. Recently, we reported increased plasma levels of MHPG in delirious patients (Nakamura et al., 1997), and we hypothesized that the hyperactivity of the noradrenergic neurons was connected to the development of delirium (Nakamura et al., 2001). The results of the present study were basically in accordance with of those our previous reports. In the present study, we demonstrated that plasma HVA, a major metabolite of dopamine, was also elevated; this finding is also considered to be reflecting of hyperactive dopaminergic neurons. The increased HVA levels in the present case did not contradict previous findings of increased HVA levels in patients with schizophrenia, mania, and psychotic depression (Yoshimura et al., 2003, 2004, 2005), as the present patient with CNS lupus exhibited a variety of psychotic symptoms such as psychosis and mood swings. In short, it is possible that the hyperactivity of the immune systems and that of the catecholaminergic neurons plays a role in inducing the development of psychotic symptoms in patients with CNS lupus.

In the present study, the oral solution of risperidone (2 mg/day) was effective for the treatment of delirium without any adverse effects. Several reports demonstrated that risperidone is effective and well-tolerated for the treatment of delirium (Horikawa et al., 2003; Han and Kim, 2004; Parellada et al., 2004). Interestingly, Nishimura et al. (2003) also reported a case of neuropsychiatric SLE presenting an acute confusional state (delirium), which was successfully managed with risperidone. Recently, we demonstrated that oral solution of risperidone is effective for the positive symptoms of acute phase schizophrenic patients, especially for excitement, hostility, and poor impulse control (Yoshimura et al., 2005). Pharmacologically, the oral solution of risperidone has the same profile as a risperidone tablet. In addition, the oral solution of risperidone has almost the same pharmacokinetic profile (the Tmax of the oral solution of risperidone is a little shorter than that of risperidone tablet) (Rispadal Package-Insert, Janssen Pharmaceutical K.K. Japan). Therefore, the oral solution of risperidone is preferable to risperidone tablet for using in a psychiatric emergency service setting (Currier and Simpson, 2001) or physically complicated patients who have difficulty in swallowing.

6. Conclusion

We reported here a case study of a patient with CNS lupus, in whom increasing plasma levels of BDNF and catecholamine metabolites were observed in parallel with increases in the severity of psychotic symptoms. We therefore propose the usefulness of measuring plasma levels of BDNF, MHPG, and HVA in patients with CNS lupus in order to predict the activity of psychotic symptoms. In addition, the present findings suggest that such measurements might also be useful for differentiating between cases of CNS lupus and steroid-induced psychosis.

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特集
精神科薬物療法の限界—そのときどうするか—
臨床精神薬理　9：1761–1766, 2006

うつ病の薬物療法の限界

——そのときどうするか——

森信　繁[1)]　田中和秀[1,2)]　市村麻衣[2,3)]　大川匡子[3)]　山脇成人[1)]

抄録：難治性・遷延性・治療抵抗性うつ病といった慣用診断名があるように，抗うつ薬治療に反応の乏しい大うつ病の存在が報告されてきている。そして抗うつ薬抵抗性の病態には，lithium・甲状腺ホルモンによる抗うつ効果に対する増強療法，電気けいれん療法，認知行動療法などが推奨されている。本稿ではこのような新たな治療を開始する前に，病態診断を再検討する必要性について論じてみた。具体的な症例報告も含め，パーソナリティ障害，広汎性発達障害，認知症との鑑別について紹介した。難治性うつ病の治療については，抗うつ薬への増強療法と抗うつ薬併用療法について，最近の総説を参考にしながら簡単に報告した。うつ病の薬物治療が奏効しない場合には，次の治療法を検討する前に，まずこれまで行ってきた診断や治療の再検討が必要であろう。

臨床精神薬理　**9：1761–1766, 2006**

Key words : *treatment–resistant depression, personality disorder, presenile dementia, pervasive developmental disorders, differential diagnosis*

はじめに

うつ病の薬物療法の限界をどのように判断するかは極めて難しい問題であり，これは難治性・治療抵抗性うつ病という病態についての診断基準が研究者によって様々であることからも示されている。治療抵抗性のうつ病を考える際に，まず治療により症状が改善するということを具体的に定義する必要がある。抗うつ薬治療に対する反応を，「治療に対して良好な結果が得られた状態の寛解群」「治療への反応が得られた群」「部分的に治療への反応が得られた群」「反応なしの群」に分類する。治療による寛解をハミルトンうつ病評価尺度（Hamilton Rating Scale for Depression；HAM–D）17項目において7点以下であると定義すると，抗うつ薬治療によって寛解に至るのは治療を受けたうつ病患者のうちわずか25～50％であるといわれる[14)]。しかも寛解の状態でもなお多くの残遺症状がみられることが多く，残遺症状が存在する群では存在しない群よりもオッズ比で3.5倍うつ病が再発しやすいことが報告されている[7)]。次に，「治療への反応が得られた群」を，抗うつ薬の治療によってHAM–D17項目の点数が50％以上減弱することと定義した場合，20～40％もの患者が初回の抗うつ薬治療に反応しないと推測されている[13)]。同様に「部分的に治療への反応が得られた群」をHAM–D17項目の点数が25％以上50％未満減弱した群と定義した場合，その割合は全体の

The limitation of pharmacotherapy for depression.

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30%程度にものぼる[10]。つまり，抗うつ薬の治療により抑うつ症状がすっきり改善する患者は決して多いとはいえず，症状が改善した患者でも50%以上がなんらかの残遺症状を有している[12]。このような統計学的結果は，我々の日々の臨床の中で交わされる患者さんとの会話の中で聞かれる，「治療前より気分は良くなりましたがまだ本来の調子ではありません」という言葉に他ならない。

本稿では今回の特集号のテーマである「精神科薬物療法の限界―そのときどうするか―」に沿い，限界と思ったその時どうするかについて，筆者らの日頃考え実践していることを紹介したい。抗うつ薬治療に抵抗性のうつ病に対しての，気分安定薬・抗精神病薬・ホルモン剤などによる増強療法や修正型電気けいれん療法の有効性などは，すでに多数の論文や著書による報告があるので本稿では詳しくは触れない。むしろ多忙な日々の臨床診療の中で，うつ病の薬物療法が奏効しない時，つぎの薬をどうするかということばかり考えがちになるが，そのような時に何を検討してみるべきかについて報告する。

Ⅰ．気分障害という診断について

標準的な薬物治療によって反応の得られない時には，まず当初の気分障害で診断は本当によいのかという疑問が提起されなければならない。抑うつ状態が前景にありDSM-IV-TRにて大うつ病と診断されても，実際には他の精神障害である可能性を忘れてはならないのではないか。例えば中・高年者のうつ病（若い頃に気分障害の既往があったとしても）の場合，認知症との鑑別が重要となってくる。一方で思春期や青年期のうつ病の場合には，境界例などのパーソナリティ障害や広汎性発達障害との鑑別が必要となってくる。同時に気分障害とこれらの疾患のcomorbidityということも，気分障害の薬物療法の限界を考える際に忘れてはならないことである。

Ⅱ．パーソナリティ障害

適応障害（抑うつ気分を伴うもの）という診断がDSM-IV-TRにみられるが，一般的に人が生きていく過程で遭遇する種々の障壁に対して克服していくことができなくなった状態を示す診断と考えられる。適応障害あるいは不適応という状態はしばしばうつ状態を呈し，また障害の発症脆弱性としてパーソナリティの未熟さによる防衛機制の不適切さがあげられる。このような事実からみて，気分障害とある種のパーソナリティ障害の合併や鑑別診断は，薬物治療の限界に大きく関与する因子の１つと考えている。最近の阿部と加藤の論文[1]にみられる，「双極性障害か境界性障害か，あるいは両者の合併かと議論するケースが増えたような印象がある」という記載は，このような問題の重要性を示唆している。

DSM-IV-TRで診断される複数のパーソナリティ障害の中でも，筆者らは境界性パーソナリティ障害や回避性パーソナリティ障害が，気分障害に対する薬物治療抵抗性を形成する頻度が大きいと考えている。境界性パーソナリティ障害に関しては慢性の空虚感や自殺・自傷行為といった診断項目があるように，大うつ病とも類似する症状を含み，また治療者との間の転移感情の変動によって双極性障害とも類似する病態を呈する。この点については先述した阿部らの論文[1]に，双極性障害が境界性人格障害といかに診断されうるかをDSM-IVの診断基準に合わせて紹介してあり，そちらを参照されたい。境界性パーソナリティ障害以外で比較的双極性障害と間違われやすい障害に，現在使用されているDSM-IV-TRからは除外されているが，かつてのDSM-IIIには記載されていたPassive-Aggressive Personality Disorder（受動-攻撃性人格障害）があげられる。この障害についてはDSM-IVに載っていないことから，多くの治療者の頭に鑑別診断としては出てこない障害であろう。相手に非があるような状況では糾弾口調で多弁に語り，自分に非のあるような状況では引きこもりを決め込むなど，気分の変動と一致した行動様式の変化と見なされ，双極性障害として治療されているケースがあると思われる。やや非定型的な双極性障害に対する薬物療法の限界を感じた時に，本障害との鑑別診断を検討するべきではないだろうか。

その他に，大うつ病や気分変調症との鑑別や合併を考えるべき，パーソナリティ障害について紹介する。その１つが，回避性パーソナリティ障害である。この障害については，恐らく日頃の臨床場面で治療者がこの診断を想起する機会が境界性に比べて少ないことにより，潜在的にはかなりの割合で「慢性うつ病」「気分変調症」と診断されているのではないかと考えている。抗うつ薬の大量投与や増強療法などを行っても，本人の葛藤は社会的批判や拒絶への不安に対する過敏性などにあるため，病状は改善されないと思われる。人間として長所がないとか他の人と比べて劣っているという考えは，大うつ病にみられる無価値感や罪責感の結果と理解されやすい。この他にも自己愛性パーソナリティ障害が，大うつ病あるいは気分変調症という表現型をとる可能性も考えられる。誇大性や賞賛されたいという欲求と共感の欠如に伴う対人様式が診断基準には記載されているが，このような行動様式が受け入れられず，結果として反応性のうつ状態を呈することも決して珍しい現象ではないと考える。大うつ病を引き起こす原因となったイベントについては詳しく情報を収集していても，それ以前の行動様式を把握していないと，自己愛性パーソナリティの診断は困難となる。

パーソナリティ障害との鑑別や合併については，幼少期からの家庭内・学校内での対人様式の取り方などに焦点を当てた病歴の聴取から検討することが望まれる。行動面での障害が気分の変動と一致している場合には特にそうであるが，治療者-患者関係の取り方などの対象恒常性に注意して，薬物治療抵抗性の症例の診断や治療に取り組むべきと思われる。

Ⅲ．広汎性発達障害

アスペルガー障害や高機能の自閉性障害を対象とした臨床研究から，うつ病が最も合併しやすい精神障害であることが報告されている[6]。疫学的な大規模研究ではなく臨床現場からの報告ではあるが，Ghaziuddin らは64名の自閉性障害を診察しその２％にうつ病の合併がみられ，最も高頻度の精神障害であったと述べている[5]。同様にWing は34名の成人期アスペルガー障害を対象に，その中の10名にうつ病の合併がみられたことを報告している[20]。総説論文としては Lainhart と Folstein による17本のケースレポートをまとめた報告から，自閉性障害にみられる気分障害への注意が喚起されている[9]。高機能の自閉性障害などでうつ病の合併が高頻度であることの原因については，遺伝的要因や環境要因の複雑な関与が報告されているものの，議論の余地のあるところである。しかしながら言語発達の遅滞に乏しいケースで，コミュニケーションの質的な障害のある場合，職場で同僚との意志疎通などにおいて様々な障害が引き起こされやすいと想像する。コミュニケーション障害に由来する現実的な問題の蓄積によって，二次的にうつ病が発症してくると考えられる。このようなケースでは一時的に抗うつ薬の投与によってうつ状態の改善は望めるが，再び職場に戻ると発症前と同じことが繰り返されるため容易に再発し，根底にある発達障害に気付かなければ難治性うつ病と診断されてしまうことになる。その他にも自閉性障害とうつ病の合併のメカニズムについて検討した Capps ら[3]や Sigman ら[18]の報告によると，高機能であればあるほど自己価値感が低くなるため，うつ病になりやすい可能性が提唱されている。

以下に，筆者の経験した症例を示す。

症例　20代後半の女性

生活歴：大学卒業後，公務員として就職。

現病歴：公務員として勤務し始めた頃は，上司や先輩の指示に従って逐一実行するだけの職場状況であったため，ほぼ支障なく勤務が可能であった。ところが自分一人で１つの企画などを担当するようになってから，企画立案の遅れ・立案上の不備などが指摘されるようになり，仕事が満足にできないと考えうつ状態となっている。このため精神科クリニックを受診し，うつ病との診断にて抗うつ薬治療を受け寛解している。しかしながら職場復帰後，再び同様の状況を繰り返すため休職となり，難治性うつ病の精査を目的に紹介されている。

初診時に，仕事の立案や実行面で様々な不備が出てしまうが，事前にそれに気づけないことが悩みとして話される。加えて，皆ができることが自分には困難で，能力が劣っているとも話す。これまでの病状経過の非定型性やあまりに状況依存的な経過から，うつ病以外の診断を疑いいくつかの心理検査を行った。その結果，Wechsler成人知能検査（WAIS）は言語性IQ（VIP）：128，動作性IQ（PIQ）：82と大きな差がみられ，AJQでも30と広汎性発達障害を示唆する所見であった。このため障害者職業センターに紹介して，認知行動療法的なアプローチからの訓練を受けるようマネージメントを行った。

Ⅳ．認　知　症

アルツハイマー型認知症の初期に抑うつ症状（精神運動抑制による意欲・興味の減退など）がみられることもあり，これに対して選択的セロトニン再取り込み阻害薬（SSRI）であるsertralineの有効性を示した論文もある[11]。仮性痴呆（pseudodementia）という用語があるように，高齢者のうつ状態に関して「うつ病」か「認知症」かの診断に困る症例は決して稀ではない。田村ら[19]も論じているように，認知症の初期症状の部分症状として「自発性の減退」が前景にみられ，この自発性の減退がうつ病に由来するのか認知症によるのか鑑別に困る病態がある。

実際Olinら[15]によって提唱された“Provisional diagnostic criteria for depression of Alzheimer disease”の田村や堀口ら[19]による邦訳である「アルツハイマー病の抑うつに対する暫定診断基準」を参考に，うつ病と認知症の鑑別を行ってみる。Olinら[15]の基準の項目Bにある「アルツハイマー型痴呆（DSM-IV-TR）のすべての基準を満たす」を十分満たさないケースで，項目Aにある10項目の抑うつ症状のうち3つ以上を呈する場合などが問題である。項目Aの（1）臨床的に著しい抑うつ気分（うつ・悲しみ・絶望・落胆・涙を流す）など大半は，DSM-IV-TRにおける大うつ病の診断基準に類似する内容であり，初診時に項目Bを満たさないと大うつ病と診断される可能性がある。この基準は必ずしも「うつ病」と「認知症」を鑑別するために作成されたものではないが，やはりOlinら[16]の提唱する「認知障害を伴ううつ病」と「アルツハイマー病の抑うつ」との鑑別点という基準をみても，複雑な状況には余り変化ないと思われる。彼らは，「アルツハイマー病の抑うつでは重症度が低く」と定義しているが，その一方で先の暫定診断基準では「臨床的に著しい抑うつ気分」と表現される項目がみられる。

このような事実は恐らく薬物への反応性も含めて臨床症状の推移を丁寧にみていくことの重要性を示唆していると考えられ，特に以前は初老期痴呆と呼ばれていた一群の存在を念頭に，頭部MRIや記銘力検査などを欠かさず行っていく姿勢が要求されると思う。

Ⅴ．難治性うつ病の治療

上述したような診断に関する再検討を行った結果，難治性うつ病と診断された場合には，（1）抗うつ薬の効果を促進する目的でのaugmentation（増強）あるいはcombination（併用）療法，（2）電気けいれん療法，（3）認知行動療法，などの治療を行うことが標準的かと思われる。冒頭にも述べたように，各治療法については多くの論文や著書が出版されているので，詳細はそれらを参照していただきたい。

Ⅵ．増強療法と併用療法

抗うつ薬の有害作用などで十分な用量の抗うつ薬投与が困難であったり，効果が不十分である場合などでは，増強療法を選択することができる。追加薬剤としてはlithium，甲状腺ホルモン，抗けいれん薬，第二世代抗精神病薬，methylphenidateなどが用いられる。ここでは紙面の都合もあり，最近報告が増えてきている，第二世代抗精神病薬の効果について報告する。

SSRIに反応しない非精神病性うつ病に対する増強療法として，risperidone，olanzapine，quetiapineなどの第二世代抗精神病薬が注目されて

いる。非精神病性の治療抵抗性うつ病患者28名をプラセボ，fluoxetine単独，fluoxetineとolanzapine併用の3群に分けて投薬を行ったところ，併用群が他の2群よりも有意に抑うつ症状の改善を示したとのRCTが報告された[17]。この併用療法にみられる臨床効果の発現機序については，fluoxetineとolanzapineの併用投与により，ラット前頭部におけるドーパミン・セロトニン・ノルアドレナリンの濃度の亢進が示されており，このような神経伝達物質の濃度変化が抗うつ薬の効果増強に関連していると推測されている[21]。

Barbeeら[2]は治療抵抗性の非精神病性うつ病に増強療法としてolanzapine，risperidone，quetiapine，ziprasidoneを投与した49例をreviewしている。第二世代抗精神病薬全体の反応率は65％であり，olanzapineが57％，risperidoneが50％と他の2剤に比べて有意に高かった。薬剤間の脱落率には有意な差はなかった。Olanzapineの平均投与量は6.48mg/日，risperidoneは0.85mg/日であり，統合失調症に対する投与量よりも少量で効果が得られた。効果発現まではolanzapineが2.27週，risperidoneが3.29週であった。これらの結果から，抗うつ薬の増強として第二世代抗精神病薬が有効である可能性があると述べている。

なお難治性うつ病の増強療法や併用療法に関してはFavaがコンパクトにまとまった総説を著しており，それによると抗うつ薬の増強療法としてはっきり推奨されるのはlithiumと甲状腺ホルモンのようである[4]。ここに紹介した第二世代抗精神病薬については，この総説以後に複数の本薬による増強療法の有効性を指摘する報告もあるが，示唆される程度の治療法と記載されている。異なった種類の抗うつ薬による併用療法については，増強療法と異なりはっきりと推奨される組み合わせはないと報告されている。三環系抗うつ薬（TCA）とSSRIとの併用も示唆される程度であり，milnacipranではなくvenlafaxineであるがセロトニン-ノルアドレナリン再取込み阻害薬（SNRI）とSSRIの併用については不確かな療法に分類されている。最近になって時々みられるようになったSSRIとSSRIによる併用療法は，この総説の判断に従うと，効果が疑わしい療法という評価になっている。

ま と め

難治性うつ病を中心に抗うつ薬の効果が限界と思われる状況になった時，すぐに併用・増強療法を試みるのではなく，やはり現病歴や発症前の生活歴を含めての診断を再検討することが必要と思われる。話は変るがマスコミの最近の報道で，団塊の世代が一挙に退職するという時勢をむかえ，退職前の職員や退職者から若手への技術伝達を強化している現状が紹介されていた。ある県警では鑑識など捜査のノウハウなどの指導が行われ，JR西日本ではATS設置に関しての指導が行われていることが報道されていた。マニュアルに頼った仕事では大事な所見を見逃すという事実があるため，ベテランの経験を伝授していく必要もあるという内容である。昨今のうつ病治療ではTCA，SSRI，SNRIという観点から抗うつ薬を選択することが当たり前のようになっているが，ひと昔前はうつ病の臨床症状を意欲・抑うつ気分・不安焦燥感に分けて評価し，Kielholzの図[8]を参考に適切な抗うつ薬を処方していた。うつ病の薬物療法の限界に際して，前に進むだけではなく温故知新も必要なのかもしれない。抗うつ薬が無効な時，するべきことは沢山あるように思われる。

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特集　ライフサイクルとうつ病

4．うつ病の病態はどこまで明らかになっているか？

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うつ病とは，抑うつ気分と意欲減退を主症状とするヘテロな症候群であるが，一定の共通する症状や治療経過を示すことなどから，何らかの生物学的基盤を共有すると考えられている。うつ病に対する生物学的研究においては，有効な動物モデルが複数，開発され，遺伝的脆弱性やうつ病の病態，抗うつ薬の作用機序に関する分子生物学的機序の解明がなされてきた。本稿では，従来の分子生物学的手法の成果と，近年，隆盛となっている脳機能画像研究による知見について概観し，その統合的理解の助けとなる，"Functional connectivity" という新しい概念について最後に取り上げた。

1．はじめに

うつ病は，抑うつ気分と意欲減退に，焦燥感や不眠，食欲低下などの精神症状を伴う状態の呼称であり，実際の臨床症状により創出された幅広い症候群と考えられる。生物学的，遺伝学的にヘテロな特徴を有しており，治療においても個々人で薬物療法や電気けいれん療法，精神療法への異なる治療反応性を示す場合も少なくない。

しかしながら，個々の患者は前述した症状の多くを共有しており，全体として捉えると，一定の治療反応性と経過をたどることから，共通した生物学的機序を根底に有すると推測される。視床下部－下垂体－副腎皮質系（HPA axis）の内分泌学的異常と，カテコラミンを媒介とする自律神経系の亢進などが古くから指摘されているが，これらがうつ病の原因であるのか，あるいは結果であるのか，随伴する変化に過ぎないのかに関して，結論は得られていない。

近年，このヘテロなうつ病という病態を単純化して捉えるため，その中間表現型（下位分類）を定義する試みも精力的に行われている[1)]。本稿では，うつ病の病態に関して，多角的な視点から現在の知見をまとめてみたい。

2．生物学的研究から見たうつ病の病態

1）動物モデル

Darwinは自著「種の起源」の中で，ヒトと最も高等な動物の心の間でさえ，大きな隔たりがあるとしながら，両者の類似した点にも目を向けなければならないと主張した。この矛盾した2つの姿勢の延長に，動物モデルの作成という医学における流れが形成されている。

げっ歯類とヒトでは，大脳皮質の占める割合が大きく異なるため，自尊心の低下，罪悪感といった微細な心理をげっ歯類でモデル化することは困難である。しかし，哺乳類は類似の脳構造と回路を持ち，海馬や扁桃体といった情動制御を司る部位は比較的，同一の機能を保持していると考えられることから，多くのうつ病の動物モデルが開発された[2)]。

代表的モデルとして，学習性無力と強制水泳，

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慢性軽度ストレスという3つが考えられ，逃避不可能で予想できないストレスを負荷することで，無気力で不安の亢進した，うつ病類似の状態を作ることに成功している。ストレス脆弱性のモデルとして，母子分離ラットといった虐待の神経発達モデルや，不安が強い個体，あるいは学習性無力になりやすい個体同士を交配した脆弱性継代モデルがあり，いずれもうつ病の分子生物学的研究と創薬の歴史に多大な貢献を果たしている。

2）神経内分泌学

Korteらは，コルチゾールやアドレナリンといったホルモンや神経伝達物質のストレスに対する適応的変化をallostasis，その持続的な変化がもたらす神経毒性機構をallostatic overloadと名付けている[3]。コルチゾールの一つであるグルココルチコイドを例にとれば，軽度のストレス時に，グルココルチコイドは蛋白の異化，食欲の亢進などを導き，闘争あるいは逃走の準備を整える適応的働きをなす反面，変化が長期にわたると，海馬や扁桃体等の機能不全をきたす神経毒性の方向に働く。すなわち，うつ病はストレス負荷時のallostatic overloadが生体にもたらす損傷の結果であると考えることができる，としている[3]。

3）遺伝的脆弱性

うつ病の遺伝的脆弱性に関しては，多因子遺伝説が優勢であり，単一原因遺伝子が見つかる可能性は少ないとされる。近年，セロトニントランスポーターの対立遺伝子（SERT）のshort formをとる多型が，うつ病発症の脆弱性因子となることが注目され，この多型を持つ被験者では，セロトニン神経系の機能低下に一致する脳機能画像所見が明らかになっている[4]。

一方，分子精神医学領域では，ゲノム自体でなく，ゲノムDNA（deoxyribonucleic acid）からRNA（ribonucleic acid）への転写を制御するepigenetic modificationという機構が，早期の養育環境に起因するストレス脆弱性の形成に関与することが発見され，話題を呼んでいる[5]。虐待など不遇な体験が，成人後のうつ病発症のリスクを高めることは，動物モデルの研究やヒトの臨床研究の結果から明らかである。

生物学的基盤として，養育行動の少ない母に育てられた仔ラットでは，海馬のグルココルチコイド受容体のゲノムDNA発現を調節するプロモーター領域のepigenetic modificationに異常のあることが確認された。不遇な早期体験を有する成人では，動物モデル類似のHPA axisの異常などが追認されており，同様にグルココルチコイド受容体のepigeneticな異常を持つ可能性が示唆されている[6][7]。

4）分子生物学的研究

1950年代後半に，最初の抗うつ薬であるモノアミンオキシダーゼ阻害剤が発見され，シナプス間隙におけるセロトニンやノルアドレナリンなどの神経伝達物質の枯渇をうつ病の本体と考えるモノアミン仮説が唱えられた。現在，市場に出回っている抗うつ薬の大半は，セロトニンやノルアドレナリン神経系の活動を増減する作用を有し，一定の治療効果を発揮している。その反面，抗うつ薬によるシナプス間隙のモノアミン量の急性回復に比し，実際のうつ病患者の症状の回復には少なくとも1，2週間は要することから，当初よりモノアミン仮説の妥当性には異議が唱えられた。

近年では，うつ病の病態あるいは抗うつ薬の作用機序の基盤を縫線核や海馬における，モノアミン受容体以降の細胞内シグナル伝達機構の変化に求める考えが大勢を占めており，中でもbrain derived neurotrophic factor（BDNF）やinsulin-like growth factor（IGF），glial cell line-derived neurotrophic factor（GDNF）などの神経栄養因子が注目されている。

ストレスやグルココルチコイドは，海馬における神経新生を抑制し，海馬や前頭葉皮質の萎縮を惹起するとされるのに対し，BDNFなどの神経栄養因子は，神経細胞の軸策伸長や樹状突起の再構成を促し，細胞の維持や分化を促進し，細胞死を抑制するという神経保護的作用を果たす。時間的経過を見ても，抗うつ薬の長期投与や電気痙攣療法により初めて，神経栄養因子の増加が見られることから，この過程がうつ病の病態あるいは抗うつ薬の作用機序に密接に関与している，と予想されている[8]。

このような神経栄養因子を介した，神経細胞の樹状突起や軸策の変化が神経回路全体の改変をもたらすという，“Remodeling of neural circuit”あるいは“Network hypothesis”という仮説が近年，

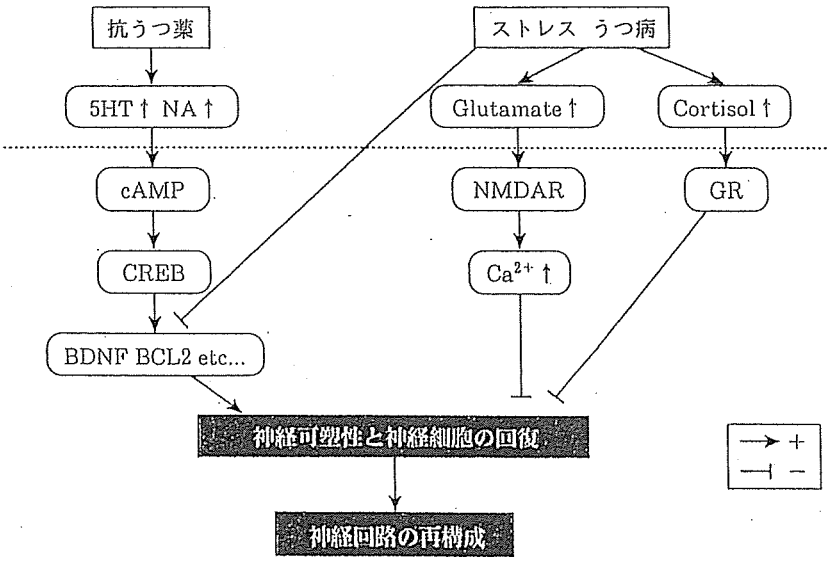

図1　うつ病に関連するシグナル伝達機構

うつ病の病態と抗うつ薬の作用機序の双方に，神経可塑性が関与している．

5HT：セロトニン，NA：ノルアドレナリン

cAMP：cyclic adenosine monophosphate

CREB：cAMP responsive element binding protein

NMDAR：N-methyl D-aspartate receptor

GR：グルココルチコイド受容体

（筆者ら作成）

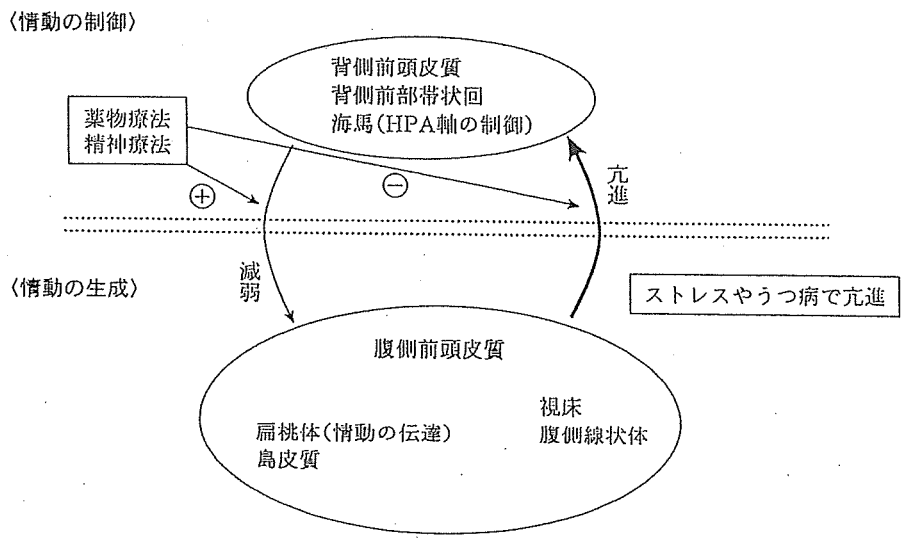

図2　うつ病に関連する神経回路

以下の神経回路の連絡異常が，うつ病であると考えられる．

① うつ病では実線のように情動の生成が亢進し，制御が低下している．

② 薬物療法や精神療法は情動の生成を減弱し，制御を強化すると予想される．

（筆者ら作成）

提唱されている[9)10)]。モノアミン以降の細胞内シグナル伝達に関しては，図1を参照されたい。

5）脳画像研究

近年の脳構造画像研究と，fMRI(functional magnetic resonance imaging)やPET(positron emission tomography) などの機能画像研究の知見の蓄積から，うつ病に関連する脳内構造物の異常としては，HPA axisの制御に関与するとされる海馬と，情動の伝達に関連する扁桃体，情動制御に深く関わる前頭葉皮質の3つの代表的部位の異常があげられ，これらを結ぶ神経回路全体の障害が，うつ病の病態形成に関与していることは確かであると思われる。

Phillipsらは，上記の神経回路をさらに細分化し，扁桃体や島皮質，腹側前頭葉皮質などの情動を生成する腹側システムと，海馬や背側帯状回，背側前頭葉皮質などの情動を制御する背側システムの二つの回路に分類して考えることを提唱している。彼らの説では，うつ病の抑うつ気分や意欲減退は，上記の背側システムによる制御能が低下し，腹側システムによる情動生成をコントロールできなくなったことによるとされ，薬物療法や精神療法が，この神経回路同士の連絡あるいはバランスを取り戻すことで症状の改善が得られる，と主張している[11)]。うつ病に関連する神経回路については図2を参照されたい。

このような，うつ病の原因を神経回路全体の連絡に求める考えは"Functional connectivity"仮説と名づけられ，脳機能画像研究の領域で検証が進められている。近年，Anandらは fMRIを用いて前部帯状回と，扁桃体や視床との血流信号の相関を調べることで，うつ病患者で情動制御に関連する神経回路の連絡が低下しており[12)]，抗うつ薬の投与後には同部位の連絡が回復することを示している[13)]。

3．おわりに

近年，抗うつ薬の作用機序を神経栄養因子による神経可塑性の回復に求める分子生物学領域の仮説と，薬物療法や精神療法の作用機序を神経回路が再度連絡されることに求める画像研究領域の仮説を統合したneuronal connectivity，あるいはremodeling of neural circuitという新しい概念が提唱されている。このように，ストレスにより失われた神経細胞の可塑性が抗うつ薬により回復することで，情動制御に関連した上述の神経回路全体の再構成が起き，うつ病の症状の改善がもたらされるという作業仮説が，分子生物学と画像研究という二つの領域から検証されつつある[9)10)]。

Nestlerは2002年の総説の中で，うつ病の生物学的研究においては，50年前の抗うつ薬の偶然の発見を越える進歩は残念ながら存在しないと指摘し，今後の課題として，① 信頼性の高い動物モデルの作成と② 遺伝的背景の把握，③ 新たな治療ターゲットの発見と④ 多様なバックグラウンドを持つ研究者の育成の4つをあげている[14)]。本稿であげたように，遅々とした歩みではあるが，うつ病の生物学的研究の前進している姿が読者に伝われば幸いである。今後は本総説で取り上げたように，臨床研究と分子生物学的研究，画像研究を統合した多面的アプローチが隆盛となることが予想される。

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