トンATPaseサブユニットとの類似点があり，dsr-2とdsm-1はD-セリンと類似した脳内分布を示す点が興味深い。現在，D-セリンの放出・取り込みを中心に代謝・機能との関連を検討中である。

おわりに

本稿で紹介したように，統合失調症におけるNMDA受容体を介したGlu伝達の低下の関与については，多くの薬理学的根拠が蓄積されつつある。ただし，現時点ではその低下を直接説明できる統合失調症患者における分子異常は明らかでない。脳脊髄液中Glu濃度の低下[29]や死後脳前頭葉のカイニン酸型Glu受容体結合の増加[36]をはじめ，NMDA受容体機能が注目される以前から，患者サンプルにおいて，Glu伝達異常を示唆する所見が得られているが，長期にわたる薬物治療の影響を除外することが難しい。また，ゲノム解析では，dysbindin，neuregulin，GRM3 (metabotropic glutamate receptor 3)，AKT1，RGS4 (regulatorof G-protein signaling 4)，D-アミノ酸酸化酵素，G72等のGlu伝達関連分子をコードする遺伝子の多型と統合失調症の相関が，複数の研究グループから報告されているものの，病因となる変化はいまだ見出されていない[40]。

NMDA受容体—D-セリンシステム系の分子機構や関連するゲノム領域における調節メカニズムに関する研究は，統合失調症の病態解明や新たな治療法開発に結びつくことが期待され，今後のさらなる発展が望まれる。

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(谷口 豪，西川 徹)

Neurobiological and Molecular Bases of Methamphetamine-Induced Behavioral Sensitization and Spontaneous Recurrence of Methamphetamine Psychosis, and its Implication in Schizophrenia

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Abstract: Spontaneous recurrence of methamphetamine- or amphetamine-induced paranoid hallucinatory psychosis (i.e., flashbacks) occasionally occurs in response to non-specific mild stress in drug-free patients with a history of methamphetamine- or amphetamine-induced psychosis. Stress sensitization associated with noradrenergic hyperactivity and increased dopamine release may be related to this flashbacks. Stressful frightening experiences as well as fear-related paranoid-hallucinatory states during methamphetamine use may be related to these stress sensitization. Robust noradrenergic hyperactivity with increased dopamine release may predicts subsequent flashback episodes. Schizophrenia-like symptoms (e.g., passivity phenomena, Gedankenlautwerden, and thought disorder such as circumstantiality and egorrhea symptoms) appear to develop related to dopaminergic hyperactivity. One of the dopamine receptor-encoding genes DRD2, TaqIA A1/A1 type, with which reduced density of the D2 receptor is associated, reduces to the risk of development of flashbacks.

Stress sensitization has been proposed as a key step in the progression from vulnerability to an overt paranoid-hallucinatory states, so that schizophrenia and flashbacks due to previous methamphetamine psychosis shares common underlying mechanisms of stress sensitization.

Compared to flashbacks due to previous methamphetamine psychosis, psychedelic drug flashbacks are the recurrence of a perception learned while an individual is experiencing high anxiety levels, and thus recur in anxiety-related situations. Anxiety or fear during drug use is an important factor in the development of flashbacks due to previous methamphetamine psychosis and also psychedelic drug flashbacks.

Dopaminergic and glutamatergic neural circuits including the striatum, nucleus accumbens and prefrontal cortex play an important role in the development of psychostimulant-induced long-lasting behavioral sensitization. Immediate early genes expression in the particular brain regions affected by the psychostimulants is involved in this process. Furthermore, recent advances in molecular analysis could shed light on the fundamental mechanism involved, by identifying specific participating molecules such as delta FosB, NAC1, G-protein b1 subunit and methamphetamine-responsive transcript 1b.

Keywords: Flashbacks, methamphetamine, stress sensitization, plasticity, gene expression, behavioral sensitization.

1. INTRODUCTION

Amphetamine (AMP) or methamphetamine (MAP) is abused primarily to enhance mental power and mood. In contrast to the multiple use of substances in other countries, MAP in Japan is taken repeatedly by intravenous injection without any other substance (no hallucinogens, cannabis, cocaine, opiates or alcohol). AMP or MAP sometimes induces paranoid-hallucinatory psychosis, closely resembling paranoid schizophrenia, in non-schizophrenic subjects [1,2].

Early studies reported that 7 % of the population had used AMP in their lives in the United States of America [3], and that one-sixth of injecting AMP users experienced psychotic states [4]. Most MAP users in Japan re-inject before the effects of the previous MAP injection were off. Such exclusive and repetitive use of MAP may easily induce psychotic states in as many as 76-92% of users, leading to engenders enduring vulnerability to paranoid-hallucinatory states [4]. A clinical study reports that a male patient developed flashbacks about 2 years after the disappearance of MAP psychosis [5]. Sensitization to MAP, which develops during abuse, is involved in susceptibility to onset and relapse of psychotic states [4]. In this regard, catecholamine metabolites such as homovanillic acid (HVA) or 3-methoxy-4-hydroxyphenylglycol (MHPG) are not related to psychiat-

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ric symptoms, and other factors such as sensitization to AMP or MAP may be more important [6]. Importantly, patients with a history of MAP psychosis occasionally undergo spontaneous recurrences of their MAP psychosis in response to stress without further MAP use after a period of normalcy, during which the pharmacological effects of MAP had worn off [1, 2, 5, 7, 8]. Indeed, a previous study reported that 3 of 235 subjects experienced spontaneous recurrence of their previous MAP psychosis in response to psychological stress, several months after resolution of MAP psychosis [7]. Spontaneous recurrences of the drug's effects are known as "flashbacks" by psychedelic drug users and researchers [9-11]. In this review, flashbacks due to previous MAP psychosis are defined according to the DSM-IV criteria for hallucinogen-persisting perception disorder and a general definition of psychedelic drug flashbacks [12] as a spontaneous recurrence of almost all aspects of MAP-induced paranoid-hallucinatory states following a period of normalcy during which the pharmacological effects of MAP had worn off. Psychedelic drug flashbacks include transient recurrences of visual effects, altered body sensations and a specific disturbing emotion, which originally occur after the immediate effects of hallucinogens had worn off [9-13]. However, the most typical form is recurrent intrusions of the frightening images into awareness for extended periods [9-13]. Flashbacks due to previous MAP psychosis mainly involve paranoid-hallucinatory states almost identical to the previous MAP psychosis as long as 2 years after disappearance of MAP psychosis [14-18]. Thus, flashbacks due to previous MAP psychosis appear to be related to persisting neurobiological alterations. Although the characteristics, symptoms and dynamics of psychedelic drug flashbacks, and several explanatory hypotheses have been studied [9-13], there is a few investigation of the neurobiological bases of both psychedelic drug flashbacks and flashbacks due to previous MAP psychosis. Recently, it has been reported that the stress sensitization associated with noradrenergic hyperactivity with dopanimergic changes, which may develop during MAP abuse, may be important in the development of flashbacks [14-18]. These findings provide useful information on the neurobiological bases of psychedelic drug flashbacks.

Schizophrenia tends to recur in response to stress such as non-specific conflict in human relations. AMP or MAP psychosis can mimic the active symptoms of schizophrenia during the acute or chronic intoxication phase in non-schizophrenic subjects [19]. Flashbacks due to previous AMP or MAP psychosis, which may occur through long-term sensitization to the psychotogenic effects of MAP, may therefore share some pathophysiology with schizophrenia [19, 20].

This review is made up of three parts. The first part addresses the nature, determinants, and significance of stress sensitization associated with catecholaminergic changes in the development of flashbacks due to previous MAP psychosis, based on the author's data (by K.Y.). The second part reviews the differences in characteristics, symptoms and etiology between psychedelic drug flashbacks and flashbacks due to previous MAP psychosis (by K.Y.). The last part focuses on molecular mechanisms of MAP-induced behavioral sensitization, based on recent findings by authors and others (Y.K. and T.N).

2. STRESS SENSITIZATION IN SPONTANEOUS RECURRENCE OF METHAMPHETAMINE PSYCHOSIS

2.1. Stress Reactivity Associated with Noradrenergic Hyperactivity and Increased Dopamine Release

AMP induces enduring sensitization to stress *via* changes in dopaminergic systems. This stress sensitization may explain why psychosis recurs only in subjects with a history of AMP psychosis following exposure to stress [21]. Previous exposure to stressful stimuli induces noradrenergic hyperreactivity to subsequent mild stress [22]. Stress-induced noradrenergic hyperactivity may be a precipitating factor in stress-related psychiatric disorders [23]. It is therefore possible that sensitization to stress associated with noradrenergic hyperactivity and dopaminergic changes are critical to the development of flashbacks due to previous AMP or MAP psychosis. The processes by which flashbacks were triggered, and related peripheral monoamine neurotransmitter function in the development of flashbacks have been studied in female subjects with flashbacks (i.e., flashbackers) [14, 15].

These subjects were 78 physically healthy females without any other psychiatric disorder in the absence of MAP use, including 44 with a history of MAP psychosis, and 34 normal controls (23 MAP users and 11 non-users, none of whom had experienced MAP psychosis or flashbacks). All subjects were recruited from inmates at a women's prison. Twenty-six of the 44 subjects with a history of MAP psychosis experienced flashbacks during their 15-20 months of incarceration; the other 18 did not (i.e., non-flashbackers). The 18 non-flashbackers were selected as having broadly similar times of resolution of MAP psychosis to the times for the 26 flashbackers (within 730 days of blood sampling; flashbackers: mean$\pm$SD=238+209.4 days; non-flashbackers: 249.7$\pm$199.1 days). All subjects had been tested as negative for other illicit drugs by the police. All subjects, except for the 11 non-user controls, had averaged 1 to 10 intravenous injections of MAP (30-60 mg per injection) per day during periods of abuse. Development of flashbacks due to previous MAP psychosis has been questioned by some researchers, because no toxicological studies to rule out unreported drug use by the subjects was conducted [24]. To further rule out candestine use of MAP, we screened for the presence of MAP in subjects' venous plasma when the flashbacks occurred; no MAP was ever found [14].

The 26 flashbackers exhibited reactivated MAP psychosis without reexperiencing the stressful events or the symptoms of post-traumatic stress disorder (PTSD) or acute stress disorder, corresponding to the DSM-IV criteria. The incidence of psychotic symptoms during flashbacks was not significantly different from that of the previous MAP psychosis. On this basis, spontaneous psychosis due to previous MAP psychosis is taken as proven. During flashbacks, the subjects continued to experience paranoid delusions, in which they developed transient auditory (96.2%) and visual hallucinations (34.7%). Auditory hallucinations lasted for 3 to 5 minutes and occurred three to five times per day. Mean Brief Psychiatric Rating Scale (BPRS) subscores for suspiciousness and hallucinatory behavior during their prominent paranoid-hallucinatory flashbacks were respectively 3.6 and 3.4.

Paranoid delusions abated after 2-282 days. Thus, the total duration of these flashbacks varied from 2 to 282 days (mean±SD=65.8±65.0 days). The flashbackers did not appear agitated, as specified by the BPRS anxiety subscores of 2 or less, and continued their light prison duties during flashbacks. Stress is usually defined as a physical or psychological factor that poses a threat to the well-being of the subjects, producing a defensive response [25]. All of the 26 flashbackers had been exposed to threatening events and fear-related psychotic symptoms during previous MAP use. The threatening events corresponded to severe or extreme types of psychosocial stressors (Table **1**). Fear-related psychotic symptoms (perception of threat) included auditory hallucinations threatening the subject with death, frightening visual hallucinations, delusions of being killed by persons concerned, or delusions of being pursued by a gangster or the police (Table **1**). Almost all subjects had been overwhelmingly threatened, taking refuge under a desk or in a closet by these fear-related symptoms. The dominant triggering factor (91.5%) was a mild fear of other people (conflicts or confrontations with inmates, 42.4%; fear of emitting body odor, 6.8%; fear of prison setting, involving fear of the prison staff, 18.6%; fear of husband, 6.6% and fear of other inmates' words and actions, 11.9%). Other factors were the obligation to perform prison labor (8.5%) and sleep disturbance due to tension (8.5%). These factors represent omnipresent psychosocial stressors in the prison.

During flashbacks, plasma norepinephrine (NE) levels were markedly increased. Moreover, a small increase in plasma levels of 3-methoxytyramine (3MT), which is indicative of dopamine (DA) [26], was related to the occurrence of flashbacks [17] (Table **2**). These findings suggest that repeated MAP use with stressful threatening experiences induces increased sensitivity to stress associated with noradrenergic hyperactivity and increased DA release to subsequent mild psychosocial stressors. Since stressful stimuli induce noradrenergic hyperreactivity to subsequent mild stress [22, 23, 27] and AMP induces enduring sensitization to stress [21], stressful threatening experiences together with MAP use may induce increased sensitivity to subsequent exposure to similar but less severe situations, so that heightened NE release would be readily elicited in response to a mild fear of other people. It is documented that 3-MT is formed peripherally and transported into the brain, implying an important correlation between plasma and brain 3-MT levels [28]. The elevated 3-MT levels during flashbacks may therefore reflect increased dopaminergic activity. Stress sensitization, acting through noradrenergic systems, may lead to pathological retrieval of traumatic memories [29]. Reproducing noradrenergic hyperactivity can elicit traumatic memories following exposure to residual traumatic memories [30]. AMP-induced sensitization to stress in dopaminergic systems may be related to the enduring hypersensitivity to the psychotogenic effects of stress in spontaneous recurrences of AMP psychosis [21]. These observations together suggest that a mild fear of other people as a triggering factor elicit memories of MAP psychosis, related to threatening experiences through increased sensitivity to stress associated with a predominance of noradrenergic over dopaminergic hyperactivity. As a result, the flashbacks may have been triggered [17]. The findings may advance our understanding of the neurobiological basis of stress sensitization in flashback phenomena, in recurrent invasive psychotic symptoms, and also in stress-related psychiatric disorders.

2.2. The Nature, Determinants, and Significance of Types of Stress in the Development of Flashbacks

This capter addresses the nature, determinants and significance of three types of stressful frightening experiences. The 26 flashbackers were classified into three subgroups according to a history of stressful events or MAP-induced fear-related psychotic symptoms (i.e., stressful events plus fear-related paranoid-hallucinatory states, stressful events, and fear-related paranoid-hallucinatory states). The numbers of stressful events and fear-related symptoms in each of the 3 subgroups of the flashbackers were significantly higher than for the 18 non-flashbackers (Table **1**).

During flashbacks, the 11 flashbackers with a history of stressful events plus fear-related symptoms had markedly increased NE levels. Both the 7 flashbackers with a history

Table 1. Stressful Experiences During Methamphetamine Use

Flashbackers	Subgroups of flashbackers[a]				Non-flashbackers
	Events plus symptoms		Events	Symptoms	
	n=26	n=11	n=7	n=8	n=18
Stressful events	18 (69.2)[d]	11 (100.0)[d]	7 (100.0)[d]	0 (0.0)	1 (5.6)
Axis IV scores	3.6±1.8[d]	4.7±0.7[d]	4.7±0.5[d]	1.3±0.4	1.2±0.9
Fear-related symptoms	19 (73.1)[d]	11 (100.0)[d]	0 (0.0)	8 (100.0)[d]	1 (5.6)
Frightening auditory hallucinations	13 (50.0)[d]	7 (63.6)	0 (0.0)	6 (75.0)[d]	0 (0.0)
Frightening visual hallucinations	6 (23.1)[c]	3 (27.3)	0 (0.0)	3 (37.5)[c]	0 (0.0)
Delusions of being killed	5 (19.3)[c]	3 (27.3)	0 (0.0)	2 (25.0)[c]	0 (0.0)
Delusions of being pursued	11 (42.3)[c]	6 (54.5)	0 (0.0)	5 (62.5)[c]	1 (5.6)

[a]Events plus symptoms: the 11 flashbackers who had been exposed to stressful events plus fear-related paranoid-hallucinatory states; events: the seven flashbackers who hade been exposed to stressful events alone; symptoms: the eight flashbackers had been exposed to fear-related paranoid-hallucinatory states alone. [b]Percentage do not total 2100 because some subjects had more than one symptoms. [c]P<0.05, [d] P<0.01 compared with the non-flashbackers (the X^2 test).

Table 2. Plasma Monoamine Metabolite Levels of Norepinephrine (NE), Epinephrine (E), 3-Methoxytyramine (3-MT), and Dopamine (DA)

Subgroups	N	Age (years)	NE	E	3-MT	DA
Flashbackers during flashbacks	26	27.5±5.2	0.58±0.55[b,d,f,h]	0.38±0.52	1.36±2.05[e]	0.08±0.15
Flashbaclers with a history of stressful events plus fear-related psychotic symptoms	11	28.3±7.4	0.66±0.46[d,e,f,h]	0.36±0.60	1.93±2.21[f]	0.15±0.19
Flasbackers with a history of stressful events	7	27.9±1.7	0.57±0.86[f,g]	0.30±0.53	1.80±2.53[e]	0.01±0.01
Flasbackers with a history of fear-related symptoms	8	26.0±5.0	0.47±0.38[e,g]	0.45±0.49	0.26±0.74	0.06±0.10
Flashbackers with a single episode	10	28.8±6.6	0.49±0.62[e,g]	0.45±0.33	1.41±2.13	0.04±0.07
Flashbackers with subsequent episode	8	26.1±3.2	0.89±0.214[b,f,h]	0.51±0.62	1.62±0.26[g]	0.07±0.13
Flashbackers during remission	26	27.7±5.5	0.31±0.32	0.35±0.48	0.61±1.23	0.22±0.55
Flashbaclers with a history of stressful events plus fear-related psychotic symptoms	11	28.5±6.7	0.29±0.23	0.47±0.65	0.72±1.61	0.20±0.61
Flasbackers with a history of stressful events	7	28.2±1.6	0.41±0.44	0.21±0.30	0.69±0.98	0.16±0.28
Flasbackers with a history of fear-related symptoms	8	26.5±5.0	0.24±0.35	0.34±0.41	0.40±0.91	0.09±0.15
Flashbackers with a single episode	10	29.1±7.0	0.24±0.25	0.24±0.41	063±0.19	0.12±0.16
Flashbackers with subsequent episodes	8	26.1±3.2	0.27±0.21	0.63±0.64	0.70±1.02[e]	0.13±0.19
Non-flashbackers	18	28.3±8.5	0.34±0.34	0.50±1.00	1.12±2.13	0.10±0.17
User controls	23	28.7±5.0	0.12±0.22	0.63±1.60	0.28±0.74	0.09±0.17
Non-user controls	11	34.7±11.7	0.10±0.13	0.34±0.42	0.85±1.42	0.18±0.27

[a]The square-root transformation was applied to all monoaminergic values. Values are means ±SD. All monoamine metabolite levels are expressed as pmol/mL. [b]P<0.01 compared with the flashbackers during remission. [c]P<0.05, [d]P<0.01 compared with the non-flashbackers. [e]P<0.05, [f]P<0.01 compared with the user controls. [g]P<0.05, [h]P<0.01 compared with the non-user controls (post hoc tests).

of stressful events alone, and the 8 flashbackers with a history of fear-related symptoms alone, had increased higher NE levels during flashbacks. However, their NE levels were lower than in the 11 flashbackers with a history of stressful events plus fear-related symptoms. Plasma 3-MT levels during flashbacks in the two subgroups with a history of stressful events (irrespective of whether they had experienced fear-related symptoms) were elevated (Table 2). These findings suggest that stressful threatening events may further induce sensitization involving DA release, indicated by slightly increased 3-MT levels, in response to mild stressors.

Fear-related symptoms met the general definition of stress [25] as described above. It has been reported that highly emotional experiences (viewing an emotionally arousing story) activate the α-adrenergic system in the regulation of memory storage [31]. Thus, fear-related symptoms may have a great impact on noradrenergic systems, inducing elevated NE levels in flashbackers having a history of fear-related symptoms alone. Collectively, fear-related psychotic symptoms during MAP use may be able to induce noradrenergic hyperreactivity to mild stress, leading to flashbacks.

2.3. Susceptibility to Episode Recurrence in Flashbacks Due to Previous MAP Psychosis and Related Factors

About 50% of subjects with flashbacks had subsequent flashbacks with shortening of remission. More psychosocial stressors are liable to be involved in the first episode of a major affective disorder than in subsequent episodes, implying an increasing susceptibility to recurrence [32]. A previous study to assess stress and symptom levels found a close similarity in the frequency or type of stress experienced by subjects who remained well, and those who relapsed, in bipolar disorder [33]. Yui *et al.* [17,18] examined whether stress reactivity associated with noradrenergic hyperactivity and dopaminergic changes in an initial episode and in any subsequent episode differ in the first flashback. They also studied which factors do and do not contribute to susceptibility to episode recurrence.

In that study, 18 of the 26 flashbackers were selected whose plasma monoamine metabolite levels were assayed during the first flashback episode, and again within 30 days of its passing. Of these, 11 experienced a single flashback episode, and the other nine also experienced subsequent episodes (two flashbacks per subject). During flashbacks, the 8 flashbackers with subsequent episodes had markedly increased NE levels and slightly increased 3-MT levels during flashbacks, whereas the 10 flashbackers with a single episode displayed less increased NE levels than the flashbackers with subsequent episodes, and also slightly increased 3-MT levels (Table 2). The 8 flashbackers with subsequent episodes had a significantly longer duration of imprisonment and significantly earlier age of onset of MAP psychosis than the 10 flashbackers with a single episode. Thus, robust noradrenergic hyperactivity with slightly increased DA release in response to mild stress may predict subsequent flashbacks. Cumulative stress effects [34] or ruminations

associated with aversive events [35] have substantial impact on the reservoir of adaptive energy that affects biological adaptation [34], and may induce further NE changes [35]. Therefore, long-term exposure to distressing situations (imprisonment) in the 8 flashbackers with subsequent episodes may reflect their robust noradrenergic hyperactivity. Evidence suggests that the earlier the age of onset of affective disorders, the higher the rate of episode recurrence [36]. Patients with early onset depression tend to experience recurrent depression [37]. Consequently, there may be a relation between early onset MAP psychosis and susceptibility to subsequent flashbacks. Overall, long-term exposure to distressing situations and early onset of MAP psychosis may be related to susceptibility to subsequent flashbacks *via* robust noradrenergic hyperreactivity.

2.4. Development of Schizophrenic Symptoms in Relation to Dopaminergic Hyperactivity

As described above, the 26 flashbackers continued to experience paranoid delusions, during which they developed transient auditory and visual hallucinations. To determine the role of DA changes in the development of schizophrenia-like symptoms, nine of the 26 flashbackers were selected who had robust increased plasma 3-MT levels during flashbacks, compared to those in the 23 MAP user and 11 non-user controls. In addition, the 7 flashbackers were selected based on the fact that they had lower levels of NE than the user and non-user controls. These 9 flashbackers with higher 3-MT levels more frequently experienced schizophrenia-like symptoms such as passivity phenomena, Gedankenlaut-werden, and thought disorder such as circumstantiality and egorrhoea symptoms. The numbers of these symptoms were significantly greater than in the 7 flashbackers with lower NE levels. Thus, dopaminergic dominance in relation to noradrenergic activity may be related to schizophrenia-like symptoms.

2.5. Involvement of Schizophrenia-Related Mechanisms in Flashbacks: The Role of Stress Sensitization

Approximately 40% of schizophrenic patients show increased psychotic symptoms after administration of CNS stimulant agents such as AMP [38]. In addition, controlled human studies involving drug-free volunteers have demonstrated that a psychotic state can be elicited by administration of small frequent oral doses of AMP [39]. Some subjects with schizophrenia exhibit emergence or worsening of their positive symptoms (e.g., paranoid-hallucinatory states), with increased DA release, following acute exposure to AMP at lower doses that induce no psychotic symptoms in healthy subjects [38]. Stress reduction strategies have a significant effect in on reducing relapse rates in schizophrenic patients [40]. Onset of schizophrenia is frequently precipitated by a stressful event, and psychological stress is well known to precipitate or exacerbate psychotic symptoms [41]. Most schizophrenic patients have enduring hypersensitivity to aversive stimuli, which may be linked to relapses [42] in response to psychological stressors [43]. Moreover, schizophrenia might be associated with chronic recurrence of intermittent sensitized states of DA systems [44]. Several lines of evidence suggest that chronic AMP effects and schizophrenia overlap in the neurobiology of idiopathic and drug-induced psychoses, specifically by augmenting dopaminergic neurotransmission within the central nervous system [45]. Clinical and preclinical data together implicate disturbances in stress-sensitive systems in the etiology of schizophrenia [38, 44]. In this respect, neurochemical sensitization of central DA systems [46], or endogenous sensitization [44] has been proposed as a key step in the progression from vulnerability to an overt symptomatology. Progressive neurochemical sensitization, which may be due possibly to aversive stimuli during early brain development, occurs with increased DA release when the capacity to compensate for perturbation in neural activity is diminished in situations of non-specific stress. This process may underlie the onset and relapse of illness [46]. Likewise, stress sensitization possibly induced by exposure to stressful experiences during previous MAP use, may be responsible for the onset of the flashbacks due to previous MAP psychosis, and further recurrences [17,18].

Although the mesolimbic DA system is implicated in neurochemical sensitization, DA hyperactivity may play only a limited role in generating positive symptoms. This is because DA mediated stimulation of D2 receptors explains only 30% of the variance in the positive symptom changes in response to AMP challenge, and patients in remission show no evidence of increased DA activity [44, 47]. A discrete neurochemical deficit could therefore account for recurrent positive psychotic episodes [44, 47]. In this regard, schizophrenic patients who showed enhancement not only in DA release and but also in NE activity during neuroleptic treatment are likely to relapse soon after neuroleptic withdrawal. This suggests that increased noradrenergic hyperactivity as well as increased DA release is related to relapse prediction [48]. In this respect, spontaneous recurrences of MAP psychosis may overlap with schizophrenia in susceptibility to paranoid-hallucinatory states. In the studies of Yui *et al.* [16, 17], stress sensitization associated with noradrenergic hyperactivity and increased DA release may be important in the development of flashbacks. The fact that robust noradrenergic hyperactivity may be related to susceptibility to further recurrences of flashbacks may parallels a previous report that increased NE levels may predict psychotic relapse in schizophrenia [48, 49]. These considerations suggest that stress sensitization associated with noradrenergic hyperactivity and increased DA release in response to mild stressors corresponds to the neurochemical or endogenous sensitization proposed by Lieberman *et al.* [46] and by Laruelle [44] as the pathophysiology of schizophrenia. Flashbacks and schizophrenia may therefore share common underlying mechanisms of susceptibility to paranoid-hallucinatory states, such as stress sensitization, noradrenergic hyperactivity and enhanced DA release.

There are several other possible discriminators between MAP psychosis and schizophrenia: speed of onset, the dream-like quality of experiences, tendency toward visual hallucinations, brisk emotional reaction (usually in the direction of anxiety), the brevity of psychotic episodes, frequent aggravation and the absence of thought disorder (i.e., fragmented and bizarre associations and disorganized speech) [20]. Although there are a number of similarities between MAP psychosis and schizophrenia, the two psychotic disorders in fact have only susceptibility to paranoid-hallucinatory states (MAP-induced abnormal behavior in experimental animals) in common. Therefore, spontaneous

recurrences due to previous MAP psychosis could act as an appropriate model of susceptibility in regard to paranoid-hallucinatory states.

Long-term use of antidepressant drugs may, in some cases, induce switching and cycle acceleration in bipolar disorder, tolerance to the effects of antidepressants during long-term treatment, onset of resistance upon rechallenge with the same antidepressant drug, all worsening the long-term outcome and withdrawal symptoms. These phenomena in susceptibile subjects can be explained by the oppositional model of tolerance. Such processes may sometimes operate unopposed and increase vulnerability to relapse. The hypothalamic-pituitary-adrenal (HPA) axis can moderate both sensitization and tolerance [50]. Moreover, it has been postulated that both sensitization to stress and episode sensitization occur in mood disorders [32]. As described above, schizophrenia might be associated with chronic recurrence of intermittent sensitized states of DA systems [44]. Progressive neurochemical sensitization is proposed as the underlying mechanism of the onset and relapse of schizophrenia [46]. Collectively, oppositional tolerance may be included in the pathophysiology of schizophrenia.

To conclude this section, flashbacks and schizophrenia share common underlying mechanisms of susceptibility to paranoid-hallucinatory states, such as stress sensitization. Moreover, stress sensitization is a common neurobiological mechanism in episode recurrence of both illnesses.

2.6. Molecular Mechanisms of Susceptibility to MAP Psychosis and Related Flashbacks

Susceptibility to MAP psychosis is related to genetic factors of the individual. Several lines of evidence suggest that MAP psychosis is related to the function of dopamine transporter protein (DAT) [51、52]. DAT is the site of presynaptic reuptake of DA, an event that terminates its synaptic activity. It is reported that DAT genotype is associated with cocaine-induced paranoia (allele frequency for allele 9 = .16 for those without paranoid experiences) [53]. Recently, Ujike *et al.* [52] investigated the association of MAP dependence/psychosis and the hDAT1 gene (SLC6A3) encoding the DAT, which is the primary site of MAP activity in the brain. They examined four exonic polymorphisms of the hDAI1 gene. Subjects with MAP psychosis, whose psychosis lasted for 1 month or more after cessation of MAP use, had a significant excess of nine- or fewer repeat alles of the a variable number of tandem repeats (VNTR) in 3'utranslated region (3'UTR) of the hDAT1 gene, suggesting that the presence of nine or few repeat alles of hDAT1 is a strong risk factor for worse prognosis of MAP psychosis [52]. Moreover, the complexes of α-synuclein and DAT facilitate membrane clustering of the DAT, thereby accelerating DA uptake *in vitro* [51]. In this respect, the α-synuclein gene may be associated with MAP psychosis and dependence in female subjects [51]. Moreover, neuroprotective effects of glutathione or its related compounds have been reported on MAP-induced neurotoxicity [54]. Gene encoding glutathione S-transferases (GSTs) have been considered as candidates for MAP psychosis [54]. Indeed, a functional polymorphism (Ile105Val) on exon 5 of the glutathione S-Transferase P1 (GSTP1) gene could be a risk factor of the development to MAP-induced psychosis [55]. Ujike *et al.* [56] further reported that one of dopamine receptor-encoding genes DRD2 of TaqIA A1/A1 type, with which reduced density of D2 receptor is associated, may reduce the risk of flashbacks.

3. COMPARISON IN CHARACTERISTICS, SYMPTOMS AND ETIOLOGY BETWEEN PSYCHEDELIC DRUG FLASHBACKS AND FLASHBACKS DUE TO PREVIOUS METHAMPHETAMINE PSYCHOSIS

3.1. Characteristics, Symptoms and Etiology of Psychedelic Drug Flashbacks

Hallucinogenic drugs include cannabis (marijuana, hashish and tetrahydrocannabinol [THC]), lysergic acid diethylamide (LSD), mescaline and psilocybin [57]. LSD is the most powerful, and marijuana the least powerful. The acute effects of these drugs includes an increased sensitivity to all variety of stimuli (e.g., prolonged visual abnormalities), hallucinations, a waxing and waning of the intensity of colors, prolonged afterimages, illusions, changes in depth perception, disturbances of body images, and alterations of cognition and judgment. Recurring drugs effects after the drug has left the body ("psychedelic drug flashbacks") date back for decades [58]. Indeed, prolonged sensitization to the delicate phenomena of perception have been reported for a long time [59].

Three types of flashback have been reported [60]: (1) "perceptual flashbacks", meaning transient recurrences of visual effects similar to the LSD experiences, ranging from flashes of light through shimmering or undulating field of vision (which psychedelic drug abusers sometimes view as "free trips"), to well-formed visual hallucination; (2) "somatic flashbacks", transient recurrent states of altered body sensations; (3) "emotional flashbacks", an intense recurrence of a specific disturbing emotion undergone during a psychedelic experience. Recent studies found that spontaneous recurrence of some of the symptoms which appear during the LSD intoxication divided fall into two types [58, 61]. The first type is psychedelic drug flashbacks as described above. The second type is hallucinogen persisting perception disorder (flashbacks) (HPPD), as recognized in DSM-III-R (1986); these include geometric hallucinations, false perceptions, flashes of color and other perceptional symptoms, but do not include psychotic paranoid hallucinatory states [62]. In general, HPPD is long-term, spontaneous, intermittent or continuous, and involves pervasive re-experiencing of one or more perceptual symptoms, causing significant distress or impairment in social, occupational or other areas of functioning [62, DSM-III-R]. Almost all previous studies were performed in the 1970s, before operational criteria for HPPD were published in DSM-III-R. It is therefore difficult to interpret whether subjects in these studies meet the criteria for DSM-III-R or DSM-IV-TR criteria for HPPD. The above mentioned type (1) symptoms may meet DSM-III-R and DSM-IV criteria A of HPPD. There is a slight prevalence of HPPD; for example, 9 of 110 LSD users (8%) exhibited specific visual phenomena, as described in DSM-III-R [63].

According to a previous study, among the military population, the fraction of responders who reported flashbacks arising from the use of LSD was 22.9%, whereas that of marijuana was 1.3% [64]. Other studies reported that, among non-military volunteers, LSD and marijuana were abused by 97% and 3% of the subjects respectively, and 57 (66%) ex-

perienced mainly perceptual flashbacks [12]. The delay between drug intake and flashback varied from a few days or a week to over 2 years [12]. Subjects continued to experience flashbacks for a long time, over 1-2 years for 82% of the subjects [12]. Previous clinical studies reported that 52% of 207 soldiers who reported the heavy use of LSD and/or marijuana experienced the perceptual flashbacks [65], and that 66 % [66] or 22.9% [67] were reported to have LSD flashbacks. When asked to rate their flashbacks (mainly LSD flashbacks) in positive or negative terms, a surprising number (70% of the 87 volunteers) perceived them as non-threatening [12]. The differing incidence of flashbacks between marijuana use and LSD flashbacks is significant ($p<0.01$) [64, 67].

Psychedelic drug flashbacks have been reported to occur during times of psychological stress [68], relaxation or everyday activities, during intoxication by alcohol, barbiturates, antihistamines, fever and flashing light [60]. Dominant factors triggering flashbacks were an anxiety-provoking situation for 20%, and pleasurable thoughts and situations for 21% of the 87 subjects [11]. A dark environment is been reported to be one of the most common triggers of visual phenomenology of flashbacks (e.g., genomic pseudohallucinations, perception of peripheral fields and flashes of color) [69].

Psychedelic drug flashbacks have been suggested to have multiple etiologies [60]. These are five main theories are: in the first, fear or anxiety is related to the development of psychedelic drug flashbacks: a) the recurrent images seem to be a return of traumatic perceptions, i.e., images of the drug experience that were overwhelmingly frightening at the time they were hallucinated [9]; b) precipitated anxiety or interferes with function may be important in spontaneous recurrence of marijuana effects such as unusual visual or somatic sensations [70]; c) a perception may be learned while an individual is experiencing high anxiety levels, and then recur in an anxiety provoking situation (learned theory) [60]; d) prolonged LSD flashbacks may persist, maintained by psychodynamic processes (i.e., conversion reactions) due to fear or anxiety during the drug experience [71]; e) if the experience is of a frightening nature, the memory of the event may be unusually intense, so that portions of the psychedelic drug experience may be easily remembered (the intensified memory theory) [60, 72]. In the second theory, once awareness of intense visual, perceptual, or body sensations has been noted, a subsequent recurrence of the same sensation may be induced when the individual attaches a negative or fearful connotation to the belief that a flashback is occurring (the sensitization theory) [60]. In the third theory, flashbacks may be related to the toxic effects of psychedelics on visual, auditory, and tactile systems, causing transient neurophysiological changes that cause recurrence of hallucinations (physiological theory) [68, 69, 73]. In the fourth theory, the psychedelic drug itself may cause a periodic release of these effects under stress (biochemical theory) [73]. In the fifth theory, LSD-related HPPD is associated with sympathetic arousal because clonidine, which decreases adrenergic activity, alleviates the symptoms [61]. Another report reclassified these theories into three principal explanations: 1) the perceptual phenomena represent a heightened awareness of normal visual phenomena; 2) some flashbacks represent merely instances of normal memory accompanied by emotional distress; 3) flashbacks are manifestations of learned, imaginative role-playing, hysterical phenomena [58]. Regarding the etiology of HPPD, HPPD is a disinhibition of visual processing related to a loss of serotonin receptors on inhibitory interneurons [62].

This diversity of theoretical speculation suggests that flashbacks are a complex phenomenon involving an interplay of physiological, personality, psychological, and social factors [11]. The flashbacks are probably primarily psychological rather than chemical in nature, and may be related to traumatic events within the LSD intoxication itself [68]. Indeed, a widely held view is that LSD flashbacks represent a novel way of reacting to stress learned while in the LSD state [68].

3.2. Comparison Between Psychedelic Drug Flashbacks and Flashbacks Due to Previous MAP Psychosis

Psychedelic drug flashbacks or HPPD include transient recurrences of visual effects, altered body sensations or a specific disturbing emotion [60]. These symptoms constitute the recurrence of some part of the psychedelic drug effect [74] and do not present disruption to the flow of normal consciousness, suggesting that they do not meet general category of dissociative phenomena [72]. An earlier study reported that the most symptomatic form of LSD flashbacks was repeated intrusions of frightening images [9]. The most psychedelic drug flashbacks do not include vivid, frightening auditory and visual hallucinations; the persisting paranoid delusions which usually occur in flashbacks due to previous MAP psychosis.

Psychedelic drug flashbacks may sometimes be related to traumatic events within the LSD intoxication itself [68], and are triggered by psychological stress [68], anxiety [12] or a dark environment [69]. Psychedelic drug flashbacks may therefore be related to frightening images experienced during the drug abuse. The etiological theories described above indicate that fear or anxiety may be related to the occurrence of psychedelic drug flashbacks. However, stressful frightening experiences described in flashbacks due to previous MAP psychosis were never reported in relation to the development of psychedelic drug flashbacks.

Psychedelic drug flashbacks may be the recurrence of a perception which was learned while an individual was experiencing heightened anxiety [60], and may therefore recur in anxiety-related situations. In contrast, in the development of flashbacks due to previous MAP psychosis, a mild fear of other people acting as a triggering factor, may have elicited memories of MAP psychosis related to threatening stressful experiences through increased sensitivity to stress associated with a predominance of noradrenergic over dopaminergic hyperactivity. Flashbacks due to previous MAP psychosis may be spontaneous psychosis *via* increased sensitivity to stress associated with catecholaminergic changes induced by stressful frightening experiences. Most studies on psychedelic drug flashbacks were performed in the 1970s, let us add that fear or anxiety during drug use is important not only in the development of flashbacks due to previous MAP psychosis, but also psychedelic drug flashbacks.

4. MOLECULAR BASES OF METHAMPHETAMINE-INDUCED BEHAVIORAL SENSITIZATION

Single or repeated exposure to psychostimulants such as amphetamines (amphetamine and methamphetamine) or cocaine results in augmented behavioral response to subsequent re-exposure to the drugs after their withdrawal. This behavioral sensitization seems to be part of the neurobiological basis involved in relapse in some cases of schizophrenia as well as amphetamine psychosis. Various lines of evidence indicate that psychostimulant-induced behavioral sensitization is a kind of neuroplasticity requiring changes in gene expression. Inhibition of de novo protein synthesis blocks establishment of the sensitization, the sensitization-inducing psychostimulants evoke expression of immediate early genes encoding transcription factors in brain regions involved in establishment of the sensitization; sensitization-specific modifications of gene expression must be identified. We review recent advances in this field below.

4.1. Neuroplasticity-Related Molecules

Long-term potentiation (LTP) is a basic model of long-lasting physiological neuronal plasticity including learning and memory. Gene expression followed by de novo synthesis of proteins is required for establishment of its late phase (L-LTP) [75]. Behavioral sensitization lasts so long that it is possible to detect the augmented behavioral response in rodents over weeks or months after its induction by pre-exposure to stimulants [76, 77]. These observations suggest that stimulant-induced behavioral sensitization also involves gene expression. Indeed, inhibition of gene expression by administration of protein synthesis inhibitors following stimulant treatment blocks sensitization, also in the case of the L-LTP [78, 79]. Dopaminergic projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) is important in initiating and establishing behavioral sensitization [76, 77]. Sorg and Ulibarri showed that injection of the protein synthesis inhibitor anisomycine into the VTA, prior to each daily pretreatment with cocaine resulted in blockade of behavioral sensitization. In contrast, administration of anisomycine into NAc, the target site of VTA dopamine neurons, did not block sensitization, indicating that changes in gene expression following repeated stimulant treatment in specific brain regions are critical in establishing the behavioral sensitization [79].

The nerve growth factor (NGF) family of neurotrophins are known to activate the Ras/mitogen-activated protein kinase (Ras/MAPK) signal transduction cascade, and accumulating evidence indicates that they have an important role in activity-dependent neuroplasticity [80, 81]. Pierce *et al.* showed that inhibition of MAPK signaling by local injection of the MAPK kinase (MEK) inhibitor PD98059 into the VTA 20 min prior to daily repeated treatment with cocaine resulted in blockade of behavioral sensitization after 14-days withdrawal [82]. Along with the sensitization-inducing property of neurotrophin-3 (NT-3) injected into the VTA [81], MAPK signaling seems to be important in the initiation of stimulant-induced sensitization.

For establishment of long-lasting behavioral sensitization, the glutamatergic projections into the VTA-NAc dopamine system and its associated structure of caudate-putamen (CPu) also have a critical role, and their major originating sites are the prefrontal cortex (PFC) and the amygdala (AMY) [83-85]. It has recently been found that tissue-plasminogen activator (tPA) is an important molecular factor in the establishment of activity-dependent neuronal plasticity [86-88]. Acute restraint stress induced tPA in the central and medial AMY of mice and the induction of tPA in AMY contribute to an increase in anxiety-like behavior [86]. The tPA has a critical role in the expression of L-LTP, through conversion of the precursor pro-BDNF to mature BDNF, which is a vital protein for the expression of L-LTP [87]. Nishikawa's research group [89] detected stimulant-induced expression of tPA mRNA in a restricted population of medial PFC neurons by in situ hybridization analysis, and confirmed that they projected into the medial striatum by using a retrogradely labeling fluorescent dye. Although the precise role of psychostimulant-induced tPA in medial PFC remains to be investigated, this protease might mediate long-lasting alternation of synaptic activity in the cortico-striatal path associated with stimulant-induced behavioral sensitization.

Collectively, these observations suggest that stimulant-induced changes in plasticity-related neural function in specific circuits are involved in the establishment of psychostimulant-induced long-lasting behavioral sensiti-zation.

4.2. Transcription Factors

Immediate early gene expression, such as c-fos or zif268, is generally a marker of activity changes in neural circuits followed by induction of specific genes. Sensitization-inducing stimulants are known to evoke c-fos gene expression in specific brain regions including VTA, NAc, CPu, PFC, and AMY [90]. Low doses of antipsychotics used for treatment of schizophrenia (4 mg/kg clozapine and 0.1 mg/kg haloperidol) attenuate amphetamine-induced c-fos expression in PFC and block the induction of behavioral sensitization [91], suggesting that changes in gene expression following antipsychotic-sensitive c-fos are important in initiating of stimulant-induced sensitization.

In the case of a short withdrawal period (less than 24h), repeated administration of with stimulants attenuates the evoking ability of immediate early genes, indicating that a homeostatic mechanism in this tolerance phenomenon to stimulants [92-94]. However, longer withdrawal periods exceeding 3 days results in enhancement of the immediate early gene expression-evoking property of the stimulants in animals pretreated with subchronic stimulants prior to their withdrawal [95-99]. Ostrander *et al.* [100] showed that environmental factors affect not only behavioral augmentation but also enhanced changes in c-fos mRNA expression elicited by amphetamine challenge after ten to twelve days of drug withdrawal. The relatively slow and progressive changes in the regulation of gene expression following subchronic treatment with stimulants, therefore, contribute to establishing of behavioral sensitization.

The c-fos gene encodes a transcription factor of AP-1 complex, and its stimulant-evoked expression in specific brain regions, including VTA, NAc, CPu, PFC, and AMY, might elicit subsequent changes in expression of various genes sustaining tolerance or sensitization. Hope *et al.* [101] identified unusually stable variant of a component of AP-1 complex encoded by fosB gene, delta FosB, after subchronic cocaine treatment [101]. Repeated treatment with cocaine

resulted in accumulation of AP-1 complex, including a stable isoform of the delta FosB molecule in the cortex and striatum [101, 102]. The abnormal accumulation of the transcription factor during subchronic drug treatment induces the following changes in gene expression during the withdrawal period from the drug. Indeed, one of the down-stream target genes, cycline-dependent kinase 5 (cdk5), was identified as being induced after subchronic cocaine treatment [103]. Cdk5 is known to mediate phosphorylation of DARPP-32 and DARPP-32, which is important in protein kinase A (PKA)-signaling from dopamine D1 receptor [104]. Increased phosphorylation of DARPP-32 by Cdk5 attenuated signaling *via* the D1 receptor and PKA. This suggests that induction of cdk5 expression by subchronic cocaine treatment *via* increased delta FosB mediates a homeostatic negative feedback response so as to minimize the behavioral impact of subsequent stimulant administration. In support of this hypothesis, administration of Cdk5 inhibitor led to enhanced the behavioral effects of repeated cocaine injection [103].

NAC-1 is a unique brain POZ (poxvirus and zinc finger)/BTB (Broad-complex, Tramtrack, and Bric-a-brac) protein of transcription factor that is upregulated in the NAc three weeks after chronic cocaine self-administration [105]. This induction of NAC-1 also seems to be part of the homeostatic response to repeated cocaine injection, because knock down of NAC-1 by microinjection of antisense oligonucleotide into NAc enhances the motor stimulant response to an acute cocaine injection [106], and virus-mediated over-expression of NAC-1 clearly prevents the development of cocaine-induced behavioral sensitization [107]. The genomic sequence of murine NAC-1 gene includes a functional AP-1 binding site with enhancer activity, suggesting that changes in AP-1 activity in NAc after discontinuation of subchronic exposure to psycho-stimulants leads to the induction of NAC-1 expression [108]. Identification of the downstream target of NAC-1 could provide clues to the prevention of ths sensitization-related psychiatric dysfunctions discussed in this article.

4.3. G-Protein Signaling

In contrast to homeostatic responses to repeated psychostimulant injection, one of the acutely induced genes, GNB1 encoding G-protein beta subunit (Gbeta1), seems to mediate the initiation of behavioral sensitization. In rats or mice, a single injection of stimulants induced GNB1 expression in the NAc or striatum 2-4 hr after administration, whereas no change was detected following subchronic treatment [109, 110]. Antisense oligonucleotide-mediated knockdown of GNB1 results in blockade of cocaine-induced behavioral sensitization [108]. Consequently, changes in G-protein signaling from G-protein coupled receptors (GPCRs), such as dopamine receptors or other unknown GPCRs, might be involved in the initiation of sensitization.

4.4. LHPA Axis

The limbic-hypothalamo-pituitary-adrenal (LHPA) axis plays an important role in stress response, and its activity seems to be closely related to the establishment of psychostimulant-induced behavioral sensitization. The Fischer 344 (F344) rat exhibits greater LHPA axis responses than the Lewis (LEW) rat. Inter-strain difference in physiological properties of the LHPA axis also show in greater sensitization in F344 than LEW [111-113]. Steckler and Holsboer [114] showed that transgenic (TG) mice expressing a neurofilament-promotor-driven antisense RNA complementary to a fragment of glucocorticoid receptor (GR) cDNA did not develop amphetamine-induced behavioral sensitization, but rather behavioral tolerance. Since the expression of GR in the TG mice was reduced to approximately 50% of that in control mice, greater stress response should result in greater sensitization [114].

Recently, glucocorticoid-induced receptor (GIR, GPR83) was studied in the rat brain. It was originally identified as an orphan GPCR induced by glucocorticoid and cyclic AMP in murine T-lymphocytes [115]. In situ hybridization data indicate that GIR mRNA is expressed mainly in neurons, with intense staining localized to the nucleus of the lateral olfactory tract, hippocampus, neocortex, and limbic cortical regions [116]. Interestingly, GIR mRNA expression was upregulated 1.7-fold compared with saline-treated controls in PFC after 7-day withdrawal from 5 consecutive daily amphetamine injections [116]. Identification of the natural ligand for this putative member of the peptide receptor family could provide new clues to the relation between LHPA axis response and psychostimulant-induced behavioral sensitization.

4.5. Developmental Regulation and Mrt1

Independent ontogenic studies in rats clearly show the existence of a critical period for induction of long-lasting behavioral sensitization to psychostimulants; pretreatment of rats before postnatal week 3 with amphetamines does not result in long-lasting behavioral sensitization [117, 108]. Nishikawa [119, 120] has hypothesized from the late-developing property of stimulant-induced sensitization that stimulant-responsive molecular and/or neuronal systems leading to the establishment of long-lasting behavioral sensitization are mature or available only after the critical period.

Based on the Nishikawa's hypothesis, his research group [120] recently performed arbitrarily primed PCR-based comparison of the partial transcriptome from rat cortices between neonatal (postnatal days 8, PD8) and young adult (PD50) rats that had received methamphetamine or saline They identified a novel molecule named methamphetamine-responsive transcript 1 (mrt1), in the rat brain [120] that shows increased cortical expression in the adult period, but not the infant period. The complete sequence of mrt1 cDNA revealed that at least two types of mrt1 mRNA, mrt1a and mrt1b, encoded isoforms of proteins, Mrt1a and Mrt1b. Expression of mrt1b, but not mrtla, in rat cortices was upregulated immediately after a single systemic injection of methamphetamine in the adult rat meocortex. The responsiveness of cortical mrt1b expression to acute methamphetamine was specifically detected after the critical period around postnatal week, for the induction of long-lasting behavioral sensitization to amphetamines, implicating this molecule in the induction of sensitization [120]. Moreover, basal expression of mrt1 in the cortex increased after 2-week withdrawal from 5 consecutive daily injection of methamphetamine, and additional induction of mrt1 by methamphetamine or cocaine challenge was not detected [121]. These data suggest that mrt1 is also important in the establishment and/or mainte-

nance of long-lasting behavioral sensitization after discontinuation of psychostimulants.

The protein encoded by mrtl (Mrtl) is a novel member of the sorting nexin family, with PDZ (Postsynaptic density 95/Discs large/Zona occludens-1), PX (phox) and RA (Ras association) domains. Proteins containing the PX module play important roles in intracellular signaling through its phosphoinositide-binding property, and the PX domain also binds to Src homology 3 (SH3) domains [122]. Also, Mrtl is mostly a RasGTP effector, because of its RA module which is found in RasGTP effectors [123]. Phosphoinositide 3-kinase (PI3-kinase) signaling is activated by calcium/calmodulin-dependent protein kinase II (CaMKII) following Ca2+ influx and the Ras/MAPK signaling is known as an information superhighway between the cell surface and the nucleus, leading to the activation of specific transcription factors as its final targets [82, 83]. These signaling cascades are believed to contribute to the establishment of both activity-dependent physiological neuroplasticity and drug-induced long-lasting changes in neuronal function [124, 125]. It follows that Mrtl should be important in establishing psychostimulant-induced long-lasting behavioral sensitization as a unique signaling molecule whereby cross talk takes place between PI3-kinase and Ras/MAPK paths.

It is also well known that the PDZ domain recognizes its specific PDZ ligand (PL), and that the PL is located at the C-terminal of the interacting target molecule [126]; PDZ-PL interactions play important roles in organizing various proteins in the same signal transducing cascade at synaptic sites [127] Recently, Joubert *et al.* showed that one of the Mrtl-associated molecules was 5-hydroxytriptamine type 4 receptor (5-HT_4) [128]. Since the central 5-HT_4 modulates dopamine transmission [130], changes in any interaction between the dopaminergic and serotonergic neuronal systems *via* Mrtl may contribute to initiation, establishment or maintenance of psychostimulant-induced behavioral sensitization.

4.6. Possible Changes in the Dendritic Cytoskeleton

Establishment of long-lasting neuroplasticity is now known to be associated with morphological changes in dendritic spines [130]. Morphological abnormalities of dendritic spines are observed in the brain in various psychiatric disorders, including mental retardation, drug or alcohol addiction and schizophrenia [131, 132]. Repeated exposure to amphetamine or cocaine increases in the density of dendritic spines and the number of dendritic branches in the PFC and NAc [133, 134]. Administration of Cdk5 inhibitor, which enhances the behavioral effects of repeated cocaine exposure, suppresses such morphological changes, which might therefore be of consequence in homeostatic negative feedback regulation [135]. More studies from the molecular viewpoints are added to settle the relation between dendritic morphological changes and psychostimulant-induced behavioral senstization.

Activity-dependent regulation of both recruitment and depolymerization/polymerization of actin molecules are critical molecular events in sustaining activity-dependent changes in dendritic spine morphology. The Rho family small GTPases and their interacting molecules are the main keys mediating the regulation of these actin cytoskeleton dynamics in spines [136]. However, the effects of single or repeated exposure to psychostimulants on activities of these molecules remain to be investigated. Various lines of evidence, described above, suggest that exposure to psychostimulants evokes changes in gene expression in specific neural circuits, followed by long-lasting functional changes associated with behavioral sensitization and tolerance. Understanding of the molecular cascade will be doubtlessly important in the treatment of relapse or recurrence of psychotic states in patients suffering from drug addiction and/or schizophrenia.

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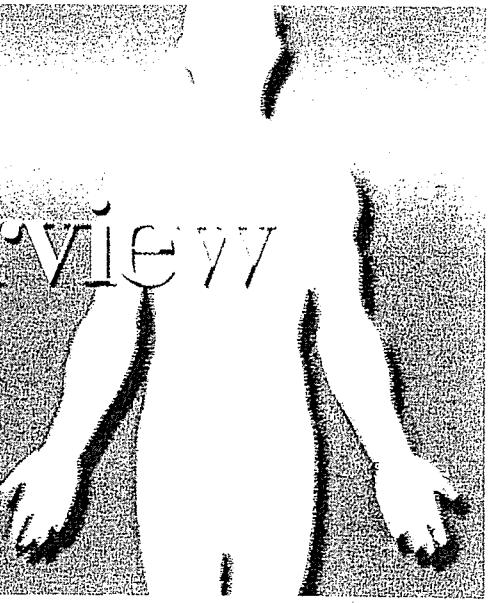
基礎研究の新たな方向性を解く25

疾患解明 Overview

統合失調症の分子機構研究の最前線

西川 徹



疾患の概要

統合失調症は，思春期・青年期を中心に0.8％の高率で発症するうえ，慢性化しやすく，幻覚・妄想などの陽性症状と感情平板化・意欲減退などの陰性症状に大別される多彩な精神症状を呈する，重大な精神疾患である．脳における明確な神経病理学的変化を欠き原因は不明であるが，治療薬や本症類似の異常を惹起する薬物の作用から，脳内のドーパミン伝達亢進およびNMDA型グルタミン酸受容体の機能低下が示唆されている．最近，こうした薬理学的所見と，ゲノム解析，脳内分子の発現・動態の解析，遺伝子操作動物の研究などの成果を取り入れた，病因・病態の分子機構と治療法開発への新たなアプローチが進展しつつある．

はじめに
—統合失調症の臨床的・生物学的特徴

統合失調症（schizophrenia）は，思春期から青年期前半を中心に0.8％の高率で発症し，慢性化しやすい重大な障害である．治療薬に抵抗する症状のため，現在もわが国だけで20万人以上が入院生活を余儀なくされている．長期予後調査によると，1952年に抗精神病薬が導入された後も，症状がほとんど消失する例は3割に満たない[1]．

本症では，思考，知覚，感情，意欲などの脳機能が広汎に障害され，多彩な精神症状が出現する．これらの症状は一般に，陽性症状と陰性症状に分類される（概念図）．陽性症状は，妄想，幻覚，統制を欠いた行動・興奮など，発症すると新たに産出されたようにみえる異常を指す．陰性症状は，諸精神機能の減弱・脱落を反映し，会話・思考内容の貧困化，感情鈍麻（感情表出の平板化と不調和），意欲減退・引きこもり（目的指向的な行動の低下）などを含む．

このように特徴的な精神機能異常が認められるにもかかわらず，脳における変性，炎症，その他の神経病理学的変化は見出されていない[1]．近年，MRI（magnetic resonance imaging）を用いた脳体積研究（voxel-based morphometry）により，左上側頭回，左内側側頭葉，前頭葉皮質各領域，視床，海馬をはじめとする特定の脳部位に体積変化が生じていることが示唆され，形態学的異常が見直されるようになった[1)~3)]．しかし，対応する神経病理学的所見を欠き，神経変性疾患に比べて軽微であり経過も異なること，可逆性の脳体積変化を示す疾患も報告されていることなどを考え合わせると，神経変性疾患と同一視することはできない．PET（positron emission tomography），SPECT（single photon emission computed tomography），近赤外線スペクトロスコピー（near-infrared spectroscopy：NIRS），functional MRIなどの脳機能画像解析技術によって検出される，脳血流，

Cuttingedge of molecular schizophrenia research
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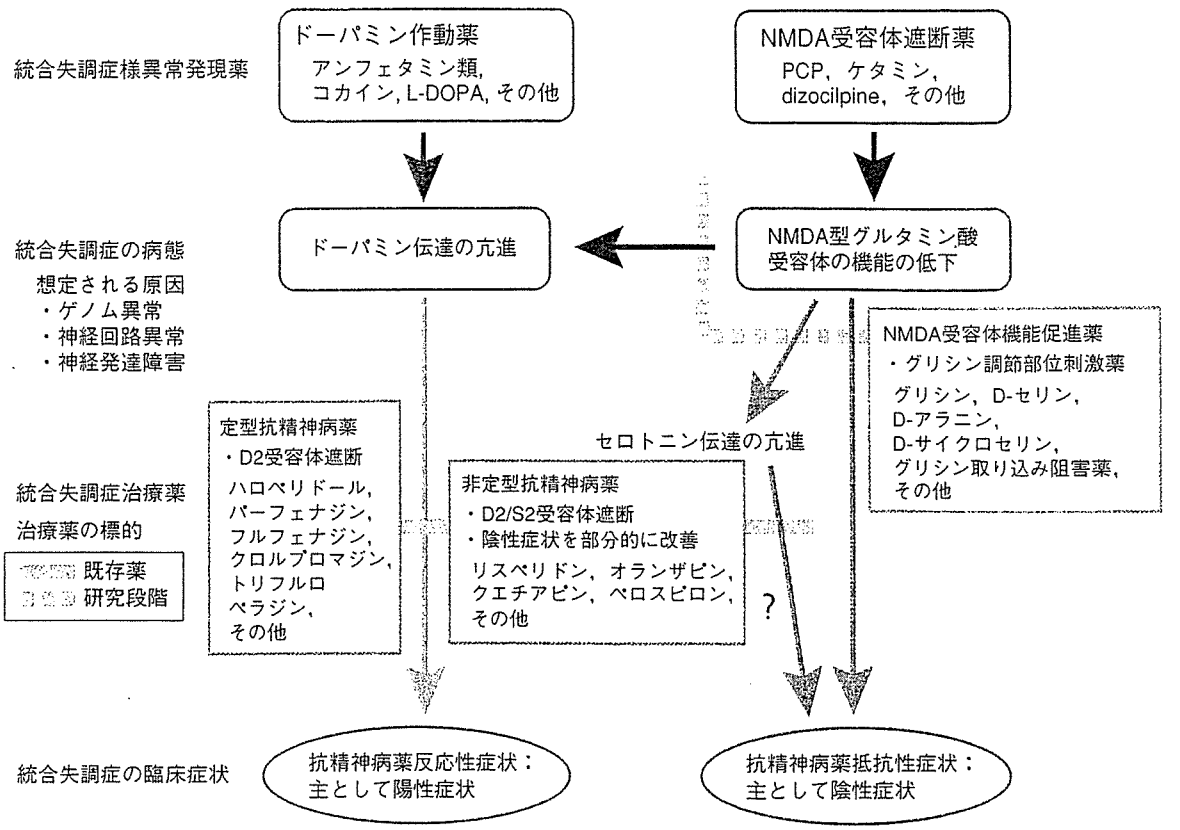
●概念図● 薬理学的にみた統合失調症状と神経伝達系との関連（仮説）



統合失調症では原因となる分子異常がいまだ同定されていないが，ドーパミン（DA）作動薬および遮断薬と，NMDA受容体の遮断薬およびグリシン調節部位に作用する機能促進薬をはじめとする種々の向精神薬の作用にもとづいて，DA伝達の亢進は主として陽性症状に，NMDA受容体を介するグルタミン酸（Glu）伝達の低下は陽性・陰性双方の発現に関与すると推察されている（図1および図2も併せて参照）．NMDA受容体の機能低下は，二次的にDA伝達を亢進させるため，陽性症状が出現することと矛盾しない．NMDA受容体機能促進薬が陰性・陽性双方の症状を改善する可能性については，現在，臨床的検証が続けられている．セロトニン伝達系の陰性症状への関与は，陰性症状を部分的に改善する薬物がS2型セロトニン受容体を強く遮断することや，NMDA受容体遮断薬投与後のセロトニン放出増加などにより示唆されるが，さらに検討が必要である（？マーク）．以上の仮説は，統合失調症の分子異常が，必ずしもDAやGluの伝達系内に限局することを意味せず，本症が異なる原因をもつ疾患群であると考えられることから（異質性），これら伝達機構の制御系を含めて複数見出される可能性がある

糖代謝，または神経伝達の状態，種々の眼球運動および事象関連電位，prepulse inhibition（突然の音や光の強い刺激への驚愕反応が，比較的弱い類似の刺激を先行させると抑制される現象で，知覚情報処理と密接に関係する）等における健常者との差異が明らかになりつつあるが[1)~3)]，生物学的マーカーとして確立されるには，さらに時間を要する．

したがって，診断は表1に示すように，臨床症状とその持続を指標とした国際的な基準によって行われている[1)]．こうした基準では，症状の特徴により，①解体型（まとまりのない行動や会話，および平板または不調和な感情が目立つ），②妄想型（妄想や幻覚が主体），③緊張型（表1下の緊張病性の行動のうち2つが優勢）などの亜型が分類されている．症状，経過，治療反応性，生物学的検査所見などから総合的にみると，統合失調症は原因の異なる複数の疾患から構成さ

表1　DSM-Ⅳによる統合失調症の診断基準

A. 特徴的症状
①から⑤の症状のうち2つ以上が，治療が成功したときを除き，おのおのは1カ月以上の期間ほとんどいつも存在
　①妄想
　②幻覚
　③まとまりのない会話（例えば頻繁な脱線または滅裂）
　④ひどくまとまりのないまたは緊張病性*の行動
　⑤陰性症状：感情の平板化，思考の貧困または意欲の欠如
B. 社会的または職業的機能の低下
C. 期間：少なくとも6カ月持続
D. 失調感情障害と気分障害の除外
E. 物質や一般身体疾患が原因となるものを除外
F. 自閉性障害や他の広汎性発達障害の既往があるときは，顕著な幻覚や妄想が1カ月以上存在

DSM-Ⅳ（diagnostic and statistical manual of mental disorders, fourth edition）はアメリカ精神医学会が作成し，国際的に広く用いられている精神疾患の診断基準．＊緊張病性の行動：①カタレプシーまたは昏迷として示される無動症，②過剰な運動活動性，③極度の拒絶症，④奇妙な随意運動（常同運動，顕著なしかめ面ほか），⑤反響言語または反響動作

れている異質性をもつ可能性がある．

統合失調症は弧発性だけでなく家族性に発症することがあり，遺伝子を多く共有するほど一致して発症する確率が高くなる[4]．患者との発症一致率は，①一般人1％，②遺伝的共通度が12.5％のいとこが2％，③共通度25％では，叔父・叔母2％，甥・姪4％，孫5％，異父母の兄弟姉妹6％，④共通度50％になると，両親6％，兄弟姉妹9％，子供13％，二卵性双生児17％，⑤共通度100％の一卵性双生児では48％に達する[4]．また，養子の研究からも，環境要因よりも遺伝的背景の方が統合失調症の発症に大きな役割を果たすことが報告され，本症では，遺伝的要因の関与が確実視されている[4]．しかし，一卵性双生児でも4～6割は一方の同胞は発症しないことから，メンデル遺伝に従う単一遺伝子疾患ではなく多因子疾患であり，非遺伝的要因も関与すると推測されている[4)~7)]．このため，分子遺伝学的解析は難航しており，統合失調症に特異的なゲノム異常は未同定である．

一方，精神神経疾患の病因・病態の解明には，死後脳の分析が欠かせないが，統合失調症では，責任病巣を特定できず，死後脳における分子変化も長期服薬の影響を除外しがたいなどの点が，疾患特異的な変化へのアプローチを阻んでいる．

薬理学的にみた統合失調症状発現の分子機構

統合失調症において，症状発現の分子機構を理解する有用な手段の1つは，本症の治療薬や，統合失調症様異常発現薬に関する薬理学的研究である．これらの研究成果から，脳内のドーパミン（dopamine：DA）伝達およびN-methyl-D-aspartate（NMDA）型グルタミン酸（glutamate：Glu）受容体機能の障害の可能性が示唆され，広く受け入れられている[1) 8) 9)]．

❶ ドーパミン伝達の亢進

統合失調症の薬物療法は，1952年にクロルプロマジンの統合失調症状改善作用が発見されことにはじまる．その後，ハロペリドールはじめ多くの異なった化学構造をもつ統合失調症治療薬が開発・導入されてきた．これらは抗精神病薬とよばれ，強力なD_2型DA受容体遮断作用をもつことが共通の特徴である．抗精神病薬は，統合失調症の主として陽性症状を改善する．しかし，陰性症状にはほとんど効果がなく（概念図），患者の十分な社会復帰を拒む主要因となっている[9) 10) 11)]．近年開発が進んだ，いわゆる非定型抗精神病薬は，それ以前に導入されていた定型抗精神病薬より，錐体外路症状，プロラクチン分泌増加等の抗DA作用による副作用を生じにくく，陰性症状評価尺度の低減効果も若干優れていることから，統合失調症の治療において中心的役割を担うようになった（概念図）．非定型抗精神病薬は，厳密に定義されていないが，相対的にセロトニン2A型受容体遮断作用が強く[11)]，D_2DA受容体から比較的解離しやすい性質をもつこと[10) 12)]などが，D_2DA受容体への親和性がその他の神経伝達物質受容体より際だって高い，定型薬との差異に関係すると推察されている．

抗精神病薬のD_2DA受容体遮断作用が臨床力価にほぼ比例する事実より（図1），統合失調症では脳内DA伝達が亢進している可能性が考えられるようになった[10) 12)]．この仮説は，アンフェタミン類（覚せい剤），コカイン，L-DOPA（l-3,4-dihydroxyphenylalanine）その他のDA作動薬が，統合失調症患者以外のヒトにしばしば本症と区別が難しい幻覚・妄想状態を引き起こすことや，症状が目立たなくなった状態の統合失調症患者に，健常者には精神変調を惹起しない少量の