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Drug Abuse and Psychosis: New Insights into Drug-induced Psychosis

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Addictive drug use or prescribed medicine abuse can cause psychosis. Some representative symptoms frequently elicited by patients with psychosis are hallucination, anhedonia, and disrupted executive functions. These psychoses are categorized into three classifications of symptoms: positive, negative, and cognitive. The symptoms of DIP are not different from the symptoms of schizophrenia, and it is difficult to distinguish between them. Due to this ambiguity of distinction between the DIP and schizophrenia, the DIP animal model has been frequently used as the schizophrenia animal model. However, although the symptoms may be the same, its causes are clearly different in that DIP is acquired and schizophrenia is heritable. Therefore, in this review, we cover several DIP models such as of amphetamine, PCP/ketamine, scopolamine, and LSD, and then we also address three schizophrenia models through a genetic approach with a new perspective that distinguishes DIP from schizophrenia.

Key words: drug abuse, psychosis, drug induced psychosis, schizophrenia, animal model

INTRODUCTION

Environmental factors such as maternal stress, traumatic brain injury, psychosocial stress, and drug abuse can instigate psychosis [1]. Among these factors, it has been shown in multiple studies that drug use can lead to psychosis without the involvement of genetic factors, especially in adult animals [2-6]. The representative drugs that can cause psychosis are amphetamine, scopolamine, ketamine, phencyclidine (PCP), and lysergic acid diethylamide (LSD) [7]. Specifically, psychosis induced by amphetamine had shed light on schizophrenia studies by transitioning the focus on psychoanalytic perspectives to the neurotransmitter perspective [8]. This relationship between drug induced psychosis (DIP) and schizophrenia has allowed researchers to utilize drugs in studying neurotransmitter roles in schizophrenia. Therefore, DIP animal models were frequently considered as schizophrenia animal models [9].

However, despite the use of DIP as a schizophrenia model, whether DIP animal models are the ideal schizophrenia models has yet to be determined. In addition, causality between drug use and psychosis cannot be established. The varying dosage and regimen of administration of drugs such as amphetamine, scopolamine, PCP, ketamine, and LSD are essential factors for inducing psychosis. On the other hand, schizophrenia is dominantly determined via genetic factors, and DIP is dependent on acquired environmental factors. Involvement of genetic factors

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on schizophrenia was supported by fact that the concordance rate for schizophrenia was reported at roughly 50% in monozygotic twins [10], leading to genome wide studies searching for common genetic factors associated with schizophrenia. As a result, about 40 candidate genes have been identified, many of which were associated with neurotransmitter release, proliferation, synaptic formation, and neuronal development, suggesting that schizophrenia is a neurodevelopmental disease [8, 11]. Current genetic studies of schizophrenia have led to the idea that genetic factors are gradually expressed by environmental factors in adolescence, leading to psychosis [8]. On the other hand, psychotic symptoms can be elicited in healthy human adults when exposed to drugs. This point that genetic factors are deeply involved in schizophrenia states that DIP animal models are distinct from schizophrenia animal models.

In this review, we cover studies with a new perspective that identifies the DIP model as distinct from the schizophrenia model. First, we will address DIP models of amphetamine, scopolamine, PCP/ketamine, and LSD. Then, we will discuss the original use of these drugs, their regimens, resulting psychotic behaviors, the mechanism of these drugs on psychosis, and the differences between DIP and schizophrenia. Lastly, we will also address genetic schizophrenia models in order to elucidate the differences between DIP and schizophrenia. In this, we will discuss the functions of the protein that the schizophrenia associated gene encodes, the expression of that protein in schizophrenia patients, the psychoses of the transgenic schizophrenia models through the investigation of gain of function or loss of function mutations, and the similarities/differences between DIP and schizophrenia.

DIP MODELS AND THEIR MECHANISM UNDERLYING PSYCHOTIC BEHAVIORS

The diagnosis of schizophrenia is given based on the demonstration of positive, negative, and cognitive symptoms in patients. Of these categories of psychosis symptoms, representative of positive symptoms are hallucinations and delusions, and of negative symptoms are flattened emotions and anhedonia. Furthermore, disorganized language use and illogical thinking are representative of cognitive symptoms. Within these three categories, psychotic symptoms can be induced in healthy animals by drug administration. However, unlike the schizophrenia model, psychoses of positive, negative, and cognitive symptoms are not observed in some DIP models. This is because the drug-induced psychosis is based on the mechanism of action of the drug. This will be discussed in detail below.

Amphetamine induced psychosis

Amphetamine was first synthesized in 1887, and was used as a stimulant to promote the performance of soldiers during World War II. Ever since its addictive properties have been found, its use was only limited to medical use. Despite strict regulations, the number of people with amphetamine induced psychosis (AIP) along with the excessive use of amphetamine has increased.

With the increase in the number of people with AIP, studies have been conducted to establish an AIP animal model, which has been further stimulated by the fact that the symptoms of AIP are similar to the symptoms of schizophrenia. According to AIP studies, temporal amphetamine administration did not produce psychosis but significant administration of amphetamine induced psychoses limited to only positive and cognitive symptoms (Table 1). Specifically, sub-chronic amphetamine administration into healthy adult rats produced amphetamine sensitization, disrupted latent inhibition, and decreased attentional vigilance, of which its effect lasted for 90 days after the last injection (Table 2) [12-14]. Also, although deficits in the attention set-shifting task were observed, spatial memory was not impaired in the Morris water maze, indicating that cognitive impairments in the AIP model appeared to be restricted to some prefrontal cortex (PFC) dependent tasks [15, 16]. Another protocol for AIP is a chronic and incremental dosage administration schedule of amphetamine, where the psychotogenic effect of this regimen is not extensively different with sub-chronic schedule (Table 2).

These psychotic symptoms within the positive and cognitive classifications were explained by the molecular function of amphetamine. Amphetamine increases the dopamine level in the synaptic cleft via inhibition of dopamine reuptake into the presynaptic neuron and facilitation of the release of vesicles containing dopamine (Fig. 1). Therefore, it has been accepted as the most plausible explanation of AIP. Amphetamine administration causes an overflow of dopamine in the striatum, which leads to excessive glutamate release into the cortex. Excess glutamate in the cortex may, over time, cause damage to cortical interneurons [7, 17]. The increase of dopamine in the striatum and the increase of glutamate in the cortex explain the positive and cognitive symptoms, respectively. On the other hand, this explanation of how molecular function of amphetamine affects psychotic behaviors has also been examined by antipsychotic drugs. The representative typical and atypical antipsychotics are haloperidol and clozapine, respectively. Haloperidol is a dopamine D2 antagonist, and clozapine is a 5-HT agonist, dopamine D2 receptor antagonist, muscarinic antagonist of the M1, M2, M3, M5 subtypes, agonist of the M4, and agonist at the glycine site of the NMDA receptor. Locomotor sensitization and latent inhibition of

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Table 1. Comparative overview of dysfunctional behaviors within categories of positive, negative, and cognitive symptoms in the drug induced psychosis model and the schizophrenia model

Animal model		Positive symptoms	Negative symptoms	Cognitive symptoms	Reference
DIP	Amphetamine	Disrupted PPI, deficit in latent inhibition, and amphetamine sensitization (1, 3 mg/kg challenge)	No effect on social interaction	Impaired working memory	[2, 9, 12, 14, 83, 84]
	Scopolamine	Disrupted latent inhibition	Social recognition deficit in 3-chamber test	Working memory deficit (T-maze spontaneous alteration)	[3, 20, 85]
	Ketamine	Hyperlocomotion	Increased immobility in forced swim test	Deficit in fear conditioning and working memory	[4, 35, 86]
	PCP	Hyperlocomotion	Reduced social interaction	Attentional set-shifting deficit (Extra dimensional shift) and disrupted working memory	[5, 32-34, 87]
	LSD	Hyperlocomotion	Decreased social behavior	Not reported Rather, the cognitive function such as increased associate learning was observed	[6, 42, 45]
Schizophrenia	DISC1	Impaired PPI and impaired latent inhibition in mice with mutation L100P	Deficit in the forced swim test in mice with mutation Q31L	Working memory deficit in mice with mutation L100P (T-maze)	[55, 57]
	Neuregulin 1	Reduced PPI in mice overexpressing cysteine-rich domain variant; hyper-locomotion and reduced PPI in Nrg1 (ΔEGF)+/- mice and typeIII Nrg1 (ΔTM)+/- mic	Social recognition deficit in Nrg1 (ΔTM)+/- mice	Inconsistent results in working memory deficit in Nrg1 (ΔTM)+/- mice	[69, 88]
	Dysbindin	Hyper responsivity to acute methamphetamine	Social interaction deficits	Impaired working memory	[75, 78]

[a]DIP, drug induced psychosis; PCP, phencyclidine; LSD, lysergic acid diethylamide; DISC1, disrupted-in-schizophrenia-1; PPI, prepulse inhibition; EGF, epidermal growth factor; TM, transmembrane; Nrg, neuregulin.

AIP was alleviated by both of these antipsychotics [18], whereas amphetamine-induced working memory impairment was improved by the clozapine, but not haloperidol [9, 19]. Although the effects of these antipsychotics may provide that positive symptoms resulted from increased dopamine, it is still not enough to explain the direct link between amphetamine and psychotic symptoms.

Despite the absence of a direct link, it is obvious that a specific amphetamine administration regimen can induce positive and cognitive symptoms, but not negative symptoms. It is because of this lack of negative symptoms that the AIP model is insufficient as an ideal schizophrenia model. In addition, it is notable that psychosis can be induced by amphetamine injection into non-transgenic animals or healthy animals whose breeding environment was not stressful, suggesting that drug abuse is sufficient to induce psychosis independently without the involvement of the genetic component of schizophrenia.

Scopolamine induced psychosis

Unlike the majority of drugs discussed in this literature, scopolamine lacks addictive properties. Rather, it is a major component of medications that treat motion sickness. However, administration of scopolamine in patients elicits prominent side effects such as hallucinations, delusions, and memory deficits. There has been an increasing effort to establish a scopolamine induced psychosis (SIP) animal model, primarily owing to the observation of muscarinic antagonists such as atropine and scopolamine inducing psychosis, and investigation into the alleviation of cognitive symptoms of schizophrenia by cholinergic stimulation.

To model SIP in animals, multiple behavioral studies have used acute injection regimens of scopolamine (Table 2). In each of these studies, disrupted behavior was found to be consistent with that of the positive, negative, and cognitive symptom categories of psychosis. For instance, behavioral changes such as impaired prepulse inhibition/latent inhibition, social recognition deficit, and working memory deficit were representative of positive, negative,

Table 2. Administration protocols of psychosis animal model of amphetamine, scopolamine, PCP/ketamine and LSD in rats and mice

Drug	Dose			Duration	Strain	Behavior test	Reference
Amphetamine	Sub-chronic and incremental dosage schedule	3 injections (06:00,12:00, and 18:00)/day for 6 days	Day 1 – 1 mg/kg, 2 mg/kg, and 3 mg/kg Day 2 – 4 mg/kg, 5 mg/kg, and 5 mg/kg Day 3-6 – 5 mg/kg, 5 mg/kg, and 5 mg/kg	90 day	Wistar rats	Amphetamine sensitization (1 mg/kg challenge)	[14]
		3 injections (08:00,14:00, and 20:00)/day for 6 days	Day 1 – 1 mg/kg, 2 mg/kg, and 3 mg/kg Day 2 – 4 mg/kg, 5 mg/kg, and 5 mg/kg Day 3-6 – 5 mg/kg, 5 mg/kg, and 5 mg/kg	28 day	Wistar rat/Male	Disrupted latent inhibition	[12]
	Chronic and incremental dosage schedule	Once daily for day, 3 times (Monday, Wednesday, and Friday) for a week	Week 1 – 1 mg/kg Week 2 – 2 mg/kg Week 3 – 3 mg/kg	22 day	Sprague – Dawley rat/Male	Disrupted PPI and amphetamine sensitization (3 mg/kg challenge)	[2]
		Once daily, 3 times (Monday, Wednesday, and Friday) for a week	Week 1 – 1 mg/kg Week 2 – 2 mg/kg Week 3 – 3 mg/kg Week 4 – 4 mg/kg Week 5 – 5 mg/kg	22 day	Sprague – Dawley rat/Male	Disrupted PPI and amphetamine sensitization (3 mg/kg challenge)	[2]
Scopolamine	Acute schedule		0.15 and 0.5 mg/kg	<1 day	Wistar rat/Male	Disrupted latent inhibition	[3]
			0.3 and 0.5 mg/kg	<1 day	C57BL/6J mouse/Female	Social recognition deficit in 3-chamber test	[20]
			0.3, 1, 2, and 3 mg/kg	<1 day	CD-1 mouse/Male	Working memory deficit (T-maze spontaneous alteration)	[85]
			10 mg/kg	<1 day	C57BL/6NCrl mice/male	PPI impairment	[21]
Ketamine	Acute schedule		100 mg/kg	<1 day	Swiss mouse/Male	Hyperlocomotion and excessive fear (latency time of fear conditioning was increased)	[4]
	Sub-chronic schedule	Once daily for 5 days	10 mg/kg	21 day	Hooded Lister rat/Male	Working memory deficit	[35]
		Once daily for 5 days	30 mg/kg	10 day	Wistar rat/Male	Hyperlocomotion	[89]
		Once daily for 5 days	30 mg/kg	21 day	Hooded Lister rat/Male	Increased immobility time in forced swim test	[86]
		2 injection for 6 days	30 mg/kg	10 day	Long Evans rat/Male	Working memory deficit (Mismatch detection test)	[89]
	Chronic schedule	Once daily for 10 days	100 mg/kg	11 day	Swiss mouse/Male	Hyperlocomotion, increased immobility time in forced swim test, and increased latency time of fear conditioning	[4]

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Table 2. Continued

Drug	Dose			Duration	Strain	Behavior test	Reference
PCP	Acute schedule		5 mg/kg	<1 day	Sprague–Dawley rat	Hyperlocomotion	[32]
			2.58 mg/kg	<1 day	Long–Evans rats	Attentional set-shifting deficit (Extra dimensional shift)	[33]
			1.5 mg/kg	<1 day	C57Bl/6J mouse/Male	Hyperlocomotion, stereotype behavior, and reduced social interaction	[87]
			2 mg/kg	<1 day	C57Bl/6J mouse/Male	Hypolocomotion and reduced social interaction	[87]
			5 mg/kg	<1 day	C57BL/6J mice/Male	Hyperlocomotion	[5]
	Sub-chronic schedule	2 injection (0800 2000) for 7 days	5 mg/kg	10 day	Long-Evans rat	Attentional set-shifting deficit (Extra dimensional shift)	[34]
	Chronic schedule	Once daily for 10 days (days 1~5, 8~12)	5 mg/kg	<1 day	C57BL/6J mice/Male	Hyperlocomotion and disrupted working memory	[5]
LSD	Acute schedule		0.03, 0.1, and 0.3 mg/kg	<1 day	Wistar Rats/ Male	Hyperlocomotion and disrupted PPI	[43]
			0.1 and 0.3 mg/kg	<1 day	Sprague-Dawley Rats	Hyperlocomotion and disrupted PPI	[43]
	Chronic schedule	Once daily and every other day for 90 days	0.16 mg/kg	1 month	Sprague-Dawley rat/ Male	Hyperlocomotion, decreased social behavior, and anhedonia	[6, 42]

[a]PCP, phencyclidine; LSD, lysergic acid diethylamide; PPI, prepulse inhibition.
This table includes the drug, administration protocol, time taken behavioral experiments after administration of the drug, strain, and psychotic behaviors that was determined by each administration protocol. The administration protocol for 10 days or less was marked as a sub-chronic schedule, and administration protocol for over 10 days was marked as a chronic schedule. In the case of behavioral testing on the day of drug administration, it was labeled as occurring for less than 1 day.

and cognitive symptoms, respectively [3, 20, 21].

Scopolamine is a non-selective antagonist of muscarinic acetylcholine receptors and binds to a group of muscarinic receptors (M1-M5) which directly modulates the release of acetylcholine or indirectly of dopamine. These receptors are classified into M1-like muscarinic receptors (M1, M3, M5) and M2-like receptors, (M2, M4) which activate and inhibit second messenger transduction via G-proteins, respectively [22, 23]. Specifically in the mesopontine nuclei, scopolamine blockade of the M2 muscarinic auto-receptor in the axon terminal is suggested to elevate acetylcholine levels in the midbrain areas of substantia nigra (SN) and ventral tegmental area (VTA), thus eliciting an increment in the striatal dopaminergic levels (Fig. 1) [24, 25]. Such activity may lead to positive symptoms of psychosis such as hyperactivity and stereotypy [26, 27]. Whereas, inhibition of M4 subtype receptors is suggested to result in cognitive deficits in memory and attention [22]. Negative symptoms of SIP can be indirectly explained by the effect of antipsychotics. Clozapine in particular was found to reverse social recognition deficit [21]. Donepezil, a cholinesterase inhibitor, was also known to restore social recognition deficit.

The SIP model shows all classifications of the symptoms of psychosis: positive, negative, and cognitive. However, the negative symptom of SIP is limited to the impairment of social recognition memory, of which is associated with cognitive function. Furthermore, in small doses, scopolamine works as rapid antidepressant [28], indicating that it may show a therapeutic effect on anhedonia which a negative symptom of psychosis. This seemingly opposite effect of scopolamine on the negative categories of psychosis suggest that the psychotomimetic effect of scopolamine is either dependent on its dose or limited to positive and cognitive symptoms. This characteristic can be observed in DIP, but not in schizophrenia.

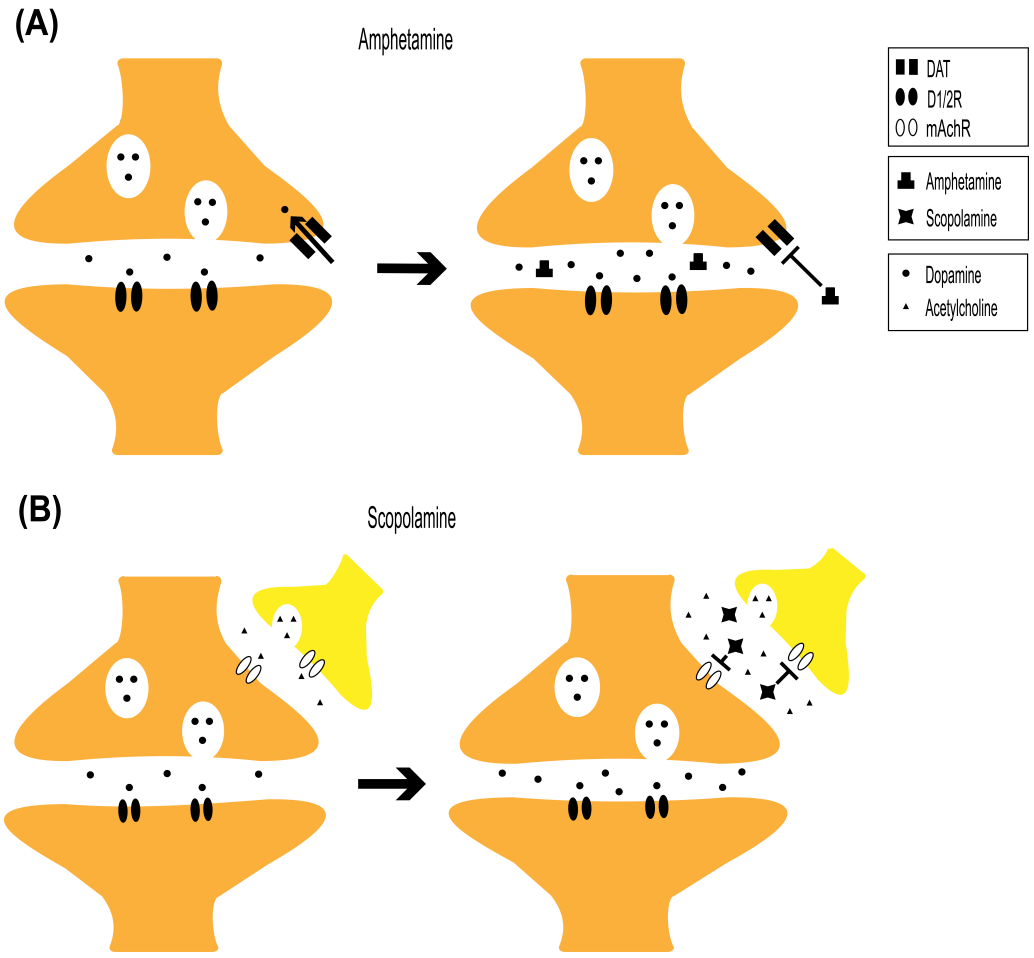

Fig. 1. Amphetamine and scopolamine alter dopamine neurotransmission. (A) Amphetamine regulates dopamine transmission. The amphetamine first binds to the dopamine DAT and vesicular monoamine transporter (VMAT) competitively with dopamine or norepineprine. Then, it faciliates DAT mediated reverse transport of DA. These functions of amphetamine result in the increase of the concentration of dopmaine in the synpatic cleft. (B) Scopolamine is invloved in acetylcholine and dopamine transmission. The scopolamine binds non-specifically to muscarinic acetylcholine receptors (M-M5) in all brain regions. Specifically, M2/M4 subtypes of mAChR that are linked to an inhibitory G-protein in the neuronal terminal of mesopotine cholinergic neurons are autoreceptors that exert negative feedback. This negative feedback is blocked by scopolamine, resulting in disinhibition of cholinergic transmission. Increased acetylcholine release into postsynaptic neurons of mesopotine, which are mainly dopaminergic neurons in VTA or substantia nigra, elevate DA release. The orange neuron located in the top-right indicates the dopaminergic presynaptic neuron whereas lower orange neuron indicates a postsynptic neron. The yellow neuron denotes the mesopotine cholinergic neuron. DAT, dopamine active receptor; D1/2R, dopamine receptor D1 and dopamine receptor D2; mAchR, muscarinic acetylcholine receptor.

PCP/ketamine induced psychosis

PCP was developed as a dissociative anesthetic agent for surgical operations in the 1950s. It is now only used in the veterinary field and is not used on humans due to its side effects. The side effects include delirium, unconsciousness, hallucinations, depression, and memory loss, which are similar to psychoses of positive and negative categories. As a result of these side effects of PCP, ketamine has been developed as a substitute for the PCP [29]. However, ketamine has also proved to have a psychotogenic effect. Although the psychotogenic effect of PCP is much stronger than that of ketamine, both drugs share similarities in the administration regimens for producing psychosis due to the fact that both drugs are NMDA receptor antagonists and share binding sites within the NMDA receptor. Thus, PCP induced psychosis (PIP) and ketamine induced psychosis (KIP) are discussed together below.

Unlike amphetamine, acute PCP and ketamine administrations are sufficient to induce psychosis in healthy people as well as in animals [4, 30, 31]. Acute ketamine administration of animals leads to hyper-locomotion when the injected animals are exposed to a novel environment [4]. On the other hand, PCP induces a more powerful psychotic response relative to ketamine. Acute

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PCP administration into animals produces hyper-activity, reduced social interaction, and decreased cognitive flexibility, and these symptoms are also shown with sub-chronic and chronic PCP administration regimens (Table 2) [9, 5, 32-34]. In KIP models using sub-chronic and chronic regimens, symptoms similar to those observed in the acute PCP model are also shown [4, 35].

As negative symptoms that were not observed in the AIP animal model were induced by PCP and ketamine, the mechanism explaining negative symptoms emerged based on the understanding that PCP and ketamine are uncompetitive antagonist of the NMDA receptor. Based on the inhibition of GABAergic interneuron in the prefrontal cortex by these antagonists, increased neuronal activity and excessive glutamate in the glutamatergic neruon of the PFC were mainly considered as the neurobiological explanation for the negative symptoms (Fig. 2) [31, 36]. The molecular function of PCP/ketamine that affects psychotic behaviors has also been examined by antipsychotic drugs. Hyper-locomotion induced by acute ketamine administration was reversed by haloperidol, clozapine, and risperidone [4]. Risperidone is an antagonist of dopamine D2 and 5-HT2A receptors, and has affinity for various receptors such as the dopamine D1 receptor, adrenergic receptors, and histamine

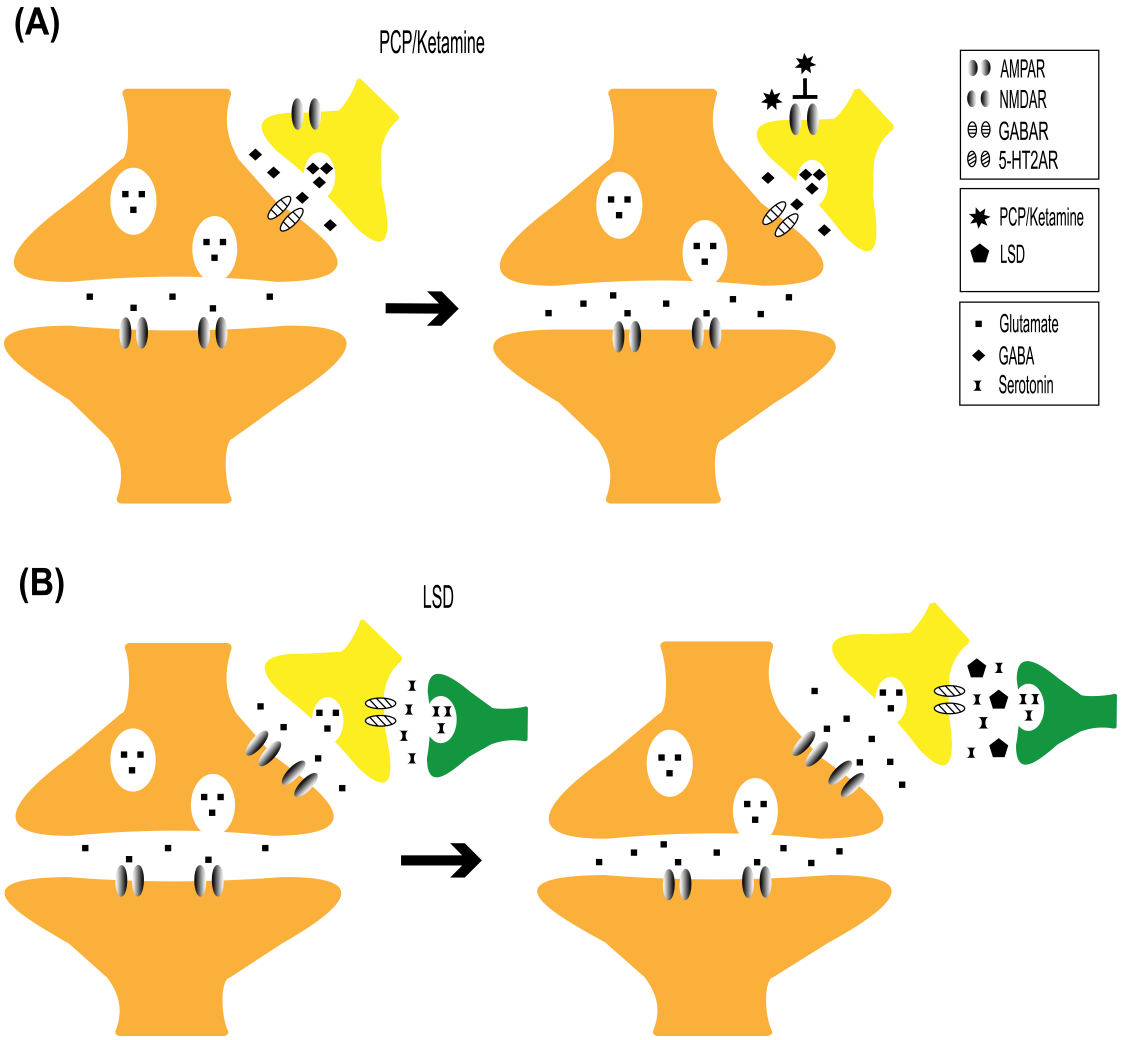

Fig. 2. PCP, Ketamine and LSD alter gluatatmate neurotransmission. (A) PCP and ketamine regulate glutamate transmission. They bind to NMDA receptors of the PFC GABAergic interneuron. The NMDA receptor hypofunction on GABAerginc neurons induces hyper-glutamatergic transmission. (B) LSD affects serotonergic transmission and gluatmate transmission. LSD binds to the 5-HT2A receptor located on thalamus glutamatergic neurons where serotonergic raphe neurons send efferent projections. Glutamate release of thalamic neuron is increased due to the effect of LSD, resulting in hyper glutamatergic transmission in the PFC. The upper orange neruon indicates presynaptic glutamatergic neuron whereas lower orange neuron indicates a postsynptic neron. The yellow neuron of figure (A) denotes GABAergic interneuron in the PFC and that of figure (B) denotes thalamic glutamatergic neuron. The green neuron is a serotonergic neuron in the raphe nucleus. AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDAR, N-methyl-D-aspartate receptor; GABAR, gamma-Aminobutyric acid receptor; 5-HT2AR, serotonin 2A receptor.

receptors [37]. Haloperidol was ineffective on cognitive deficits in behavioral tests such as set-shifting task, reversal learning, and novel object recognition in the sub-chronic PIP and KIP models, whereas clozapine was effective on some cognitive symptoms such as reversal learning and novel object recognition [4, 34, 38, 39]. Although the function of PCP and ketamine as a NMDA receptor antagonist has been stressed, these drugs also bind to a variety of receptors [40]. Furthermore, the positive symptoms in PIP and KIP models were explained by an increase of dopamine level in the PFC, not by a hyper-glutamatergic state [31]. This increased dopamine level in the PFC can be explained by the affinity of ketamine at the dopamine receptor (ketamine acts as partial of D2 agonist), which is similar to that at the NMDA receptor [41]. However, in the case of PCP, the affinity at the 5-HT receptor is similar to that at the NMDA receptor, and its affinity at the dopamine D2 receptor is lower than at both NMDA and 5-HT receptors [41]. Therefore, the explanation for the positive symptoms in the PIP and KIP models by dopamine transmission may be consistent with the amphetamine model, but further studies are needed to confirm its validity.

The PCP/ketamine model may be the most accessible model that shows schizophrenia-like behavior. However, since PCP and ketamine bind to various receptors, PIP and KIP have complex mechanisms underlying psychoses; which are further complicated by the absence of a concrete understanding of its mechanisms. Therefore, it is still uncertain whether PIP and KIP, with the assumption that they are based on the identical mechanism, will provide meaningful contributions to the study of schizophrenia.

LSD induced psychosis

LSD was synthesized for therapeutic purposes by Albert Hoffman. In 1938, he accidentally discovered the hallucinatory properties of LSD [7]. To date, LSD is the most powerful hallucinogen known that can distort the perception of time and space at very low doses compared to other drugs [6, 42, 43]. Due to its strong psychotomimetic effects, recreational use of the LSD has been increasing [44]. As a result, LSD has never been distributed for medicinal purposes, and has been illegally used. Although there are fewer studies on LSD compared to other drugs due to legal limitations, LSD was also presented as a drug of schizophrenia model when amphetamine induced psychosis received attention in the late twentieth century in schizophrenia studies [7].

There have been a significant number of studies that have investigated the psychosis induced by LSD. Across many of these studies, acute injection of LSD into animals at very low doses induced psychotic behaviors that were classified into positive symptoms [43], whereas chronic LSD administration with a low dosage (0.16 mg/kg) elicited positive symptoms as well as negative symptoms (Table 2) [42]. Such positive symptoms were hyper-locomotion and disrupted PPI. Negative symptoms were decreased social behavior and reduced sucrose preference (Table 1). It is interesting to note that the cognitive symptoms were not observed in the LSD induced psychosis animal model. Rather, cognitive function was improved by LSD. According to a paper by Hervey on the relation of serotonin receptors and learning, LSD injection at a dose of 0.013 mg/kg into rabbits enhanced associative learning [45, 46].

Although the specific mechanisms of action of LSD are not yet fully understood, numerous studies have pointed to the modulatory effect of LSD on the receptors of various systems including the serotonergic, dopaminergic systems, and to its affinity for 5-HT2A and dopamine D2 receptors as an starting point for investigation [47]. As a localization point for serotonergic neurons, the raphe nucleus projects to the thalamic regions. The agonist action of LSD on the 5-HT2A receptors of the thalamic afferents is responsible for the increase in glutamate levels in the corticocortical and corticosubcortical transmissions (Fig. 2) [48]. Thus, the usage of LSD has been shown to increase glutamate release onto the layer V pyramidal neurons of the PFC [49]. It appears that the elevated level of extracellular glutamate in the PFC region is associated with the symptoms of psychosis [42]. There are studies that test whether LSD-induced psychosis (LIP) is alleviated by antipsychotic drugs. Haloperidol failed to reverse disruption of PPI in the LIP model [43]. In contrast, hyperirritability, hyper-locomotion, anhedonia, and decreased social interaction were transiently reversed by haloperidol and olanzapine [42]. Olanzapine is an atypical antipsychotic drug and it has a higher affinity for 5-HT2A serotonin receptors than the D2 dopamine receptors [42]. Also, head-twitch response, a rapid side-to-side head movement, was alleviated by long term administration of clozapine in the LIP animal model [50].

LSD is a drug of weak addictive properties and at the same time is the most potent hallucinogen. In addition, LSD modulates the serotonergic, dopaminergic neurotransmission systems which are major targets of typical and atypical antipsychotics. Although this may indicate that the LIP model is most suitable for studying psychosis as it does not induce drug effects such as dependence of amphetamine and antidepressant effect of ketamine/scopolamine, LSD enhances cognitive function. This means that LIP is, unfortunately, not adequate for schizophrenia research like the other four DIP models. Meanwhile, it also indicates that LIP is isolated set of symptoms that can be differentiated from schizophrenia.

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SCHIZOPHRENIA MODELS AND THEIR MECHANISMS UNDERLYING PSYCHOTIC BEHAVIORS

While DIP is a result of environmental factors, schizophrenia is highly heritable and a considerable number of genetic components are involved in the development of schizophrenia. Therefore, we defined schizophrenia models as models that incorporated altered genes, many of which were identified from schizophrenic patients. To identify schizophrenia associated genes, genome-wide association studies have been attempted [51-53]. As a result, several susceptibility genes for schizophrenia have been discovered [52, 53]. The major genes of schizophrenia were identified as DISC1, Neuregulin, and Dysbindin [9], and we will investigate how the schizophrenia associated genes may affect schizophrenic behaviors.

Disrupted-in-schizophrenia-1

It is known that Disrupted-in-schizophrenia-1 (DISC1) carries out multiple functions in coordination with numerous interacting partners. These partner proteins were mostly involved in axon elongation, radial migration, cortical development, and synaptic plasticity [54, 55]. Interestingly, although DISC1 is the most representative of the associated genes of schizophrenia, the expression of DISC1 in schizophrenics showed no difference with that in the healthy group [54]. Despite of the normal expression of DISC1 in schizophrenia patients, the mouse model overexpressing full-length human DISC1 showed abnormal wake/sleep patterns which were a characteristic of schizophrenia [56]. Whereas, reduced expression of proteins interacting with DISC1 was observed in the schizophrenia patients. Consistent with this data from patients, reduced interaction between DISC1 and PDE4B, a partner protein of DISC1, was also observed in two schizophrenia models that had a point mutation (Q31L and L100P, respectively) within the DISC1 sequence. However, interestingly, these two transgenic mice did not exhibit symptoms that covered the entire psychosis spectrum of schizophrenia. Mice with mutations of Q31L exhibited deficit in the forced swim test, whereas L100P mice showed impaired PPI and impaired latent inhibition [55, 57].

DISC1 contributes to these schizophrenic behaviors by affecting neurotransmission and brain development. According to recent studies, DISC1 was involved in dopamine and glutamate transmissions [58-60], which overlaps with mechanisms that underlie psychotic behaviors of DIP. Animals with overexpressed full length DISC1 showed altered dopamine homeostasis such as an increased affinity to dopamine D2 receptors and increased dopamine turnover [60]. Mice with mutant human DISC1 exhibited a hypofunction of NMDA receptors [58]. These recent results suggest that the roles of DISC1 in neurotransmission are similar to the dopamine and glutamate transmissions in AIP and PIP/KIP, respectively. Whereas, the fact that DISC1 affects brain development emphasizes the distinction of DIP. DISC1 is a scaffold protein that is associated with synaptic pruning, astrogenesis, cortical development, and hippocampal development [61-64]; processes which continue until adolescence. Consistent with the roles DISC1 is presumed to be involved in, administration of immune-stimulants into pregnant DISC1 L100P heterozygous mice induced schizophrenic behaviors [65], which suggest that genetic factors of schizophrenia were continuously affected by environmental factors during the developmental period. Therefore, the schizophrenia model has not only commonalities but also differences with the DIP models.

Neuregulin 1

Pro-neuregulin is a transmembrane protein that contains extracellular epidermal growth factor (EGF) domains. The pro-neuregulin 1 undergoes proteolytic cleavage by three transmembrane proteases (ADAM17, BACE, and ADAM19) [66] forming Neuregulin (Nrg 1), and of which binds to the ErbB4 receptor. Previous studies have associated Nrg 1 with synaptic plasticity, neurotransmitter transmission, and nervous system development [67, 68]. However, there have been inconsistencies in certain studies that the expression of these two proteins was either decreased or increased in the brain of patients with schizophrenia [66, 69]. In addition, there are many kinds of mouse models of which Nrg 1 is genetically engineered due to its numerous isoforms (at least 31 isoforms) and its multiple cleavage sites [66]. Among isoforms of Nrg 1, cysteine-rich domain Nrg 1 isoform is the most prominent neuregulin 1 variant in the brain, and mice overexpressing this isoform showed elevated anxiety and reduced PPI [69]. While, hyper-locomotion and reduced PPI were observed in mice with deletions of the Nrg 1 EGF domain and of the transmembrane domain of Nrg 1 [55, 67].

Nrg 1 contributes to schizophrenic behaviors via various mechanisms which may overlap or are completely separate with the mechanisms of DIP. These two mechanisms of Nrg 1 are connected with each other intricately. Likewise with the DIP models, the schizophrenia associated Nrg 1 is also involved in dopamine transmission. Nrg 1 and ErbB4 receptors expressed on membrane of dopaminergic neurons modulate dopaminergic transmission via downstream signaling of mGluR1 [70]. Interestingly, this regulation of neurotransmission is limited to adolescent mice (postnatal day 24~48), but not to adult mice. Systemic injection of ErbB kinase inhibitor into an adolescent mouse increases striatal dopamine levels, reduces sucrose

preference, and induces deficit in the T-maze reversal learning task later during adulthood [71]. In addition, neonatal Nrg 1 injection into mice induced altered properties of the dopaminergic neuron at an adult stage [72]. Together, schizophrenia and DIP share altered neurotransmission as a contributor to schizophrenia. Also, whereas causative factors of schizophrenia affect emergence of schizophrenic behaviors for a long period, drugs of DIP quickly act on the emergence of psychotic behaviors.

Dysbindin

Dysbindin is primarily located on axonal bundles and axonal terminals [73], and regulates neurotransmitter release in the presynaptic neuron while playing a role in receptor trafficking in the postsynaptic neuron [74, 75]. The expression of dysbindin is decreased in the PFC and the hippocampus of schizophrenia patients [76, 77]. Furthermore, reduced dysbindin expression was observed in dysbindin mutant mice, and these mice showed a decrease in NMDA-dependent glutamate receptor signaling and exhibited impaired working memory [78]. Whereas mice overexpressing human dysbindin exhibited increased locomotion by acute amphetamine administration [75].

How dysbindin affects schizophrenic behaviors can be explained by altered neurotransmission, in particular by dopaminergic transmission [79, 80]. Increased number of dopamine D2 receptors on the cell membrane was observed in Sandy (Sdy) mice with a mutation in the DTNBP1 gene that resulted in the reduced expression of dysbindin protein [79, 81]. In addition, effects of D2 receptor antagonists have been examined. Unsurprisingly, schizophrenia-like behaviors such as hyperactivity, impaired working memory, and spatial memory deficit were rescued by D2 receptor antagonists in the Sdy mouse model. However, this rescue effect was limited to the adolescent period (postnatal day 21~35 in mice) [79]. These results indicate that dysbindin plays a role in regulating functions of the dopamine D2 receptor. Furthermore, mutation in the DTNBP1 gene inhibits D2 receptors on the mPFC GABAergic neurons, resulting in an altered glutamatergic system [82]. In conclusion, mechanisms of schizophrenia based on dysbindin mutation also partially share those of DIP, especially in neurotransmission. Schizophrenic behaviors resulting from dysbindin mutation are expressed depending on the developmental stage of the animal.

CONCLUSION

Schizophrenia and DIP cannot be differentiated simply through observing symptoms. This implies that common mechanisms underlie schizophrenia and DIP and it is due to this that the DIP model was used in schizophrenia research. While previous studies have converged on the similarities of DIP and schizophrenia, in this review we aim to focus on the differences between the DIP and schizophrenia models. In terms of etiology and mechanisms, it is clear that DIP and schizophrenia are isolated. To specify, DIP is caused by drugs and schizophrenia is thought to develop due to genetic causes, indicating different mechanisms underlying their psychotic or schizophrenic behaviors. Also, most DIP studies have explained psychotic symptoms by altered neurotransmitter systems, whereas most schizophrenia model studies have described schizophrenic symptoms based on functional changes of genes identified from schizophrenia patients. Knowing the distinction between the DIP and schizophrenia models will inevitably reduce misinterpretation of results in future studies that utilize DIP models in schizophrenia research. Along with distinguishing animal models, further studies should focus on discovering the exact mechanisms for specific symptoms stemming from either drugs or genetic factors, which may provide a more effective treatment of drug induced psychosis or schizophrenia.

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