

REVIEW

SIGNIFICANCE OF DYSFUNCTIONAL GLUTAMATERGIC TRANSMISSION FOR THE DEVELOPMENT OF PSYCHOTIC SYMPTOMS

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It has been postulated that disturbances in glutamatergic transmission may contribute to the pathophysiology of schizophrenia. This view is based on several findings: (1) the noncompetitive NMDA receptor antagonists, phencyclidine and ketamine, induce both positive and negative psychotic symptoms in humans, which closely resemble those observed in schizophrenia; (2) a number of animal studies have shown that neuroleptics that ameliorate symptoms of schizophrenia (e.g. clozapine) also inhibit the effects of NMDA antagonists; (3) *postmortem* and *in vivo* studies have revealed alterations in ionotropic glutamate receptors (NMDA, AMPA, KA) and their modulatory sites in schizophrenia; (4) compounds enhancing the function of NMDA receptors potentiate the antipsychotic effects of neuroleptics in schizophrenic patients.

Key words: schizophrenia, glutamate, NMDA receptors, phencyclidine

Introduction

The generally accepted dopamine hypothesis of schizophrenia was mostly based on studies into the mechanism of action of neuroleptic drugs. Clinically efficient antipsychotic drugs are antagonists of dopamine receptors [9, 169]. Moreover, a positive correlation was found between the ability of neuroleptics to weaken psychotic symptoms and the degree of blockade of postsynaptic dopamine D₂ receptors [168, 169]. The dopamine hypothesis of schizophrenic psychoses is also substantiated by the development of psychotic symptoms in users of amphetamine which is well known to increase dopamine release [41].

However, the dopamine hypothesis of schizophrenia which postulated the hyperactivity of the dopaminergic system in limbic structures to be its cause, proved to be unsatisfactory, as it could not explain all aspects of the disease. In particular, it was emphasized that that theory was not able to account for low efficacy of typical neuroleptics in moderating negative symptoms [9, 88, 128]. Furthermore, paradoxical alleviation of negative symptoms was reported after dopamine receptor agonists [209]. To explain these discrepancies, it was recently suggested that psychotic symptoms could result from the unsettled balance between cortical and subcortical dopaminergic systems. Hypofunction of cortical dopaminergic system (prefrontal cortex) may be responsible for the development of negative symptoms, while positive symptoms could be attributed to its enhanced activity in the limbic system [87, 95, 209]. Cortical and subcortical dopaminergic systems are functionally linked *via* the glutamatergic system, and it was recently suggested that its dysfunction could also precipitate psychotic symptoms.

Contribution of aberrant glutamatergic system function to the development of psychotic symptoms has been the target of extensive studies in many research centers in recent years.

Psychotomimetic effects of NMDA receptor antagonists

Glutamate is a primary excitatory neurotransmitter in the brain. Glutamate acts on target cells through specific receptors, belonging to two distinct classes: ionotropic (NMDA, AMPA and kainate (KA)) and metabotropic glutamate receptors

coupled with second messenger system through G-proteins [cf. 149, 163].

The first evidence pointing to the role of glutamatergic system in schizophrenia came from the observations of the effects of NMDA receptor blockers in humans. Phencyclidine (PCP) and ketamine, noncompetitive antagonists of NMDA receptor complex, exacerbated psychotic symptoms in the patients suffering from schizophrenia and induced schizophrenia-like symptoms in healthy individuals [1, 6, 111, 115]. These compounds precipitated positive symptoms, and contrary to dopaminomimetics (e.g. amphetamine), they also induced negative symptoms [1, 6, 41, 111, 115]. Psychotic symptoms in humans can be elicited also by compounds binding to other sites at the NMDA receptor complex and blocking its function (e.g. CPP, CPPene, CGS 19755) [cf. 140].

The demonstration of psychotomimetic properties of NMDA receptor blockers was an important argument substantiating the role of abnormalities in glutamatergic transmission in schizophrenia. These findings prompted researchers to put forward the hypothesis linking pathomechanism of this disease with hypofunction of glutamatergic system. However, it has recently been emphasized that the problem is more complex, since PCP and ketamine increase glutamate release in the prefrontal cortex, which is a compensatory reaction to NMDA receptor blockade [131, 132]. In this situation, glutamate released from presynaptic endings excessively activates non-NMDA receptors (AMPA and/or KA), which is supposed to lead to cognitive dysfunctions [131, 132]. Hence, it was recently proposed that psychotic symptoms could be produced by a disturbed balance between pre- and postsynaptic parts of a glutamatergic synapse rather than by simple NMDA receptor hypofunction [131, 132, 141].

Changes in glutamatergic transmission in schizophrenic patients

The investigation of different markers of glutamatergic system showed its anomalous function in schizophrenic patients. However, the results were not unequivocal. *In vivo* and postmortem studies yielded incoherent results showing both lowering [93, 194] and lack of any changes [97, 150, 197] in the level of glutamate in the cerebrospinal fluid, cerebral cortex and hippocampus of schizophrenics. A cause of such discrepancies is not clear. More-

over, interpretation of the results of both postmortem examination of the brain tissue and *in vivo* studies is difficult, as they determine the whole glutamate pool. Glutamate fulfils a role of neurotransmitter in the brain, but it is also a precursor of GABA and an intermediate in some metabolic pathways in neurons and glial cells [52]. The neurotransmitting pool constitutes only 20–30% of the total glutamate content in the brain [52]. Therefore, changes in its level not necessarily indicate dysfunctions in glutamatergic transmission.

Some authors have suggested that abnormal glutamatergic transmission in schizophrenic patients can result from the altered metabolism of dipeptide NAAG (N-acetyl-aspartyl-glutamate) which occurs at high concentrations in glutamatergic neurons. NAAG is a NMDA receptor antagonist [30]. Furthermore, this dipeptide is catabolized to glutamate and N-acetyl-aspartate (NAA) by glutamate carboxypeptidase II (GCP II) [30]. Postmortem studies have demonstrated an increased NAAG level as well as a decreased GCP II activity and glutamate level in schizophrenic brain, which might cause dysfunction of glutamatergic transmission [196]. Recent studies have also shown elevated cerebrospinal [43] and cortical [165] levels of another endogenous NMDA receptor antagonist, kynurenic acid, in schizophrenic patients. Kynurenic acid is an antagonist of glycine site on NMDA receptor complex, but at higher concentrations it is also able to block AMPA and KA receptors [181]. Although under normal conditions its brain concentration is probably too low to significantly modulate NMDA receptor function [181, 185], it cannot be excluded that its elevated level observed in schizophrenic subjects is sufficient to block NMDA receptors and cause dysfunction of glutamatergic transmission.

Glutamate receptors in the brains of schizophrenic patients

Receptor binding analysis and assays of the level of mRNA for different glutamate receptors showed the changes in their expression in the cerebral cortex and limbic structures in schizophrenic patients.

Due to psychotomimetic effects of NMDA receptor antagonists, they became primary focus of researchers' attention. NMDA receptors are coupled to ion channels permeable to calcium, sodium

and potassium ions. The NMDA receptor complex has a glutamate binding site and a number of modulatory binding sites [cf. 32, cf. 149]. The strychnine-insensitive glycine binding site is very important for NMDA receptor function, since its occupation is required simultaneously with the stimulation of a glutamate site in order to activate NMDA receptors [cf. 32, cf. 149]. Besides, the NMDA receptor complex has also polyamine binding site and the binding site of noncompetitive NMDA receptor antagonists located inside ion channel. The function of this receptor is also determined by magnesium and zinc ions and pH of the milieu [cf. 32, cf. 149].

NMDA receptors can be composed of different protein subunits. Two main families of NMDA receptor subunits have been distinguished and designated as NR1 and NR2. The NR1 subunit is present in all NMDA receptors and is indispensable to their proper function. It exists in 8 variants resulting from alternative mRNA splicing. The NR2 subunit, which is also included in the NMDA receptor, is encoded by 4 distinct genes: NR2A, B, C and D [cf. 32, cf. 149]. In addition to NR1 and NR2, a novel inhibitory subunit, named NR3, has recently been described [33, 123]. Combinations of different protein subunits produce NMDA receptors differing in their affinity for agonists and antagonists, e.g. receptors composed of NR1/NR2A or NR1/NR2B bind more potently MK-801 than do receptors built of NR1/NR2C or NR1/NR2D [19, 32, 101, 149]. On the other hand, receptors containing NR1/NR2B subunits show high affinity for the antagonist of polyamine binding site ifenprodil, while NR1/NR2A receptors bind more potently the competitive antagonist CGP 39653 [19, 49, 101, 149]. Thus, a change in subunit composition can lead to significant alterations in the receptor function.

NMDA receptor density in schizophrenic patients was studied using ligands labeling different sites on the complex: the glutamate binding site was labeled with [³H]glutamate, or [³H]CGP 39653 (a competitive antagonist); the glycine site was quantified using [³H]glycine or its antagonists ([³H]L-689,560 and [³H]MDL 105,519); the polyamine site was labeled with its antagonist [³H]ifenprodil, while the intrachannel PCP-sensitive site with [³H]MK-801 or [³H]TCP (Tab. 1).

In schizophrenic patients, NMDA receptor density was increased and proportions of different protein subunits (NR2) were changed in different areas of the cerebral cortex (prefrontal, parietal, temporal

Table 1. Expression of NMDA receptors in schizophrenic patients

Receptor binding sites	Brain structure	References
Glutamate site		
[³ H]glutamate [³ H]CGP 39653	↔ hippocampus, frontal cortex, temporal cortex, thalamus, caudate, putamen, nucleus accumbens	[56, 64, 73, 91, 127]
<i>Glycine site</i>		
[³ H]glycine	↑ prefrontal cortex, parietal cortex, occipital cortex,	[77]
[³ H]L-689,560	↑ temporal cortex, ↔ frontal cortex ↑ putamen, ↔ caudate, nucleus accumbens	[64, 138] [8]
[³ H]MDL105,519	↓ thalamus ↔ caudate, putamen, nucleus accumbens	[73] [127]
Polyamine site		
[³ H]ifenprodil	↑ temporal cortex; ↔ frontal cortex ↓ thalamus ↔ caudate, putamen, nucleus accumbens	[64] [73] [127]
Intrachannel PCP-sensitive site		
[³ H]MK-801	↑ putamen; ↔ frontal cortex, hippocampus, amygdala ↑ parietal cortex, temporal cortex; ↔ prefrontal cortex ↔ caudate, putamen, nucleus accumbens ↔ thalamus	[96] [194] [127, 136] [73]
[³ H]TCP	↑ frontal cortex; ↔ temporal cortex, amygdala	[175]

↑ – increased, ↓ – decreased, ↔ – unchanged

and occipital fields) [4, 35, 64, 77, 138, 175, 194]. However, the obtained results were not coherent (Tab. 1 and 2). The studies of NR1 mRNA yielded opposing results demonstrating increases [27, 35], decreases [72, 178] or lack of any changes [4] in its cortical levels. In addition, some authors observed an increased number of NMDA receptors in the putamen [8, 96] and their decrease in the thalamus [73]. However, these data were not confirmed by other authors [127, 136]. Moreover, there was no change in NMDA receptor density in the hippocampus, although mRNA encoding the NR1 and NR2B subunits was reduced and increased, respectively [56, 91].

Besides the changes in NMDA receptor, also AMPA and KA receptor expression was found to be altered in schizophrenic patients (Tab. 2 and 3).

Kainate receptors are functionally connected with ion channel permeable to Na⁺, Ca²⁺ and K⁺ ions, while AMPA receptors are coupled to ion channel permeable to Na⁺ and K⁺ ions, acquiring permeability to Ca²⁺ only when built of certain configurations of protein subunits [cf. 149]. Four subunits of AMPA receptor (GluR1-GluR4) and 5 subunits of kainate receptor (GluR5-GluR7, KA1 and KA2) have been cloned [cf. 149]. AMPA and KA receptors form homo- or heteromeric structures, and differences in their subunit composition account for their physiological properties, like in the case of NMDA receptors [cf. 149].

The expression of AMPA and KA receptors in schizophrenic patients was abnormal mainly in the hippocampus. Their density and mRNA levels in that structure were decreased [15, 38, 39, 67, 91,

Table 2. Expression of NMDA receptor subunits

Subunit mRNA expression	Brain structure	References
NR1, NR2A-C, NR2D	↔ prefrontal cortex, parietotemporal cortex, ↑ prefrontal cortex	[4]
NR1	↓ temporal cortex	[72]
	↓ frontal cortex	[178]
	↑ temporal cortex	[27]
NR1	↑ prefrontal cortex, occipital cortex	[35]
NR2A	↑ occipital cortex; ↔ prefrontal cortex	
NR2B	↔ prefrontal cortex, occipital cortex	
NR1	↓ CA3; ↔ CA1, CA2, DG	[56]
NR2A	↔ CA1, CA2, CA3, DG	
NR2B	↑ CA2, CA3; ↔ CA1, CA2, DG	
NR1, NR2B,C	↓ thalamus	[73]
NR2A,D	↔ thalamus	
NR1, NR2A-D	↔ caudate, putamen, nucleus accumbens	[127]

↑ – increased, ↓ – decreased, ↔ – unchanged

153], though not all authors confirmed that observation [16, 137] (Tab. 2 and 3). On the other hand, elevated levels of kainate receptors [34, 135, 194] and an unchanged density of AMPA receptors [53, 68, 99] were found in the cerebral cortex (Tab. 4). However, Akbarian et al. [3] found a tenfold increase in the unedited form of the GluR2 subunit of AMPA receptors in the prefrontal cortex of patients with schizophrenia. It has been suggested that the increased proportion of this subunit can lead to the raised number of Ca²⁺-permeable AMPA receptors, and consequently, to neuronal damage [3].

The number of AMPA and kainate receptors was generally not changed in the nucleus accumbens [53, 68, 127, 136] and thalamus [73], although a lowered expression of mRNA for protein subunits of those receptors was observed in the latter structure [73]. Moreover, there were no changes in the level of kainate receptors in schizophrenic striatum [127, 136, 137], whereas studies of AMPA receptors yielded conflicting results which showed

either an increase [136], a decrease [137], or a lack of changes [53, 68, 127] in their level in that structure.

Besides ionotropic receptors, there are also metabotropic receptors whose activation – *via* G-proteins – leads to stimulation of the second messenger system [cf. 163]. These receptors are encoded by 8 genes, designated as mGlu1-mGlu8, which are divided into 3 groups according to their sequence homology and pharmacological profile. Group I comprises mGluR1 and mGluR5 receptors, which are linked to the phospholipase C pathway. On the other hand, stimulation of group II (mGluR2 and mGluR3) and group III (mGluR4, 6, 7 and 8) receptors leads to inhibition of adenylyl cyclase [cf. 163]. However, only a few studies concerned with metabotropic receptors in schizophrenia have been published so far. No changes in their expression were found in the thalamus [155], while mGluR5 level was increased in the cerebral cortex without any changes in mGluR2 and mGluR3 [31, 139].

The above-discussed literature data indicate that glutamatergic system function can be disorganized in schizophrenia. Moreover, it appears that the changes in this system function can be specific for certain areas of the brain, i.e. cerebral cortex, hippocampus, or, possibly, thalamus. In these structures, density of glutamate receptors and proportion of protein subunits building these receptors alter, which can lead to serious functional anomalies. However, the obtained results are not unequivocal, and they do not provide solid evidence, but only indications confirming the glutamate theory of schizophrenia. Moreover, interpretation of clinical data is complicated by the fact that schizophrenic patients are often treated with neuroleptics for many years, which may also change glutamatergic transmission.

Influence of neuroleptics on the behavioral effects of NMDA receptor antagonists

Typical antipsychotic drugs like haloperidol block with high affinity dopamine D₂ receptors and also inhibit though with lower affinity D₁, D₃, and D₄ receptors. Such neuroleptics are effective in improving positive psychotic symptoms, however, they have little, if any, effect on negative symptoms. Atypical neuroleptics such as, e.g. clozapine, olanzapine or risperidon also block dopamine receptors (D₂, D₁, D₃ or D₄), with diverse potency, though [9, 168, 169]. In this respect, clozapine is an

Table 3. Expression of AMPA receptors in schizophrenia patients

Receptor binding sites	Brain structure	References
$[^3\text{H}]\text{CNQX}$	↓ CA4, CA3; ↔ CA1, CA2, CA3	[91]
	↑ caudate; ↔ putamen, nucleus accumbens	[136]
	↓ caudate, nucleus accumbens	[137]
	↔ hippocampus, amygdala	
$[^3\text{H}]\text{AMPA}$	↔ frontal cortex, parieto-temporal cortex, occipital cortex, putamen, nucleus accumbens	[53, 68, 99]
	↓ CA2, ↔ CA1, CA3, CA4, DG	[56]
	↔ thalamus	[73]
	↔ caudate, putamen, nucleus accumbens	[127]
Subunit mRNA expression		
GluR1	↓ CA3; ↔ CA1, CA4, DG	[67]
GluR1, 2	↓ CA3, CA4, DG, ↔ CA1	[39]
GluR1	↓ frontal cortex	[178]
GluR2 (unedited)	↑ prefrontal cortex	[3]
GluR1, 3	↓ thalamus	[73]
GluR2, 4	↔ thalamus	
GluR1,2,3,4	↔ caudate, putamen, nucleus accumbens	[127]
Subunit protein expression		
GluR2/3	↓ CA4; ↔ CA1, CA3, DG	[38]
GluR1,2,3	↔ hippocampus, cingulate cortex	[16]

↑ – increased, ↓ – decreased, ↔ – unchanged

exceptional drug, as it shows relatively low affinity for D_2 , but high for D_4 receptors [169]. Apart from dopamine receptors, atypical neuroleptics also display high affinity for, among others, noradrenergic and serotonergic receptors, in particular for 5-HT_{2A} ones [9]. It has been suggested that relatively weak blockade of dopamine D_2 receptors, concurrent with profound blockade of 5-HT_{2A} ones, may result in a low incidence of extrapyramidal side-effects produced by atypical neuroleptics, as well as in a higher efficacy of these neuroleptics in comparison with typical ones in alleviation of negative symptoms [9, 128, 129, 158].

Experimental studies with animals have shown that atypical neuroleptics (e.g. clozapine) are also more effective than typical ones in relieving effects exerted by PCP-like drugs in some tests.

A vast body of evidence indicates that non-competitive antagonists of NMDA receptors (MK-

801, PCP) increase the locomotor activity of animals and induce stereotyped behavior [26, 70, 124, 182, 192]. According to some authors, this behavioral activation may represent an animal model of schizophrenia [26, 131, 159, 192]. Both typical (e.g. haloperidol, raclopride) and atypical (e.g. clozapine, olanzapine, risperidone) neuroleptics reduce the locomotor response produced by NMDA receptor antagonists, which indicates involvement of a dopaminergic component in this behavioral activation [26, 70, 79, 124, 192; also see below]. Acute administration of PCP and other NMDA antagonists also leads to a deficit in working memory performance [131, 132, 202]. A number of studies have demonstrated that working memory processes are associated with the prefrontal cortex, dopaminergic transmission playing a significant role therein [10, 63, 82]. Single treatment with NMDA receptor antagonists increases dopamine release in the pre-

Table 4. Expression of kainate receptors in schizophrenic patients

Receptor binding sites	Brain structure	References
$[^3\text{H}]\text{KA}$	↑ frontal cortex; ↔ striatum, temporal cortex	[34, 135]
	↓ CA1, CA2, CA3, CA4, DG	[91]
	↑ prefrontal cortex, parietal cortex; ↔ occipital cortex	[194, 195]
	↔ CA1, CA2, CA3, CA4, DG	[56]
	↔ caudate, putamen, nucleus accumbens, amygdala	[127, 135, 136]
	↔ thalamus	[73]
Subunit mRNA expression		
GluR6	↓ CA3, DG	[153]
KA2	↓ CA2, CA3, DG	
GluR7, KA1	↓ frontal cortex	[178]
KA2	↓ thalamus	[73]
GluR5-7, KA1	↔ thalamus	
Subunit protein expression		
GluR5,6,7	↓ hippocampus	[15]

↑ – increased, ↓ – decreased, ↔ – unchanged

frontal cortex; moreover, dopamine D₂ antagonists such as, e.g. haloperidol and raclopride have been reported to ameliorate the working memory deficit evoked by these compounds, which suggests that the enhanced dopaminergic transmission may, at least partly, contribute to such impairment [82, 202].

There are, however, differences between effects of typical and atypical neuroleptics administered acutely regarding the sensorimotor gating deficit induced by PCP and the social behavior altered by this compound.

Prepulse inhibition is a model of sensorimotor gating, which uses the reflex startle response to brief stimuli as a behavioral measure. In this model, a weak acoustic stimulus, which cannot induce a startle response *per se*, inhibits the reaction of the organism to strong sensory stimulation. The degree to which a weak sensory stimulus (prepulse) inhibits the reflex motor reaction to an intense stimulus (pulse) is considered to reflect sensorimotor gating [58, 187].

A disruption of prepulse inhibition has been observed in schizophrenic patients [cf. 58]. In rats, prepulse inhibition (PPI) is disrupted by dopaminomimetics (apomorphine, amphetamine) [116, 156, 188], NMDA receptor antagonists (PCP, MK-801) [11, 12, 71, 186], and compounds stimulating 5-HT₂ receptors (e.g. DOI) [9], which suggests that deficits in PPI may be attributed to dopaminergic, glutamatergic or serotonergic system dysfunctions.

Acute treatment with either typical or atypical neuroleptics can reverse the dopamine agonist-induced PPI deficits [116, 158, 188]. Contrariwise, the disruption of PPI induced by PCP is antagonized by acute treatment with some atypical neuroleptics such as clozapine [12, 186], olanzapine [11], seroquel [186] or remoxipride [85], whereas some typical neuroleptics (e.g. haloperidol) with high affinity for dopamine D₂ receptors are ineffective [71, 89, 206]. However, some recent evidence indicates that long-term treatment with haloperidol attenuates the PCP- or the MK-801-induced PPI deficits [49, 121, 152].

The mechanism responsible for the PPI deficit induced by PCP-like drugs has not been fully elucidated as yet. A potential mechanism by which PCP may produce a deficit in PPI consists in the influence exerted by this compound on serotonergic transmission. PCP, as well as other NMDA antagonists increase 5-HT release in the brain, and 5-HT₂ antagonists diminish the PCP-induced deficit in this test [57, 120, 201]. However, a role of other neurotransmitter systems, e.g. glutamatergic or noradrenergic ones, in these effects has also been suggested [cf. 57].

As has already been mentioned elsewhere, the negative symptoms of schizophrenia in humans are produced by non-competitive NMDA receptor antagonists (PCP and ketamine); whereas dopaminomimetics are devoid of such activity. Experimental studies on rats have also demonstrated that PCP, but not amphetamine, disrupts social interaction, which is considered to be an animal model of negative symptoms [26, 159, 161]. The effects of NMDA receptor antagonists in this model are diminished by some atypical neuroleptics, such as clozapine, olanzapine, or remoxipride [26, 159, 160]. Typical neuroleptics (haloperidol, raclopride), which have little, if any, effect on negative symptoms in schizophrenic patients, do not reduce, either, the deficits in social interaction produced by NMDA receptor antagonists [26, 159, 160].

Behavioral impairment induced by NMDA receptor antagonists: the role of dopaminergic and non-dopaminergic transmission

There exists anatomical and functional evidence that glutamate interacts with the nigrostriatal and the mesocorticolimbic dopaminergic systems, and that the dysregulation of one of them may alter the neurotransmission of another. In the striatum, GABAergic projecting neurons receive two major regulatory inputs: a dopaminergic input from the substantia nigra, and a glutamatergic input from the cerebral cortex [21, 143, 144]. Those GABAergic projecting neurons form the so-called 'direct' and 'indirect' strio-thalamic pathways. Glutamate exerts stimulatory action on these neurons, while dopamine – *via* D₂ receptors – inhibitory one [21, 144]. Carlsson and Carlsson have suggested that 'indirect' strio-thalamic pathways have inhibitory influence on glutamatergic thalamo-cortical afferents, and thus 'gate' the sensory information coming into the cortex [21]. Disruption of such an inhibitory gating mechanism, induced by the hyperfunction of dopaminergic transmission or by the hypofunction of NMDA receptors, may lead to behavioral activation in animals and psychotic symptoms in humans [21].

It is noteworthy that the hypofunction of NMDA receptors evoked by PCP-like drugs may also induce a hyperfunction of dopaminergic transmission. A number of studies indicate that the behavioral activation evoked by PCP or MK-801 in rodents may be mediated by a dopamine-dependent mechanism. Acute treatment with these compounds increases dopamine release in the prefrontal cortex, nucleus accumbens and striatum, [122, 131, 132, 176, 206] and enhances the firing rate of dopamine neurons in the midbrain [54, 133, 183, 213]. Furthermore, the locomotor response produced by NMDA receptor antagonists can be diminished by catecholamine depletion [113, 208] or – as has been mentioned above – by dopamine receptor antagonists administered either systemically or directly into the nucleus accumbens [26, 70, 79, 113, 124, 192, 208].

A potential mechanism by which PCP may enhance dopaminergic transmission in the brain consists in inhibition of dopamine re-uptake [125]. However, such a mechanism cannot account for all PCP effects on dopaminergic neurons. As has al-

ready been mentioned earlier, PCP and MK-801 which do not bind to dopamine uptake carriers, increase the firing rate of dopamine neurons [54, 125, 133, 183, 213]. Thus, the increased activity of dopaminergic neurons in the ventral tegmental area (VTA) and substantia nigra would lead to enhancement of dopaminergic transmission in the target structures, nucleus accumbens and striatum, respectively, and to stimulation of locomotor activity [122, 134, 183]. In line with the above assumption, the GABA_B receptor agonist baclofen, which inhibits dopaminergic neuronal activity [142], diminishes the locomotor response evoked by NMDA antagonists when it is administered directly into the VTA [134].

In support of the role of dopaminergic transmission in the NMDA antagonist-induced behavioral stimulation, recent studies have shown that glycine, an agonist of glycine site at the NMDA receptor complex, diminishes both the PCP-induced dopamine release in the nucleus accumbens and the hyperlocomotion evoked by this compound [80].

Recently, it has been postulated that the disinhibition of glutamatergic transmission induced by PCP-like drugs can account for the enhancement of dopaminergic transmission [122, 131, 132, 183]. As has been mentioned above, the hypofunction of NMDA receptors produced by these compounds leads to an increase in glutamate release (in different brain regions, e.g. in the prefrontal cortex, VTA, striatum and hippocampus), which in turn may facilitate dopamine release *via* stimulation of AMPA/KA receptors [110, 131, 132, 183]. This hypothesis is based on the observation that AMPA and/or KA receptor antagonists, administered either systemically or directly into the VTA, antagonize both the stimulation of dopamine release in the nucleus accumbens and the hyperlocomotion evoked by NMDA receptor antagonists [18, 122, 208]. Likewise, local or systemic pretreatment with AMPA/KA receptor antagonists reduces the PCP-induced dopamine release in the prefrontal cortex [132]. It is unlikely, however, that the elevated glutamate level is the only factor responsible for such an effect, since recent studies have shown that LY 354740, an agonist of group II metabotropic glutamate receptors, reduces the PCP-induced glutamate efflux without blocking the increased dopamine release in this structure [131].

Other findings suggest that PCP or MK-801 can diminish GABA transmission by blocking NMDA

receptors, which leads to disinhibition of dopaminergic transmission in the prefrontal cortex [162, 211]. Microdialysis studies have demonstrated that PCP and MK-801, applied directly into the prefrontal cortex, decrease GABA release, but increase dopamine efflux in this structure [211]. Furthermore, local application of GABA receptor agonists, or systemic pretreatment with γ -vinyl GABA, an irreversible inhibitor of GABA catabolizing enzyme (GABA-AT) which increases GABA level in the brain, diminishes the PCP-induced increase in dopamine release in the prefrontal cortex [162, 211]. Hence, a cortical glutamate/GABA/dopamine interaction may, at least partly, underlie the enhanced dopaminergic transmission in this structure [162, 211].

Although the hypofunction of NMDA receptors evoked by acute treatment with PCP or MK-801 may enhance dopaminergic transmission both in subcortical structures and in the prefrontal cortex, repeated PCP administration induces a hypofunction of dopaminergic transmission in the latter structure. Subchronic PCP or MK-801 administration decreases dopamine utilization and release in this structure [81, 82, 84]. Moreover, after such treatment, a decrease in dopamine D₁ receptor mRNA level is observed in rat prefrontal cortex [82]. On the other hand, subchronic treatment with PCP enhances dopaminergic transmission in subcortical structures. A more pronounced dopamine release and amphetamine-induced hyperlocomotion have been found in rats treated repeatedly with PCP in comparison with control ones [13, 83]. Interestingly, recent *in vivo* studies have shown that also amphetamine releases dopamine more intensely in schizophrenic patients than in healthy controls [17, 100], as is the case in PCP-treated animals. Thus, the chronic PCP model of schizophrenia is in line with the latest dopamine hypothesis about this disease (see above), and suggests that the hypofunction of NMDA receptors can induce secondary disturbances in cortical and subcortical dopaminergic functions.

The influence exerted by NMDA antagonists on dopaminergic transmission cannot, however, account for all the effects of these compounds, since they can also evoke behavioral impairment *via* a dopamine-independent mechanism. For example, it has been reported that destruction of dopaminergic neurons in the nucleus accumbens by 6-OHDA does not inhibit the locomotor response induced by MK-801 [148]. Furthermore, NMDA antagonists

can elicit locomotor stimulation in animals pretreated with α -methyl-p-tyrosine (α -MT) [184], or with reserpine given jointly with α -MT [20, 22]. The locomotor response evoked by PCP in dopamine-depleted rats can be diminished by LY379268, a group II metabotropic glutamate receptor agonist, and by LY293558, an AMPA/KA receptor antagonist, which suggests involvement of glutamatergic transmission in the behavioral effect of NMDA antagonists [184]. As has already been mentioned above, AMPA/KA receptor antagonists also diminish the hyperlocomotion [18, 122, 208] and cognitive disruption [132] evoked by PCP-like drugs in normal rats. Moreover, agonists of group II metabotropic glutamate receptors (e.g. LY379268 or LY354740) also suppress the effects of NMDA antagonists (locomotor stimulation, stereotypy, and cognitive disruption) in normal rats [24, 132, 184], probably by decreasing glutamate release, since it has been demonstrated that LY354740 reduces both the PCP-induced behavior and glutamate release without blocking dopamine efflux [132]. The inhibitory effect of LY354740 on glutamate release is probably mediated by the activation of group II mGluRs on glutamatergic terminals. Therefore, PCP may enhance glutamate release which, in turn, activates AMPA/KA receptors and finally induces behavior impairment.

PCP-like drugs also increase 5-HT release, and the behavioral effect of these compounds can be suppressed by 5-HT_{2A} receptor antagonists in both normal and dopamine-depleted rats, which also suggests a role of serotonergic transmission in the behavioral impairment induced by NMDA receptor antagonists [23, 120, 124, 204]. Interestingly, electrophysiological studies have indicated that 5-HT increases glutamate release in the cerebral cortex *via* 5-HT_{2A} receptors [2, 118, 119]. Therefore, it is supposed that PCP may also enhance glutamate release in cerebral cortex *via* a serotonergic mechanism and this effect can be suppressed by 5-HT_{2A} antagonists [2].

It has also been suggested that NMDA antagonists can facilitate, at least partly, glutamate release by decreasing the excitatory transmission onto inhibitory GABAergic neurons [140]. The reduced GABAergic transmission may lead to disinhibition of glutamatergic neurons and a subsequent increase in glutamate release. In line with this assumption, the electrophysiological studies conducted in the hippocampus have shown that NMDA receptor an-

tagonists reduce local GABAergic transmission in the CA1 area [66]. In the prefrontal cortex, PCP increases glutamate efflux [131, 132], but reduces GABA release [211]. Furthermore, a reduced level of GAD₆₇, an enzyme responsible for GABA synthesis [154], as well as a hypofunction of GABA_A receptors [212] have been found in the cerebral cortex and limbic structures after PCP administration.

The dysfunction of GABA transmission has also been implicated in schizophrenia. For example, both the uptake and the release of GABA are diminished in the cerebral cortex of schizophrenic patients [92, 172, 174]. Moreover, the activity of glutamic acid decarboxylase (GAD), an enzyme responsible for GABA synthesis, as well as the expression of GAD₆₇ mRNA are reduced in the prefrontal cortex of schizophrenic patients [92], as is the case in animals treated with NMDA antagonists.

Hence, the hypofunction of NMDA receptors evoked by PCP-like drugs can induce disturbances in different neurotransmitter systems, e.g. glutamatergic, dopaminergic, serotonergic and GABAergic, which are also affected in schizophrenia. The disturbed function of these neurotransmitter systems by PCP may induce behavioral impairment in animals and psychotic symptoms in humans. Since the agents that interfere with the serotonergic system (e.g. antagonists of 5-HT_{2A} receptors), as well as with the glutamatergic one (e.g. agonists of the glycine site at the NMDA receptor complex, antagonists of AMPA/KA receptors, and agonists of group II metabotropic glutamate receptors), diminish the PCP-induced effect in animals, they may help to work out a novel strategy in the treatment of schizophrenia [98, 130, 131, 183].

Morphological changes in neurons induced by NMDA receptor antagonists

PCP and other noncompetitive NMDA receptor antagonists, administered at high doses or repeatedly, cause neuronal damage in the cerebral cortex and limbic structures [28, 42, 47, 48, 86, 171]. The distribution of neuronal degenerations induced by NMDA receptor antagonists in rat brain is similar to the localization of abnormalities reported in patients with schizophrenia, which indicates that the damage may be caused by dysfunctional glutamatergic transmission [42, 140, 141].

The mechanism responsible for NMDA receptor antagonist-induced pathological changes in neu-

rons has not been fully elucidated as yet. However, it has recently been suggested that this effect is mediated by the influence of these antagonists on glutamate and acetylcholine release [28, 47, 141]. The hypofunction of NMDA receptors produced by these antagonists leads to an excessive release of both the above neurotransmitters [94, 131, 132] and overstimulation of postsynaptic neurons, which has been suggested to cause neuronal damage [47]. Several classes of drugs, e.g. GABA_A agonists, AMPA/KA antagonists and muscarinic antagonists, as well as such typical antipsychotics as haloperidol and thioridazine, and atypical ones such as clozapine and olanzapine, are effective in preventing the neurotoxicity induced by NMDA antagonists [26, 46–48, 140, 171].

Influence of neuroleptics on glutamatergic transmission

In recent years, a number of studies have indicated that typical and atypical neuroleptics can modulate NMDA receptor function by their direct effect on these receptors [14, 51, 76, 104], or indirectly *via* intracellular mechanisms triggered by their influence on other receptors, e.g. dopamine receptors [102]. These drugs have been suggested to act as partial agonists of a glycine site or another modulatory site in the NMDA receptor complex [14, 51, 104]. Moreover, *in vitro* studies have shown that neuroleptics administered at low micromolar concentrations displace [³H]MK-801, [¹²⁵I]MK-801 and [³H]TCP from the binding site inside an NMDA receptor ion channel, and [³H]ifenprodil from the polyamine site of this receptor [14, 29, 104, 112].

Repeated treatment with neuroleptics produce adaptive changes in the glutamatergic system by modulating glutamate release and altering the number of glutamate receptors and the expression of their mRNAs.

In vivo microdialysis experiments have revealed differences in the effects of typical and atypical neuroleptics on glutamate release in various brain structures. Typical neuroleptics, e.g. haloperidol or fluphenazine, but not atypical ones, e.g. clozapine, increase extracellular glutamate level in the striatum and alter the morphology of neurons in this structure, which is associated with the development of neuroleptic-induced extrapyramidal effects [117, 130, 166, 167, 210]. On the other hand, opposing

Table 5. Influence of the repeated treatments with neuroleptics on NMDA receptor density in animals

Neuroleptic	Receptor binding sites	Brain structure	References
Glutamate site			
Haloperidol (3 weeks)	[³ H]glutamate	↑ parietal cortex; ↔ hippocampus, thalamus	[200]
Haloperidol (6 months)		↔ hippocampus	[56]
Haloperidol (3 months)	[³ H]CGP39653	↑ frontal cortex, parietal cortex, insular cortex	[147]
Clozapine (3 months)	[³ H]CGP39653	↑ parietal cortex, insular cortex; ↔ frontal cortex	
Intrachannel PCP-sensitive site			
Haloperidol (6 weeks or 3 months)	[³ H]MK-801	↔ striatum	[145]
Haloperidol, clozapine (4 weeks)		↔ striatum	[130]
Haloperidol (3 weeks)	[³ H]MK-801	↑ prefrontal cortex	[55]
Sulpiride (3 weeks)		↔ prefrontal cortex	
Clozapine (3 weeks)	[³ H]MK-801	↓ frontoparietal cortex; ↔ prefrontal cortex, NA, striatum, hippocampus	[59]
Haloperidol 4 weeks or 8 months	[³ H]MK-801	↓ prefrontal cortex; ↔ striatum, hippocampus, NA, SN, VTA ↔ prefrontal cortex, striatum	[189]
Clozapine 4 weeks or 8 months		↓ prefrontal cortex, striatum, ↔ hippocampus, NA, SN, VTA ↓ striatum; ↔ prefrontal cortex	
Raclopride (4 weeks or 8 months)		↔ prefrontal cortex, striatum, hippocampus, NA, SN, VTA	
Haloperidol, clozapine (3 weeks)	[³ H]MK-801	↔ frontal cortex, striatum, NA	[179]
Haloperidol, clozapine (3 months)	[³ H]MK-801	↔ frontal cortex, parietal cortex, insular cortex	[147]

↑ – increased, ↓ – decreased, ↔ – unchanged; NA – nucleus accumbens, SN – substantia nigra, VTA – ventral tegmental area

effects of typical and atypical neuroleptics on glutamic acid release have been observed in the cerebral cortex [151]. Chronically administered haloperidol raises, while clozapine lowers, the extracellular level of this neurotransmitter in the frontoparietal cortex, which may be important for a higher efficacy of clozapine in abolishing some effects of NMDA receptor antagonists [151].

Both typical and atypical neuroleptics administered repeatedly also cause adaptive changes in the NMDA receptor complex. These drugs affect the

density and expression of mRNA for protein subunits composing this receptor in different brain structures (Tab. 5 and 6). However, the results obtained so far are not coherent and depend on the used neuroleptic and treatment duration [25, 146, 157, 189, 191]. In addition, they also depend on the compound used for labeling the NMDA receptor; for example, long-term treatment with neuroleptics (3 months) increases the binding of the competitive antagonist of NMDA receptor [³H]CGP39653, being without effect on the binding of its noncom-

Table 6. Influence of repeated administrations of neuroleptics on expression of protein subunits of NMDA receptor in animals

Neuroleptic	Subunit mRNA expression	Brain structure	References
Haloperidol (3 weeks)	NR1, NR2A-C	↑ striatum, ↔ frontal cortex, hippocampus, NA	[157]
Clozapine (3 weeks)	NR1	↓ NA, ↔ frontal cortex, hippocampus, striatum	
	NR2A-B	↔ frontal cortex, hippocampus, striatum, NA	
	NR2C	↓ frontal cortex, NA ↔ hippocampus, striatum	
Olanzapine (3 weeks)	NR1, NR2A-C	↔ frontal cortex, hippocampus, striatum	[190]
Guetiapine (3 weeks)	NR1	↓ NA; ↔ hippocampus, striatum	[191]
	NR2A-B	↔ NA, hippocampus, striatum	
	NR2C	↑ striatum; ↓ NA, ↔ hippocampus	
cis-Flupenthixol (1, 2, 4, 8, 12, 24 weeks) (2 weeks) (12–24 weeks)	NR1	↓ frontal cortex, parietal cortex, subcortical structures	[25]
	NR2B-2D	↑ frontal cortex, parietal cortex, subcortical structures	
	NR2A-2C	↓ frontal cortex, parietal cortex, subcortical structures	
Haloperidol (3 months)	NR1	↓ frontal cortex, parietal cortex, striatum;	[146]
Clozapine (3 months)	NR1	↑ CA1; ↔ NA, insular cortex	
		↑ NA, insular cortex; ↔ frontal cortex, parietal cortex, hippocampus	
Subunit protein expression			
Haloperidol (4 weeks)	NR1	↑ striatum; ↔ prefrontal cortex, NA, hippocampus	[50]
Clozapine (4 weeks)	NR1	↔ prefrontal cortex, NA, hippocampus, striatum	

↑ – increased, ↓ – decreased, ↔ – unchanged; NA – nucleus accumbens

petitive antagonist [³H]MK-801 in the cerebral cortex [147]. This may be due to the existence of a variety of NMDA receptor subtypes, which as mentioned above can show diverse affinity for different compounds [19, 90, 101].

There is a variety of opinions about the effect of chronic neuroleptic treatment on AMPA receptors [50, 126, 145, 179, 189, 190, 191]. Some authors found that the atypical neuroleptic clozapine, but not the typical one, haloperidol, increased the level of AMPA receptors [179], whereas others observed that haloperidol raised their number in rat brain [126]. On the other hand, Tarazi et al. [189] did not report any changes in AMPA receptor density after chronic treatment with haloperidol or clozapine. Long-term treatment with neuroleptics evoked no effect, either, on KA receptor density [179, 189].

Recent evidence indicates that chronic treatment with neuroleptics causes adaptive changes in group II metabotropic receptors. Clozapine and olanzapine, but not haloperidol, elevate mGluR3 mRNA level in rat frontal cortex [190].

Significance of impaired glutamatergic transmission at early developmental stages for subsequent psychotic symptoms

The hypothesis that schizophrenia may be a neurodevelopmental disease has been discussed for some time. It is argued that the exposure to factors damaging neurons at early developmental stages may culminate in schizophrenia in adulthood [40, 74, 75, 141]. Glutamic acid is regarded as one of such neuron-damaging factors. Glutamatergic neu-

rotransmission, in particular activation of NMDA receptors, plays an important role in the neuronal growth and formation of a network of synaptic connections between neurons [cf. 74]. However, changes in glutamatergic transmission can cause neuronal damage and degeneration. The blockade of NMDA receptor during synaptogenesis by treatment with noncompetitive (PCP, MK-801, ketamine) or competitive (CPP) antagonists produces a wave of apoptotic processes which eliminate neurons in many brain structures, including different cortical fields, limbic structures, the thalamus and striatum [74, 75]. In this case, degeneration affects neurons bearing NMDA receptors, which may lead to dysfunction of glutamatergic neurotransmission and manifestation of psychotic symptoms in adulthood. The above assumption was corroborated by recent studies, which demonstrated that several doses of PCP administered to animals on days 7, 9 and 11 after birth caused degeneration of cortical neurons and development of deficits in information processing, characteristic of schizophrenia at later stages of animal life [204]. Importantly, PCP effects were reversed by the atypical neuroleptic olanzapine [204].

As has already been mentioned above, glycine plays an important role in NMDA receptor function [149]. However, it seems that its too high concentration in the brain and the resultant excessive stimulation of NMDA receptors can also lead to neuronal degeneration. Experimental studies demonstrated structural brain changes resembling those observed in schizophrenics, i.e. enlarged cerebral ventricles and decreased volume of the hippocampus in those rats whose mothers were fed on a glycine-rich diet, and which themselves were on a similar diet after birth [205]. Furthermore, those animals exhibited deficits in information processing, measured by a sensorimotor gating test [205]. Although in those studies glycine was administered to animals until adulthood, it was postulated that it caused neurodegeneration at early developmental stages [205], since treatment of adult animals with high doses of glycine for 3–5 months did not produce degeneration of cortical and hippocampal neurons [173]. Thus, glycine effects appear to be paradoxical, since the drug was shown to be neurotoxic at early developmental stages, but exerted therapeutic action in adulthood (see below).

In line with the hypothesis that schizophrenia may be a neurodevelopmental disease, it has also been demonstrated that neonatal excitotoxic lesions of the ventral hippocampus (VH), which destroy a great number of glutamatergic projections, lead to an increased dopaminergic transmission in subcortical structures in early adulthood and alter functions of the glutamatergic system, thus mimicking abnormalities observed in schizophrenia [5, 106, 108, cf. 109, 164]. For example, animals with neonatal ventral lesion show an enhanced sensitivity to stress, novel environment, dopamine agonists and NMDA receptors antagonists [5, 106, 108, cf. 109, 164]. Moreover, such treatment leads to working memory impairment, disruption of latent inhibition, and sensory motor gating deficit [105, 107, cf. 109]. Some of these abnormalities can be ameliorated by neuroleptics and, interestingly, by AMPA/KA receptor antagonists [5, 108]. Thus, the latter animal model suggests that defects in the development of the hippocampus may lead to psychotic symptoms after puberty. It is noteworthy that a number of studies have reported abnormalities in schizophrenic hippocampus, suggesting that they may be of developmental nature [207].

Manipulation of glutamatergic transmission and therapeutic effects

In line with the hypothesis that the hypofunction of NMDA receptors is implicated in the pathomechanism of schizophrenia, it has been suggested that the compounds enhancing the function of these receptors may be therapeutically beneficial.

Agonists of the glutamate binding site on the NMDA receptor complex (glutamate, NMDA) could not be used in the clinic due to their neurotoxic effects. Hence, the first clinical trials were carried out with agonists of the glycine site on this complex, such as glycine, D-serine and D-cycloserine. It was found that glycine administered for 6–8 weeks jointly with neuroleptics alleviated negative symptoms in patients suffering from schizophrenia [69, cf. 78]. Unfortunately, the therapeutic effect was relatively weak, which could be due to poor penetration of the blood-brain barrier by glycine. However, recent reports have indicated that combined treatment with neuroleptics and D-serine, another endogenous agonist of the glycine site on NMDA receptors, alleviated not only negative, but also positive symptoms of schizophrenia and im-

proved cognitive functions [198]. D-serine crosses the blood-brain barrier more readily than glycine, and its distribution in the brain correlates better with the distribution of NMDA receptors than that of glycine [177]. The use of the partial agonist of glycine site D-cycloserine in a neuroleptic therapy also has a beneficial effect on the relief from negative symptoms [44, 60, 61].

The ability of the compounds augmenting NMDA receptor function to enhance antipsychotic effects of neuroleptics makes them very attractive. However, for reasons unknown, the compounds acting through the glycine site do not enhance the effects of the atypical drug clozapine [45, 62, 199].

Another pharmacological strategy is based on the observation that some effects of PCP and other psychotomimetic compounds belonging to NMDA receptor antagonists may depend on the augmentation of glutamatergic transmission at AMPA/KA receptors. As has already been mentioned above, these compounds increase glutamate release in the cerebral cortex, which leads to overstimulation of non-NMDA receptors (AMPA/KA) and, in consequence, to cognitive impairment [131, 132]. These experimental studies have inspired hope that the compounds that lower glutamate release and/or block postsynaptic AMPA/KA receptors can be efficient also in schizophrenic patients.

Until now, only preliminary clinical trials of the efficacy of glutamatergic transmission-diminishing compounds have been carried out. One of the tested drugs, lamotrigine, reportedly lowers glutamic acid release by blocking sodium channels, P- and N-type calcium channels and potassium channels [65, 180, 203], while another compound, topiramate, blocks AMPA and kainate receptors and enhances GABAergic transmission [cf. 170].

It has been shown that lamotrigine alleviated psychotic symptoms and improved the impaired cognitive functions evoked by ketamine in healthy volunteers [7]. Those findings confirmed the suggestion that the compounds lowering glutamate release could be beneficial to schizophrenic patients. However, the first clinical trial which included lamotrigine in the neuroleptic therapy did not yield satisfactory results, since that drug attenuated psychotic symptoms only when it was administered jointly with clozapine, but not with any other neuroleptic (haloperidol, olanzapine, risperidone, or flupenthixol) [37, 193]. Initial clinical trials with topiramate did not yield conclusive results, either,

as both reduction of negative symptoms [36] and lack of therapeutic effects upon combined treatment with neuroleptics were reported [37].

In the aforementioned preliminary clinical trials only a very limited number of participants were examined, so it is difficult to determine whether a combined therapy with neuroleptics and compounds lowering glutamatergic transmission is successful in terms of therapeutic efficacy. Multi-center large-scale trials of many glutamatergic system modulators are required to obtain an unequivocal answer to this question.

Conclusion

The hypothesis attributing decisive role in the development of psychotic symptoms in schizophrenia exclusively to dysfunction of dopaminergic transmission has been gradually relinquished over recent years. As mentioned above, a neuroleptic therapy targeted at this system only has proven to be insufficient to abolish all psychotic symptoms, while atypical neuroleptics, which, besides their dopaminergic effects, also bind to other receptor types, have been reported to be more efficient than typical ones in alleviating at least some psychotic reactions in patients suffering from schizophrenia [9, 128, 129]. Hence, new concepts are emerging which link the pathomechanism of this disease to the dysfunction of different neurotransmitter systems. The list of such systems has recently been supplemented with the serotonergic and GABAergic systems whose anomalous function may be implicated in the development of psychotic symptoms [92, 103, 158]. The results of clinical and experimental animal studies presented in this article indicate that also dysfunction of glutamatergic transmission may lead to psychotic reactions. An aberrant function of this system, both in adulthood and at early stages of brain development, may produce psychotic symptoms. Hence a better understanding of the structure and function of glutamate receptors under physiological conditions and in the course of schizophrenia may contribute to elucidation of the pathomechanism of this disease and facilitate the development of more effective therapeutic strategies.

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