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Therapeutic targets for schizophrenia

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CONTENTS

Abstract

Schizophrenia is a psychiatric illness characterized by disturbances of cognition and thought, affecting language, perception and sense of self. The treatment of schizophrenia involves drug therapy to relieve symptoms and prevent relapse, education and psychosocial intervention to help both patients and their families to cope with the illness, and rehabilitation to facilitate reintegration of patients into the community. The search for effective treatment strategies for schizophrenia continues, with special attention focused on the identification of novel targets for drug development. In order to facilitate access to information on the major targets for therapeutic intervention, this article presents those that are currently under active investigation.

Introduction

Schizophrenia is a common and severe, often disabling psychiatric illness that is characterized by extreme disturbances of cognition and thought, affecting language, perception and sense of self. It is a chronic disorder typified by a life-long pattern of acute psychotic episodes superimposed upon chronically poor psychosocial adjustment. No simple, single causative factor of schizophrenia has been identified, and it is conceivable that no such factor exists. Both genetic liability and nongenetic (e.g., environmental) risk factors appear to be involved. This psychiatric disorder does not know ethnic, economic or cultural boundaries and has a prevalence worldwide of approximately 1%. It is characterized by positive symptoms (auditory hallucinations, disorganized or bizarre thoughts, delusions and irrational fears) and negative symptoms (social withdrawal, loss of will or drive, poverty of speech, apathy and lack of energy). Positive symptoms appear to reflect an excess or distortion of normal functions, while negative symptoms reflect a decrease or loss of normal functions. Many patients also experience cognitive dysfunction ranging from impaired attention to abnormal executive function, as well as memory impairment, depression and/or anxiety. Given the extensive heterogeneity of symptoms among individual patients, schizophrenia can be considered a clinical syndrome rather than a single disease entity (1-3).

Although the pathophysiology of any given clinical feature of schizophrenia may differ from one individual patient to another as a result of the various possible combinations of environmental and genetic risk factors, there are certain molecular changes in critical cellular pathways that are conserved and are common to individuals sharing that particular feature. If these alterations, which have been referred to as “molecular hubs”, can be pinpointed, they can be expected to provide targets for therapeutic intervention (4).

The treatment of schizophrenia involves three main components: 1) drug therapy to relieve symptoms and prevent relapse; 2) education and psychosocial intervention to help both patients and their families cope with the illness; and 3) rehabilitation to facilitate reintegration of patients into the community. Identifying schizophrenic patients in the earliest stages of the disorder so that treatment can be initiated promptly decreases the risk of recurrence or serious residual damage. Although a cure has not yet been found for the disease, a plethora of treatments have become available to help patients control their symptoms, improve quality of life and restore productive lives (5).

The most relevant drug targets for schizophrenia have been suggested to be those involved in the pathophysiology of prefrontal dysfunction. Antipsychotic drug development over the past 40 years has been based on the “hyperdopaminergic hypothesis” of schizophrenia, which suggests that excessive production of dopamine (presynaptic dopamine overactivity) and/or increased D_2 receptor density or increased postreceptor action (postsynaptic dopamine overactivity) is implicated in the pathogenesis of the disorder. The earliest discovered neuroleptic agents, or *typical antipsychotics,* act on dopamine receptors and relieve only the positive symptoms of schizophrenia. Agents discovered later that also act on serotonergic receptors were shown to improve negative symptoms of the disease as well, and led to the development of a new generation of *atypical antipsychotics* that

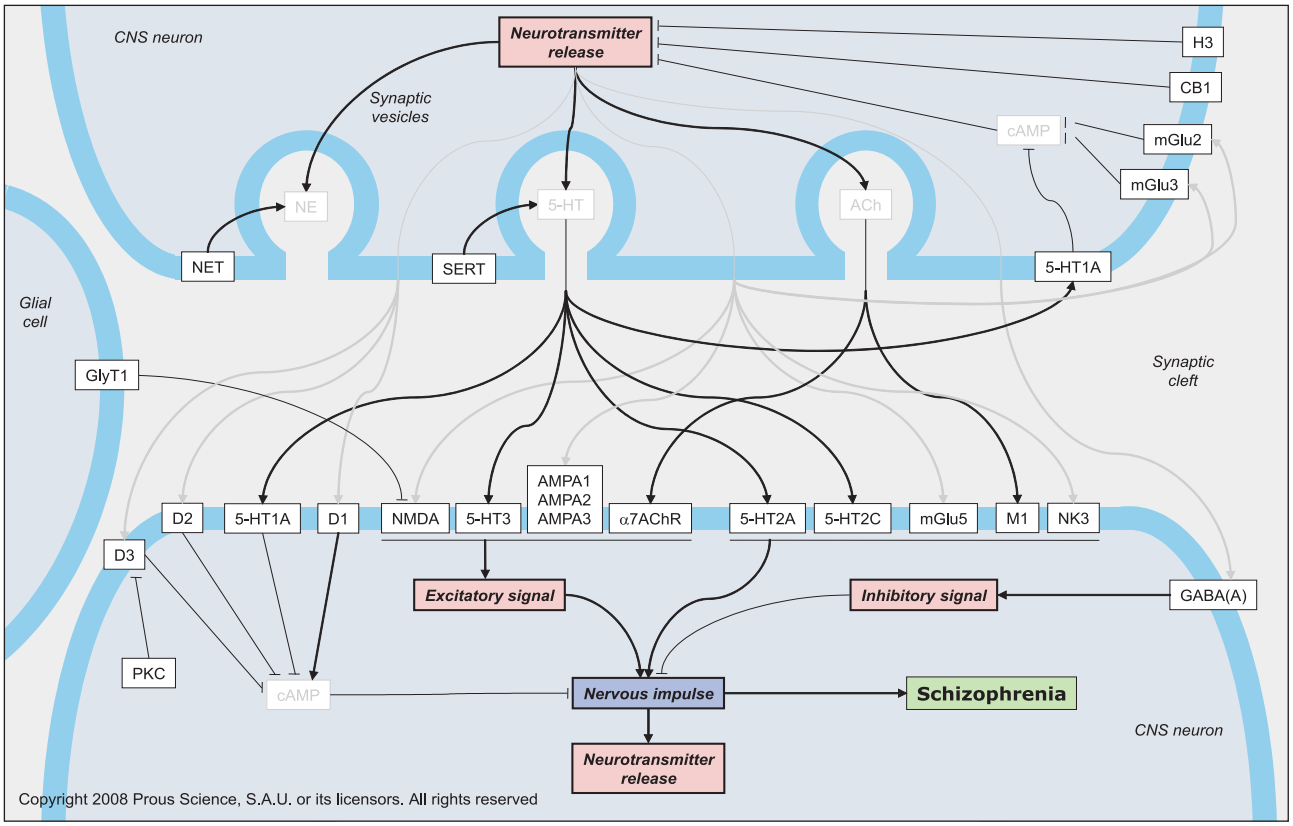

Fig. 1. Schizophrenia targetscape. A diagram showing an overall cellular and molecular landscape or comprehensive network of connections among the current therapeutic targets for the treatment of schizophrenia and their biological actions. Arrow, positive effect; dash, negative effect; 5-HT1A, serotonin receptor subtype 1A; 5-HT2A, serotonin receptor subtype 2A; 5-HT2C, serotonin receptor subtype 2C; 5-HT3, serotonin receptor subtype 3; AMPA1, ionotropic glutamate AMPA receptor subtype 1; AMPA2, ionotropic glutamate AMPA receptor subtype 2; AMPA3, ionotropic glutamate AMPA receptor subtype 3; CB1, cannabinoid receptor type 1; D1, dopamine receptor subtype 1; D2, dopamine receptor subtype 2; D3, dopamine receptor subtype 3; GABA(A), GABA receptor subtype A; GlyT1, glycine transporter 1; H3, histamine H3 receptor; M1, acetylcholine (muscarinic) M_1 receptor; mGlu2, metabotropic glutamate receptor type 2; mGlu3, metabotropic glutamate receptor type 3; mGlu5, metabotropic glutamate receptor type 5; NET, norepinephrine transporter; NMDA, NMDA glutamate receptor; PKC, protein kinase C; SERT, serotonin transporter; NK3, tachykinin NK_3 receptor; α7AChR, acetylcholine (nicotinic) α7 receptor.

cause fewer extrapyramidal side effects than classical neuroleptics. Other agents targeting different pathways were also developed, but nowadays most of the marketed antipsychotic drugs that are capable of reducing the symptoms of schizophrenia act at least in part by decreasing dopaminergic neurotransmission. The search for effective treatment strategies for schizophrenia continues, with special attention focused on the identification of novel targets for drug development (2-4). Those targets that are currently under active investigation are discussed below (see Figure 1). Table I shows a selection of products under active development for each target.

Targets

5-HT_{1A} receptor

Serotonin (5-HT) is a biogenic amine neurotransmitter involved in a wide variety of behaviors, including affective state, hallucinogenesis and memory. The 5-HT_{1A} receptor is a G protein-coupled receptor (GPCR) component of the 5-HT system that is present both pre- and postsynaptically in different brain areas. The 5-HT_{1A} receptor is G_i/G_o-coupled and acts by decreasing cellular levels of cAMP by inhibiting adenylate cyclase activity. 5-HT_{1A} receptor binding is altered in the hippocampus, cortex and amygdala in the schizophrenic brain. There is evidence that decreased 5-HT_{1A} receptor binding in the amygdala may trigger the negative symptoms in schizophrenia related to affective components. Moreover, 5-HT_{1A} receptor agonists possess anticataleptic properties and could attenuate extrapyramidal side effects induced by dopamine D_2 receptor blockade. For this reason, agents that combine dopamine receptor partial agonism and 5-HT_{1A} receptor agonism are possible therapies for schizophrenia (6-8).

5-HT_{2A} receptor

The 5-HT_{2A} receptor is a GPCR (G_q/G_{11}) for 5-HT that belongs to the class of phosphoinositide-specific phospholipase C (PLC)-linked receptors that lead to mobilization of intracellular calcium and activation of protein

Table I: Select targets and products launched or being actively investigated for schizophrenia (from Prous Science Integrity®).

Target	Product	Source	Phase
5-HT_{1A} receptor	Aripiprazole	Bristol-Myers Squibb/Otsuka	L-2002
	Bifeprunox mesilate	Solvay	Prereg.
	SLV-313	Solvay/Wyeth	II
	AV-965	Avera Pharmaceuticals	I
5-HT_{2A} receptor	Risperidone	Janssen/Schering Pough	L-1993
	Olanzapine	Lilly	L-1996
	Quetiapine fumarate	AstraZeneca	L-1997
	Ziprasidone HCl	Pfizer	L-2000
	Aripiprazole	Bristol-Myers Squibb/Otsuka	L-2002
	Sertindole	Lundbeck	L-2006
	Blonanserin	Dainippon Sumitomo Pharma	L-2008
	Iloperidone	Vanda Pharmaceuticals	Prereg.
	Lurasidone HCl	Dainippon Sumitomo Pharma	III
	Norclozapine	ACADIA	II
	Pimavanserin tartrate	ACADIA	II
	TGOF02N	Fabre-Kramer	II
	YKP-1358	SK Bio-Pharmaceuticals	II
	ITI-007	IntraCellular Therapies	I
	YKP-1447	SK Bio-Pharmaceuticals	Preclinical
5-HT_{2C} receptor	TGOF02N	Fabre-Kramer	II
	Vabicaserin HCl	Wyeth	II
5-HT_3 receptor	Tropisetron	National Institute of Mental Health	III
	MEM-3454 (R-3487)	Memory Pharmaceuticals/Roche	II
	Ondansetron	National Institute of Mental Health	II
Cannabinoid CB_1 receptor	Drinabant	sanofi-aventis	II
Dopamine D_1 receptor	Asenapine maleate	Schering-Plough	Prereg.
Dopamine D_2 receptor	Amisulpride	sanofi-aventis	L-1986
	Risperidone	Janssen/Schering-Plough	L-1993
	Olanzapine	Lilly	L-1996
	Quetiapine fumarate	AstraZeneca	L-1997
	Ziprasidone HCl	Pfizer	L-2000
	Aripiprazole	Bristol-Myers Squibb/Otsuka	L-2002
	Sertindole	Lundbeck	L-2006
	Paliperidone	Johnson & Johnson	L-2007
	Blonanserin	Dainippon Sumitomo Pharma	L-2008
	Asenapine maleate	Schering-Plough	Prereg.
	Bifeprunox mesilate	Solvay	Prereg.
	Iloperidone	Vanda Pharmaceuticals	Prereg.
	Lurasidone HCl	Dainippon Sumitomo Pharma	III
	Cariprazine HCl	Forest/Gedeon Richter/Mitsubishi Tanabe Pharma	II
	Norclozapine	ACADIA	II
	Perphenazine 4-aminobutyrate	BioLineRx	II
	SLV-313	Solvay/Wyeth	II
	TGOF02N	Fabre-Kramer	II
	YKP-1358	SK Bio-Pharmaceuticals	II
	RGH-363	Gedeon Richter	I
	SLV-314	Solvay	I
	ST-2472	Sigma-Tau	Preclinical
	YKP-1447	SK Bio-Pharmaceuticals	Preclinical
Dopamine D_3 receptor	Amisulpride	sanofi-aventis	L-1986
	Cariprazine HCl	Forest/Gedeon Richter/Mitsubishi Tanabe Pharma	II
	Norclozapine	ACADIA	II
	TGOF02N	Fabre-Kramer	II
	RGH-363	Gedeon Richter	I
$GABA_A$ receptor	L-830982	Merck & Co.	II
	MK-0777	University of California, Los Angeles	II
	Perphenazine 4-aminobutyrate	BioLineRx	II
Glycine transporter GlyT1	R-1678	Chugai Pharmaceutical/Roche	II
	DCCCyB	Merck Sharp & Dohme	I
	GSK-1018921	GlaxoSmithKline	I
	R-231857	Johnson & Johnson	I
	SSR-103800	sanofi-aventis	I

Continuation

Table I (Cont.): Select targets and products launched or being actively investigated for schizophrenia (from Prous Science Integrity®).

Target	Product	Source	Phase
Histamine H_3 receptor	Tiprolisant HCl	Bioprojet	II
	SAR-110894	sanofi-aventis	Preclinical
Ionotropic glutamate AMPA receptor	Farampator	Schering-Plough	II
	GSK-729327	GlaxoSmithKline	I
Ionotropic glutamate NMDA receptor	D-Serine	National Institute of Mental Health	III
	Neboglamine	Rottapharm/Xytis	I
Metabotropic glutamate $mGlu_{2/3}$ receptor	LY-2140023	Lilly	II
Metabotropic glutamate $mGlu_5$ receptor	ADX-63365	Addex	Preclinical
Muscarinic acetylcholine M_1 receptor	Norclozapine	ACADIA	II
	NGX-267	TorreyPines	I
	NGX-292	TorreyPines	Preclinical
Nicotinic acetylcholine α7 receptor	AZD-0328	AstraZeneca	II
	MEM-3454 (R-3487)	Memory Pharmaceuticals/Roche	II
	TC-5619	Targacept	I
	SAR-130479	sanofi-aventis	Preclinical
	XY-4083	Xytis	Preclinical
Protein kinase C (PKC)	Chelerythrine chloride	Marinus Pharmaceuticals	Preclinical
Serotonin transporter (SERT)	SLV-314	Solvay	I
Tachykinin NK_3 receptor	SSR-241586	sanofi-aventis	I

kinase C (PKC). The 5-HT_{2A} receptor is localized in postsynaptic neurons of limbic areas and prefrontal cortex, as a monomer, a homodimer or even forming functional complexes with other proteins (e.g., the metabotropic glutamate $mGlu_2$ receptor). The major effect of 5-HT_{2A} receptor antagonists is the reduction of extrapyramidal side effects observed with typical antipsychotics. Agents that combine dopamine receptor partial agonism and 5-HT_{2A} antagonism are well-known therapies for schizophrenia. Selective 5-HT_{2A} antagonists are also being developed for treating this disorder (9-12).

5-HT_{2C} receptor

The 5-HT_{2C} receptor is another GPCR (G_q/G_{11}) member of the 5-HT receptor family which, like the 5-HT_{2A} receptor, signals through PLC in neurons. 5-HT_{2C} receptors have been implicated as potential targets for diseases, including obesity and schizophrenia. The difficulty in developing agents that selectively bind to this receptor has kept its biological effects unclear for many years. There is evidence that 5-HT_{2C} antagonism by some atypical antipsychotic drugs may be related with the increase in dopaminergic activity in the prefrontal cortex. On the other hand, 5-HT_{2C} agonists have also shown antipsychotic actions, highlighting the 5-HT_{2C} receptor as an interesting target for schizophrenia (10, 13).

5-HT_3 receptor

The 5-HT_3 receptor is a ligand-gated, cation-selective ion channel; its activation by 5-HT triggers rapid membrane depolarization and synaptic transmission in neurons of limbic areas and prefrontal cortex. It has been proposed that activation of the 5-HT_3 receptor can regulate the release of other neurotransmitters, such as dopamine, acetylcholine, GABA and norepinephrine, modulating the anxiolytic, antipsychotic and procognitive effects of these compounds. In particular, 5-HT_3 receptor antagonists are being developed for the treatment of schizophrenia because there is evidence showing a role in reversing the deficit in P50 auditory sensory gating which is present in most schizophrenic patients. This action could be mediated through the release of acetylcholine which activates the α7 nicotinic acetylcholine receptor (nAChR) in the hippocampus (11, 14, 15).

Cannabinoid CB_1 receptor

Cannabinoids are terpenophenolic compounds that have been speculated to exert neuroprotection against excitotoxicity and acute brain damage, among other properties. The CB_1 receptor is a GPCR ($G_{i/o}$) which together with the CB_2 receptor has been identified as the receptor for cannabinoids. Its mechanisms of action include inhibition of adenylate cyclase and activation of mitogen-activated protein (MAP) kinase. CB_1 is preferentially expressed in the brain, where it mediates the psychoactivity of cannabinoids. High levels of CB_1 receptors are found in the basal ganglia, hippocampus, cerebellum and cortical structures. Activation of presynaptic CB_1 receptors inhibits N-type Ca^{2+} channel activity, which in turn reduces excitatory neurotransmitter release to the synaptic cleft, thus allowing the excitatory signals to activate the

postsynaptic cell. CB_1 receptor activation would protect hippocampal or granule cerebellar neurons from excitotoxicity and from hypoxia and glucose deprivation through inhibition of the release of glutamate. The CB_1 receptor is also implicated in learning and memory, and antagonism of this receptor may improve cognitive deficits present in psychiatric diseases such as schizophrenia. The limitation on the use of these agents is the desensibilization that may occur because of further loss of inhibition of CB_1 receptors by antagonists or chronic exposure to cannabinoids. This desensibilization could contribute to distractibility and the occurrence of hallucinations in schizophrenic patients (16, 17).

Dopamine D_1 receptor

The D_1 receptor is a GPCR ($G_{s/olf}$) that binds the neurotransmitter dopamine, present in the central nervous system (CNS) in basal ganglia. Dopamine is the precursor of norepinephrine and epinephrine and accounts for 90% of all catecholamines. The D_1 receptor transduces their signals by increasing intracellular cAMP levels, mainly via coupling to $G_{\alpha s}$ proteins in neurons. Hypofunctionality of the D_1 receptor has been postulated to play a key role in the pathophysiology of both positive and negative symptoms of schizophrenia. Agonists of the D_1 receptor exhibit antipsychotic activity with very few extrapyramidal side effects (18, 19).

Dopamine D_2 receptor

The dopamine D_2 receptor is a GPCR ($G_{i/o}$) that, like the D_1 receptor, binds dopamine present in the CNS in basal ganglia. The D_2 receptor can suppress cAMP production by coupling to $G_{\alpha i/o}$ proteins in neurons. The D_2 receptor has also been shown to regulate calcium and potassium ion channels through PLC when it forms hetero-oligomers, especially with the D_1 receptor. This D_1–D_2 receptor hetero-oligomer has been proposed to facilitate a distinctive dopamine-mediated calcium signal, with important effects on synaptic plasticity. The D_2 receptor is the most widely studied target of antipsychotic drugs and D_2 antagonists are validated drugs for the treatment of schizophrenia. Many of the agents that are in active development also act on 5-HT receptors (18, 20).

Dopamine D_3 receptor

The D_3 receptor is the longest isoform of the D_2-like receptor subfamily, all of which can not only reduce cAMP production by coupling to $G_{\alpha i/o}$ proteins, but have also been shown to regulate calcium and potassium ion channels, as seen for the D_2 receptor. The D_3 receptor has been implicated in the control of drug-seeking behavior, and may play a role in the pathophysiology of impulse control disorders and schizophrenia. D_3 modulators have shown antipsychotic properties and reverse cognitive deficits, and they are currently being investigated for the treatment of schizophrenia (18, 21).

$GABA_A$ receptor

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain and spinal cord and acts via $GABA_A$, $GABA_B$ and $GABA_C$ receptors. These receptors are ionotropic and can be activated by several different compounds. The $GABA_A$ receptor is widely distributed throughout the CNS. It is suggested to be involved in the modulation of vigilance, anxiety, muscle tension, epileptogenic activity and memory functions. It has been shown that the $GABA_A$ receptor is upregulated in post mortem brains from schizophrenic patients, especially in pyramidal cells. Enhancement of $GABA_A$ receptor-mediated fast synaptic inhibition may be effective in improving cognition in schizophrenia patients. $GABA_A$ agonists also decrease catalepsy, exhibiting antischizophrenic efficacy with reduced extrapyramidal effects (22, 23).

Glycine transporter GlyT1

GlyT1 is a sodium- and chloride-dependent glycine transporter that may play a role in glutamatergic neurotransmission via activation of NMDA receptors. GlyT1 is expressed mainly in glial cells that surround neurons which primarily express NMDA receptors in regions of the brain, including cerebellum, spinal cord, cortex and hippocampus. GlyT1 both imports and exports glycine, depending on its extracellular concentration, modulating its concentration in the synaptic cleft. Glycine acts as a coagonist of the NMDA receptor and enhances its excitatory postsynaptic currents. Since deficits in NMDA receptor function are related with the pathophysiology of schizophrenia, GlyT1 inhibitors are being developed for the treatment of this disease and other psychiatric disorders associated with NMDA receptor hypofunction (24, 25).

Histamine H_3 receptor

Histamine is a biogenic amine that can also act as a neurotransmitter. The H_3 receptor is a GPCR ($G_{i/o}$) for histamine that acts on several signal transduction pathways, i.e., inhibiting adenylate cyclase, activating phospholipase A_2 (PLA_2), AKT and MAP kinase, as well as inhibiting the Na^+/H^+ exchanger and K^+-induced Ca^{2+} mobilization. Activation of this receptor affects physiological and pathological processes such as obesity, cognition, the sleep–wake cycle and epilepsy. In contrast to other histamine receptors, the H_3 receptor is predominantly expressed in the CNS. Due to its location, it has been speculated that the H_3 receptor mediates various CNS functions by modulating brain histaminergic tone, and possibly through an interaction with H_1 and H_2 receptors. The H_3 receptor has been shown to act as an autoreceptor in presynaptic neurons and to control histamine turnover, and it also acts as a heteroreceptor in dopamine-, serotonin-, norepinephrine-, GABA- and acetylcholine-containing neurons. A role for H_3 receptors has been suggested in schizophrenia, since relative increases in the levels of dopamine in the brain can be

induced by either decreasing histamine receptor density or by increasing histamine degradation. Thus, H_3 receptor antagonists may be effective in the treatment of cognitive dysfunction in schizophrenia and other psychiatric and neurological disorders (26-28).

Ionotropic glutamate AMPA receptor

The AMPA receptor is a non-NMDA-type ionotropic transmembrane receptor for glutamate, which is the main excitatory neurotransmitter in the CNS and is involved in learning and memory. AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) is the synthetic ligand for these receptors. Studies have shown that changes in the number of synaptic AMPA receptors may be responsible for synaptic plasticity (e.g., the neuronal mechanism required for learning and memory). AMPA receptors mediate fast excitatory neurotransmission, as well as activation of co-localized *N*-methyl-D-aspartic acid (NMDA) receptors, through partial depolarization of the postsynaptic membrane. Allosteric modulators of the AMPA receptor facilitate hippocampal long-term potentiation and also improve short-term memory. AMPA modulators could potentially help combat cognition deficits associated with schizophrenia and other psychiatric disorders (29 30).

Ionotropic glutamate NMDA receptor

The NMDA receptor is a subtype of the ionotropic glutamate receptors that binds the excitotoxic amino acid NMDA in neurons and also has a site to bind glycine as co-activator. Activation of the NMDA receptor results in the opening of an associated ion channel pore, allowing inflow of Na^+, K^+ and Ca^{2+}, of which the last one is thought to play a critical role in synaptic plasticity. The receptor activation mediates long-term potentiation of the signaling involved in learning, memory and cognition, but synaptic overactivity may induce neuronal cell injury and death. Studies on the deregulation of neurotransmission mediated by the NMDA receptor have contributed to the understanding of the pathogenesis of schizophrenia and it has been proposed that the putative dopamine imbalance related with the development of the disease could be the result of NMDA receptor hypofunction in the prefrontal cortex. Currently, positive allosteric glycine site-specific modulators of the NMDA receptor are being studied for the treatment of the negative symptomatology and cognitive impairment of this and other psychiatric disorders (24, 31, 32).

Metabotropic glutamate $mGlu_2$ receptor

The $mGlu_2$ receptor is a GPCR (G_i/G_0) member of the type II family of metabotropic receptors for glutamate. mGlu receptors have a ubiquitous distribution throughout the CNS and present multiple roles, including neuronal and glial functions (modulation of neuronal excitability and synaptic transmission), as well as various metabolic functions. $mGlu_2$ signals via inhibition of the cAMP cascade and serves to modulate the function of other receptors (such as NMDA receptors), changing the synapse's excitability. Activation of mGlu type II family receptors decreases glutamate release from presynaptic neurons, affecting NMDA neurotransmission. Deregulation of $mGlu_2$ is implicated in schizophrenia and studies in animal models have indicated that it may be responsible for the pharmacological action of nonspecific mGlu receptor agonists. Dual $mGlu_{2/3}$ agonists have shown significant improvements in both positive and negative symptoms and are being studied as potential antipsychotic drugs (33-35).

Metabotropic glutamate $mGlu_3$ receptor

The $mGlu_3$ receptor is a GPCR (G_i/G_0) for glutamate (type II) that, like $mGlu_2$, signals via inhibition of the cAMP cascade in glia and presynaptic neurons of wide brain areas. It has been shown that the dimeric $mGlu_3$ receptor may be reduced in post mortem brains from schizophrenic patients and its gene (*GRM3*) polymorphisms were related with psychosis. As explained for the $mGlu_2$ receptor, dual $mGlu_{2/3}$ agonists are being investigated for the treatment of schizophrenia (33, 35, 36).

Metabotropic glutamate $mGlu_5$ receptor

The $mGlu_5$ receptor is a GPCR (G_q), a member of the type I family of metabotropic receptors for glutamate. $mGlu_5$ activates PLC. It is also associated with Na^+ and K^+ channels and, like other mGlu receptors, it is involved in changing synapse excitability. The $mGlu_5$ receptor can increase both excitatory presynaptic potentials and inhibitory postsynaptic potentials. Activation of $mGlu_5$ by selective agonists potentiates NMDA-induced responses and can be effective as therapy for diseases affected by NMDA hypofunction. In accordance, $mGlu_5$ receptor positive allosteric modulators are in development for the treatment of schizophrenia and other psychiatric disorders (33, 37).

Muscarinic acetylcholine M_1 receptor

The M_1 receptor is one of five subtypes of membrane-bound GPCR AChR proteins that have been identified and found to be predominantly expressed within the parasympathetic nervous system, which exerts inhibitory and excitatory control over central and peripheral tissues and plays a role in physiological functions, such as heart rate, arousal, cognition, learning, hippocampal-based memory, short-term memory, sensory processing and motor control. The M_1 receptor is activated by acetylcholine and the highly toxic exogenous alkaloid muscarine, thus distinguishing it from the unrelated nAChRs that respond to nicotine but not muscarine. Activation of the stimulatory M_1 receptor results in mobilization of intracellular calcium and may be related with loss of cholinergic function, causing cognitive impairment. The M_1 receptor is known to play a role in hippocampal-based memory,

learning and short-term memory. Disruptions in the balance of acetylcholine and dopamine are of critical importance in the pathology of schizophrenia. The cholinergic system tends to suppress positive side effects that are exacerbated by an increase in dopaminergic activity, and the corresponding increase in cholinergic activity then leads to an intensification of negative schizophrenic symptoms in the acute phase of the illness. The M_1 receptor protein and mRNA levels have been shown to be altered in post mortem brains of schizophrenic patients, supporting the role of the cholinergic system in the pathogenesis of the disease. Anticholinergic agents may therefore be indicated for the treatment of some symptoms of schizophrenia (38, 39).

Nicotinic acetylcholine receptor α7

The nAChRs are pentameric ion channels expressed in the central and peripheral nervous systems and in the periphery, including skeletal muscle, epithelial, endothelial and immune cells. Nicotine has well-documented effects on cognitive and motor function and cerebral blood flow. The α7 subunit is the main component of brain nicotinic receptors present at high density in areas involved in learning and memory. This subunit displays marked permeability to calcium ions and seems to be essential for inhibiting cytokine synthesis by the cholinergic antiinflammatory pathway. Variants in the corresponding gene (*CHRNA7*) are associated with the genetic transmission of schizophrenia, related neurophysiological sensory gating deficits and cognitive impairment. Agonists for the α7 receptor have positive effects on cognitive dysfunction associated with psychosocial disability in schizophrenia and other psychiatric disorders (40, 41).

Norepinephrine transporter (NET)

The NET is a solute carrier Na^+/Cl^--dependent transporter for norepinephrine (NE). NET is a target of psychomotor stimulants such as amphetamines or cocaine. Monoamine transporters in general act in neuronal membranes by sequestering monoamines from nerve terminals. The NET regulates NE signaling in central and peripheral nervous systems by mediating its clearance and modulating its presence in the synaptic cleft. Selective NET inhibitors produce an increase in NE in brain and a secondary increase in prefrontal dopamine, and thus, NET inhibitors are being developed as treatments for schizophrenia and other disorders affected by dopamine dysregulation (42, 43).

Protein kinase C (PKC)

PKC belongs to a family of enzymes that phosphorylate proteins on serine or threonine residues. PKC is involved in a wide range of physiological processes, including differentiation, proliferation, gene expression, cytoskeletal organization, brain function and protein transport. It is ubiquitous and can be activated by membrane phospholipids that are involved in intracellular signaling. The classical PKC isoforms (α, β1, β2 and γ) are calcium-dependent and can be activated endogenously by diacylglycerol or nonphysiologically by phorbol esters. Several calcium-independent isoforms have also been identified. PKCγ is exclusively expressed in neurons and is involved in various neuronal functions. Among other actions, PKC regulates the intracellular trafficking of the dopamine D_3 receptor in the CNS through sequestration and further desensitization by phosphorylation. The D_3 receptor is expressed mostly in parts of the brain that control the emotional behaviors and its dysregulation has been involved in the pathophysiology of schizophrenia. Thus, inhibitors of PKC are being studied for the treatment of this disorder (44, 45).

Serotonin transporter (SERT)

The SERT is a membrane uptake carrier dependent on Na^+ and Cl^- that transports 5-HT from the extracellular synaptic space back to the inside of 5-HT nerve terminals. SERT is a mediator in the termination of serotonergic transmission in the nervous system. SERT inhibitors increase extracellular concentrations of 5-HT and amplify signals sent by 5-HT neurons. Altered serotonergic neurotransmission and 5-HT have long been associated with psychiatric disorders, including schizophrenia. Polymorphic regions in the SERT promoter and variations in its gene (*5-HTTLPR*) have been implicated in neuropsychiatric and mood disorders. Agents that block SERT, such as selective 5-HT reuptake inhibitors, may be effective in the treatment of schizophrenia and other conditions such as depression and anxiety (42, 46).

Tachykinin NK_3 receptor

The NK_3 receptor is a GPCR for tachykinins that appears to modulate synaptic transmission, nociception and neuroimmunomodulation. NK_3 receptors are expressed in both the peripheral and central nervous systems and particularly in neurons from forebrain areas and basal ganglia. Tachykinins (neurokinin B, neurokinin A and substance P) are excitatory neuropeptides synthesized in neuronal and glial cells that bind the NK_3 receptor with a decreasing order of affinity. Activation of NK_3 by tachykinins induces the stimulation of the PLC cascade and stimulates cell division and proliferation. It has been shown that NK_3 receptor activity can modulate monoaminergic and amino acid neurotransmission and that NK_3 receptor agonists are reportedly able to potentiate dopamine release. Antagonists of NK_3 receptor activity have shown therapeutic efficacy in treating the positive symptoms of schizophrenia and other affective disorders (47, 48).

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