Schizophrenia: Neurobiology and Targets for Drug Treatment

Justin M. Saunders and Javier González-Maeso
Department of Physiology and Biophysics, Virginia Commonwealth University School of Medicine, Richmond, VA 23298, USA

Schizophrenia is a severe mental disorder that affects approximately 1% of the population worldwide. The symptoms of this psychiatric condition can be divided into three broad categories: positive symptoms, such as hallucinations and delusions; negative symptoms, such as social withdrawal, diminished affective response and lack of interest; and cognitive symptoms, such as disordered speech, memory problems and attention deficits. Its etiology remains unknown, although there is evidence suggesting that schizophrenia results as a consequence of complex interactions between genetic factors and environmental influences.

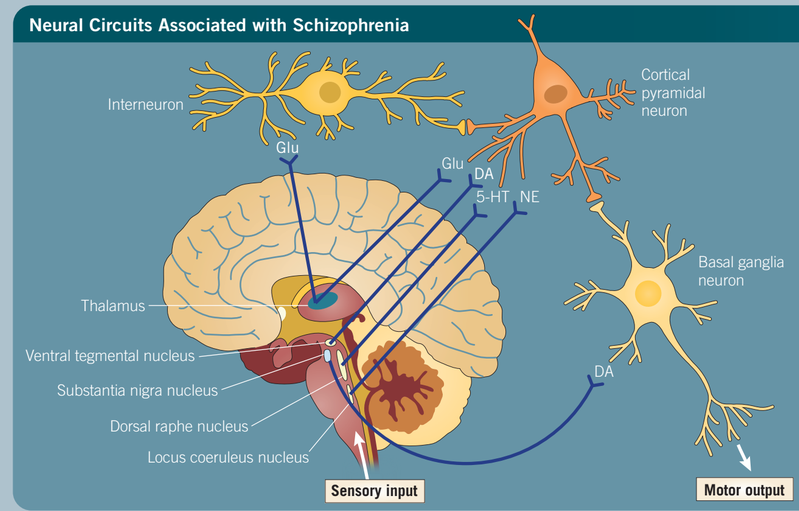
Genetic Factors

Schizophrenia has traditionally been considered a genetic disorder, with rates of heritability estimated at 73-90%. This hypothesis was strengthened by genome-wide association studies (GWAS) in the mid-2000s showing schizophrenia-associated genetic alterations that included large recurrent microdeletions, copy number variations, as well as rare chromosomal microdeletions and duplications, especially in neurodevelopmental pathways. These genomic studies also suggested that the risk of schizophrenia is associated with polygenic pathways involving thousands of common alleles, each with a very small effect. More recent GWAS have narrowed down the list of genetic loci potentially associated with schizophrenia. These genes include those encoding dopamine D_2 (*DRD2*) and serotonin 5-HT_{2A} (*HTR2A*) receptors, as well as genes encoding proteins involved in glutamatergic neurotransmission, voltage-gated ion channels, and the signaling complex formed by activity-regulated cytoskeleton-associated scaffold protein (*ARC*) at the postsynaptic density. Schizophrenia-associated loci are not randomly distributed throughout genes of separate classes and function. On the contrary, they coincide with genes expressed in certain cell types and tissues. Schizophrenia associations are also enriched among genes expressed in tissues with important immune functions.

Susceptibility Genes

GAD67	GABA biosynthesis
IGSF9B	Expressed in GABAergic neurons
DISC1	Cell proliferation and migration
GRIN2A	Member of NMDA receptor complex
ACTN1	Member of NMDA receptor complex
GRIA1	Member of NMDA receptor complex
BAIAP2	Member of the ARC complex
NCKIPSD	Dendritic spines
CACNA1I	Synaptic plasticity
NLGN4X	Synaptic plasticity
RIMS1	Presynaptic plasticity
DRD2	Neurotransmitter receptor
HTR2A	Neurotransmitter receptor
GRM3	Neurotransmitter receptor
HSP90AA1	Glutamate neurotransmission
CLCN3	Voltage-gated chloride channel
MEF2C	Transcription and neurogenesis

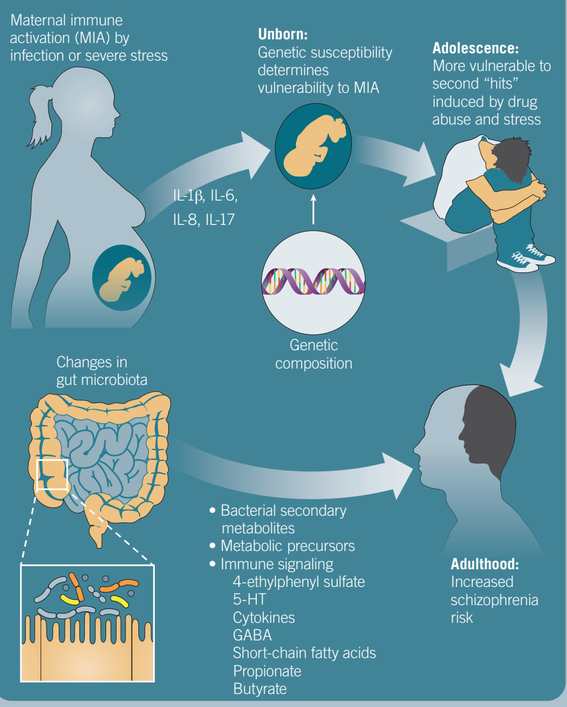
Neural Circuits Associated with Schizophrenia



The thalamus plays a fundamental role in the bidirectional flow of cellular signaling between cortical and subcortical brain areas. Pyramidal neurons are the principal source of glutamatergic (Glu) excitatory axon terminals in the cortex. Axons from neurons in the thalamus and from dopaminergic (DA) neurons in the mesencephalon innervate targets in the frontal cortex. An excessive response of pyramidal neurons in the frontal cortex has been proposed as a putative mechanism of psychosis. The release of dopamine from the ventral tegmental nucleus activates dopamine D_1 and D_2 receptors that increase the pyramidal neuronal response to glutamate. Serotonin (5-HT) release from the dorsal raphe activates cortical 5-HT_{2A} receptors, promoting the release of glutamate. Antipsychotic drugs modulate the effects of both dopamine and serotonin, as well as block dopamine signaling in the substantia nigra, which has been implicated in movement disorders. Antipsychotics modulate the release of acetylcholine from the basal forebrain nucleus, and increase interneuron activity by blocking noradrenaline (NA) receptors in the locus coeruleus. Interneurons themselves in the frontal cortex regulate glutamate release and therefore the excitation of cortical pyramidal neurons.

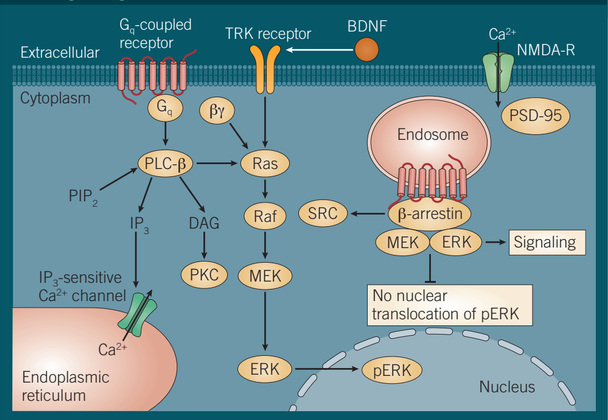
Environmental Events

Although genetics play a fundamental role in the etiology of schizophrenia, genetic aberrations are not the only factor responsible for this psychiatric phenotype. The concordance rates of schizophrenia for monozygotic twins, whose DNA sequences are ~100% identical, have been found to be about 40 to 50%, which favors a significant contribution of environmental events in the development of schizophrenia. Epidemiological studies indicate that maternal infection with a wide variety of microbial agents, including influenza virus, increases the risk of developing schizophrenia in later life. Similarly, severe adverse life events during pregnancy, such as war, famine, and death of a close relative, have been associated with schizophrenia risk in the adult offspring. Animal models of maternal influenza viral infection and maternal stress support a uniform conclusion that schizophrenia-related physiological and behavioral changes in the offspring are related to inflammatory mediators found in maternal blood and amniotic fluid. Whether these proteins cross the placenta and act directly upon the fetal brain remains unknown. Nevertheless, these animal models have identified several cytokines as critical mediators of maternal immune activation, which has been suggested to induce dysbiosis of the offspring gut microbiota. These changes associated with prenatal insults affect schizophrenia-related phenotypes in the adult offspring.



Current and Emerging Targets for Schizophrenia

Cell Signaling



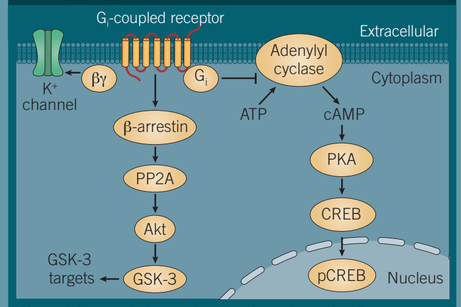
A number of G_q protein-coupled receptors, including the serotonin 5-HT_{2A}, metabotropic glutamate 5 ($mGlu_5$), and acetylcholine muscarinic M_1, have been proposed as direct targets of either antipsychotic drugs or drugs that induce antipsychotic-related behaviors in rodent models. Activation of G_q protein-coupled receptors elicits the phospholipase C (PLC)-catalyzed hydrolysis of phosphatidylinositol 4,5 bisphosphate (PIP2), which ultimately induces a transient increase in the concentration of intracellular calcium $[Ca^{2+}]_i$ through the release of Ca^{2+} from the endoplasmic reticulum.

Adding or removing phosphates is a fundamental mechanism for altering the shape and therefore the function of a protein. The MAPKs are a family of serine/threonine kinases that include extracellular signal-regulated kinases such as ERK1/2. The downstream effectors of MAPKs modulate a number of cellular functions, including cell cycle, transcriptional regulation, and apoptosis. Both G protein- and β-arrestin-mediated signaling cascades might lead to ERK activation. However, the sub-cellular distribution of activated ERK1/2 downstream of these two pathways are different. Whereas phosphorylated ERK1/2 mediated via heterotrimeric G protein signaling translocates into the nucleus, the phosphorylated ERK1/2 induced by β-arrestin remains in the cytoplasm.

Glutamatergic Hypofunction

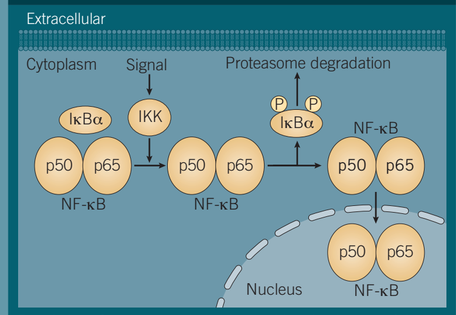
Glutamatergic hypofunction is one of the main hypotheses underlying the pathophysiology of schizophrenia. Noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine (PCP) are used as pharmacological models of schizophrenia in mice and rats because of their capacity to evoke psychotic symptoms in humans, as well as deficits in sensorimotor gating resembling those observed in the disease. The use of NMDA-enhancing agents, such as glycine, D-Serine and sarcosine, has been proposed as a potential pharmacological tool to augment the therapeutic potential of currently available antipsychotic medications. Genes that form part of the postsynaptic NMDA receptor-PSD95 signaling complex have been associated with the etiology of schizophrenia.

Adenylyl Cyclase



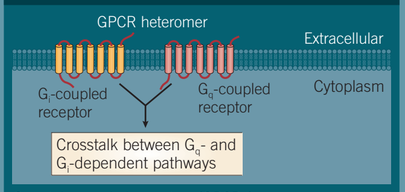
$G_{i/o}$ protein-coupled receptors, such as dopamine D_2, metabotropic glutamate 2 ($mGlu_2$), acetylcholine muscarinic M_4, and α_{2A} adrenergic, have been shown behave as direct targets of antipsychotic drugs. Activation of $G_{i/o}$ protein-coupled receptors leads to both inhibition of adenylate cyclase activity by the $G_{\alpha i}$ subunit and positive regulation of K^+ channels by the $G_{\beta\gamma}$ subunit. This affects the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), and consequently the activity of protein kinase A (PKA).

Regulation of Gene Transcription



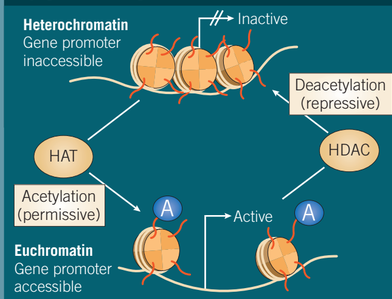
Regulation of gene transcription is considered to be one of the mechanisms involved in psychiatric disorders. Transcription factors such as cAMP response element binding protein (CREB) and nuclear factor kappa B (NF-κB) have roles in different processes of the brain that might be dysregulated in schizophrenia patients, such as neurogenesis, synapse regulation, neural migration and synaptic plasticity.

GPCR Dimerization



G protein-coupled receptors (GPCRs) were assumed to function as monomers. This model of receptor signaling is supported by the demonstration of G protein coupling via a single purified class A GPCR, such as the adrenergic β_2 receptor. However, it has been demonstrated that class C GPCRs, such as mGlu and $GABA_B$ receptors, function as dimers. Additionally, more recent findings support the hypothesis that family A GPCRs form heterodimers or even higher order oligomers. Examples of GPCR heterodimers/heteromers potentially involved in schizophrenia and its treatment include 5-HT_{2A}-$mGlu_2$, dopamine D_2-adenosine A_{2A}, and μ-opioid-α_{2A}-adrenergic receptor complexes.

Epigenetic Targets



Covalent modifications of the N-termini of histones correlate with open or closed states of chromatin depending on the type of modification. Acetylation (A) of histone H3 (H3ac) and histone H4 (H4ac) creates a more open chromatin architecture. Histone acetylation is catalyzed by histone acetyltransferases (HATs), and this modification can be reversed by the enzymatic action of histone deacetylases (HDACs), which fall into four different phylogenetic classes. Findings in preclinical models suggest that HDAC inhibitors might emerge as a new pharmacological approach to treat cognitive deficits in schizophrenia patients.

Product listing

Dopamine Receptors	
D_1 and D_5	Dihydrexidine, SKF 81297, SKF 82958, SCH 39166
D_2	(-)-Quinpirole, Aripiprazole
D_3	Rotigotine, SB_277011A
D_4	PD_168077, L-745,870
Transporters	GBR_12909, FFN 102
Non-selective Dopamine	NPEC-caged dopamine, Lisuride, Clozapine, L-DOPA
Adenosine A_{2a} Receptors	
CGS_21680, LUF 5834, ZM_241385	
LRRK2	
PF 06447475, MLi-2, CZC 25146	
GABA Receptors	
$GABA_A$ Receptors	Muscimol, Bicuculline, SR_95531, Allopregnanolone
$GABA_B$ Receptors	(*R*)-Baclofen, CGP 35348, CGP 55845
Glutamate Receptors	
NMDA Receptors	Glycine, D-Serine, Sarcosine, Ketamine, Hydroxynorketamine, MNI-caged-NMDA
AMPA Receptors	NBQX, GYKI_53655, Naspm, Cyclothiazide
Kainate Receptors	Kainic acid, GYKI_53655, ACET
mGlu Group I	MPEP, MTEP, VU 0360172, VU 0409551
mGlu Group II	LY_379268
mGlu Group III	L-AP4, (*S*)-3,4-DCPG
Serotonin Receptors	
5-HT_{1A}	(*S*)-WAY 100135, WAY 100635
5-HT_{1B}	GR 55562, SB_224289
5-HT_{2A}	TCB-2, MDL 11,939, Risperidone, MDL 100907
5-HT_{2C}	Ro 60-0175, SB_242084
Muscarinic Receptors	
M_1	Xanomeline oxalate, VU 0255035
M_4	PD 102807, VU 152100
Adrenergic Receptors	
α_{2A}	B-HT 933, Atipamezole
β_2	Formoterol, ICI 118,551
Opioid Receptors	
μ Receptors	DAMGO, CTOP
δ Receptors	SNC 80, BMS 986187
κ Receptors	U-50488, Salvinorin B
Histone Deacetylases	
Valproic acid, MC 1568, SAHA	
MAPK Pathway	
U0126, SB239063, FR180204	

Schizophrenia antibodies from our sister brands

R&D Systems®

hDopamine D_2 R MAb (MAB9266)
hDISC1 PAb (AF6699)

Novus Biologicals®

NMDAR1 Mab (NB300-118)
BDNF Mab (NBP2-42215)

References

Gaitonde and Gonzalez-Maeso (2017) *Curr.Opin.Pharmacol.* **32** 23
Hanks and Gonzalez-Maeso (2013) *ACS.Chem.Neurosci.* **4** 33
Holloway and Gonzalez-Maeso (2015) *ACS.Chem.Neurosci.* **6** 1099
Ibi and Gonzalez-Maeso (2015) *Cell.Signal.* **27** 2131
Kurita *et al* (2016) Novel Targets for Drug Treatment in Psychiatry. In: Fatemi and Clayton eds. *The Medical Basis of Psychiatry.* Springer, New York
Moreno and Gonzalez-Maeso (2013) *Int.J.Neuropsychopharmacol.* **16** 2131

For copies of this poster, please visit **tocris.com**