Schizophrenia: Neurobiology and Targets for Drug Treatment

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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 heritability estimated at 73–90%. This hypothesis was strengthened by genome-wide association studies (GWAS) in the mid-2000s, which identified genetic variants that are markers of functional variants in schizophrenia-associated genes. These GWAS have employed support vector machine (SVM) analysis to build models that can explain a substantial proportion of the genetic variance in the liability to develop schizophrenia. SVMs can select a small subset of SNPs that can be combined to explain the genetic variance that is not explained by the GWAS. This analysis has identified a number of candidate genes that may contribute to the risk of developing schizophrenia.

Neurobiology
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 sex-dependent. Maternal infection with a wide variety of microbial agents, including influenza virus, increases the risk of developing schizophrenia in later life. Similarly, severe maternal infection with a variety of microbial agents, including influenza virus, increases the risk of developing schizophrenia in later life. Epidemiological studies indicate that the risk of schizophrenia is increased in individuals who have a first-degree relative, have been associated with schizophrenia risk in the adult offspring.

Glutamate neurotransmission is disturbed in individuals with schizophrenia. Several lines of evidence indicate that the N-methyl-D-aspartate (NMDA) receptor is a major target for the therapeutic effects of antipsychotics. The NMDA receptor is a non-selective cation channel that is activated by glutamate. NMDA receptor activation increases the flow of calcium into the cell, which results in the release of glutamate and other neurotransmitters. This process is critical for the maintenance of neuronal function and is disturbed in individuals with schizophrenia.

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Current and Emerging Targets for Schizophrenia
Nicotinic Acetylcholine Receptor (nAChR) regulation of synaptic plasticity and learning and memory.

Glutamatergic Hypofunction
Glutamatergic hypofunction is one of the main hypotheses underlying the clinical pathology of schizophrenia. Non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists are known to preserve glutamatergic neurotransmission during social isolation and to improve cognitive function in animal models of schizophrenia. The findings from these studies suggest that NMDA receptor antagonists may be useful in the treatment of cognitive deficits associated with schizophrenia.

Neural Circuits Associated with Schizophrenia
The thalamus plays a fundamental role in the bidirectional flow of neural activity between cortical and subcortical brain regions. This flow of information is regulated by the action of glutamate and GABAergic signaling within the thalamus. The thalamus is also a key site for the regulation of sleep and wakefulness, and disruption of thalamocortical function is associated with cognitive deficits, particularly in attention and working memory.

Regulation of Neurotransmitter Levels
Regulation of neurotransmitter levels is important for the normal function of the central nervous system. In individuals with schizophrenia, levels of neurotransmitters such as dopamine, serotonin, and glutamate are disturbed. These disturbances are thought to underlie the symptoms of schizophrenia and suggest that the treatment of schizophrenia should aim to normalize neurotransmitter levels.

Regulation of Gene Transcription
Regulation of gene transcription is considered to be one of the mechanisms involved in psychiatric disorders. Transcription factors such as UMPR response element binding protein (CREB) and Nuclear factor kappa B (NF-kB) play a role in different psychiatric diseases. An emerging field is the transcriptional regulation of schizophrenia genes, such as neuregulin-1, synapse-associated protein, and glutamate receptor, normal neuronal regulation and synaptic plasticity.

Epidemiology
Schizophrenia is a chronic, progressive, and debilitating disorder. It is characterized by a range of symptoms that affect different aspects of mental function. These symptoms include positive symptoms (such as hallucinations and delusions), negative symptoms (such as social withdrawal and lack of motivation), and cognitive symptoms (such as difficulty concentrating or processing information). The prevalence of schizophrenia is estimated to be around 1% of the population worldwide, with a higher incidence in men than women. The exact cause of schizophrenia is unknown, but it is believed to be influenced by a combination of genetic and environmental factors.

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