



FIGURE 28-1 Neurobiology of schizophrenia.

Neurotransmitters

A number of neurotransmitters have been implicated in the etiology of schizophrenia. These include dopamine, norepinephrine, serotonin, glutamate, and GABA. The dopaminergic system has been most widely studied and closely linked to the symptoms associated with the disease.

Areas of the Brain Affected

- Four major dopaminergic pathways have been identified:
 - *Mesolimbic pathway*: Originates in the ventral tegmentum area and projects to areas of the limbic system, including the nucleus accumbens, amygdala, and hippocampus. The mesolimbic pathway is associated with functions of memory, emotion, arousal, and pleasure. Excess activity in the mesolimbic tract has been implicated in the positive symptoms of schizophrenia (e.g., hallucinations, delusions).
 - *Mesocortical pathway*: originates in the ventral tegmentum area and has projections into the cortex. The mesocortical pathway is concerned with cognition, social behavior, planning, problem solving, motivation, and reinforcement in learning. Negative symptoms of schizophrenia (e.g., flat affect, apathy, lack of motivation, and anhedonia) have been associated with diminished activity in the mesocortical tract.
 - *Nigrostriatal pathway*: originates in the substantia nigra and terminates in the striatum of the basal ganglia. This pathway is associated with the function of motor control. Degeneration in this pathway is associated with Parkinson's disease and involuntary psychomotor symptoms of schizophrenia.
 - *Tuberoinfundibular pathway*: originates in the hypothalamus and projects to the pituitary gland. It is associated with endocrine function, digestion, metabolism, hunger, thirst, temperature control, and sexual arousal. Implicated in certain endocrine abnormalities associated with schizophrenia.
- Two major groups of dopamine receptors and their highest tissue locations include:
 - The D₁ Family:
 - D₁ receptors: basal ganglia, nucleus accumbens, and cerebral cortex
 - D₅ receptors: hippocampus and hypothalamus, with lower concentrations in the cerebral cortex and basal ganglia
 - The D₂ Family:
 - D₂ receptors: basal ganglia, anterior pituitary, cerebral cortex, limbic structures
 - D₃ receptors: limbic regions, with lower concentrations in basal ganglia
 - D₄ receptors: frontal cortex, hippocampus, amygdala

Antipsychotic Medications

Type	Receptor Affinity	Associated Side Effects
Conventional (typical) antipsychotics: Phenothiazines Haloperidol Provide relief of psychosis, improvement in positive symptoms, worsening of negative symptoms.	Strong D ₂ (dopamine) Varying degrees of affinity for: (cholinergic) Ach α ₁ (norepinephrine) H ₁ (histamine) Weak 5-HT (serotonin)	EPS, hyperprolactinemia, Neuroleptic Malignant Syndrome Anticholinergic effects Tachycardia, tremors, insomnia, postural hypotension Weight gain, sedation Low potential for ejaculatory difficulty
Novel (atypical) antipsychotics: Clozapine, Olanzapine, Quetiapine, Aripiprazole, Risperidone, Ziprasidone Provide relief of psychosis, improvement in positive symptoms, improvement in negative symptoms.	Strong 5-HT Low to Moderate D ₂ Varying degrees of affinity for: Ach α adrenergic H ₁	Sexual dysfunction, GI disturbance, headache Low potential for EPS Anticholinergic effects Tachycardia, tremors, insomnia, postural hypotension Weight gain, sedation