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# Neurobiological Role Of Chemical Imbalances In The Brain In Schizophrenia

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## I. Introduction:

A chemical imbalance in the brain is a phenomenon of psychopathology that takes place when the brain possesses either an excess or deficit of chemical messengers, called neurotransmitters, the activity of their respective receptors is adversely impacted or their transmission through the complex neural networks is altered. Neurotransmitters—like serotonin, dopamine, glutamate, norepinephrine, and GABA (gamma-aminobutyric acid)—are chemical messengers: diverse chemical substances that convey information between nerve cells by producing rapid excitatory or inhibitory postsynaptic as well as slow-onset biochemical changes in the membrane potential of the receiving neuron (via ligand-gated channels).

When the number of neurotransmitters present within our bodies either exceeds or falls short of the requisite amount for chemical and neurobiological equilibrium, chemical imbalances occur in the brain. The idea of a "chemical imbalance" underlying mental disorder (the chemical imbalance theory) is pervasive in our society and aberrations in various neurotransmitter systems have been implicated in conditions like schizophrenia, depression and anxiety disorders. Chemical imbalances are also often critically related to physical health conditions. For example, polycystic ovary syndrome (PCOS) occurs with a hormonal imbalance due to excessive androgens (male hormones) in females, in turn putting the person at risk for other conditions, includingType 2 diabetes and infertility.

## II. Neurotransmitters

Neurotransmitters are endogenous chemicals that allow neurons to communicate with each other throughout the body. Otto Loewi discovered the first neurotransmitter in 1926 when he demonstrated that acetylcholine conducted a chemical signal from the vagus nerve to the heart that decelerated the cardiac rhythm. Since then, more than one hundred substances and many receptors have been implicated in synaptic transmission. However, as a result of the remarkably diverse effects of neurotransmitter-mediated signalling at the receptor and post-receptor levels, the number of neurotransmitters, as large as it is, vastly understates the complexity of signalling in the brain.

In a classic prototype of chemical transmission systems, a presynaptic neuron releases a neurotransmitter which binds to receptors on it. These receptors are often localized on dendrites – filamentous extensions from the neuron's cyton that are responsible for receiving and transmitting impulses or signals throughout the complex neural structures of the nervous system. Receptors and associated proteins convert the chemical information received into electrical information by the activation of ion channels. At rest the neuronal membrane is polarized, bearing a negative charge. Neurotransmitter binding can activate ion fluxes across the membrane. Depending on which types of channels are activated, either 'hyperpolarizing' negative charges or 'depolarizing positive charges' may enter the cell. The equilibrium of negative and positive charge is integrated within the dendrites and cyton of the neuron, and on achieving a threshold of depolarization, specialized voltage-gated $Na^+$ channels open in succession, generating a wave of depolarization down the axon, an 'action potential'.

When an action potential arrives at the distal end of the axon – the presynaptic terminals – the inrush of positive charge activates voltage-sensitive $Ca^{2+}$ channels. $Ca^{2+}$ entry then initiates processes by which neurotransmitters are released into the synaptic cleft. When neurotransmitters, such as acetylcholine or glutamate, activate cation (for example $Na^+$ or $Ca^{2+}$) channels, and are thus depolarizing, they can be described as excitatory; when neurotransmitters, such as GABA, activate anion (for example $Cl^-$) channels, they can be described as inhibitory.

Some important neurotransmitters and their functions are given below –

- Serotonin (5-hydroxytryptamine or 5-HT; more precisely, 3-(2-Aminoethyl)-1*H*-indol-5-ol): It is a monoamine neurotransmitter that modulates multiple neuropsychological processes and neural activity. Serotonin also has implications that affect gastrointestinal processes like bowel motility, bladder control, cardiovascular function, bone health and sexual desire/attraction.

- Dopamine (a contraction of 3,4-dihydroxyphenethylamine**)**: It is a neuromodulatory molecule of the catecholamine and phenethylamine families that plays an essential role in several brain functions, including learning, motor control, reward, emotion, and executive functions. Dopamine has been implicated in psychiatric and neurological disorders.
- Glutamate (2-azaniumylpentanedioate): It is the divalent anion of glutamic acid that serves as the principal excitatory neurotransmitter used in the brain. It is also the primary mediator of nervous system plasticity. It has been implicated in modifiable synapses, which researchers suspect are the memory-storage elements of the brain.
- Norepinephrine(4-[(1R)-2-amino-1-hydroxyethyl]benzene-1,2-diol): It is a monoamine of the catecholamine family that functions as both a neurotransmitter and a hormone and,chemically, is demethylated epinephrine. It impacts stress, sleep, attention, focus, and inflammation. It also plays a role in modulating the responses of the autonomic nervous system.
- Histamine (2-(1H-Imidazol-4-yl)ethanamine): Derived from the decarboxylation of the amino acid histidine,it is another neurotransmitter that mediates homeostatic functions in the body, promotes wakefulness, modulates feeding behaviour, and controls motivational behaviour.

The neurotransmitters and their functions are critically responsible for our development.Chemical imbalances are rendered when the levels of various neurotransmitters are altered, their 'communication systems' are adversely impacted, or their functioning is impaired, in the following ways.

(a) Receptors become oversensitive or insensitive to a specific neurotransmitter, causing them to respond too much or too little to the release of the neurotransmitter.
(b) The originating cell pumps out too little of a neurotransmitter, resulting in the message getting weakened.
(c) An overly efficient reuptake takes place that reabsorbs too much before the molecules have the chance to bind to the receptors on other neurons, thus weakening the message.

In addition, other factors could change the levels of chemicals in your brain. For example, some researchers suggest that mitochondrial disease – caused by mutations in mitochondrial DNA – could contribute to a chemical imbalancethat could be linked to depression. Chronic stress can also change the levels of neurotransmitters in your brain and the inflammation that accompanies chronic stress can also adversely impact brain chemistry. Lastly, drugs and alcohol use also affect neurotransmitters. They can mimic neurotransmitters and change the levels of your natural neurotransmitters. This is one of the reasons why people become addicted to drugs and alcohol.

## III. Schizophrenia

Schizophrenia is a neurodevelopmental syndrome – a collection of signs and symptoms of unknown aetiology – predominantly defined by observed signs of psychosis, and often characterised by a loss of touch with reality.

Schizophrenia is known for its psychopathology and involves a fundamental but not pathognomic disturbance of personality, a more or less characteristic disordering of the process of thought, a frequent sense of being controlled by outside forces, bizarre perceptions and delusions and inappropriate emotions. At the same time, what makes it truly peculiar is that a clear conscience and intellectual capacity are, by and large, maintained, and the person usually considers their behaviour natural and rational. The neuropathological defect involved in schizophrenia was called 'intrapsychic ataxia' by an early researcher in the field.

Schizophrenia symptoms generally fall into three main categories: psychotic/ positive, negative, and cognitive.

1. **Psychotic or positive symptoms** include changes in the way a person thinks, acts, and experiences the world. People with psychotic symptoms may lose a shared sense of reality with others and experience the world in a distorted way.
   - **Hallucinations**: When a person sees, hears, smells, tastes, or feels things that are not there. People who hear voices may hear them for a long time before family or friends notice a problem.
   - **Delusions**: When a person has strong beliefs that are not true and may seem irrational to others. These may be bizarre delusions such as delusions of being controlled, thought broadcasting, thought insertion or thought withdrawal. Alternatively, they may be somatic, grandiose, religious, nihilistic or persecutory.
   - **Thought disorder**: When a person has ways of thinking that are unusual or illogical. People with thought disorders may have trouble organizing their thoughts and speech.
   - **Movement disorder**: When a person exhibits abnormal body movements. People with a movement disorder may repeat certain motions over and over.
2. **Negative symptoms** include loss of motivation, anhedonia, loss of interest or enjoyment in daily activities, withdrawal from social life, difficulty showing emotions, and difficulty functioning normally.
3. **Cognitive symptoms** include problems in attention, concentration, and memory. These symptoms can make paying attention, following a conversation, processing information to make decisions, learning new things, or remembering appointments difficult. A person's level of cognitive functioning is one of the best

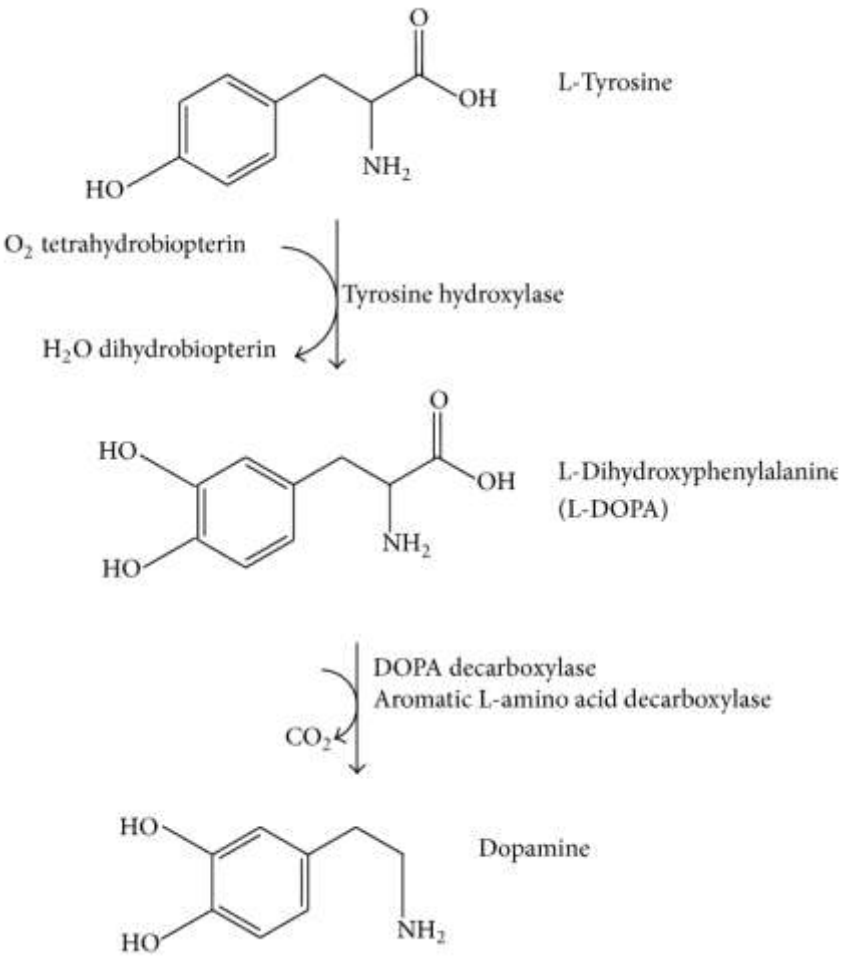
predictors of their day-to-day functioning. Healthcare providers evaluate cognitive functioning using specific tests.

## IV. Role of chemical imbalances in schizophrenia.

**The Dopamine Hypothesis**

Dopamine (3,4-dihydroxyphenethylamine)is an important neurotransmitter of the catecholamine and phenethylamine family that is produced in the substantia nigra and ventral tegmental regions of the brain.

A dopamine molecule consists of a catechol structure (a benzene ring with two hydroxyl side groups) with one amine group attached via an ethyl chain. As a result, it is the simplest possible catecholamine. The presence of a benzene ring with this amine attachment also makes it a phenethylamine. Dopamine is synthesized by removing a carboxyl group from a molecule of its precursor chemical, L-DOPA, as follows:




As a critical neurotransmitter, dopamine plays important roles in executive functioning, motor control, motivation, arousal, reinforcement, and reward through signalling cascades that are exerted via binding to dopaminergic receptors at the projections found in the substantia nigra, ventral tegmental area, and arcuate nucleus of the hypothalamus of the human brain.

Dopamine alterations and impairments in the dopamine system as a result of dopamine dysfunctions in the substantia nigra, ventral tegmental region, striatum, prefrontal cortex, and hippocampus, have been historically related to schizophrenia. The original dopamine hypothesis was proposed as early as the 1960s. This hypothesis posits that hyperactive dopamine transmission results in schizophrenic symptoms. It rested on the foundations of the discovery of dopamine as a neurotransmitter in the brain by ArvidCarlsson. However, it was consolidated when, during this time, doctors noticed that an antipsychotic drug called chlorpromazine, which reduces dopamine activity, effectively treated some types of schizophrenia symptoms.Another antipsychotic agent, haloperidol, which was also implicated in dopamine receptor blockade, was found to be able to manage positive symptoms of schizophrenia, such as hallucinations and delusions.

A link was observed between various schizophrenia symptoms and the activity of dopamine receptors. The positive symptoms of schizophrenia – hallucinations and delusions –are a result of the increased release of dopamine in the subcortex, due to a disturbed cortical pathway through the nucleus accumbens (neural interface between motivation and action), which augments the activation of the $D_2$ receptor. On the other hand, research suggests that the negative symptoms of schizophrenia – anhedonia, lack of motivation, poverty of speech etc.– result from reduced $D_1$ receptor activation in the prefrontal cortex and decreased activity of the caudate nucleus. Alterations in $D_3$ receptors might also be involved in the negative symptoms of schizophrenia.

Over time, the original dopamine hypothesis came into question, particularly because some schizophrenia symptoms may be triggered when certain areas of the brain have high levels of dopamine activity while others have lower levels of activity. Further, clozapine, which is a very effective antipsychotic in patients with resistant schizophrenia, has rather a low affinity to dopamine $D_2$ receptors. Moreover, some patients with schizophrenia also have normal levels of dopamine metabolites in cerebrospinal fluid or serum. The theory was, thus, revised.

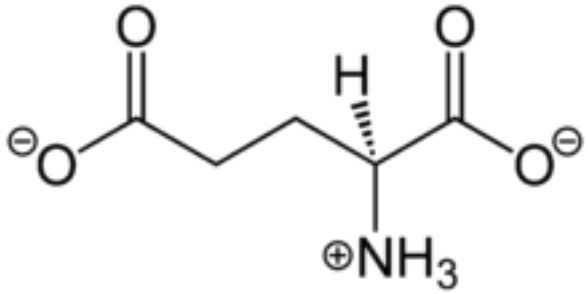
The revised dopamine hypothesis proposes that schizophrenia in patients is characterized by hyperactive dopamine transmission in the mesolimbic areas and hypoactive dopamine transmission in the prefrontal cortex. Moreover, they linked the positive symptoms of the disease with the striatal dopamine $D_2$ receptor overactivation resulting from hyperactive mesolimbic dopamine projections while negative and cognitive symptoms resulted from the prefrontal cortex dopamine $D_1$ receptor hypostimulation due to diminished mesocortical dopamine projections.

Thus, the revised hypothesis suggests that dopamine dysregulation is not restricted to the mesolimbic areas – dopaminergic 'reward' pathways – but is also observed in brain regions like the amygdala – whose responses represent a critical nexus between the propensity for emotional experience and emotional interactions with perceptual encoding – and the prefrontal cortex – which is involved in planning complex cognitive behaviour, personality expression, decision making, and moderating social behaviour. PET (positron emission tomography) studies have identified differences in dopamine contents in the prefrontal cortex, cingulate cortex, and hippocampus between schizophrenia patients and neuropsychiatric healthy control subjects. In particular, the dopamine system in the hippocampus is overactive in schizophrenia patients.

The aberrant salience hypothesis of psychosis most commonly links the dopaminergic system with the symptoms of schizophrenia. Salience governs attention, affects decision-making and functioning, and how your brain attaches importance to something. For example, when you're crossing the street, the cars, traffic and avoiding accidentsconstitute your most salient thoughts. The foundation of the aberrant salience hypothesis is the incentive salience hypothesis, which suggests that mesolimbic dopaminergic neurotransmission is crucial in the attribution of salience. The aberrant salience hypothesis assumes that excessive dopamine firing in psychotic episodes disturbs the attribution of salience leading to the psychotic symptoms that generally characterise schizophrenia.

## V. The Glutamate Hypothesis

Glutamate is a major excitatory neurotransmitter of the healthy mammalian brain, as the most profuse free amino acid that happens to sit at the intersection between several metabolic pathways.
It is the divalent anion of glutamic acid, and its structure is as follows:




It is involved in the rapid production of excitatory postsynaptic potentials at axospinous synapses and in slowly developing neuroplasticity associated with learning, memory, and neuronal development at glutamatergic synapses in the hippocampus, neocortex, and other parts of the brain. Glutamate is unique among neurotransmitters in that it plays a prominent role in intermediary metabolism, protein synthesis, and neurotransmission.

Most cells in the central nervous system (CNS) express at least one type of glutamate receptor. These include the ionotropic NMDA (N-methyl-D-aspartate), AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), and kainite receptors, which mediate fast excitatory transmission; in addition to the family of

eight metabotropic glutamate receptors (mGluR1-8), which are located pre-, post-, and extra-syntactically throughout the CNS.

Glutamatergic pathways linking to the cortex, the limbic system, and the thalamus regions are important in schizophrenia. Disturbances in glutamatergic neurotransmission may influence synaptic plasticity and cortical microcircuitry, especially NMDA receptor functioning. NMDA-receptor hypofunction state can lead to morphological and structural brain changes which can result in the development of psychosis. Thus, the glutamate theory of schizophrenia proposes that schizophrenia symptoms and cognitive impairment are due to hypofunction of NMDA receptors and excessive glutamate release, especially in brain areas such as the prefrontal cortex and hippocampus. This theory emerged from the discovery that open-channel NMDA receptor antagonists – drugs that bind to the NMDA receptor either on the primary site or on another site, which all together stop the receptor from producing a response – and dissociative anaesthetics–psychedelic drugs that are subclasses of hallucinogens, distorting the perception of sight and sound and producing feelings of detachment from the environment or self – such as phencyclidine (PCP) and ketamine, induced negative symptoms and cognitive dysfunction resembling schizophrenic phenotypes in healthy subjects. In schizophrenic subjects, on the other hand, subanesthetic doses of ketamine could exacerbate psychotic and cognitive symptoms.

In animal studies, suppression of NMDAR function by pharmacological or genetic approaches leads to schizophrenia-like behaviours. Schizophrenia is also associated with the dysregulation of some genes and/or proteins involved in glutamate transmission.High extracellular glutamate levels lead to hypermetabolism, structural disorganization, and eventually hippocampal volume reduction. Each of these dysfunctions is associated closely with disease progression from prodromal symptoms (early signs or symptoms indicating the onset of a disease before more diagnostically specific symptoms) to psychosis.In addition, genome-wide association studies have reported that the NMDAR subunits encoding genes, GRIN2A and GRIN2B, are schizophrenia-related genes; in fact, two de novo mutations in GRIN2A were found in sporadic schizophrenia patients. Moreover, in postmortem studies, some disturbances in glutamatergic receptor density and subunit composition in the prefrontal cortex, thalamus, and temporal lobe – brain regions with distorted stimulation while cognitive actions are performed by schizophrenia patients – were found.

Research has also found that the peptide transmitter *N*-acetylaspartylglutamate (NAAG) activates a group II metabotropic receptor, mGluR3. Metabotropic receptors are large monomeric transmembrane proteins containing seven-transmembrane domains that initiate intracellular signalling via coupling to G proteins, and mGluR3 is a metabotropic glutamate receptor whose polymorphisms (variations of specific DNA sequences) are genetically associated with psychosis, with the risk alleles also being associated with schizophrenia-related endophenotypes such as impaired cognition, cortical activation and glutamate markers.

## VI. Other Neurotransmitters

While research suggests that the neurotransmitters dopamine and glutamate play the most significant role in the chemical imbalances characterizing schizophrenia, other neurotransmitters like serotonin and gamma-aminobutyric acid (GABA) may also be involved.

Studies suggest that an overload of serotonin from the dorsal raphe nucleus (DRN) – a heterogeneous brainstem nucleus located in the midbrain and pons – resulting from stress may disturb the activity of cortical neurons in schizophrenia. Moreover, long-lasting extensive stress-derived serotonergic overload in the cerebral cortex, particularly in the anterior cingulate cortex (ACC) and dorsolateral frontal lobe (DLFL), may play a role in developing some schizophrenic symptoms.

Indeed, despite a glaring lack of absolute evidencepointing to the importance of serotonin signalling aberrance in the pathomechanism of schizophrenia, serotonin receptors, particularly 5-$HT_3$ and 5-$HT_6$, still represent promising drug targets for the discovery of antipsychotic agents which can alleviate cognitive and negative symptoms of the disease.

Gamma-aminobutyric acid (GABA) is also an important inhibitory neurotransmitter. GABAergic interneurons play a vital role in the suppression of the CNS, and synchronization and oscillations of neurons are critical for perception, learning, memory, and cognition. As a result, disturbances in the GABA signalling may cause an imbalance between excitation and inhibition in the cerebral cortex,which is an important factor in the pathomechanism of schizophrenia. Changes in GABA neurotransmission were found in basic and clinical research on schizophrenia and animal models.

## VII. Conclusion

Schizophrenia is a debilitating mental illness affecting about 1% of the population. While several studies have been useful in obtaining valuable insights into the pathomechanism of schizophrenia, in particular, the chemical imbalances due to deviations in the working of neurotransmitters like dopamine, glutamate, serotonin etc., that cause this disorder, it is not yet fully understood.

Research suggests that several neurotransmitters interact with each other to form a network of psychotogenic pathways that together may produce schizophrenia symptoms.

This research supports an earlier hypothesis (Carlsson, 1988)that suggested that psychomotor activity and psychotogenesis depend on mutual interactionsbetween dopamine and glutamate projecting to the striatum from the lower brainstem and cortex, respectively. These neurotransmitters are predominantly antagonistic to each other, that is, when they act on striatal GABAergic projection neurons, they produce opposite effects – the former is inhibitory and the latter stimulating. These GABAergic projection neurons of indirect striatothalamic pathways, exert an inhibitory action on thalamocortical glutamatergic neurons, thereby filtering off part of the sensory input to the thalamus to protect the cortex from a sensory overload and hyperarousal. Hyperactivity of dopamine or hypofunction of the cortico-striatal glutamate pathway should reduce this protective influence and could thus lead to confusion or psychosis – positive effects of schizophrenia.

This may provide a holistic overview of the process on a larger level, however, it too remains merely a theory. The actual pathomechanism of complex mental disorders like schizophrenia is very sophisticated and nuanced, which makes it difficult for scientists to ascribe with absolute certainty cause-and-effect relationships to describe it.

The current antipsychotics for schizophrenia are also characterized by several limitations. Firstly, these treatments are only efficient for about 50% of patients. Secondly, they ameliorate mainly positive symptoms (e.g., hallucinations and thought disorders which are the core of the disease) but, by and large, leave negative (e.g., flat affect and social withdrawal) and cognitive (e.g., learning and attention disorders) symptoms untreated. Thirdly, they involve severe neurological and metabolic side effects and may lead to sexual dysfunction or agranulocytosis (clozapine).

Emerging knowledge about the interactions between different neurotransmitters in complex neurocircuits opens up possibilities for achieving antipsychotic activity by helping develop new drugs that specifically counteract hypo- or hyperactivity in various neurotransmitter systems. Most intriguing is the finding in animal experimental models, indicating that it should be possible to alleviate psychotic conditions by stabilizing rather than paralyzing neurocircuits, thus avoiding the risk of motor and mental side effects of the currently used drugs. Such new research could be pivotal in increasing our understanding of schizophrenia, working towards reducing its harmful consequences and ultimately, destigmatizing this disorder.

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