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Schizophrenia: Interaction between Dopamine, Serotonin, Glutamate, GABA and Norepinephrine

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ABSTRACT

Research has implicated dysfunction of various neurotransmitters in the pathophysiology of schizophrenia. This review evaluates evidence from preclinical and clinical studies that five major neurotransmitters in brain are altered in schizophrenia, may affect symptom expression, and requires modulation by antipsychotic drugs. A comprehensive review of scientific articles published that address the role of Dopamine, Serotonin, Glutamate, GABA and Norepinephrine (NE) in the pathophysiology of schizophrenia was carried out. Dopamine and serotonin are the major neurotransmitters that have been implicated in schizophrenia. Several studies have revealed alterations in Glutamate, GABA and NE neurotransmission in several brain regions in schizophrenia. Agents that enhance NMDA receptor function reduce negative symptoms and variably improve cognitive functioning in schizophrenic subjects. GABA_A agonists alleviate schizophrenic symptoms. Raised levels of Norepinephrine in the CSF of schizophrenic patients raise the doubt about its association with the disease. Apart from dopamine and serotonin, dysfunction of glutamate, GABA and NE neurotransmission may play an important role in the pathophysiology of schizophrenia, especially of the negative symptoms and cognitive impairments associated with the disorder, and is a promising target for drug development.

Keywords: Schizophrenia, Dopamine, Serotonin, Glutamate, GABA, Interactions.

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INTRODUCTION

Schizophrenia is a mental disorder characterized by a breakdown of thought processes and deficit of typical emotional responses. Combination of positive and negative symptoms characterizes it. Common symptoms are delusions and disorganized thinking including auditory hallucination, Paranoia, bizarre delusions, disorganized speech, and it is accompanied by significant social or occupational dysfunction. The onset of symptoms typically occurs in young adulthood, with a global lifetime prevalence of about 0.3–0.7%. [1] Generally considered a biochemical disorder of the brain.

This review will briefly summarize the interaction between Dopamine, Serotonin, Glutamate, GABA and Norepinephrine in the pathophysiology of schizophrenia

Dopamine and Schizophrenia

Various studies are available which shows dopamine as the major neurotransmitter behind the pathophysiology of Schizophrenia. A major line of evidence that supports the hypothesis of dopamine overactivity in schizophrenia is the psychomimetic potential of agents such as amphetamine that stimulate dopamine outflow. [2] Dopamine receptor antagonist improves Psychotic symptom it created. Abi-Dargham A et al measured *in vivo* occupancy of striatal D₂ receptors and found increased stimulation of D₂ receptors by dopamine in schizophrenia, consistent with increased phasic activity of dopaminergic neurons. [3] Potency of D₂ receptor antagonist and levels of homovanillic acid (HVA), a breakdown product of D (Dopamine), has positive correlation.[4]

Imaging studies showed increased densities of D₂-like receptors in the basal ganglia and also in limbic system, substantia nigra, thalamus and striatum. D₂ receptor antagonists, such as typical antipsychotics, block nigro-striatal and are responsible for motor disorder symptoms and extrapyramidal side effects which again prove the dopamine blocking action of typical antipsychotic. Though D₂ receptors are high, Levels of D₁ receptors in prefrontal cortex is less. Subcortical mesolimbic DA projections might be hyperactive, resulting in hyper stimulation of D₂ receptors and positive symptoms, whereas mesocortical DA projections to the prefrontal cortex might be hypoactive, resulting in hypo stimulation of D₁ receptors, negative symptoms, and cognitive impairment. [5] Mesolimbic dopamine system now seems responsible for changes in psychotic features.

Serotonin and Schizophrenia

Dopamine hyperactivity remains viable explanation but only for positive symptoms. Newer atypical antipsychotics improve negative symptoms which has less action on D₂ receptor, raising the question of role of serotonin. LSD (D-lysergic acid diethylamide) competes for and occupies serotonin's receptor and produce psychosis. James A. Nathanson et al found similarity of Serotonin with LSD and LSD acts through Serotonin sensitive adenylyl cyclase. [6] Also atypical antipsychotic drugs like clozapine and risperidone improved symptoms in those resistant to other medications. Both drugs have weak D action and acts by different mechanism (probably serotonin antagonism). This is confirmed when Typical Antipsychotics are combined with 5HT-2 antagonist, negative symptoms and motor side-

effects reduced. Now theorized that increased levels of serotonin in the prefrontal cortex will result in lower dopamine levels in the area.[7] This lead to increased levels of dopamine in secondary dopaminergic systems (positive symptoms). This interaction theory has been widely accepted now.

GABA and Schizophrenia

GABA an inhibitory aminoacid control dopamine levels in brain. The interaction between GABA glutamate and Dopamine can be understood better by the following figures. Fig.1. GABA is synthesized from Glutamate with the help of vit B6 (Pyridoxine) and Glutamic acid Decarboxylase (GAD).[8] Fig.2. In case of Pyridoxine deficiency, synthesis of GABA is impaired due to less activity of Glutamic acid Decarboxylase (GAD). Due to decreased levels of GABA the inhibitory action of it on Dopamine will reduce thereby increasing the levels of Dopamine leading to Confusion and irritability. GABA has two types of receptors GABA_A and GABA_B. GABA_A receptor is more consistent with schizophrenia. D₂ agonists reduced the postsynaptic response to a GABA_A agonist. D1 and D2 receptors therefore regulated GABAergic activity in opposite manners and through different mechanisms in prefrontal cortex.[9] Benzodiazepine which increases the affinity of GABA to its binding sites alleviates schizophrenic symptoms. Iodine-123-labeled iomazenil ([123 I] iomazenil), a radioligand that selectively binds with high affinity to the benzodiazepine subunit of the GABA_A receptor complex in the human brain also has similar effect. [10]

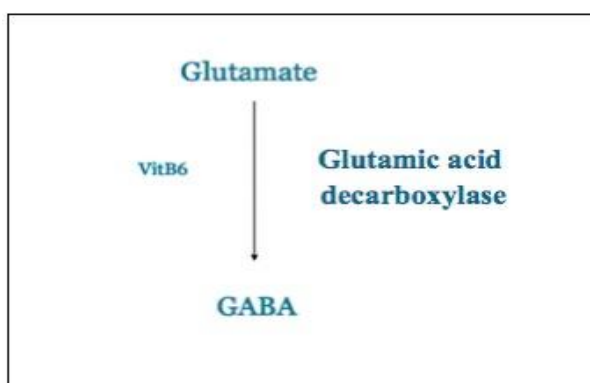


Fig.1. GABA synthesis

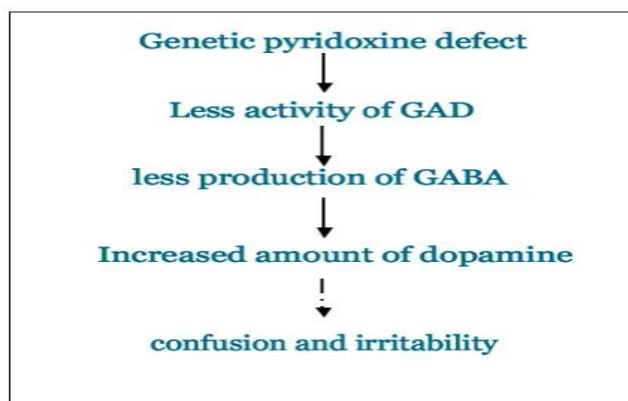


Fig.2.GABA Dopamine interaction

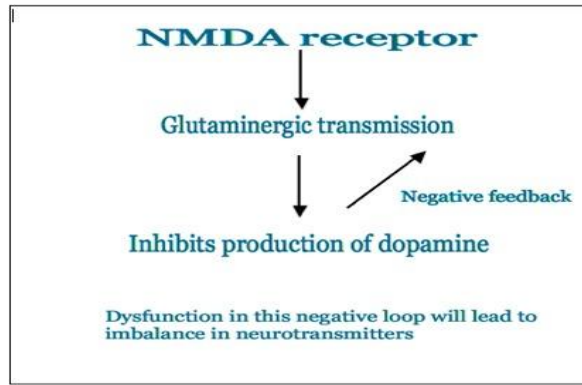


Fig.3. Glutamate Dopamine interaction

Glutamate and Schizophrenia

Glutamatergic neurons are the major excitatory pathways linking the cortex, limbic system, and thalamus, regions that have been implicated in schizophrenia. Postmortem studies have revealed alterations in pre- and postsynaptic markers for glutamatergic neurons in several brain regions in schizophrenia. Phencyclidine (PCP, angel dust) a NMDA receptor antagonist produce toxicity which mimics positive and negative symptoms of Schizophrenia. [11] The NMDA subtype of glutamate receptor may be particularly important, as blockade of this receptor by the dissociative anaesthetics reproduces in normal subjects the symptomatic manifestations of schizophrenia, including negative symptoms and cognitive impairments, and increases dopamine release in the mesolimbic system. Agents that indirectly enhance NMDA receptor function via the glycine modulatory site reduce negative symptoms and variably improve cognitive functioning in schizophrenic subjects. [12] Fig.3. illustrates the relation between *N*-methyl-d-aspartic acid (NMDA) receptor, Glutaminergic transmission and inhibition of dopamine. NMDA receptor induces glutaminergic transmission and inhibits production of dopamine. Low dopamine level induces negative feedback to glutaminergic transmission and GABA synthesis (fig.1.).

Norepinephrine and Schizophrenia

Increased level of NE creates heightened autonomic arousal. [13] NE reward system consists of positive and negative feedback circuits. Alpha and beta receptors modulate this. Schizophrenia may be related to a defect in this noradrenergic reward system. Evidence of norepinephrine's involvement in schizophrenia is weak. Clonidine was effective in lowering NE. [14] But the relief of symptoms was only marginal compared to antipsychotics. Clonidine is largely unsuccessful as augmenting agent. But Kemali et al confirmed raised levels CSF norepinephrine in schizophrenic patients.[15] What norepinephrine's role is, what part its reward system plays, and to what extent it modulates dopamine levels is still a big question.

CONCLUSION

Schizophrenia has great human and economic costs. [1] It results in a decreased life expectancy of 12–15 years, primarily because of its association with obesity, sedentary lifestyles, with an increased rate of suicide playing a lesser role. [1] These differences in life expectancy increased between the 1970s and 1990s, and between the 1990s and first

decade of the 21st century did not change substantially.[16] Which clearly indicates we are stuck with dopamine and serotonin theory. Multiple lines of evidence have linked abnormalities in Dopamine, Serotonin, Glutamate, GABA and Norepinephrine in the pathophysiology of schizophrenia. However currently available antipsychotic drugs, apart from action on serotonin and dopamine, also alter glutamatergic activity in multiple ways by enhancing release of glutamate in the striatum, directly interacting with NMDA receptors, altering glutamate receptor density, and changing the subunit composition of glutamate receptors. [12] Association of GABA with schizophrenia is clear while that of NE has to be explored further. In a longer perspective, drugs interfering with Glutamate, GABA and Norepinephrine function via different mechanisms may also turn out to be useful, especially in the control of negative symptoms. Thus, drugs that modulate glutamatergic, GABA and NE neurotransmission hold promise for novel treatments for schizophrenia, especially for the cognitive impairments and negative symptoms associated with the disorder.

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