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Schizophrenia: The Ambiguous Mechanism behind the Disorder

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ABSTRACT

Background: Schizophrenia is considered one of the top 10 conditions that cause disability worldwide. Regardless of its low prevalence, it negatively impacts the quality of life not only for patients but also for families and society. The present antipsychotic therapies provide relief only for the positive symptoms, but they do not improve the negative or cognitive symptoms of schizophrenia. Extensive research is being conducted to discover new medications that can treat or prevent the illness. This can only be achieved by fully understanding the underlying mechanism behind the illness.

Methods: Four hypotheses which explain the possible mechanisms that might be involved in the development of schizophrenia have been discussed in this review. The effect of vitamin D and iron deficiencies, infection, and paternal age on the development of schizophrenia in the offspring were also reviewed, in addition, to the demonstration some of the clinical studies and their outcomes.

Results: The exact cause of schizophrenia is still not fully known. The disease might develop as a result of neurotransmitter dysfunction, receptor hypofunction, environmental factors, or other factors which might play a role in the etiology and course of schizophrenia.

Conclusion: All these factors which might be involved in the development of the illness are required to be investigated in order to provide new hope for people suffering from schizophrenia. Numerous studies are in progress to find the exact pathophysiology of the disease, but despite such progress, there are still many questions are required to be answered in order to assist us in developing the appropriate therapy for treating the illness.

Keywords: Antipsychotic, disability, hypotheses, mechanisms, schizophrenia.

1. INTRODUCTION

The term schizophrenia which means split mind comes from Greek roots schizo (split) and phrene (mind) (1). It is a mental disorder wherein the person split from reality. Schizophrenia is often confused with dissociative identity disorder in which the patient has more than one identity or personality where these identities take part in the patient's life (2). The concept of the disease can be difficult to understand. Healthy individuals who are not suffering from schizophrenia have little idea about the illness. Schizophrenia is a chronic psychotic disorder that affects how people think, live, and see the world. It is characterized by three symptoms: positive symptoms like hallucination and delusion, negative symptoms like social withdrawal and reduce interest in everyday activities and cognitive symptoms including reduced attention and memory changes (3, 4). The severity of the disorder, signs, symptoms, and the effect of the disease on the patient's quality of life may vary among individuals (5). Schizophrenia generally starts to develop in late adolescence and early adulthood, it impacts both genders equally. However, men usually start to experience the symptoms earlier at the age of 15-25, whereas women tend

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to develop the symptoms at the age of 25-35 (6).

Schizophrenia has been around for a long time, but due to its nature, the exact statistic is difficult to be obtained. Approximately 1% of the population worldwide are suffering from the disease (7). It is estimated that the illness costs the society US$94 million to US$102 billion per annum in United States. It imposes a burden on the society which finds it difficult to provide support for those patients through family and social bonds (8). Most of the developing countries suffer from high rate of mental illnesses (9). The majority of patients and their families are not aware of the severity of the disorder; they find that this disease is a stigma and should be hidden from the society. As a consequence, many patients who suffer from schizophrenia refuse to get appropriate treatment in order to protect themselves from being stigmatised as a maniac by the community (10). The etiology and pathophysiology of schizophrenia remain unclear but numerous theories have been suggested to illustrate the possible mechanisms involved in the development of the illness. This review highlights some of these theories (Fig. 1) and demonstrates their point of view in explaining the underlying mechanism of schizophrenia.

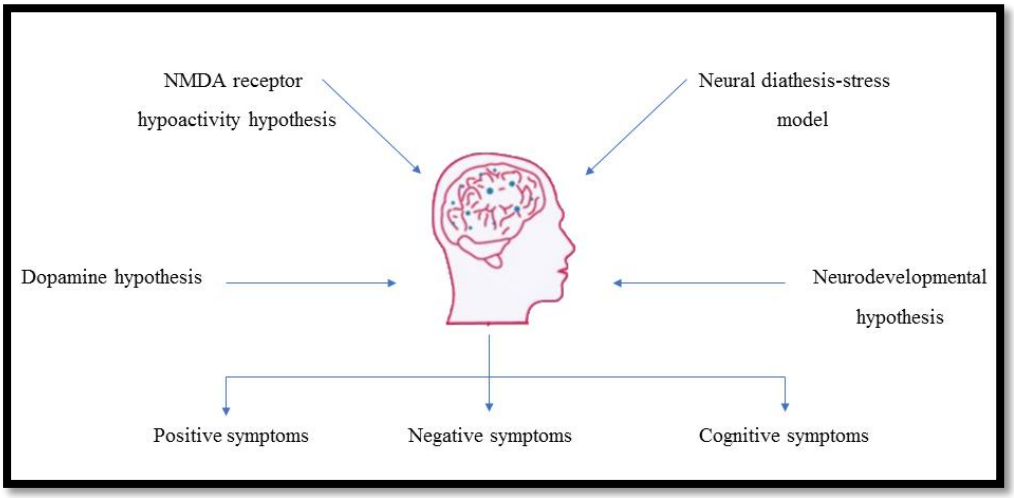

Fig. 1. Schizophrenia hypotheses. Some of the hypotheses that explain the possible mechanisms involved in the development of schizophrenia.

2. THE POSSIBLE UNDERLYING MECHANISMS INVOLVED IN THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

2.1 Dopamine Hypothesis

This hypothesis is the oldest neurochemical theory of the pathophysiology of schizophrenia (11). It was proposed as a consequence of discovery that the antipsychotic drugs block the dopamine (DA) receptors in animal experiments (12). The usefulness of antipsychotic treatment was observed prior to the explanation of how it works. Studies later discovered the correlation between the clinical effectiveness and antipsychotics affinity for DA receptors (13). So far, the dopamine hypothesis provides the best explanation for the psychotic episode of schizophrenia; it suggests that the unusual behaviour and psychosis experienced by schizophrenic patient might be related to changes in DA level in the brain (14).

The early formulated hypothesis attributed the symptoms of schizophrenia to hyperactivity of DA transmission based on the observations that

psychostimulants activate the DA receptors and the important role of DA in the extrapyramidal motor system (15). The classical DA hypothesis was reformulated over the years, due to the increased awareness of the importance of persistent negative and cognitive symptoms in this disease and their resistance to antipsychotics. Brain imaging studies proposed that the patient develops the symptoms of schizophrenia due to the imbalance in DA in the brain (16). The positive symptoms arise as a result of over-activity of DA in subcortical mesolimbic pathway which augments D2 receptor activation in the brain. The DA hyperactivity can be attributed to either excessive release of DA from the presynaptic cell or pathological raise in D2 receptor on postsynaptic end (17). In addition, the positive symptoms might also develop due to the disturbance in the cortical pathway through the nucleus accumbens (18). On the other hand, the negative symptoms and cognitive impairment of schizophrenia result from the hypoactivity of mesocortical DA projections to the prefrontal cortex which leads to hypostimulation of D1 receptors in the brain (19, 20).

Recently, a comprehensive study conducted by researchers at Columbia University Irving Medical Center and New York State Psychiatric Institute found that people with schizophrenia who experience auditory hallucinations tend to hear what they expect. Those patients are known to have elevated levels of DA in the brain, where the elevation of DA could make some patients rely more on expectations, which could then result in hallucinations. Cassidy et al. have reported the dopamine-dependent mechanism that explains the reason of hallucination in psychotic patients. They induced auditory illusions in untreated patients with schizophrenia who experience varying degrees of hallucination and healthy volunteers to test a dopamine-dependent gain-control mechanism of hallucinations. They have requested the participants to judge the length of a target tone that preceded by context tones which were in three different conditions: shorter, same length, or longer than the target tone. The context tones were applied for the reason of setting up an expectation in the participants of hearing tones of a certain length, which biases subsequent perception of the target tone. Critically, as mentioned earlier, the influence of expectation on perception in health is dictated by how strong or reliable the expectation is. Cassidy and colleagues have manipulated this aspect by changing the variability of the context tones, in which all context tones were either the same length or fluctuated around the mean. The study results have reported that, in healthy participants, the influence of expectation on perception was modulated by this manipulation; the perceptual bias that was induced by the context tones was less strong in the condition with high variability compared to the one without. This finding suggests that when generating percepts, the auditory system of a healthy person weights the influence of expectation on perception according to its reliability. A different pattern emerged in untreated patients with schizophrenia: the higher the severity of hallucination, the stronger the biasing effect of expectation on perception; moreover, the reliability of the expectation had little or no modulatory influence on this bias. This finding indicates that, in schizophrenia, hallucination severity is associated with a stronger perceptual bias toward expected states and with failures to inhibit this perceptual bias in uncertain contexts. In order to study the DA role in this process, a subsample of participants was given a low dose of amphetamine, which develops the positive symptoms by increasing the DA levels in the nucleus accumbens. Participants, whose perception had previously been sensitive to the reliability of their expectation, became less sensitive after this pharmacological challenge due to the elevation in DA levels. Thus, the more DA a participant's brain generated, the less their auditory system down-weighted the influence of expectation when its reliability was low. These findings propose that increased DA levels lead to an overestimation of the reliability of expectation. This process disturbs the flexible integration of expectations into perceptual

experience, which might ultimately lead to hallucinatory percepts (21).

The typical and atypical antipsychotics have proven to be the best available treatment for schizophrenia so far. However, the treatment of the disease with antipsychotics is not definitive due to the fact that these medications treat only the positive symptoms by blocking the D2 receptors (Fig. 2), without improving the negative symptoms or cognitive impairments of the disorder (22). Further, typical antipsychotics are commonly cause extrapyramidal side effects due to excessively blockage of D2 receptors resulting in either DA blockade or depletion in basal ganglia (23, 24). To date, no therapy has been found for alleviating the negative symptoms and cognitive impairments of schizophrenia. Thus there is an urgent unmet medical need, which must be fulfilled by discovering newer therapies (25).

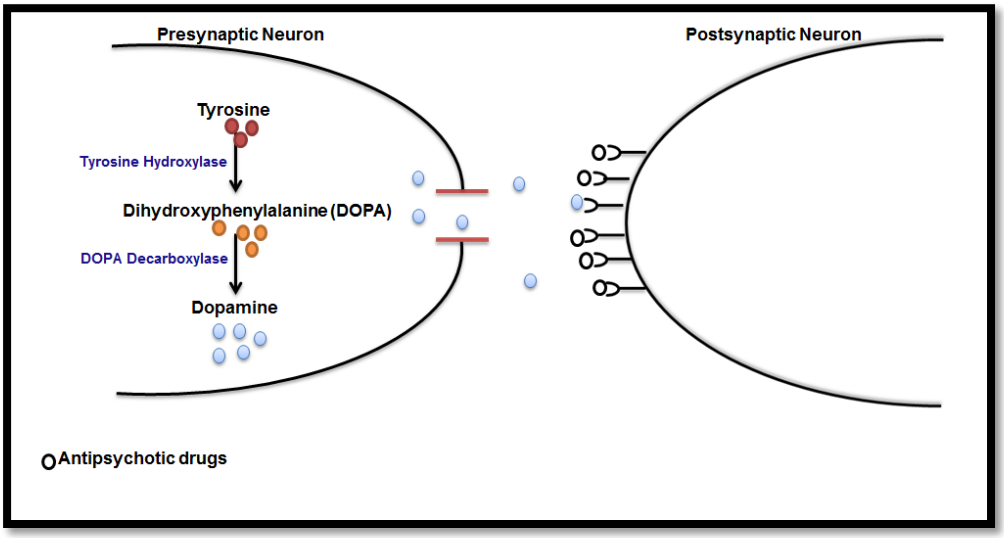

Fig. 2. Antipsychotic drugs and dopamine compete for the same receptor sites. The principle mechanism of action of typical and atypical antipsychotics is activation of indirect pathway by blocking D2 receptors.

2.2 The N-methyl-D-aspartate Receptor Hypoactivity Hypothesis

N-methyl-D-aspartate (NMDA) receptors belong to the glutamate receptor family; they are considered the most important excitatory neurotransmitter receptors in the brain. The expression and regulation of NMDA receptors properly in the brain are crucial for cortical plasticity, maturation, learning and memory processes. This hypothesis postulates that NMDA receptor hypofunction, which is a condition that induced in human or animal brain by using NMDA receptor antagonist, might be viewed as a model for a disease mechanism, where the course of schizophrenia may be attributed to either dysfunction or blocking of the NMDA receptors (26, 27). Glutamate and acetylcholine which are excitatory neurotransmitters in the brain are excessively released in the cerebral cortex as a consequence of NMDA receptors blockage. Studies reported that, the cognitive and behavioural disturbances associated with NMDA receptor hypofunction explained by the excessive release of excitatory neurotransmitters and overstimulation of postsynaptic neurons (28). It has been assumed that both genetic and environmental factors can participate in the NMDA receptor hypofunction condition where this condition established in the brain early in life as a latent state which trigger psychotic manifestation during the adulthood life but not before that because, the pathological potential

can be expressed after the occurrence of certain maturational changes in the circuitry of the brain. When these maturational changes have taken place, the NMDA receptor hypofunction has the potential to trigger the symptoms of schizophrenia and in advance cases, to cause ongoing structural deterioration (26).

In the past two decades, evidences from both human subjects and animal models revealed that different aspects of molecular, cellular, and behavioural abnormalities related to schizophrenia are due to the aberration in the function of NMDA receptor in the limbic region of the brain (29). The NMDA hypothesis was based on the experimental observation, in which the NMDA receptor antagonists such as phencyclidine (PCP) and ketamine can produce schizophrenia-like symptoms in healthy people (30). Evidence has suggested that the intoxication with PCP can trigger the positive and negative symptoms of schizophrenia. In addition, the PCP and its analog compounds can produce exactly the same metabolic, neurochemical, and behavioural changes that are seen in schizophrenic patients (Fig. 3). This observation was very important, it emphasized the role of NMDA receptor hypofunction in the development of the disease (29). On the other hand, ketamine showed different effects on healthy individuals, these effects are based on the dose used: at low doses, both psychotic features and cognitive deficits were observed, whereas, anaesthetic effects were present at high doses (31). Post-mortem studies of brain subjects with schizophrenia revealed an increased level of N-acetylaspartylglutamate (NAAG) which is an endogenous NMDA receptor antagonist that binds to glycine site of the receptor in order to prevent NMDA receptor-dependent long-term potentiation (LTP) in hippocampus (LTP: is a kind of synaptic plasticity, where the synapses are being strengthening persistently, it plays important role in memory). They also show decline in the GCPII (a catabolizing enzyme that catabolizes the degradation of NAAG to N-acetylaspartate and glutamate) amount in limbic regions in brain individuals with schizophrenia. All these evidences point to the role of NMDA receptor hypofunction in schizophrenia (32).

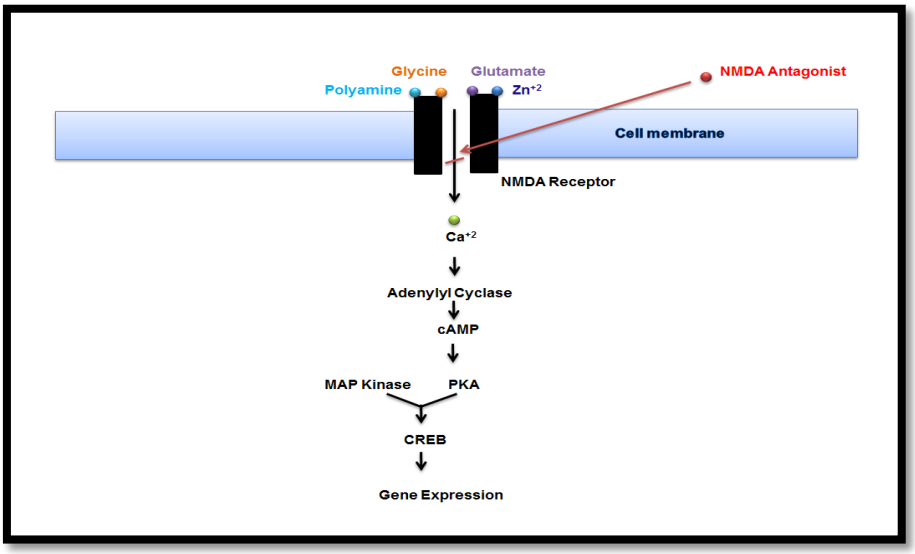

Fig. 3. NMDA antagonist blocks the entry of Ca^{+2} into the cell. The effect of NMDA antagonist on normal receptor transmission.

In the hippocampus, NMDA contributes to the initiation rather than maintenance of LTP. The induction of LTP is prevented by NMDA receptor antagonists, but if these antagonists are added after the induction of LTP, no effect is produced. Consequently, individuals with schizophrenia have a problem with memory formation, not retention since the NMDA mediated part is only affected, while the hippocampus is structurally stable (31). Extensive postmortem and *in vivo* neuroimaging research has described the involvement of the hippocampus in the pathophysiology of schizophrenia. Lieberman and co-workers developed a pathophysiologic model that characterizes the progression of schizophrenia from the premorbid through the prodromal stages to syndromal psychosis. Their longitudinal study of high-risk patients exposed a specific spatiotemporal pattern of hippocampal dysfunction that progresses in the transition from pre-syndromal stages to syndromal psychosis. Their model assumes that, during pre-syndromal stages, dysregulation of glutamate neurotransmission occurring in the CA1 region of the hippocampus which elevates neuronal activity reflected in metabolism and blood flow. As this persists, it drives the transition process to the later prodromal stage and subsequently syndromal psychosis. As the incipient illness progresses, this pathologic process spreads from CA1 to the subiculum and likely beyond the hippocampus and causes an atrophic process in which the neuropil of hippocampal cells is reduced and interneurons are lost. They examined this pathophysiological hypothesis in a rodent model with three experiments. First, they discovered that ketamine-evoked increases in extracellular glutamate in mice mirrored the evoked fMRI pattern, with maximal changes found in the CA1 and subiculum hippocampal subregions. Second, they found that the ketamine-induced effects were associated with atrophy in a spatial-temporally concordant manner. Third, they discovered that the sustained basal hypermetabolism and hippocampal atrophy were decreased or inhibited when the extracellular glutamate efflux was prevented by pretreating with an agent that inhibited ketamine-induced extracellular glutamate efflux, before the intermittent ketamine administration. Therefore, reducing extracellular glutamate is a valid target for preventing or ameliorating the onset of illness and limiting hippocampal atrophy. Thus, It is possible, to design a study in subjects at high risk for psychotic disorders to test whether the glutamate reducing agents i.e. lamotrigine or gabapentin normalize hippocampal hypermetabolism and prevent progression to psychosis and hippocampal atrophy (33).

2.3 Neural Diathesis-Stress Model of Schizophrenia

This model attempts to explain the role of biological (pre-existing vulnerability) and environmental (stress) factors in the etiology and course of the disorder (34). It suggests that people who experience schizophrenia are born with certain genetic or biological predisposition to the disease (Fig. 4), but not all individuals with this genetic or biological susceptibility will develop the illness (35, 36). The diathesis-stress model tends also to explain the relationship between stress and schizophrenia (37). In healthy individuals, stress stimulates cortisol production from HPA axis. The hypothalamus and anterior pituitary stimulate cortisol release from the adrenal glands that lower stress reactivity (Fig. 5). Through a negative feedback loop, high plasma cortisol lowers hypothalamus and pituitary activity (38). In individual with schizophrenia, the homeostasis of the HPA axis is disturbed. This disturbance results in HPA axis hyperactivity and elevated cortisol level that triggers the symptoms of schizophrenia (39).

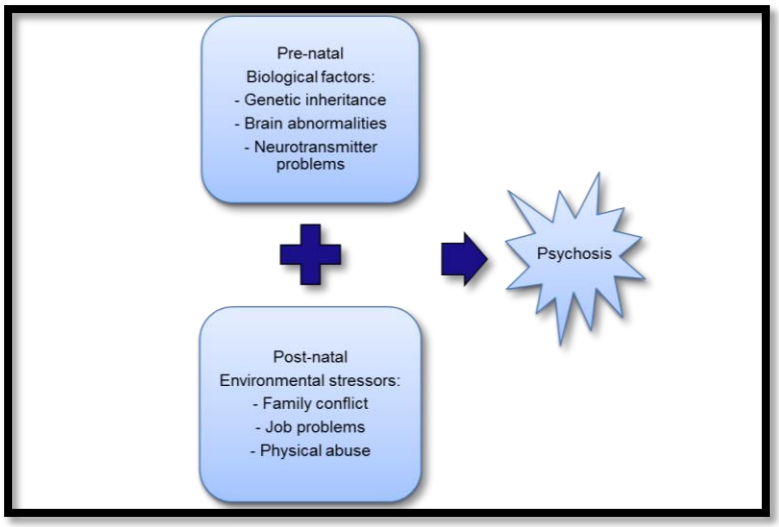

Fig. 4. The neural diathesis stress model. The role of biological and environmental factors in the etiology and course of schizophrenia.

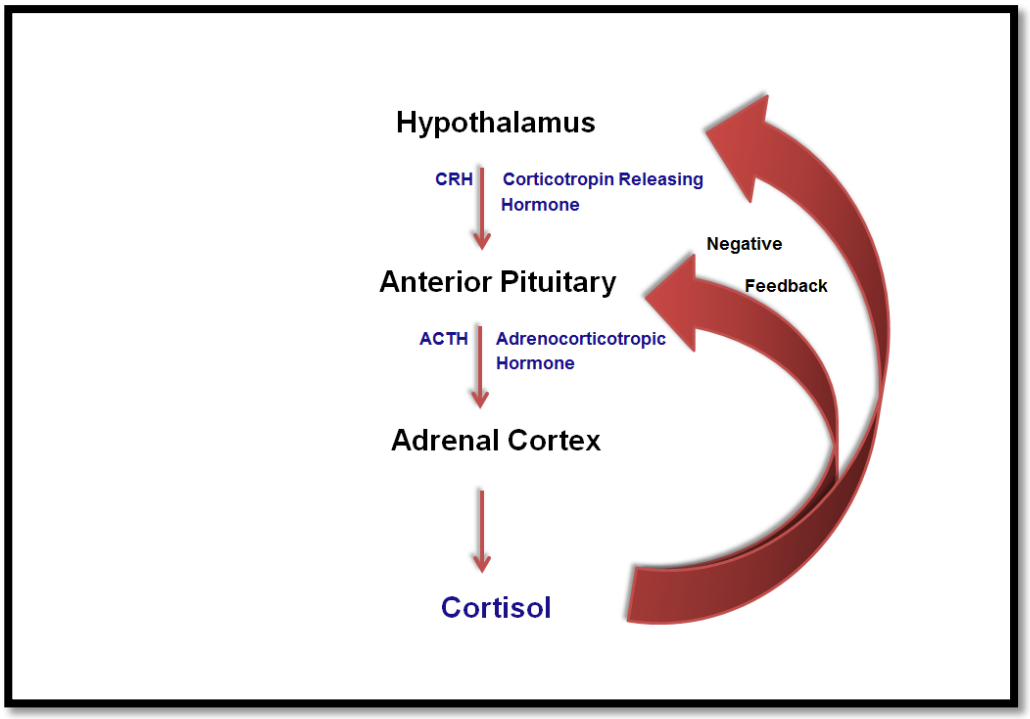

Fig. 5. Regulation of cortisol secretion by HPA axis.

Three chemical messengers are released from HPA axis upon its activation. The binding of these messengers to their corresponding receptors result in secretion of cortisol from adrenal cortex. HPA axis: hypothalamic

pituitary adrenal axis, CRH: corticotropin releasing hormone, ACTH: adrenocorticotropic hormone.

Pituitary volume is reflective of HPA axis structure and function, stress and psychosis severity. Greater perceived distress from adverse life events relates to smaller pituitary volume in people who have a first or second degree relative with schizophrenia. Greater pituitary volume associated with higher nocturnal cortisol in patients with depression or bipolar disorder. In schizophrenia, the pituitary enlarges at the prodromal and early stages and atrophies at the chronic stage. Furthermore, pituitary enlargement is associated with a minimal improvement of psychotic symptoms in early psychosis. Premkumar and colleagues have carried out a study to determine whether cognitive behavioural therapy for psychosis (CBTp) reduces pituitary volume in patients with schizophrenia, and whether pre-therapy memory relates to CBTp-led pituitary volume reduction. They hypothesized that CBTp would reduce pituitary volume and pre-therapy memory would relate to a significant reduction in pituitary volume in patients receiving CBTp. In their study, the pituitary volume was measured at baseline prior to the therapy in 40 patients with schizophrenia and 30 healthy individuals. Later on, pituitary volume was measured again 6–9 months in patients who had received either CBTp with standard care (SC) or SC alone. Both groups were compared based on the change in the pituitary volume from baseline to follow-up. The results showed that the pituitary volume was decreased over time in CBTp + SC patients. In addition, the pre-therapy verbal learning correlated more strongly with the pituitary volume reduction in the CBTp + SC group than the SC group. As hypothesized, pituitary volume reduced over time in the CBTp + SC group relative to the SC group as CBT assists patients to find stress regulation strategies and reduces cortisol level in which lower cortisol relates to lower pituitary volume. In addition, pre-therapy memory related to CBTp-led pituitary volume reduction, such that the association was stronger in the CBTp + SC group than the SC control group, because good memory in patients receiving CBTp could lower stress-related cortisol level (38).

Another research was conducted by Franzen to find the relation between the cortisol release and the severity of symptoms of schizophrenia. He studied this relation in 10 schizophrenic patients. He measured the levels of serum cortisol in these patients while they were on medication, then withdrew the medication and measured the cortisol levels again after 5 weeks. He found increase in the levels of cortisol over the last 5 weeks period which was associated with increase in psychotic episodes (40). This finding was supported by Sachar et al. who carried out similar study on 4 non-medicated patients. They measured the daily cortisol levels in urine over 2-3 month period. They reported that the cortisol levels rose significantly immediately before the psychotic periods. They were higher by 250% compared to the recovery period levels (41).

Numerous animal experiments and human researches proposed that not only cortisol but also DA release are elevated in response to stress (42). Studies have revealed that the glucocorticoids increase the activity of DA in mesolimbic system, while the DA synthesis and receptors increase through activation of HPA. In laboratory animals, the administration of corticosterone augments the rate of DA synthesis in the brain due to the corticosteroids' effects on tyrosine hydroxylase (TH), which is the main enzyme involved in the biosynthesis of catecholamine. Corticosteroids have various effects on TH, they raise not only the enzyme levels but also the rate of transcription of TH gene, the levels of TH messenger RNA, as well as the levels of TH enzyme protein (43). Several studies proposed that activation of HPA axis could alter the DA receptors. They suggested that the prenatal exposure to stress results in no change in D1 receptors, increase in D2 receptors, and declined in D3 receptors in the rats. These effects were not noticed until the animals reached adulthood (35). Antipsychotic treatments reduce dopamine level as well as corticosteroids level. Experiments showed that the longer the duration between onset of schizophrenia

and initiation of the treatment, the worse the course of the disorder and the long-term outcome. The antipsychotic treatment has a protective function, by decreasing the HPA activation that results in the reduction in elevated cortisol level associated with psychosis and inhibiting the response to biological stress which related to psychotic episodes. Therefore, the shorter the non-medicated period of the disease, the less likely of permanent changes in HPA axis; these changes can augment stress sensitivity and symptoms severity (35).

2.4 Neurodevelopmental Hypothesis

This hypothesis was presented in its current formulation by Weinberger, Murray, and Lewis nearly a quarter of century ago (44). The idea that severe mental illness disrupts the normal development of the nervous system had been discussed before, but new evidences have been found that support these findings (45). Firstly, in neuroimaging studies, abnormal brain structure was observed at the onset of the illness, so far no evidence for neurodegeneration was found in post-mortem studies. Secondly, patients with clear illness were suffering from frequent occurrence of cognitive and motor abnormalities at a young age. Lastly, research on primates have demonstrated that the neonatal lesions could have effects later on behaviour, this supports the idea that adult mental illness may have its origin in developmental stages (44, 46).

According to the neurodevelopmental hypothesis, the genetic or environmental factors during crucial early periods of development before the brain approaches its adult anatomical state have adverse impact on the adult mental health (47). It hypothesizes that schizophrenia is the behavioural outcome of an aberration in neurodevelopmental processes that begins long before the onset of clinical symptoms, and that core cognitive deficits are the outcome of an abnormal development of the brain, leading to problems in acquiring cognitive abilities (48-50). The abnormality in brain development and maturation begins prenatally, the brain cells start to generate during the fetal development in the uterus. Neurons build particular pathways in the brain during the second trimester where they start to migrate to their final positions and connect to other neurons (5). This is considered as a critical period in neuronal development, any abnormality in this stage will affect the structural organizations of the brain cells and lead eventually to the development of schizophrenia in young adulthood (Fig. 6) (51). It has been found that early motor disorders and delayed developmental milestones i.e. walking, crabbing and lifting the head are present in those children who later developed schizophrenia (52). This can be seen as early signs of neuropathology and an indication of non-specific neurocognitive abnormalities specific for schizophrenia (53, 54). Walker analysed home videos taken at the early age of people who had later developed schizophrenia and their healthy siblings. Experts who analysed the videos identified those later developing schizophrenia. They found neuro-motor abnormalities especially on the left side of the body and poor motor skills. These deviations were most prominent in the first two years of life where motor skills are developing at the fastest rate (50, 55).

Early studies in experimental neuropsychology and psychopathological research laid the groundwork for subsequent neurocognitive studies. Comprehensive studies proved that cognitive deficits are relatively stable for a long time after onset. These cognitive impairments are present in a milder form in the premorbid and prodromal phase. Moreover, there are some delays in cognitive and neuro-motor skills in those children who later develop schizophrenia. These findings provide solid evidence that there is no neurodegeneration in schizophrenia, and that this disease fits better into what is called a neurodevelopmental disorder. But we still have a limited understanding of what triggers the deviant development in cognitive functioning, and why symptoms do not appear before early adulthood (50).

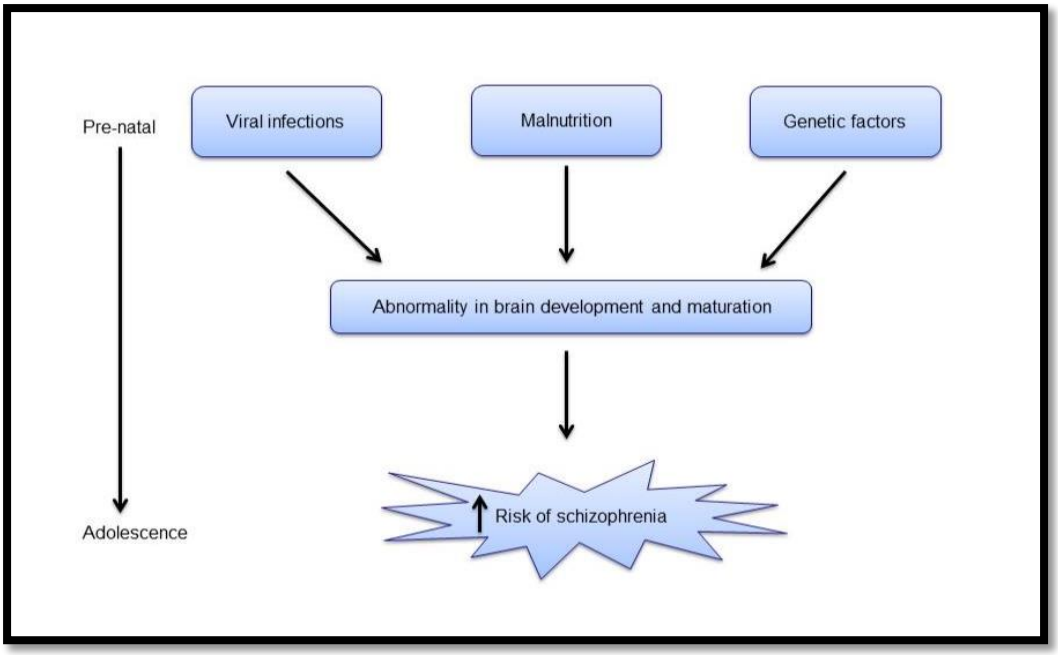

Fig. 6. Neurodevelopmental model of schizophrenia. The adverse impact of genetic or environmental factors on brain maturation during prenatal period and development of schizophrenia.

2.4.1 Risk Factors for Schizophrenia that Impact the Early Brain Development

2.4.1.1 Vitamin D Deficiency

The link between vitamin D deficiency and a wide range of psychiatric illness has become an area of interest for researchers. Prenatal vitamin D deficiency has been suggested as a risk factor for schizophrenia. Evidence from rodent experiments demonstrates that persistent change in the structure and neurochemistry of adult brain results from transient prenatal deficiency in vitamin D (56). In the period between 1988 and 2013, 19 studies were reviewed by one meta-analysis. This review found a strong relationship between schizophrenia and deficiency in vitamin D. In these studies, 2,804 patients with schizophrenia have participated, more than 65% of the patients had deficiency of vitamin D. Individual with vitamin D deficiency are 2.16 times at higher risk of developing schizophrenia compared to individual with sufficient vitamin D (57).

The risk of schizophrenia and status of vitamin D is affected by birth season, high latitude, and skin pigmentation (58). Individuals who are born in winter are more likely to develop schizophrenia later due to reduced exposure to the UV rays that are required for the synthesis of vitamin D. The new-borns in January and February are exposed to lower UV radiation levels during their prenatal and perinatal period. The rate of schizophrenia rises also at high latitudes; this may again be due to lower UV availability and status of vitamin D. At higher latitudes, a comparison between dark-skinned individual and lighter skinned individual shows pronounced reduction in vitamin D in dark-skinned individual, because the individual with lighter skin has less melanin, this allows more effective absorption of UV rays by the skin (Figure 7). It is estimated that at higher latitudes darker skin individuals are more likely to have schizophrenia than the general population (59).

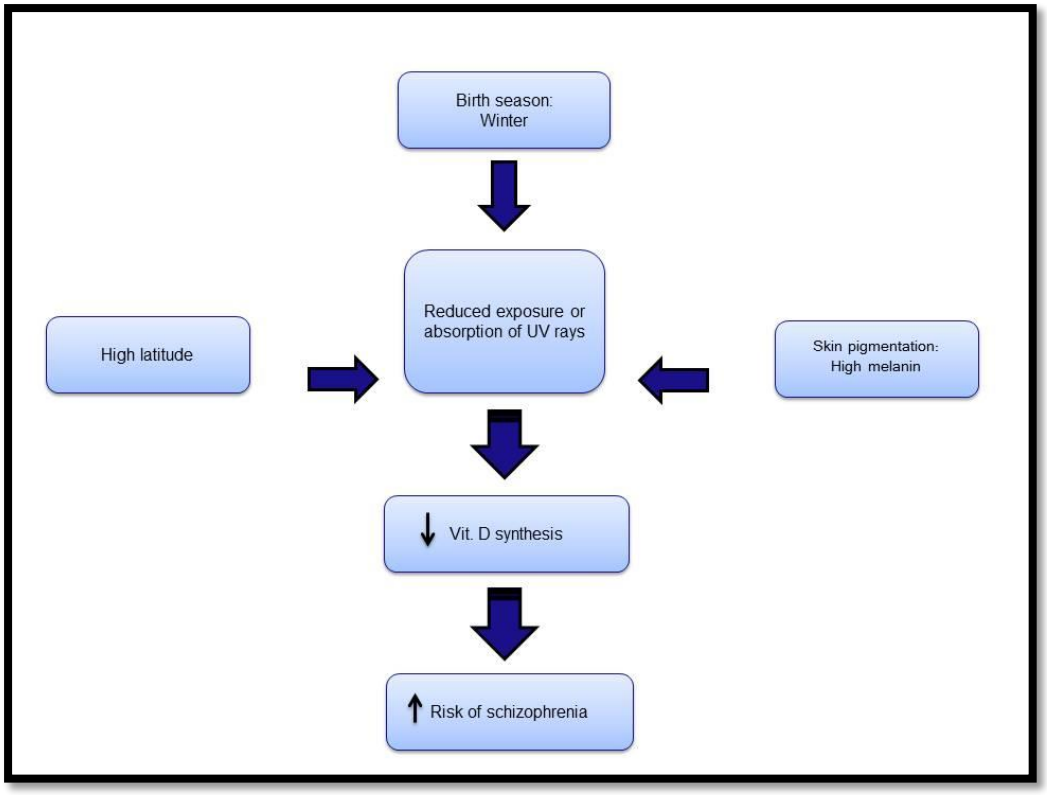

Fig. 7. The link between Vit. D deficiency and risk of schizophrenia. Effect of birth season, high latitude, and skin pigmentation on the status of Vit. D and schizophrenia.

2.4.1.2 Iron Deficiency

Evidence suggests that prenatal nutritional factors may play role in the etiology of schizophrenia (60). During pregnancy, the maternal iron deficiency is the most common nutritional deficiency that adversely affects neurodevelopment which might lead to the development of schizophrenia. Iron is important for the development and maintenance of the functions and structures of the brain, it is essential for myelination and dopaminergic neurotransmission (61). Iron deficiency leads to anemia, where the mother's oxygen-carrying capacity is impaired which results in the reduction of oxygen delivery to the fetus and might cause neurodevelopment disruption through its effect on birth outcomes (62). The risk of iron deficiency depends on the imbalance between iron supply and demand. Research has been conducted on the effect of failure to meet the iron requirements of developing brain on the possibility of developing psychiatric illness. Studies reported that the possibility of developing schizophrenia-spectrum disorder (SSD) in the offspring of low maternal haemoglobin concentration (≤ 10.0 g/dl) is higher by 4 fold compared to the offspring of maternal with mean concentration (≥ 12.0 g/dl). This proposed that the maternal iron deficiency is a risk factor for developing (SSD) among offspring (61).

2.4.1.3 Infection

Over recent decades, evidence demonstrating the relation between prenatal infection and increased risk of schizophrenia has been accumulated (63). The risk of schizophrenia is raised among individuals with prenatal exposure to influenza, rubella, or toxoplasmosis gondi (64). Initially, this evidence was based on ecologic studies,

but recently more studies access the biobanks to examine these hypotheses in analytical settings (56). Individuals who were exposed to infection or immune activation during their fetal life have higher risk of abnormalities in the brain structure and function related to schizophrenia (65). The link between prenatal infections and schizophrenia might be explained by cytokines and chemokines, which are known to mediate the host response to infection. A birth cohort study in northern California concluded that the level of chemokine interleukin-8 in second-trimester pregnant women was 2 fold higher for offspring who developed schizophrenia later compared with controls (66). Yolken and co-workers applied a number of laboratory techniques to examine the effect of infection on the development of schizophrenia. They tested the cerebrospinal fluids (CSFs) that obtained from patients with early stage of schizophrenia. They found increased rate of transcription of HERV-W which is an endogenous retrovirus in the RNA extracted from these fluids. The HERV-W transcription was detected in 30% of the patients with recent onset of schizophrenia and 5% of patients with chronic disease. A number of infectious agents can activate the transcription of endogenous retroviruses. Yolken et al. also examined the presence of active infection in different stages of schizophrenia. The results of their study reported that increased levels of Toxoplasma gondii's antibodies were found in individuals with recent onset of schizophrenia. They also found that serological evidence of infection with Toxoplasma gondii and Herpes Simplex Virus type 1are related to increased levels of cognitive impairments in patients with early stage schizophrenia (67).

In childhood, the CNS viral infections have been linked to increased risk of adult psychotic illness via two mechanisms, direct effects of pathogenic microorganism, and the effects of inflammatory response on the brain (68). Inflammation leads to release of peripheral inflammatory cytokines, including IL-6 or tumor necrosis factor alpha (TNF-α), these cytokines communicate with the brain via three different ways: vagus nerve, active transport, or enter through a leaky circumventricular area in blood-brain barrier. When these inflammatory cytokines reach the brain, their signals stimulate the microglia to secrete local inflammatory mediators (cytokines, chemokines, and proteases) from their monocyte and macrophage lineage. These local inflammatory mediators have several effects: First, they affect the function of the neurons and synaptic plasticity, second, alter the metabolism and reuptake of neurotransmitters i.e. dopamine and serotonin. Finally, they stimulate the HPA axis (69). In older adults, the cognitive and functional decline after systematic infection might be associated with a systematic proinflammatory response in the brain (70). The activation of peripheral immunity in healthy volunteers showed raised levels of circulating cytokines, induced anxiety, low mood, and declined cognitive performance (65).

2.4.1.4 Advancing Paternal Age

Advanced paternal age has been linked to a range of neurodevelopmental disorders including autism and schizophrenia (56). During early childhood, the offspring of older fathers have impaired neurocognitive development. A meta-analysis demonstrated that the risk of schizophrenia increased in the offspring of older fathers (aged $\geq$ 30 years) compared with younger fathers (aged $\leq$ 29 years) (71). The greatest risk was found in fathers aged $\geq$ 50 years. Moreover, it was reported that schizophrenic patient without family history of schizophrenia is more likely to have older father than schizophrenic patient with family history of the disease. Therefore, advanced paternal age is argued to be critical risk factor for schizophrenia (72). Wu and colleagues studied the relation between advanced paternal age and schizophrenia. Their research was conducted in a Chinese Han population where 351 schizophrenic patients and 238 healthy volunteers were participated in their study. They investigated the effect of age and sex on the risk for development the illness in the offspring. The result of the study reported an association between advanced paternal age and increased risk for

schizophrenia, and the risk for the illness in offspring both grew in synchrony with advanced paternal age. They found that the higher risk of schizophrenia is associated with later beginning of fatherhood, where the risk of the disease rose from 2.660 to 10.183 in the paternal age range of 30-34 and ≥ 35. On the other hand, they found no association between maternal age at birth and increased risk for schizophrenia in offspring. They also found that there is no significant difference in the effect of advanced paternal age and risk of development schizophrenia in the male and female offspring (73). This finding was supported by another population based cohort study that conducted by Sipos et al. where they also reported no difference in the effect of advanced paternal age on the risk of schizophrenia for both male and female offspring (74). However, the mechanisms behind these linkages remain unclear, but several hypothesised mechanisms suggest that there is a causal relation, whereas others argued that the linkage can be explained by unmeasured disturbing (75).

3. CONCLUSION

This review presents a summary of the available hypotheses and theories that are related to schizophrenia. Each hypothesis proposes a different mechanism that might involved in the development of the illness. The dopamine hypothesis suggests that the schizophrenia develops due to dopamine abnormality in basal ganglia. This theory was supported by the fact that so far D2 receptor antagonists are considered the best available treatment for schizophrenia. As for NMDA hypo activity hypothesis, it has been argued that NMDA hypofunction involves in the pathophysiology of the disease due to the fact that NMDA receptor antagonists produce schizophrenia-like symptoms in healthy individuals. In addition, an increased level of NAAG and decreased level of GCPII were found in brain individuals with schizophrenia. These two theories provided insufficient facts about the etiology of the disease, which led to a conclusion that it is most likely a combination of both theories might explain the etiology of schizophrenia since both neurotransmitters have influence on each other. Later on, a new theory was developed which pointed to the role of genetic and environmental factors in the pathophysiology of schizophrenia. This hypothesis was known as a neural diathesis-stress model of schizophrenia. However, evidences form genetic studies indicated that the adult mental illness may have its origin in development. As a consequence, additionally, to neurotransmitter dysfunction, receptor hypofunction, and environmental factors, other causes may play a role in the etiology and course of schizophrenia i.e. vitamin D and iron deficiencies, infection, paternal age and etc. All these factors are required to be investigated in order to provide a new hope for the people suffering from the illness. Numerous studies are in progress to find the exact pathophysiology of schizophrenia, but despite such progress, there are still many questions that need to be answered. Why it takes more than two decades for the symptoms to be developed? Why the disease not noticed until the patient reach adulthood? What are the exact changes that happened in the brain? All these questions and more require to be answered in order to help us in developing the appropriate therapy for treating the disease.

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الفصام: آلية المرض المبهمة

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ملخص

الخلفية: يعد مرض الفصام واحدا من أشد الاضطرابات التي تعيق حياة الأشخاص المصابين بالمرض. على الرغم من معدل انتشاره المنخفض، إلا انه يؤثر سلبًا على حياة المرضى، عائلاتهم والمجتمع. تعالج مضادات الذهان المتوفرة حاليا الأعراض الإيجابية فقط، ولكنها لا تحسن الأعراض السلبية أو المعرفية لمرض الفصام. لذلك، يتم إجراء أبحاث مكثفة من أجل اكتشاف مركبات داوئية جديدة لمعالجة مرض الفصام والسيطرة على أعراضه لكن لن يتحقق ذلك إلا من خلال الفهم الكامل لآلية المرض المبهمة.

الطرق: لقد تمت مناقشة أربعة فرضيات تشرح الآليات المحتملة التي قد تكون متضمنة في تطور مرض الفصام في هذه المقالة حيث تمت الإشارة إلى تأثير نقص فيتامين دال والحديد، الإصابة بالالتهابات، بالإضافة الى عمر الآباء على احتمالية إصابة الأبناء بمرض الفصام، وقد تم أيضا مناقشة بعض الدراسات السريرية ونتائجها.

النتائج: لا يزال السبب الرئيسي للإصابة بمرض الفصام غير معروف بشكل دقيق. حيث تشير بعض الدراسات ان المرض قد يحدث نتيجة لخلل في الناقل العصبي، أو نقص في الأداء الوظيفي للمستقبلات، أو العوامل البيئية، أو عوامل أخرى قد تلعب دورًا في ظهور هذا المرض وتطوره.

الخاتمة: كل العوامل التي تم مناقشتها في هذه المقالة قد تكون سببا في حدوث مرض الفصام، مع ذلك يجب التحقق من دور هذه العوامل في ظهور المرض من أجل توفير أمل جديد للأشخاص الذين يعانون من مرض الفصام، لذلك فان العديد من الدراسات الحالية تهدف لمعرفة الفيزيولوجيا المرضية الدقيقة للفصام، ولكن على الرغم من هذا التقدم، لا تزال هناك العديد الأسئلة التي يجب الإجابة عليها لتساعدنا في تطوير العلاج المناسب لهذا المرض.

الكلمات الدالة: مضادات الذهان، الإعاقة، الفرضيات، الآليات، الفصام.

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