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Review Article

Metabolic and Molecular Aspects of Schizophrenia: A Review

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Abstract

Despite decades of research, the causes and biology of schizophrenia remain unknown. The condition is associated with metabolic symptoms such as hyperinsulinemia, dyslipidaemia, type 2 diabetes (T2DM), and obesity. These sensations are a prevalent side effect of the new antipsychotic medications. Nevertheless, metabolic dysfunction in schizophrenia has been studied before the antipsychotic phase, and it has also been documented in patients with first- onset schizophrenia prior to antipsychotic treatment. We investigate the evidence for metabolic abnormalities in schizophrenia patients, both in the central and peripheral nervous systems. Post-mortem brain tissue molecular analysis indicated alterations in glucose metabolism and insulin signalling pathways, whereas blood-based molecular profiling revealed hyperinsulinemia and abnormalities in insulin and co-released factor synthesis after the development of symptoms. Yet, such features are not seen in all patients with the disorder, and not all people with such defects have schizophrenia symptoms. One explanation of these facts is the presence of an underlying metabolic sensitivity in a subset of persons that interacts with environmental or hereditary factors to create the disorder's overt symptoms.

Keywords: Schizophrenia, Hyperinsulinemia, T2DM, Metabolism, Genetics.

INTRODUCTION

Schizophrenia is a chronic idiopathic neuropsychiatric illness which affects the patient's social and professional life [1]. The lifetime morbid risk of Schizophrenic patients is roughly one percent [2]. The disease is characterised by positive symptoms such as lack of insight, hallucinations, delusions, thought disorders, etc. and negative symptoms including demotivated and disorganized behaviour, reduced emotional behaviour, anhedonia etc. [3]. The processes driving the development, relapse, symptomatology, and management of schizophrenia (SZ) have eluded researchers for many years [4]. Schizophrenia patients have anomalies in brain glutamatergic metabolism, mitochondrial metabolism and redox balance (NAD+/NADH ratio) [5].

Knowing that schizophrenia is indeed a neurological condition characterised by brain functional impairments and neurochemical changes, and at least two neurotransmitters i.e. glutamate and dopamine have emerged as major contenders for its neuropathophysiology [6]. N-methyl-D aspartate receptors hypofunctional on -aminobutyric acid interneurons in the prefrontal cortex, which cause glutamate transmission to the ventral tegmental region to be overactivated or downregulated, may result in higher dopamine via the mesolimbic pathway in the ventral striatum. Positive symptoms of schizophrenia are hypothesised to be connected with evidence of enhanced synthesis capability of dopamine or dopaminergic mesolimbic circuit's hyperactivation [7]. Other neurotransmitters and neuropeptides involved in the neuropathophysiology of schizophrenia include oxytocin, cortisol, serotonin, cannabinoid, neurotensin, GABA, neuropeptide Y, corticotropin-releasing factor, cholecystokinin and orexin [8, 9]. When compared to the healthy individuals, people with schizophrenia have a hazard ratio of 3.1 for standardised mortality [10] and

14.5 years i.e. a weighted average life expectancy [11]. Obtaining full remission of symptoms is one of the most difficult tasks in people with schizophrenia, despite the fact that they have a high degree of illness stability and their symptoms tend to remain stable over time [12]. Over the previous two decades, there has been a significant improvement in years of possible life loss for people with schizophrenia due to suicide and accidents. However, this progress has been offset by an increase in the number of life-years lost due to preventable chronic physical disorders [13, 14].

Subjects with schizophrenia have hypertension, a heightened risk of heart disease, hypercholesterolemia, elevated concentrations of deposition of visceral fat, insulin resistance (IR), poor glucose tolerance, and T2DM [15]. The greater proportion of metabolic syndrome correlated with psychiatric diseases is primarily determined by characteristics such as the population's average BMI, age, and ethnicity [16]. Improved diagnostic along with therapeutic options depend on an approach i.e., personalised medicine, could result from a better knowledge of the function of metabolic disturbances in schizophrenia and their link with mental symptoms. Though the brain accounts for 2% of total body mass only, it is predictable that it can use up to 65% of total daily glucose consumption provided by the peripheral [17]. Homeostasis of glucose is ultimately monitored by central nervous system (CNS) mediated by leptin and insulin signalling mechanisms, as well as the impacts of other diffuse neuroendocrine system components. Thus, peripheral and CNS metabolic activities are fundamentally related.

Schizophrenia is thought to be caused by a number of variables including genetic, environmental, and societal influences [3]. In fact Gene-environment interactions and epigenetic alterations may be a part of the overall risk, according to recent studies [18, 19]. The detail of these factors is shown in Table 1.

Table 1

Factors responsible for schizophrenia	Types	Reference
Environmental	Drug abuse, viral exposure	[3]
adverse gestational events	Perinatal hypoxia, maternal infection, obstetric complications	[20]
Genetic	Mutation in genes involved in neuron development	[21]
Societal atmosphere	Migration, persecution, isolation, urban life style physical abuse, ethnic minorities	[22] [23]

Genetic Discernment of Schizophrenia

Two methods i.e. Linkage statistics and logarithm of the odds ratio (LOD) score are popularly used to determine the gene involved in any disease [21] . Schizophrenia very rarely exhibits traditional Mendelian inheritance patterns and majority of schizophrenia cases are still sporadic in the general population [24]. There are several hypothesis such as missense and nonsense mutation in D5 dopamine receptor gene play crucial role in the development of schizophrenia [21].

Our knowledge of the molecular genetics of schizophrenia is rapidly evolving due to genome-wide research [24]. However, finding the genes and DNA markers for Schizophrenia is still a challenging task as multiple genes associated with this disorder and each gene only minimally affects phenotype. Linkage based molecular genetic studies suggested that there are various locus on chromosomes which can be utilized as DNA markers for detection of Schizophrenia (Table 2). For instance, The role of 22q11.2 deletion is found to be clinically relevant for Schizophrenia [2]. Further, quantitative Reverse Transcriptase Polymerase Chain Reaction (RTPCR) and Western Blot analysis based data suggested that altered expression of (CAP2) mRNA and Cyclase-associated protein 2 levels are also associated with Schizophrenia [25]. Moreover, mutation in genes involved in neuronal metabolism and brain development also play crucial role in the development of Schizophrenia. For instance, SETD1A, a histone methyl transferase gene is linked to the schizophrenia as its mutation leads to its loss of function which further reduced the neuronal development [26].

However, mutation of multiple genes is involved in the development and progression of Schizophrenia but not all population exhibit similar gene mutation. For example mutation in gene NRG 1 is most prevalent in Icelandic and Scottish population [27].Similarly, deletion mutation in α-7 nicotinic receptor gene is widely seen in US population.

Table 2 described some important gene and their functions and mutation associated with schizophrenia disease.

Table 2

Location of gene	Gene associated	Type of mutation	Function	References
15q13–q15	α-7 nicotinic receptor gene	Deletion	Neuronal death/survival and synaptic plasticity.	[21, 1],
11p15	tryptophan hydroxylase (*TPH*) and	Point mutation	TPH maintains the serotonergic functions by limiting biosynthesis of 5-HT	[21, 28]
11q23	D2 dopamine receptor gene (*DRD2*)		*DRD2 participate in* neuronal signaling and inhibits adenylyl cyclase activity	[21]
22q11	catechol-*O*-methyl transferase (*COMT*)	Deletion	metabolizing various catecholamine neurotransmitters, such as epinephrine and dopamine	[2]
8p22–p21	neuregulin 1 (*NRG1*)		participates in glutamatergic signaling by regulating the N-methyl-D-aspartate (NMDA) receptor	[3]
6p22.3	dysbindin (DTNBP1)		Neuronal development,	[19]

Indicators of Metabolism in Schizophrenia

Current investigations of individuals with schizophrenia have directly examined metabolic indicators such as glucose of blood and insulin levels, either at the time of onset prior to treatment of antipsychotic or in persistently sick drug-free patients. Interestingly, one of these investigations [29] discovered reduced glucose tolerance in first degree relative's patients as compared to controls, and results was repeated in additional small study [30]. Hyperinsulinemia and IR have also been found in patients with antipsychotic naive [31, 29, 32] and drug-free chronic [33, 34] schizophrenia, as well as first-degree relatives of schizophrenia patients [29]. Surprisingly, the majority of these individuals' metabolite profiles normalised after a nine-day course of antipsychotic medication. A following research [35] looked at metabolic variables in first-episode individuals during 10 days of antipsychotic medication and did not observe any significant changes in any variable, comprising lipid metabolites, baseline glucose, insulin levels, and glucose tolerance, among patients and control subjects. Studies on peripheral cells collected from schizophrenic patients have also revealed metabolic abnormalities. Microarray investigation of glucose-deprived lymphoblastoid cells revealed that glucose responsive genes were expressed differently in patients with schizophrenia as compared to controls [36]. We recently performed proteome profiling of stimulated peripheral blood mononuclear cells (PBMCs) and discovered aberrant expression of glycolytic proteins among drug-naive schizophrenia patient's cells versus controls, implying a functional impairment in glycolysis [37]. This conclusion was corroborated by higher intensities of the glucose transporter-1 (GLUT1/ SLC2A1) while lower intensities of the insulin receptor, implying that certain patients with schizophrenia may be IR, at least in the early stages of the condition.

Secretion of Insulin in Schizophrenia

Another recent research revealed that 66 first and current onset individuals with schizophrenia had greater concentrations of various proteins and co-peptides released with insulin from beta cells of pancreatic than 68 control subjects [38]. These molecules were recognised as des 31,32 proinsulin, mature insulin, , chromogranin A (CHGA), and C peptide. Interestingly, author noticed that the growth of these compounds was frequently linked with extremely low glucose concentrations. Higher CHGA and insulin levels were seen in a current follow-up study of 236 antipsychotic naïve patients with schizophrenia vs 230 control participants, despite the fact that levels of glucose were not documented for the majority of individuals [39].

The Effects of Metabolic Changes on Brain Function

For knowing the relationship among peripheral and CNS mechanisms of metabolic homeostasis with schizophrenia, as in other neuropsychiatric illnesses with a metabolic component, may be crucial for developing treatment options [40]. Schizophrenia is known as the "diabetic brain condition" [41]. This has been interpreted as poor utilisation of glucose, which results in anaerobic respiration, production of lactate and tissue acidosis [42]. Nevertheless, given that neurons employ lactate in addition to glucose as an energy source, this may be an oversimplification. As astrocytes take up glucose, it's converted to lactate, which is subsequently delivered to neurons in an activity-dependent manner, which is especially important when glucose supplies are low. Lactate can even reach directly to the brain under specific situations. Peripheral fatty acid mobilisation evidence from ketone bodies has also been observed in schizophrenia [43], indicating that in schizophrenia, a scarcity of glucose might thrust the brain concerning this energy source. Prolonged dysregulation of metabolic pathways for energy might also produce

dysfunction with brain, resulting in schizophrenia-like symptoms such as decreased synaptic plasticity, decreased neuronal growth, transmission, abnormal glutamate, dopamine release, and myelination abnormalities. Variations in energy source, as well as inherent inter-individual variation in brain chemistry and connectivity, might lead to symptom presentation differences in patients with schizophrenia. This is consistent with research indicating that acute metabolic stress affects function of brain and hormonal responses differently in patients with schizophrenia than in controls, implying that these effects are connected to dopamine [44], serotonin [45], and noradrenaline function abnormalities [46].

Improper production and/ or signalling of insulin can induce peripheral as well as CNS disturbances, subsequent in straight alterations in cellular function and energy supply. The discovery that some type 2 diabetes patients and insulin resistant persons with high circulating insulin levels have diminished hippocampus sizes provides indirect evidence for the impact of aberrant insulin signalling on the brain [47]. Hyperinsulinemia has been linked to Alzheimer's disease pathogenesis, including abnormal phosphorylation of filamentous proteins, signalling molecule translocation, increased CNS inflammation, b-amyloid plaque deposition, and neuronal apoptosis [48], though GSK3 activity may vary in the converse way in Alzheimer's disease as well as schizophrenia, according to research [49].

The Role of Metabolic Dysregulation in the Development of Psychiatric Disease

This fits with the idea that schizophrenia is a multidimensional condition with subtypes presenting at the genetic, phenotypic, and molecular levels. As a result, a conservative interpretation of the findings would be that a subtype of schizophrenia is caused by a combination of systemic metabolic abnormalities and one or more additional risk factors, such as obstetric difficulties or genetic predisposition. One study compared glucose metabolism in persons with deficit schizophrenia (primarily negative symptoms) to non-deficit schizophrenia (mainly positive symptoms) [50]. When compared to non-deficient individuals, deficit patients exhibited considerably lower glucose tolerance and higher fasting insulin levels. Malnourishment, diabetes, obesity, or neuroendocrine stress throughout pregnancy can all result in metabolic dysfunction in the child, possibly due to abnormalities in the formation of the hypothalamic link [51].

Conventional Vs Molecular Diagnostic Tools

The conventional methods to evaluate Schizophrenia is positron emission tomography (PET), single photon emission computed tomography (SPECT) [5] and Magnetic resonance (MR) spectroscopy, computed Tomography (CT). Some biochemical markers such as C- Reactive protein responsible for inflammation have also been correlated with schizophrenia [52]. The conventional methods are not only indefinite but also diagnose disease at very late stage. Apart from that the conventional methods are not predictive in nature. As we are gradually shifted in the direction of preventative psychiatry, it is essential to adopt more sensitive predictive diagnostic techniques [53]. Molecular techniques such as multiplex immunoassay [53]. Polymerase chain reaction and restriction fragment length polymorphism (PCR–RFLP) methods [54], RT PCR and Western Blot methods [25] are widely used to decipher specific mutation involved in Schizophrenia disease. PCR RFLP based methods are helpful in the detection of single nucleotide polymorphism. Further, RT PCR predict the gene expression of disease related genes through evaluation of m RNA levels. Moreover, nucleotide and protein Microarray, whole genome sequencing, DNA barcoding, Next generation sequencing can also unfold the causes of Schizophrenia. The molecular techniques are able to detect Single nucleotide polymorphism (SNPs), copy number variations (CNVs), upregulation and downregulation of gene expressions, tissue specific gene expression, epigenetics etc. There are several studies available where Schizophrenia have been associated with different genes and proteins on the basis of molecular techniques (Table 3).

Table 3

Methods/ Techniques	Targets	References
Sequencing-based-typing (PCR-SBT)	major histocompatibility complex class I polypeptide-related sequence A (MICA) polymorphisms	[55]
direct sequencing of the promoter region	5' regulatory region of GABRB3 (gamma-aminobutyric acid type A receptor beta 3, subunit gene).	[56]
PCR–RFLP	DRD2 gene polymorphisms	[54]
Whole genome sequencing	Whole genome	[57]
RT PCR	**CAP2, DLG1 and ADAM10 Genes**	[25]
Western Blot	**CAP2, DLG1 and ADAM10 protein**	[25]
mRNA expression arrays	**GSE93987 and GSE38485**	[58]
Solexa sequencing, TaqMan Low Density Array and qRT-PCR	**MiRNA**	[59]
real-time PCR analysis	**Catechol-O-methyltransferase gene expression level**	[60]
Q-RT-PCR	**SNPs and CNVs of cell cycle related genes**	[61]

The molecular methods are more specific and sensitive. Further, it opens the option for genetic counselling and preventive medicine [2]. However, the Molecular techniques are expensive and required trained and expertise personal. The gene targets have been investigated which could be potentially utilized for molecular diagnosis of Schizophrenia.

CONCLUSION

Since there is no primary preventive or cure for schizophrenia, and the basic pathophysiological mechanisms underlying it are still unclear. Therefore, understanding the Molecular genetics of schizophrenia can help the modern health system to diagnose the disease in its early phase. However, the diagnosis should be appropriately sensitive, specific and inexpensive. Research should also be navigating to find new genetic markers in order to prevent progression of this devastated mental disease. Such studies will surely open the path for prediction, counselling and potential therapeutic targets for Schizophrenia.

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