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REVIEW ARTICLE

Schizophrenia as metabolic disease. What are the causes?

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Abstract
Schizophrenia (SZ) is a devastating neurodevelopmental disease with an accelerated ageing feature. The criteria of metabolic disease firmly fit with those of schizophrenia. Disturbances in energy and mitochondria are at the core of complex pathology. Genetic and environmental interaction creates changes in redox, inflammation, and apoptosis. All the factors behind schizophrenia interact in a cycle where it is difficult to discriminate between the cause and the effect. New technology and advances in the multi-dispensary fields could break this cycle in the future.

Keywords Schizophrenia · Neuroinflammation · Mitochondria · Aging · Gene-environment · Oxidative stress

Schizophrenia is a devastating developmental and chronic disease with the onset starting in late childhood (Jaaro-Peled and Sawa 2020). This complicated disorder is an outcome of gene-environment interactions (Wahbeh and Avramopoulos 2021). Nongenetic components include drug abuse, parasitic infestations and stress, are apparent risk factors for developing schizophrenia in young adults (Janoutová et al. 2016). This disease represents 1% of the population in most countries and, unfortunately, is represented in both sexes. It is well-known that schizophrenic parents are more susceptible to having schizophrenic children than others. Other than the common environmental risk factors**,** genetic and epigenetic mechanisms can explain this trend (van de Leemput et al. 2016).

The current review studies cell danger markers as a potential mechanism behind schizophrenia (SZ). It is proposed, in this review, that schizophrenia may result from known or hidden factors that induce neuronal danger responses. Hopefully, we are tracking different cell danger markers related to SZ here.

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Immune injury-inducing cell danger in Schizophrenia

There is strong evidence from postmortem brain examination of schizophrenic candidates, that neuroinflammation response is a component of schizophrenia pathology with evident increased microglial activity (van Kesteren et al. 2017; Trépanier et al. 2016). To tack this hypothesis in more depth, schizophrenia is associated with an inflammatory response in the white matter, representing aging criteria in the white matter with more activity in astrocytes and microglia (Najjar and Pearlman 2015; Wright et al. 2014). Here, it is suggested that schizophrenia has a double pathology pattern with an inflammatory senescence component and a neurodevelopmental component. The cognitive impairment is caused by a mismatch between chronological age and biological component (Wang et al. 2021). However, it is not well known whether white matter ageing induces inflammation in the brains of people with schizophrenia or quite the opposite. Studies conclude that white matter ageing is associated with blood–brain barrier defects. Such an imbalance creates disharmony between the central and peripheral immune machinery (Müller 2019). Such split may be associated with cell danger response to the genetic and environmental phenomenon.

Infection risk factor as a possible cause of Schizophrenia

As mentioned before, the immunological response has been associated with psychotic pathology. Studies suggest that perinatal viral infections may be implicated in SC

pathology. Aftab et al. (2016) claimed human endogenous retroviral infections to be a risk factor for SC's neurodevelopmental and neuroinflammatory components. Other research work demonstrated the comorbidity between hepatitis C and SZ. A recent study created a relationship between the Zika virus and SZ. Furthermore, there is strong evidence that maternal herpes simplex is another risk factor (Šprah et al. 2017; Davies et al. 2020; Pierson et al. 2020). The polymorphism in the immunoglobulin genes explains the interaction between environmental and genetic etiologies of schizophrenia. Genetic surveillance demonstrated the correlation between immunoglobulin genes and the risk of developing SC due to an incorrect response to viral infections (Pandey et al. 2016).

Toxoplasmosis has been extensively studied as a risk factor for neuropsychiatric disorders, especially SZ. Possible mechanisms include immunopathology and blood–brain barrier disruption (Xiao et al. 2018). The parasitic infestation has been considered a risk factor for SZ.

Studies demonstrated that unlucky mothers exposed to infections showed increased maternal blood levels of immune antibodies that are considered a potential cause of neuropathology. The scope of developmental disorders includes SZ, autism, and other psychiatry profile. The evidence of this hypothesis is based on experimental animal work supported by clinical statistical data (Estes and McAllister 2016). Many viruses are claimed for this chronic brain insult including flu, measles, mumps, and others (Reisinger et al. 2015). The incidence of SZ increases from 1 to 20% on maternal infectious exposure. The rates of autistic insults raise 13 times because of maternal infection. The strong association between infection and developmental injury was recorded not only by high maternal blood levels of antibodies but also by high CSF levels of cytokines (Patterson 2009). It seems that the immune system produces a variable response to pathogens in combination with other multifactorial risk factors including chronic intoxications (Knuesel et al. 2014). Indeed, it is not clear why 80% of infected mothers deliver healthy individuals (Selten and Morgan 2010). The scientists proposed autoimmunity as a model of schizophrenia to explain how diverse pathogens produce the same pathology (Endres et al. 2020). Another hypothesis concluded that SZ is a heterogeneous disorder of different pathogenesis factors (Winship et al. 2019).

Recently, during the COVID-19 pandemic, many cases infected with the coronavirus developed psychosis. The viral infection is known to induce an aberrant immune response that ends the state of neuroinflammation explaining a potential mechanism explaining psychosis (Watson et al. 2021). Individual cases in the 40 s developed new-onset psychotic episodes without any history and responded to classic antipsychotics (Kozato et al. 2021). It is important to notice that mild neuroinflammatory findings were recorded in toxoplasmosis and proposed to be part of schizophrenia pathogenesis. However, Toxoplasmosis was reported in a third of the community with no explanation of individual risk factors of specific induction of psychosis by parasitic infestation (Fuglewicz et al. 2017).

On the other hand, it was reported that SZ patients were considered a vulnerable group and more susceptible to catching corona infection. It can be said that infection increases the risk of psychosis and schizophrenic candidates are more susceptible to infection (Barlati et al. 2021).

Mitochondrial Disorders as a risk factor for SZ

Mitochondrial proteins, either nuclear transcribed or mitochondrial coded, have been implicated in the pathogenesis of SZ. These polymorphisms affect metabolic pathways and synaptic functions in SZ and bipolar disorders (Schulmann et al. 2019). Dysfunctional mitochondrial function, either inherited or induced, creates oxidative stress load and accelerates the ageing process, which has been seen in degenerative diseases, and is a component of the pathogenesis of SZ. The defective mitochondrial adaptation was associated with the inflammatory and apoptotic endpoints, suggesting that loss of function is part of SZ (Wu et al. 2019). Studies showed impaired mitochondrial activity with disrupted redox status, induced endothelial dysfunction and atherosclerosis (Morris et al. 2020). Hypo-functioning mitochondria impair synaptic trafficking, calcium metabolism, and activity of action potentials, resulting in dysfunctional neuronal activity. It can be said that schizophrenia is impaired dynamics of neurons that are essentially dependent on energy (Vanden Berghe et al. 2002; Montalvo et al. 2006).

Purigenic signaling as a mechanism is Schizophrenia

ATP and adenosine work as neurotransmitters. ATP plays the role of the excitatory transmitter, while adenosine plays the opposite. This machinery regulates energy from one side and neurons' activity, including synaptic trafficking and plasticity (Lindberg et al. 2015). ATP helps release excitatory glutamic acid, and later ATP is metabolised to adenosine as a regulatory mechanism (Burnstock 2008). The receptors affected by purines and pyrimidines are P1, P2, and P2Y. These receptors are essential for ischemia, aging, and neuroinflammation (Burnstock 2008 Optimal mitochondrial function is essential for keeping an ATP/Adenosine balance during activity and rest (Barraco et al. 1993). Disrupted mitochondrial control of pyrogenic metabolism induces increasing intracellular calcium, ending in apoptosis, hindering synaptic plasticity, a feature

of schizophrenia and other psychiatric disorders (Mattson et al. 2008; Cheng et al. 2010; Manji et al. 2012). Excess dopamine activity, an essential parameter in schizophrenia, impairs mitochondrial activity. Experiment results showed that dopamine has a negative effect on cellular metabolism, particularly complex activity (Brenner-Lavie et al. 2009).

Oxygen consumption

As mentioned before, impaired mitochondrial function, either degenerative or developmental in the case of excess dopamine, is associated with low oxygen consumption. This defective machinery is a cause of increased dissolved oxygen with increased oxidative stress creating a cycle of cell destruction, inflammation, or aging (Lu 2013).

An experimental study on cerebral organoids derived from schizophrenic candidates showed disturbed mitochondrial oxidation detected by transcriptomic analysis (Kathuria et al. 2020). Complex 1 deformities have been reported in schizophrenic patients, unlike bipolar disease. It is possible to consider reduced oxygen consumption as a marker of schizophrenia (Rosenfeld et al. 2011). Experimental transplantation of mitochondria to the forebrain to animals showed an improved psychotic profile at the level of proteomic level. The transplantation of the healthy mitochondrial was considered a therapeutic test of the schizophrenic animal model (Ene et al. 2022). An extensive study on a family suffering from SZ showed higher mitochondrial bulk, increased lactate level in the blood, and low mitochondrial DNA. The mitochondrial enzymes were defective and the oxygen consumption was low (Torrell et al. 2017).

The NMDA receptors are downregulated in SZ candidates and these findings in conjunction with decreased antioxidant capacity are associated with disturbed redox balance, oxidative stress, and neuroinflammation (Beeraka et al. 2022).

Studies showed that exercise improved the performance of SZ candidates and recommended strength exercise as adjuvant therapy (Keller-Varady et al. 2016). MRI examination of sports-practicing SZ patients showed evidence of improved structural changes in the hippocampus (Malchow et al. 2016).

Cysteine and sulfur metabolism

Glutathione synthesis depends on cysteine as a substrate. This amino acid is considered a semi-essential amino acid, produced endogenously and supplied by food. The endogenous source comes from the essential amino acid methionine. The process of glutathione synthesis is essential for both the antioxidant capacity and methylation of the DNA, which is a crucial factor in epigenetic risk factors in many diseases, including SZ. (Matsuzawa et al. 2008; Aldini et al. 2018).

Cases suffering from homocystinuria manifested with lens dislocation and mental retardation. These patients developed schizophrenic criteria in adolescence. The mechanism behind psychosis can be explained by the fact that methionine and homocysteine with the oxidation product as agonists for the excitatory glutamate receptors (Eschweiler et al. 1997). These psychotic episodes do not respond to conventional antipsychotics. Vitamin supply of folic acid and pyridoxine improves the delusional spectrum (Colafrancesco et al. 2015).

Vitamin D metabolism

Studies raised concern about the role of Vitamin D deficiency in the pathogenesis of SZ. Normal levels of vitamin D are essential for brain development in neonates. Experimental animal depletion of neonatal vitamin D altered the dopaminergic system in a manner comparable to SZ pathology (Cui et al. 2021).

Vitamin D3 is generated by the effects of skin sun exposure in addition to dietary sources. This vitamin is subjected to hydroxylation into active vitamin D that can pass through the blood–brain barrier and bind the vitamin D receptors (Eyles et al. 2005; Cui et al. 2013). On exposure to cell stress, the activity of the mitochondrial 24 hydroxylase increases, contributing to vitamin D deficiency. This emergency condition may explain the inflammatory status associated with SZ (Kivity et al. 2011; Shanmugasundaram and Selvaraj 2012).

Folic acid and B12 metabolism

Early-onset psychotic patients have been examined for folic acid, vitamin B12, and cortisol level assays. Those untreated candidates suffered from low folate and vitamin B12, in contrast to higher cortisol and homocysteine levels, suggesting cellular stress as part of the neuropathology. To complete the picture, SZ is associated with dietary insufficiency with lower levels of B12 and folate, creating a cycle of vitamin depletion (Kale et al. 2010; Yazici et al. 2019). The mitochondrial Krebs cycle, methylation of DNA or histones, and methionine synthesis are all linked to folic acid and B12 (Naviaux 2008; Smiraglia et al. 2008).

Genetic polymorphism of genes involved in vitamin B12 absorption and metabolism has been claimed to cause cognitive decline in psychiatric disorders like SZ. Further studies are needed to explain the possible mechanisms (Mitchell et al. 2014).

Metabolomics features in Schizophrenia

The metabolic profile of SZ showed accelerated ageing and inflammatory response. These data are supported by proteomic studies (Campeau et al. 2022). An experimental study

examined the metabolic profiles of chronically hospitalised SZ candidates and showed lower glutamate and urea cycle metabolism (Okamoto et al. 2021). On the other hand, a research study showed increased glutamate metabolism in SZ and, at the same time, lower polyunsaturated fatty acids, vitamin E, and creatinine. The differences in glutamate metabolism suggest heterogeneity of SZ, or the presence of different phases of the pathology over time (Davison et al. 2018. Even with antipsychotic treatment, the amino acid metabolome was altered, suggesting redox, inflammation, lipid peroxidation, DNA damage, mitochondrial injury, and apoptosis pathways. The metabolomics profile showed decreased plasma levels of valine, aspartate, citrulline, glycine, arginine, and ornithine in schizophrenic patients (Davison et al. 2018).

Microbiota and Schizophrenia

Experimental fecal transplantation of microbiota from schizophrenic patients to mice, showed significant alterations in the animal behavior corresponding to SZ. The animal brain had abnormal tryptophan and dopamine activity (Zhu et al. 2020). Gut flora was a critical factor in oxidative inflammation and the permeability of the intestine, making a model for what happened distantly in the brain (Konjevod et al. 2021). The gut-brain axis is strongly linked to SZ. The process of the pathogenesis of psychosis was associated with changes in the gut microbiome. Adjuvant therapy with probiotic therapy has not been proven for SZ. Such a line of treatment partially modifies the pathology. The activity of the intestinal flora was associated with a concurrent modification of the inflammatory status of the brain. It is not clear what the causal relationship of this axis is (Mangiola et al. 2016; Helaly et al. 2019; Samochowiec and Misiak 2021). Enterobacteriaceae and Enterobacteriods strains were associated with high-risk SZ in contrast to Gammaproteobacteria. These results could be related to Flora's production of serotonin. Excess serotonin-producing strains were more related to increased rates of SZ (Zhuang et al. 2020).

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Metals and Schizophrenia

Exposure to heavy metals for a long time, like lead and arsenic, is blamed for being associated with an increased risk of SZ. In utero and young, exposure to these oxidative pressures may induce neurodevelopmental-aging combinations of the SZ pathology (Opler and Susser 2005, Ma et al. 2019). Furthermore, sustained metal toxicity creates chronic inflammatory status in the brain and impaired dopamine receptor function. Neuroinflammation and disrupted dopamine function are core mechanisms in SZ, arsenic has extra hyperphosphorylation of the cytoskeletal proteins, contributing to degenerative diseases in the brain (Finefrock et al. 2003; Vahidnia et al. 2007; Jomova and Valko 2011).

Nutritional metals like iron are essential for dopamine signaling, synaptogenesis, and myelination, energy metabolism. Several studies have found a link between iron deficiency during pregnancy and an increased risk of SZ later in life (Bastian et al. 2020; Maxwell and Rao 2021).

The causality of Schizophrenia

In summary, schizophrenic patients have cell stress for many interacting causes, whether genetic or environmental. Indeed, it is part of a metabolic disease with an energy disorder. However, the cause-effect is challenging to analyze. Many pathological elements can be both a cause and an effect at the same time, making the

Table 1 Showed a summary of Insilco studies in relation of SZ

Type of study	Insilco	References
Immune	Gene mutations associated with aberrant immune response	Tsavou and Curtis 2019
infection	Dihydroorotate dehydrogenase (DHODH) is a target for SZ and COVID-19	Berber and Doluca 2021
mitochondria	*Celastrus paniculata* extract is known to modulate ATPase function	Venkataramaiah 2020
Methylation	APC, CACNB2, and PRKN, genes-and transcription factors, such as FOXO1, MYB, and ZIC3	Forero and González-Giraldo 2020
Catecho-lamine metabolism	Animal and in silico studies showed impaired metabolism of biological amines	Venkataramaiah et al. 2021
bioavailability	Sulpiride has low bioavailability that increases the toxicity	Kecel-Gunduz et al. 2020
metals	Copper and Iron is implicated in the pathology of neurodegenerative disease and also in SZ	Kumar et al. 2019

Table 2 Showed summary of studies done on SZ either clinical or non-clinical exploring the pathogenesis and the possible risk factors

Type of study	In vitro	preclinical	Clinical study
immune	Maternal immune response disrupts neural progenitor cells (Couch et al. 2021)	T regulatory cells I a new model to treat psychosis (Corsi-zuelli et al. 2021)	SZ patients have higher blood levels of IL8 (Arabska et al. 2022)
infection	Type coxsackieviruses induce psychosis after children's infection (Jmii et al. 2021)	Maternal pathogens stimulate endocannabinoids to produce a model of psychosis (Guo et al. 2018)	Anti-inflammatory drugs have a potential role in treating psychosis (Khandaker et al. 2015) COVID-19 induced psychosis (Watson et al. 2021)
mitochondria	Stem cells model to test mitochondrial function in SZ (Srivastava et al. 2018)	Clozapine support mitochondria in an animal model of SZ (Amiri et al. 2021)	1- Post mortem brain study in SZ showed a 40% decrease of content mitochondria in the caudate nucleus and putamen (Roberts 2017)
Vitamin	The carbonyl stress was demonstrated in in-vitro studies suggesting pyridoxal in the development of SZ (Arai et al. 2014)	Vitamin deficiency showed brain defects in the animal model for psychosis (Schoenrock and Tarantino 2016)	Vitamin D deficiency may be a risk to develop SZ in children later on (Cui et al. 2021) Vitamin D defects increase the susceptibility to COVID-19 (Viani-Walsh
Microbiota	High-resistant colonies of amoebic blastocysts derived from SZ were tested in vitro (Franklin et al. 2022)	Germ-free animals are used to test the effective probiotic therapy for psychiatric disease (Luczynski et al. 2016)	An altered microbiome has been linked to SZ (Li et al. 2021) Probiotic therapy improves the metabolic profile of olanzapine treatment of SZ (Pu et al. 2021)
Metal	Zinc modulates synaptic activity in excitatory neurons of neurodevelopmental disorders (Arons et al. 2016)	Zinc altered the hippocampus function in the SZ model (Camacho-Abrego et al. 2021)	Heavy metal intoxication was associated with neurotransmitter disturbance in psychiatric disorders including SZ (Cao et al. 2020)

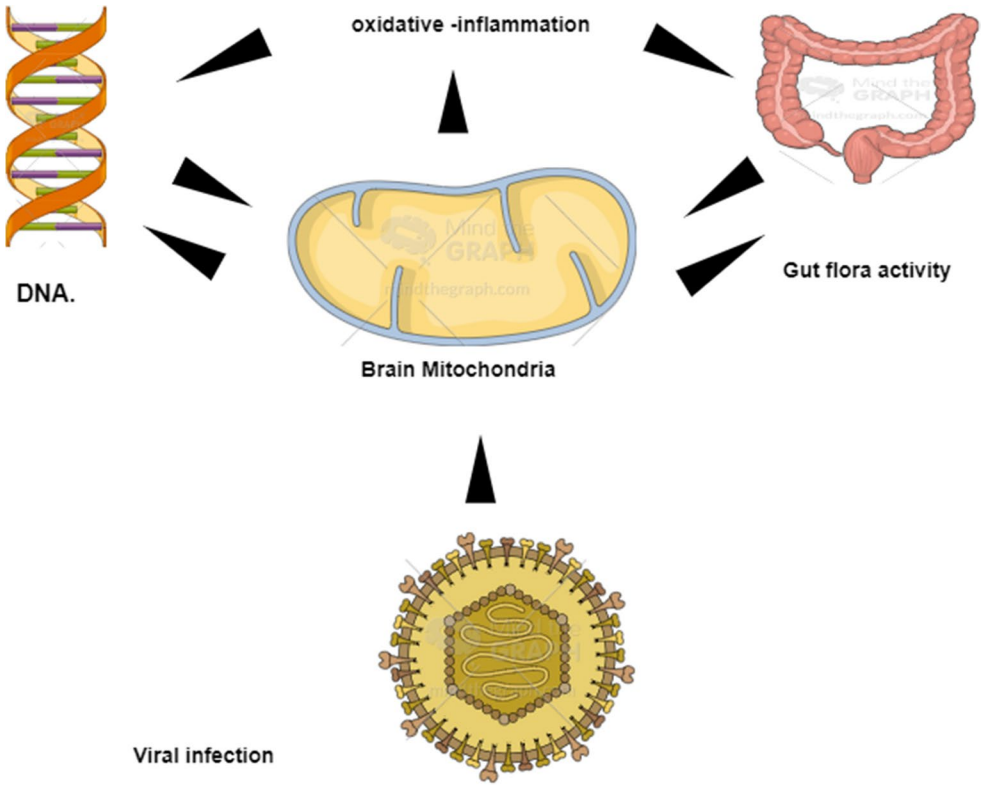

Fig. 1 Showed the interaction between causes and effects in relation to SZ

etiology of this profound disorder and other chronic diseases difficult to determine. Here, we hope for advances in physics to provide a new perspective. The discovery of gravitation waves in 2015 can explain or add a new horizon to understanding space–time at the molecular level (Vitale 2021). It is postulated that a strong gravitational field can modify the dynamics and energy functions of the cells. It is possible to track the medical records of psychiatric patients, the visits to the clinics, and the relapse in a timetable in correlation to the activity of LIGO records, hoping to create an association. This hypothesis can explain the dual pathology of SZ as the candidates suffer from biological ageing and developmental components at the same time. The activity of Wnt signalling in SZ supports the trophic component (developmental) (Inestrosa et al. 2012) (Tables 1 and 2, Fig. 1).

Conclusion

Schizophrenia is a developmental disorder with associated cell danger factors. It is not known what is the starting point of that response like any multifactorial disease. Multiple factors like an immune response, infection and mitochondrial dysfunction have been proposed to explain SZ. Metabolic abnormalities of cysteine, Sulphur were suggested as a theory of psychosis besides vitamin deficiency. New tools in physics could add potential explanation to solve the such dilemma. Gravity risk factor may open new scope to overcome such chronic psychiatric diseases.

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Code availability (software application or custom code) Not applicable

Declarations

Ethics approval (not applicable)

Consent to participate (not applicable)

Consent for publication (not applicable).

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