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Defects in bioenergetic coupling in schizophrenia

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Abstract

Synaptic neurotransmission relies on maintenance of the synapse and meeting the energy demands of neurons. Defects in excitatory and inhibitory synapses have been implicated in schizophrenia, likely contributing to positive and negative symptoms as well as impaired cognition. Recently, accumulating evidence suggests bioenergetic systems, important in both synaptic function and cognition, are abnormal in psychiatric illnesses such as schizophrenia. Animal models of synaptic dysfunction demonstrate endophenotypes of schizophrenia, as well as bioenergetic abnormalities. Here we report findings on the bioenergetic interplay of astrocytes and neurons and discuss how dysregulation of these pathways may contribute to the pathogenesis of schizophrenia, highlighting metabolic systems as important therapeutic targets.

Keywords

bioenergetic coupling; schizophrenia; glucose utilization; lactate shuttle; metabolism; mitochondria

Introduction

Schizophrenia is a devastating illness that affects over 2 million people in the U.S. and displays a wide range of psychotic symptoms, as well as cognitive deficits and profound negative symptoms that are often treatment resistant [1–6]. This illness is highly heritable, suggesting a major role for genetic variants in its complex pathophysiology. Large genome-wide association studies (GWAS) have reported over 100 genetic loci containing common alleles conveying minor schizophrenia associations [7], while rare de novo copy number variations (CNVs), which often span multiple genes, confer higher effects on risk [8, 9]. There is accumulating evidence of bioenergetic dysfunction in chronic schizophrenia, including deficits in energy storage and usage in the brain. While it is possible that genetic variation in metabolic genes contributes to these energetic deficits, genetic risk for

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schizophrenia is conferred by a large number of alleles, with risk variants each typically conferring a small portion of overall risk [10]. Interestingly, these studies demonstrate a convergence of de novo mutations and altered gene expression on sets of functionally related proteins, pointing to the regulation of plasticity at excitatory synapses as a pathogenic mechanism in schizophrenia [9]. Taken together, the bioenergetic deficits and genetic risk for synaptic dysfunction in schizophrenia lead to the following question: how do defects in bioenergetic function develop and contribute to the pathophysiology of this illness?

In this review, we will describe bioenergetic coupling in detail and discuss, in turn, how metabolic dysfunction may contribute to impaired synapse activity and maintenance. We will discuss the role of glucose/lactate utilization in cognition, as well as evidence for bioenergetic changes in schizophrenia. We will consider possible drivers of abnormal bioenergetic coupling, including genetic risk factors for schizophrenia, metabolic consequences of abnormal glutamatergic brain development, and the effects of antipsychotic medications. We will integrate these data into a working model to understand the bioenergetic interplay of astrocytes and neurons in psychiatric disorders (such as schizophrenia) characterized by synaptic dysfunction, and possible treatment strategies.

Bioenergetic coupling and energy supply at the synapse

Bioenergetic coupling in the brain requires the coordination of multiple systems and cell types to deliver energetic substrates in a spatio-temporal manner. There are multiple mechanisms in the brain to meet neuronal energy demands, including glycolysis, oxidative phosphorylation, and lactate uptake. Additionally, glutamate released at the synapse signals increased energetic demand to astrocytes and enhances production of bioenergetic substrates via increased glucose uptake, glycolytic rate, and lactate generation [11–13]. In order to shape plasticity, glutamate levels in the synapse are normally tightly controlled by astrocytes, which remove extracellular glutamate via excitatory amino acid transporters (EAATs)[14]. These transporters rely on the electrochemical gradient maintained by the adenosine triphosphate (ATP) dependent Na^+/K^+ ATP pump. Thus, the clearance of synaptic glutamate is bioenergetically costly as well.

While the role of glutamate clearance in bioenergetic homeostasis is generally well understood, the principal mechanism fulfilling the energy requirements of neurons has been debated. Two bioenergetic ideologies offer viable energy production pathways under normal and pathological conditions. An early hypothesis stated that the main mechanism of energy production for neurotransmission was systemically derived glucose taken up by neurons and metabolized by oxidative phosphorylation [15]. Conversely, a more recent and well-supported hypothesis suggests that astrocytes produce lactate in aerobic conditions (Warburg effect), with lactate shuttling from astrocytes to meet the bioenergetic needs of neurons. Pellerin and Magistretti have termed the net flow of lactate from astrocytes to neurons the “astrocyte-neuron lactate shuttle” (Figure 1), which may help fuel neuronal oxidative phosphorylation [16, 17]. This hypothesis posits that neuronal activation increases the concentration of glutamate in the synapse, activates glycolysis in glycogen rich glial cells even in the presence of normal oxygen levels, and generates lactate which is transported out of astrocytes and into neurons via monocarboxylate transporters (MCTs)[15, 18, 19]. For

example, lactate generated by glycolysis in glial cells constitutively supports synaptic transmission even under conditions in which a sufficient supply of glucose and intracellular ATP are present [16]. Lactate production in astrocytes and the lactate shuttle are now thought to be the main mechanisms supporting bioenergetic coupling [20–22]. We discuss both hypotheses in detail in the supplement.

Glucose/lactate utilization in normal cognition

The importance of glucose/lactate utilization in cognitive function is more resolved. The coupling mechanism between neuronal activity and astrocyte lactate production is essential for working memory performance and long-term memory formation in rodents, which is impaired following disruption of the MCTs and bioenergetic coupling [23, 24]. “Breaking” the lactate shuttle disrupts synaptic transmission, resulting in cognitive impairment [25, 26]. Patients with schizophrenia experience a wide range of psychotic symptoms, as well as profound negative symptoms and cognitive deficits [1–6]. Since bioenergetic coupling and neurotransmission are tightly coupled to cognitive function, these pathways could be important pathophysiological substrates in schizophrenia.

Evidence for abnormal bioenergetic function in schizophrenia from transcriptomic and proteomic studies

Schizophrenia pathology features a number of abnormalities associated with glucose metabolism, the lactate shuttle, and bioenergetic coupling, suggesting energy storage and usage deficits in the brain in this illness (Table 1)[27–40]. Studies employing microarrays found significant decreases in the expression of genes encoding proteins involving the malate shuttle, tricarboxylic acid (TCA) cycle, ornithine–polyamine, aspartate–alanine, and ubiquitin metabolism in the dorsolateral prefrontal cortex (DLPFC) in schizophrenia. These changes were not attributable to antipsychotic treatment, which may have a restorative effect [37]. Alterations in these genes might have significant implications for oxidative phosphorylation, which is a key mechanism of ATP production for neurotransmission. Other studies implicate mitochondrial dysfunction in the pathophysiology of schizophrenia [39, 40]. Further, a genetic study demonstrated evidence in schizophrenia for linkage between enzymes that control glycolysis, such as 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2 (PFKFB2), hexokinase (HKK) 3, and pyruvate kinase (PK) 3, suggesting that genetic risk for this illness includes bioenergetic substrates [41].

Consistent with these findings, three other groups found cell-specific changes in gene expression of bioenergetic factors in schizophrenia [42–45]. Using dentate granule neuron samples from the hippocampus, one group observed decreases in mRNA expression for clusters of genes that facilitate mitochondrial oxidative energy metabolism, ubiquitin–proteasome systems, and synaptic plasticity [42]. This included transcripts for lactate dehydrogenase A, NADH dehydrogenases, and ATP synthases. Most schizophrenia subjects in this study were on antipsychotic medication at the time of death, although unmedicated and medicated subjects contributed almost equally to these findings. Changes were not observed in bipolar disorder (BPD) or major depression disorder (MDD) subjects, some of which were also on psychotropic medications [42]. Another group found marked decreases

in mitochondrial and ubiquitin related genes in layer 3 and 5 pyramidal neurons in the DLPFC of schizophrenia subjects (n=36, n=19)[43, 44]. These results also did not extend to a cohort of BPD or MDD subjects (n=19), suggesting that cell-subtype specific alterations of metabolic gene expression may be unique to schizophrenia. Authors posit these changes in schizophrenia are not due to medication effects, since this cohort of BPD and MDD subjects also included patients on antipsychotic medication, and changes in these transcripts in pyramidal cells in the DLPFC of antipsychotic-treated monkeys were not detected [43]. These findings support a molecular link between signatures of mitochondrial dysfunction and spine pathology in schizophrenia, which is well-documented in this brain region [46–49]. Supporting this hypothesis, ubiquitin-proteasome systems are strongly linked to metabolics and the control of synaptic protein connectivity, signaling, and turnover [50–54]. For instance, degradation of the main positive regulator of glycolysis (PFKFB3) in neurons through the ubiquitin–proteasome pathway would result in an inability to upregulate glycolytic flux during increased synaptic activity [55].

We have recently demonstrated similar metabolic deficits in pyramidal neurons from the DLPFC, including decreases in mRNA expression of glycolytic enzymes (HXK1, PFK1) and glucose transporters (GLUT1, GLUT3) in schizophrenia [45]. These changes were not detected in pyramidal neurons from antipsychotic treated rats, suggesting a neuron-specific deficit in glucose uptake and metabolism in schizophrenia that is not due to medication effects. Alternatively, this finding may reflect a compensatory mechanism for neurons to maintain adequate amounts of glucose entering the pentose pathway, slowing glycolysis in favor of supporting mechanisms that protect from oxidative damage [55]. Decreased glycolysis in neurons could increase the strain on metabolic systems, such as the lactate shuttle, to meet energetic demands. These data are consistent with a hypothesis put forth by McDermott and Silva, who postulated that impaired neuronal uptake of glucose through GLUT1 and GLUT3 could contribute to the pathogenesis of schizophrenia [56]. Taken together, these findings suggest that bioenergetic pathways function differently across different brain regions and are cell-subtype specific. The differential involvement of brain regions, circuits, and cell types is in keeping with the diversity of cognitive symptoms in schizophrenia, since persons afflicted with this illness have heterogeneity in the onset, prognosis, and phenotype of cognitive impairment.

Proteomic analyses also highlight the abnormal expression of bioenergetic targets in schizophrenia [33]. In the posterior superior temporal gyrus, 11 downregulated and 14 upregulated proteins were found in schizophrenia. About half of these hits are enzymes involved the regulation of energy metabolism, such as aldolase C and glyceraldehyde-3-phosphate dehydrogenase, likely to impact bioenergetic systems. The same study also reported differentially expressed ATP synthase subunits, which may result in altered ATP metabolism and ultimately contribute to bioenergetic uncoupling in schizophrenia. Importantly, all schizophrenia subjects in this study were treated with antipsychotic medication. Some proteomic studies suggest that these metabolic abnormalities could be an effect of medication, while others implicate bioenergetic dysfunction as a central element of the disease [36, 41].

Several other postmortem studies have found abnormalities in the activity of metabolic enzymes in schizophrenia. For instance, there is a decrease in first half and an increase in second half TCA cycle enzyme activity in the DLPFC of schizophrenia [27]. Most of these subjects (9/13) were off of antipsychotic medications for at least 6 months prior to death, suggesting that alterations in TCA cycle enzyme activity are a core feature of the illness [41]. We also found decreases in the activity of two glycolytic enzymes, HXK and PFK, in the DLPFC of schizophrenia subjects (n=16)[57]. Other studies have also shown a decrease in specific activity of mitochondrial respiratory chain enzymes in the frontal cortex [58, 59]. These data suggest that functionality of metabolic proteins, and not expression levels alone, could be important in the pathophysiology of chronic schizophrenia.

Postmortem studies have several limitations, such as postmortem interval, mRNA/protein integrity, lifetime effects of medication on brain neurochemistry, and samples that reflect the later or more “mature” stages of the illness. These factors may variably impact dependent measures, including mRNA, protein, and receptor binding site expression [60]. One way to circumvent many of these challenges is to perform studies in living patients. In vivo proton magnetic resonance spectroscopy (MRS) studies offer a noninvasive approach to directly study brain bioenergetics in schizophrenia. Interestingly, a study employing phosphorous spectroscopy (31P-MRS) found a decrease (22%) in creatine kinase activity in schizophrenia, an enzyme critical for maintaining stable ATP levels during altered neuronal activity [29]. Other MRS studies in medication naïve patients also implicate abnormal bioenergetic pathways in schizophrenia, suggesting that decreases in the availability of high-energy phosphates may be a common feature of the illness [61]. For example, using high field MRS, one study demonstrated elevated in vivo brain lactate levels in patients with schizophrenia, possibly indicating metabolic dysfunction with a shift towards anaerobic glycolysis [62]. However, MRS studies also face limitations. This includes large voxel sizes unable to differentiate contributions from white or gray matter, low signal to noise ratio, long acquisition times, and (often) small sample sizes. Patient variability and methodological differences could contribute to the inconsistent reports from imaging studies on bioenergetics in schizophrenia. However, MRS studies overall have provided meaningful indexes of brain activity and disruption of metabolic energy pathways in schizophrenia at a macroscopic level.

Do certain cell-subtypes exhibit greater bioenergetic susceptibility in schizophrenia?

Apart from pyramidal cells, another class of neurons raises interest due to its particularly high-energy usage and susceptibility to oxidative stress: GABAergic interneurons. Parvalbumin positive (PV+) interneurons are highly sensitive to redox states and reactive oxygen species signaling, and oxidative stress is linked to long lasting PV+ interneuron defects and cognitive deficits in adulthood [63]. Particularly, there is evidence that oxidative stress during the critical window in development leads to loss of PV+ interneurons, and may contribute to abnormal brain development and schizophrenia pathology [63, 64]. Early in development, the accumulation of Cl⁻ by Na-K-Cl cotransporter (NKCC1) results in GABAA receptors exhibiting excitatory properties, stimulating synaptic growth and

requiring large amounts of energy. Later in life, GABAA receptors become inhibitory due to the delayed expression of the chloride exporter K-Cl cotransporter (KCC2)[65]. We previously found decreases in KCC2 protein in the DLPFC in schizophrenia, possibly reflecting higher cortical energetic demands similar to that of early in life [66]. Another study found increased mRNA expression of two chloride channel regulatory kinases (OXSRI and WNK3) in the DLPFC in schizophrenia, suggesting a further dysregulation of chloride transport and energy consumption [67]. Together, these findings suggest abnormal an abnormal GABAergic metabolic profile in schizophrenia, which could be due to oxidative stress.

A brain with dysfunction in multiple brain regions and cell-subtypes such as in schizophrenia may not have the reserve capacity to compensate for this deficit. While there is strong evidence for disruption of limbic circuits in schizophrenia (including frontal cortex, hippocampus, striatum, and thalamus), nearly every brain region has been implicated to an extent (including cerebellum) in schizophrenia pathology. This supports the idea that chronic schizophrenia, often viewed as a developmental illness with synaptic abnormalities, could be accompanied by widespread metabolic dysfunction, attributable to high metabolic demands placed on neurons by the processes involved in neurotransmission.

Glia are another cell type with vital role in bioenergetic homeostasis that may be abnormal in schizophrenia. For instance, a recent study shows that childhood-onset patient derived induced pluripotent stem cells (iPSCs) show delayed differentiation into astrocytes with glial pathology [68]. However, limited work has been done examining bioenergetic processes of glial cells in schizophrenia, and there is little direct evidence for cell-subtype metabolic dysfunction in astrocytes in this illness. However, astrocyte and neuron metabolics are tightly coupled via the glutamate/glutamine cycle, and extensive work has been done examining these substrates in schizophrenia.

The metabolic role of astrocytes in glutamatergic function

It is well established that glutamatergic systems are disrupted in schizophrenia. In normal brain, neurons have lower capacity than astrocytes for glutamate reuptake. Astrocytes are responsible for the majority of glutamate uptake (about 75%) via EAATs and recycle glutamate to the precursor glutamine, which neurons can readily transport [69–71]. This is referred to as the glutamate/glutamine cycle, and is bioenergetically costly. However, glutamate entering astrocytes can meet several metabolic fates, including entering the TCA cycle or lactate/ATP production [72–74]. Studies have confirmed that a significant amount of glutamate is oxidatively metabolized in astrocytes to lactate (by glutamate dehydrogenase and the TCA cycle) when energetic demand is high, and that the amount converted to glutamine is proportionately decreased [70, 73, 74]. Interestingly, EAATs are co-expressed with Na⁺/K⁺ ATPases, mitochondria, and glycolytic enzymes to signal rapid glycolysis and lactate generation when neuronal activity is high [75, 76]. Since the glutamate/glutamine cycle in astrocytes is tightly linked to both metabolics and neurotransmission, alterations in this cycle may indicate disrupted bioenergetics coupling between neurons and astrocytes.

We and other groups have found changes in cellular and subcellular localization of glutamate transporters in schizophrenia [75, 77–80]. Abnormal EAAT expression on astrocytes may lead to pathological glutamate spillover, as well as a decrease in the generation of bioenergetic substrates for neuronal consumption [79]. Localization of EAATs impacts synaptic plasticity [77], and changes in localization suggest uncoupling of glutamate transporter protein complexes from mitochondria [78]. Supporting this hypothesis, one study demonstrated decreased labeling of astrocytes adjacent to blood vessels in schizophrenia, suggesting decreased access to the vascular space, which is the primary source of glucose. Such changes could contribute to diminished metabolic capacity [81]. Since astrocytes are integral to the bioenergetic homeostasis and fidelity of synaptic function, targeted studies examining changes in these cells is a promising avenue for understanding the pathophysiology of schizophrenia [82].

What drives metabolic abnormalities in schizophrenia?

Pharmacologic, genetic and theoretical considerations suggest schizophrenia as a developmental disorder with synaptic dysfunction [83–87]. The accumulating evidence discussed above suggests metabolic disturbances are also a key feature of this illness. As the brain develops, bioenergetic organization and the formation of synapses occur simultaneously, creating a fundamentally interdependent system. Reflecting the heterogeneous nature of schizophrenia, some “indirect” cases may develop an intermediate metabolic phenotype secondary to inherited genetic risk for synaptic dysfunction, while some “direct” cases may have genetic risk for impaired bioenergetic systems, leading to the inability of cells to meet the energy demands of synaptic machinery. Thus, metabolic dysfunction may be a primary cause of schizophrenia and/or an intermediate phenotype secondary to synaptic dysfunction.

Genomic variation of synaptic and metabolic systems confers risk for schizophrenia

The genetic risk for schizophrenia is complex and includes numerous synaptic risk factors that appear to contribute to its pathophysiology. For example, genetic susceptibility factors include genes that play roles in NMDAR function, synapse development/plasticity, and postsynaptic pathways [7–9, 84, 88–97]. These prominent abnormalities are part of a complex genetic profile that includes genomic variation in other functionally related groups such as metabolic proteins [37–44]. Thus, the metabolic phenotype observed in schizophrenia could be driven by inherited synaptic and metabolic risk factors, including single-nucleotide polymorphisms or rare CNVs. The combination of synaptic and metabolic genetic insults could coalesce over development, resulting in a brain with synaptic disturbances and diminished bioenergetic capacity. This could contribute to abnormalities described in this illness such as decreased spine density [46, 98], loss of neuropil [99], decreased expression of glutamate transporters [80, 83–87, 100–102], altered expression of glutamate receptors, and other changes [100, 103]. This hypothesis is also supported by genetic linkage studies and numerous findings of abnormally regulated transcripts related to mitochondrial function, glucose utilization, and other high-energy pathways [37–44].

Does synaptic dysfunction during brain development yield an intermediate metabolic phenotype?

Although alterations in metabolic gene expression may confer some risk for schizophrenia, it is also possible that genetic risks culminating in synaptic dysfunction could be driving perturbations of metabolic systems. Metabolism is intimately linked to normal synaptic function and abnormal synapses are likely to have altered bioenergetic capacity. Developing a brain with synaptic dysfunction could result in an intermediate metabolic phenotype in schizophrenia, which may contribute to cognitive symptoms (Figure 2). This coincides with the developmental nature of schizophrenia, where the age of onset is typically later in life (18–25 years)[104]. Taken together, these data raise the question of whether or not metabolic dysfunction in schizophrenia is genetic, an intermediate phenotype acquired secondary to antipsychotic treatment, or some combination of those factors.

Changes in metabolic systems in schizophrenia due to antipsychotic drug treatment

It is possible that metabolic abnormalities in schizophrenia are due to the high percentage of subjects taking antipsychotic medications, often for several decades. Antipsychotic drugs are known to have potent interactions with metabolic pathways in the brain. We discuss this important topic, as well as other drugs that have metabolic effects, in detail in the supplement.

Metabolic abnormalities in drug-naïve patients

Studies in drug-naïve patients offer valuable information on the pathophysiology of schizophrenia. Several studies account for this potential limitation through unmedicated patient populations, which we discuss in detail in the supplement. However, animal models may inform the specific mechanisms underlying these effects.

Animal models as a valuable tool

Given the complex and heterogeneous nature of schizophrenia, it is likely that metabolic genetic predisposition, an intermediate metabolic phenotype secondary to genetic risk for synaptic dysfunction, and treatment with antipsychotic drugs may all contribute to the bioenergetic deficits observed in this illness. Multifaceted contributions can make interpreting human results challenging, highlighting the utility of animal models to better investigate these important questions. Animal models of synaptic dysfunction may provide a tool to address the hypothesis that metabolic disturbances may be an intermediate phenotype secondary to genetic risk for synaptic dysfunction. The evidence suggesting a central role for the glutamatergic system in this illness has led to development of several animal models of synaptic dysfunction. Specifically, defects in NMDARs in schizophrenia [105–113] have led to generation of NMDA receptor hypofunction models [114–120]. For example, the NMDA receptor GluN1 subunit knockdown model demonstrates impaired social interaction, increased stereotypic behaviors, decreased performance in spatial and working memory tasks, and increased auditory and visual event related potentials (suggesting decreased

inhibitory tone)[116, 118, 120–122]. Other targeted mutations in genes encoding glutamate receptors result in similar schizophrenia-like phenotypes, several of which have been implicated in schizophrenia (reviewed in [123]). In addition to genetic models, pharmacological models such as administration of phencyclidine, MK-801, and other NMDA-receptor antagonists can induce positive and negative symptoms associated with schizophrenia [124, 125]. NMDA receptor hypofunction models are widely used in schizophrenia research, but are not the only models of dysfunctional synapses. Several other genetic models also exhibit behavioral abnormalities considered endophenotypes for schizophrenia (including astrocyte pathology models), such as GluR-A knockout mice, disrupted in schizophrenia 1 (DISC1) transgenic mice, serine racemase knockout mice, nicotinic receptor knockout mice, and SynGAP heterozygotes (Table 2)[120, 126–130].

Models informing antipsychotic treatment on metabolic systems

An alternate approach to the challenge of medicated patient populations is using model systems to probe for the effects of antipsychotic drugs on metabolic systems. We discuss this in the supplement.

Evidence for an intermediate metabolic phenotype in genetic models of synaptic dysfunction

There is evidence suggesting developing a brain with synaptic dysfunction yields an intermediate metabolic phenotype. This may be due to failure of astrocytes to develop or maintain metabolic coupling with neurons. There is strong evidence linking glycolysis/lactate shuttle defects to developmental NMDA receptor dysfunction in GluN1 subunit KD mice, including abnormal mitochondrial PK protein expression [30, 131]. It is unclear which isoform (PKM1 or PKM2) is abnormally expressed, an important consideration as isoform expression varies in cells with different glycolytic profiles. We have also shown marked decreases in two metabolic transporters important in this pathway in the frontal cortex of GluN1 KD mice (MCT4, 63% and GLUT3, 60%)[132]. MCT4 plays a vital role in transporting lactate generated from glycolysis in astrocytes into the synaptic cleft for neurons to take up, while GLUT3 transports glucose directly into neurons to be metabolized [133]. Neurons are unable to sustain a high glycolytic flux during prolonged synaptic activity and instead meet their bioenergetic requirements from other sources such as the lactate shuttle, suggesting that defects in lactate transporter MCT4 could lead to bioenergetic uncoupling between cell types [55]. Both synaptic function and meeting of energetic demands are essential for cognition, and failure of either could contribute to the cognitive symptoms seen in schizophrenia. It is possible that defects in excitatory synapses in the GluN1 KD model could lead to a metabolic intermediate phenotype and contribute to poor cognitive performance in these animals. Similar metabolic phenotypes are seen in pharmacological models of NMDA receptor dysfunction.

Conclusions

This review highlights recent work in both human and animal models implicating bioenergetic dysfunction in schizophrenia. Pathogenic mechanisms underlying metabolic

defects in schizophrenia are complex and not readily explained by genetic variance or neurochemical changes alone. Adding to this complexity, antipsychotic medications appears to interact with metabolic systems in diverse ways. In vivo and postmortem studies have begun to reveal the consequences of abnormal metabolic gene expression and developing a brain with dysfunctional synapses. In addition, reverse translational approaches have become increasingly valuable, as it is likely that a combination of diverse variables contributes to the bioenergetic deficits in schizophrenia. Teasing apart primary versus secondary causes also poses a challenge not easily overcome by human studies alone, particularly between intertwined entities such as metabolic and synaptic systems. Some bioenergetic disturbances in schizophrenia may be cell or cell-subtype or micro-domain specific, leading to recent studies examining specific cortical lamina, cell subtypes, and microdomains. Collectively, these findings highlight the importance of synaptic and metabolic interplay in the pathophysiology of schizophrenia and provide the framework for future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Bioenergetic coupling in normal brain. Glycolysis and oxidative metabolism via tricarboxylic acid (TCA) cycle are key pathways in maintaining synaptic function. Both neurons and astrocytes undergo glycolysis even during aerobic conditions. Glucose, which feeds the glycolytic pathway, can enter cells through glucose transporters (GLUTs) or be derived from the breakdown of glycogen in astrocytes. Meeting the energy demand of neurons is highly reliant on the metabolic coupling of neurons to glycolysis and lactate production in astrocytes. There are several key enzymes in glycolysis, including hexokinase (HK) and lactate dehydrogenase (LDH). This metabolic coupling also requires monocarboxylate transporters (MCTs), which rapidly transport lactate generated by astrocytes into the extracellular space and into neurons. Here lactate is converted back to pyruvate by LDH, which may enter the TCA cycle and oxidative phosphorylation to generate 30–36 molecules of adenosine triphosphate (ATP). This net flow of energetic substrates from astrocytes to neurons to support neuronal activity is termed the “astrocyte–neuron lactate shuttle.”

Figure 2.

Genetic and environmental risk factors for schizophrenia include genomic variants and stressful events that impact the NMDA receptor signaling complex. There is a close interrelationship between the development of glutamatergic synapses and the meeting of bioenergetic demands, which if disrupted could in return affect synaptic function, generating a pathological cycle and possibly an intermediate metabolic phenotype. This phenotype could include a metabolic uncoupling of astrocytes and neurons, affecting pathways such as the astrocyte neuron lactate shuttle, and result in an inability to support increases in neuronal activity. There is evidence that the astrocyte neuron lactate shuttle is necessary for cognitive functions such as long-term memory, suggesting bioenergetic uncoupling could contribute to cognitive deficits in adulthood in this illness. Abbreviations. Dorsolateral prefrontal cortex (DLPFC); hippocampus (HC).

Summary of metabolic abnormalities in schizophrenia and models of schizophrenia.

Table 1

Model	n #	Brain region	Cell specific?	Finding	Method	Antipsychotic effect	Reference
Human	13/group	DLPFC	No	Abnormal TCA cycle activity	Enzyme assays	9/13 off medication	27
Human	3–7/group	Striatum	No	20% fewer mitochondria	Electron micrographs	May normalize	28
Human	26/group	Frontal lobe	No	22% reduction in creatine kinase kf	31P-MRS	Unknown	29
Human	6–9/group	Wernicke’s area	No	Abnormal expression of metabolic enzymes	2D-GE-MS	Unknown	33
Human	10/group	Prefrontal cortex	No	Mito. function and oxidative stress protein/gene changes	2D-DIGE and microarrays	7/10 off medication	34
Human	10/group	Prefrontal cortex	No	Decreased TCA/metabolic genes	Microarrays	May normalize	37
Human	12–13/group	Context, BG, cerebellum	No	Defects in mitochondrial respiratory chain	Enzyme assays	Unknown	58
Human	15/group	CSF	No	Elevated CSF lactate	Metabolite analyzer	Trend with decreased CSF lactate	32
Human	35/group	DLPFC	No	Abnormal synaptic and metabolic proteins	2D-GE-MS	Affects some proteins	35
Human	15/group	ACC	No	Altered TCA/glycolysis/gluconeogenesis proteins	2D-GE-MS	Some proteins correlate	36
Human	13–15/group	ALIC	No	Decreased lactate (19%)/alanine (24%)	1H-NMR	Unknown	38
Human	987	n/a	No	PFKFB2, HXK3, PK3 linked to SCZ	Linkage analyses	Minimal	41
Human	22–24/group	Hippocampus	Yes	Decrease in mito. oxidative metabolism genes	LCM-microarray	Unlikely	42
Human	36/group	DLPFC	Yes	Decrease in mito. and ubiquitin-proteasome genes	LCM-microarray	No	43
Human	19/group	DLPFC	Yes	Decrease in mitochondrial energy production genes	LCM-microarray	Unlikely	44
Human	16/group	DLPFC	Yes	Decrease in glycolytic/glucose transport genes	LCM-qPCR	Possible	45
Human	9–33/group	Nucleus caudatus/cortex gyrus frontalis	No	63%/43% reduction in COX activity	Assays/PCR	Unknown	59
Human	12–19/group	PBMCs	No	Altered glycolytic pathway proteins	LC-MS/assays	Used APD naïve patients	61 S.L.
Human	7–9/group	DLPFC	No	Abnormal energy metabolism proteins	2D-DIGE-MS	Unknown	53 S.L.
Human	48–62/group	Serum/urine	No	Increased pyruvate	NMR	Unknown	86 S.L.
MK-801 treated rat	5–6/group	Context	No	Increased lactate levels	1D/2D in vivo NMR	No	42 S.L.
MK-801 treated rat	12/group	Cerebral cortex	No	Abnormal energy metabolism protein expression	2-DE-MS	No	30
MK-801 treated rat	11–12/group	Cortex/hippocampus	No	Disturbed TCA cycle	1H-MAS-NMR	No	31
MK-801 treated rat	4–7/group	Sensory cortices/limbic structures	No	Region specific changes in metabolism	quantitative [14C]2-deoxyglucose autoradiographic	No	43 S.L.
MK-801 treated rat	9/group	Cortico–striato–thalamo–cortical loop	No	Decreased lactate, reduced glycolysis in parietal/temporal cortex	13C-NMR-HPLC	No	45 S.L.
PCP treated rat	8/group	Frontal cortex	No	Decreased pyruvate and PK, altered complex I subunits	1H-NMR, LCMS, assays	No	85 S.L.
NR1 KD mouse	12/group	Frontal cortex and hippocampus	No	Increased PK, abnormal glycolysis/gluconeogenesis/TCA	LCMS	No	131
NR1 KD mouse	5/group	Cortex	No	Decrease glucose/lactate transporter expression	qPCR	No	132

Abbreviations. Dorsolateral prefrontal cortex (DLPFC); tricarboxylic acid cycle (TCA); forward rate constant (kf); magnetic resonance spectroscopy (MRS); 2 dimensional gel electrophoresis (2D-GE); 2 dimensional difference gel electrophoresis (2D-DIGE); mass spectrometry (MS); mitochondrial (mito.); basal ganglia (BG); cerebral spinal fluid (CSF); anterior cingulate cortex (ACC); anterior limb of the internal capsule (ALIC); nuclear magnetic resonance (NMR); 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2 (PFKFB2); hexokinase 3 (HXK3); pyruvate kinase 3 (PK3); schizophrenia (SCZ); laser-capture microdissection (LCM); quantitative polymerase chain reaction (qPCR); cyclooxygenase (COX); peripheral blood mononuclear cell (PBMC); antipsychotic drug (APD); magic angle spin (MAS); high-performance liquid chromatography (HPLC); liquid chromatography–mass spectrometry (LCMS); phenylclidine (PCP); pyruvate kinase (PK); supplementary information (S.I.).

Table 2
 Characteristics of Selected Animal Models of Schizophrenia with “Synaptic Dysfunction”

Animal model	Transgenic?	Memory deficit?	PPI deficit?	Social deficit?	Novel object deficit?	Metabolic disturbance?	Reference
GluR-A knockout	Yes	Yes	Yes	Yes	No	Unk	128, 77 S.I.
DISC I transgenic	Yes	Females	Yes	Males	No	Unk	129, 130
SynGAP heterozygotes	Yes	Yes	Yes	Yes	No	Unk	126
NR1 knockdown	Yes	Yes	Yes	Yes	Yes	Altered glycolytic enzymes/glucose transport	131, 132
$\alpha 7$ nicotinic receptor knockout	Yes	Yes	No	Unk	Unk	Unk	79 S.I., 80 S.I.
$\alpha 5$ nicotinic receptor knockout	Yes	No	No	No	Unk	Unk	81 S.I.
Serine racemase knockout mice	Yes	Yes	Yes	Some	No	Unk	82 S.I.
Acute NMDA antagonism	No	Yes	Yes	Yes	Yes	Increased lactate and glucose utilization	119
Chronic PCP administration	No	Yes	Yes	Yes		Mitochondrial abnormalities, decreased pyruvate kinase	85 S.I.
Ketamine administration	No	Yes	Varies	Varies	Varies	Altered PPP and glycolysis/gluconeogenesis metabolites	84 S.I.
MCT4 conditional knockout	No	Yes	Unk	Unk	Unk	Impaired lactate shuttle	23, 24
Dominant-negative SNARE mice	Yes	Yes	Unk	Unk	Unk	Abnormal ATP/adenosine	83 S.I.

Abbreviations. Disrupted in schizophrenia (DISC); synaptic ras GTPase-activating protein (SynGAP); N-methyl D-aspartate (NMDA); pentose phosphate pathway (PPP); monocarboxylate transporter (MCT); soluble attachment protein receptor (SNARE); unknown (Unk); supplementary information (S.I.).