Neuron-specific deficits of bioenergetic processes in the dorsolateral prefrontal cortex in schizophrenia

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Abstract

Schizophrenia is a devastating illness that affects over 2 million people in the U.S. and costs society billions of dollars annually. New insights into the pathophysiology of schizophrenia are needed to provide the conceptual framework to facilitate development of new treatment strategies. We examined bioenergetic pathways in the dorsolateral prefrontal cortex (DLPFC) of subjects with schizophrenia and control subjects using western blot analysis, quantitative real-time polymerase chain reaction, and enzyme/substrate assays. Laser-capture microdissection-qPCR was used to examine these pathways at the cellular level. We found decreases in hexokinase (HXK) and phosphofructokinase (PFK) activity in the DLPFC, as well as decreased PFK1 mRNA expression. In pyramidal neurons, we found an increase in monocarboxylate transporter 1 mRNA expression, and decreases in HXK1, PFK1, glucose transporter 1 (GLUT1), and GLUT3 mRNA expression. These results suggest abnormal bioenergetic function, as well as a neuron-specific defect in glucose utilization, in the DLPFC in schizophrenia.

Introduction

A growing body of evidence suggests abnormal bioenergetic function in chronic schizophrenia, including deficits in energy storage and usage processes in the brain. Microarray studies found significant decreases in expression of genes encoding proteins involving the malate shuttle, tricarboxylic acid (TCA) cycle, as well as the ornithine–polyamine, aspartate–alanine, and ubiquitin metabolism groups in the dorsolateral prefrontal cortex (DLPFC)(1-13). These changes were not attributable to antipsychotic treatment, which may have a restorative effect (11).Further, a genetic study demonstrated evidence for linkage between enzymes that control glycolysis, such as 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2 (PFKFB2), hexokinase 3 (HXK3), and pyruvate kinase 3 (PK3),suggesting that genetic risk for this illness includes bioenergetic substrates (14).

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Several postmortem studies have also found abnormalities in metabolic enzyme activity. In schizophrenia, there was decreased first half and increased second half TCA cycle enzyme activity in unpooled DLPFC samples (n=13), as well as decreased specific activity of mitochondrial respiratory chain enzymes in the frontal cortex (1, 15, 16). In vivo studies also implicate alteration of bioenergetic pathways in schizophrenia. Direct evidence for bioenergetic dysfunction as a core feature of schizophrenia was reported using magnetic resonance spectroscopy (MRS). A decrease (22%) in creatine kinase activity was found in schizophrenia (3), an enzyme critical for maintaining stable adenosine triphosphate (ATP) levels during altered neuronal activity (3, 17, 18). Other MRS studies in medication naïve patients suggest that decreases in the availability of high-energy phosphates may be a core feature of the illness (19-21).

While compelling, prior work has not explored critical elements of bioenergetic pathways for glucose utilization in schizophrenia. In normal brain, ~80% of the energy consumed supports neurotransmission and neurotransmitter cycling (22). Abnormalities in bioenergetic function are likely to have implications for neuronal and circuit activity. Glucose is converted to glucose-6-phosphate (G6P) via HXK in the first step of glycolysis, where it may be further converted to other bioenergetic intermediates by highly regulated enzymes, such as phosphofructokinase, ultimately yielding pyruvate and ATP (23). Pyruvate may be converted to lactate by lactate dehydrogenase (LDH) and shuttled via monocarboxylate transporters (MCTs) into neurons, providing energy for receptor trafficking, spine formation and other neurotransmission events (24, 25). In schizophrenia, cognitive impairment correlated with decreases in striatal cytochrome oxidase and cortical glucose utilization (26, 27). Motivated by these findings, we investigated key metabolic proteins, transcripts, and enzyme activities to assess glycolysis and glucose uptake in severe mental illness. Specifically, we hypothesize that cell-subtype specific abnormalities in glucose utilization pathways may contribute to a common pathophysiology found in chronic schizophrenia.

Methods

Tissue acquisition and preparation

Dorsolateral prefrontal cortex (DLPFC, Brodmann area 9) postmortem brain samples originated from the Maryland Brain Collection and were distributed by both the Maryland Brain Collection and the Alabama Brain Collection. Rationale for the choice of this brain region is provided in the supplement. The cohort consisted of subjects with schizophrenia (n=16) and nonpsychiatrically ill comparison subjects (n=16) (Table 1, eTable 1). Thirteen control subjects and twelve subjects with schizophrenia were common to all experiments (Table 1). Subjects were diagnosed with schizophrenia based on DSM-IV criteria. The medical records of the subjects were examined using a formal blinded medical chart review instrument, as well as in person interviews with the subjects and/or their caregivers, as previously described (28). Schizophrenia, depression, and comparison groups were matched for sex, age, pH, and PMI (Table 1).

In this study, there were two overarching experiments:1) A region-level analysis of mRNA and protein levels, as well as enzyme activity and substrate levels. This experiment utilized DLPFC brain tissue sections scraped from glass slides and homogenized. We used real time

quantitative polymerase chain reaction (RT-qPCR), Western blot analyses, and enzyme assays to generate this data. 2) A cell-subtype specific analysis of mRNA expression in DLPFC pyramidal neuron and astrocyte enriched samples. This experiment utilized cells cut using laser capture from fresh frozen tissue sections. We used laser capture microdissection (LCM) coupled with qPCR to generate this data.1000 cells were cut from each subject, and all of the cells were used for the qPCR analyses. The tissue sections used for each of these experiments (14 um) were cut from tissue blocks, and a number of the subjects from experiments 1 and 2 overlap, as detailed in Table 1. There was no pooling of subjects in any of our experiments.

We performed western blot analyses (29-31), LCM-qPCR (32-34), and rodent antipsychotic studies (33) as previously described. Briefly, western blot analyses were run in duplicate using the following antibodies optimized for postmortem brain: monocarboxylate transporter 1 (MCT1), lactate dehydrogenase (LDH), LDHA, LDHB, hexokinase 1 (HXK1), glucose transporter 3 (GLUT3). For LCM-qPCR, enriched populations of pyramidal neurons or astrocytes (1000 of each cell type per subject) were identified from Nissl-stained slides and cut from superficial (2-3) and deep (5-6) layers of DLPFC by LCM using the Veritas Microdissection instrument and CapSure Macro LCM caps (Life Technologies, formerly Arcturus, Mountain View, CA, USA). RT-qPCR targets included MCT1, MCT4, HXK1, HXK2, LDHA, LDHB, phosphofructokinase 1 (PFK1), GLUT1, and GLUT3. Enzyme activity and lactate/glucose-6-phosphate levels were measured in tissue homogenates using commercially available kits adapted to postmortem brain. For enzyme assays, each sample was assayed with and without an inhibitor. Full details of these methods are provided in the eMethods. A full list of primers and antibodies is available in the eMethods and eTable 2.

Statistical analysis

Data were analyzed using Statistica 13.0 (Statsoft, Tulsa, Oklahoma, USA). Outliers were removed from data sets using the ROUT method (Q = 5%). Data were tested for normality using D'Agostino & Pearson omnibus normality test. If data were not normal, Y values were transformed using $Y=Log(Y)$ and retested for normalcy. When data were normal, student's t test (enzyme/substrate assays) and ANOVA (qPCR and protein studies) was used ($\alpha=0.05$). If data were not normal, Mann-Whitney (enzyme/substrate assays) or Kruskal-Wallis test (qPCR and protein studies) was used. Correlation analyses were performed to probe for associations between the expression of our dependent measures and tissue pH, age, and postmortem interval. Additional details regarding our statistical approach are provided in the eMethods section.

Results

No significant associations were found between pH, post-mortem interval (PMI), RNA integrity number (RIN), or age and any of our dependent measures (mRNA, protein, enzyme activity, or substrate levels). We adapted all enzyme assays to postmortem brain and used inhibitors to demonstrate specificity of our assays. Enzyme inhibitors used were able to achieve near complete inhibition, similar to 95°C heat inactivation (eFigure 1).

Region-level Studies

We detected a significant decrease in phosphofructokinase 1 (PFK1) mRNA expression (24%) in DLPFC in schizophrenia (t=2.16, p<0.05). We did not detect any changes in transcripts for monocarboxylate transporter 1 (MCT1), MCT4, lactate dehydrogenase A (LDHA), LDHB, hexokinase 1 (HXK1), HXK2, glucose transporter 1 (GLUT1), or GLUT3 in schizophrenia versus control at the region-level (eFigure 2). Since transcript expression is not always indicative of protein levels, we also measured protein expression for these genes (35). We did not detect any changes in LDH, LDHA, LDHB, HXK1, MCT1, or GLUT3 protein levels in the DLPFC in schizophrenia (Figure 1).

Next, we assayed enzyme activity for key pathways in glucose utilization in the brain. In subjects with schizophrenia, we found decreases in HXK (26%) and PFK (16%) activity, but not LDH, in the DLPFC (Figure 2). We also found a decrease in HXK (27%) activity normalized to protein expression in the DLPFC (t=1.68, p<0.05) (eFigure 3). We were unable to assess PFK activity normalized to protein expression due to lack of working PFK antibody for human brain. We did not find any changes in LDH, HXK, or PFK enzyme activity in rats treated with 28.5 mg/kg haloperidol-decanoate or vehicle every 3 weeks for 9 months (Figure 2). In rats with varying PMIs, no changes were detected in LDH, HXK, or PFK activity in rat brain samples at 4, 8, or 12 hour time points compared to 0 hours (Figure 2). At 24 and 48 hour time points, we detected increases in LDH and PFK activity. To address if the changes in enzyme activity were disease specific, we also examined HXK and PFK activity in a cohort of subjects with major depressive disorder (MDD) (n=20) and did not detect any differences (eFigure 4). Finally, we did not find any changes in lactate or G6P levels in subjects with schizophrenia or rats treated with haloperidol-decanoate (Figure 3). Postmortem enzyme activity and substrate levels were not associated with PMI or pH (Figure 2, eFigure 5).

Cell-level Studies

To address the possibility that changes in expression may be cell-subtype specific, we used LCM-qPCR to assess mRNA expression of our metabolic targets in enriched populations of astrocytes and pyramidal neurons. We have previously shown our LCM samples are enriched for specific cell-subtypes using neurochemical markers (32-34). In a sample enriched for pyramidal neurons, we found an increase in MCT1 mRNA expression (22%, p=0.038), as well as decreases in HXK1 (p=0.023, t=3.18, 19%), PFK1 (p=0.003, t=3.20, 22%), GLUT1 (p=0.008, t=2.78, 20%), and GLUT3 (p=0.023, t=2.66, 20%) mRNA expression (Figure 4 and eFigure 6, p<0.05). We did not detect any significant changes in mRNA expression in samples enriched for astrocytes (eFigure 7). Since 11/16 of our schizophrenia subjects were on typical antipsychotic medications, we assessed MCT1, HXK1, PFK1, GLUT1, and GLUT3 transcripts in enriched populations of pyramidal neurons from rats treated with 28.5 mg/kg haloperidol-decanoate or vehicle every 3 weeks for 9 months to see if our findings in pyramidal neurons in schizophrenia were secondary to a medication effect. We found increases in MCT1 (17%, t=2.52, p<0.05) and GLUT3(20%, t=2.41, p<0.05), but no changes in HXK1, PFK1, or GLUT1, mRNA expression in enriched pyramidal neuron samples of antipsychotic treated rats (Figure 4 and eFigure 8). All LCM-qPCR pyramidal neuron findings remained significant after applying the FDR correction.

Discussion

To our knowledge, this study is the first to suggest cell-subtype specific changes in glucose utilization in postmortem brain in severe mental illness. In a laser-captured cell populations enriched for pyramidal neurons from superficial (2-3) and deep (5-6) layer DLPFC, we found significant decreases in mRNA expression of two glycolytic enzymes (HXK1 and PFK1), two glucose transporters (GLUT1 and GLUT3), and an increase in lactate/pyruvate transporter MCT1 mRNA expression in schizophrenia. We did not detect any changes in a cell population enriched for astrocytes, suggesting our findings are cell-subtype specific. In normal brain, glucose enters cells through GLUT1/GLUT3 and is processed by both HXK1 and PFK1 via glycolysis to produce pyruvate. Pyruvate can then be converted to lactate and transported between cells or intracellularly by MCTs to be oxidized in the TCA cycle when neuronal energy demand is high (36, 37). Our data suggests a decrease in the capacity of pyramidal neurons to generate bioenergetic substrates from glucose via glycolytic pathways. Additionally, if neurons were unable to take up adequate amounts of glucose for glycolysis, the intracellular pool of available pyruvate/lactate for transport into mitochondria may be diminished, ultimately impacting energy supply. Under aerobic conditions, pyruvate generated from glycolysis is oxidatively decarboxylated to form acetyl CoA, which serves as the main input into the TCA cycle. Our data suggests this mechanism is impaired in neurons, which could result in TCA cycle abnormalities and impaired oxidative phosphorylation.

Consistent with this hypothesis, other studies demonstrated decreases in genes related to oxidative phosphorylation in LCM captured pyramidal neurons in schizophrenia (38-40). Decreases in clusters of genes that encode for mitochondrial oxidative energy metabolism were found in dentate granule pyramidal neurons from the hippocampus. This included transcripts for lactate dehydrogenase A, NADH dehydrogenases, and ATP synthases. These changes were not found in MDD or bipolar affective disorder, suggesting possible specificity for schizophrenia (38). Other studies also observed decreases in mitochondrial related genes in pyramidal neurons in the DLPFC of schizophrenia subjects (39, 40). Metabolic systems are strongly linked to the control of synaptic protein connectivity, signaling, and turnover (41-45). Thus, decreases in mitochondrial function coupled with abnormal glucose utilization in neurons could reduce the capacity of pyramidal cells to sustain a normal complement of dendritic spines, contributing to the lower DLPFC spine density reported in schizophrenia (38, 46, 47).

Neurons are unable to synthesize glucose and thus are fully dependent upon glucose transporters for glucose uptake/supply (48). Although not usually considered the rate-limiting step in glucose utilization in normal brain, in pathological states decreased GLUT1 and GLUT3 expression may diminish glucose transport capacity to a threshold resulting in impaired glucose metabolism (49). Interestingly, decreases in GLUT1 and GLUT3 and impaired brain glucose utilization have been reported in other cognitive disorders. For instance, a reduction in GLUT1/GLUT3 expression has been implicated as a possible cause, rather than a consequence, of neurodegeneration in Alzheimer's disease (49-51). Our finding of decreased GLUT1 and GLUT3 transporter expression in neurons suggests a similar impairment in glucose uptake and metabolism as a key feature of chronic schizophrenia, possibly contributing to cognitive impairment. However, it is important to consider mRNA

changes in neurons may not have an effect on protein levels or transport activity. Interestingly, McDermott and deSilva hypothesized that genetic deficits in GLUT1/GLUT3 and poor uptake of glucose in the brain would result in a backlog effect and mild systemic hyperglycemia (52), which has been reported in schizophrenia (53, 54). Reduced glucose availability in neurons may disrupt bioenergetic coupling systems such as the glutamine/ glutamate cycle, which is also perturbed in this illness (55, 56). For example, elevated glutamine to glutamate ratio in the CSF of schizophrenia first episode drug naïve patients suggests endogenous substrates which communicate between neurons and glia are altered (55).

Since most subjects (11/16) in our cohort were taking typical antipsychotics, we examined our dependent measures in haloperidol treated rats. Increases in GLUT3 transcripts in pyramidal neurons following haloperidol treatment suggest our finding of decreased GLUT3 mRNA in schizophrenia is not due to a medication effect. In contrast, our findings of increased MCT1 transcripts in pyramidal neurons in schizophrenia could be secondary to the administration of typical antipsychotic medications. However, it is possible that there is a disease x drug interaction that may not be appreciated in our rodent studies. To address this limitation, we performed additional *in silico* analyses using a publically available online database (eTable 3). In brain samples from subjects with schizophrenia on versus off medications, we found no changes in MCT1, HXK1, or PFK1, and increased levels of the glucose transporters GLUT1 and GLUT3. These changes are in the opposite direction of our findings in schizophrenia, and for GLUT3 mirror our findings in antipsychotic treated rats. Interestingly, these increases in glucose and lactate transporters following antipsychotic drug administration offer a novel mechanism for haloperidol's antipsychotic effect. Increased glucose transporter expression could restore intracellular glucose levels in neurons, while increases in monocarboxylate transporters could circumvent bioenergetic deficits by scavenging extracellular lactate generated by astrocytes.

We detected decreased HXK (26%) enzyme activity in the DLPFC of schizophrenia, possibly indicating a functional defect in glucose utilization in this brain region, impacting ATP production, oxidative phosphorylation, and synaptic events. HXK1 is normally localized to the outer membrane of mitochondria through specific binding to voltage dependent anion channel (VDAC), where it couples cytosolic glycolysis to mitochondrial ATP production and interacts with the Na+/K+ ATPase (23, 57). This confers HXK1 direct access to ATP generated by mitochondria and facilitates increased activity/high glycolytic rates when needed. Previous studies reported altered subcellular localization of HXK1 in schizophrenia, with a shift in HXK1 partitioning from the mitochondrial fraction to the cytosolic fraction in the DLPFC and parietal cortex (30, 58). Such a shift may diminish ATP production and increase vulnerability to oxidative damage. This functional uncoupling in schizophrenia may contribute to our finding of decreased HXK activity. Such a decrease in HXK activity could further diminish the capacity of cells to coordinate oxidative phosphorylation and glycolysis, which is necessary to respond to bioenergetic demands during neuroplastic events (59).

Our finding of decreased PFK activity (16%) in schizophrenia also supports the hypothesis of impaired glycolytic function in neurons. Increased rates of glycolysis and lactate

production (below toxic levels) are necessary for long-term memory formation (60-62). A decrease in PFK activity could slow the rate of glycolysis to avoid lactate accumulation under resting conditions, but may influence the ability of cells to meet energy demands during neuronal activation. These findings are consistent with previous reports of abnormal enzyme activity in metabolic pathways in schizophrenia, such as decreased creatine kinase activity, as well as a decrease in cytochrome-c oxidase activity in the caudate nucleus (63%) and frontal cortex (43%) (3, 15, 16). Interestingly, similar changes in enzyme activity were not found in a cohort of MDD subjects. Many complex yet subtle abnormalities underlie severe psychiatric illnesses, and while many of these changes may be shared between MDD and schizophrenia, our findings do not appear to extend to unipolar depression. However, in MDD there are also metabolic abnormalities such as alterations in high-energy phosphate metabolism and regulation of oxidative phosphorylation (63). It may be important to examine our dependent measures in other illnesses, such as bipolar disorder, that share high levels of genetic and environmental risk with schizophrenia.

Postmortem interval might impact enzyme activity; however, our HXK and PFK enzyme activity findings do not appear to be due to a PMI effect (Figure 2). The average PMI in our brain samples was 12-13 hours. Although we found increases in LDH and PFK activity at 24 and 48 hour time points in our PMI rodent studies, these changes are in the opposite direction of our findings in schizophrenia. We also did not detect any changes in lactate or G6P levels in the DLPFC in schizophrenia (eFigure 5), or an effect of PMI on these factors. It may not be possible to detect localized or cell-specific changes in substrate/product levels in whole tissue homogenates. Techniques that may provide such specificity have not yet been adapted to postmortem substrate.

A common limitation to region-level studies is the inability to determine the cell type or types in which changes are occurring. Our study addresses this concern using a cell-level approach to assess metabolic pathways in schizophrenia, as well as extensive rodent studies to probe for possible medication and PMI effects. The present study is not without limitations. First, the LCM technique does not produce entirely homogeneous samples. We have previously used neurochemical markers to demonstrate enrichment of populations of pyramidal neurons and astrocytes (32-34). Due to the labor-intensive nature of the LCM studies presented here, we have not yet examined our dependent measures at the cellular level in multiple brain regions, other cell-subtypes, a non-schizophrenia disease cohort, or rats with varying PMIs. Additionally, our findings need to be replicated in an independent sample set and a sample set with additional female subjects. The present study would also be strengthened by examining our dependent measures in an animal model of schizophrenia treated with antipsychotics. Finally, schizophrenia is characterized by hypofrontality and thus the impaired glucose metabolism in pyramidal neurons reported here could be causative or a consequence of this abnormality. Further studies are needed to determine if glycolytic disturbances are a primary or secondary effect.

The cell-subtype specific nature of the bioenergetic defects observed here suggest other cell types may have unique bioenergetic profiles in schizophrenia. GABAergic interneurons, particularly fast-spiking interneurons, may be particularly susceptible due to their high-energy processes. Studies suggest that in normal brain, GABAergic neurons consume a

substantial fraction of glucose, and glucose metabolism might be higher in GABAergic neurons than in glutamatergic neurons, making them more vulnerable to bioenergetic insults (64, 65). Additionally, there is evidence that glucose metabolism increases during long-term recurrent inhibition of hippocampal pyramidal cells, and decreases in GABAergic inhibitory tone in schizophrenia might reflect a decrease in glucose utilization (66). Abnormal bioenergetic function in these cells could further disrupt excitatory/inhibitory balance in schizophrenia. Further studies examining glycolytic pathways in interneurons could provide insight into the circuity involved.

Taken together with previous studies, the findings reported here suggest metabolic systems are an important target in delineating the pathophysiology of schizophrenia. Augmenting affected systems such as glucose utilization pathways could offer a novel approach to restoring cognitive function in schizophrenia. This could include targeting pro-metabolic substrates pharmacologically. Pioglitazone (Pio), a synthetic ligand for peroxisome proliferator-activated receptor gamma (PPARγ), can alter the transcription and expression of GLUT1, leading to changes in glucose uptake through PPARγ and other mechanisms (67, 68). An increase in glucose uptake stimulates glycolytic pathways and may restore some cognitive deficits. Previously, pioglitazone was assessed in 42 Alzheimer's patients accompanied with type II diabetes mellitus for 6 months. Interestingly, patients receiving pioglitazone treatment had increased regional cerebral blood flow in the parietal lobe and cognitive improvement, as well as enhanced insulin sensitivity (69). Pioglitazone has also been used as an adjunct to antipsychotics, resulting in the reduction of negative symptoms in schizophrenia (70, 71). Other studies administering similar drugs, such as the antibiotic ceftriaxone, which increases glucose metabolism via increased glutamate transporter 1 expression and glutamate uptake, have shown modest decreases in psychotic symptoms in schizophrenia subjects (72-74).

In summary, our novel data implicate functional deficits of glucose metabolism and a cell-subtype specific defect of glycolytic processes in the DLPFC in schizophrenia, possibly impacting the ability of neurons to respond to the high energy demands associated with neuroplastic events (1, 30, 75). Since bioenergetics are tightly coupled to cognitive function, abnormal metabolism in the prefrontal cortex may directly impact cognitive tasks such as working memory in schizophrenia (60-62). There remain significant challenges in developing high efficacy therapeutics for schizophrenia, but substrates modulating bioenergetic systems such as glycolysis and oxidative phosphorylation could offer plausible avenues for development of novel pharmacological interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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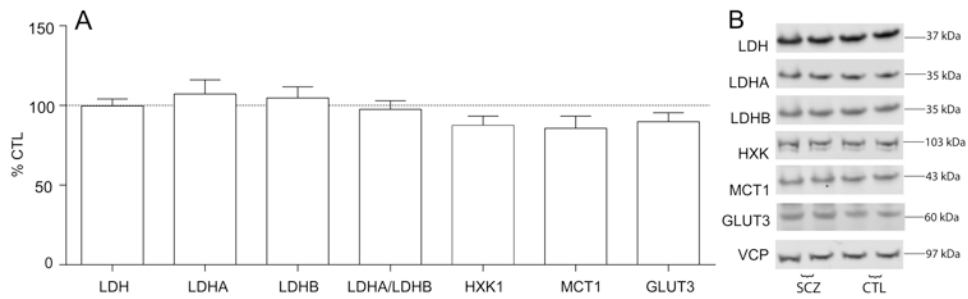
Figure 1.
Region-level protein expression. Expression of lactate dehydrogenase (LDH), lactate dehydrogenase A (LDHA), lactate dehydrogenase B (LDHB), LDHA:LDHB, hexokinase 1 (HXK1), monocarboxylate transporter 1 (MCT1), and glucose transporter 3 (GLUT3) in the dorsolateral prefrontal cortex (DLPFC) of schizophrenia patients (SCZ) normalized to valosin-containing protein (VCP) and expressed as percent control (CTL) (A). Western blot representation of LDH, LDHA, LDHB, HXK1, MCT1 and VCP expression at predicted band weights in SCZ and CTL subjects (B) (n=16 per group). Data are expressed as mean ± SEM.
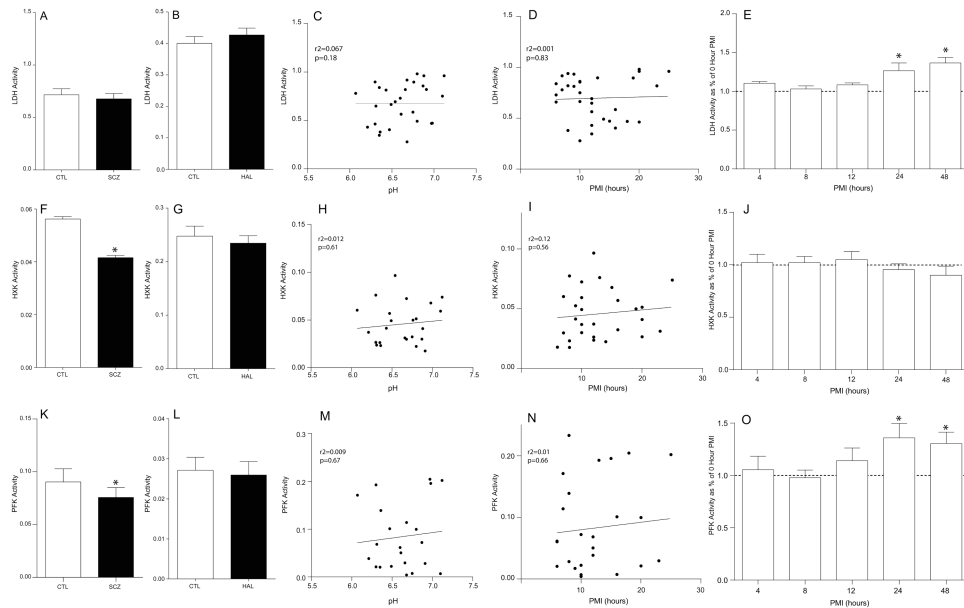
Figure 2.
Enzyme activity. Lactate dehydrogenase (LDH), hexokinase (HXK), and phosphofructokinase (PFK) activity in the dorsolateral prefrontal cortex (DLPFC) in control subjects (CTL) and subjects with schizophrenia (SCZ) measured in nmoles nicotinamide adenine dinucleotide hydrate (NADH) over time (A, F, K). LDH, HXK, and PFK activity in rat prefrontal cortex (n=10 per group) treated with haloperidol-decanoate (28.5 mg kg−1) (HAL) or vehicle (CTL) for 9 months (B, G, L), and LDH, HXK, and PFK activity in rats simulating varying postmortem intervals (PMIs) expressed as percent of 0 hour PMI (E, J, O). Correlation of LDH, HXK, and PFK activity and pH (C, H, M) or PMI (D, I, N) in CTL subjects and subjects with SCZ. Data are expressed as mean ± SEM (n=16 per group).*P<0.05.
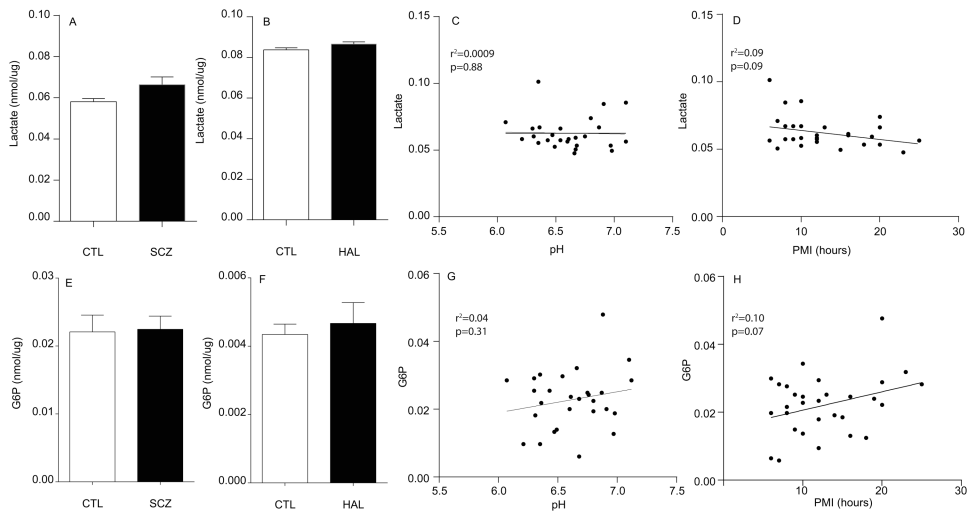
Figure 3.
Substrate concentrations. Lactate (A) and G6P (E) concentration measured in the dorsolateral prefrontal cortex (DLPFC) of control subjects (CTL) and subjects with schizophrenia (SCZ) expressed as nmoles/μg protein. Lactate (B) and G6P (F) concentration in rat prefrontal cortex treated with haloperidol (HAL) or vehicle (CTL) for 9 months. Correlation of lactate (C) and G6P (G) concentration and pH in CTL subjects and subjects with SCZ. Correlation of lactate (D) and G6P (H) concentration and PMI in CTL subjects and subjects with SCZ. Data (A-F) are expressed as mean ± SEM (n=10 per group).
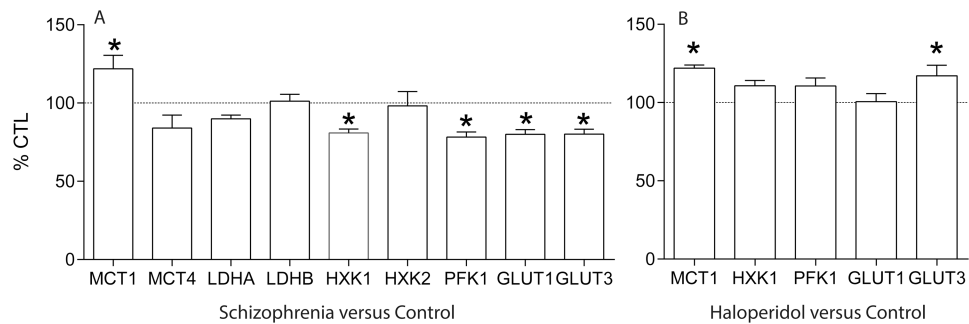
Figure 4.
Relative expression levels of lactate dehydrogenase A (LDHA), LDHB, hexokinase 1 (HXK1), HXK2, phosphofructokinase (PFK), monocarboxylate transporter 1 (MCT1), MCT4, glucose transporter 1 (GLUT1), and GLUT3 transcripts in enriched pyramidal neuron populations from schizophrenia (SCZ) and control (CTL) subjects (A). Relative expression levels of HXK1, PFK1, MCT1, GLUT1, and GLUT3 transcripts in enriched pyramidal neuron populations from haloperidol and control treated rats (B). Data from pyramidal neuron enriched samples were normalized to the geometric mean of three housekeeping genes. Data are expressed as percent control ± SEM. *P<0.05.

Table 1

Subjects Table

	mRNA		Enzyme/Protein	
	CTL	**SCZ**	**CTL**	**SCZ**
N	16	16	16	16
Sex	14m,2f	14m,2f	12m,4f	13m,3f
pH	6.6±0.2	6.6±0.3	6.6±0.2	6.6±0.3
PMI	13±4	15±5	12±5	13±6
Age	44±9	45±11	43±9	45±11
Rx	0/16	3/11/2	0/16	2/11/3

Subject demographics. Control subjects (CTL), schizophrenia (SCZ), postmortem interval (PMI), male (m), female (f), off or unknown / on typical / atypical antipsychotics (Rx).