Metabolic Insights into Neuropsychiatric Illnesses & Ketogenic Therapies: A Transcriptomic View

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INTRODUCTION

The disruption of brain energy metabolism, leading to alterations in synaptic signaling, neural circuitry, and neuroplasticity, has been implicated in severe mental illnesses such as schizophrenia, bipolar disorder, and major depressive disorder [1].

The therapeutic potential of ketogenic interventions in these disorders suggests a link between metabolic disturbances and disease pathology [2]; however, the precise mechanisms underlying these metabolic disturbances, and the therapeutic effects of metabolic ketogenic therapy, remain poorly understood.

In this study, we conducted an in silico analysis of transcriptomic data to investigate perturbations in metabolic pathways in the brain across severe mental illnesses via gene expression profiling. We also examined dysregulation of the same pathways in rodent or cell culture models of ketosis, comparing these expression profiles to those observed in the disease states.

METHODS

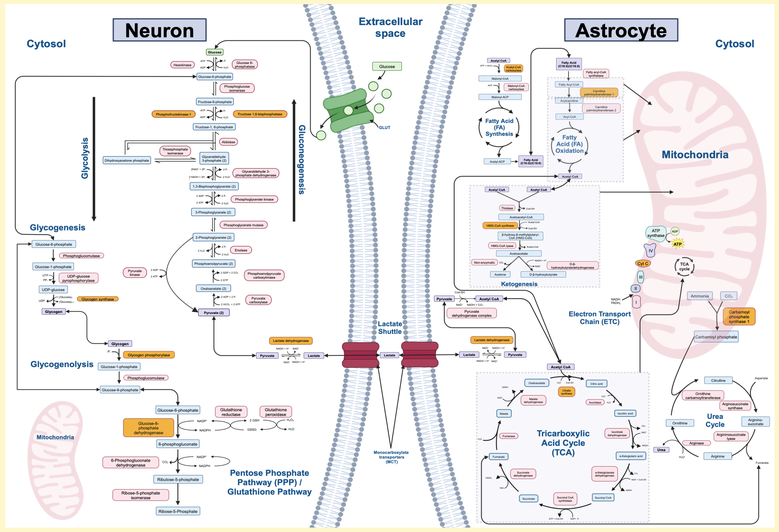
First, a literature search was performed to select major biochemical pathways involved in mammalian cellular metabolism. The gene annotation tool, Gene Ontology (GO), was used to obtain the gene symbols associated with enzymes in metabolic pathways. The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database within Kaleidoscope was used to refine final gene sets for each pathway.

Next, the Gene Expression Omnibus (GEO) data repository was used to filter datasets that assessed the effects of various ketogenic interventions. These datasets were processed utilizing Galaxy and EdgeR and were uploaded to the "ketosis" module within the Kaleidoscope Lookup tool [3].

Finally, gene sets associated with each metabolic pathway were queried within Kaleidoscope Lookup and analysis of the differentially expressed genes was performed among all schizophrenia, bipolar, depression, and ketosis datasets.

Side-by-side comparisons of the differentially expressed genes in schizophrenia vs. ketosis, bipolar vs. ketosis, and depression vs. ketosis were performed to assess patterns of dysregulation among pathways for each comparison

RESULTS



Metabolic Pathway (n=12)	Rate-Limiting Enzyme	Final Gene List (Output from Kaleidoscope STRING)	Number of Genes (n=242)
Gluconeogenesis	Fructose-1,6-bisphosphate	PC, PCK1, PCK2, FBP1, FBP2, G6PC1, G6PC2, G6PC3, PFKFB2	9
Glycolysis	Phosphofructokinase	HK1, HK2, HK3, GCK, GPI, PFKL, PFKM, PFKP, ALDOA, ALDOB, ALDOC, TPI1, GAPDH, GAPDHS, PGK1, PGK2, BPGM, PGAM1, PGAM2, PGAM4, ENO1, ENO2, ENO3, ENO4, PKLR, PKM	27
Lactate Shuttle (Neuron-Astrocyte)	Lactate dehydrogenase	SLC2A3, LDHA, LDHC, LDHD, SLC16A1, SLC16A3, GLS, GLS2, GLUL, SLC2A1, SLC2A10, SLC2A11, SLC2A12, SLC2A14, SLC1A1, SLC1A2, SLC1A3, SLC1A6	18
Tricarboxylic Acid (TCA) Cycle	Citrate Synthase	CS, ACLY, ACO1, ACO2, IREB2, IDH1, IDH2, IDH3A, IDH3B, IDH3G, OGDH, OGDHL, SUCLA2, SUCLG2, SUCLG1, SDHA, SDHB, SDHC, SDHD, SDHAF1, SDHAF4, ALDH5A1, FH, MDH1B, MDH2, PDHA1, PDHA2, DBT, DLAT, DLD	30
Electron Transport Chain (ETC)	Cytochrome C oxidase	NDUFA8, NDUFS4, NDUFV3, NDUFA11, NDUFS5, NDUFC1, NDUFC2, NDUFS1, NDUFV2, NDUFV1, NDUFA12, NDUFB5, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND5, MT-ND6, MT-ND4L, SDHA, SDHB, SDHC, SDHD, SDHAF1, SDHAF2, SDHAF3, SDHAF4, UQCRB, UQCRQ, UQCRC1, UQCRC2, UQCR10, MT-CYB, CYC1, UQCRFS1, UQCRH, UQCR10, UQCR11, COX4I1, COX4I2, COX5A, COX5B, COX6A1, COX6A2, COX6B1, COX6B2, COX6C, COX7A1, COX7A2, COX7B, COX7B2, COX7C, COX8A, COX8C, MT-CO1, MT-CO2, MT-CO3, COQ4, COQ7, COQ10A, COQ10B, CYCS, ATP5F1A, ATP5F1B, ATP5F1C, ATP5F1D, ATP5F1E, MT-ATP6, MT-ATP8	69
Fatty Acid Synthesis	Acetyl-CoA carboxylase	ACACA, ACACB, MCAT, FASN, OXSM, DECR1, HADH, ELOVL1, ELOVL3, ELOVL6, OLAH, PPT1, PPT2	13
Fatty Acid Oxidation	Carnitine Palmitoyltransferase I	SLC27A2, ACSBG2, ACSBG1, ECI1, ECHS1, HADHA, HSD17B10, HADH, HADHB, ACAA2, SCP2, VLCAD, SCAD, MCAD, LCAD, CPT1C, CPT2	17
Ketogenesis	HMG-CoA synthase	ACAT1, ACAA1, ACAA2, HMGCS1, HMGCS2, HMGCL, HMGCLL1, BDH2, BDH1	9
Glycogenesis	Glycogen synthase	ADPGK, GCKR, HK1, HK2, HK3, PGM1, PGM2, UGP2, GYS1, GYS2, GSK3A, GSK3B, GBE1	13
Glycogenolysis	Glycogen phosphorylase	PYGL, PYGM, PYGB, AGL, PGM1, PGM2, G6PC1, G6PC2, G6PC3	9
Urea Cycle	Carbamoyl phosphate synthetase I	OTC, OAT, CPS1, CAD, ASS1, ASL, ARG1, ARG2, AGMAT, NAGS, ACY1	11
Pentose Phosphate/ Glutathione Pathways	Glucose-6-phosphate dehydrogenase	HK1, HK2, HK3, G6PD, PGD, TKT, TKTL1, TKTL2, TALDO1, GPI, GCLC, GSS, GSR, SOD1, RPE, RPIA, RGN	17

Metabolic Pathway	Significant Genes by Pathway in Schizophrenia (SCZ) Datasets (n=35)	SCZ Average LFC Values	Significant Genes by Pathway in Ketogenic Intervention (KI) Datasets (n=8)	KI Average LFC Values
Gluconeogenesis	Upregulated: PC, PCK1	1.08	Upregulated: PC	0.23
	Downregulated: G6PC3, PFKFB2	-0.32	Downregulated: PCK2	-1.56
Glycolysis	Upregulated: ALDOA, ALDOB, ALDOC, GAPDHS, PGAM2, ENO1, ENO3, PKLR, PKM	0.68		
	Downregulated: GAPDH, PFKM, PFKP, PGK1, PGK2	-0.58	Downregulated: ENO1, GAPDH, PFKP	-0.56
Lactate Shuttle (Neuron-Astrocyte)	Upregulated: GLUL, LDHC, SLC16A3, SLC1A2, SLCIA3, SLC2A1	0.58	Upregulated: SLC16A1	0.29
	Downregulated: GLS2, LDHA, SLC1A1, SLC2A11, SLC2A14	-0.23		
Tricarboxylic Acid (TCA) Cycle	Upregulated: ACO1, ACO2, CS, DBT, IDH2, SDHA, SUCLG2	0.39		
	Downregulated: DLD, IDH1, IDH3B, MDH2, SDHB, SDHD, SUCLA2	-0.33	Downregulated: CS, IDH3G, SDHA, SDHB, SUCLG2	-0.67
Electron Transport Chain (ETC)	Upregulated: COX4I2, COX6B2, SDHA, UQCR10	0.56	Upregulated: CYCS, COX4I2, SDHAF3	0.40
	Downregulated: ATP5F1A, ATP5F1B, ATP5F1C, ATP5F1E, COQ10B, COQ4, COQ7, COX5A, COX5B, COX6A1, COX6B1, COX6C, COX7A1, COX7A2, COX7B, COX7C, COX8A, CYC1, NDUFA12, NDUFA8, NDUFB5, NDUFC2, NDUFS4, NDUFS5, NDUFV1, NDUFV2, NDUFV3, SDHAF3, SDHB, SDHD, UQCR11, UQCRB, UQCRC1, UQCRFS1, UQCRQ	-0.30	Downregulated: ATP5F1C, ATP5F1D, COX411, COX5B, COX6C, CYC1, SDHA, SDHB, NDUFV2, UQCRC1, UQCRFS1	-0.62
Fatty Acid Synthesis	Upregulated: ACACB, DECR1, FASN, HADH	0.50	Upregulated: ACACB, HADH	0.70
	Downregulated: ELOVL1, MCAT, OLAH, OXSM	-0.68	Downregulated: DECR1, PPT1	-0.69
Fatty Acid Oxidation	Upregulated: ACAA2, CPT1C, CPT2, HADHA, HSD17B10	0.56	Upregulated: HADH	0.41
	Downregulated: SCP2	-0.48		
Ketogenesis	Upregulated: ACAA2, BDH1, BDH2, HMGCLL1	0.82		
	Downregulated: ACAA1, HMGCS1	-0.30		
Glycogenesis	Upregulated: HK2	0.33		
	Downregulated: GBE1, GSK3A, GSK3B, GYS1	-0.22	Downregulated: PGM1	-0.50
Glycogenolysis	Upregulated: PYGL	0.54	Upregulated: PYGL, PYGM	0.56
	Downregulated: G6PC3	-0.36	Downregulated: PGM1	-0.50
Urea Cycle	Upregulated: ACY1, AGMAT, CAD	0.90		
	Downregulated: ARG2, ASS1, CPS1, OAT	-0.32	Downregulated: OAT	-0.56
Pentose Phosphate/ Glutathione Pathways	Upregulated: G6PD, GPI, HK2, RPE, TKT	0.52		
	Downregulated: GCLC, GSS, RPIA, SOD1, TALDO1	-0.26	Downregulated: G6PD, GSR, RPIA	-0.73

DISCUSSION

- The observed metabolic perturbations from this study reveal a multifaceted disruption of brain energy metabolism across neuropsychiatric illnesses.
- We found significant perturbations across all metabolic pathways, with the greatest perturbations in glycolysis, the tricarboxylic acid (TCA) cycle, and the electron transport chain (ETC) across all three disorders.
- We also observed discordant gene expression patterns between disease states and ketogenic intervention studies, suggesting a potential role for ketone bodies in modulating pathogenic metabolic changes
- These findings highlight the importance of understanding metabolic dysregulation in severe mental illnesses and the potential therapeutic benefits of ketogenic interventions in restoring metabolic homeostasis.
- These findings also provide a basis for understanding the heterogeneity of cell type etiology and behavioral phenotypes seen in severe mental illnesses.

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