Metabolic dysfunction, aging and cognition

Norman J. Haughey
Johns Hopkins University School of Medicine
Metabolic Aging

Metabolic age is a comparison between a person's basal metabolic rate (BMR) against the average BMR for that person's age.

Calculate your BMR (basal metabolic rate): Women: \( \text{BMR} = 655 + (4.35 \times \text{weight in pounds}) + (4.7 \times \text{height in inches}) - (4.7 \times \text{age in years}) \) 
Men: \( \text{BMR} = 66 + (6.23 \times \text{weight in pounds}) + (12.7 \times \text{height in inches}) - (6.8 \times \text{age in years}) \)
Metabolic rate decreases and percentage of fat increases with age.
Insulin Resistance and Metabolic Syndrome

In non-diabetic individuals, insulin resistance commonly clusters with:

- upper body fat distribution
- glucose intolerance
- relative hypertension
- dyslipidemia
- age
- sex
- ethnicity
- sub-clinical inflammation
- circulating adipokines
- intracellular lipid accumulation in liver and skeletal muscle

- Strong association with Alzheimer’s disease
- Growing association with CI in HIV

The NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders
Human studies showing metabolic changes with HIV

Role of **obesity, metabolic variables, and diabetes** in HIV-associated neurocognitive disorder. *Neurology* 2012

**Cerebral metabolite changes** prior to and after antiretroviral therapy in primary HIV infection. *Neurology* 2014
Andrew C. Young, Constantin T. Yiannoutsos, PhD, Manu Hegde, MD, PhD, Evelyn Lee, Julia Peterson, Rudy Walter, Richard W. Price, MD, Dieter J. Meyerhoff, PhD and Serena Spudich, MD

Cerebrospinal fluid **metabolomics** implicate bioenergetic adaptation as a neural mechanism regulating shifts in cognitive states of HIV-infected patients. *AIDS* 2015
Alex M. Dickens; Daniel C. Anthony; Reena Deutsch; Michelle M. Mielke; Timothy D.W. Claridge; Igor Grant; Donald Franklin; Debra Rosario; Thomas Marcotte; Scott Letendre; Justin C. McArthur; Norman J. Haughey

**Abdominal obesity** contributes to neurocognitive impairment in HIV-infected patients with increased inflammation and immune activation. *JAIDS* 2015

**Complement Component 3** Is Associated with **Metabolic Comorbidities** in Older HIV-Positive Adults. *AIDS Res* 2016
Bryant AK1, Fazeli PL2, Letendre SL1, Ellis RJ1,3, Potter M1, Burdo TH4, Singh KK5, Jeste DV2,6, Grant I1,2, Moore DJ1,2.
IR associated with NCI in HIV

Insulin resistance associated with NCI

Valcour et al., JAIDS 2006

HOMA associated with NCI in WISE

Valcour et al., AIDSrhs. 2012

BMI < 18.5 and obese BMI (higher BMI = better performance)

Valcour et al., J Neurovirol. 2013
Plasma metabolic measures in the discovery cohort (CHARTER n=47)

A. Insulin (pmol/L)***
B. C-peptide (ng/mL)***
C. C/I Molar Ratio (C:I)
D. Cholesterol (mg/dL)
E. HDL (mg/dL)***
F. LDL (mg/dL)
G. TC/HDL Ratio
H. LDI/HDL Ratio
I. Triglycerides (mg/dL)***
J. Adiponectin (ug/mL)***

Khuder et al., 2018 under review

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Plasma metabolic measures in the validation cohort (MACS n=72)

Khuder et al., 2018 under review

The NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders
Insulin signaling

- Glucose neogenesis
- Glucose genolysis
- Lipolysis
- Ketogenesis
- Proteolysis

- Glucose uptake
- Glycolysis
- Glycogen synthesis
- Protein synthesis

The NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders
Evidence for alterations of energy metabolism in HIV and NC

- Skeletal muscle is hypermetabolic in patients with HIV lipodystrophy.
- Possibly an adaptive thermogenesis in response to an inability to store triglyceride fuel in a normal manner.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Gene Title</th>
<th>HAND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trks</td>
<td>TRF1-interacting ADP-ribose pol</td>
<td>1.179 0.018</td>
</tr>
<tr>
<td>Mthfd1l</td>
<td>methylenetetrahydrofolate DH 1L</td>
<td>1.423 0.020</td>
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<tr>
<td>Arl5b</td>
<td>ADP-ribosylation factor-like 5B</td>
<td>1.142 0.021</td>
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<tr>
<td>Mthfd2l</td>
<td>methylenetetrahydrofolate DH 2L</td>
<td>1.406 0.107</td>
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<tr>
<td>Atp6v1g1</td>
<td>ATPase, lysosomal V1 subunit G1</td>
<td>1.195 0.128</td>
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<tr>
<td>Atp1b3</td>
<td>ATPase, beta 3 polypeptide</td>
<td>1.215 0.473</td>
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<tr>
<td>Atp5f1</td>
<td>ATP synthase, mitochondrial F1 c, G1</td>
<td>1.069 0.724</td>
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<tr>
<td>Tiparp</td>
<td>TCDD-inducible poly(ADP-ribose) pol</td>
<td>1.521 0.039</td>
</tr>
<tr>
<td>Abcg1</td>
<td>ATP-binding cassette, sub-family G,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>class VI, type 11C</td>
<td></td>
</tr>
<tr>
<td>Atp1ic</td>
<td>ATPase, class II, type 9B</td>
<td>1.140 0.163</td>
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<tr>
<td>Atp15</td>
<td>ADP-ribosylation factor related 1p</td>
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<td>Atp9b</td>
<td>ATPase, class II, type 9B</td>
<td>1.131 0.075</td>
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<td>Atp15</td>
<td>ADP-ribosylation factor related 15</td>
<td>1.183 0.033</td>
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<td>Atp2b4</td>
<td>ATPase, Ca++ transporting 4</td>
<td>1.060 0.044</td>
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<td>Atp6v1g2</td>
<td>ATPase, lysosomal V1 sub G2</td>
<td>1.812 0.007</td>
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<td>Glutamine/glutamate/glutaminase</td>
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<tr>
<td>Glib1</td>
<td>galactosidase, beta 1</td>
<td>1.019 0.020</td>
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<tr>
<td>Gct1</td>
<td>glut oxaloacetate transaminase 1</td>
<td>1.071 0.508</td>
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<td>Gclm</td>
<td>glut-cysteine ligase</td>
<td>1.312 0.038</td>
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<td>Gftp1</td>
<td>glutamine fructose-6P transaminase1</td>
<td>1.003 0.927</td>
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<td>Qser1</td>
<td>glutamine and serine rich 1</td>
<td>1.093 0.030</td>
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<tr>
<td>Tgm2</td>
<td>transglutaminase 2</td>
<td>1.054 0.419</td>
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<tr>
<td>Tgm3</td>
<td>transglutaminase 3</td>
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<td>Tgm5</td>
<td>transglutaminase 5</td>
<td>1.091 0.142</td>
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<tr>
<td>Cytochrome/mitochondria</td>
<td></td>
<td></td>
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<tr>
<td>Sod2</td>
<td>superoxide dismutase 2</td>
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<td>Me2</td>
<td>malic enzyme 2, mitochondrial</td>
<td>1.052 0.164</td>
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<td>Cox11</td>
<td>cytochrome c oxidase 11</td>
<td>1.121 0.308</td>
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<td>Mdh2</td>
<td>malate dehydrogenase 2, NAD</td>
<td>1.177 0.522</td>
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<td>Cox5a</td>
<td>cytochrome c oxidase, subunit Va</td>
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<tr>
<td>Ucp2</td>
<td>Uncoupling protein 2</td>
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<td>Cyp46a1</td>
<td>cytochrome P450, f46, sfa</td>
<td>2.020 0.0001</td>
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<tr>
<td>Glycolysis/Glc</td>
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<tr>
<td>Ugcg</td>
<td>UDP-glucose ceramide</td>
<td>2.232 0.007</td>
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<td>Pfkfb3</td>
<td>6-PF-2-kinase/fructose-2,6-biP 3</td>
<td>1.138 0.001</td>
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<tr>
<td>Pgpk1</td>
<td>phosphoglycerate kinase</td>
<td>1.337 0.336</td>
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<tr>
<td>Pkm2</td>
<td>pyruvate kinase</td>
<td>1.147 0.194</td>
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<tr>
<td>Ugp2</td>
<td>UDP-glucose pyrophosphorylase 2</td>
<td>1.108 0.653</td>
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<tr>
<td>Insulin</td>
<td></td>
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<tr>
<td>Igfals</td>
<td>insulin-like growth factor binding</td>
<td>1.162 0.058</td>
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<tr>
<td>Igfbp4</td>
<td>insulin-like GF binding p4</td>
<td>1.058 0.296</td>
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<tr>
<td>Igfbp6</td>
<td>insulin-like GF binding p6</td>
<td>1.198 0.019</td>
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</table>


The NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders
Cerebrospinal fluid metabolomics implicate bioenergetic adaptation as a neural mechanism regulating shifts in cognitive states of HIV-infected patients

NOSEY and 2D COSY $^1$H-NMR spectroscopy enabled the identification of energy metabolites.

Dickens et al., AIDS; 29 (2015) 559-569
Prognostic markers for neurocognitive decline

**Prognostic**

N = 50

- **Nadir CD4**
  - <322
  - ≥322

- **Current CD4**
  - <136
  - ≥136

- **Stably Normal**

- **Worsening**

- **Plasma viral load**
  - Detectable
  - Undetectable

- **Antiretroviral status**
  - Off
  - On

- **Glutamine**
  - >25.04x10^5
  - ≤25.04x10^5

- **Citrate**
  - >3.12x10^5
  - ≤3.12x10^5

- **Creatinine**
  - >2.11x10^5
  - ≤2.11x10^5

- **Creatine**
  - >2.11x10^5
  - ≤2.11x10^5

- **Acetate**
  - >8.24x10^6
  - ≤8.24x10^6

- **Citrate**
  - >5.01x10^5
  - ≤5.01x10^5

**Change**

N = 50

- **Plasma viral load**
  - No change
  - Change

- **Creatine**
  - Stably Normal

- **Creatine**
  - Stably Normal

- **Acetate**
  - Stably Normal

- **Citrate**
  - Stably Normal

**Predictive accuracy 86%**

**Sensitivity 96%**

**Specificity 76%**

Dickens et al., AIDS; 29 (2015) 559-569

The NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders
Cognitive worsening: Excessive glycolysis

Citrate accumulates when the glycolytic rate exceeds the capacity of the TCA cycle

Adapted from: Ramsköld et al. Wikipathways

The NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders
Lower cognitive reserve when aging with HIV

Age-Dependent Increases in Brain Activation

Chang et al., Neurobiol of Aging 2013
Prognostic markers for neurocognitive improvement

Prognostic

N = 48

Current CD4 Count

<176

≥176

Improving

Plasma viral load

Detectable

Undetectable

Improving

Stably impaired

Glucose

<3.54x10^-4

≥3.54x10^-4

≥5.54x10^-5

<5.54x10^-5

≥5.01x10^-5

<5.01x10^-5

Improving

Stably impaired

Lactate

≥6.43x10^-4

<6.43x10^-4

≥6.41x10^-5

<6.41x10^-5

Improving

Stably impaired

HCV status

-ve

+ve

Acetate

<2.04x10^-5

≥2.04x10^-5

Glutamine

≥6.41x10^-5

<6.41x10^-5

Improving

Stably impaired

Predictive accuracy 92%
Sensitivity 87%
Specificity 96%

Longitudinal change in metabolites and clinical features

N = 48

myo-Inositol

<5.01x10^-5

≥5.01x10^-5

Glutamine

≥5.54x10^-5

<5.54x10^-5

Improving

Age

<47

≥47

Improving

Stably Impaired

β-Glucose

≥1.07x10^-4

<1.07x10^-4

Improving

Stably Impaired

Creatinine

<4.21x10^-5

≥4.21x10^-5

Antiretroviral status

On-On/Off-Off

Off-Off

Improving

Stably Impaired

Predictive accuracy 92%
Sensitivity 100%
Specificity 84%

The NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders
Cognitive improvement is associated with a shift to anaerobic glycolysis in the CNS

- Key metabolite changes:
  - Decreased glucose
  - Decreased acetate
  - Increased lactate
How can we regulate CNS energy metabolism to promote anaerobic glycolysis?

• Exercise: Kelly O’Brien, U of Toronto
  Meilissa Wilson, U of Colorado

• Intranasal delivery of insulin could promote the utilization of available glucose and the brain must then shift to alternate energy sources
## Summary of past and ongoing human intranasal insulin trials

<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>DOSE OF INTRANASAL INSULIN TESTED</th>
<th>PATIENT POPULATION</th>
<th>ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benedict, 2004</td>
<td>160 IU (long-term)</td>
<td>Healthy</td>
<td>Word list (immediate recall)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Word list (delayed recall)</td>
</tr>
<tr>
<td>Reger, 2006</td>
<td>20 or 40 IU (acute)</td>
<td>Probable AD or MCI vs. healthy</td>
<td>Story recall (immediate + delayed recall)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Word list (immediate + delayed recall)</td>
</tr>
<tr>
<td>Benedict, 2007</td>
<td>20 IU Aspart* vs. 20 IU Regular (long term)</td>
<td>Healthy men</td>
<td>Word list (immediate recall)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Word list (delayed recall)</td>
</tr>
<tr>
<td>Benedict, 2008</td>
<td>160 IU (acute)</td>
<td>Healthy, normal weight, with no medications</td>
<td>Digit span (immediate recall)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Object location (immediate recall)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mirror tracing (immediate recall)</td>
</tr>
<tr>
<td>Hallischmid, 2008</td>
<td>160 IU (long-term)</td>
<td>Obese men</td>
<td>Word list (delayed recall)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Word list (immediate recall)</td>
</tr>
<tr>
<td>Reger, 2008</td>
<td>20 IU (long term)</td>
<td>AD or MCI</td>
<td>1. Memory score (immediate/delayed recall ratio)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2. Voice onset time (immediate/delayed recall ratio)</td>
</tr>
<tr>
<td>Reger, 2008</td>
<td>10, 20, 40, 60 IU (acute)</td>
<td>AD or MCI</td>
<td>1. Story recall (immediate recall or delayed recall)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Story recall learning (immediate recall, delayed recall)</td>
</tr>
<tr>
<td>Krug, 2010</td>
<td>160 IU (acute)</td>
<td>Healthy postmenopausal women</td>
<td>1. Digit span (immediate recall)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Object location (immediate recall)</td>
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<tr>
<td>Fan, 2012</td>
<td>140 IU (acute)</td>
<td>Schizophrenic</td>
<td>1. Hopkins Verbal Learning Test (Immediate recall)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Hopkins Verbal Learning Test (Delayed)</td>
</tr>
<tr>
<td>Craft, 2012</td>
<td>10 or 20 IU bid</td>
<td>AD or MCI</td>
<td>1. Verbal Memory Composite</td>
</tr>
<tr>
<td>Craft, 2012</td>
<td>20 or 40 IU</td>
<td>AD or MCI</td>
<td>Story recall (delayed recall)</td>
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<tr>
<td>McIntyre, 2012</td>
<td>40 IU (long term)</td>
<td>Euthymic with bipolar disorder</td>
<td>California Verbal Learning Test, second edition</td>
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<td>Process Dissociation Task</td>
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<td>Burns, 2012</td>
<td>40 IU (acute)</td>
<td>Early AD</td>
<td>fMRI activation</td>
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<td></td>
<td></td>
<td></td>
<td>Cognitive battery</td>
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<tr>
<td>Novak, 2013</td>
<td>40 IU (long term)</td>
<td>Diabetic</td>
<td>Brief Visuo-spatial Memory Test-Revised</td>
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<td></td>
<td></td>
<td></td>
<td>Verbal fluency measures</td>
</tr>
<tr>
<td>Fan, 2013</td>
<td>40 IU (long term)</td>
<td>Schizophrenic</td>
<td>Cognitive battery</td>
</tr>
<tr>
<td>Craft, 2013</td>
<td>20 IU bid</td>
<td>AD or MCI</td>
<td>3. Cognitive battery</td>
</tr>
</tbody>
</table>

### The NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders
Intranasal insulin trial for NC in HIV

To examine whether intranasal insulin is safe and well tolerated in individuals with HAND

To examine whether intranasal insulin improves neuroimaging markers of CNS injury.

To examine whether intranasal insulin improves CSF surrogate markers of oxidative stress, axonal injury, inflammation and abnormal amyloid metabolism.

10 subjects enrolled – 2 completed
Intranasal insulin delivery in mice

- NMR measures of energy metabolites
- RNAseq - (hippocampus)
  - Time course and n=3/condition
- RNAseq – neurons
- RNAseq – astrocytes
- RT-PCR validation of gene expression
  - Energy Metabolism
- Untargeted Lipidomics
- Developed method to quantitatively measure fatty acids
- Direct measures of fatty acid oxidation
- Mitochondrial function
Intranasal insulin mouse (hippocampus)

2 SD = 236 transcripts
181 transcripts up regulated
55 transcripts down regulated

2 SD = 313 transcripts
173 transcripts up regulated
140 transcripts down regulated

2 SD = 241 transcripts
164 transcripts up regulated
77 transcripts down regulated

Total protein-protein coding genes 21,917 genes

The NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders
### Genes that regulate Oxidation

<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Gene Symbol</th>
<th>Encoded Product</th>
<th>Function</th>
<th>Astro 6hr</th>
<th>Astro 12hr</th>
<th>Neuron 6hr</th>
<th>Neuron 12hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>stearyl-CoA desaturase</td>
<td>SCD</td>
<td>Enzyme stearyl-CoA desaturase</td>
<td>This gene encodes an enzyme involved in fatty acid biosynthesis, primarily oleic acid. Regulate fatty acid and cholesterol metabolism</td>
<td>+3</td>
<td>+6</td>
<td>+1</td>
<td>+2</td>
</tr>
<tr>
<td>sterol regulatory element binding transcription factor 1</td>
<td>Srebf1</td>
<td>Sterol regulatory element binding protein-1 (SREBP-1)</td>
<td>This gene encodes a transcription factor that binds to the sterol regulatory element-1 (SRE1).</td>
<td>+3</td>
<td>+1</td>
<td>-2</td>
<td>-1</td>
</tr>
<tr>
<td>Fatty Acid Binding Protein 3</td>
<td>FABP3</td>
<td>Protein FABP3</td>
<td>The intracellular fatty acid-binding proteins (FABPs) belong to a multigene family. They are thought to participate in the uptake, intracellular metabolism and or transport of long chain fatty acids.</td>
<td>+3</td>
<td>+0.5</td>
<td>+0.5</td>
<td>-1</td>
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<tr>
<td>Acyl-CoA Synthetase Long-Chain Family Membrane 4</td>
<td>Acs4</td>
<td>Long-chain fatty acid-CoA ligase 4</td>
<td>The protein encoded by this gene is an isozyme of the long-chain-fatty-acid-coenzyme A ligase.</td>
<td>+2</td>
<td>+0.5</td>
<td>+2</td>
<td>+0.5</td>
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<tr>
<td>protein kinase AMP-activated non-catalytic subunit beta 1</td>
<td>Prkab1</td>
<td>5'-AMP-activated protein kinase subunit beta-1</td>
<td>The protein encoded by this gene is a regulatory subunit of the AMP-activated protein kinase (AMPK), an important energy-sensing enzyme that monitors cellular energy status.</td>
<td>+2</td>
<td>+2</td>
<td>-0.5</td>
<td>+0.5</td>
</tr>
<tr>
<td>Ubiquinol-Cytochrome C Reductase Core Protein I</td>
<td>Uqcr1</td>
<td>Cytochrome b-c1 complex subunit, mitochondrial</td>
<td>This is a component of the ubiquinol-cytochrome c reductase complex (complex II), which is part of the mitochondrial respiratory chain. This protein may mediate formation of the complex between cytochromes c and c1.</td>
<td>+2</td>
<td>+1</td>
<td>-1</td>
<td>-1</td>
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<tr>
<td>Fatty acid synthase</td>
<td>FASN</td>
<td>Fatty acid synthase (FAS)</td>
<td>The enzyme encoded by this gene catalyzes the synthesis of palmitate from acetyl-CoA and malonyl-CoA, in the presence of NADPH, into long-chain saturated fatty acids.</td>
<td>+1</td>
<td>+2</td>
<td>+0.5</td>
<td>+1</td>
</tr>
<tr>
<td>Carnitine Palmitoyltransferase 1</td>
<td>CPT1C</td>
<td>Carnitine palmitoyltransferase 1</td>
<td>The encoded protein regulates the beta-oxidation and transport of long-chain fatty acids into mitochondria.</td>
<td>+1</td>
<td>+2</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>acetyl-CoA acetyltransferase 2</td>
<td>ACAT2</td>
<td>Acetyl-CoA acetyltransferase, cytosolic</td>
<td>The product of this gene is an enzyme involved in lipid metabolism and it encodes cytosolic acetoacetyl-CoA thiolase.</td>
<td>+1</td>
<td>+2</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Protein Kinase CAMP-Activated Catalytic Subunit Alpha</td>
<td>PRKACA</td>
<td>Catalytic subunit α of protein kinase A</td>
<td>This gene encodes one of the catalytic subunits of protein kinase A.</td>
<td>+1</td>
<td>+1</td>
<td>-0.5</td>
<td>-1</td>
</tr>
<tr>
<td>Protein Kinase AMP-Activated Non-Catalytic Subunit Gamma</td>
<td>Prkag1</td>
<td>5’AMP-activated protein kinase subunit gamma-1</td>
<td>The protein encoded by this gene is a regulatory subunit of the AMP-activated protein kinase (AMPK).</td>
<td>+1</td>
<td>+1</td>
<td>-2</td>
<td>-2</td>
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The NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders
Validations of gene expression
(Astrocytes - FA metabolic pathways)

Fatty Acid Uptake and Biosynthesis

Fatty Acid Oxidation

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β-oxidation of fatty acids

- Occurs largely in peroxisomes and mitochondria
- Inside the cell fatty acids are elongated, desaturated and conjugated with CoA
- Long-chain acyl-CoAs are converted to a long-chain Acyl carnithines for transport into mitochondria
- Inside mitochondria Acyl carnithines are converted back into long-chain acyl-CoAs
- Metabolized by β-oxidation into acetyl CoA for TCA cycle

Glycolysis – 4 ATP total (2 used)

β-oxidation (palmitate) – 131 ATP (2 used)
Evidence for fatty acid utilization in astrocytes

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Summary/Discussion

- Metabolic abnormalities are common with HIV infection
  - Contribution of HIV
  - Contribution of ART
- Often are subclinical

- Promoting anaerobic metabolism is neuroprotective

- Intranasal delivery of insulin shifts brain utilization to β-oxidation of fatty acids
  - Produces 50X more ATP
The NIMH Center for Novel Therapeutics of HIV-associated Cognitive Disorders

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