The Molecular Link Between Metabolic Imbalance and Cognitive Function

Sangwon F. Kim, PhD
Department of Psychiatry and Pharmacology
Center for Neurobiology and Behavior
Perelman School of Medicine
University of Pennsylvania

Clinical Neurosciences Training Seminar Series
April 3rd, 2015
Research Focus in the Laboratory

Energy Metabolism

- Energy Balance/Nutrient Sensing
- Neuronal/Cellular Metabolic stress and neural circuit/behavior
- The Effects of Periphery Energy Balance on the Brain Function
OUTLINE

1) Adverse Metabolic Side Effects of Second Generation Antipsychotic Drugs

2) Effect of Periphery Energy Imbalance on Brain Function
OUTLINE

1) Adverse Metabolic Side Effects of Second Generation Antipsychotic Drugs

2) Effect of Periphery Energy Imbalance on Brain Function
Psychotic disorders

• **What is a psychotic disorder?**
Psychotic disorders are mental disorders in which the personality is seriously disorganized and *a person's contact with reality is impaired*. During a psychotic episode a person is confused about reality and often experiences delusions and/or hallucinations.

• **What characteristics/symptoms are associated with psychotic disorder?**
Some of the characteristics associated with psychotic disorders include delusions, hallucinations, bizarre behavior, incoherent or disorganized speech, disorganized behavior and/or a lack of emotion/motivation.

• **At what age do psychotic disorders appear?**
Generally, the first signs of most psychotic disorders appear when a person is in his/her late teens, twenties, or thirties.

• **How common are psychotic disorders in society?**
Psychotic disorders are actually quite common worldwide. About one percent (1%) of the population is thought to have some form of psychotic disorder.
Conventional (Typical) Antipsychotic Drugs

1. History

- The first antipsychotic drugs were discovered by accidents in the 1950s when a putative antihistamine (chlorpromazine) was observed to have antipsychotic effects when tested in schizophrenia patients.
- Chlorpromazine has antihistaminic activity, but its therapeutic actions in schizophrenia are not mediated by this property.
- Early in the testing process, Chlorpromazine and other antipsychotic agents were all found to cause neurolepsis, known as an extreme slowness or absence of motor movements as well as behavioral indifference in experimental animals as well as human.

2. Mechanism

- By the late 1960s and 1970s it was widely recognized that the key pharmacologic property of all neuroleptics with antipsychotic properties was their ability to block dopamine 2 receptors. This action provided to be responsible not only for efficacy of conventional antipsychotics but also for most of their undesirable side effects, including neurolepsis.
Atypical Antipsychotic Drugs (AAPDs)

1. Definition
   - a pharmacological perspective: the atypical antipsychotics may be defined in part as serotonin-dopamine antagonists (SDAs).
   - a clinical perspective: an atypical antipsychotic is defined in part by the clinical properties that distinguish such drugs from conventional antipsychotics. - low extrapyramidal symptoms (EPS) and efficacy for negative symptoms.

2. Mechanism

???
Side Effects of Antipsychotic Drugs

• Typical (conventional) drugs: Extrapyramidal symptoms (EPS) → general term for a number of disorders caused by abnormalities of the basal ganglia or certain brain stem or thalamic nuclei; characterized by motor deficits, loss of postural reflexes, bradykinesia, tremor, rigidity and various involuntary movement. cardiac effects, weight gain, elevation of prolactin secretion.

• Atypical drugs: EPS, glucose intolerance, diabetes and weight gains
Proposed Mechanisms Of Weight Gain

1. Inhibition of brain serotonin system which appears to modulate eating behavior.

2. Dysregulation of leptin which regulates eating habit and energy metabolism.
   - Elevated leptin level reduces food intake.
   - Clozapine-treated patients show the increased leptin level in serum but do not show the loss of appetites.

3. Abnormal lipid/glucose metabolism.
AAPDs Induces Lipid Synthesis

Fatty acid synthesis ($^{14}$C)

Cholesterol ($^{3}$H)

Triacylglycerol
Fatty acids
Cholesterol
Olanzapine Induces Fatty Acid Synthesis In Hela Cells

![Graph showing fatty acid synthesis with Olanzapine concentration and CPM/ug of protein. The EC50 is 48 nM.](image)
AMPK In The Brain

AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus

Yasuhiro Minekoshi¹, Thierry Alquier¹, Noboru Furukawa¹, Young-Bum Kim¹, Anna Lee¹, Bingzhong Xue¹, James Mu¹, Fabienne Faurel², Pascal Ferre², Morris J. Birnbaum², Bettina J. Stuck¹ & Barbara B. Kahn¹

¹Division of Endocrinology, Diabetes and Metabolism, Beth Israel Deaconess Medical Center and Department of Medicine, Harvard Medical School, Boston, Massachusetts 02215, USA
²Howard Hughes Medical Institute, The Fox Institute, University of Pennsylvania Medical School, Philadelphia, Pennsylvania 19104, USA
³Unit 465 INSERM, Centre de Recherches Biomédicales des Cordeliers, 75270 Paris Cedex 6, France

Obesity is an epidemic in Western society, and causes rapidly accelerating rates of type 2 diabetes and cardiovascular disease. The evolutionarily conserved serine/threonine kinase, AMP-activated protein kinase (AMPK), functions as a ‘fuel gauge’ to monitor cellular energy status¹. We investigated the potential role of AMPK in the hypothalamus in the regulation of food intake. Here we report that AMPK activity is inhibited in arcuate and paraventricular hypothalamic (PVH) by the anorexigenic hormone leptin, and in multiple hypothalamic regions by insulin, high glucose and refeeding. A melanocortin receptor agonist, a potent anorexigen², decreases AMPK activity in PVH, whereas agouti-related protein, an orexigen³, increases AMPK activity. Melanocortin receptor signalling is required for leptin and refeeding effects on AMPK in PVH. Dominant negative AMPK expression in the hypothalamus is sufficient to reduce food intake and body weight, whereas constitutively active AMPK increases both. Alterations of hypothalamic AMPK activity augment changes in arcuate neuropeptide expression induced by fasting and feeding. Furthermore, inhibition of hypothalamic AMPK is necessary for leptin’s effects on food intake and body weight, as constitutively active AMPK blocks these effects. Thus, hypothalamic AMPK plays a critical role in hormonal and nutrient-derived anorexigenic and orexigenic signals and in energy balance.

pAMPK up  →  an increase of appetite
pAMPK down  →  a decrease of appetite
AMP-Activated Protein Kinase (AMPK)

Why sensing AMP (e.g. AMP:ATP)?

- ATP → ADP → AMP
  - Pi
  - It is because of Adenylate Kinases.
    - (2ADP → ATP + AMP)

- TAK1 (MEKK7): a protein kinase downstream from cytokine receptors. TNF-related apoptosis inducing ligand (TRAIL) can activate AMPK and yet physiological significance of this mechanism is not clear.
Antipsychotic Drugs Activate AMPK Via Histamine H1 Receptor

**A.**

- CTL
- Clozapine
- Olanzapine
- Quetiapine
- Risperidone
- Ziprasidone

**B.**

- CTL
- Clozapine
- Haloperidol
- Aripipirazole

**C.**

- CTL
- Tri (50, 500)
- Clozapine

**D.**

- CTL
- Clozapine
- CLO 200 nM

**Drugs**

- Clozapine
- Olanzapine
- Quetiapine
- Risperidone
- Ziprasidone
- Haloperidol
- Aripipirazole

**IC50 (nM)**

- Clozapine: 9
- Olanzapine: 13
- Quetiapine: 40
- Risperidone: 80
- Ziprasidone: 150
- Haloperidol: 2000>
- Aripipirazole: 3000>

**Orexigenic Effects**

- Clozapine: ++++
- Olanzapine: +++
- Quetiapine: ++
- Risperidone: +/-
- Ziprasidone: -
- Haloperidol: -
- Aripipirazole: -
Clozapine Activates Hypothalamic AMPK via Histamine H1 Receptor
Clozapine Increases Food Intake In Mice During Light Cycle

Fig.5. Clozapine has an effect on neuropeptides in the hypothalamus and food intake during light cycle. A. Mice (n=6/group) received clozapine (3 mg/kg) and were sacrificed at 3 h. Hypothalami were removed and mRNA levels were measured by real-time PCR. B. C57BL/6J Mice (8 weeks of age, n=6/group) were individually housed at 22°C, maintained on a 12-h/12-h light/dark cycle (lights off at 9:00 AM.) Mice were administered with 1 mg/Kg clozapine and food intake was measured for 24 hr. C. Mice were injected with clozapine (1 mg/Kg) at 9:00AM and food intake was measured for indicated time periods.
• AAPDs (clozapine, olanzapine) up-regulate AMPK in the hypothalamus through Histamine H1 Receptor.
How?
IPMK and Energy Metabolism


The *IHPK1* gene is disrupted at the 3p21.31 breakpoint of t(3;9) in a family with type 2 diabetes mellitus


Requirement of Inositol Pyrophosphates for Full Exocytotic Capacity in Pancreatic β Cells


Inositol polyphosphate multikinase is a physiologic PI3-kinase that activates Akt/PKB

Maag et al (2011) PNAS

Amino Acid Signaling to mTOR Mediated by Inositol Polyphosphate Multikinase

Reciprocal Regulation of IPMK and AMPK in the Hypothalamus and Cell Line in Response to Energy Balance

Fasted vs. Refed

- pAMPK (Thr172)
- pS6K (Thr389)
- pS6 (Ser235/236)
- IPMK

IPMK mRNA levels

Fasted: 20
Refed: 60

P < 0.005

WT vs. KO

- pAMPK
- AMPK
- IPMK

Glucose

H L H L

- Glucose

WT KO

WT: H L H L
KO: H L H L

fl/fl KO

- pACC
- ACC
- pAMPK
- AMPK
- IPMK
- LKB1

Metformin (4 mM)

- Metformin
- Control
IPMK Mediates Clozapine-Induced AMPK In Hypothalamus

GFP or Cre-GFP

WT vs. IPMK-/- (hypo) with Cloz (3 mg/Kg)

Hypothalamus (ARC)

Food Intake (g)

WT Sal | WT CLOZ | KO Sal | KO CLOZ

GFP or Cre-GFP

Food intake

* *
Summary II

- IPMK mediates AAPDs-induced activation of hypothalamic AMPK.
Expression of nSREBP is Reduced In Animal Models of Schizophrenia

**WT**  **Dys-/-**
- P-AKT (S473)
- P-AKT (T308)
- P-AMPK
- full-SREBP
- nSREBP
- HMGCR
- FASN
- GAPDH

**Brain**

**WT**  **DISC1-/-**
- nSREBP
- GAPDH

**Brain**

![Graph showing nSREBP expression in different animal models.](image-url)
Regulation of SREBP activation
Neuronal Activity Modulates SREBP Processing

A. KCl (50 mM)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>fSREBP</th>
<th>nSREBP</th>
<th>ARC</th>
<th>GAPDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Differentiated PC12 cells

B. SREBP1

0 min

30 min

60 min

Depolarization

C. CTL  TEA

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>fSREBP</th>
<th>nSREBP</th>
<th>ARC</th>
<th>GAPDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Differentiated PC12 cells

D. Norm  Enrich

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>nSREBP</th>
<th>GAPDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2 weeks

E. KCl (50 mM)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>KCl</th>
<th>PF429242 (10 µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>60</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

nSREBP1

F. nSREBP-myc

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>nSREBP-myc</th>
<th>ACC</th>
<th>ARC</th>
<th>GAPDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Inhibition of SREBP Processing Blocks LTP

Frontiers in Bioscience (2011) 16: 49

PF-429242
SREBP Maturation and ARC Activation were Impaired in Sandy (Dys-/-) Mice

![Image](image_url)

SREBP activation by antipsychotic- and antidepressant-drugs in cultured human liver cells: Relevance for metabolic side-effects?

Maria B. Raeder, Johan Fernø, Audun O. Vik-Mo and Vidar M. Steen

1Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Helse, Bergen HF, Norway;
2Dr. Einar Martens’ Research Group for Biological Psychiatry and Bergen Mental Health, Research Center, Section for Medical Genetics and Molecular Medicine, University of Bergen, Norway
Positive Impacts of Serum Lipid on Cognition in SZ (N=578)

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Predictors</th>
<th>Beta*</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal memory</td>
<td>Triglyceride</td>
<td>0.07</td>
<td>1.72</td>
<td>0.086</td>
</tr>
<tr>
<td></td>
<td>LDL cholesterol</td>
<td>0.03</td>
<td>0.79</td>
<td>0.428</td>
</tr>
<tr>
<td></td>
<td>HDL cholesterol</td>
<td>-0.05</td>
<td>-1.12</td>
<td>0.263</td>
</tr>
<tr>
<td>Vigilance</td>
<td>Triglyceride</td>
<td>0.10</td>
<td>2.29</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>LDL cholesterol</td>
<td>0.09</td>
<td>2.10</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>HDL cholesterol</td>
<td>0.04</td>
<td>0.88</td>
<td>0.379</td>
</tr>
<tr>
<td>Processing speed</td>
<td>Triglyceride</td>
<td>0.09</td>
<td>2.25</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>LDL cholesterol</td>
<td>0.09</td>
<td>2.51</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>HDL cholesterol</td>
<td>0.02</td>
<td>0.57</td>
<td>0.570</td>
</tr>
<tr>
<td>Reasoning (Executive function)</td>
<td>Triglyceride</td>
<td>0.13</td>
<td>3.09</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>LDL cholesterol</td>
<td>0.10</td>
<td>2.57</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>HDL cholesterol</td>
<td>-0.06</td>
<td>-1.36</td>
<td>0.174</td>
</tr>
<tr>
<td>Working memory</td>
<td>Triglyceride</td>
<td>0.07</td>
<td>1.71</td>
<td>0.087</td>
</tr>
<tr>
<td></td>
<td>LDL cholesterol</td>
<td>0.10</td>
<td>2.49</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>HDL cholesterol</td>
<td>-0.03</td>
<td>-0.67</td>
<td>0.505</td>
</tr>
</tbody>
</table>

*aAdjusted for age, gender, race, years of education and abdominal obesity

Is lipogeneic effect of AAPDs a part of therapeutic action?
**Acknowledgment**

**Center for Neurobiology and Behavior**
- Sookhee Bang, Ph.D.
- Yong Chen, Ph.D.
- BoRan Choi, VDM
- Catherine Steenstra

**DERC/IDOM**
- Rexford S. Ahima, M.D., Ph.D.
- Ravindra Dhir, Ph.D.
- Raina Dhir

**Steven Arnold, MD**
- Hala Kazi

**Irwin Lucki, Ph.D.**
- Bethany Brookshire, Ph.D.

**National Institutes of Health Grant** DK 084336
**American Federation of Aging Research**
**Penn DRC Pilot Grant** NIH DK 19525
**NARSAD Young Investigator Grant**