Hypothalamic obesity: a window on the neuroendocrinology of energy balance

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The First Law of Thermodynamics

Calories In

Calories Out

Weight Gain

Obesity as a Philosophical Paradigm

1. Obesity is a behavior

Stedman's Medical Dictionary

Def. A stereotyped motor response to a physiological stimulus
Obesity as a Philosophical Paradigm

1. Obesity is a behavior
2. Obesity is a disease
3. Obesity is a phenotype

Obesity as a Philosophical Paradigm

1. Obesity is a behavior
2. Obesity is a disease
3. Obesity is a phenotype

Hypothalamic Obesity

Incidence of obesity in survivors of ALL

- Sainsbury et al. Arch Dis Child 60:832, 1985 (ALL, n = 86)
  - Wt/Ht within 1 year of Rx, did not improve after Rx stopped
  - Did not standardize for Rx, XRT, steroids
  - 38% with BMI > 80th percentile, correlated with CrXRT
  - 38% obesity by adulthood
  - Correlated with CrXRT, younger age at Dx
  - Mean BMI continued to increase especially in females
  - 46% obesity (BMI > 85th percentile) by adulthood, esp. in women
  - Correlation with chemotherapy, 18 vs. 24 Gy no difference
  - French, not British normal reference population
### Incidence of Obesity in Adult St. Jude Alumni

(n=1721)

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>Mean BMI (±SD)</th>
<th>BMI &gt; 25 (%)</th>
<th>BMI &gt; 30 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-malignant dis.</td>
<td>98</td>
<td>24.1 ± 6.7</td>
<td>33</td>
<td>12</td>
</tr>
<tr>
<td>Solid Tumors</td>
<td>805</td>
<td>24.1 ± 5.8</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>ALL — CrXRT</td>
<td>246</td>
<td>25.0 ± 6.0</td>
<td>41</td>
<td>17</td>
</tr>
<tr>
<td>Other Leukemia</td>
<td>51</td>
<td>25.6 ± 6.5</td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td>ALL + CrXRT</td>
<td>400</td>
<td>26.5 ± 6.2*</td>
<td>52</td>
<td>22</td>
</tr>
<tr>
<td>CNS Tumors</td>
<td>80</td>
<td>26.4 ± 6.3*</td>
<td>54</td>
<td>27</td>
</tr>
</tbody>
</table>

*P < 0.0001 versus non-cranial insult patients, ANOVA with post-hoc testing

### Incidence of Obesity in Adult CNS Tumor Survivors

(n=80)

<table>
<thead>
<tr>
<th>Location</th>
<th>N</th>
<th>Mean BMI (±SD)</th>
<th>BMI &gt; 25 (%)</th>
<th>BMI &gt; 30 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulloblastoma</td>
<td>26</td>
<td>23.8 ± 4.6</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Other Post. Fossa</td>
<td>23</td>
<td>25.0 ± 5.8</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>Hemispheric</td>
<td>16</td>
<td>25.8 ± 6.0</td>
<td>56</td>
<td>19</td>
</tr>
<tr>
<td>Thalamic</td>
<td>4</td>
<td>27.2 ± 4.0*</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>Hypothalamic</td>
<td>15</td>
<td>33.0 ± 5.9*</td>
<td>82</td>
<td>64</td>
</tr>
</tbody>
</table>

*P = 0.015 versus other CNS, ANOVA with post-hoc testing

### Final height and BMI after brain tumor in the Childhood Cancer Survivors Study

Gurney et al. JCEM 88:4731, 2003

- 921 adults surviving childhood brain tumor, age 20-45
- Height and weight in adulthood obtained by telephone interview
- 40% had short stature; correlated with
  - younger age at Dx
  - craniospinal radiation and PNET histology
  - growth hormone therapy
- Obesity correlated with
  - younger age at Dx
  - female gender
  - cranial radiation, only in females

### Obesity in survivors of adult brain tumors

OBRISK
A retrospective analysis of BMI velocity after therapy in survivors of brain tumors

St. Jude Brain Tumor Registry 1975 — 1995

Inclusion Criteria:
• Age < 14 at diagnosis
• No spinal cord involvement
• Therapy and follow-up at St. Jude
• Either 5 years of disease free follow-up after initial therapy (n = 148);
  or 5 years of follow-up after first recurrence (n = 41)
• Ambulatory
• Not on chronic dexamethasone or prednisone (hydrocortisone OK)

Risk factors assessed
• Location
• Histology
• Age at diagnosis
• Extent of surgery
• Initial high-dose glucocorticoid therapy
• Radiation therapy
• Intrathecal or peripheral chemotherapy
• Hypothalamic endocrinopathy

Lustig et al. JCEM 88:611, 2003

OBRISK; Effect of Tumor Location

OBRISK; Effect of Tumor Histology
OBRISK; Effect of Extent of Surgery

- Biopsy: 35
- None: 0
- Gross total resection: 30
- Subtotal resection: 25

BMI vs. Time from Diagnosis (months)

OBRISK; Effect of Cranial Radiation

- No Radiation therapy: 35
- Radiation therapy: 0

BMI vs. Time from Diagnosis (months)

OBRISK; Effect of Radiation Dosimetry to the Hypothalamus

- Less than 51Gy: 35
- 51-55Gy: 30
- Greater than 55Gy: 25

BMI vs. Time from Diagnosis (months)

p=0.0018

p=0.031

OBRISK; Effect of Residual Endocrinopathy

- Any hormone replacement: 35
- No hormone replacement: 0

BMI vs. Time from Diagnosis (months)

p=0.0018

p=0.031
OBRISK

No effect on BMI velocity:

- Initial high-dose glucocorticoid therapy
- Intrathecal chemotherapy
- Peripheral chemotherapy
Attempts to control weight gain in hypothalamic obesity

1. Diet and exercise
2. Appetite suppressants (Bontril, Didrex)
3. Phen-Fen
4. Phen-Pro
5. Pro-Adderall
6. Dextroamphetamine
7. Sibutramine
8. $T_3$
9. Octreotide
10. Pancreatic vagotomy
11. Roux-en-Y gastric bypass

Craniopharyngioma: caloric intake and energy output
Müller et al. JCEM 89:3298, 2004

The neuroendocrinology of energy balance

The Starvation Response
Lustig, Ped Clin NA 48:909, 2001
SB 1049: Mean Weight During 1-Year Trial

<table>
<thead>
<tr>
<th>Mean Weight (kg)</th>
<th>Treatment Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>88</td>
</tr>
<tr>
<td>Sibutramine 10 mg qd</td>
<td>89</td>
</tr>
</tbody>
</table>

P<0.001 for months 1 to 12, sibutramine vs placebo.

*very low calorie diet.

Efficacy: Orlistat

Mean Percent Change From Initial Body Weight Over 2 Years

- Diet + placebo (n=234)
- Diet + orlistat 120 mg tid (n=240)

Hypocaloric diet

"Eucaloric" diet

**P<0.0001; least squares mean difference from placebo.

Orlistat NDA, data on file, Roche Laboratories, Inc.
Why the negative plateau with weight loss?

Because of decreased energy expenditure, to offset the decreased caloric intake

• Decreased non-exercise associated thermogenesis (NEAT)
• Decreased resting energy expenditure
  • Decreased thermic effect of food
  • mitochondrial adaptation (UCP’s?)

Weight loss lowers REE/FFM by 20%

Decreased resting energy expenditure in hypothalamic obesity

Energy Expenditure = “Quality of Life”

Decreased energy expenditure:

• hypothyroidism
• starvation

Increased energy expenditure:

• exercise
• caffeine
• ephedrine (banned)
Defective Autonomic Innervation of the Adipocyte

Leptin stimulates the SNS


Decreased adrenergic activity in craniopharyngioma with hypothalamic involvement

Schofl et al. JCEM 87:624, 2002
Decreased adrenergic metabolites in craniopharyngioma with hypothalamic involvement

Roth et al. Ped Res. 61:496, 2007

Defective Autonomic Innervation of the β-cell

Regulation of Insulin Secretion

Vagal Modulation of Insulin Secretion

Lustig, Rev Endo Metab Dis 4:23, 2003
**Autonomic Function in Hypothalamic Obesity**

In response to defective central leptin signaling:

- Reduced sympathetic activity
  - decreased lipolysis
  - decreased gluconeogenesis
  - decreased skeletal muscle conversion of T4 to T3
  - decreased energy expenditure

- Increased vagal activity
  - reduced myocardial oxygen consumption
  - increased adipocyte insulin sensitivity
  - increased insulin secretion
  - increased energy storage

**Attempts to control weight gain in hypothalamic obesity**

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11. Laparoscopic adjustable gastric banding
12. Pancreatic vagotomy

**Insulin dynamics in hypothalamic obesity**

<table>
<thead>
<tr>
<th></th>
<th>Craniopharyngioma</th>
<th>Obesity</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Secretion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Phase</td>
<td>4456 ± 2084</td>
<td>3028 ± 1335</td>
<td>0.03</td>
</tr>
<tr>
<td>Second Phase</td>
<td>1091 ± 479</td>
<td>737 ± 311</td>
<td>0.03</td>
</tr>
<tr>
<td>Insulin Sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting Insulin</td>
<td>242.2 ± 160</td>
<td>161.3 ± 84.3</td>
<td>0.11</td>
</tr>
<tr>
<td>WBISI</td>
<td>5.2 ± 4.7</td>
<td>6.9 ± 5.9</td>
<td>0.11</td>
</tr>
<tr>
<td>FSIGT Si</td>
<td>0.96 ± 0.34</td>
<td>1.67 ± 0.7</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Attempts to control weight gain in hypothalamic obesity

1. Diet and exercise
2. Appetite suppressants (Bontril, Didrex)
3. Phen-Fen
4. Phen-Pro
5. Pro-Adderall
6. Dextroamphetamine
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Dextroamphetamine in hypothalamic obesity


Attempts to control weight gain in hypothalamic obesity

Vagal Modulation of Insulin Secretion

Lustig, Rev Endo Metab Dis 4:23, 2003
Hypothalamic Obesity Pilot Study—

**Purpose**

1. To assess the insulin secretory dynamics of patients with hypothalamic obesity
2. To assess the efficacy of octreotide in reducing basal and glucose-stimulated insulin release in patients with hypothalamic obesity
3. To assess the efficacy of octreotide in promoting weight loss in patients with hypothalamic obesity

### Weight and BMI Change

![Graph](Lustig et al. J Pediatr 138:162, 1999)

### Effects on Glucose and Insulin Responses

![Graphs](Lustig et al. J Pediatr 138:162, 1999)

### Weight Loss Versus:

**Change in Insulin response on octreotide**

\[ y = 45.8 + 19.4x \\
\text{r}^2 = 0.524 \\
\text{P} = 0.04 \]

**Change in Leptin levels on octreotide**

\[ y = 7.403 + 2.2x \\
\text{r}^2 = 0.571 \\
\text{P} = 0.03 \]
Octreotide treatment of hypothalamic obesity

Demographics

• Double-blinded, 6 month placebo-controlled trial of octreotide
• 20 subjects with pediatric hypothalamic obesity
  ages 8-18; 11M, 9F
  2 from St. Jude
  18 from other institutions
  13 with craniopharyngioma
  4 with hypothalamic astrocytoma, optic pathway glioma
  1 with suprasellar germinoma
  2 with ALL, S/P cranial XRT and chemotherapy
• Weight 96.8 ± 5.7 kg, BMI 36.3 ± 1.3 kg/m2, annualized weight gain 15.9 ± 2.9 kg

1 subject with tumor recurrence at Month 2 (on drug)
1 subject with diabetic hyperosmolar non-ketotic coma at Month 4 (on placebo)


Octreotide treatment of hypothalamic obesity
1st Window (6 Months)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>P = 0.0008</td>
</tr>
<tr>
<td>BMI</td>
<td>P = 0.0005</td>
</tr>
</tbody>
</table>


Insulin dynamics during OGTT (1st Window)

Pediatric Cancer Quality of Life
PCQL-32, Version 1

32-item proctored questionnaire
Patient and parent reports on:
  Cognitive functioning
  Physical functioning
  Psychological functioning
  Social functioning

Validated for ages 8-18 yr

Octreotide Treatment of Hypothalamic Obesity
PCQL-32 (6 months – 0 months)

<table>
<thead>
<tr>
<th>Functioning</th>
<th>Placebo</th>
<th>Octreotide</th>
<th>Intergroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Child</td>
<td>Parent</td>
<td>Child</td>
</tr>
<tr>
<td>Cognitive</td>
<td>0.33</td>
<td>0.22</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>-1.33</td>
<td>NS</td>
</tr>
<tr>
<td>Physical</td>
<td>0.33</td>
<td>-1.44</td>
<td>1.78</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>-2.22</td>
<td>NS</td>
</tr>
<tr>
<td>Psychological</td>
<td>0.11</td>
<td>-1.89</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td>-0.11</td>
<td>-2.11</td>
<td>2.00</td>
</tr>
<tr>
<td>Social</td>
<td>0.22</td>
<td>-1.89</td>
<td>2.11</td>
</tr>
<tr>
<td></td>
<td>-1.22</td>
<td>-1.56</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Correlation between Quality of Life and Insulin Response (6 Months – 0 Months)

Attempts to control weight gain in hypothalamic obesity

1. Diet and exercise
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Roux-en-Y Gastric Bypass for Hypothalamic Obesity

- 15 yo otherwise healthy boy with fatigue, somnolence, vomiting
- CT = Suprasellar mass
- Resection/irradiation for craniopharyngioma
- Developed panhypopituitarism
- Developed severe hyperinsulinemia
- Gained massive amounts of weight

**Roux-en-Y Gastric Bypass for Hypothalamic Obesity**

- Gained 300 pounds/2yr without Octreotide-LAR
- Gained only 30 pounds/2yr on Octreotide-LAR
- Discontinued drug due to lack of weight loss and expense (approx. $500 per day)
- Surgical Referral for Gastric Bypass
  - Little published experience
  - Informed consent very honest about uncharted territory!
**LAGB for hypothalamic obesity due to craniopharyngioma**

<table>
<thead>
<tr>
<th>Dx (yr)</th>
<th>Surgery (yr)</th>
<th>F/U (yr)</th>
<th>BMI-SDS Pre-op</th>
<th>Delta BMI-SDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>13</td>
<td>3.5</td>
<td>+12.35</td>
<td>-5.1</td>
</tr>
<tr>
<td>12</td>
<td>17</td>
<td>0.5</td>
<td>+10.36</td>
<td>-1.1</td>
</tr>
<tr>
<td>12</td>
<td>21</td>
<td>1.0</td>
<td>+11.74</td>
<td>-3.6</td>
</tr>
<tr>
<td>20</td>
<td>23</td>
<td>0.5</td>
<td>+7.30</td>
<td>-1.8</td>
</tr>
</tbody>
</table>

Muller et al. Int Soc Ped Neuro-Oncol, June 2008 (abstr)

**Attempts to control weight gain in hypothalamic obesity**

1. Diet and exercise
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**Vagotomy: Weight Loss Mechanisms**

- Decreased acid production
  - Reduces absorption
- Increased gastric tone
  - Fullness occurs earlier, lasts longer
- Dumping syndrome and rapid liquid emptying
  - Discourages high sugar-content foods
- Reduces deposition of energy into adipose tissue
- Interrupted ghrelin signal
  - Reduced hunger sensation
- Reduces diabetes, hypertension through PPARα

**History of Vagotomy for Obesity**

- **Open truncal vagotomy + pyloromyotomy for ulcer disease**
  - Introduced by Dragstedt in 1943
  - Found that obese patients lost weight
  - Dumping syndrome and other sequelae
- **Open truncal vagotomy study for morbid obesity**
  - Weight-loss out to 5 years, minimal sequelae.
- **Anecdotal open truncal vagotomy for “hypothalamic obesity”**
  - However, further anecdotal experience yielded inconsistent results
Surgical Gastric Drainage Procedures

- Vagotomy results in gastric stasis
- Solved by surgical drainage (pyloroplasty or pyloromyotomy)
- But can result in "dumping syndrome" secondary to rapid efflux into duodenum
- Gastric stasis may help in satiety
- We chose to perform vagotomy alone without pyloromyotomy

LTV for children with hypothalamic obesity following brain tumors

- UCSF CHR approved, informed consent
- Compassionate use protocol
- Obtained insurance approval
- 4 children with massive and intractable weight gain after brain tumor and its therapy
- 3/4 children started on dextroamphetamine pre-op to increase energy and activity, and prevent further weight gain

Laparoscopic Truncal Vagotomy in Adults (UCSF and U. Rochester)

- Boss et al., SAGES 2007
- UCSF CHR approved, informed consent
- Compassionate use protocol
- Compassionate use protocol
- Increase energy and activity, and prevent further weight gain
Insulin dynamics in children with hypothalamic obesity

<table>
<thead>
<tr>
<th>Pt</th>
<th>Fasting Insulin</th>
<th>HOMA</th>
<th>Time to peak</th>
<th>Peak Insulin</th>
<th>CIR (secretion)</th>
<th>CISI (resistance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (cranio)</td>
<td>17.2</td>
<td>3.36</td>
<td>30 min</td>
<td>571</td>
<td>3.83</td>
<td>1.1</td>
</tr>
<tr>
<td>2 (cranio)</td>
<td>5.4</td>
<td>1.00</td>
<td>60 min</td>
<td>497</td>
<td>3.92</td>
<td>4.3</td>
</tr>
<tr>
<td>3 (pituitary adenoma)</td>
<td>22.6</td>
<td>5.02</td>
<td>60 min</td>
<td>748</td>
<td>6.74</td>
<td>1.5</td>
</tr>
<tr>
<td>4 (cranio)</td>
<td>7.4</td>
<td>1.42</td>
<td>30 min</td>
<td>206</td>
<td>1.82</td>
<td>3.3</td>
</tr>
</tbody>
</table>

NL <20 <2.5 60 min <150 <1.5 >2

Weight, BMI, and BMI z-score before and after LTV for hypothalamic obesity

<table>
<thead>
<tr>
<th>Age at Dx</th>
<th>Annualized weight gain pre-Vx</th>
<th>BMI and BMI z-score pre-Vx</th>
<th>ΔWeight post-Vx</th>
<th>ΔBMI and BMI z-score post-Vx</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 3/12 yr (cranio)</td>
<td>15 kg/yr over 1.5 yr</td>
<td>32.2 kg/m2 +2.82*</td>
<td>-3.3 kg in 11 mos*</td>
<td>-3.3 kg/m2 -0.34</td>
</tr>
<tr>
<td>13 yr (cranio)</td>
<td>15.2 kg/yr over 2 yr</td>
<td>46.8 kg/m2 +2.68*</td>
<td>+2.9 kg in 11 mos*</td>
<td>-1.1 kg/m2 -0.10</td>
</tr>
<tr>
<td>11 3/12 yr (pit adenoma)</td>
<td>7.5 kg/yr over 4 yr</td>
<td>48.4 kg/m2 +2.98*</td>
<td>+1.0 kg in 10 mos*</td>
<td>+0.1 kg/m2 +0.06</td>
</tr>
<tr>
<td>6 6/12 yr (cranio)</td>
<td>16 kg/yr over 5 yr</td>
<td>44.5 kg/m2 +2.87</td>
<td>-9.7 kg in 7 mos</td>
<td>-5.9 kg/m2 -0.23</td>
</tr>
</tbody>
</table>

* Also receiving dextroamphetamine 5 mg PO bid

Change in BMI

HbA1c (%)

<table>
<thead>
<tr>
<th>Pt</th>
<th>First seen UCSF</th>
<th>Pre-vagotomy</th>
<th>Most recent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.9</td>
<td>6.8</td>
<td>5.6</td>
</tr>
<tr>
<td>2</td>
<td>4.7</td>
<td>5.3</td>
<td>5.1</td>
</tr>
<tr>
<td>3</td>
<td>5.5</td>
<td>6.1</td>
<td>5.7</td>
</tr>
<tr>
<td>4</td>
<td>5.1</td>
<td>5.1</td>
<td>5.0</td>
</tr>
</tbody>
</table>
Complications

- All patients with reduced hunger
- 2 patients with burping (resolved by 6 months)
- 2 patients with intermittent diarrhea (resolved by 6 months)
- None with dumping
- None with dysphagia
- None with vitamin deficiency
- All patients said that in retrospect they would undergo the procedure again

Conclusions: Hypothalamic Obesity

- Hypothalamic obesity results in defective leptin signaling, which manifests as:
  - sympathetic reduction, reducing lipolysis and energy expenditure.
  - vagal activation, increasing insulin secretion and energy storage.
- Decreased energy expenditure yields decreased quality of life.
- Blocking insulin release decreases appetite, promotes weight loss (or stabilization), increases physical activity, and improves quality of life.
- Pharmacotherapy should be considered early, but effects may be salutary; may be a preventative temporizing measure.
- Bariatric surgery (RYGB, LAGB, LTV) should also be considered, but may not completely reverse the obesity.

Collaborators

St. Jude Children’s Research Hospital
Melissa Hudson, M.D. —Heme/Onc
Kleebsahai Srivanaboon, M.D. —Heme/Onc
Pam Hinds, Ph.D. —Nursing
Robbin Christensen, D.Ph. —Pharmacy
Richard Heideman, M.D. —Neuro/Onc
Larry Kun, M.D.—Rad/Onc
Tom Merchant, D.O., Ph.D. —Rad/Onc
Alex Sanford, M.D. —Neurosurgery
Susan Post, MSII, Chicago Medical School
Sue Kaste, D.O. —Diagnostic Imaging
Karen Smith, R.D. —Clinical Nutrition
Xiaoping Xiong, Ph.D. —Biostatistics
Shesh Rai, Ph.D. —Biostatistics
Dana Jones-Wallace, M.S. —Biostatistics
Shelly Lensing, M.S. —Biostatistics
Shengjie Wu, M.S. —Biostatistics
St. Jude Clinic Nurses and Staff

U. Tennessee —Ped. Endocrine
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Susan Rose, M.D.
George Burghen, M.D.
Robert Danish, M.D.
Pisit Pitukcheewanont, M.D.
U.T. Pediatric CRC Nurses

UCSF
Nalin Gupta, M.D., Ph.D. —Neurosurgery
Rose Du, M.D. —Neurosurgery
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