Neurobiology of Obesity: Food for Thought

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Objectives:

1. Identify effective methods for the practical application of concepts related to improving the delivery of services for persons with developmental disabilities

2. Identify advances in clinical assessment and management of selected healthcare issues related to persons with developmental disabilities

3. Discuss the ethical issues related to persons with developmental disabilities

4. Discuss new scientific research regarding obesity in people with IDD

Notes:
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Goals
• Provide an overview of the complex neurobiology of obesity, focusing mainly on gene-environment interactions
• Review current information about the relationship between the regulation of hunger, satiety, metabolism and obesity
• Neurobiology of treatment- can we lose weight without effort?

Epidemiology
• BMI -overweight 25 kg/m; obesity: 30
• 65% of adults are overweight, rates have doubled since the 1960’s
• Racial, SES, ethnic differences - length of time in the US, “fast foods”- super-sizing America
• The fastest growing group - those BMI > 50
• Special problem posed by childhood obesity
**Why We Gain Weight**

- More calories than can be metabolized
- 1-2 pounds per year at 100-200 extra cal/day
- Genes- hypercellular versus hypertrophied fat cells
- Thyroid problems are uncommon
- Energy metabolism -
- Evolution - unpredictable access at high caloric costs -

**Brain, Gut and Feeding**

- Flight or Fight v feed or breed
- Gut actions- full stomach and the Vagal n.; satiety signals; delayed action of regulatory peptides
- Ghrelin- hunger in spite of food, PWS
- MC-4r/CCK/peptide YY/ GLP-4-, serotonin, hormones and proteins, leptin, insulin and effects on hormone activity

**Fat Cells- The Devil Is in the Details**

- Genes- number of fat cell (hyper); size of fat cells, metabolically active; insulin, FA metabolism
- Endocrine activity- converting (aromatases), leptins/adiponectins, cytokines and immune system activation
- Regulation of insulin activity, Ob-Ob rats, leptin hyperactivity-receptor-down regulation
Why Is It So Hard to Lose Weight

• Environmental factors-biology
• More than hormones, will power
• Chronic lifelong condition- relationship to addiction, relapse is likely
• 5-10%- wt loss most diets and medications, total lifestyle change
• Bypass surgery - most effective but difficult to get for individuals with IDD

My Whole Family Is Overweight- I Don’t Stand a Chance

• Early environmental experiences shape the regulation of food intake and activity level
• Obesity during early childhood is most problematic, genes are regulation of hunger/satiety and food preferences (hi cal/lo cal; fat; sweet tooth
• Eating when hungry or when food is present
• Food as reinforcement- hunger cues v stress

Complications of Obesity

• Metabolic syndrome - psychotropic drugs
• Dyslipidemias, insulin resistance, fat distribution, noninsulin dependent diabetes mellitus (Type II or NIDDM)
• CAD, CVD, hypertension
• Cancer
• OSAS - sleep apnea
• Neuroendocrine abnormalities- fat cells are metabolically active, converting estrogen to testosterone (aromatases)
Obesity and Developmental Disorders

- Specific behavioral phenotypes - Prader-Willi, Trisomy 21, Laurence Moon Bidel
- Hormonal disorders - thyroid disorders are blamed but actually uncommon; Cushing’s
- Lower levels of exercise or caloric expenditure
- High use of orexigenic side effects from various psychotropic drugs
- Dietary factors - calorie restrictions may shift thermogenesis and psychosocial/environmental issues

Genetic Disorders

- Hypothalamic dysfunction – lesions associated with cognitive changes, hormones, OC, rage outbursts, excessive thirst, engorgement
- Short stature, dysmorphic features, hypogonadism
- Prader Willi - 15q deletion, genomic imprinting, inherited segment from father
- Delayed or failure to experience puberty
- Distribution of fat
- Food preferences, binge eating; imbalance between pos/neg feedback factors

My Genes Made Me Do It

- Genes play a role but genetic determinism is not it
- Entrainment (environmental effects) begin in utero, shaped by parents, change through time by influencing when certain genes are turned on or off
- In some respects, obesity resembles drug addiction/behaviors
New Ideas

• H. pylori and regulation of ghrelin activity- GERD/PUD and overpopulation
• Brown or metabolically active fat (body temp regulation)- exercise and conversion of white to “tan” fat
• Obesity is a drug of addiction- sugar craving, opiate release, withdrawal; Rimonabant, endocannabinoid (CB1) inh; combined bupoprion-naltrexone

New Ideas- continued

• High fructose corn syrup- increases adiposity and increases TGA, relationship to addiction
• Pregnant mothers on high fat diet can shape the risk for obesity for several generations- epigenetic changes
• Rou-en-Y bariatric surgery, increases glucagon like peptide-1 and PYY3 release during feeding- shut down feeding
• Prader Willi- ghrelin excess, HGH deficiency

New ideas- continued

• Melanocortin 4 receptor suppress appetite, activated by aMSH
• Obesity in KO mice for MC4R (exenatide, laraquitide- block degradation enzyme)
• Oxyntomodulin- delays gastric emptying time, reduces gastric acid, dec food intake, increase energy expenditure
• Inh of carbonic anhydrase promote fat breakdown - topamax
Even more new ideas

- Stimulants affect neurotransmitter regulation of food intake/hunger, beta AR activity
- Food as an addiction - decrease reward potential for food or compete with stimulation of reward pathways
- Enhancing thermogenesis - brown fat activity via beta 1 adrenergic receptor
- DA1 suppress food intake in hungry animals

Treatment Approaches

- Too much food too little exercise
- Obesity plus?
- Actual efficacy of meds depends on mechanisms of action
- Sustained weight loss is not easy
- Life style changes
- Psychiatric disorders are common
- Treatment-related weight gains

Pharmacological Approaches to Obesity

- Chronic relapsing disorder
- Appetite suppressants – hunger, satiety - 5HT2c activation;
- Absorption - orlistat
- Topiramate - side effects higher doses
- Rimonabant - cannabinoid antagonist, Leptin/CNF axokine)
- Must be added to exercise, lifestyle changes