Pathways to Obesity: Implications of a Shifting Obesity Paradigm for Nursing Research

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Obesity is a global health problem.

- More than 500,000,000 adults have BMI > 30 Kg/m² (WHO, 2013).
- More than 40,000,000 children < 5 years old are overweight or obese (WHO, 2013).
Problem

* Calories in - calories out paradigm of weight regulation
Obesity classification systems are based on:

- Degree of adiposity
  - BMI classification
  - Percent body fat.

- Adipose distribution
  - Visceral, abdominal, or android
  - Peripheral, subcutaneous, or gynoid
Purpose

To identify and organize a new theoretical model of factors associated with the development and progression of obesity based on the pathophysiological bases for adipogenesis.
Theory synthesis (Walker & Avant, 2010, 1983) was utilized to organize research findings of adipogenic factors into a taxonomy of obesity pathophysiology.
Methodology

* Literature search > 863 articles

• Primary search terms
  ▪ Obesity etiology
  ▪ Obesity pathophysiology
  ▪ Adipogenesis

• Secondary search terms
  ▪ Leptin
  ▪ Mitochondria + obesity
  ▪ PPAR-γ + obesity
  ▪ Sleep and obesity
Methodology

* Heirarchy of research evidence:

- Human subjects
- Animal studies
- Cellular studies
- Random control studies
- Association studies – longitudinal
- Comparative studies
- Case studies
Results

* Initial taxonomy categories

- Genetics
- Hypothalamic dysfunction
- Adipose cell dysfunction
- Mitochondrial dysfunction
- Other unclassified
Results: Pathways to Obesity

* Genetic vs epigenetic effect

* Physiological process
  • Neuroendocrine signaling
  • Adipose cell dysfunction
  • Mitochondrial alterations
  • Gastrointestinal microbiota
Pathways to Obesity

Neuroendocrine Signaling

- 7 genes deleted or unexpressed, Chromosome 15q11-q13 (Prader-Willi syndrome)
- Resistance to leptin
- Leptin receptor homozygous & heterozygous mutations
- Leptin receptor polymorphisms
- MCR3 & MCR4 polymorphisms
- BDNF gene & its TrkB receptor variants
- Bardet–Biedl syndrome (BBS) gene mutations

Genetic

- MCR4 autoantibodies
- Medications (Atypical antipsychotic drugs, antihistamines; cortisol)
- MCR4 autoantibodies
- Stress
- Sleep deprivation

Epigenetic
Pathways to Obesity

Adipose Tissue

- Failure to liberate fatty acids (β-adrenergic receptor polymorphisms)
- Leptin homozygous & heterozygous mutations
- ? Lipase

- PPAR-γ activation (adenovirus-36, medications [TZDs], fatty acids)

- Brown fat deficiency
  - ? Vitamin D deficiency

Genetic

Epigenetic
Pathways to Obesity

Skeletal Muscle Mitochondria

Genetic
- mtDNA mutations
- Uncoupling proteins 2 & 3 polymorphisms
- Failure to metabolize fatty acids
- Excess free fatty acids
- Failure to metabolize glucose at aconitase in TCA cycle
- Pro-inflammatory cytokines, including TNF-α and IL-6
- Dioxin
- Dichloracetonitrile (H₂O₂ disinfectant)

Epigenetic
- Decreased carnitine palmitoyltransferase 1 (CPT1)
- Impaired mitochondrial biogenesis
Pathways to Obesity

Gastrointestinal Microbiota

- ↑Firmicutes ↓Bacteriodetes
  - Caesarean birth
- H. pylori eradication
- Lipopolysaccharide activation of innate immune system
Pathways to Obesity

Neuroendocrine
- Resistance to leptin
- Leptin receptor polymorphisms
- MCR3 & MCR4 polymorphisms
- MCR4 autoantibodies
- Leptin receptor deficiency
- BDNF gene & its TrkB receptor variants
- Hyperinsulinemia
- Medications (Antipsychotic drugs, antihistamines; cortisol)

Gastrointestinal Microbiota
- ↑Firmicutes ↓ Bacteriodetes,
- H. pylori eradication
- Lipopolysaccharide activation of innate immune system

Skeletal Muscle Mitochondria
- Failure to metabolize fatty acids
- Failure to metabolize glucose at aconitase in TCA cycle
- Increased AMPK production
- Medications (Statins, B-blockers)
- Impaired mitochondrial biogenesis

Adipose Tissue
- Failure to liberate fatty acids (β-adrenergic receptor polymorphisms)
- Lipase
- PPAR-γ activation (adenovirus-36, medications [TZDs], fatty acids)
- Brown fat deficiency
Conclusions

* Benefits of the taxonomy

- Requires health care providers to more thoroughly assess patients for “noncaloric” factors contributing to weight gain.
  - History of exposures – medications, toxins
  - Life events – stress, sleep
  - Diagnostic testing
Conclusions

* Benefits of the taxonomy
  
  • Changes how students and patients are taught about obesity.
    ▪ Obesity is more complex than calories in and calories out.
    ▪ Patients can try and fail to control their weight without being hedonistic
    ▪ The role of genetic counseling in diagnosing and treating obesity.
Conclusions

* Benefits of the taxonomy

- Expands research options
  - Environmental epidemiology
    - Environmental effects on neuroendocrine signaling, fat cell metabolism, mitochondria, and GI microhabitat.
- Interactions between genetics, environment, and weight control interventions.
Conclusions

* More than 350 genes or gene markers have been associated with obesity and may contribute to the etiology of obesity in humans.

* There may be thousands of different types of obesity (Atkinson, 2005).
References


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Thank You