Remodeling in Our Brain and Nervous System: Connections to Obesity and Diabetes

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Our Lab’s Focus:
Neurobiology and Energy Balance

“PNS Team”

“CNS Team”
Obesity and Diabetes Are Worldwide Pandemics
Obesity rates continue to climb in the U.S.
Mortality With Increasing Body Mass Index (BMI)

BMI = weight (kg)/height (m)^2

BMI Categories: under 18.5 (underweight); 18.5-24.9 (‘normal’), 25-29.9 (overweight), over 30 (obese)

From Adams 2006 NEJM – Male data (female data are similar)
Obesity: Numerous co-morbidities, affecting nearly every organ system in the body

- Cardiovascular/vascular complications; stroke
- Type 2 diabetes mellitus; inflammation
- Cancers (breast, kidney, pancreatic, etc.)
- Asthma, sleep apnea, lung disease
- Hepatic steatosis
- Gallbladder disease; pancreatitis
- Bone/joint problems, arthritis
- Reproductive dysfunction
- Depression, learning/memory problems
- Gout, skin problems
Obesity: Connections to Cardiovascular Disease and Type 2 Diabetes

Metabolic Syndrome:
- Hypertension
- Diabetes
- High triglycerides
- Low HDL, high LDL cholesterol
- Impaired fibrinolysis
- Inflammatory markers
- Decreased adiponectin
- Non-alcoholic fatty liver

Better than BMI:
- Waist circumference (abdominal adiposity matters more!)
- Tissue distribution (imaging) – lean vs fat
Genetics of Obesity

Twin Studies

Monozygote – share environment and genes

Dizygote – share environment
Genetic Predisposition and the Complex Genetics of Obesity

Illness, medications, viruses, antibiotics, stress, sleep, maternal environment...

Andersson-Assarsson et al. 2011
The Environment and Obesity

Over 50 ‘obesogens’ implicated

- Fungicides
- Endocrine Disruptors
- Arsenic, Lead
- Plasticizers (BPA, phthalates)
- Parabens, PCBs, PFCs
- Nicotine
- Air Pollution

Modified from: Heindel, NIEHS
Hippocrates (father of medicine) correctly identified the energy equation:

- Laws of Thermodynamics: Energy cannot be created or destroyed & Energy is either used or stored.
- Hippocrates: health changes brought about by change of diet
- When “calories in” are greater than “calories out” then body weight increases.
- When “calories in” are less than “calories out” then body weight decreases.
Energy Balance

Energy IN

Energy OUT

POLYGENIC + ENVIRONMENT

Appetite, food intake, nutrient absorption & nutrient sensing

White Adipose Tissue (WAT)

Brown Adipose Tissue (BAT)

Energy expenditure: physical activity, BMR (mitochondria), thermogenesis, muscle efficiency
Brain ← → Tissue/Organ Communication

Peripheral Nerves

Circulatory System (endocrine, nutrients)
VIDEO: Peripheral Innervation
Brain-Adipose Communication:

Regulation of calorie burning (energy expenditure), such as in adipose/fat tissue

Sympathetic Nerves

Sensory Nerves

Energy Sensing (ie: fuel stores), Appetite Regulation
Synapses: Nerve cell communication is electrical and chemical.

Electrical Impulse Travels Down Axon

Release of Neurotransmitter at Synapse
Our Nervous System is Not Static: Neural Plasticity

Even in adulthood, when development is done, most tissues remain ‘plastic’ and can remodel/regenerate in response to stimuli.

1. Nerve/Neuron survival
2. Neurogenesis – more/new neurons
3. Extension of neurites (axons, dendrites)
4. More synaptic connections between nerves and their targets
Appetite Control: The Hypothalamus

The Brain’s center for energy balance regulation
Appetite Regulation

Konturek et al. 2005
Anorexigenic Neurons

Orexigenic Neurons

Mouse Coronal Brain Slice

LEPTIN (from fat)

GHRELIN (from gut)

Appetite Regulation in Hypothalamic Neurons
Bone Morphogenetic Proteins (BMPs) – Growth Factors Regulating Energy Balance

BMP7

Energy in

Energy out

BMP7
The anorectic & weight-lowering effects of BMP7 do not require leptin

*Obese ob/ob* mice genetically lack leptin (produced by adipose and signals hypothalamus to decrease appetite)
VIDEO: PDB of BMPR1A

Type II receptor: BMPR2

Type I receptor: IE: BMPR1A

BMP7 ligand
BMPs, like BMP7, affect both arms of energy balance in the hypothalamus

Townsend et al, FASEB 2012

Ligand administration

Townsend et al, Endocrinology 2017

Central ablation of the receptor for BMP ligands

Anorexigenic (POMC) Neurons

BMPR1A KO

+ 

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Fries
Hypothalamic Tanycytes – Neural Plasticity in Energy Balance?

Maggi et al. 2015 Frontiers in Neuroscience

Brain Ventricle – cerebrospinal fluid (CSF) circulates
Does deletion of BMPR1A in tanycyte subsets affect neural plasticity and energy balance?

Tanycytes co-localized with BMPR1A

Hypothalamic serial sections, immunostaining

Vimentin (tanycyte marker)

DAPI (nuclear marker)

BMPR1A

α

β

Noelle Leon-Palmer, Callie Greco, Cameron Fudge
Adult Neurogenesis and Neural Plasticity: Who and Where are the Adult Stem Cells?

Open Questions:
- Is there adult neurogenesis in the hypothalamus? Does it contribute to the regulation of energy balance?
- Do adult stem cells in the brain have a unique and specific marker that would allow us to better study them?

Modified from: Crews and Nixon, 2004
Fat Tissue = adipose tissue
Making more fat cells = adipogenesis
Measure of amount of fat = adiposity

- **Hypertrophy** (cells get bigger – ie: more stored lipid)
- **Hyperplasia** (cells increase in number) = HEALTHIER
Differences between white (WAT) and brown (BAT) adipose tissues

**WAT:**

**Function**
- energy storage

**Morphology**
- Unilocular - single large lipid droplet

**Beige/Brite:**

**Function**
- energy expenditure

Inducible/recruitable brown adipocytes appearing in WAT

Most of adult human BAT is this type

**BAT:**

**Function**
- energy expenditure

**Morphology**
- Multilocular - several small lipid droplets
- Densely packed with mitochondria (UCP1+) - for thermogenesis
HUMAN Brown Adipose Tissue (BAT):
Interscapular main depot at birth; main adult depots along spine, clavicle, neck:
I = interscapular; PR = perirenal; C = cervical; PV = paravertebral; CI = clavicular; H = heart; U = underarm

MOUSE Brown Adipose Tissue (BAT):
Interscapular main depot all of life:
I = interscapular; PR = perirenal; M = mediastinic; A = axillary, C = cervical

Townsend and Tseng; Int. J. Obesity; 2014
Brown and White Adipose Tissues are Innervated Organs with Numerous Cell Types

Adipose Tissue roles: endocrine, metabolic, immune

Art credit: Magda Blaszkiewicz
Development of adipose tissue and cellular turnover: Plasticity/Remodeling

- Preadipocyte (precursor)
- Spillover of lipid to liver, muscle, heart
- proliferation
- differentiation
- Small adipocyte
- lipogenesis
- Lipolysis
- fasting
- fed
- Large Adipocyte (more stored lipid)
Adipose Tissue Nerve Remodeling (plasticity) Affects Metabolic Health??

Central Nervous System (CNS) → Peripheral Nervous System (PNS) → Norepinephrine → Adrenergic Receptors Mediate Effects

Adipogenesis → Lipolysis → Browning

Energy
Adipose Tissue has Heterogeneous Nerve Distribution

Are adipose tissue nerves dynamic?

Could neuropathy and neural plasticity underlie changes in metabolic health?

2D representation of 3D tiled z-stacks reconstructing mouse subcutaneous adipose depot

β3-Tubulin
Pan-Neuronal Marker
Heterogeneity of Adipose Nerves

PGP9.5 – nerve bundle

PGP9.5 – fine neurites around adipocytes

MPZ – myelinated nerves

PGP9.5

Myelin Protein Zero (MPZ)

Magdalena Blaszkiewicz, Jake Willows, Cory Johnson
Towards a Neuroanatomy of Adipose Depot Innervation

“Subiliac Transverse Nerves”

Subiliac Lymph Node

Thoracoepigastric Vein
Peripheral Neuropathy

• Dying back of peripheral nerves – loss of proper tissue communication with brain
• Caused by over 30 medical conditions
• Diabetes alone – over 30 million patients in US
• Skin → inward
• Pain, numbness, often leads to amputation
• Difficult to diagnose early, small fiber
• No therapeutic options aside from analgesics
Peripheral Neuropathy in Adipose: aging, certain diets, obesity/diabetes

Disease Progression

Summary of data from Blaszkiewicz et al, BioRxiv 2018
Cold-Exposure Promotes Adipose Neural Plasticity and Increases Innervation

3-Day Cold Exposure
scWAT PGP9.5

Local Growth Factor Involvement – including from resident immune cells

Blaszkiewicz et al., BioRxiv 2018

β3-tubulin (pan-neuronal)
Science, not Stigma. Health, not BMI.
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