Myokines, Exercise, Metabolism

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Overview:

• **Why?** Evolutionary perspective
• **How?** Myokines: what they are and what they do
• Exercise and physiology | Energy restriction
  ○ Similarities between both on health
  ○ May work through myokines
• Energy dysfunction
• Neurodegenerative Disorders
Evolutionary Perspective: Hunger Games

- **Ancestors**
  - High competition for food
  - Limited supply

- **Advantages**
  - Travel long distances
  - Mapping skills
  - Communication

- **Energy intake** ↓  **Energy expenditure** ↑
  - Brains evolved to favor this

- **Recent technological developments**  →  **sedentary lifestyle**

- **What now??**
Myokines - An Overview

- Specific type of cytokine that is secreted by skeletal muscles
  - Cytokines are broadly involved in cell signaling; leptin and ghrelin are considered cytokines
- Myokines are induced by specific exercise
- Typically have a positive effect on physiology
  - Counteract pro-inflammatory adipokines
  - Act through familiar cellular pathways
- Myokines may have pleiotropic effects
  - The main effects of each are discussed
Muscle Hypertrophy

- Leukemia Inhibitory Factor (LIF)
  - Injury response myokine: mRNA upregulated following muscle injury
    - Muscle injury: muscle growth model
  - Induces cell proliferation through JAK/STAT & PI3K pathways

- SPARC: Secreted Protein, Acidic and Rich in Cysteine
  - Typically known to modulate cell surface interactions in connective tissue and bones.
  - Involved in muscle tissue remodeling

- Irisin - Myostatin feedback
  - Myostatin: the only myokine that is decreased in response to exercise, and causes reduced growth
    - Passively secreted by muscles, and is downregulated by irisin
    - Popular therapeutic target for correcting muscle dystrophies
  - Irisin: more typically related to metabolism; IGF-1 enhances muscle growth
Plasticity & Exercise

- Running rats display greater LTP than non-running rats
- Early-phase LTP is impaired in sedentary rats as opposed to non-sedentary rats
- Exercising neurons without aerobic exercise can also enhance plasticity
Plasticity & Energy Restriction

- Important for learning, memory, and brain restoration
- Aging causes a decrease in LTP in the hippocampus and can be increased with ER
- ER in old rhesus monkeys results in enlarged hippocampus, amygdala, PFC
Neurogenesis

- **What is Neurogenesis?**
  - The formation of a neuron from a stem cell
  - Develops new neuron circuits

- **Voluntary exercise stimulates hippocampal neurogenesis**
  - Enhances memory
  - Integration into functional existing circuits

- **ER enhances survivability of new hippocampal neurons**
- **ER and exercise upregulates BDNF, IGF-1, VEGF**
Memory & ER

Evidence suggests ER and exercise can enhance brain function and slow cognitive decline

- Elderly experiment: 30% ↓ in calories → ↑ in memory tests
Memory & Exercise

- Mice that ran regularly showed better spatial pattern separation in the dentate gyrus
  - Hippocampal neurogenesis
  - Exercise up = hippocampal neurogenesis up

- Exercise enhances memory
  - Adolescent rat exercise v. adult rat exercise saw better memory retention for adolescent rats
  - Critical period for protection from deterioration

- Adolescents that exercise regularly displayed better cognitive performance relative to those not under aerobic exercise
  - studied MRI scans
  - Increased brain region size
  - Increased grey & white matter
Endurance Exercise v. Energy Restriction

**Endurance Exercise:**
- Comparatively little effect on aging
- Stimulates hippocampal neurogenesis
- Increased brain region size
- Increased grey & white matter (aerobic)

**Energy Restriction:**
- Slows aging
- Lower core body temp
- Lower sex hormone

**Similarities in both:**
- Better cognitive performance
- Increased plasticity
- Increased insulin sensitivity
- Increased heart rate variability
- Reduced central adiposity
- Upregulation of neurotrophic factors & myokines
- Resistance to age-related diseases
Glucagon like Peptide-1

- Hormone for neuroprotection/neurorestoration
- GLP-1 → cAMP production → CREB → BDNF
  - CREB = cyclic AMP response element-binding = transcription factor
- Food ingestion: gut epithelial cells release GLP-1 to act on liver and muscle cells to increase insulin sensitivity
- GLP-1 increased in exercise
  - Improve learning and memory
- Lacking GLP-1R exhibit impaired hippocampal synaptic plasticity, learning, memory
- Can also exhibit antidepressant actions
Glutamate Activation
- Glutamate → NMDAr → Ca influx → CAMK & MAPK → CREB → BDNF
- CAMK2 & MAPK used for synapse strengthening & cellular stress resistance

Exercise & ER Activation
- Induces BDNF & IGF-1
- 3 months of exercise v. sedentary sees higher BDNF release from the brain

CREB, PGC-1α, NF-κB, Nrf-2, & HSF-1 are used to express proteins used for plasticity
PGC-1a & Mild Energetic Stress Response

- Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
- Increased metabolism
- Activation depends on exercise intensity
- Treadmill running
  - for 1hr/day over 8 weeks = PGC-1a upregulation in many brain regions
  - Rats: After stroke = upregulation of PGC-1a
- BDNF can stimulate PGC-1a
Glucose Enhancement & Lipid Metabolism

**AMPK Pathway**

**IL-6**
- Glucose homeostasis
- Increases lipolysis & FFA oxidation in adipocytes

**SPARC**
- Muscle: Development, Regeneration, Hypertrophy
- Prevents weakening of fiber-like preadipocytes

**BDNF**
- Role in central metabolic pathways and regulators of skeletal muscles
- mRNA increase after contraction

**BAIBA**
Paracrine effect on muscles
Insulin signaling

**Irisin**
- Regulator of energy metabolism
- Response to “acute” exercise
- Control of mitochondrial biogenesis
Glucose Uptake

LIF
- P13K/mTORC2 pathway
- May potentially have an effect in muscle through cell signaling and/or detonation of a hormone
- Stimulate the group of cells functioning during osteoblast

IL-15
- JAK3/STAT3
- Stimulates muscle fibers and cells which lead to accumulation of contractile proteins
- Leads: Less fat accumulation and more muscle
Amelioration of Insulin Signaling

BAIBA

- IRS1/Akt pathways
- Present after extended periods of exercise

Presence leads to mitochondrial FFA oxidation

Better insulin signaling

Endocrine side: upregulation of mitochondrial FFA oxidation

Less fat accumulation
Inflammatory and oxidative protections

- **IL (Interleukin) 6**: the “prototypical” myokine
  - Involved in many of the different effects of myokines
  - Inhibits pro-inflammatory cytokines TNF-alpha and IL-1-beta

- **BAIBA (beta-aminoisobutyric acid)**
  - Activation of AMPK-PPARdelta has anti-inflammatory effects
  - AMPK also alleviates hepatic stress and apoptosis

- **IL-15**
  - Alleviates peroxide oxidative stress, and has PPARdelta activity

- **BDNF & IGF-1**
  - Protect neurons against both metabolic and oxidative stress
Chronic Positive Energy Balance (CPEB)

- Higher BMI was associated with less cerebral blood flow in PFC
- Less white matter integrity
  - Frontal, parietal, and temporal white matter and frontal gray matter in middle age human subjects
- Less N-acetylaspartate (indication of neural metabolic health)
- Reduced neurotrophic factor signaling, oxidative damage, chronic inflammatory state
- CPEB can also affect those not overweight: central adiposity is a risk for normal-weight women
CPEB cont.

- Fast-food diet in rats showed impaired hippocampal plasticity and cognitive performance
  - Negative correlation to insulin sensitivity
  - Could not be reversed to insulin administration
- Leptin receptor mutant rats develop impaired synaptic plasticity, and reduced neurogenesis in hippocampus
  - Increased corticosterone levels
- Diet induced Insulin resistance also inhibits cognitive performance
- Genetic predisposition to obesity → perform more poorly on verbal memory recollection even without clinically apparent cognitive impairment
Energy Restriction & Exercise Increase Brain Activity

- Diabetes-induced defects can be made better via ER and exercise
- Increased hippocampal blood flow in 4 months exercise in elderly
  - Increased connectivity to the anterior cingulate cortex
- Relative deactivation in overfed v. lean minipigs
- ER over 1 year showed improved mood, WM, and cognitive processing speed (low fat or low carb)
Neurodegenerative Disorders

- Energy balance influences vulnerability of the brain to injury and neurodegenerative disorders
- Traumatic brain injury (TBI) and stroke
  - Leading causes of death
- Energy Restriction
  - Improves functional outcome + reduces neuronal damage
  - Deficits in motor function and cognition
- Exercise
  - Rats on treadmill → reduced brain damage + improved functional outcome
Neurodegenerative Disorders

- Alzheimer’s Disease (AD)
  - What is it?
    - Progressive cell death & degeneration
    - Amyloid beta protein buildup
  - ER
    - More resistant to cognitive impairment & hippocampal degeneration
  - Exercise
    - Can reduce risk of age-related cognitive impairment & AD

- Parkinson’s Disease (PD)
  - Progressive fatal movement disorder
  - Decrease in dopamine
  - Running can help with deficits in rodents
Sources


will result in improved brain health. Examples of potential prescriptions can be readily incorporated into the work and family life schedules in ways that not only improve (brain) health but also enhance productivity and leisure activities include (1) alternating days of fasting and ad libitum eating, with a daily exercise period; (2) eating only during a short time period each day (e.g., not eating breakfast or lunch) and exercising every other day; and (3) eating in the morning and late afternoon/evening, and exercising at midday. The impact of such intermit-
MYOKINES NOTES

- Muscles as a secretory organ: myokines are specific cytokines. Cytokines: broad term for type of immune (not necessarily function) signalling molecules. Counteract pro-inflammatory adipokines, also a type of cytokines. etc. Leptin and ghrelin are both considered cytokines.

- Hypertrophy mech? Muscle types and specifics? **Myokines are induced by specific exercise.** Molecular targets: ppar, tnf, pgc1alpha

- IL-6: prototypical, more notes in 2nd paper. Interleukins: just another type of cytokine. **IL-15:** contractile protein increase, glut4 transporter/glucose uptake. May be associated with either resistance or endurance, but in rats may modulate glucose tolerance.

- BDNF: based on name: has neurotrophic effects, not explored here. Food intake and glucose level reduction - anorexigenic? Increased in response to contraction: AMPK and ACC. Skeletal BDNF not released into circulation. Actually decreased following resistance exercises. Overexpressed in t2 diabetes soleus> compensatory effect?

- LIF: enhances hypertrophy and recovery, upregulated in response to injury. Namesake: differentiation of cells arrests continued proliferation. While mRNA increases in response to endurance and resistance, unclear effect bc protein half life. Following long term endurance of mdx mice, mRNA drops (does this matter)?


- SPARC: typically linked to osteogenesis linkage. Muscle development, regeneration, and hypertrophy. Levels increase increases in acute exercise, further with continued training. Downregulates adipogenesis. AMPK signaling
**MYOKINES PT 2 NOTES**

- Why/background: biomarkers and therapies. Acute chronic, aerobic, resistance exercise -- associated energy usage. Endurance: PGC1-alpha = key factor leading to mitochondrial genesis and metabolism and muscle fiber composition (1, 2a, 2b, 2x). Resistance: mTOR = hypertrophy.
  - Re: counters adipocytes
- Re: IL-6 as the prototypical myokine. Anti inflammatory, insulin sensitivy. Lipolysis, adipose browning through uncoupling.
- Re: Irisin: has a few biochem pathways linked, as a mitochondrial browner, but is this myokine important to mention? YES. linked with GLP-1 agonist drug in anti diabetic action.
- Myostatin: the only myokine downregulated in response to exercise (both types). Negatively regulates muscle growth. Inhibition of this has several therapeudic effects against muscle degeneration, and is down regulated by irisin -- pathway to target. Extensively studied to find therapeudics against
  - Re: IL-15: oxidative stress tolerance, WAT mass reduction.
- Re: BDNF: fat browning, irisin upregulation. Brain effects on memory: reduction of A beta proteins?
- BAIBA: auto/paracrine effects on muscles. FFA oxidation. AMPK, ppar-delta protection against inflammation. Reduction of liver lipogenesis and stress.
  - Re: LIF: hypertrophy through JAK/STAT PI3K pathways. Acute glucose uptake. Increases osteoblast proliferation (bone building), inhibits adipocyte proliferation -- unknown if this effect is related to exercise.
- Re: SPARC: modulates cell surface interactions (collagen, vitronectin). Leads to skeletal tissue remodeling (how?). Inhibits adipogenesis through beta catenin pathway. AMPK for glucose metabolism.
- Other myokines: being discovered through transcriptome and secretome analysis, and their roles are still being figured out.
- GROUPING: BASED ON OVERALL EFFECT OF THAT MYOKINE?
- Certain compounds are being developed to regulate myokine release (ex: metformin AMPK action implicated in IL-6)
will result in improved brain health. Examples of potential prescriptions can be readily incorporated into the work and family life schedules in ways that not only improve (brain) health but also enhance productivity and leisure activities include (1) alternating days of fasting and ad libitum eating, with a daily exercise period; (2) eating only during a short time period each day (e.g., not eating breakfast or lunch) and exercising every other day; and (3) eating in the morning and late afternoon/evening, and exercising at midday. The impact of such intermit-