Exercise

Neurotransmission
What is Exercise?

- Participants in studies were given regimens of various types of cardio and resistance exercise
- Some examples include Treadmill running for 60 minutes for 5d/week for 8 weeks, and 3d/w of 6-10 reps of 70% one rep max of resistance exercise.
What actually happens inside your body?

- When muscles contract they release myokines and other signaling proteins
- Receptors are located on muscle, fat, liver, pancreas, bone, heart, immune, and brain cells, which explains why exercise has effects on the entire body
What are myokines?

- We discussed cytokines in discussion previously, which are used to signal neighboring cells.
- Myokines are very similar, as they also signal the body about changes to the environment.
- The difference is that myokines are secreted from the muscles.
- “Myo-” meaning muscle in Greek.
Effects on Metabolism

Brain Derived Neurotrophic Factor (BDNF)

- Recently it has appeared to have strong effects on peripheral metabolism including fat oxidation, and have a subsequent effect on the size of adipose tissue.
- Skeletal Muscle BDNF has been shown to be a key modulator in metabolic diseases.
- BDNF in skeletal muscle may be expressed as a compensatory neurotrophic factor against diabetic neuropathy or myopathy.
- IGF-1 is also a key protein that is upregulated with exercise along with BDNF.
Effects on Metabolism

Interleukin-15 (IL-15)

- Regulates metabolic diseases like obesity and diabetes
- Modulates glucose uptake in skeletal muscle
- Important regulator of skeletal muscle fiber growth, hypertrophy and glucose uptake.
- Exercise alters IL-15 concentration at the mRNA level.
- Most notably after moderate intensity resistance training, but some studies showed an increase from aerobic training
- Controls glucose and lipid metabolism
Effects on Metabolism

Fibroblast Growth Factor-21 (FGF-21)

- Levels increased during starvation and ketogenic state and returned to normal after feeding.
- Administration into diabetic rats increased insulin sensitivity.
- Stimulates glucose uptake in adipocytes.
- Other studies have shown that it is elevated in humans after exercise.
- The increase was also accompanied by an increased lipolytic response leading to the release of free fatty acid and glycerol.
Effects on Metabolism

Secreted Protein Acidic and Rich in Cysteine (SPARC)

- Levels are decreased immediately after exercise.
- It is also increased in the serum of young healthy males.
- Reduces fat accumulation.
- It is also involved in glucose metabolism via the AMPK signaling pathway.
- AMPK plays a critical role in regulating glucose and fat metabolism in skeletal muscle during exercise.
Diseasome of Inactivity

Real life implications

Physical inactivity → abdominal adiposity → macrophage infiltration of visceral fat → chronic systemic inflammation → insulin resistance, neurodegeneration, tumor growth
Some effects of physical inactivity

- Study that examined what would happen in men when reducing the number of steps they took from 10,000 steps per day to 1,500 steps per day
  - Results: Men had developed impaired glucose tolerance and a decrease of postprandial lipid metabolism.
  - In addition: there was a 7% increase in intra-abdominal fat-mass and a follow-up post-study noted a decline in peripheral insulin and a 7% decrease in VO2 Max and a decline in leg muscle
TNF-α

- Tumor Necrosis Factor
  - Cell signalling protein involved in systemic inflammation, but also has roles in immune response
- For systemic inflammation: TNF is secreted from macrophages
  - This can cause damage to arteries as well as insulin resistance in muscles
IL-6 Release: The Champion against Inflammation

• Increase of IL-6 up to 100-fold during exercise, when expressed by type-1 and type-2 (aka slow-twitch and fast-twitch) muscle fibers, IL-6 exerts its effect both locally within the muscle and act in a hormone-like fashion when in circulation.

• Muscular derived IL-6 mediates anti-inflammatory effects by inhibiting endotoxin-induced TNF production and stimulate the occurrence of anti-inflammatory cytokines, such as IL-1 receptor antagonist and IL-10 and also through a direct inhibition of IL-6 on TNF-alpha and IL-1 production.
Support for IL-6 as TNF-α inhibitor

- “Low-grade inflammation” model: low dose of Escherichia Coli endotoxin was administered to healthy volunteers
  - The volunteers were randomly separated into two conditions: rest or exercise prior to administration
- Results:
  - For resting subjects the endotoxin induced a 2-3 fold increase in circulating TNF-α levels
  - For exercise subjects that performed 3h of ergometer cycling or received a 3h infusion of recombinant human IL-6 prior to administration saw TNF-α response completely blunted
The Importance of Context with Myokines

- IL-6 was originally thought to be pro-inflammatory
  - How is this possible?
- IL-6 is a classic example of the importance of context
  - Where IL-6 is secreted from makes a HUGE difference
- Example: when IL-6 comes from macrophage, it is released along side TNF-α to create an inflammatory response
  - IL-6 that comes from muscles aids in an anti-inflammatory response by inhibiting TNF-α
Not Losing Weight but Getting Healthier?

- A couple of studies had men and women with abdominal obesity exercised under supervision and were required to consume extra food to inhibit weight loss from exercise.
- Results: after 12-16 weeks of chronic exercise the participants didn’t see weight loss.
- However, there was a considerable reduction in total fat, abdominal fat (especially visceral fat, which decreased by 12-18%), and waist circumference.
- Additionally, increased skeletal muscle mass and cardiorespiratory fitness.
Brain Health and Cognitive Function: The idea of Reserve

• Reserve: Capacity of the brain to function in the face of acute injuries or Neurodegenerative Disease:

  • Biological Reserve: "structural integrity" of the brain – ex: Volume
  • Cerebrovascular Reserve: capacity of the blood vessels of the brain to maintain blood flow in response to chemical, mechanical or neural stimuli
  • Cognitive Reserve: capacity for compensatory brain function in order to maintain cognitive performance

• Main Idea: The brain can adapt through these different reserves but these reserve are variable between people → Our experiences and lifestyle
The Ischemic Stroke example:

**PRE**

EXERCISE:

- Increase TNF-a levels
- Downregulating TNFRI and TNFRII

**STROKE**

**POST**

EXERCISE:

- Levels of pro-inflammatory cytokines
- Decrease Infarct Volume
- Levels of cell stress markers
Study of Metabolic Disorders and Cognitive Decline in elderly Latinos!

Significant negative association with 3MS:

- Metabolic Disorder Group:
  - C-reactive Protein (Inflammation level)
  - Impaired Glucose Control
  - High Blood Pressure

Baseline → 3 years

Cognitive Function | Metabolism

The Metabolic Syndrome:

Brain Health

- Hyper tension
- Hyper glycemia
- Dys lipidemia
- Insulin resistance

Systemic inflammation → CNS inflammation → Cognitive Decline
Growth Factors and Exercise:

- BDNF/TrkB
- Calmodulin KII
- MAPKII
- LTP
- Proliferation of Neural cell Precursors
- Angiogenesis
- Neurogenesis
- IGF-1
- Survival Promoting Effect
- VEGF
- Proliferation of Neural cell Precursors

Exercise induced retention
Exercise induced recall

Survival Promoting Effect
Proliferation of Neural cell Precursors

Regulation of NT release at synapses
Exercise Enhances Neurogenesis in Middle Aged Mice

Some Facts:

- Compared to young mice, new neuron formation is significantly decreased in middle to old aged mice.

- Neurogenesis in this area (DG) has been shown to help hippocampal dependent learning and memory

Why is this important?
Key Terms

Neural progenitor cells/stem cells (DCX+antibody): used interchangeably - refers to undifferentiated cells

BrdU - marker for mitotic cells (diving); incorporates a synthetic nucleotide

Dentate gyrus: part of the hippocampus, thought to help with formation of new episodic memories

BDNF - Brain derived neurotrophic factor - member of the neurotrophin family of growth factors

TrkB - Tyrosine Kinase Receptor; Binds BDNF

Serum corticosterone: elevated levels in older mice - can contribute to decline of neurogenesis

Subgranular Zone (SGZ): region in the hippocampus where adult neurogenesis occurs.
Objective

To examine the effects of Treadmill Running (TR) on neurogenesis in middle aged mice

Why Treadmill?

What are they measuring/looking at?
Methods

- Cell proliferation was measured at 3, 7, 9, 13 and 24 mo of age.

- All other aspects of the environments were controlled: controlled temperature, sleep cycles, consistent food and water. Specific Male c57b/6J mice used.

- Mitotic cells were traced with daily injections of BrdU. The TR started at 8 or 12 months (middle aged). Running speed was set to 10m/min and the duration of running increased 10 min/day until a max of 60min/day. This fulfilled intensity criteria of approx 70% of the mouse's maximal oxygen consumption
Methods cont.

-Mice were sacked and brains were post fixed in PBS and paraformaldehyde. In order to image the tissue, the brains were sliced into 30 micron sections and stored in a cryoprotectant until further use.

-Immunohistochemistry brains were stained with a anti goat DCX primary antibody and and a goat anti rabbit secondary antibody. To identify DG slices were counterstained red and incubated.

-Each brain had about 90 coronal sections and every 6th section was counted for DCX and BrdU positively labeled cells. What does this mean?

-Dendritic lengths were imaged and analyzed for their length using NIH Image Software
Serum Corticosterone

Recall * Corticosterone levels are known to increase in middle aged mice. Previous papers have shown age related decline of neurogenesis has been linked to this rise.

Researchers wanted to make sure that exercise itself was increasing neurogenesis, not another factor.

Why is this important?

People could argue that the neurogenic and neurotrophic effects of exercise is due to a decrease in the serum corticosterone. If corticosterone concentration is kept at a basal level, it's been shown to reverse the age related decline of hippocampal neurogenesis.
Quantification of BDNF and TrkB

- ELISA commercial kit to measure protein concentration

- Western Blotting and Band density and intensity measured with image analysis

- Statistical Analysis 2 way ANOVAS (p<.05)
Results

1) First they want to statistically show that neurogenesis is dramatically decreased in middle aged mice. Compared with a 3 month old mice, the number of mitotic and neural progenitor cells (BrdU+ and DCX+) decreased to 8% of that level in 24 mo old mice.

2) In the critical period (middle age) for neurogenesis, 5 weeks of TR increased the number of BrdU and DCX+ neurons in the DG. P value was <.001 so the results are highly significant. Different ages are affected differently by TR. (TR has a more pronounced effect on younger animals)

3) TR promotes neurite outgrowth in the immature neurons of middle aged mice (not only do they extend farther but the location of branching is more complex)
Dendrites surpass SBZ and Granule Cell Layer
-Neural progenitor cells DCX+ extend farther/ branch more
Results cont

- TR improves the survival of newborn neurons in middle aged mice. In TR mice the survival rate of new neurons increased from 30% to 50%
- TR does not change the basal level of serum corticosterone in middle-aged mice. Basal levels of serum corticosterone of middle-aged mice are not changed by 5 wk of TR. Therefore, although corticosterone is a strong negative regulator for adult hippocampal neurogenesis, it contributes little to reducing neurogenesis during aging
- TR stimulates BDNF and TrkB expression in hippocampus of middle aged mice (promotes differentiation and survival)
- Application:
Exercise and Alzheimer’s

- At risk: (AD)-related genes
  - Specifically Apolipoprotein (ApoE)-4 allele carriers
    - Carriers and exercise positively correlated with:
      - Better auditory, visual and spatial performance
      - Stronger temporal cortex activation during learning activities than non-carriers
      - Decreased depressed symptoms*
      - Active lifestyle may benefit at-risk population
      - Reduction of Amyloid B plaques in AD aged mice
- Intermittent Fasting/ Caloric Restriction
  - Limited caloric intake = reduced risk for AD

*results as to the specific cause for this need further investigation ???
Brain Fuel

● How neurons fuel themselves during exercise
  ○ Astrocytes
  ○ Glycogen storage
● Microwave irradiation to freeze glycogen
  ○ Study deceased rats
  ○ Glycogen levels pre/post exercise
Brain Fuel

- Single bout of exercise
  - Overcompensated glycogen by astrocytes
- Consistent multi-weekly exercise
  - Aerobic/ Cardiovascular exercise
  - Supercompensation becomes normal
  - Increases in critical learning and memory formation
- Frontal Cortex and Hippocampus
  - Increasing cortex and hippocampus has huge correlation to improved thinking and memory*

*in mice, studies on human glycogen levels are difficult to produce
Exercise and Cognition

- Correlation between exercise and intelligence in children and adult
- Areas affected:
  - Hippocampus
  - Frontal Cortex
- Techniques to measure neurophysiological data
  - EEG, ERP, MRI
  - Positive outcome of physical activity measured by these neurophysiological measures
- New tasks and learning decreases with age
  - Plasticity of synaptic contacts, synaptic strength reduced in hippocampus and cortex
- Children/ adults displayed high correlation between exercise and higher intelligence scores, learning, retention and brain resilience
Neurogenesis and Synaptic Plasticity

● Hippocampus
  ○ Neurogenesis linked to enhancement of learning and memory via the effects on the hippocampus and cortex*
  ○ Strongest neurogenic stimulus is exercise
  ○ Wheel running had 3-4-fold increase in production and survival of neurons**

● Synaptic Plasticity
  ○ 3-4-fold increase in plasticity of cells in dentate gyrus
  ○ Upregulate genes related to synaptic plasticity - glutamatergic system enhanced

● Dendritic spines
  ○ Exercise affects the properties
  ○ Actin-rich protrusions on the dendrites that contain excitatory synapses
  ○ Spine changes associated with LTP and synaptic strength
  ○ Exercise accelerates maturation of dendritic spines in new neurons

*Debatable, needs further research  **Not including mice with early onset AD or Huntington's
Active Lifestyle Implications

● The observations
  ○ Memory/learning improvement
  ○ Prevents/delays loss of cognitive functioning
  ○ Prevents/delays neurodegenerative diseases
  ○ Results shown for both voluntary and forced exercise, but voluntary exercise yields stronger results

● Improvements
  ○ Prevents:
    ■ Hypertension, Heart Disease, Type II Diabetes, Osteoporosis and Depression
  ○ Efficiency in the elderly with reasoning, memory and reaction times
Depression

- Mood Disorder that can lead to behavioral and physical symptoms:
  - Worldwide health burden
  - Hard to assess because depression is linked to cognitive decline.
- Human study:
  - Aerobic (2-4mo) → Treatment for both young and older depressed subjects
  - General adherence across studies: Up to more than 50% continue after the study.
- Rodents:
  - Exercise reduced stress-induced learned helplessness
Putative mechanism

Hypothalamic-Pituitary-Adrenal Axis → Anti-Depressant Effects

Leptin → Neurogenesis ?

BDNF → IGF-1
Exercise in Pregnant mice and their offspring

- HFD mice without exercise
  - Displayed an increase in fat mass, body weight and had poorer glucose tolerance and disposal
  - HFD mice had a lower proportion of phosphorylated AKT in adipose tissue compared to HFD mice who exercised
  - These findings show that mice who did not exercise were more likely to have insulin insensitivity, decreased glucose tolerance and were more likely to become obese or diabetic and have hyperglycemia
    - These findings could be due to increased fat mass which contributes to glucose insensitivity
Mother who were fed a HFD but exercised had significantly better outcomes

- Mice that were fed the same HFD but exercised had similar weight, fat volume, insulin sensitivity, and glucose tolerance as mice who were fed a standard diet but didn’t exercise.
- With exercise, mice had improved glucose tolerance, returning to baseline after a glucose test in half the time as HFD mice without exercise.
- Exercise can protect against impaired glucose disposal caused by a HFD because muscles during exercise require glucose uptake and dispose of glucose.
Mother who were fed a HFD but exercised had significantly better outcomes

- Phosphorylation of AKT in adipose tissue between HFD groups were equal until there was insulin introduced.
- When insulin is introduced there are significantly increased levels of phosphorylated AKT compared to the HFD mice without exercise. This shows that there may be better insulin signaling.
Mother who were fed a HFD but exercised had significantly better outcomes

- Mothers who exercised and were fed HFD showed improved resilience to the effects of obesity and other effects of fat accumulation such as insulin resistance.
- Insulin resistance can cause a proinflammatory environment that release cytokines and reduce the body's ability to signal for insulin which would keep the glucose levels high.
- A hyperglycemic state is friendly towards cancer cells because cancer cells thrive in high glucose environments, this is not to say that obesity and hyperglycemia cause cancer but they create environments that are friendly towards it.
Mother who were fed a HFD but exercised had significantly better outcomes

- Exercise can ensure that in mothers with diabetes and even pregnancy induced diabetes they may be able to increase insulin sensitivity and glucose disposal and ultimately ensure that their offspring are not predisposed to diabetes or a higher likelihood to become obese
- HFD fed mice have been shown to have detrimental effects to offspring with effects including, hypertension, impaired glucose tolerance,
What happens to offspring when a mother is fed a HFD without exercise?

- Unfortunately the positive effects of exercise are limited if your mother had a HFD and did not exercise suggesting that diet and lack of exercise can play a role in offspring susceptibility to obesity, and Type 2 Diabetes.
- But although the effects are less significant in the mice who had HFD fed mothers there still is improvements compared to those that did not exercise.
- Weight gain, glucose tolerance, and insulin sensitivity fall to the baseline for mice with mothers fed standard diets that are not exercising.
- Glucose uptake and therefore performance on exercise tasks is reduced in mice with mothers that were fed HFD.
Exercises role in ameliorating the effects of a HFD in offspring

- HFD mice resulted in offspring that had significantly higher body fat within the first year of age
- The offspring of HFD mice also had impaired glucose tolerance and decreased insulin sensitivity
- But when exercise is introduced the effects of the HFD is almost entirely ameliorated and the offspring do not have decreased glucose tolerance and are also less likely to have higher body fat
Exercises role in ameliorating the effects of a HFD in offspring

- Offspring of exercise trained HF mice were found to have similar results on insulin and glucose testing as SD and have improved glucose tolerance even in comparison to SD mice.
- Remarkably the insulin sensitivity and glucose tolerance was nearly identical to that of mice that were fed regular diets while those that didn’t exercise had nearly 3 times worse insulin sensitivity.
- So if the mother was fed a HFD but exercised nearly all the negative effects of a HFD are ameliorated, it is only in the absence of exercise that there is a plethora of negative effects displayed in offspring.
- Offspring of sedentary dams had a worsening of glucose tolerance as they aged but both exercise conditions had these effects completely negated.
Timing of exercise for mothers matters

- In order to have the largest effects it is important that dams exercise before pregnancy and during pregnancy, so in humans the mother should exercise while attempting to become pregnant and while pregnant.
- If mothers exercise before and during pregnancy there are marked improvements in glucose tolerance to the ova.
- Glucose tolerance has protective factors towards obesity, Type 2 Diabetes, and fostering an environment that is friendly to cancerous cells.
- In addition exercise mitigates all negative factors that offspring of HFD mice face including, body weight, glucose tolerance, and peripheral insulin sensitivity.
- Offspring of HFD fed mothers who exercised also able to have the same glucose uptake in skeletal muscles as offspring of mothers who were fed standard diets and exercised and were better off than those that did not regardless if they were fed lower fat diets.
What does this mean for mothers and offspring of mothers who are obese or diabetic?

- A HFD does not doom offspring so long as the mothers exercise and even if they don't exercise in offspring still helps.
- Furthermore if the mother has diabetes or is obese a regular regimen of exercise may improve their health as well as the health of their offspring.
- However even if a mother is not obese or diabetic if she consumes a HFD without exercise she will be causing her offspring to face limited positive effects of exercise in the future.
- The findings of exercise in all conditions suggest anti-inflammatory effects from exercise and may be protective towards diabetes, obesity, hyperglycemia and may be beneficial for cognitive function.
Diet and Cognition

- Synergy between diet and exercise
  - Reduce inflammation
  - The effects of exercise on cognition are enhanced when immediately followed with proper diet yet the process does not work in the opposite order
- Diet
  - Alone does not have a large effect on cognitive functioning
  - Enhances neurite outgrowth
  - Spine density increased in hippocampal granule cells
Diet and Cognition

- **Flavanols**
  - Plant polyphenols, subclass of phytochemical flavonoid
  - Mediates cognitive effect from exercise
  - Neuroprotective, antioxidant, antiapoptotic
  - Enhance synaptic plasticity and learning
  - Effect on angiogenesis to improve cardiovascular function and lower blood pressure, more beneficial than exercise, but stronger when coupled with exercise

- **(-)epicatechin**
  - Improves insulin sensitivity, regulates blood sugar and stimulates muscle protein synthesis
  - Consumption - improved retention of spatial memory better than AD meds (rats)
  - Memory function and synaptic plasticity enhanced when coupled with voluntary exercise
Inflammation

- Age-related cognitive decline
- Neurodegeneration (AD, PD)
- Neurotrophin resistance

Exercise

- Metabolic syndrome
- Hypertension
- Insulin resistance

↑ Growth factor induction and signaling cascades

↑ Brain health
- ↑ Cognition
- ↑ Plasticity
- ↑ Neurogenesis
- ↑ Vascular function