Intermittent Metabolic Switching

By Got My Ion You (Andy, Lexi, Ryan, Sofia, Vicky & Yuval)
Introduction
Agenda

1. Introduction to **Intermittent Metabolic Switching** (IMS)
   → Different IMS protocols
2. Dive into IMS physiology
3. Neuronal adaptation
   → Animal models of IMS
4. Signaling pathways affected by IMS
5. How IMS relates to neurological disorders
6. Conclusions & Future Directions
IMS - The Big Picture
Today

- 700-900 calories
- 10-14 hours without exercise
Why Fast?

- Historically sporadic food access
- A brain and body that functions better during a fast will be more capable of:
  - Acquiring food
  - Surviving
  - Reproducing
What Happens in Fasting: Metabolic Switch!

1. Glycogen depleted
2. Adipose cells release fatty acids
3. Converted to ketone bodies
   - b-hydroxybutyrate (BHB)
   - acetoacetate (AcAc)
4. Used by neurons as energy substrate

G-to-K Switch

Low circulating glucose

Released into blood
Switching Back: Eating and Rest

- Switching results in cellular and molecular adaptations in brain neural networks
  - Enhances functionality
  - Improves resistance to:
    - Stress
    - Injury
    - Disease
What is Intermittent Metabolic Switching (IMS)?

- Ketosis induced
- G-to-K and K-to-G switches
- Possible:
  - Brain health and resilience optimization
  - Cognitive and physical performance enhancements
  - Cognition and mood circuit benefits
  - Neuroplasticity and resilience promotion
IMS Animal Protocols

1. Intermittent Fasting (IF)

2. Alternate-Day Fasting (ADF)
   a. 24 hr deprivation every other day

3. Daily Time-Restricted Feeding (TRF)
   a. Set time period deprivation
      OR
   b. Caloric restriction (CR)
      i. 20-22 hr fast
What you saw in the video:

16:8 Fasting Clock
The Rest of the Presentation:

Molecular and cellular adaptations to IMS

Cognition, mood regulation & motor control

- Enhanced insulin sensitivity
- Reduced abdominal fat
- Muscle mass maintenance
- Reduced resting HR & BP
Key Terms Review

TERMS TO RECOGNIZE:

● IF- simly intermittent fasting

● K->G switch

● ketones
  ● b-hydroxybutyrate (BHB)
  ● acetoacetate (AcAc)
WTF Happens When I Eat?

- We eat 3-4 times daily
- Each time replenishes our glycogen stores which should give us **700-900 calories of energy**
- This equates to 10-14 hours of energy (if you are not exercising)
- Is this **too much energy?**
## Benefits of IMS - The Claims

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Changes</th>
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<tbody>
<tr>
<td>Neuroplasticity → learning / memory, mental acuity, cognitive performance</td>
<td>↑↑</td>
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<td>Resting heart rate &amp; blood pressure</td>
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<td>Insulin sensitivity</td>
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<td>Abdominal fat</td>
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<td>Resistance of nervous system to injury / disease</td>
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<td>Anxiety / depression</td>
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G-to-K and K-to-G Switch
Energy Expenditure - The Physiology
Fasting vs. Not Fasting

- Fasting → **deplete** liver glycogen stores
  - Production of ketone bodies
    - β-Hydroxybutyrate
    - Use as energy source
- Breaking fast (by eating) → **replenish** liver glycogen stores
  - Liver glycogen → provide ~700-900 calories of energy, last for 10-14 hours if not exercising
What do we mean by “depleting” liver glycogen?

**Glycogen** = stored glucose

Depletion → through fasting OR exercise

- **Connection to video**: Sofia saying she is in “just as much pain as [the fasters]”

**HOW?**

- **Glycogenolysis** (fancy speak for breaking down glycogen) - how we use that stored glucose
Hepatic Glycogenolysis: The Bare Bones

Glycogenolysis = biochemical breakdown of glycogen (stored glucose) - just know that it involves a bunch of enzymes

Hepatic → refers to the liver

(b) Fasted state: glucagon dominates

↑ Glycogenolysis
↑ Gluconeogenesis
↑ Ketogenesis
So what happens when we use up all our glycogen?
Let's make it a party

**Lipolysis Party**

**WHEN:** After liver glycogen stores have been depleted

**LOCATION:** Adipocytes

**WHAT:** Let's cleave some fat cells! We'll be breaking down TAGs and DAGs to make Free Fatty Acids (FFA's) and then using these to make ketones for energy! It's sure to be a great time!

BYOB.
Lipolysis (in adipocytes) begins only after liver glycogen is depleted

Recall: It takes at least 10-14 hours for this to occur!

Generate **FFA’s** → generate acetyl CoA for **Kreb’s cycle** (from fatty acyl-CoA)
WHAT'S HAPPENING:

Stored glucose stores (glycogen) depleted in fasted state (hepatic glycogenolysis)

Once depleted → G-to-K switch can occur (generate ketones from fatty acids) → alternate energy source
WHAT'S HAPPENING:

Cleave DAG’s/TAG’s in adipocytes to form free fatty acids (FFA’s) = lipolysis

Can then be transported to liver or astrocytes via the bloodstream & converted to fatty acyl-CoA and subsequently acetyl CoA to use in the Kreb’s cycle
KEY TAKEAWAYS:

● Glucose = body’s *preferred* energy source
  ○ Will utilize ketones if ↓↓ blood glucose

● “G-to-K Switch” = transition from using glucose → fatty acids & ketones (energy)
  ○ IF protocols **INDUCE** this metabolic effect (why it requires fasting *at least* 10-14 hours)
Neuronal Adaptation to IMS
Behavioral Adaptations

Animal Models
Behavioral Adaptations - Young Mice

- Weaning age mice:
  - Daily TRF at 40% caloric restriction
  - Learning/memory remain unaffected by age
  - Locomotor performance improvement with age when compared to control mice
Behavioral Adaptations - Young Mice

- 14-month-old mice:
  - 10 months of fasting led to improved (relative to control mice):
    - Spatial navigation
    - Working memory
    - Strength
    - Coordination
Behavioral Adaptations - Older Mice

- Adult mice:
  - Daily TRF at 40% caloric restriction showed (relative to controls):
    - No hippocampal spatial learning/memory deficits
    - Lack of anxiety-related behaviors
  - Low-calorie diet for 4 consecutive days every other week for 7 months (relative to controls):
    - Elevated levels of ketones
    - Improved spatial learning/memory in maze tasks
    - Elevated performance in object recognition/working memory in novel object recognition tasks
Networks, Plasticity, & Neurogenesis

Animal/human models
Neuronal Network Activity - Epilepsy

- Human patients
  - Suffer from seizures - sudden excessive neural activity
    - Can lead to loss of consciousness, loss of bladder control, muscle spasms
  - Ketogenic diets benefit epileptic patients
  - Increase in ketones controls neuronal network activity
- Animal models
  - Rats exposed to alternate-day fasting exhibit ability to resist damage to hippocampus resulting from seizures.
Synaptic Plasticity

● IMS resulting from IF or exercise:
  ○ Rats and mice display (relative to controls) increased long-term potentiation in hippocampus
    ■ Forming basis for improved learning/memory

● Daily TRF (22 hours of fasting/day for three weeks):
  ○ Rats show improved maze task performance
  ○ Increased dendritic spine density and LTP in CA1 region of hippocampus

● Daily TRF (30% CR)
  ○ Control and diabetic mice displayed increased hippocampal dendritic spine density
  ○ Effects can be optimized by combining with exercise
Neurogenesis

- New hippocampal neurons constantly born in mammalian adult life.
- Running and IF:
  - Running increases proliferation of stem cells and strengthens connections between new neurons and brain areas important for learning/memory (entorhinal cortex & basal forebrain)
  - IF increases survival rate of new neurons
- Role of G-to-K switch on adult neurogenesis, and relationship with running/IF still being studied.
Signaling Pathways Affected by IMS
Glutamate

- Primary excitatory neurotransmitter in the central nervous system (brain)
  - Responsible for:
    - Triggers $\text{Ca}^{2+}$ influx into postsynaptic neuron $\Rightarrow$ dendritic spine growth, synaptogenesis, and long-term potentiation/depression
      - LTP and LTD important for balance
      - Downstream pathway: $\text{Ca}^{2+} \Rightarrow \text{CaMK + PKC + CREB + NF-kB}$
“Increased activity in neuronal circuits that occurs during exercise and fasting contribute to mitochondrial biogenesis via \( \text{Ca}^{2+} \)-CaMKII-CREB-PGC1\( \alpha \) pathway”
Proteins and Factors Involved in IMS

**BDNF (brain-derived neurotrophic factor)**
- Involved in **synaptic plasticity, neurogenesis**, and **neuronal stress resistance**

**BHB (β-hydroxybutyrate)**
- Involved in **regulating gene transcription, synaptic plasticity**, and **cellular stress resistance**

**SIRT3**
- Involved in **protecting neurons from mitochondrial stress and apoptosis** by deacetylating superoxide dismutase 2 and cyclophilin D

**IGF1 (insulin-like growth factor 1)**
- Involved in **enhancing neuroplasticity** and **protecting neurons against metabolic and oxidative stress**

**FGF2 (fibroblast growth factor 2)**
- Involved in **stimulating neural stem cell proliferation**, protecting neurons against **metabolic and oxidative stress**, and **regulating neurite outgrowth/cell survival during break development**

**PGC-1α**
- Transcription factor
- Involved in **mitochondrial biogenesis** through (nuclear respiratory factor) NRF1/NRF2
**β-hydroxybutyrate**

- Induces expression of BDNF (when glucose levels are low)
- Inhibits HDAC (histone deacetylase)
  - HDAC usually repressed BDNF
- Exercise decreases HDAC
- Fasting increases acetylation
  - Acetylation = proteins can be translated from RNA
- Triggers activation of NFkB
  - Goes to nucleus to induce BDNF expression
- Precursor to oligodendrocytes = myelination
- Research:
  - Oral administration of a BHB ester to rats for 5 days improved their spatial learning and memory, and enhances their endurance on a treadmill test!
mTOR

Mammalian/mechanistic target of rapamycin

- Protein kinase
- **Mediates local synthesis of proteins in dendrites**
- **Fasting/extended exercise:**
  - mTOR is inhibited because of an increase in AMPK
    - Intermittent AMPK activation = **enhance** neuroplasticity
    - Sustained AMPK activation = **impaired** axonal and dendritic plasticity
- **Short and intense exercise, eating, resting, and sleeping:**
  - mTOR is active ⇒ protein synthesis
    - Critical for learning, memory, and synaptic plasticity
Exercising and Fasting... Similar effects?

Exercise
- Uses liver glycogen stores
- Fuel source: Glucose $\Rightarrow$ FA $\Rightarrow$ Ketones
- Similar proteins released (BDNF, FGF2)
- mTOR activity decreases
- CREB activation (downstream of Ca$^{2+}$ pathway)
- Mitochondrial biogenesis (needed to use fats for energy)

Fasting
- Passive process
- Many types of fasting: Too many to name

Active process
- 2 types of exercise: (1) anaerobic (2) aerobic

Passive process
- Many types of fasting: Too many to name
Using Fats for Energy
Using Fats for Energy
Key Components:

- Mitochondrial biogenesis
  - Ca\(^{2+}\)/calmodulin-dependent protein kinase type II gamma (CaMKII)
  - AMPK
  - PGC-1\(\alpha\)
    - Transcription factor that can enhance BDNF expression
PGC-1α knockdown = basal synapse formation reduced and synaptogenesis reduced

Need mitochondria to maintain/support the function of synapses
MITOCHONDRIAL BIOGENESIS IS GOOD
Optimization through IMS

**Fasting and exercise**

- **Glucose-to-ketone switch (bioenergetic challenge)**
  - ↑ Ketones
  - ↑ Ghrelin
  - ↑ Myokines
  - ↓ Glucose
  - ↓ Leptin
  - ↓ Insulin
  - ↓ Cytokines

- **Cellular stress resistance (molecular recycling and repair pathways)**

**Eating, resting and sleeping**

- **Ketone-to-glucose switch (recovery period)**
  - ↓ Ketones
  - ↓ Ghrelin
  - ↓ Myokines
  - ↑ Glucose
  - ↑ Leptin
  - ↑ Insulin
  - ↑ Cytokines

- **Cell growth and plasticity pathways (mitochondrial biogenesis, synaptogenesis and neurogenesis)**

- **IMS**

**Enhanced synaptic plasticity and neurogenesis**
- **Enhanced performance (cognition, mood, motor and ANS function)**
- **Resistance to neuronal degeneration and enhanced recovery from injury**
Visualizing the effects of IMS

**EFFECTS OF INTERMITTENT FASTING ON THE BODY AND BRAIN THAT MAY THWART OBESITY AND CHRONIC DISEASES**

**BRAIN**
- Improved cognitive function
- Increased neurotrophic factors
- Increased stress resistance
- Reduced inflammation

**HEART**
- Reduced resting heart rate
- Reduced blood pressure
- Increased stress resistance

**LIVER**
- Increased insulin sensitivity
- Ketone body production
- Decreased IGF-1 levels

**FAT CELLS**
- Lipolysis
- Reduced leptin
- Increased adiponectin
- Reduced inflammation

**INTESTINES**
- Reduced energy uptake
- Reduced inflammation
- Reduces cell proliferation

**MUSCLE**
- Increased insulin sensitivity
- Increased efficiency
- Reduced inflammation
WTF DOES THIS HAVE TO DO WITH COGNITION
- glutamate is one of the body's key excitatory hormones
- it plays a role in synaptic activation and plasticity
- mouse studies of increased dendritic spines
Dendritic Spines

- products of excitatory signals
- can be increased through training
- however, same chemicals are released in training yet more are released through IF
-also shown to be beneficial in the formation of dendritic spines

-agonists easily cross BBB
-shock tests with mice who were also administered ghrelin agonist
corticotropin releasing hormone/ACTH system has role in anxiety
-shock mazes show that animals experienced more anxiety after their first treatment with ghrelin but these side effects went away
AMPK Pathways

- Play key role in energy balance and detecting levels of ATP.

- Other mice studies where AMPK was administered saw upregulation of mitochondrial genes in hippocampal areas.
- Suppression of pro-inflammatory cytokines
- Elevation of IL-1 alpha, IL-1 beta, and TNF alpha levels
- Prevents reduction of BDNF in hippocampal areas
- This reduces effects of systematic inflammation
We know:
IMS -----> Positive Brain Health

What About:
IMS --------> Acute Injury?
Findings:

Seizures

Factors for Injury:
- Excitotoxicity
- Metabolic Failure
- Oxidative Stress

Rats on IF:
- Exposure to the seizure ----> reduced loss of hippocampal pyramidal neurons + improved performance in a water maze test of spatial learning and memory
- daily IF ----> elevates circulating BHB levels + also suppresses seizures
Findings:

Strokes

Factors for Injury:
- Excitotoxicity
- Metabolic Failure
- Oxidative Stress

Rats on IF:
- On IF prior to cerebral vessel occlusion -----> reduced death of cerebral cortical neurons
- IF initiated either before or after a injury to the thoracic spinal cord significantly improves recovery of motor function
Conclusions

From strokes and seizures

- These findings demonstrate that IMS can protect neurons and enhance resilience following injury.
- Can IF help patients who suffered from stroke?
Findings

Cellular and Molecular mechanisms

**IF upregulates:** resistance to proteotoxic stress, neurotrophic factor signalling, DNA repair, mitochondrial metabolism and bioenergetics, antioxidant defences

**IF downregulates:** pro-inflammatory cytokines
IMS -----> Neurological Disorders

- Alzheimer disease (AD) and Parkinson disease (PD)
- Depression and anxiety disorders
- Autism spectrum disorder (ASD)
Alzheimer disease and Parkinson disease

- Major risk: aging
- How IF helps:
  - Extend lifespan by up to 40% and protect against chronic diseases
  - Overindulgent lifestyles are at increased risk of developing AD and PD
Alzheimer

Features of AD:
- β-amyloid (Aβ) plaque
- neurofibrillary tangle-like pathologies
- cognitive impairment
- Daily TRF (time restricted feeding) reduced the accumulation of Aβ plaques in App-mutant mice
- Long-term IF prevented development of cognitive impairment in AD mice that express beta amyloid precursor protein (APP)

Parkinson

- Selective degeneration of dopaminergic neurons, induced by administration of mitochondrial toxins that selectively accumulate in dopaminergic neurons.
- When mice are maintained on an IMS regimen before neurotoxin administration, their dopaminergic neurons are relatively resistant to degeneration and their motor deficits are reduced
Depression and Anxiety Disorder

- Overindulgent lifestyle ---> increases risk of anxiety disorder and depression.
- IMS by exercise or IF can improve mood and make anxiety and depression better
Depression and Anxiety Disorder

- BHB induces BDNF expression in hippocampal and cortical neurons----> ketones mediate the antidepressant effects of exercise and IF
Autism Spectrum Disorder

- Link b/w increase childhood obesity and autism
- Neurobiological mechanisms may include reduced BDNF expression and excessive mTOR pathway activation.
- Consistent with a potential benefit of IMS, exercise is effective in reducing behavioural issues in many children with ASD
WTF / Conclusion & Future Directions
-general anxiety and tiredness caused by the system “recalibrating”

-most of the subjects did not participate for a long enough time to see the cognitive benefits

-perhaps it is only in mice

-general reduction of body weight shows that's the first effect of IF

-questions!
Criticisms
- This study claimed general cognitive benefit
- Read between the lines
- Most studies point to better spatial awareness
- Lots of training of the mice also increases synaptic plasticity/ perhaps a better test can be used

Ideas for Future Studies
- Do studies that incorporate student/athlete/working professional lifestyle
- Recognize that the brain needs calories!
- Standardize sleep and other aspects that could affect cognition across studies