Inflammation: Obesity and Metabolic Syndrome

Week 6
Gaba-Daba-Doo
AGENDA

Introduction
● Obesity, metabolic syndrome, inflammation

Inflammatory Response
● Normal acute response
● Anti-inflammatory
● Response in obesity and metabolic syndrome
● Adipocyte dysfunction, visceral obesity, diet, and microbiota

Mediators
● IL-6
● CRP
● Adiponectin

Additional Studies

The Big Picture
Agenda

1. Obesity
2. Metabolic Syndrome
3a. Inflammation
3b. Inflammatory Response
4. Microbiota & Adipocyte Dysfunction
5. IL-6
6. CRP
7. Adiponectin
8. Additional Studies
9. Big Picture

FOCUS PAPER FIGURE

the relationship between obese-metabolic syndrome patients and the chronic inflammation of adipose tissue
TNF-alpha: tumor necrosis factor
CRP: C-reactive protein
SFA: saturated fatty acids
• TLR: toll-like receptors
AD: adipocyte dysfunction
IL: inter-leukin
JNK: C-Jun N-terminal kinase
IKK: IkB kinase
PKC: protein kinase B

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*TLR’s activation further synthesizes pro-inflammatory factors

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• Obesity
• Metabolic Syndrome
• Inflammation
Source: Behavioral Risk Factor Surveillance System

*Sample size < 50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%
obesity

- What is it?
- What causes it?
- How can we stop it?
What is Obesity?

- 39.8% of Americans, 93 million Americans
- Leading cause of death worldwide
- Heart disease, stroke, type 2 diabetes, and certain types of cancer

Obesity

- A medical condition in which excess body fat has accumulated to an extent that it may have a negative effect on health
- BMI greater than or equal to 30
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Causes of Obesity

- **Sedentary Lifestyle** → worldwide trends toward less physically demanding work and insufficient amounts of exercise
  - Excessive food intake
  - Easily accessible and palatable diet
  - Increased reliance on cars
  - Mechanized manufacturing

- Insufficient sleep, endocrine disruptors (environmental pollutants that interfere with lipid metabolism), increased use of medications that cause weight gain
Causes of Obesity cont.

- Genetics
  - Two copies of FTO gene (fat mass and obesity associated gene)
  - Two obese parents → 80% chance of obese child

- Thrifty Gene Hypothesis
  - Due to dietary scarcity during human evolution, people are prone to obesity. Their ability to take advantage of rare periods of abundance by storing energy as fat would be advantageous during times of varying food availability, and individuals with greater adipose reserves would be more likely to survive famine
How we can stop obesity
How we can prevent Obesity

- Prevention in Children and Adolescents
  - Gradually work to change family eating habits and activity levels
  - Encourage physical activity
  - Encourage children to eat only when hungry, and to eat slowly
  - Avoid the usage of food in terms of reward/punishment

- Prevention of Obesity in Adults
  - Eat 5-6 servings of fruits and veggies daily
  - Whole grains
  - Exercise!!!!!!!!!!!!!!! 30 minutes or more of exercise daily
metabolic syndrome

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**TLR’s activation further synthesizes pro-inflammatory factors**

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2. Metabolic Syndrome
3a. Inflammation
3b. Inflammatory Response

- Metabolic overload (one of many factors of obesity)
  - 1. Obesity
  - 2. Metabolic Syndrome

3a. Inflammation
- 3a. Inflammation

3b. Inflammatory Response
- 3b. Inflammatory Response

4. Microbiota & Adipocyte Dysfunction
- 4. Microbiota and AD

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- 5. IL-6

6. CRP
- 6. CRP

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- 7. Adiponectin

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- 8. Additional Studies

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what is MetS?
aka American Syndrome, syndrome X, IR syndrome

A medical condition *identified by the combination of the following comorbidities:

1. Glucose Intolerance
2. Central Obesity
3. Dyslipidemia
4. ↓↓ High-Density Lipoprotein
5. Hypertension

Kinda.

*Oxidative Stress, Inflammation and Angiogenesis in the Metabolic Syndrome
what is MetS?
aka American Syndrome, syndrome X, IR syndrome

That definition is fairly controversial

- Debate on the gravity of the components
- Monteiro & Azevedo include a chronic proinflammatory state
- Obesity and MetS don’t completely overlap
  - Adipose cell size might matter more
What causes MetS?

\-_-\(ツ\)_/\-

But seriously, we don’t know.
possible culprits:

- Chronic low-grade inflammation
- Excess adiposity
  - Relationship between adiposity and inflammation
  - FTO gene & melanocortin receptor 4
- Insufficient adiposity
- ‘Modern Western Lifestyle’
  - Chronic psychological stress
  - Positive energy balance
  - Low quality diet
  - Chronobiological disruption
- Allostatic Dysregulation
  - It’s like a Domino Effect, but they reset to get knocked over again.
- Mood disorders
- Psychotropic medication
- Genetics
- Excessive alcohol use
- Age
- Gender
how can we stop MetS?

- Healthier lifestyle (increased physical activity, higher quality food, reduced calorie intake)
- Paleolithic Diet Pattern
- Drink more milk/eat more dairy products

Remember: MetS is not a single disease or disorder. It’s a constellation of comorbid diseases which feed into each other.
Inflammation

- What is it?
- What causes it?
- Why should we care?
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What is inflammation?

- An ordered sequence of events engineered to maintain tissue and organ homeostasis
- A physical, biological, or chemical reaction in response to a noxious stimulus

TWO TYPES

- **Normal acute inflammation**
  - Short time
  - Characterized by edema and migration of leukocytes
- **Chronic inflammation**
  - Happens if acute inflammatory response process is unsuccessful
  - Long time
  - Characterized by presence of lymphocytes, macrophages, and proliferation of blood vessels
Types of Inflammation

Acute
- Cuts, Laceration, Stabbing
- Frostbite
- Chemical irritants
- Trauma (bruises, sprains, strains, broken bones)
- Allergic Reaction
- Burn (sun, fire, touching hot objects)

Inflammation

Chronic
- Cardiovascular Disease
- Autism
- Rheumatoid Arthritis
- Autoimmune Disease
- Depression
- Cancer
- Alzheimer
- Neurological Disease
What causes inflammation?

- Inflammation can come from internal AND external factors
- Leading factors that cause inflammation:
  - Eating inflammatory foods
  - Blood sugar imbalances
  - Leaky gut syndrome
  - Chronic stress
  - Poor sleep habits
  - Environmental toxins
  - Chronic infections

TAKEAWAY: Inflammation can be triggered by numerous factors. The best way to prevent is to have a balanced immune system (AKA - healthy living)
Why is the inflammatory response important?

- Inflammation is the body’s response in healing itself!
  - It is a **vital immune response** if harmful stimuli enters the body
- Inflammation has been shown to be associated with numerous diseases/disorders → helps us understand them!
  - FUN FACT: researchers are trying to find a link between inflammation and cancer too
5 Classic Signs of Inflammation

1. **Heat** (Calor)
2. **Redness** (Rubor)
3. **Swelling** (Tumor)
4. **Pain** (Dolor)
5. **Loss of Function** (Functio Laesa)
Inflammatory Response

1) Normal acute response
2) Anti-inflammatory
3) Response in obesity and metabolic syndrome
4) Adipocyte dysfunction, visceral obesity, diet, and microbiota
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Normal Acute Inflammatory Response

1. Platelets from blood release blood clotting proteins to wound
2. Delivery of plasma components and leukocytes to injury site
   a. Initiated by macrophages and mast cells
3. Mast cells produce different types of pro-inflammatory mediators
   a. Cytokines
   b. Chemokines
   c. Vasoactive amines
   d. Eicosanoids
   e. Products of proteolytic cascades
Acute Inflammatory Response Cont’d

4. Neutrophils AND Macrophages attack the invading pathogen and release the mediators
   a. Pyrogenic cytokines increase blood vessel permeability and induces acute phase response proteins

5. IF SUCCESSFUL = injurious agent is eliminated and anti-inflammatory process occurs

6. IF UNSUCCESSFUL = chronic inflammation and autoimmunity
Anti - Inflammatory Response

1. Successful inflammatory response → apoptosis of inflammatory cells
   a. Removes dead cells
   b. Macrophages acquire a phenotype conductive to resolution
2. Macrophages release anti-inflammatory signals
   a. IL-10
   b. TGFβ
   c. Adiponetin
3. Final clearance and neutralization of toxic stimuli!
Response in Metabolic Syndrome

- Metabolic Syndrome:
  - “Low-grade” chronic inflammation because it does not show infection or signs of autoimmunity
    - Can also be called “metaflammation” or “parainflammation”
  - Modern western lifestyle shows an increase incidence of metabolic syndrome
    - Stress
    - Positive energy balance
    - Low quality food
    - Disruption of chronobiology
Response in Obesity

Importance of Catecholamines and Insulin

- Regulates blood flow into the adipose tissue
  - Inadequate blood supply → reduced oxygenation → possible inflammation
- Can alter adipocyte metabolism

Role of Adipocytes

- Obese individuals secrete large amounts of pro-inflammatory cytokines (IL-6, TNFα, and IL-1β) from adipocytes but not enough of the anti-inflammatory adiponectin to complete the response → can lead to numerous obesity linked diseases
Summary: Inflammatory Response

- Inflammation: A response to any harmful stimuli
  - Successful: elimination of stimulus
  - Unsuccessful: chronic inflammation
- Key Players:
  - Platelets
  - Macrophages
  - Cytokines
  - Neutrophils
- MetS and Obesity
Inflammatory Response PT II

1) Adipocyte Dysfunction

2) Visceral Obesity

3) Diet and Microbiota
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What’s Adipocyte Dysfunction?

- Characterized by:
  - ↓ insulin sensitivity
  - ↑↑ parameters of intracellular stress
  - ↑↑ autophagy and apoptosis
  - ↑↑ inflammation
Where does AD come from?

1. **Overload**
   - visceral and subcutaneous adipose tissue, lipid/nutrient accumulation
   - apo-Bs, TLRs and IKKB

2. **Stressors**
   - Oxidative stress, inflammatory cytokines, elevated fatty acids/cases of obesity
   - Organelle dysfunction
AD and Inflammation

1. OVERLOAD: Inc NEFA(elevated nonesterified fatty acids)--stimulate dyslipidemc effect
   a. Adipose tissue can’t buffer excess nutrient intake = metabolic overload
      i. Inc apo-B--low density lipoprotein formation)--Adipose Tissue Dysfunction!!
      ii. Activate TLR2 and TLR4 synthesize proinflammatory factors IL-6 and TNF-a--Metabolic syndrome!
      iii. Metabolic dysfunction--mediated by dec IKKB--inhibitory serene phosph. Of IRS and attenuation of insulin signaling-- Inc inflammation
AD and Inflammation

1. METABOLIC STRESS: on adipose tissue--organelle dysfunction
   a. Mediated by kinase--stress receptor impaired--inactive IRS--activate AP-1 and NFK-B-- inc inflamm!
   b. Body Response: ER signals PKR-like eukaryotic factors in Kinase PERK, IRE-1 and activates ATK-6--induce repair--cell death or biogenesis
What is Visceral Obesity

- Predictor of:
  - Insulin sensitivity
  - Impaired glucose tolerance
  - Elevate blood pressure
  - Dyslipidemia
Visceral Obesity and Inflammation

- Note: NOT all people with the syndrome have a proinflammatory response
- When does it occur?
  - Adipocyte size enlarged (not just overload)—likely rupture—inflammation—IR
  - proinflammatory—increase metabolic syndrome—dense vascular abdominal adipose
  - Positively correlated with TNF-a, IL-6 and CRP, Negative correlation with adiponectin
- Subcutaneous vs Visceral Adipocytes
- Adipocyte Instability
- Visceral tissue growth depends on location
Diet and Inflammation

- Total dietary fat and saturated fat--insulin resistance/blood pressure/inflammation
  - aP2 association with insulin resistance and inflammation
- Study:
  - People put under saturated high sugar weight loss diet inc inflammation marker (not dep on oxidative stress)
  - People under monosaturated fatty-acid rich diet--anti-inflammatory
- Note:
  - inflammatory markers have been found to increase in a mixed meal as well!
Microbiota and Inflammation

- Microbiota! What are they?
  - microorganisms that contribute to digestion and metabolism
- What happens when there are diff levels of microbiota?
  - Obese individuals and nonobese have been found to have diff levels of microbiota
  - Speculation, but unsure of what this may indicate
- Changes in gut microbiota control metabolic endotoxemia and inflammation
ujjayi

time
Inflammatory Mechanisms:

- IL-6
- CRP
- Adiponectin
Interleukin-6

- IL-6 acts as a pro-inflammatory cytokine in immune and adipose tissue
- IL-6 gene
- Produced by adipocytes
- Secreted by macrophages in response to PAMPs → inflammatory cytokine production
- Dysregulated continual production of IL-6 → development of disease
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IL-6 Signaling

Classic: Anti-Inflammatory Response

- IL-6 stimulates target cells via a membrane bound IL-6 receptor
- Upon ligand binding → gp130
- Gp130 dimerizes → activation of Janus kinases (JAK) → phosphorylation of tyrosine
- Engagement of phosphatase Src homology domains (SHP-2) → MAP kinase pathway

Trans-Signaling: Pro-Inflammatory Response

- Soluble form of the IL-6 receptor
- Enlarges the spectrum of the IL-6 target cells
- Mediates gp130 activation

The therapeutic blockade of IL-6 by neutralizing anti-IL-6 monoclonal antibody has been approved for the treatment of inflammatory diseases
Trans-Signaling

**IL-6 Classic Signaling**

- IL-6
- gp130
- IL-6R
- Signaling

**IL-6-Trans-Signaling**

1. sIL-6R
2. ADAM17

Classically, IL-6 binds to gp130 and IL-6R to initiate signaling. In trans-signaling, sIL-6R and ADAM17 are involved in the process.
Regulation of IL-6 Synthesis

- Infectious lesion → warning signal to body
- PAMPS are recognized by PRRs of immune cells
- Stimulate signaling pathways → enhance the transcription of IL-6

- IL-6: warning signal in the event of tissue damage
- DAMPs are released from damaged or dying cells
- Promote inflammation
Adipose Tissue and IL-6

- Adipose Tissue
  - “Body fat”
  - Energy storage
  - Cushions and insulates the body
- Produces and releases pro-inflammatory and anti-inflammatory factors:
  - Leptin, adiponectin, as well as other cytokines and chemokines
- Obesity and plasma IL-6 levels
  - $\frac{1}{3}$ of the total circulating concentration of IL-6 originate from adipose tissue
- Inadequate blood supply $\rightarrow$ reduced oxygenation $\rightarrow$ inflammation
Obesity and IL-6

- Overexpression of pro-inflammatory cytokines → link between inflammation, obesity and Metabolic Syndrome
- Adipocyte enlargement + obesity → adipocyte blood supply reduced → hypoxia

- Hypoxia
  - Inciting etiology or necrosis, and macrophage infiltration into adipose tissue
  - Localized inflammation propagates overall systemic inflammation associated with obesity-related comorbidities
- Inflammatory mediators produced by macrophages
  - TNF-alpha
  - IL-6
- IL-6 strongly stimulates hepatocytes to produce and secrete CRP, indicating a state of inflammation
- Accumulation of free fatty acids → activation of pro-inflammatory serine kinase cascades which promote adipose tissue to release IL-6 → triggers secretion of CRP
Abdominal Obesity and Metabolic Syndrome via Inflammatory Mediators

- Excess of macronutrients → Obesity

  - Adipocyte hypertrophy/hyperplasia
  - Hypoxia/necrosis
  - Macrophage infiltration

  - Activation of JNK, IKK, PKR
  - Activation of Toll-like receptor

  - Alteration in lipid and glucose metabolism
  - Pro-inflammatory state
  - Atherosclerosis
  - Insulin resistance
  - Hypertension
  → Metabolic syndrome

- Pro-inflammatory state
  - ↑ TNF-α, ↑ IL-6, ↓ Adiponectin

- Endothelial/microvascular dysfunction
  - ↓ NO, ↑ ROS
Molecular Link of IL-6 and CRP

● C-Reactive Protein
  ○ Synthesized and secreted in hepatocytes
  ○ Regulated by IL-6 and IL-1
● Highly expressed in the liver, intestine, kidney, and adrenal glands
● Inhibited by the farnesoid X receptor (FXR)
● Free fatty acid accumulation in obesity
  ○ Activates pro-inflammatory serine kinase cascades, (IκB kinase and c-Jun N-terminal kinase)
  ○ → promotes adipose tissue to release IL-6
  ○ Which triggers hepatocytes to synthesize and secrete CRP
Summary: IL-6

- Has pro-inflammatory properties
- Lets CRP know it's time to go spread the word about inflammation
- Main inflammatory mediator → links obesity, metabolic syndrome, and inflammation
(1) What is it?
(2) How does it relates to chronic inflammation in obesity and the metabolic syndrome?
(3) Fun facts and cool stuff
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**Obesity**
- **Metabolic Syndrome**
  - Microbiota and AD
  - Intestine
  - SFA
  - TLR

**Inflammation**
- IL-6
- TNF-α
- Adiponectin
- Hypertrophied adipocytes
- JNK
- IKK
- PKC
- TNF-α
- IL-n

**Inflammatory Responses**
- TLR
- Hemokines
- Macrophages

**Additional Studies**
- TLR's activation further synthesizes pro-inflammatory factors

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What is CRP?

- Marker of systemic inflammation synthesized by the liver
- * Traditionally used to detect acute injury, infection, and inflammation

* CRP’s functionality is actually really complex
CRP and Inflammation

- **IN GENERAL**, CRP levels will rise if there is inflammation
- If bacterial: CRP levels will sky-rocket
- If viral: CRP levels will increase slightly
CRP and Inflammation

<table>
<thead>
<tr>
<th>LEVELS</th>
<th>RANGE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 3 mg/L</td>
</tr>
<tr>
<td>Oh No</td>
<td>3 mg/L - 10 mg/L</td>
</tr>
<tr>
<td>Danger</td>
<td>10 mg/L +</td>
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[chuckles] I'm in danger
What does a high (resting) CRP level mean?
CHRONIC INFLAMMATION!!!!

ACUTE INFLAMMATORY RESPONSE ➔ Macrophages ➔ IL-6 ➔ Hepatocytes ➔ CRP
What does chronic inflammation have to do with metabolic overload?
1. Lack of space for Adipose Tissue
2. Hypertrophic growth of adipocytes
CRP and its other functions: In Vitro ("within the glass")
CRP other than a marker....

- Can only bind to damaged tissues and cells
- Can recognize pathogens and activate the classical component pathway
- CRP can interact with immunoglobulin receptors to elicit a response from phagocytic cells
- Part of the innate immune response
CRP can do both!!!

<table>
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<th>Pro-Inflammatory</th>
</tr>
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<tbody>
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<td>Can induce expression of IL-1 antagonist</td>
<td>Activation of classical complement pathway</td>
</tr>
<tr>
<td>Signal the release of anti-inflammatory cytokine IL-10</td>
<td>Enhances pathocyte activity</td>
</tr>
<tr>
<td>Repression of interferon-γ</td>
<td>Increase release of IL-6</td>
</tr>
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</table>
CRP and its other functions: In Vivo ("within the living")
CRP in Mice

- Protects against bacterial infection but is not limited to bacteria
- Protection of various mediators of inflammation ($PAF$, $TNF-\alpha$, $IL-1\beta$)
- Has been found to delay onset and development of the mice version of multiple sclerosis
- Inhibits influx of neutrophils and protein in the lungs
CRP + SLE (NEW STUFF!!!)

- SLE = systemic lupus erythematosus
- Injection of CRP into mice with SLE, found to have slight delay in mortality
- Lower basal levels of CRP associated with increased risk of developing SLE

Conclusion:
- Decreased amounts of CRP may contribute to the pathogenesis of SLE
Summary: CRP

- CRP is a marker of inflammation
  - Production signaled by IL-6
- Part of the innate immune response
- Role in Metabolic Overload
  - Adipocyte Hypertrophy
  - Lipotoxicity
- Both pro- and anti-inflammatory
- Protector of inflammatory mediators
ADIPONECTIN AND METABOLIC SYNDROME

- CHRONIC INFLAMMATION
- OBESITY
- INSULIN-RESISTANCE

[Symptoms of Mets]
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REFRESHER

• **Adiponectin:**
  • A *protein hormone*
  • Abundantly secreted by adipose tissue
  • Expressed all around the body (liver, muscle, hypothalamus, adipose tissue, vasculature)
  • (in healthy humans/rodents) Extremely abundant in plasma levels
  • Binds to Adipor2 and Adipor1 (in different parts of the body)
• **Function:**
  • Regulates *glucose metabolism* (increases energy expenditure)
  • Regulates *fatty acid oxidation* (increases oxidation process)
  • Regulates *insulin sensitivity*
  • *Anti-inflammatory* mediator
ADIPONECTIN LEVELS IN HEALTHY/UNHEALTHY

Healthy patients = high levels of adiponectin

MetS patients = low levels of adiponectin

Obese/Insulin-resistant patients = low levels of adiponectin

Obese/Insulin-resistant mice = low levels of adiponectin
HIGH ADIPONECTIN LEVELS = PROTECTIVE FACTOR

• If there’s high adiponectin levels…
  • anti-inflammatory effect of T2DM (type 2 diabetes mellitus)
  • inhibits plaque initiation and thrombosis (blood clots)
  • reduced risk of atherosclerosis (plaques in arteries)
    • And coronary artery calcification
    • And other cardiovascular diseases
  • improves insulin sensitivity
  • reduces gluconeogenesis
  • reduced risk of myocardial infarction (heart attack)
LOW ADIPONECTIN LEVELS = MANY COMPLICATIONS

- If there’s low adiponectin levels… (hypoadiponectinemia: low adiponectin in blood)
  - Increased levels of TG (triglycerides)
  - Increased levels of FBG (fasting blood glucose) (less insulin produced)
  - Decreased HDL-c (high density lipoproteins = good cholesterol)
  - Increased risk of hypertension (high blood pressure)
  - **Increased risk of metabolic syndrome**
  - 2x risk of atherosclerosis (plaques in arteries)
RECALL: PRO AND ANTI-INFLAMMATORY MEDIATORS

In these MetS/obese/insulin-resistant/chronically inflamed patients:

- pro-inflammatory IL-6 levels are high
- pro-inflammatory CRP levels are high
- anti-inflammatory adiponectin levels are low

It would make sense that we get chronic inflammation since adiponectin levels are low, and can’t “anti-inflammate” these adipocytes.
SO WHY ARE ADIPONECTIN LEVELS LOW IN OBESE PATIENTS?

It’s important to find out why, or what mechanism is going on because:

* if we discover the mechanism, we discover possible therapeutic interventions*

- Answer: unfortunately unclear…

- **BUT**: A theory involving **adiponectin, TNF-alpha**, and **PPARy**.

A POSSIBLE THEORY WHY LOW ADIPONECTIN LEVELS IN OBESE PATIENTS

PPARγ Ligands Increase Expression and Plasma Concentrations of Adiponectin, an Adipose-Derived Protein

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insulin resistance. In this study, we demonstrate the inducing effects of thiazolidinediones (TZDs), which are synthetic PPARγ ligands, on the expression and secretion of adiponectin in humans and rodents in vivo and

PPAR: peroxisome-proliferator-activated receptors

Mediates: insulin sensitivity and glucose and lipid metabolism

Answer: PPARy RECEPTORS AND TNF-alpha.
So maybe along this pathway in METs patients…

1. Faulty PPARγ mechanism
2. PPARγ can’t inhibit TNF-alpha
3. TNF-alpha proliferates
4. Lower adiponectin levels.
Additional Studies

- Depression and Obesity: Integrating the Role of Stress, Neuroendocrine Dysfunction and Inflammatory Pathways
Depression, Obesity, and Inflammation

- Major life stressors can result in a homeostatic imbalance
- Patients with depression displayed evidence of high levels of inflammatory markers
- Across 24 different replicatory studies, patients with MDD had higher levels of TNF-a and IL-6
  - The unstimulated cytokine concentrations of patients with major depression were measured.
Inflammatory Mechanisms

1. Initial Immune Response
   a. Macrophages release pro-inflammatory cytokines
      - Occurs in response to the recognition of pathogens, tissue damage or destruction via cell surface Toll-like receptors (TLRs)
   b. TLRs activate NF-κB induces an innate inflammatory response involving the release of pro-inflammatory cytokines such as IL-1, IL-2, IL-6 and TNF-α

2. Cytokines access the brain via leaky regions in BBB
NEUROTRANSMITTER METABOLISM AND INFLAMMATION

1. Cytokines influence the manifestation of depression through metabolic alterations of neurotransmitters
   a. including serotonin (5-HT), dopamine (DA), noradrenaline (NA)
1. In the Th1 response
   a. microglia and macrophages secrete IL-1, IFN-γ and TNF-α
   b. induces indoleamine 2,3-dioxygenase (IDO) expression
   c. favors conversion of tryptophan into quinolinic acid, a N-Methyl-D-aspartic acid (NMDA) agonist, and kynurenic acid, NMDA antagonist.
NT Response

1. DA Implicated in MDD
2. Pro-inflammatory cytokines influence DA synthesis and reuptake
3. Kynurenine is converted into kynurenic acid, an NMDA antagonist, which antagonizes alpha-7 nicotinic acetylcholine (ACh) receptors and can reduce dopamine release.
   a. Dopamine reuptake is increased through phosphorylation of the dopamine transporter (DAT) by mitogen-activated protein kinase kinase (MAPKK)
Conclusion

- While TNF-a and IL-6 are both involved with areas involved with mood regulation, inflammation alone can’t be the sole cause of MDD.
- Inconclusive as to whether one causes the other.
- Childhood adversity may predispose individuals to develop depression with inflammation.
  - Inflammation may trigger a cycle that prevents recovery from depression in these predisposed individuals.
- Difficult part about studying this: different immune profiles
- While NA is also thought to be involved in the pathogenesis of depression, the role of inflammation in the reduction of NA has not yet been established in humans with MDD.
Conclusion
References:

**FOCUS PAPER:**

**ADDITIONAL RESOURCES:**
References:

- Xia, Dongyuan, and David Samols. "Transgenic mice expressing rabbit C-reactive protein are resistant to endotoxemia." Proceedings of the National Academy of Sciences 94.6 (1997): 2575-2580.
Adiponectin

produce adiponectin

Adipocytes