Stressin’ with Ghrelin

Peptide Pods: Lara, Elijah, Karen, Brandon, Milena, Max & Lucile
Agenda

- Ghrelin Essentials Review
- Associations of Ghrelin with eating, stress, metabolic factors, etc.
- High-fat diet increases ghrelin-expressing cells in stomach
- Ghrelin, Stress, and Food-Reward Behavior
- Ghrelin, Growth Hormone, and Fear
- Ghrelin and Addiction
- Significance and Importance of Ghrelin
Ghrelin and Stress: Recap

Important Points:

- Orexigenic - Anabolic
- “Flip Side” of Leptin
- Produced in Stomach
- Acts through the GHS-R1a on NPY/AgRP Neurons; Inhibits POMC and CART Neurons
- Hypothalamic Regions of Interest: ARC, VMH, BLA
- VTA, NAcc, LTDg also stimulated by Ghrelin
- GOAT activates Ghrelin

NPY = Neuropeptide Y  
AgRP = Aguoti Related Peptide  
ARC = Arcuate Nucleus  
VMH = Ventromedial Hypothalamus  
BLA = Basolateral Amygdala  
VTA = Ventral Tegmental Area  
GOAT = Ghrelin O-acyl Transferase
Ghrelin and Stress: Recap

Important Points:
- Liver: increase fat production/storage
- WAT: increase fat production/storage; decrease fat oxidation; where Leptin is produced
- BAT: decrease in thermogenesis and energy expenditure

Ghrelin’s Effects on Several Tissues via the Sympathetic Nervous System (SNS)

WAT = White Adipose Tissue
BAT = Brown Adipose Tissue

Figure Courtesy of: Martinez de Morentin et al. 2013
Ghrelin and Stress: Important Anatomy, HPA Axis

- Primary Stress Pathway
- Dysregulation leads to many anxiety related diseases
  - I.e. PTSD
- Activated by both psychosocial and physical stress
- How does this relate to Ghrelin?
Associations of ghrelin with eating behaviors, stress, metabolic factors, and telomere length among overweight and obese women: Preliminary evidence of attenuated ghrelin effects in obesity?
Before we start, just a lil review

- Ghrelin
  - Only known appetite-stimulating hormone in humans
- Ghrelin’s receptor is GHS - R1
  - Otherwise known as Growth Hormone Secretagogue receptor 1
- Ghrelin signals to the Arcuate Nucleus in the hypothalamus to increase appetite/food intake when energy supply is low (affects the two orexigenic neurons shown here →)
New fun facts about Ghrelin being discussed today

- Ghrelin appears to play a role in hedonic eating, food-induced reward
  - Ghrelin affects dopaminergic neurons in the Ventral Tegmental Area and Nucleus Accumbens
- Ghrelin also affects glucose, insulin, and insulin resistance
  - Elevated Ghrelin $\Rightarrow$ elevated glucose in blood, less insulin and insulin resistance
  - Ghrelin also regulates growth hormone secretion, which controls secretion of insulin-like growth factor-1 (IGF-1)
- Increased Ghrelin may mediate the motivation to eat under stress
  - Ghrelin increases in humans when we’re stressed out
  - Possible explanation for comfort eating when stressed?
Now back to the experiment

- Studies on diet-induced obese mice have shown many different ways obesity can cause Ghrelin to become dysfunctional in your body:
  - Hypothalamic resistance to Ghrelin
  - Decreases transcription of Ghrelin and GOAT*
  - Decreases the expression of GHSR** in the hypothalamus
  - Decreased Ghrelin activity can also influence the activity of other metabolic factors, such as insulin-like growth factor-1 (which I’ve already touched on.)

*GOAT = Ghrelin o-acyltransferase
  Enzyme that converts ghrelin to its active acylated form

**GHSR = Growth Hormone Secretagogue Receptor
  Ghrelin Receptor in Hypothalamus
So what did the experimenters do?

- For our purposes, the experimenters were concerned with the total plasma levels of ghrelin, insulin, and glucose in overweight and obese women
  - Wanted to look at the association between ghrelin and other factors, including participant’s diet and cortisol levels
- Participants were given forms to document their own specific diet for 3 days
  - Recorded what type of food she ate and the portion size of the meal
Time for Results!

• As expected, total ghrelin was lower in the obese group than the overweight group.
• The obese women and overweight women had similar daily calorie intake
  • Differed in what type of calories they were getting
• The obese women also had higher levels of insulin and insulin resistance than the overweight women
  • Negative correlation between ghrelin and insulin, insulin resistance

Fig. 1. Scatterplot of the relation between weight (kg) and plasma ghrelin.
Time for More Results!

- In terms of hedonic eating attitudes, ghrelin was positively associated with giving into palatable foods in the overweight, but not in the obese group.
- Palatable foods are normally high in sugar and high in fat.

Table 2
Pearson correlations of ghrelin with eating, stress, and metabolic factors, and telomere length by group.

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* a Excluding participants taking anti-hypertensive medication.
* * p < .10.
* * * p < .05.
* ** p < .01.
Discussion of these Findings

- So by now, we all know that obese people have lesser amounts of ghrelin than overweight or lean people
  - But we still don’t know what comes first
- The results (shown in Table 2) provide support for the notion that ghrelin may promote hedonic eating in the overweight
  - However, these results don’t hold when applied to the obese, possibly due to ghrelin resistance
- Also, more cortisol concentrations was associated with higher ghrelin levels among overweight women.
  - Not consistent with the obese group either.
  - More research needed on the relationship between ghrelin and cortisol/stress and how it relates to weight status
Discussion of these Findings cont.

- Ghrelin is negatively correlated with Insulin Resistance and Insulin
  - Higher amounts of acylated ghrelin ⇒ Insulin Resistance
  - Acylated Ghrelin : Deacetylated Ghrelin (AG: DAG) ratio must stay consistent to maintain insulin sensitivity

![Graphs showing correlation between ghrelin and insulin resistance](image)

*Fig. 6.* Scatterplots of the relation between insulin resistance (log transformed HOMA) and plasma ghrelin by BMI group.
Takeaways from this paper

- Ghrelin has an effect on dopaminergic cells in the Ventral Tegmental Area and Nucleus Accumbens
  - Ghrelin in overweight people may contribute to hedonic eating and eventual weight gain
- As a person approaches obesity and his or her ghrelin levels decrease, this could be an indicator of insulin resistance
  - Even though ghrelin levels decrease in obesity, the ratio of acylated ghrelin actually rises
  - The ratio between acylated ghrelin and deacylated ghrelin matters!

"I matter!"
-Acylated Ghrelin
High-fat diet increases ghrelin-expressing cells in stomach, contributing to obesity

- This paper looked at the role of ghrelin in a high fat diet (HFD)
- Preproghrelin + ghrelin-O-acyltransferase (GOAT) = Ghrelin
- Ghrelin-reactive immunoglobulins (IgGs)
  - Transport Ghrelin around body without disturbing its functionality
- In this experiment, the researchers looked at different groups and different factors when inducing obesity in mice
  - Groups
    - Standard chow-fed control group
    - High-fat diet
    - Genetically obese
  - Factors they looked at:
    - Body weight and composition, preproghrelin mRNA-expressing cells, total amount of plasma ghrelin, and IgGs
HFD effects on body weight and composition

- Starting week 5, high fat diet fed mice showed significantly more weight gain than their control group counterparts.
- At 12 weeks, body composition analysis showed that HFD mice had significantly more fat body mass than their control group counterparts.
Preproghrelin mRNA expression

• The average number of proproghrelin mRNA-producing cells per millimeter (mm) was 15% higher in the HFD mice, compared to the control group.
• The avg. number of proproghrelin mRNA-producing cells per mm was 41% lower in the genetically obese mice than in the control mice.

*ob/ob = Genetically obese mice
Total Plasma Ghrelin Concentration

- Total plasma ghrelin concentrations did not differ significantly across the three groups
  - However, the HFD mice and the genetically obese mice showed significantly lower levels of deacylated ghrelin than the control mice
  - While the ratio between acylated ghrelin and deacylated ghrelin did not differ significantly between the HFD mice and the control mice, this ratio did differ significantly when the ob/ob mice were compared to the control.
Ghrelin-reactive IgG

- There were no real significant differences in how the IgGs functioned between the HFD mice and the control mice, except for one!
- There was a significant difference for the affinity of ghrelin sensitive immunoglobulin
  - 150% increase in ghrelin-reactive IgGs affinity in HFD mice compared to the control
  - More protection for acylated ghrelin when transported
Discussion of findings / Main takeaways

- Study revealed that HFD leading to obesity causes changes in the ghrelin system that favors development of obesity
  - Ghrelin plays a role in high fat diet induced obesity
- HFD appears to create favorable conditions for ghrelin precursor expression
- Increased protection for IgGs in HFD can lead to larger orexigenic effects
- Any questions regarding these papers? (: 

THANKS FOR LISTENING
Paper #1: Ghrelin mediates stress-induced food-reward behavior in mice
Chuang et al., 2011
Feeding Behavior Changes with Stress & Depression

Upon stress and/or depression people report an increase in the intake of highly palatable food independent of being hungry or not (hyperphagia/hypophagia)

Human Studies :

A. “Longitudinal study from New Zealand showed that major depression in late-adolescent girls was associated with increased risk in adulthood & commonness of obesity in adulthood was positively correlated with the number of major depressive episodes during adolescence in these girls.”

B. Subjects with atypical depression reported increased body weight

C. Combined overweight and obesity prevalence in a sample of US veterans with PTSD was found in a chart review study to exceed that within the US general population by 20%
Previous Animal Models

Used to explore the mechanism responsible for stress-induced and depression-associated eating behaviors.

Previously included:

A. bouts of restraint in rats -> increase of intake of freely available lard- and sucrose-based chow
B. Visible burrow system in rats -> increased meal size in subordinate males
C. Measuring intake of high-fat diet pellets to which mice exposed to stress were given limited access along with preweighed regular chow

- Mice with genetic deletion of corticotropin-releasing factor receptor-2 (which results in an exaggerated hypothalamic-pituitary-adrenal response to stress) showed an increase in HFD consumption during chronic variable stress

- Wild-type mice that previously had been calorically restricted and then allowed to recover body weight consumed a significantly greater proportion of high-fat calories during chronic variable stress than did wild-type mice without calorie restrictions

these models provided insights into stress-induced changes in feeding
Ghrelin is involved in food-reward behaviors and human appetite regulation

Ghrelin’s role: promote food intake by enhancing the rewarding properties of certain food

- Conditioned place preference (CPP) for High-fat diet (HFD): animal gravitating toward a chamber with environmental cues it has associated with HFD reward and operant nose poking for HFD in which a motivated animal will exert increase effort (by poking a button with its nose) to receive a HFD reward

^induced by peripheral ghrelin injection and prolonged caloric restriction (=increase plasma ghrelin)
GHSR antagonist administration and genetic deletion of GHSRs prevents
- caloric restriction-associated CPP for HFD in mice
- prevents caloric restriction-associated level pressing for sucrose in rats
=> role for ghrelin in caloric restriction-associated food-reward behaviors

Ghrelin injection preferentially enhances
- fat intake over carbohydrate intake in rats

w/o GHSR= effects of ghrelin ↓ = animal preference for HFD ↓

- Ghrelin administration to human subjects during fMRI increases the neural response to food pictures in brain regions implicated in hedonic (relating to pleasant sensations) feeding
=> importance of ghrelin in human appetite regulation
CSDS (chronic social defeat stress) is considered a model of prolonged psychosocial stress in humans featuring aspects of major depression and posttraumatic stress disorder.

- subjects male mice to repeated periods of social subordination by an older and larger aggressor male.
- After CSDS, most male mice exhibit lasting depression-like behavioral deficits (social withdrawal (measured using a social interaction task))

CSDS-->plasma ghrelin elevations VS. Genetic deletion of GHSR-->depression-like behaviors

CSDS
Ghrelin elevations produce antidepressant-like behavioral effects

CSDS  --> ghrelin ↑→ hyperphagia (hunger, eating) → weight gain
-→less depression-like behavior
CSDS  --> no GHSR -> not detecting ghrelin→hypophagia
(not feeling hungry) -> not eating + not gaining weight
Objective of Research Article

- New model of food-reward behavior measured after CSDS
- Relationship of stress-induced food-reward behavior to increased ghrelin levels
- Ghrelin-enhanced preference, operant responding for energy-dense foods (CSDS increases both CPP for and intake of HFD)
- Ghrelin signaling specifically in catecholaminergic neurons mediates orexigenic, antidepressant-like and food-rewarding behavioral effects
- Ghrelin is sufficient to mediate stress-induced food-reward behavior
Terminology includes:

- **Wild-type** = Normal mice without genetic alterations
- **GSHR-null** = Ghrelin Receptor (GHSR) is deficient in function
- **CSDS** = Chronic Social Defeat Stress
- **CPP** = Conditioned Place Preference
- **HFD** = High Fat Diet
Chronic Social Defeat Stress (CSDS)

Smaller Mice develop Chronic Social Defeat Stress:

Smaller mice become less social, and develop depressive symptoms

Aged and Aggressive:
Older and more aggressive mice interact with smaller, younger ones and exert pressure on them
Experiment 1: Effects of CSDS in social behavior and Ghrelin

Wild and GSHR-null mice introduced to CSDS condition with non-CSDS for comparison

- Stress increases activated ghrelin levels
- Corticosterone is the main hormone found in rodents that is released in response to stress

Demonstration that there is an effect on social behavior caused by CSDS that exhibits depressive symptoms and the endocrine system reflects this effect

CSDS: chronic social defeat stress condition
Conditioned Place Preference (CPP)

Chow Diet

High Fat Diet

Chow is alright, but fat tastes better and makes me feel good!
Experiment 1 Cont.: Effects of CSDS in diet behavior

Dieting behavior in stress
- Wild types exhibit significant preference for HFD due to effects of CSDS
- GHSR-Null has no change in diet preference after CSDS

Dieting behavior in non-stress
- Preference in HFD is still apparent, but not as exaggerated since there is not as much motivation to seek out high reward food
Experiment 2: Assess the role of direct action of ghrelin on the VTA and other catecholaminergic neurons

- GHSRs have a well-defined central expression pattern which includes tyrosine-hydroxylase expressing (TH-expressing) ventral tegmental area (VTA) neurons
  - Tyrosine-hydroxylase (TH) is the rate limiting enzyme of catecholamine biosynthesis
  - VTA is a dopaminergic projection and has an extensive role in mediating both reward behavior of various types and mood regulation
- Ghrelin can act on VTA neurons and influence food intake and food reward
Experiment 2 Cont: Mouse Groups Studied

- Wild-type
  - Normal mice without genetic alteration
- GHSR-null
  - Ghrelin receptor-deficient
- GHSR-null/TH
  - Express endogenous levels of GHSRs only in TH-containing neurons programmed to express both GHSR and TH
Experimnet 2 Cont: Observe GHSR expression in brain structures of mice

- In order to study role of ghrelin in VTA alone, researchers compared wild-type mice, GHSR-null mice, and GHSR-null/TH mice.
- GHSR-null/TH mice
  - GHSR expression observed in the VTA and arcuate nucleus (ARC) in the hypothalamus, but not in sites known to lack TH-expressing neurons and/or GHSR-expressing neurons within wild-type mice (dentate gyrus, nucleus accumbens)
- GHSR expression levels in the VTA and ARC is higher in wild-type mice than in GHSR-null/TH mice
  - Signalling that GHSR expression also happens in other, non-TH cell types
Experiment 2 Cont: Direct action of ghrelin effects

- Wild-type
  - Responded to injections of ghrelin by increasing food intake of freely available chow
- GHSR-null
  - Re-expression of GHSR in TH-containing neurons partially restored ghrelin-induced food intake
  - Fasting blood glucose levels were lower than that in wild-type littermates
- GHSR-null/TH
  - Similar fasting blood glucose levels to those of GHSR-null littermates
    - Suggests that direct action of ghrelin on catecholaminergic neurons does not mediate its modulatory effects on glycemia
  - Selective catecholaminergic GHSR expression shown to mediate ghrelin’s pharmacological ability to induce CPP for HFD
Experiment 2 Cont: Analyze effects of CSDS on social interaction and food intake by GHSR-null/TH mice

- Increased social isolation after CSDS compared with that of wild-type littermates in GHSR-null mice
  - Re-expression of GHSR in TH-containing neurons improved social interaction scores to levels similar to those of wild-type littermates
    - Suggests catecholaminergic GHSR expression is sufficient to mediate ghrelin’s antidepressant actions
- Assessment of the performance of a separate cohort of mice in the CPP for HFD protocol for CSDS showed that selective catecholaminergic GHSR expression was sufficient to restore the chronic stress induction of CPP for HFD
Takeaway Message

- Ghrelin can act on VTA neurons and influence food intake and food reward
- GHSR expression levels in the VTA and ARC is higher in wild-type mice than in GHSR-null/TH mice
  - Signalling that GHSR expression also happens in other, non-TH cell types
- GHSR-null/TH
  - Suggests that direct action of ghrelin on catecholaminergic neurons does not mediate its modulatory effects on glycemia
- Re-expression of GHSR in TH-containing neurons improved social interaction scores to levels similar to those of wild-type littermates
  - Suggests catecholaminergic GHSR expression is sufficient to mediate ghrelin’s antidepressant actions
Paper #2: A ghrelin-growth hormones axis drives stress-induced vulnerability to enhanced fear

Meyer et al., 2014
Purpose

• To determine the role of ghrelin when it comes to stress-induced susceptibility to fear.
Hypothalamus-Pituitary Adrenal (HPA) Axis

• HPA axis: secretes stress hormones such as adrenal and corticosterone
• Both high and low levels of HPA activity have been linked to stress sensitive mental disorders
• HPA has been linked to heightened fear in rodents, there are no clinical applications...
• ...Therefore, it may be time to look elsewhere...
  • Ghrelin has been found to be affected by stress
Inducing Fear into Rats (PTSD for rodents)

Repeatedly exposed to stress then went through pavlovian fear conditioning
Experiment 1

**Purpose:** Find out if adrenal stress hormones are separate from fear and ghrelin

**Results:** Yes! Adrenal Stress hormones are separate from fear and Ghrelin
Experiment 2

**Purpose:** To determine if activating the ghrelin receptor is sufficient in enhancing fear memory on its own.

**Results:** Repeated activation of the ghrelin receptor can create enhanced fear without changing other stress hormones.
Experiment 3: is the ghrelin pathway *sufficient*?

**Purpose**: determine GHSR activation in the BLA is sufficient to enhance fear memory

**Result**: repeated activation of the GHSR directly in the BLA triggers a heightened response to the tone

**Conclusion**: long-term pharmacological stimulation of GHSR activity in the amygdala enhances fear memory, so *yes*

VEH: vehicle (control)  
MK: ghrelin receptor agonist  
GHSR: ghrelin receptor  
BLA: basolateral amygdala

**Experiment 4: sufficient, but is it necessary?**

**Purpose:** determine if ghrelin signalling is necessary for enhanced fear memory

**Result:** GHSR antagonism during chronic stress suppresses enhanced fear memory and is independent of corticosterone release

**Conclusion:** ghrelin signalling is necessary for mediation of enhanced fear memory

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GHSR: ghrelin receptor  
VEH: vehicle (control)  
DLys3: highly specific GHSR antagonist  
NS: nonstressed group  
STR: stressed group
Experiment 5: Role of GH, part 1

**Background:** GH interacts with ghrelin in the amygdala to enhance fear memory

**Purpose:** Establish the role and importance of growth hormone in the ghrelin pathway that mediates fear

GH: growth hormone
BLA: basolateral amygdala
NS: nonstressed group
STR: stressed group
CON: GFP-only control virus
rGH: recombinant rat GH virus

Experiment 5: Role of GH, part 2

- GHSR stimulation triggers GH release in the amygdala
- Antagonizing the activity of GH prevents the fear enhancing effects of GHSR stimulation

Experiment 5: summarizing the role of GH

Amygdalar growth hormone is increased by chronic stress, is sufficient to enhance fear memory and is necessary for the fear-potentiating effects of ghrelin receptor stimulation

- GH was significantly upregulated in the BLA post-exposure to chronic stress
- Overexpression of GH in the amygdala enhanced long-term fear memory
- When GHSR was stimulated GH was released
- Antagonizing GH also downplays the fear-enhancing effects of GHSR stimulation
Summary

1. The ghrelin-GH axis acts in parallel to the HPA axis in response to stress
2. Ghrelin receptor activity plays a key role in enhancing fear-related effects of stress
3. The ghrelin pathway is necessary for vulnerability to fear
4. GH is a key co-mediator of stress-induced fear learning and memory

So what?

- Identified a separate hormonal axis that mediates the stress-related fear response
  - Behavioral effects of ghrelin that lead to disorder
- New understanding of the underlying mechanisms that contribute to the development and prolongation of stress-related disorders

No current treatments exist for preventing stress-related affective disorders, suggesting that our most intriguing and important finding is that blockade of ghrelin signaling during stress is sufficient to prevent stress-related vulnerability to excessive fear. This raises the possibility that such a strategy might reduce or prevent the development of stress-sensitive affective disorders like PTSD during prolonged or extreme stress load.

Ghrelin and Addiction
Ghrelin and Addiction: Which Substances?

- Ghrelin has only been implicated in addiction behaviors for certain substances of abuse:
  - Alcohol, Nicotine, and Stimulants are implicated
  - Cannabis and Opioids are not implicated
Ghrelin and Addiction: Alcohol

In animals:

- **Length of Exposure key to effects of Ghrelin on Alcohol Consumption**
  - 9-week alcohol treated mice had an increase in alcohol consumption after VTA, LTDg or ICV ghrelin administration
  - 3-day alcohol treated mice had no change in alcohol consumption when treated with peripheral ghrelin
  - Prolonged exposure to alcohol reduces total ghrelin levels in high-preference strains more than low-preference strains

- **GHS-R1A antagonists reduce Alcohol Consumption and Preference**
  - In both normal and alcohol preferring mice, the antagonists lowered the preference of alcohol over water and the consumption of alcohol
  - Intake was also lowered in 8-month exposed mice after a 10 day treatment with antagonists
  - Antagonist treatment also shows a Length of Exposure preference, with 5-month exposed mice having a greater reaction to treatment than 2-month exposed mice

VTA = Ventral Tegmental Area
LTDg = Laterodorsal Tegmental Area
ICV = Intracerebroventricular
Ghrelin and Addiction: Alcohol

In animals (cont’d):

- GHRL KO mice show reduced Consumption and Preference
  - GHRL KO mice have a lowered release of Dopamine in the NAcc
  - ICV administered ghrelin still stimulated the effects of increased consumption on GHRL KO mice
  - CPP for alcohol is also reduced in GHRL KO mice

- GHS-R1A expression increased in high-consuming rat strains compared to low-consuming rat strains
  - The increased expression was found in the NAcc, VTA, amygdala, pre-frontal cortex, and hippocampus
  - Also ghrelin is reduced less after alcohol exposure for high-consuming strains

- Of note: a negative correlation of GHSR expression in the VTA and alcohol intake was observed
  - This was after a 10 month exposure and treatment with GHS-R1A antagonist

GHRL = ghrelin/obestatin prepropeptide gene
KO = knockout, gene deletion
NAcc = Nucleus Accumbens
ICV = Intracerebroventricular
Ghrelin and Addiction: Alcohol

In Humans:

- Ghrelin has been shown to increase cue-dependent cravings in heavily-dependent drunks
  - Fasting acyl-ghrelin levels and craving scores positively correlated
  - Fasting Acyl ghrelin levels higher in male patients with alcohol dependence after a 30-day abstinence than those without dependence who had not drank for 72 hours
- *However, other studies have shown conflicting results

- Acute administration of an oral dose of alcohol reduced fasting total and acyl-ghrelin
  - Healthy (non-dependent) volunteers showed a reduction that lasted 5 hours
- IV administration of Alcohol to healthy social drinkers resulted in a blunting of the fasting-induced increase of acyl ghrelin and total ghrelin
Ghrelin and Addiction: Nicotine

In animals:

- Acyl-ghrelin was increased in response to inhalation of nicotine
- Des-acyl ghrelin levels were unchanged
  - Proposed reasoning: the “smoker” group had a lower relative energy balance as opposed to the “non-smoker” group
- GHS-R1A antagonists once again reduced CPP, nicotine-induced locomotor stimulation, and release of extracellular dopamine in the NAcc
Ghrelin and Addiction: Nicotine

In humans:

- Oftentimes ghrelin was looked at as a secondary effect
  - Many tests focused on cardiovascular or other endocrine factors
- However: smoking was associated with higher levels of acyl-ghrelin up to one hour after smoking
- After 2 months of abstinence, acyl-ghrelin levels were reduced in smokers
- Prolonged nicotine exposure could lead to ghrelin resistance?

- Due to inconsistent methodologies, more work needs to be done on human nicotine-ghrelin interactions
Ghrelin and Addiction: Stimulants

In animals:

- Acyl-ghrelin may reduce the threshold for establishment of CPP for cocaine
  - When pretreated with ghrelin, higher doses of cocaine showed no CPP, unknown why
- Ghrelin pretreatment also enhances locomotor stimulation of cocaine
- Ghrelin may also enhance drug-seeking behavior in response to food-deprivation

- Administration of methamphetamine raises circulating ghrelin for mice with free-access (ad-libitum) to food but ghrelin was decreased if administered before food presentation
- MDMA abuse raises total ghrelin, but total ghrelin returns to baseline after 24 hours
In animals (cont’d):

- GHRL KO mice exhibited reduced locomotor activity in response to cocaine administration
- GHS-R1A antagonists reduced the locomotor activity as did GHSR KO rats
- Furthermore GHS-R1A antagonists can reduce the effects of CPP and extracellular dopamine release in the NAcc
Ghrelin and Addiction: Stimulants

In humans:

- Only a small study which showed a link between a GHRL SNP and methamphetamine dependence in a population of Swedes.
- More testing and more accurate testing must be done in order to find links between animal findings and human applications.
Ghrelin and Addiction: Opioids

In animals:

- Despite mu-opioid receptor agonists increasing food intake, palatability and willingness to work for food (and antagonists having the opposite effects) there was no difference in the amount of self-administration of heroin.
- Also, GHS-R1A antagonists did not influence self-administration of heroin.

In humans:

- No pertinent publications found for the interactions of ghrelin and opioid.
Ghrelin and Addiction: Cannabinoids

In animals:

- CB1 antagonists can reduce circulating acyl-ghrelin in hungry rats
  - Endocannabinoids are involved in the regulation of food intake and antagonizing their receptors may influence ghrelin levels
- Rimonabant, the cannabinoid antagonist, can block orexigenic the effects of central ghrelin
- GHSR KO mice had no increase in hypothalamic AMPK in response to both ghrelin and CB1 agonists

In humans:

- Only one study which showed hedonic eating was associated with increased peripheral levels of ghrelin and the endocannabinoid 2-arachidonoylglycerol
- Although the endocannabinoid and ghrelin systems interact to regulate appetite more research must be done with respect to cannabinoid abuse

CB1 = cannabinoid 1 receptor
Why do we care?

Ghrelin is an important hormone for energy homeostasis. Evolutionarily, ghrelin acted as a way to store energy efficiently as fat to maintain a “positive energy state” during times without food. This hormone also has implications in stress pathways as hunger is an essential stressor for survival.

As we have shown, an understanding of ghrelin can have preventative care and therapeutic uses to prevent Stress, Metabolic and Addiction Disorders.
Questions?
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