PHY3102
Nutrition, Metabolism and Body Weight

The Hypothalamic Regulation of Energy Homeostasis

Energy Homeostasis

Energy homeostasis is a biological process through which the body matches energy intake and expenditure in order to maintain equilibrium or balance of body weight

- Sensory detector → Processor → Effector → Negative or Positive feedback to Sensory Detector
- Molecules from peripheral tissues feedback to the brain
- If you have not eaten, you will go into storage mode and conserve energy

Genome Wide Association Studies

- Obesity is a genetic disorder effecting neuronal control
- Evolution evolved during food scarcity
- Therefore, the brain ensures we have a drive to eat

Hypothalamus

- Responds to signals to automate autonomic function functions
- Can influence pituitary hormones once hormones are detected by the hypothalamus
    - Feedback loop to stimulate or inhibit their release

VMH

- Lesions caused obesity → Satiety Centre

LH

- Lesions caused starvation → Feeding Centre

Note: Lesioning VMH obesity reversed obesity with lesions in LH
Therefore, the urge to eat overrides the urge of satiety

The Arcuate Nucleus

Neuropeptide Y (NPY)/ Agouti-related peptide (AgRP) neurons → Increase Food Intake
POMC neurons releasing a-MSH → Neurons suppress food intake

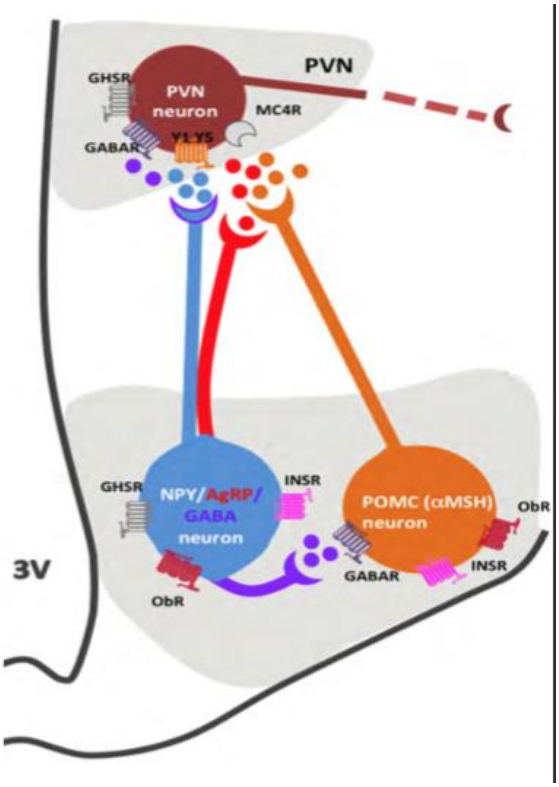
- AgRP neurons are very close to the blood and cerebrospinal fluid
- Ablation of AgRP stopped feeding and caused starvation
- Neurons are active when hungry and drives motivation for food

AgRP/NPY/GABA Neurons

- Favour energy conservation
- Suppress BAT thermogenesis and energy expenditure
- Sense acute and chronic negative energy balance
- Activated by Ghrelin and inhibited by leptin
- More active during negative energy balance (calorie restriction)

Actions

- Antagonises MC4R
- Activation of Y receptors
- Activation of GABA to inhibit POMC



POMC Neurons

- Favour energy dissipation and suppress' feeding
- Increases energy expenditure and maintains appropriate blood glucose concentrations
- Sense acute and chronic positive energy balance and are very sensitive
- Sense: glucose, leptin, insulin
- Ablation causes obesity and glucose intolerance
- More active during positive energy balance (after a meal and in obesity)

Inhibition

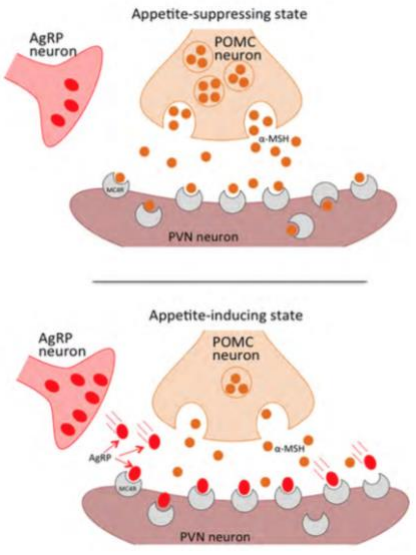
- AgRP inhibit POMC neurons via GABA
- Ensures a stronger drive for food
- POMC cannot inhibit AgRP

Note: Activation of both neurons at the same time leads to increased food intake

- Highlighting a stronger drive for food intake

The Paraventricular Nucleus (PVN)

- A-MSH from POMC neurons activates melanocortins 4 receptors to suppress food intake
- NPY activates Y1 and Y5 to increase food intake (rapid)
- GABA acts on GABA receptors
- AgRP antagonises MC4R and prevents anorectic effects of a-MSH (delayed effect on food intake)



Hormonal Regulation of NPY/AgRP and POMC Neurons

NPY/AgRP

- NPY/AgRP neurons express ghrelin, leptin and insulin receptor
- Ghrelin binds to GHSR and activates NPY and AgRP neurons to increase appetite
- Leptin binds to leptin receptors and inhibits NPY/AgRP neurons
- Insulin binds to the insulin receptor and inhibits NPY/AgRP

Ghrelin

- Increases in plasma during fasting, calorie restriction, starvation and anorexia
- Increases food intake, reduces fat utilisation and increases fat storage and increases glucose production

POMC

- Express the leptin receptor and insulin receptor
- Leptin binds to the reception and activation POMC neurons
- Ghrelin does not directly effect it, but if the concentration is high enough, it will activate NPY/AgRP which will inhibit POMC indirectly through GABA

Leptin and Insulin Signal Positive Energy Balance

- Acutely and chronically (in postprandial state and in obese state)
- Leptin and insulin suppresses food intake and increases energy expenditure
- This is done by activating POMC and inhibiting AgRP
- Their actions are more effective together, than alone (synergistic)

Ventromedial Nucleus

- Express leptin receptors
- Prevents obesity by increasing activity of POMC neurons in the hypothalamus
- Leptin regulated brain derived neurotrophic factor
- BDNF signalling in the VMH prevents obesity

Reward Pathways

Hedonic is defined as related to pleasure and hedonism is defined as devoted to pleasure
Homeostatic eating is a need to eat, rather than a want to eat

Satiety

- Satiety messages are slow and therefore, people over eat
- Need to eat slow for messages to get to the brain
- Development in a mother of stress and hunger is seen in the offspring

Mesolimbic

- Dopamine as neurotransmitter
- Dopamine cell bodies are located in the ventral tegmental area
- Dopamine projections to the nucleus accumbens
- Dopamine deficiency demotivates urge to eat and mice will die unless given L-DOPA

Incentive Salience

The motivational "wanting" of a stimulus or goal under certain circumstances which is different to liking

- If very hungry, you may want to eat Brussel sprouts

Wanting and Liking

***Liking**: An objective affective reaction that is mediated for taste in the brain from the brain stem to the nucleus accumbens*

- It is hedonic
- Mediated by mu opioid receptors in the nucleus accumbens
- Antagonists reduce the liking of previously sweet solutions
- Endocannabinoids are also distributed in this region and may also increase appetite

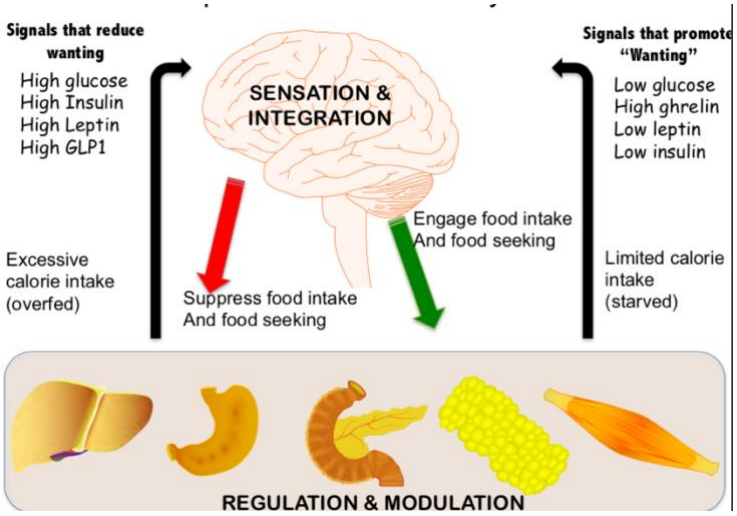
***Wanting:** An objective motivational process that is often termed incentive salience (importance of motivation) that is attached to attaining a reward, not the hedonic impact*

- May be due to the environment (negative energy balance)
- Removing liking can help, but it increases

Note: Increasing dopamine levels in the nucleus accumbens does not change "liking" but increases the motivational component of reward or "wanting". Calories can influence the reward system, which is signalled by the gut and the neural circuits of wanting and liking can be separated

Electrical Self Stimulation

- Rats with electrodes in the reward pathway centre and in a box
- Rats will repeatedly stimulate electrodes that are placed in the nucleus accumbens
- Excitation of dopaminergic neurons increase dopamine release



Dopamine in Reward

The reward skeleton primarily driving wanting and motivation, upon which other neural systems act to drive hedonistic behaviours or "liking"

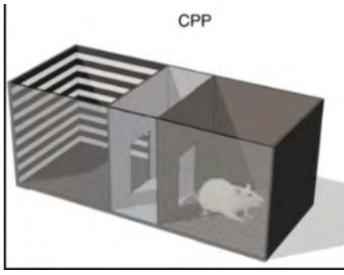
- Opioid and endocannabinoid system interact with the mesolimbic dopamine system
- Metabolic information can also effect this system

Ghrelin

- Interacts with dopamine neurons in the VTA
- There are ghrelin receptors on dopamine neurons
- Ghrelin injections in the VTA or N.A. increases food intake
- If given, it increases the reward value of the food compared to when it's not
- If brain perceives high glucose and high ghrelin, glucose is more effective and overrides hunger caused by ghrelin → Low motivation or low wanting
- Therefore, glucose is more influential than ghrelin

Ghrelin and Place Coding

- Conditions a place preference for when it is given with food compared to with no food
- If mice given a high fat diet, no place preference
- Therefore, motivation and homeostasis are closely entwined and metabolic state is very important



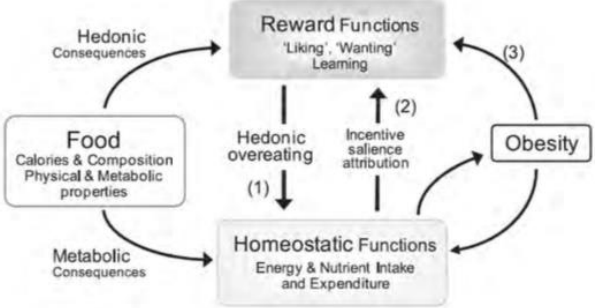
Leptin

- Microinjections of leptin (and insulin) abolish *conditioned place preference in rats*
- Leptin receptors are present on dopamine containing neurons
- These cause a reduction in firing rate and food intake
- Knock down the leptin receptor leads to an increase in food intake

Leptin impinges on dopamine and neural pathways to change the attractiveness of food and degree of wanting

AgRP

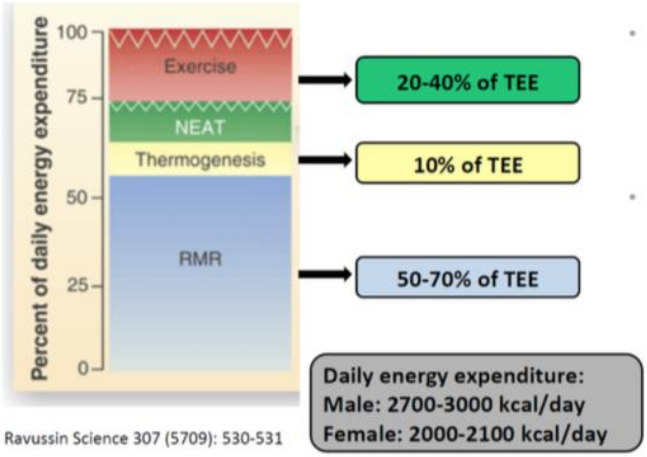
- Activation of AgRP neurons drives a condition place preference when animals conditioned with food
- Activation of them is almost the same as overnight fasting
- Activation of AgRP neurons drives a conditioned place aversion when conditioned without food and mice will walk around more as motivation to obtain food is high



Energy Expenditure – Physical Activity

Energy Expenditure

- Exercise and NEAT is activity expenditure (20-40%)
- Thermogenesis is only 10% of TEE
- 50-70% RMR
- 31% do not meet activity guidelines, and 80% of adolescence don't
- May be due to different guidelines
- Women are less active than men
- Inactivity increases with age

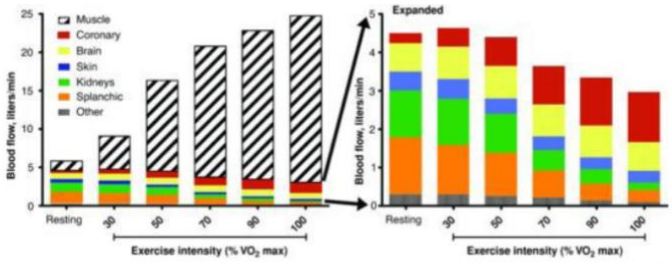


Ravussin Science 307 (5709): 530-531

At Rest

Accounts for 70% of Total Energy Expenditure

- ATP synthesis
- Protein synthesis
- Function of heart, lungs and brain, kidney and liver
- Skeletal muscle is only 20% of REE even though its 50% of mass
- However, it dramatically increases during exercise
- Brain blood flow remains constant
- During exercise, and increase in metabolism is matched by an increase in blood flow



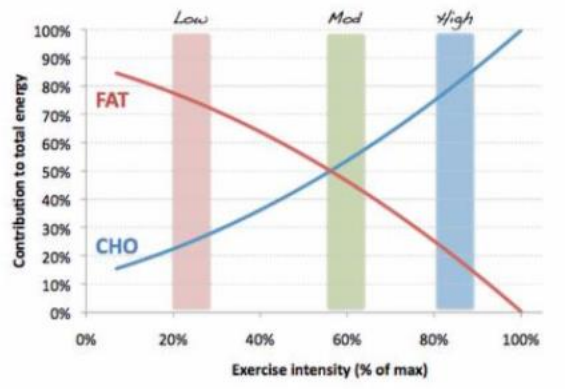
Laughlin et al. Compr Physiol 2012, 2: 321-447

Duration and Intensity

Energy expenditure dependent on both these factors
Duration – The longer you exercise, the more energy you will expend
Intensity – Positive correlation between exercise intensity and energy expenditure
Body mass – More energy is needed as heavier people have a higher energy cost

Intensity

- Fat is the primary fuel source at low intensities (Lipolysis)
- Can only produce energy via aerobic pathways
- Higher intensities increase CHO metabolism
- Aerobic or anaerobic pathways (efficient but slow; fast but lactic acid)



Duration

- Increase in plasma FFA
- Decrease in muscle glycogen and blood glucose
- Shift to fats (lipolysis) as time increases

Genetic Variation

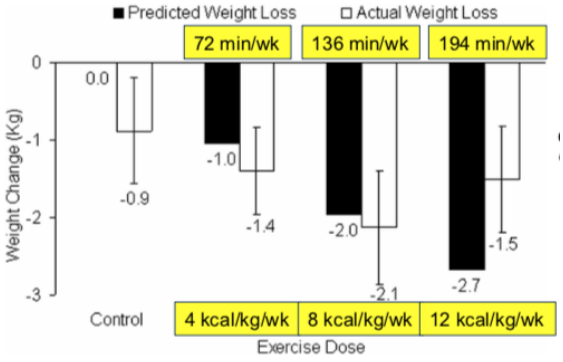
- Twins in studies lost similar amounts of weight between each other
- Diversity across the cohort, accounted for by the genetic diversity
- Genetics determine if exercise is effective for weight loss

Exercise for Weight Loss

- Clinically significant weight loss is a loss of 10% of body weight
- More exercise is needed to prevent weight gain after loss than normal prevention of weight loss
- This is because the body wants to go back to its set point

H.I.I.T

- Greatest change in central abdominal fat
- More effective than long steady state endurance exercise
- The longer extended duration exercise, the less weight loss
- High dose exercise produced half the predicted weight loss
- May be due to a metabolic compensation with a decrease in thermogenesis
- May be a response by a decrease in NEAT

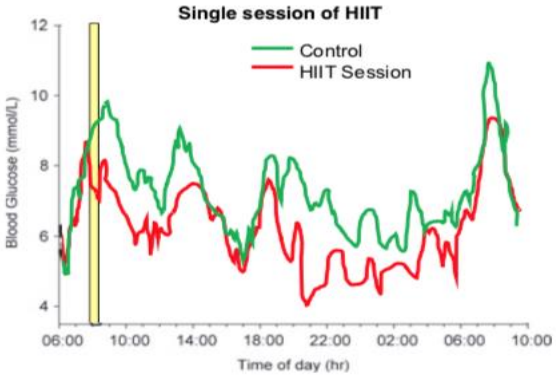


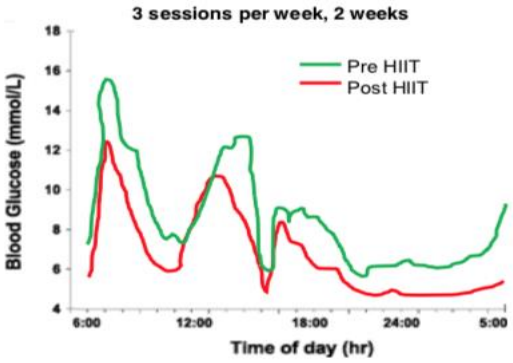
Compensatory Changes to Weight Loss

- Weight loss increases NPY and AgRP neurons
- This caused a drive in hunger to eat
- This is because of a decrease in fat mass

Study With H.I.I.T

- Glucose is reduced and maintained with 1 session which is effective for diabetes by improving glucose tolerance and insulin sensitivity
- Even though insulin levels are lower, there is a greater glucose uptake even with no change in body weight
- With many sessions, it reduces it long term





Exercise and Neuroprotection

Promotes Neuroplasticity and Neurogenesis

- Increases BDNF and neurotransmitters (D.A and 5-HT)
- Improves brain health (cognitive function, learning, memory, mood and arousal)
- Indirect effects cause a chronic increase in blood flow and decreases CNS inflammation

Low Intensity Physical Activity – NEAT

Non-Exercise Activity Thermogenesis

- Overeating decreases NEAT
- Regular exercise in the long term increases NEAT
- Lean people spend more time standing than sitting compared to obese people
- Increase BMR in obese people. But NEAT was the difference
- Lean people who were overfed increased NEAT to lose the weight and keep it off
- Indicates that NEAT is a physiological response by the body to increase energy expenditure

Orexin Increases NEAT

- Distinct, as it increases arousal, food intake and energy expenditure
- Increases spontaneous activity and mutations leads to a decrease in arousal and weight loss

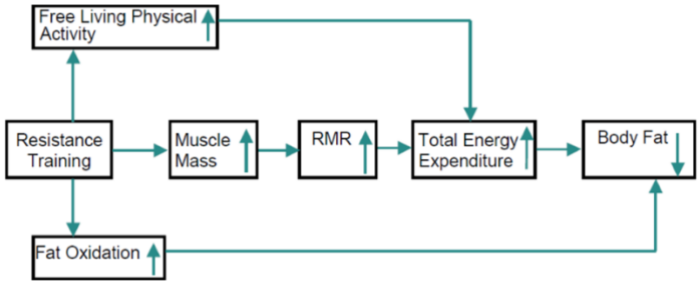
Energy Expenditure 2 – Non-Exercise Aspects of Energy Expenditure

Energy Expenditure

- Changes in E.E cause a susceptibility to weight gain
- Genetic predisposition to is NEAT and Adaptive Thermogenesis
- Adaptive Thermogenesis: Regulated by neurons that also control feeding

Basal Metabolic Rate

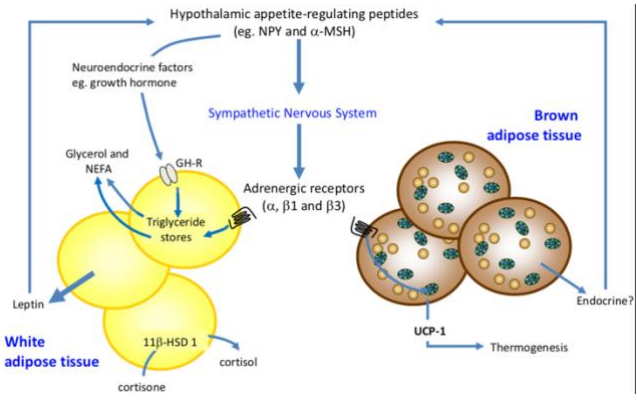
- Correlated to lean body mass and reduces with age
- Resistance training increases muscle mass, fat oxidation and BMR
- Men have a higher BMR than women



Thermogenesis

White Adipose Tissue

- Primary organ for storage and leptin production and secretion
- It is an endocrine organ
- Produces cortisol from cortisone
- Acted upon adrenergic receptors (sympathetic nerves)
- Unilocular (One large fat droplet)
- 50g of WAT stores 300-500 calories in energy

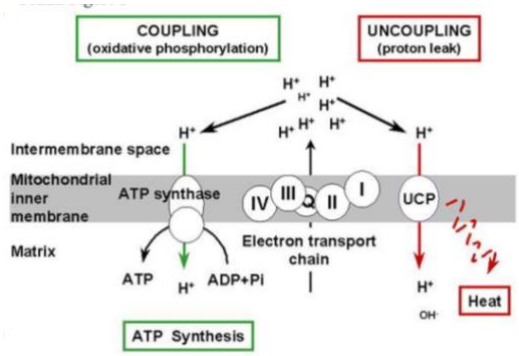


Brown Adipose Tissue

- Functions for heat production
- Enriched with mitochondria and Uncoupling Protein -1 (UCP-1)
- Expends energy, does not store it
- Multilocular (Many fat droplets)

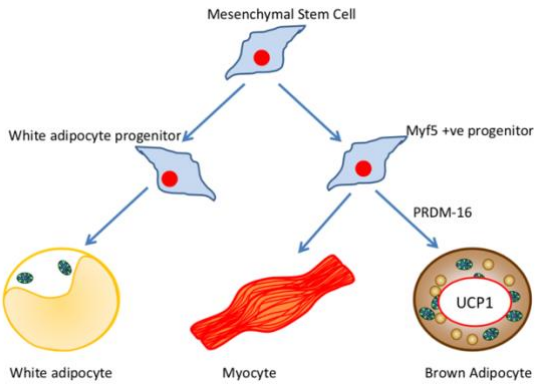
UCP-1

- A protein embedded on the inner mitochondrial membrane
- The protein gradient that is created by the ETC now has a leak
- H+ now goes either to ATP synthase or UCP-1
- When H+ goes to UCP-1, it releases ATP and heat → thermogenesis



Mesenchymal Stem Cells

- White adipocyte derived from white adipocyte progenitor
- Brown adipocyte and myocyte derived from Myf5 progenitor
- What determines if it will be muscle or fat is PRDM-16



Brown Adipose Tissue

- PET scan measures radio-ligand glucose uptake
- Mainly on neck, clavicle, interscapular and visceral organs
- 50g of BAT burns 100-300 calories/day
- Declines with obesity
- BAT is high when you're born as we cannot shiver
- Declines until adolescence, with a reinstatement of BAT
- This occurs to increase muscle mass

Thermography

- Changes in skin colour
- Compared to the negative control (Manubrium)
- Manubrium has very little tissue and fat and therefore acts as a control

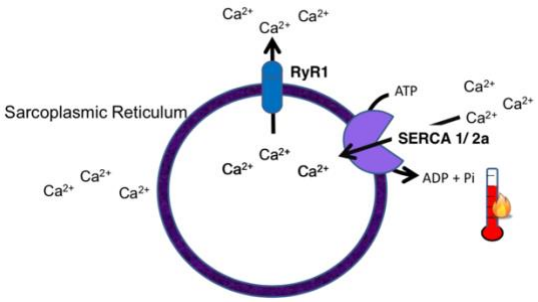
Activators of BAT

- Cold temperature is the main activator
- After eating, BAT increases but other tissues are also thermogenic
- Skeletal muscle is very thermogenic after a meal

Other Tissues

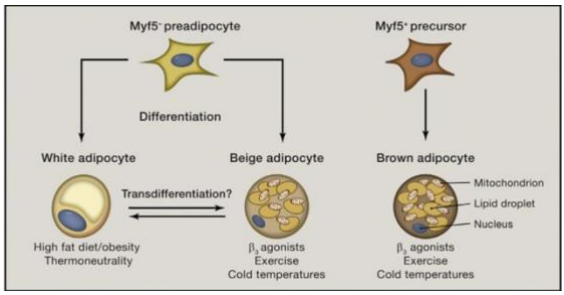
UCP-1 → BAT
UCP-2 → BAT, WAT and Muscle (Buffers R.O.S)
UCP-3 → BAT and Muscle (Not as strong as UCP-1)

Alternate Heat Pathway – Calcium Cycling



- Calcium entering the cell acts on Sarcoplasmic Reticulum
- This causes calcium release through the Ryanodine receptor
- SERCA protein drives calcium back in, but requires ATP
- This ATP → ADP + Pi releases heat → Thermogenesis

Beige Adipocytes



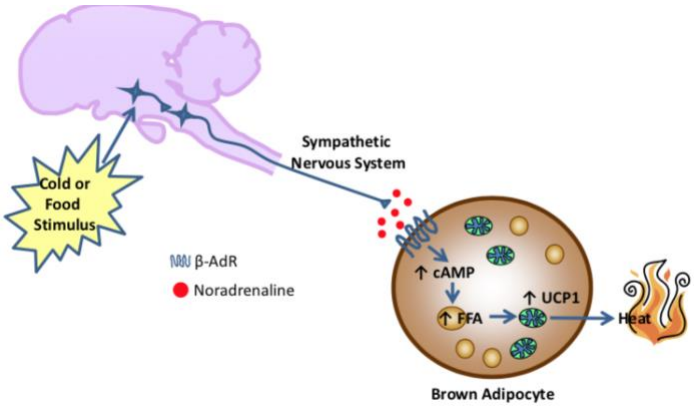
- More mitochondria than WAT but less than BAT
- Derived from Myf5- progenitor like white adipocyte
- Activated by B3 agonists, exercise and cold temperatures
- Multilocular but not as much as BAT
- Can have transdifferentiation from white to beige

Thermogenesis is Driven by the Sympathetic Nervous System

- Adaptive thermogenesis is controlled by the SNS
- Noradrenaline acts on beta adrenoceptors on BAT
- This increases cAMP which causes lipolysis and increase in Free Fatty Acids
- FFA are the main energy fuel for thermogenesis
- This drives UCP-1
- K.O of beta adrenoceptors show to increase body weight and decrease UCP-1 and lose BAT
- Hypothalamus is important in regulating thermogenesis
- **Leptin** acts at the brain to increase thermogenesis in BAT and skeletal muscle via melanocortins system (NPY/AgRP)

Brain and Hormones

- Factors that stimulate food intake inhibit energy expenditure
- Factors that inhibit food intake stimulate energy expenditure
- Only orexin increases both



Hormonal Regulation of Body Weight

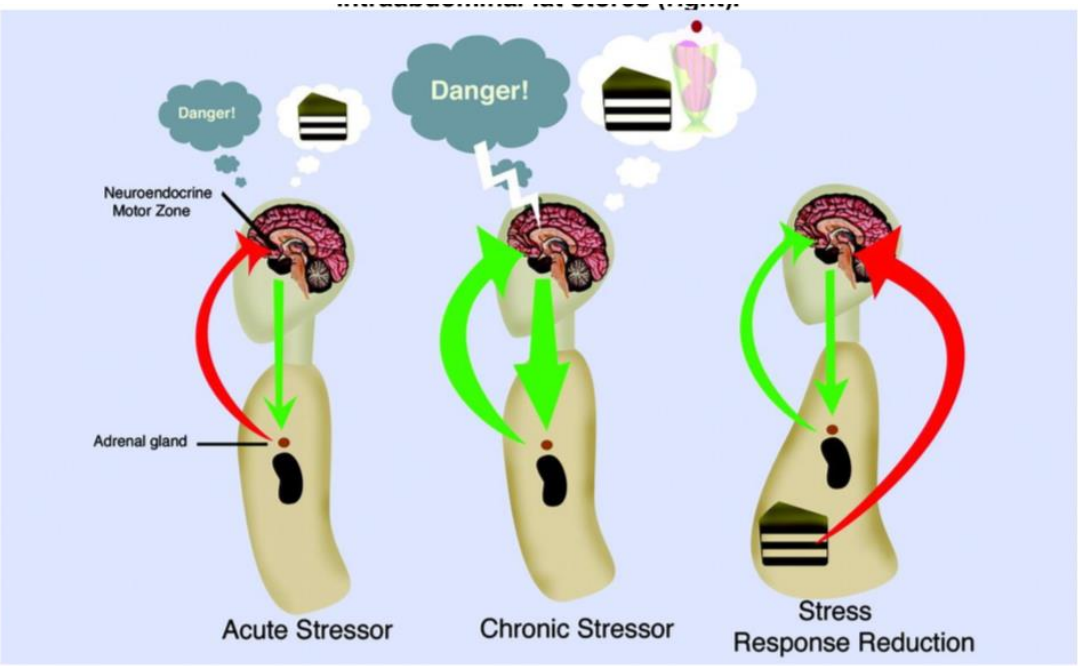
Increased levels of circulating sex steroids increase the predisposition to gain weight

Cushing's Syndrome

- Excess cortisol production
- Due to a pituitary tumour that produces excess ACTH
- This acts on the adrenal gland to secrete cortisol in excess
- Characterised with abdominal obesity and moon faces
- Can be treated with an antagonist, but the body won't respond to stress

Comfort Food Hypothesis

- The majority of people increase food intake in response to stress
- Only a small subset of people (10-15%) reduce food intake when stressed
- The increased glucocorticoids stimulate the increased intake of caloric dense high fat/sugar
- This is done to suppress the stress response
- In an acute setting, glucocorticoids will signal danger and inhibit ACTH release
- In chronic stress, they lose their ability to negative feedback
- As a result, increased food intake acts as a feedback mechanism to decrease the stressor response
- This is characterised with a decrease in glucocorticoid

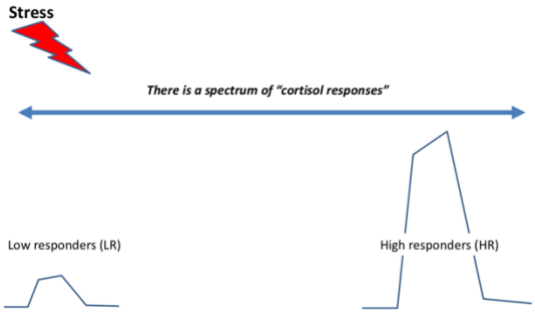


Stress and Ghrelin

- Released during psychosocial stress, caloric restriction and cachexia
- Attenuates stress response to increase food intake
- Acts as an anti-depressant and anxiolytic

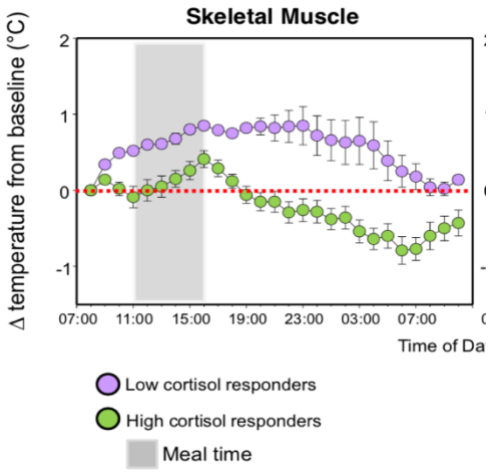
Types of Responders

- Some people have large amount of cortisol or low amount released when stress occurs
- Innate differences in cortisol responsiveness influence energy homeostasis and metabolism
- High responders and low responders eat the same normally, but only high responders will over eat after a stressful situation



Genetic Selection for Obesity and Cortisol

- No differences in food intake
- High responders however are more likely to gain weight and be obese



Thermogenic Divergence

- Occurs only in skeletal muscle, not retroperitoneal fat
- It is higher for low responders

Neuroendocrine Differences in Responders

- Both high and low responders are **not leptin resistant**
- They are however **resistant to aMSH**
- **The MC4R receptor is lower** in high responders than low in the PVN
- High responders have a **reduction in physical activity**

Orexin

- High responders have **reduced post-prandial thermogenesis** in skeletal muscle
- Attenuated catabolic state in response to stress

Oestrogen and Fat

- Change of fat distribution from hips and glutes to upper body after menopause
- This is due to a lack of oestrogen
- Weight gain is both steroid dependent and independent

Menstrual Cycle

- Different stages of food cycle changes food intake
- During ovulation, food intake is lowest when oestrogen is naturally at its highest
- This is when oestrogen is at its highest

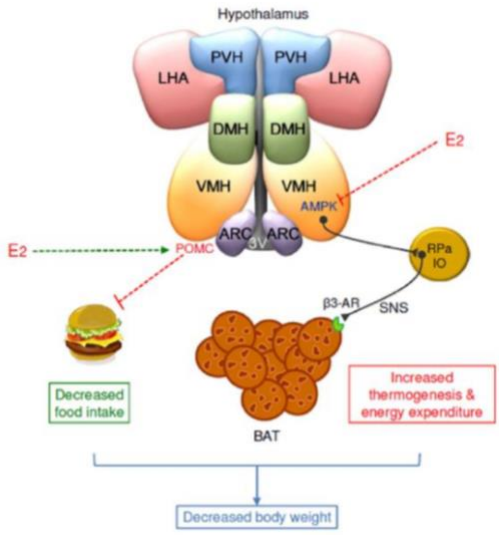
Studies and Facts

- Decreased oestrogen in rats increases body weight
- Overiectomy rats and HFD increases food intake, body weight and gonadal fat weight
- Oestrogen alone is the same as high fed rat, yet the weight loss is due to thermogenesis
- Therefore, oestrogen also impacts energy expenditure via UCP-1

Neural Circuitry with Oestrogen

Oestrogen…

- Activate POMC neurons in the arcuate nucleus to reduce food intake
- AMPK neurons in the VMH to increase thermogenesis and energy expenditure
- Lower leptin levels in the brain in women than male sheep
- This is because oestrogen sensitises the brain to leptins effects, making it more enhanced
- Oestrogen abolishes Orexigenic effects of ghrelin



Androgens

- Testosterone is considered anabolic
- The benefits in the table is mostly due to aromatisation and therefore, oestrogens effects
- It decreases energy expenditure with no change to intake
- DHT increases body weight
- Lower thermogenesis than in control

Estrogen	Androgen
Reduce food intake	Little effect on food intake
↑ energy expenditure (thermogenesis)	↓↔ energy expenditure (thermogenesis)
Prevents accumulation of visceral adipose tissue	↑ Muscle protein synthesis and muscle mass

Aging

- Both decrease Growth hormone → which induces lipolysis normally
- Both increase cortisol
- Both decrease oestrogen or free testosterone
- No change or increase in DHT
- These changes are associated with increased susceptibility to weight gain

Females	Males
• ↓ Growth Hormone	• ↓ Growth Hormone
• ↑ Cortisol	• ↑ Cortisol
• ↓ Estrogen	• ↓ Free testosterone
	• ↔↑ DHT