**Obesity**

**Part 4: Mechanisms: Basic Principles**

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**Satiation**

- Satiation is the perception of fullness that leads to meal termination.
- Gastric distension is sensed by mechanoreceptor neurons in the stomach and relayed to the brain.
- Satiation peptides released from the gut include cholecystokinin (CCK), glucagon-like-peptide (GLP-1), along with amylin from the pancreas.
- CCK is released from the duodenal and jejunal mucosa (response to fat and protein ingestion) - decreases food intake rapidly but transiently via activation of vagal afferents. Meal size is increased by intervention that disrupt CCK. GLP-1 and amylin also affect satiation.

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**Ghrelin**

- Ghrelin is a peptide secreted from the gastric mucosa that stimulates feeding and meal initiation (hunger hormone).
- Ghrelin peaks just before a meal and decline rapidly afterwards.
- Afferent signals involved in satiety are processed initially in the hindbrain.

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**Long term regulation of Food Intake and Energy Balance**

- Leptin is secreted by adipocytes in proportion to body fat mass and plays a key role in energy homeostasis by informing the brain of changes in both energy balance and the amount of fuel stored as fat – controls fat set point.
- Leptin acts in the brain as a negative feedback regulator of adiposity, constraining fat mass by limiting energy intake and supporting energy expenditure.
- Decreased leptin signaling promotes increased food intake, positive energy balance and fat accumulation.

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**Leptin**

- Leptin's effects on energy balance are mediated by leptin receptors in the hypothalamus.
- The nucleus of the solitary tract (NTS) and midbrain regions central to reward and motivation are also leptin sensitive.
- The hypothalamus senses and integrates signals including hormones (leptin, insulin and ghrelin) and nutrients (fatty acids, amino acids and glucose).
**Leptin resistance**

- Obesity is characterised by increases in fat mass and circulating leptin.
- Leptin resistance is a plausible mechanism to explain the defense of an elevated fat set point.
- Leptin resistance seems to be required for diet-induced obesity to occur.
- Inflammatory signalling has emerged as a potentially important mediator of leptin resistance. Some researchers suggest lectins and fructose may also contribute to leptin resistance. Exercise helps to maintain leptin sensitivity.

**Body fat set point**

- If obesity involves the biological defense of an elevated level of body fat advice to eat more and move more can't be expected to work. This is because the body will defend the elevated fat mass and elicit compensatory responses to restore fat mass and are difficult to consciously override.

**Adaptive response to fat loss induced by calorie restricted diets**

- Negative energy balance and loss of body fat lowers levels of the feedback mechanisms for adiposity (e.g., leptin and insulin) and raise ghrelin (hunger hormone). In response the brain strongly promotes increased food intake, positive energy balance and recovery of lost fat so hunger is increased and metabolism is lowered.

**Effect of intentional weight loss**

- In the Finnish twin study - Subjects included 4129 individual twins from the population-based FinnTwin study (90% of twins born in Finland 1975–1979).
- Due to genetic confounders Finnish twins were studied on the effects of intentional weight loss showed a dose dependent association between the number of lifetime weight losses, gain in BMI and risk of overweight in a large population based cohort.
- In monozygous cotwins who were discordant for IWLs, twin pair members with IWLs 0.4 BMI units heavier (approx. 1.2kg in a person 170cm tall) at 25 years than those who had never lost weight despite similar BMI at 16-18 years.

**Intentional weight loss**

- Most dieters rapidly re-gain achieved weight loss or even more.
- In prospective studies, weight control efforts have predicted future weight gain.
- Suppression of metabolic rate and loss of lean mass by negative energy balance may facilitate post dieting weight rebound.
- In worst case net weight gain is accompanied by undesirable changes in body composition with disproportionate replenishment of fat stores.

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**Muscle mass**

- Weight loss - loss muscle and fat – lean mass loss ranges from 14% to 23% of total weight loss. Loss of lean mass can be associated with adverse health events especially in older adults – has an effect on metabolic rate and can lead to increased frailty.
- In one study on postmenopausal women – for each 1kg of weight lost, 0.32 kg lean tissue was lost. For every 1kg weight regained over the following year only 0.06kg lean tissue regained.
- Women became more sarcopenic obese.
- However, intentional weight loss of this magnitude can improve many obesity-related risk factors for coronary heart disease and diabetes. Studies have shown that 6 mo weight loss intervention in older adults showed greater fat loss associated with greater gains in muscle strength and quality despite loss of lean body mass.
- Increasing protein intake during weight loss can offset the deleterious effects on muscle mass by maintaining more muscle relative to weight lost.

Beavers KM et al 2011 Am J Clin Nutr

**Protein and muscle mass**

- Postmenopausal women supplemented with whey protein (0.8g/kg body weight dietary protein plus additional 45g a day of whey protein) showed maintenance of muscle mass relative to weight lost and lower subcutaneous fat tissue compared to control (Mojtahedi MC et al 2011. J Gerontol)

**The Minnesota Starvation Study**

- The Minnesota Starvation Study on 36 normal weight men put on a restricted diet providing only half calorie needs for 6 months – the men became severely obsessed with overeating which continued in the rehabilitation phase with the restoration of energy needs.

**Food intake determinants**

*“The initiation and maintenance of ingestive behavior is co-determined by metabolic and non-metabolic factors.”*

<table>
<thead>
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<th>Non metabolic factors</th>
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<td>Environmental cues</td>
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<td>Insulin</td>
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<td>Ghrelin</td>
<td>Cognitive</td>
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<td>Emotional</td>
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**Food intake: non homeostatic**

- **Environmental cues** - Abundance of food cues in the modern environment. The easy availability (low physical effort and cost) of palatable, energy dense foods (snacks) in a socially enhanced environment.
- **Cognitive**
- **Reward**
- **Emotional**
- **Reward** - Palatability and pleasantness are arguably the most powerful determinants of food intake.


**Food reward**

- Palatability is the hedonic or pleasure value associated with food and influences meal size.
- In rodents provided with human junk food as well as standardised chow overconsume the junk food at the expense of the more nutritious chow and susceptible rat strains develop obesity quickly.
- Rats will also endure foot shocks or extreme cold in order to obtain the junk food.

**Learning/ reinforcing aspects of eating - Food reward**

- Reward is the process whereby behaviours are reinforced in response to certain stimuli.
- Taste, smell and environmental cues are associated with food properties that reinforce behaviours related to acquisition and consumption of rewarding food.
- Relevant food properties include caloric density, texture, content of fat, starch, sugars, salt and free glutamate which can influence food intake and body fatness.


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**Rewarding Foods**

- Fat
- Starch / carbohydrates
- Sugar
- Salt
- MSG – processed foods, crisps, Chinese
- The absence of bitterness
- Certain textures – THINK PRINGLES!
- Certain tastes – CHINESE? CHEESE & ONION CRISPS, JAFFA CAKE?
- High calorie food

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**Food reward**

- Dopamine signalling relates to the wanting or food, whereas opioids are implicated in the liking of food i.e. hedonic value, palatability.
- Obesity can arise when animals or humans are confronted with foods whose palatability or reward value greatly exceeds that to which they are genetically adapted and hence that interventions that inhibit food reward can prevent fat gain and promote fat loss.
- A change in the reward value of a diet impacts on the energy homeostasis system.


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**Paleo vs Mediterranean**

- Patients with type 2 diabetes advised to eat a Palaeolithic diet, based on lean meat, fish, fruits, vegetables, root vegetables, eggs and nuts as staple foods, while avoiding cereals, dairy products, refined fat, sugar and salt. Control subjects, who were advised to follow a Consensus (Mediterranean-like) diet based on whole grains, low-fat dairy products, fish, fruits and vegetables, did not significantly improve their glucose tolerance despite decreases in weight and waist circumference.

- The Paleo diet showed:
  - Improved glucose tolerance
  - Greater abdominal fat loss and a trend toward greater weight loss
  - Lower caloric intake (total intake paleo= 1,344 kcal; Med= 1,795)
  - An increase in insulin sensitivity (HOMA-IR)


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**Highly Rewarding Food Changes The Brain**

- Overconsumption of highly rewarding food causes changes in the brain that regulates body fatness:
- An inherited or acquired reduction of dopamine signalling in discrete CNS regions influences systems governing energy homeostasis in a way that favours fat accumulation.
- This dopaminergic defect might be caused by desensitization of specific dopamine circuits caused by overexposure to highly palatable/rewarding food. And/or the suppressive effect of elevated leptin and insulin on reward regions in obese


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**Addiction**

- Addiction is what happens when the reward system is over-stimulated by drugs, sex, food or other high-reward stimuli.
- In susceptible people highly palatable/rewarding foods are addictive, leading to binge eating behavior.
- This can lead to compulsive relationships with food.
- Combination of highly accessible highly addictive food and stressful lifestyles

Addiction and obesity

- Behavioral changes, which are similar to behavioral changes observed in drug use/addiction, can be observed with food. Drug addiction and food overconsumption share similar behavioral features, such as lack of control over initiation and termination of eating/drug use, compulsive behavior, and adaptation/sensitization to rewarding stimulus. These altered behaviors seen in both obesity and drug addiction may in part be explained by inappropriate functioning of the brain reward system and associated dopaminergic circuitry.
- Several researchers have pointed to similarities between addiction and obesity.
- Palatable food is a potent reinforcer
- Neuronal mechanisms underlying addiction-like behavior after repeated food overconsumption and drug use are similar, and likely involve the dopaminergic reward pathway.


Opiates and sweets

- A common variant of the OPRM1 (G/G) Genotype of the A118G marker is associated with higher preferences for sweet and fatty foods and is related to all measures of overeating and BMI.
- Some of the individual differences in the preference for highly palatable foods can be explained by genotypic differences in the regulation of mu opioid receptors that play a key role in the appetite and reward system (in addition, these receptors may also have a role in regulating the homeostatic system).


Modern environments

- Level of body fat is important for survival and so it is suggested that the energy homeostasis systems has evolved to maintain an appropriate level of adiposity for the ecological niche and is controlled by feedback systems.
- The modern environment poses a number of challenges to these feedback systems.