Neurophysiology of the Regulation of Food Intake and the Common Reward Pathways of Obesity and Addiction

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The Brain as the Regulatory Center for Appetite

- The brain is the integration center for appetite
- Produces a coordinated
  - behavioral,
  - Endocrine, and
  - autonomic response
- Under normal conditions, there is a homeostatic control of food intake and metabolism, however malfunction in reward pathways can be linked to the growing problem of obesity
- Obesity can lead to:
  - cholelithiasis [5],
  - osteoarthritis [6],
  - infertility [7],
  - stroke [8],
  - cutaneous infections
  - wound healing deficiencies [10],
  - general increase in mortality [11]
Complex Homeostatic Mechanisms of Appetite

- The metabolic mechanisms of the brain
- The input stations in the hypothalamus and brainstem sensitive to metabolic signals
- The link between food intake and energy expenditure
- The neural framework for integrating metabolic cues and reward properties
- The common pathways of drug addiction and increased food intake
- Novel therapeutic strategies for obesity using the model of drug addiction
Complex Homeostatic Mechanisms of Appetite
Homeostatic regulation of Appetite and Feeding

- appetite and feeding is regulated via homeostatic regulation with the brain as the central processor
- peripheral metabolic signals to the brain:
  - Leptin
  - Insulin
  - peptide YY
- Additional signals:
  - ghrelin and lipid mediators
  - vagus nerve
- hormonal signals reflecting the availability and demand for metabolic fuel is relayed via neurons in the
  - Arcuate nucleus (Arc) of the hypothalamus
  - Nucleus of the solitary tract (nTS) of the brainstem
Leptin

- appetite-regulating endocrine signal from adipose tissue
- feeding-inhibitory messenger through a decrease of appetite and increase of metabolism
- combination of hyperleptinaemia and hyperphagia: led to the suggestion that obesity is characterized by leptin resistance
Insulin

- glucostatic regulator
- decreases food intake
- Operates via insulin receptors expressed on Arc neurons
- modulates peripheral energy metabolism by inhibiting liver gluconeogenesis
Endocrine Peptides

- Cholecystokinin (CCK),
- Peptide tyrosine-tyrosine (PYY)
- peptides produced by enteroendocrine cells in the lining of the gut
- most prominently important feedback signal from the gut to the hypothalamus.
- release stimulated by the presence of lipids and carbohydrates in the lumen of the distal ileum and colon
- inhibit food intake
Ghrelin

- first hormone shown to stimulate food intake
- Produced in the epithelium of the stomach and small intestine
- stimulation of feeding and gastric emptying
- increase food intake and increase fat mass
- activates the mesolimbic cholinergic-dopaminergic reward network
OEA and the Vagus Nerve

- Oleoylethanolamide (OEA)
- fatty acid
- chemically, but not pharmacologically similar to endogenous cannabinoids
- role in the modulation of synaptic transmission
- produced in the duodenum and acts via the vagus nerve
- decrease body weight through activation of the nTS to decrease appetite
Signaling of the Hypothalamus and Brainstem

- peripheral signals act upon the Arc and nTS
- influence the central pathways regulating energy balance.
- In the Arc, receptors for leptin and insulin found on Neuropeptide Y (NPY) neurons
- Pro-opiomelanocortin (POMC) neurons inhibit transcription of NPY and increase POMC mRNA levels via second messenger systems
Integrating Center Signaling

- Neuropeptide Y (NPY): one of the most potent stimulators of feeding known
  - central in leptin signalling.
- Stimulation of feeding is transduced predominantly via postsynaptic NPY Y1 receptors,
- Pro-opiomelanocortin (POMC): large precursor protein which gives rise to melanocortin peptides
  - a- and c-melanocyte-stimulating hormone have been shown to exert potent anorexigenic effects
Integration Center Signaling

- NPY neurons to control the activity of the POMC cells via multiple mechanisms.
  - Coexpression of agouti gene-related peptide (AGRP)
    - endogenous melanocortin antagonist
  - POMC neurons are innervated by NPY-ergic terminals
    - NPY causes a powerful membrane potential hyperpolarization

- Inhibitory influence over the NPY neurons via PYY
  - selective agonist of the inhibitory Y2 autoreceptors
Integration and Coordination of Brain-Mediated Responses

- **Balance of two systems**
  - Hypothalamus monitors the periphery for signals alerting central circuits to diminishing energy stores
    - long-term control orchestrating meal initiation
  - Brainstem, receiving oral and gastrointestinal information
    - short-term control for meal termination

- Leptin activates the same medial region of the nTS that is stimulated by gastric distension
  - anatomical site of integration of long- and short-term feeding controls.

- Melanocortin agonists can reduce feeding and body weight by brainstem mechanisms

- Orexigenic effects of Ghrelin are also seen with selective local administration both in the hypothalamus and in the brainstem
Regulation of Behavioral, Autonomic, and Endocrine Responses

- Arc and nTS and ultimately engage regions that initiate and organize
  - behavioral,
  - Autonomic, and
  - endocrine response patterns.

- Organized by a collection of cell groups within the medial hypothalamus area, collectively termed the hypothalamic visceromotor pattern generator network

- Paraventricular nucleus (PVH) is a control column module for ingestive behavior.

- Output from the PVH employs
  - endocrine via neuroendocrine neurons controlling pituitary hormone release
  - autonomic via direct projections to preganglionic neurons in the spinal cord
    - intermediolateral cell column (sympathetic)
    - dorsal motor nucleus of the vagus (parasympathetic),
  - behavioural (i.e. somatomotor) via pathways innervating the brainstem
Regulation of Behavioral, Autonomic, and Endocrine Responses
The motivational state is a product of limbic influences relayed by the amygdala, and reward factors.
The concept of reward is intimately linked to that of addiction, and it has been suggested that obesity is a consequence of an addiction to food.
Drugs of abuse converge upon the mesolimbocortical system.
produce reward by enhancing dopamine release in the nucleus accumbens (Acb) of the forebrain.
Reward and Reinforcement

- Drug and Food Reinforcement leads to an increase in the release of dopamine from the presynaptic neuron.
- Dopamine reuptake is blocked at the synapse leading to an accumulation in the synaptic cleft.
- Coupled, these lead to an increased stimulation of dopamine receptors.
Dopamine Receptors

- D2-like dopamine receptors inhibit cAMP formation via Gi and Go proteins.
- A common mechanism of drug and food reinforcement has been hypothesized at the postreceptor, signal-transduction level.
- Gi and proteins, and the cAMP second-messenger and protein-phosphorylation system, may represent a final common intracellular pathway utilized in reinforcement patterns observed in drug addiction as well as obesity.
Novel Approaches to the Treatment and Prevention of Obesity

- Overlap of the motivational mechanisms of obesity and drug addiction
- Product of Neuroadaptations resulting from excessive intake
- Pharmacological Interventions that are currently being used to treat drug addiction may be useful for the treatment and prevention of obesity
- Although there is no current treatment of obesity using this approach, further research could potentially lead to changes in the approach to treating eating disorders
Broberger C et al. Subtypes Y1 and Y2 of the neuropeptide Y receptor are respectively expressed in pro-opiomelanocortin- and neuropeptide- Y-containing neurons of the rat hypothalamic arcuate nucleus. *Neuroendocrinology* 1997; 66: 393–408.

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