Internal Regulation II

Energy

Reading:
BCP Chapter 16

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Homeostasis

Biologically, what is necessary for life is a coordinated set of chemical reactions. These reactions take place in water at a rate dependent on the temperature of the solution, concentration of the solutes and availability of energy.

Homeostasis refers to biological processes that keep body variables within a fixed range.

The process of homeostasis includes:
- sensory transduction of a variable
- detecting changes from the optimal range
- integrated response (humoral, visceromotor and somatic) to restore parameter back to optimal (called negative feedback)

The hypothalamus plays a key role in the regulation of body temperature, fluid balance, and energy balance.
The brain’s requirement for energy, in the form of glucose, is urgent: even a few minutes of deprivation will lead to loss of consciousness and death.

The body’s energy stores are replenished during and immediately after consuming food. During the parandial state, glucose is stored (via anabolism) in the form of two macromolecules: glycogen (in liver and skeletal muscles) and triglycerides (in fat). During the fasting state, stored glycogen and triglycerides are broken down (via catabolism) to provide nutrients to the body.

Energy balance and body fat:
- normal: intake = expenditure
- obesity: intake > expenditure
- starvation: intake < expenditure

Homeostatic (long- and short-term) and hedonic mechanisms regulate energy reserves and feeding.
Body weight is normally very stable in the long-term. Weight lost during a period of starvation is gained rapidly when food is available. Similarly, if an animal is force fed, it will gain weight, but the weight is lost if the animal can regulate its own food intake.

→ Lipostatic hypothesis (Kennedy 1953): the brain monitors the level of body fat and “defends” this source against perturbation.

Evidence suggests that fat cells release the hormone leptin to communicate the level of fat to the brain, thus regulating body mass. In particular, mice lacking both copies of the ob gene (which codes for leptin) are obese, whereas deficient mice which receive daily doses of leptin are normal in size.

Leptin deficiency is rare in humans; rather obesity may be caused in part by decreased penetration through the blood-brain barrier; reduced receptors; altered CNS response.
Studies show that bilateral lesions of the hypothalamus have large effects on feeding behavior and adiposity.

Lateral hypothalamic syndrome: lesions in this region cause anorexia, a severely diminished appetite and reduced fat stores

Ventromedial hypothalamic syndrome: lesions in this region (specifically of the arcuate nucleus) cause obesity, severe overeating and weight gain

- Together, the arcuate nucleus and lateral hypothalamic area regulate energy balance
The arcuate nucleus of the hypothalamus is considered to be the “master area” for control of appetite.

It has two sets of neurons: one set sensitive to hunger signals (purple; low leptin) and one set sensitive to satiety signals (green; high leptin).

When activated, hunger-sensitive neurons release AgRP (agouti-related peptide) and NPY (neuropeptide Y) onto their targets (the paraventricular nucleus and lateral hypothalamic area), whereas satiety-sensitive neurons release αMSH (alpha-melanocyte-stimulating hormone) and CART (cocaine- and amphetamine-regulated transcript) into the same targets.
Hunger

A reduction in the blood levels of leptin is detected by neurons in the arcuate nucleus that contain the neuropeptides NPY and AgRP (called orexigenic:appetite peptides).

These arcuate nucleus neurons:

- **(humoral)** inhibit the paraventricular cells that control the release of TSH (thyroid-stimulating hormone) and ACTH (adrenocorticotropic hormone) which decreases metabolic rate
- **(visceromotor)** activate the paraventricular cells that control the parasympathetic system (stimulate saliva; gastric peristalsis)
- **(somatic)** stimulate feeding behavior in the lateral hypothalamic region
Satiety

An increase in the blood levels of leptin is detected by neurons in the arcuate nucleus that contain the neuropeptides αMSH and CART (called anorectic:satiety peptides).

These arcuate nucleus neurons:
• (humoral) excite the paraventricular cells that control the release of TSH and ACTH to increase metabolic rate
• (visceromotor) activate the paraventricular cells that control the sympathetic system to increase blood flow to skeletal muscles
• (somatic) suppress feeding behavior in the lateral hypothalamic area
Long-term Hunger and Satiety

Arcuate (AR)

αMSH and AgRP are literally antagonistic on same MC₄ receptor

NPY/AgRP/GABA POMC/CART

Medial PVN

dorsal/ventral PVN

Arcuate nucleus response

Humoral response
medial PVN

Visceromotor response

dorsal/ventral PVN

Somatic motor response
LHA
orexin: initiates meal
MCH: prolongs consumption

Paraventricular (PVN)

Lateral hypothalamic area (LHA)
In addition to the long-term regulation of feeding behavior by leptin, the motivation to eat depends on short-term factors such as the length of time since the last meal and how much was consumed at that time.

A model of the short-term regulation of feeding involves interactions among orexigenic and satiety signals. When orexigenic signals (red) are high and satiety signals (dash) are low, food consumption ensues. Conversely, when orexigenic signals are low and satiety signals are high, food consumption is inhibited.
Short-Term Factors

Hunger/satiety is regulated by a variety of short-term factors including signals from the stomach, intestines, and the composition of chemicals in the blood.

Stomach:
- hormone ghrelin (hunger)
- distention (vagus nerve) (satiety)

Intestines:
- hormone cholecystokinin CCK (satiety) (also stimulates vagus nerve, and closes exit of stomach)

Blood:
- hormone insulin (pancreas) low = hunger; high = satiety
Short-term hunger/satiety signals activate neurons in the arcuate nucleus in much the same way as leptin.

- Like low leptin levels, high ghrelin, low CCK, insulin and gastric tension (via activity in the nucleus solitarius NS in the medulla) activates the NPY/AgRP-containing (orexigenic or hunger) neurons.
- Like high leptin levels, high CCK, insulin and gastric tension activate the αMSH and CART-containing (anorectic or satiety) neurons.
Hedonic Regulation of Feeding

Food is consumed in order to maintain energy balance at homeostatic levels. In addition, palatable food is also consumed for its desirable “hedonic” properties independent of energy status.

Certain foods, particularly those rich in sugars and fat, are potent rewards that promote eating (even in the absence of an energetic requirement). In evolutionary terms, this property was advantageous because it ensured that food was eaten when available.

Hedonic hunger incorporates motivational (reward) and emotional influences on eating. Evidence suggests that dopamine (ventral tegmental area) and serotonin (Raphe nucleus) modulate, respectively, these hedonic effects of food.
In 1954, Olds and Milner discovered that brain circuitry exists that reinforces behaviors. In particular, animals will administer brief bursts of weak electrical stimulation to specific sites in their own brains. This phenomenon is known as intracranial self-stimulation (ICSS), and the brain sites capable of mediating the phenomenon are called pleasure centers.

The mesocorticolimbic pathway (specifically the ventral tegmental area and the nucleus accumbens) is the major “reward” pathway for ICSS and natural rewards (and site of action of addictive drugs).

**Mesocorticolimbic Dopamine System**
The mesocorticolimbic dopamine system is involved more-so in anticipatory pleasure (i.e., wanting or craving: reward prediction), as opposed to actual pleasure (i.e., liking).

Events (e.g., the sight or smell of pancakes) cause dopamine neurons to fire, thus inciting appropriate behaviors (in this case, to feed).
Mood and food are connected (e.g., grouchy on a diet; happy eating a cookie).

Serotonin provides one link between food and mood. The level of serotonin in the hypothalamus increases during meal time. Serotonin is derived from the amino acid tryptophan, which must be consumed. It is found in proteins; however, tryptophan levels in the blood vary with the amount of carbohydrates in the diet (high levels → high insulin → amino acids absorbed in muscle → more tryptophan to cross BBB).

Serotonin acts like a short-term regulator of hunger/satiety in the arcuate nucleus, but also reduces the level of dopamine release from the ventral tegmental area. However, abnormal low serotonin levels (dysregulation; stress) can override homeostatic mechanisms and cause overeating (e.g., obesity, bulimia).