ENERGY BALANCE

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Energy balance

- Peripheral or afferent system generates signals from various sites:
- Leptin and adiponectin are produced in fat cells
- Ghrelin is produced in the stomach
- Peptide Y (PYY) is produced in the ileum and colon
- Insulin is produced in the pancreas
- The arcuate nucleus integrates the peripheral neurohumoral signals and generates efferent signals.

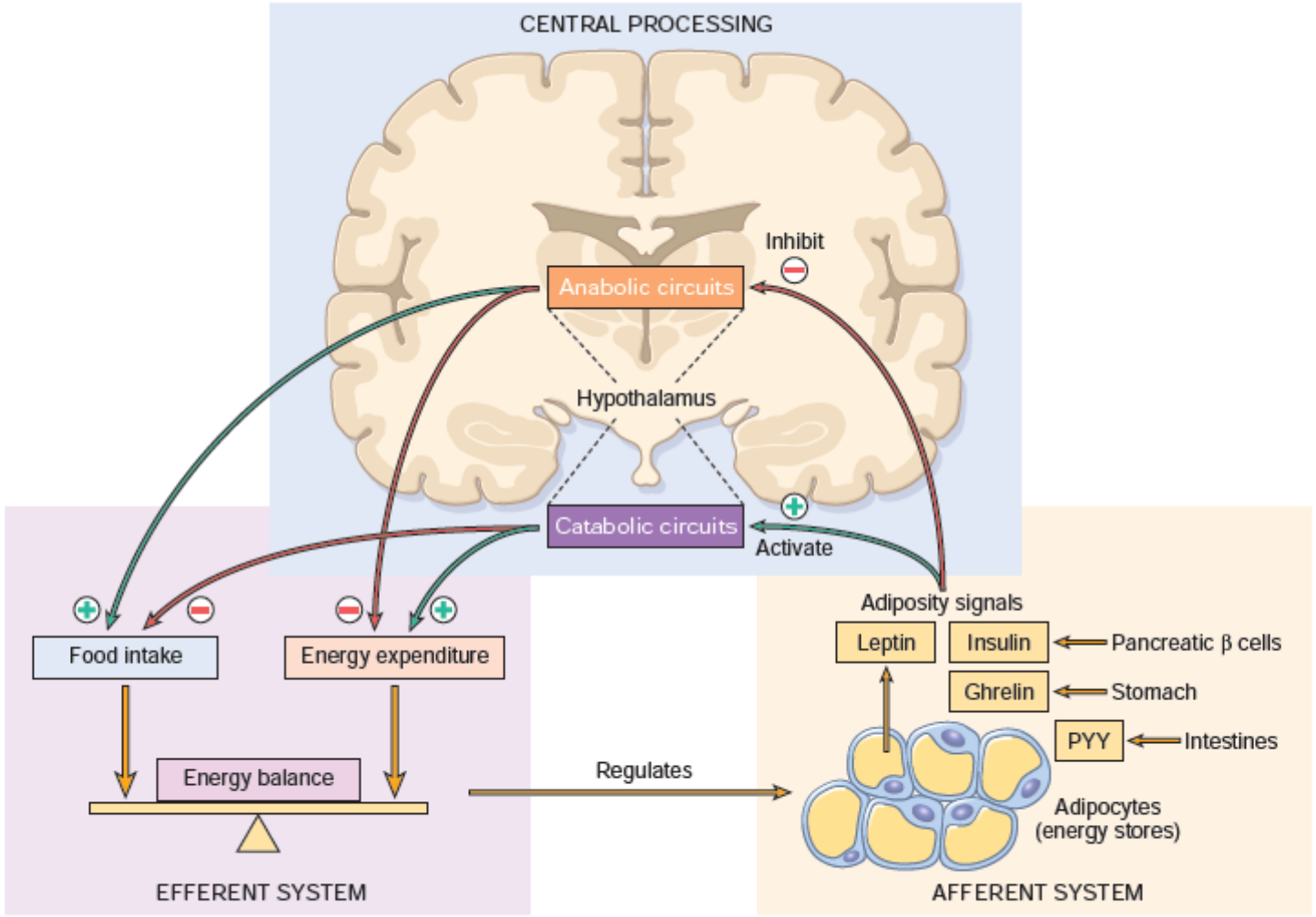

Figure 9-30 Regulation of energy balance. Adipose tissues generate afferent signals that influence the activity of the hypothalamus, which is the central regulator of appetite and satiety. These signals decrease food intake by inhibiting anabolic circuits, and enhance energy expenditure through the activation of catabolic circuits. PYY, Peptide YY. See text for details.

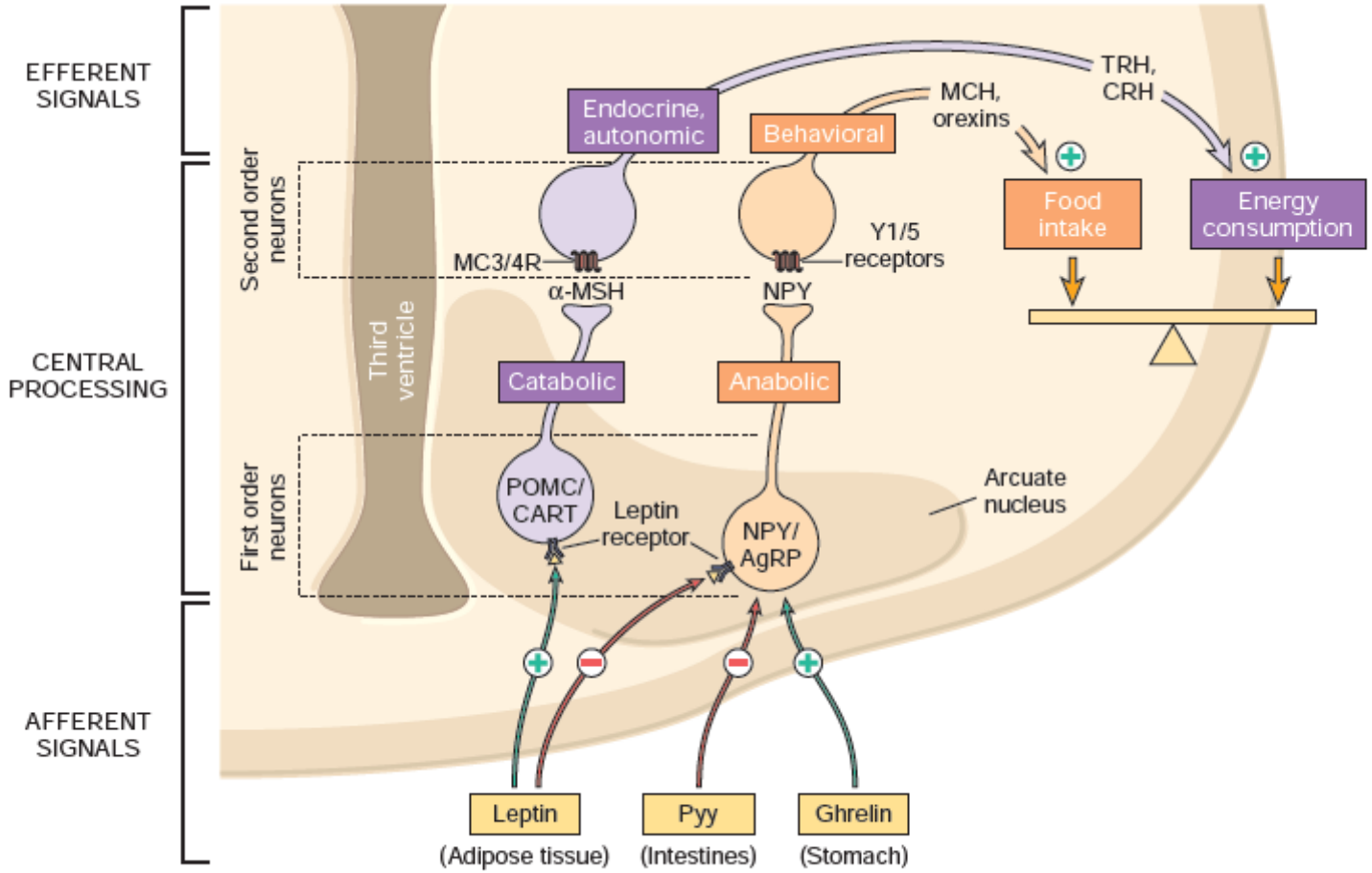

Figure 9-31 Neurohumoral circuits in the hypothalamus that regulate energy balance. Shown are POMC/CART anorexigenic neurons and NPY/AgRP orexigenic neurons in the arcuate nucleus of the hypothalamus, and their pathways. See text for details.

Energy balance

- First order neuron subsets include POMC (pro-opiomelanocortin) and CART (cocaine and amphetamine-regulated transcripts) as well as neurons containing neuropeptide (NP) Y and agouti-related peptide (AgRP).
- POMC/CART neurons lead to the production of α-MSH (anorexigenic) and the activation of melanocortin receptors (MC3/4) in second order neurons.
- NPY/AgRP neurons activate Y1/5 receptors in second order neurons (orexigenic).

Energy balance

- Leptin is a product of the LEP gene at 7q32.1.
- Production stimulated when fat stores are abundant
- Regulated by insulin-stimulated glucose metabolism.
- Leptin stimulates POMC/CART and inhibits NPY/AgRP neurons.
- Regulates food intake and energy expenditure.
- Leptin receptor is the product of the diabetes gene (LEPR) at 1p31.3 and belongs to the type I cytokine receptor superfamily (IL-2, IL-6, GCSF).
- Activates jak/stat pathway.

Energy balance

- Adiponectin directs fatty acids to muscles for oxidation.
- Receptor binding leads to inactivation of acetyl-CoA carboxylase.
- Adipose cells also produce TNF-α, IL-1, IL-6, IL-18, and steroid hormones.
- Relative overproduction (obesity) induces a chronic inflammatory state.

Energy balance

- Ghrelin is the only gut hormone that is orexigenic.
- Ghrelin is also produced in the arcuate nucleus (orexigenic).
- Binds growth hromone secretagogue receptor and stimulates NPY/AgRP neurons.
- PYY and amylin stimulate POMC/CART neurons.

Protein Energy Malnutrition

- BMI <16kg/m^2
- Marasmus results from inadequate caloric intake
- Associated with loss of muscle mass and subcutaneous fat
- Serum albumin normal; leptin levels low; cortisol production elevated
- Kwashiokor results from protein depletion
- Generalized or dependent edema (serum albumin low) and fatty liver (diminished synthesis of apolipoproteins)
- Hyper and hypo-pigmented hair and skinwith desquamation (“flaky paint”)

Cachexia

- Cachetic agents produced by tumors include:
- Proteolysis inducing factor (glycosylated polypeptide) leads to skeletal muscle breakdown through degradation of myosin chain as well as through loss of dystrophin
- Lipid mobilizing factor increases fatty acid oxidation and production of TNF-α, IL-2, and IL-6, creating a chronic inflammatory state.
- TNF-α activates NF-κB and initiates transcription of ubiquitin ligases.
- Albumin levels diminish.

Obesity

- Don’t blame it on leptin.
- Produced in adipocytes
- Signals hypothalamus that adipose stores are sufficient.
- Interacts with POMC (anorexigenic) and arginine related protein (orexigenic as it blocks α-MSH) as well as the abundant Neuropeptide Y (orexigenic).
- Normal BMI >18-25 kg/m^2
- Overweight children if weight >85^{th} percentile; obesity if >95^{th} percentile

Obesity

- Definition of obesity differs among those of Asian ancestry (>25), European ancestry (>30), and African ancestry (>34).
- Waist circumference greater discriminator in Hawaiian-Phillipine Islander populations (>88cm in women, 90cm in men)
- An elevated BMI is associated with a health risk comparable to tobacco use
- Obesity is associated with 2-4 years loss of life expectancy
- A BMI>40, a loss of 8-10 years

Obesity

- Any diet to which the patient adheres is more effective than no intervention
- Exercise diminishes resistance to endogenous insulin
- However, not associated with weight loss

Effective diet approaches

- Forks over Knives
- Plant based diet
- Requires vitamin B_{12} supplementation
- Minimize or avoid meat, poultry, seafood, eggs, cheese and milk, oils, refined sweeteners, bleached flour, white bread, white rice
- Sparingly use almond milk or soy milk
- Sparingly use whole grain breads

Effective diet approaches

- Emphasize potatoes, sweet potatoes, brown rice, quinoa, black beans, kidney beans, lentils, pinto beans, and chickpeas
- Broccoli, carrots, kale, cauliflower, lettuce, squash, corn, green peas
- Bananas, blueberries, oranges, strawberries

Effective diet approaches

- Other diets with short-term success
- NOOM
- Low calorie diet with cognitive behavioral therapy
- Lengthen time of eating
- Half diet
- Halve the portions normally eaten
- When weight loss plateaus, halve the portions once again
- Avoid white at night
- No food after 6pm
- Avoid potatoes, rice, white bread, sugar

Effective diet approaches

- Weight Watchers
- Low calorie diet
- My Fitness Pal
- Low calorie diet
- F factor
- High fiber, low calorie diet
- Not for those on low carbohydrate diets
- Adkins/South Beach/Keto
- Constipation, hydration common
- Intermittent Fasting

Drug use in associated disorders

- Not associated with weight gain:
- Lamotrigine, phenytoin, and carbamazepine
- Bupoprion
- Carvedilol
- Ranitidine
- Metformin, GLP1, DD4, and SGLT2
- Sulfonylureas are associated with weight gain

Drug use in diabetes mellitus type 2

- GLP1 agonist
- Effective in inducing and sustaining weight loss
- 5-10% weight loss independent of glycemic control
- Liraglutide is a weekly subcutaneous injection
- Not for use in MEN2
- Semaglutide as daily subcutaneous injection more effective than pill
- Diminishes gastric emptying
- Neuroprotective
- Diminishes incidence of adverse cardiovascular events

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Drug use in diabetes mellitus type 2

- SGLT2
- Works in proximal tubule
- Block Na^+-glucose transport protein as well as Na^+-HCO_3^- transport.
- May lead to acidosis.
- Promotes osmotic diuresis (rapid weight loss)
- Diminishes hyperfiltration
- Dafagliflozin if established coronary artery disease, diminished ejection fraction
- Canagliflozin if renal disease, heart failure, and preserved ejection fraction as well

Drug use in diabetes mellitus type 2

- PPARy (glitazones) and SGLT2 diminish LDL clearance
- GLP1 and SGLT2 associated with improved HbA_{1c} and blood pressure control

Bariatric surgery

- Decrease all cause incidence of mortality
- Criteria:
- BMI >40 or 45 kg (100 pound) overweight
- BMI >35 if co-morbidities
- BMI 30-35 if with diabetes despite optimal medication control