Palliating Cancer-Associated Anorexia/Cachexia: Sated but not Satisfied

Palliative Care ECHO Session

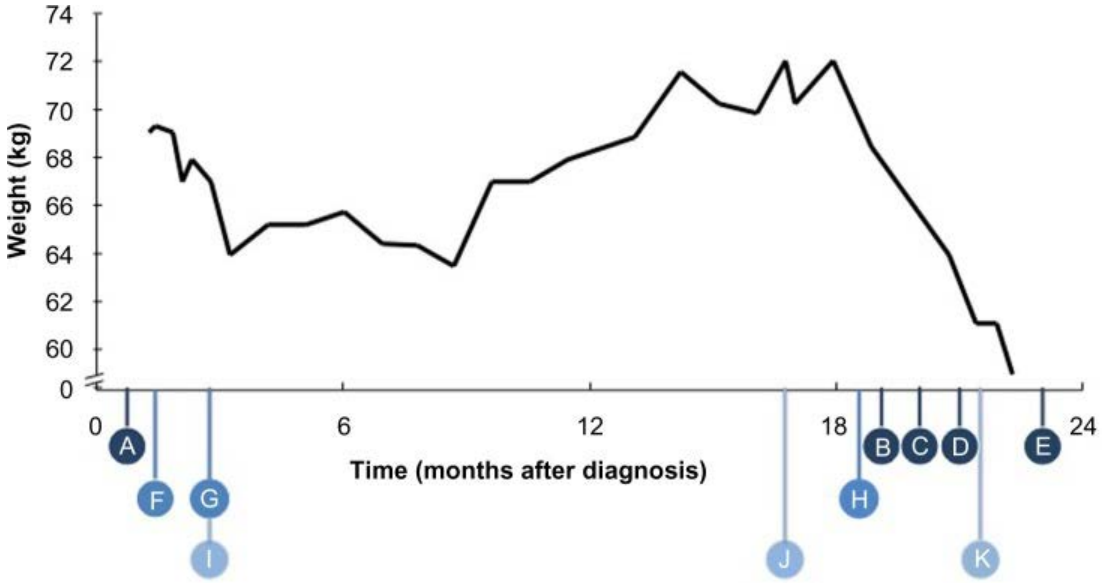
5/24/23

Learning Objectives

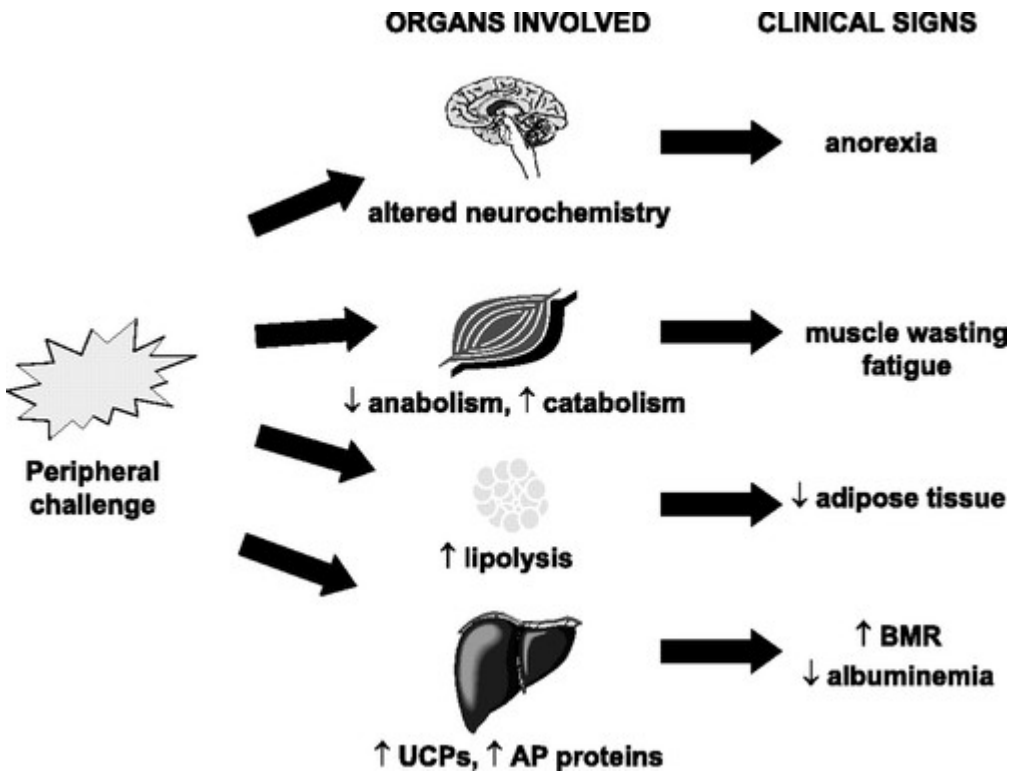
- Describe the pathophysiology of anorexia in cancer patients
- Employ tools and assessment scales for diagnosing cancer-associated anorexia/cachexia
- Understand and apply pharmacotherapy options for anorexia/cachexia in cancer patients
- Instruct on non-pharmacological interventions to address anorexia/cachexia.

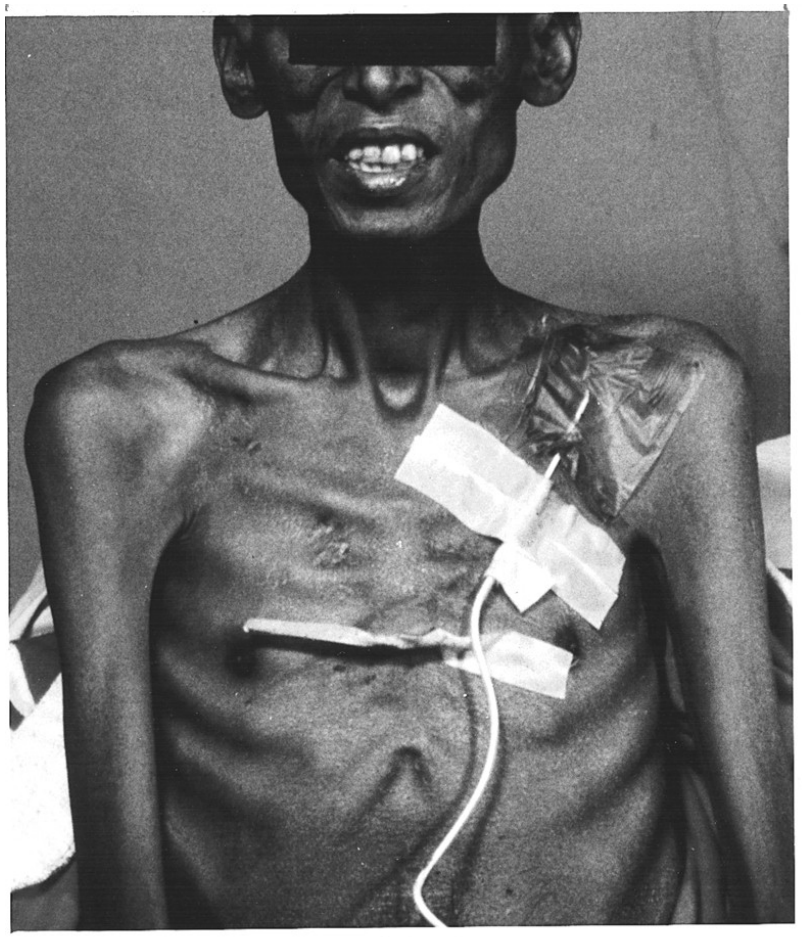
Case Example

- 63 M, metastatic pancreatic adenocarcinoma.
- Clinical Course: weight loss c/b gastric outlet obstruction, protein-calorie malnutrition.
  - s/p PEG-J. On FOLFOX.
- Weight loss: affected by clinical events, medical intervention, and surgical intervention.
- Potential correlations among growth of metastatic tumor burden and cachexia.



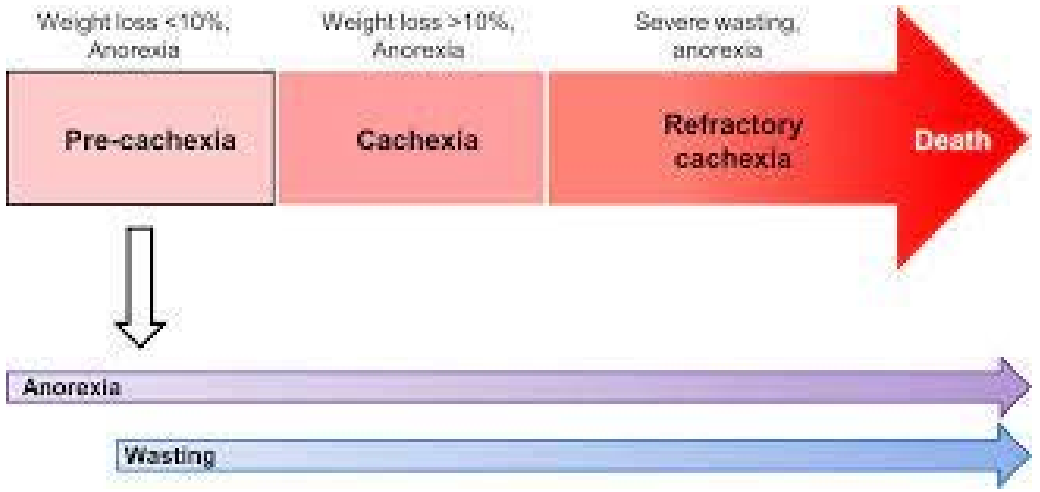
Introduction





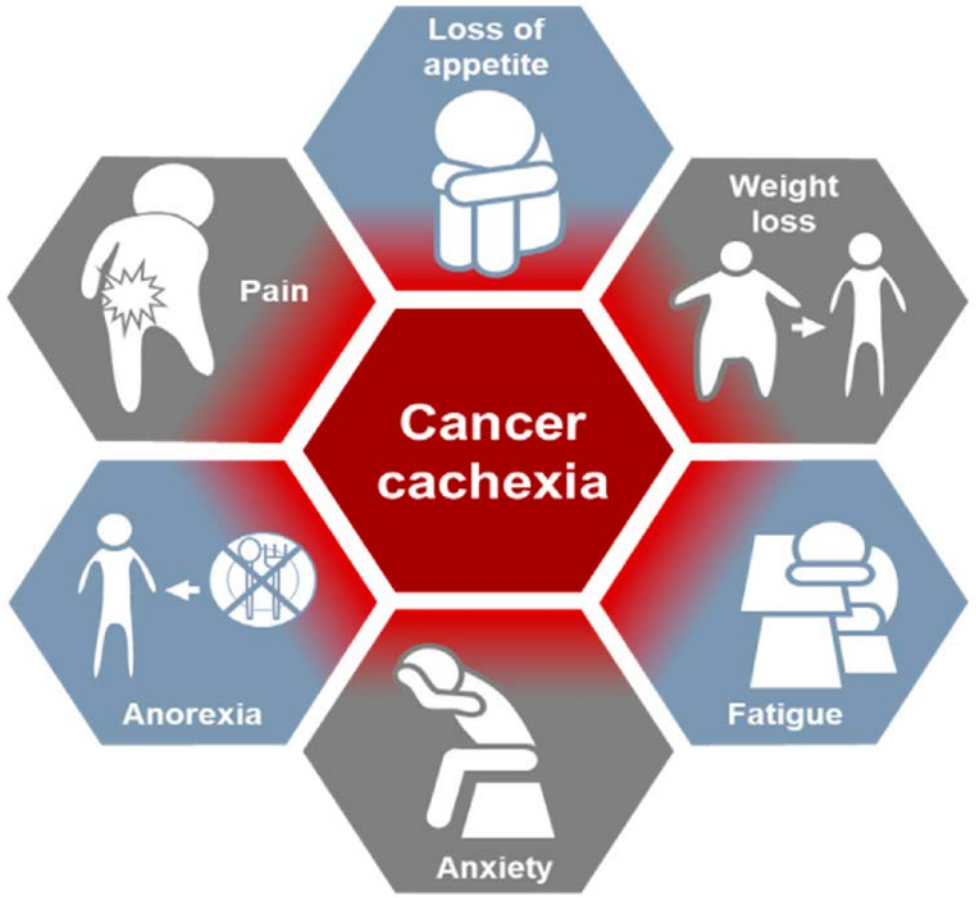
Introduction

- Anorexia: loss of desire to eat→ reduced food intake.
- **Prevalence**: among patients with advanced cancer--39% -81.5% for weight loss and 30%-80% for anorexia.
- Degree of weight loss significantly affects prognosis or performance status.
- 2.5 kg weight change over 6–8 weeks→ significant changes in performance status.
- Death at 30% weight loss.

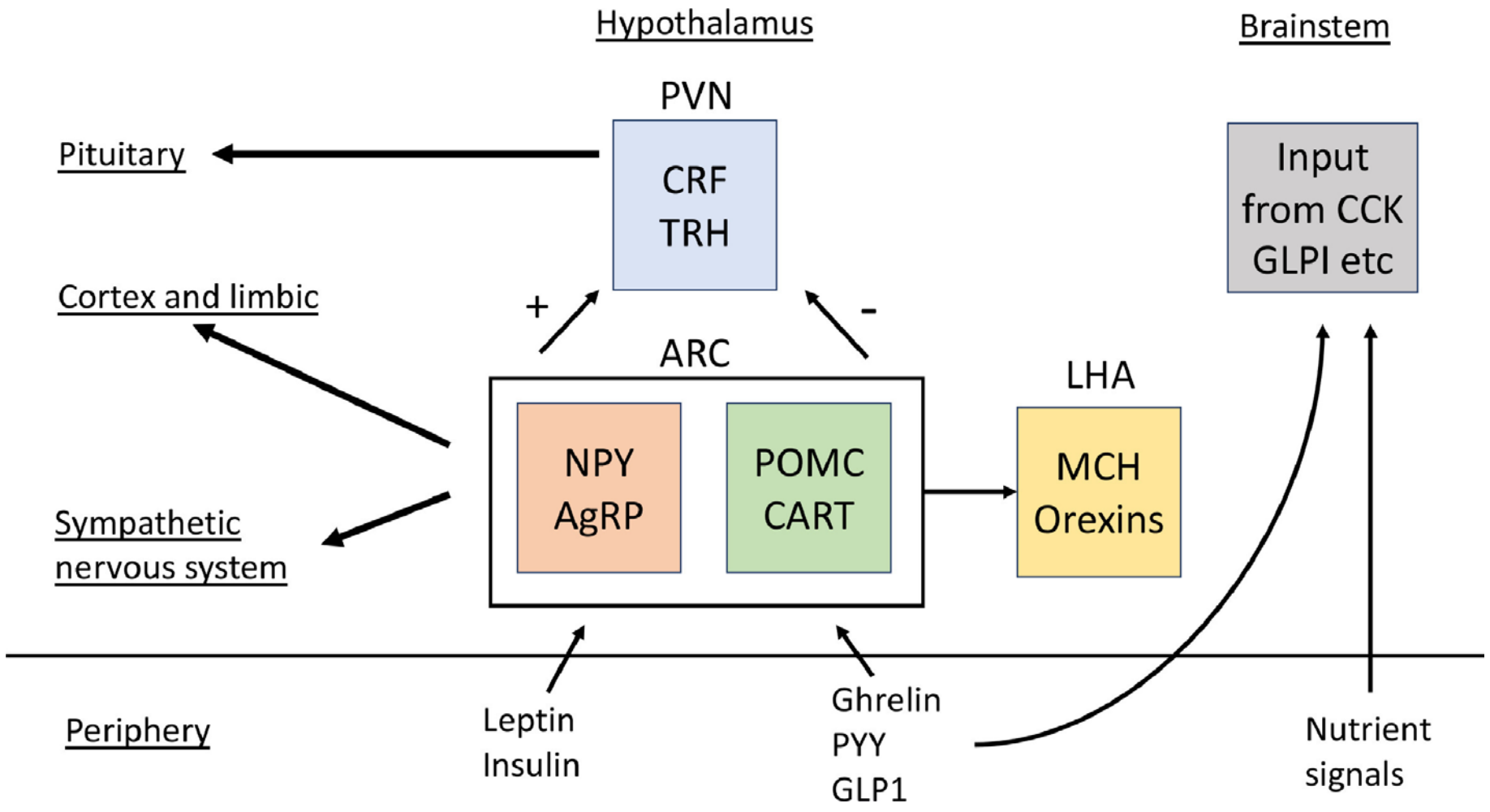


Introduction

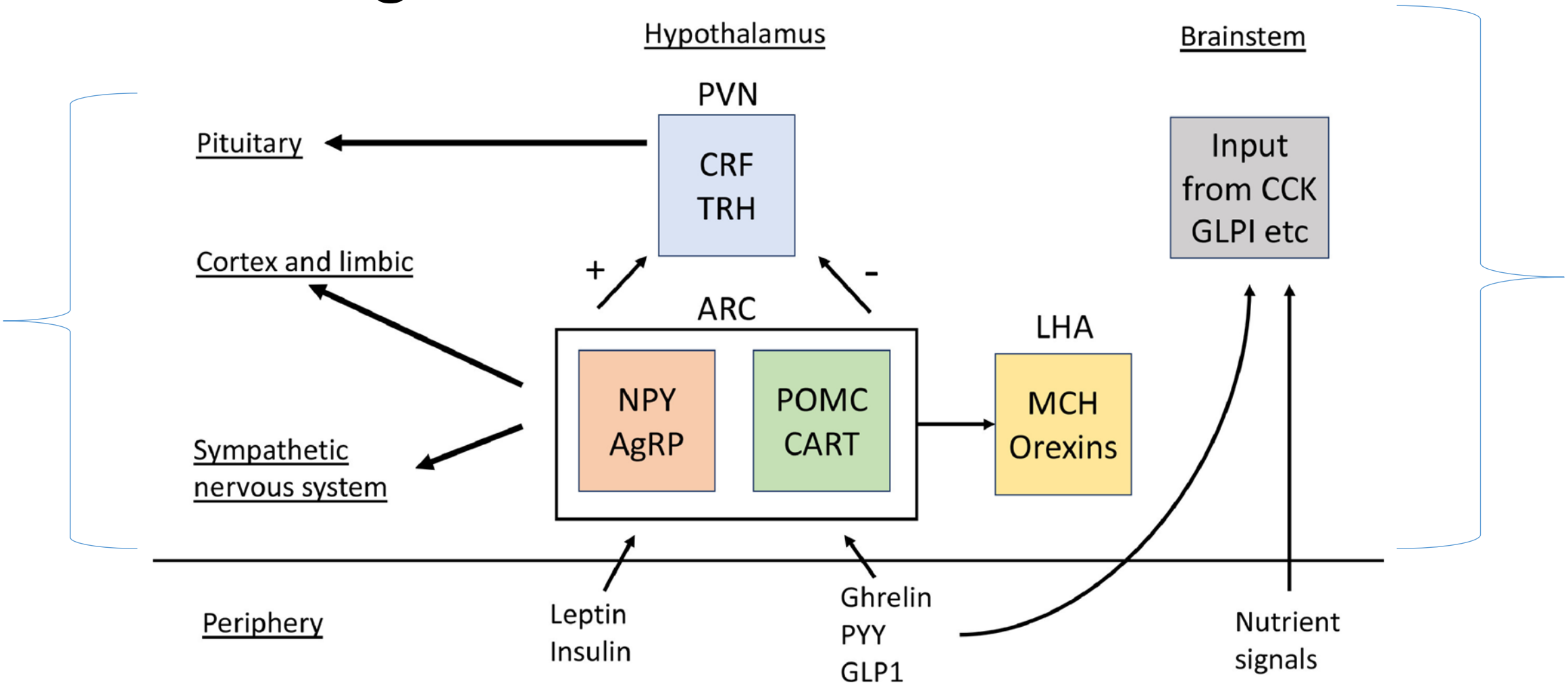
- Anorexia components: nausea, altered taste sensation, swallowing difficulties, or depression.
- Failure of nutritional supplementation to reverse weight loss→ cancer cachexia.
- Loss of appetite reported to be most important factors in physical and psychological aspects of quality of life (QOL).
- Loss of appetite and resultant decrease in energy intake→ loss associated with cancer malnutrition and cachexia.
- Lack of appetite impacts QOL, overall symptom distress.



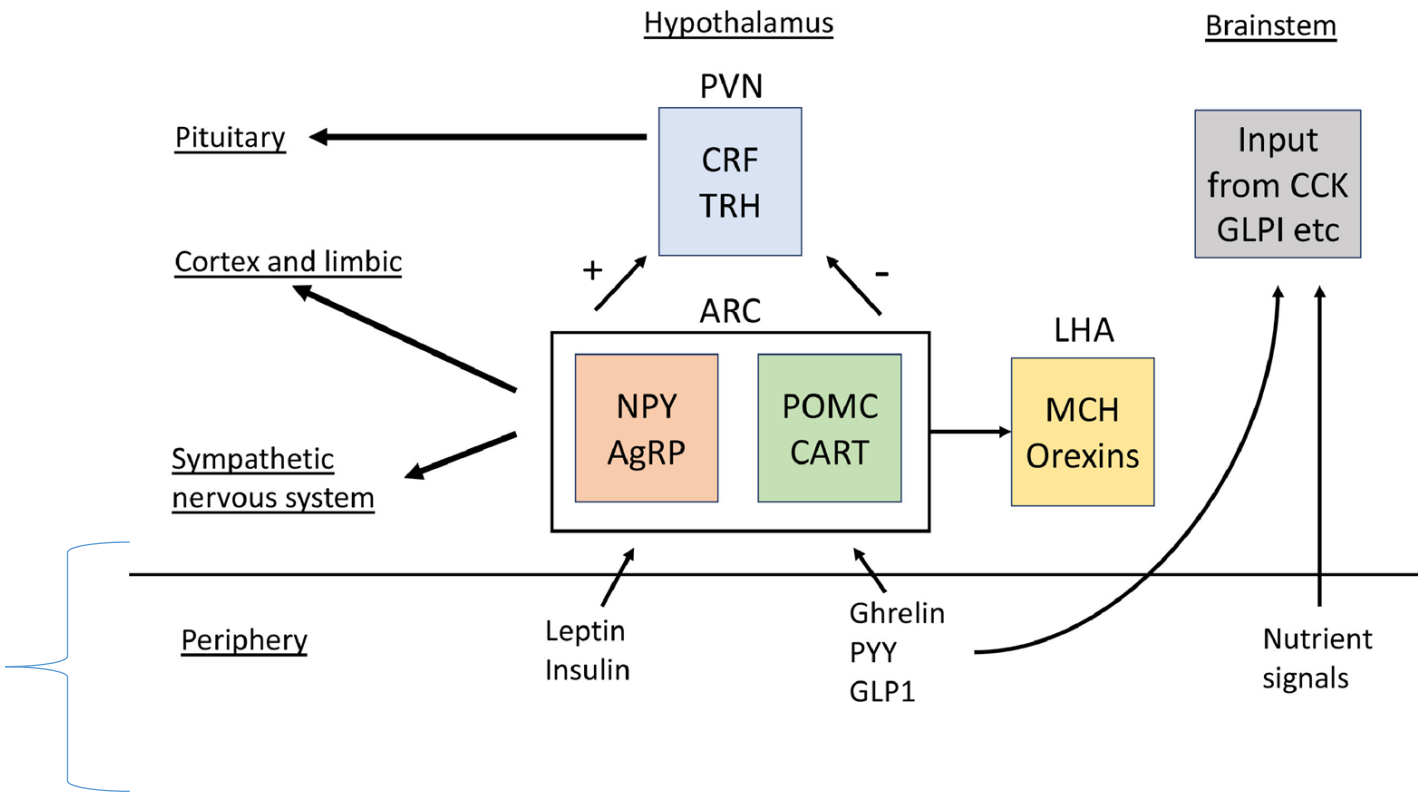
Physiology of appetite

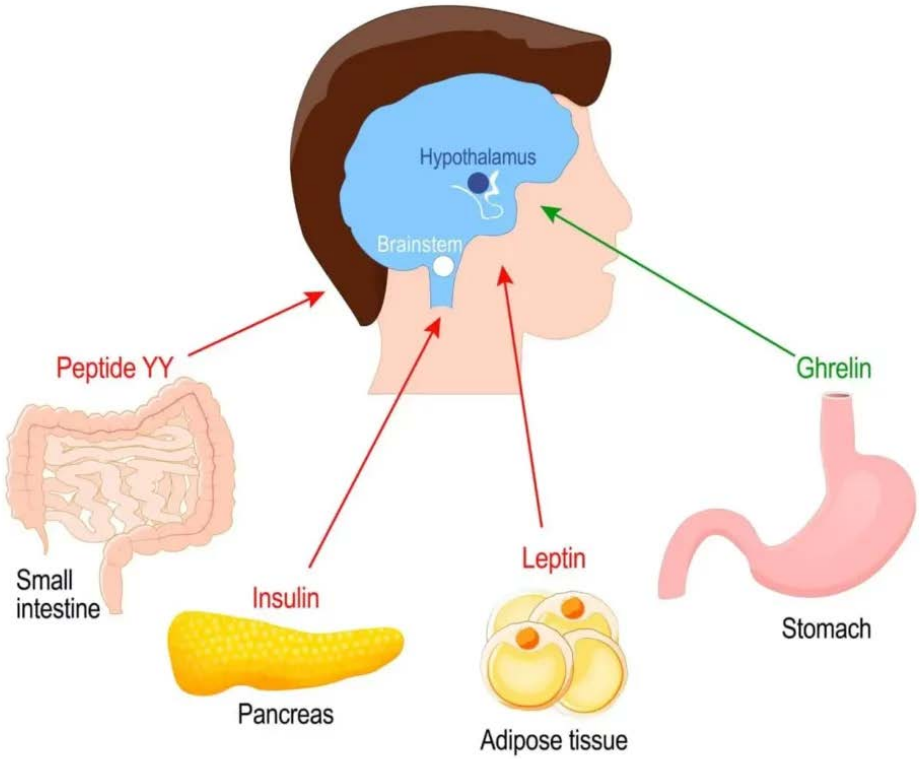


Central Regulation

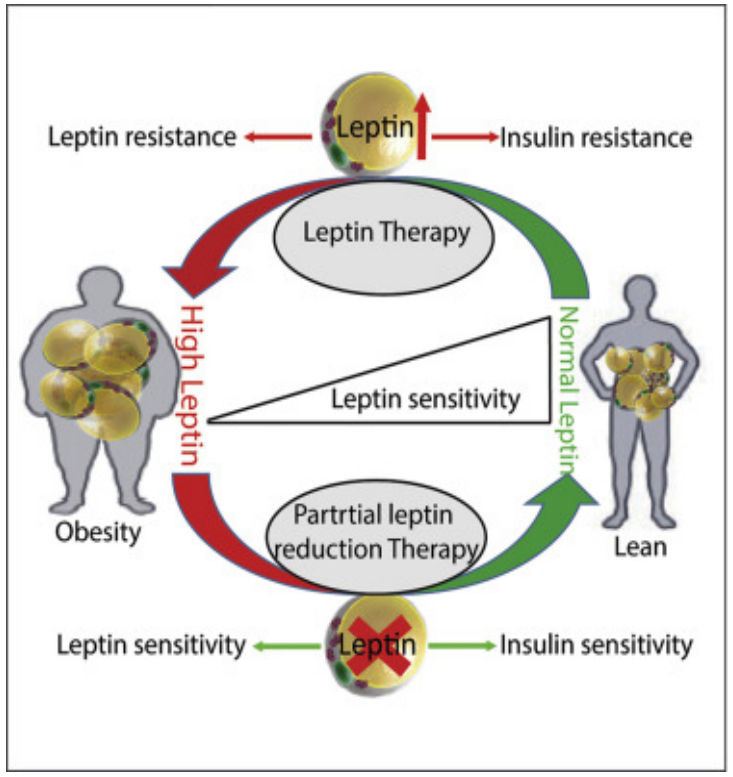


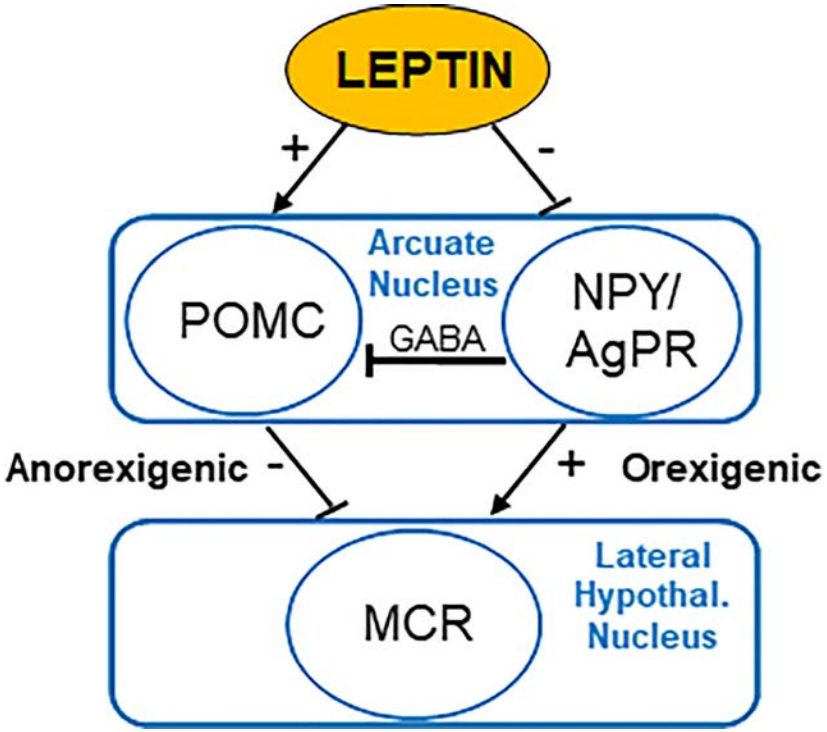
Peripheral Regulation





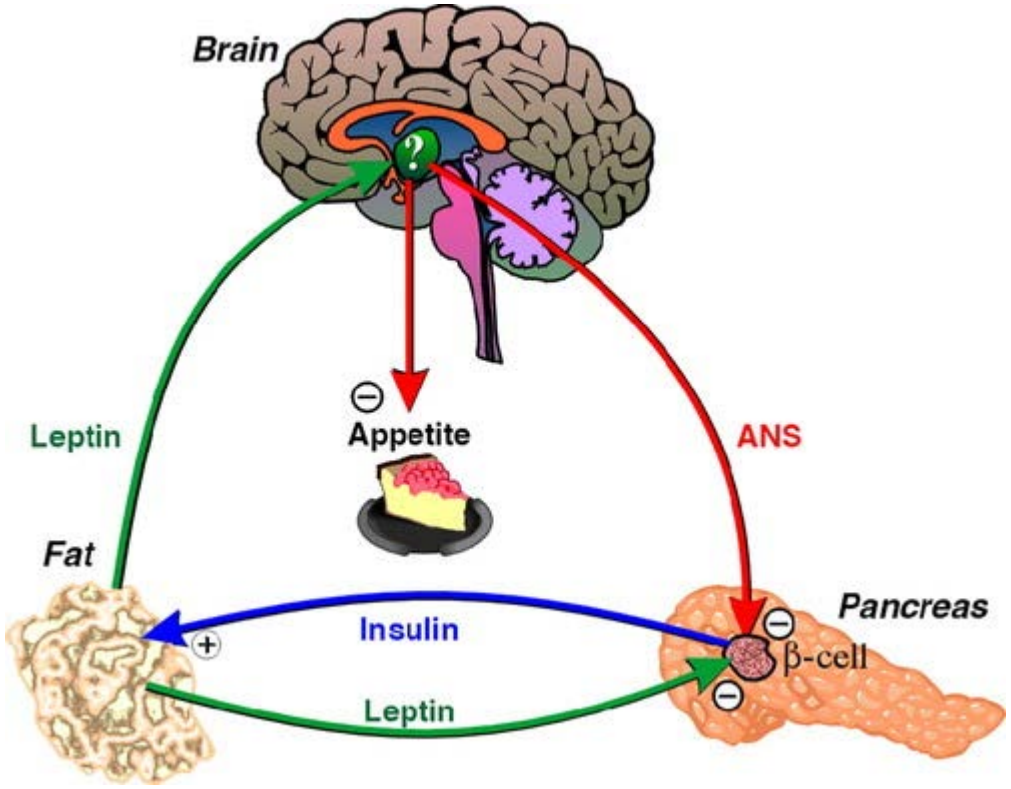
Peripheral Regulation: Leptin





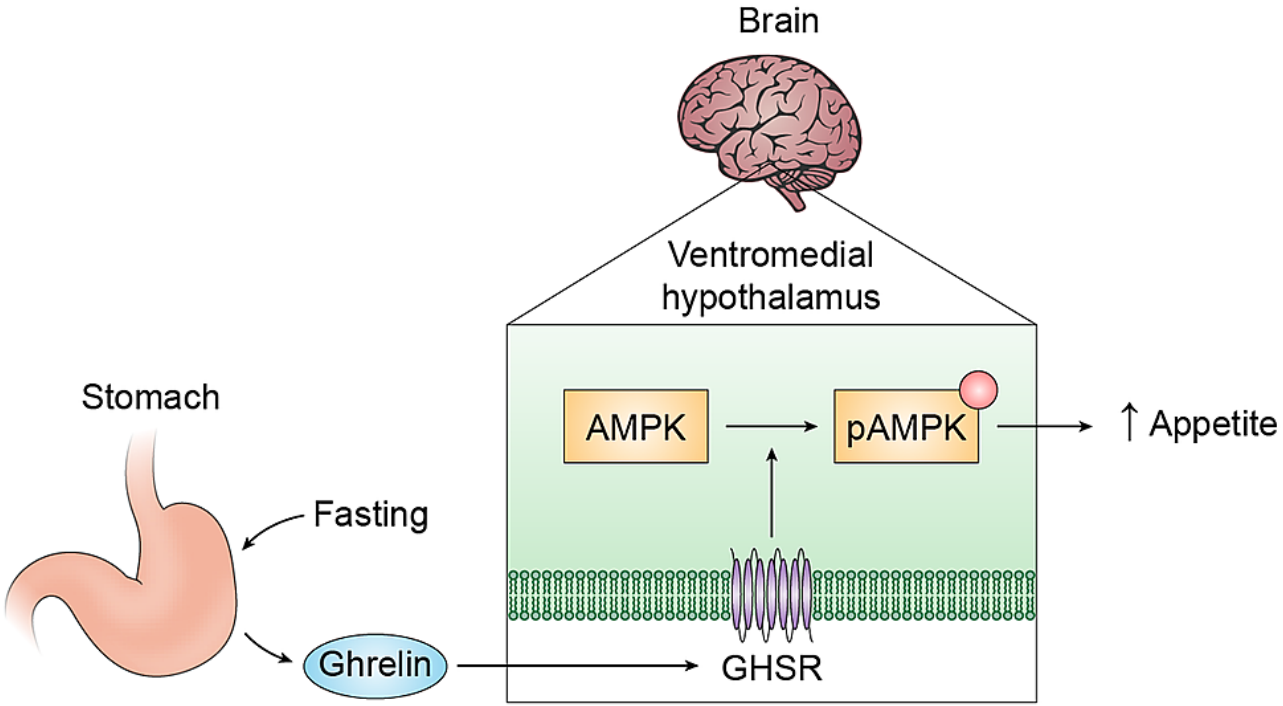
Peripheral Regulation: Insulin

- Lipostatic role similar to leptin
- Central effects on food intake and energy homeostasis less efficient.
- Circulates at levels proportional to fat mass; crosses blood–brain barrier.
- Insulin receptors expressed by brain neurons involved in energy intake.
- Exerts effects by inhibiting NPY/AgRP co-expressing neurons.
- Stimulates synthesis and secretion of leptin from white adipose tissues through feedback loop→ **adipo-insular axis.**



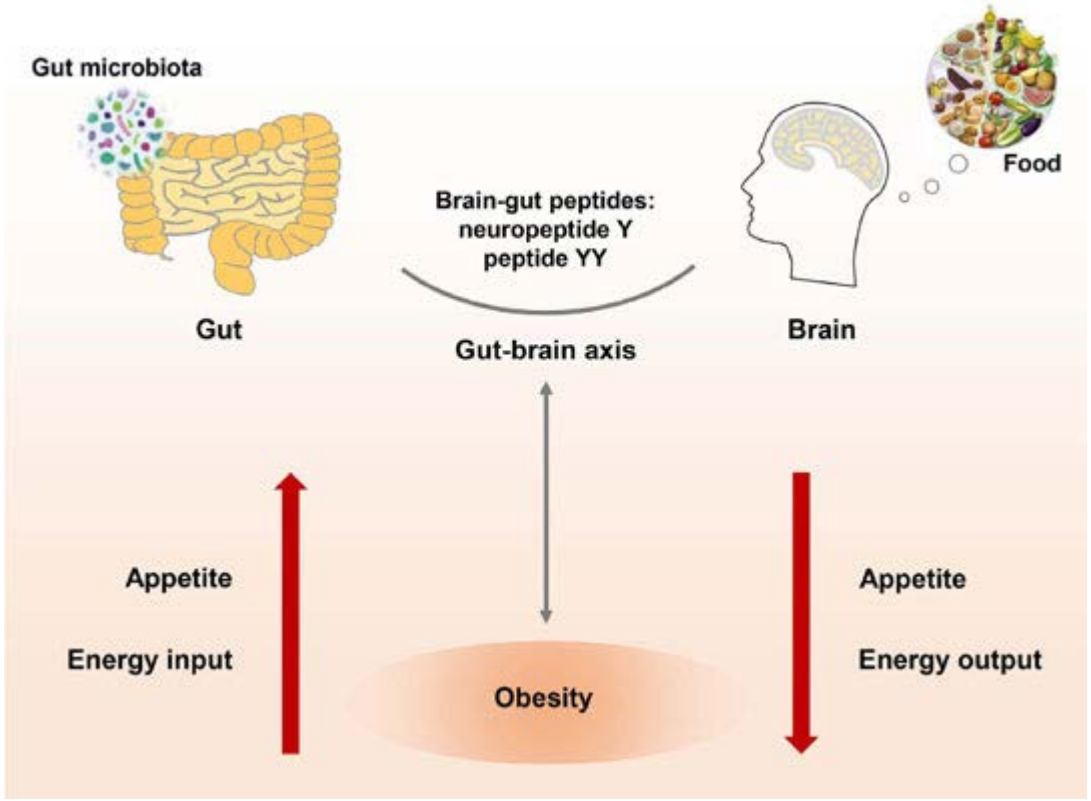
Peripheral Regulation: Ghrelin

- Synthesized by stomach [mostly]
- Endogenous ligand for growth hormone secretagogue receptor (GHSR)→expressed in brain stem and hypothalamic nuclei, including ARC.
- Expression of GHSR demonstrated in NPY neurons, and NPY and AgRP antagonists abolish ghrelin-induced feeding.



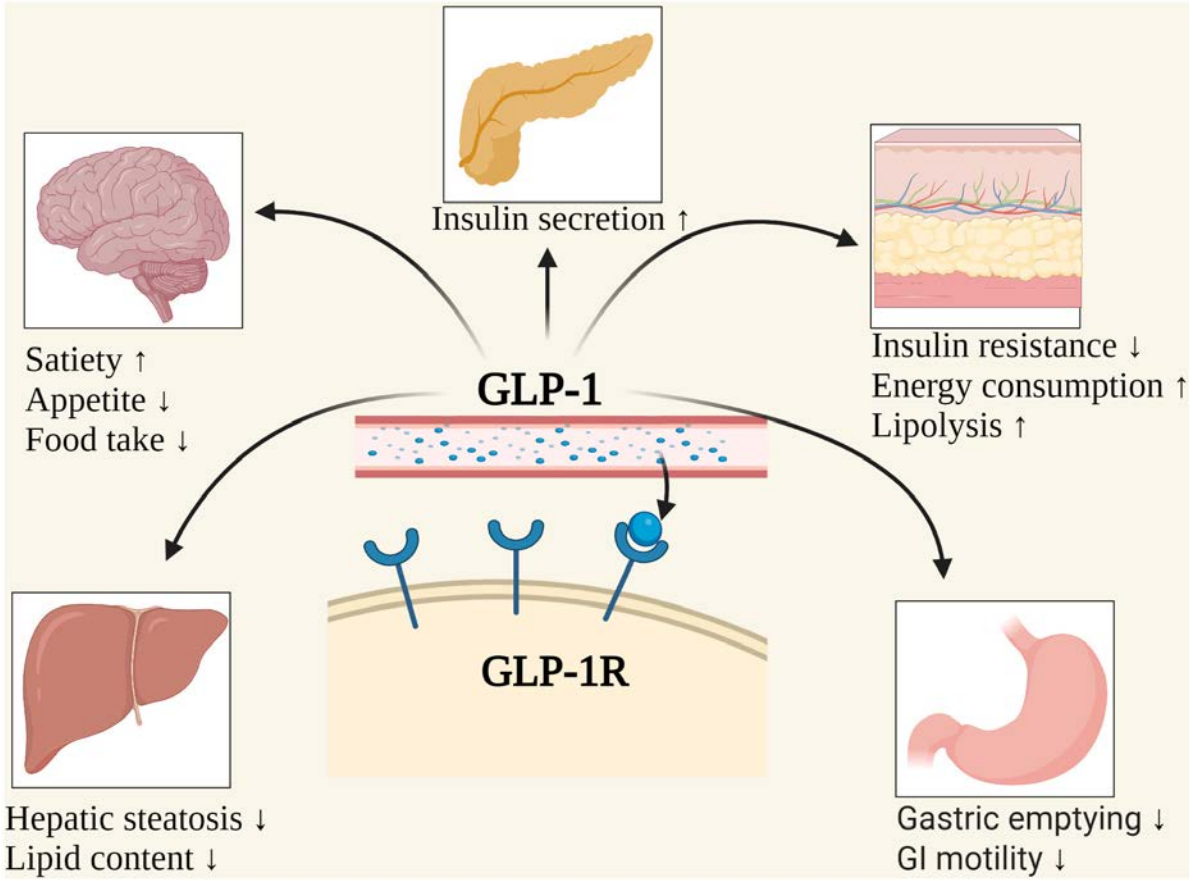
Peripheral Regulation: Peptide YY

- Produced by l-cells of gastrointestinal tract, esp. distal intestine
- Released into circulation after meals in proportion to calories ingested.
- Peripherally administered PYY3−36 exerts food intake–inhibiting effects via Y family of G protein-coupled receptors [preferentiality for Y2 receptor]
- Inhibition of food intake in response to administration of selective Y2 agonist, and attenuation of inhibitory effect in response to Y2 antagonists

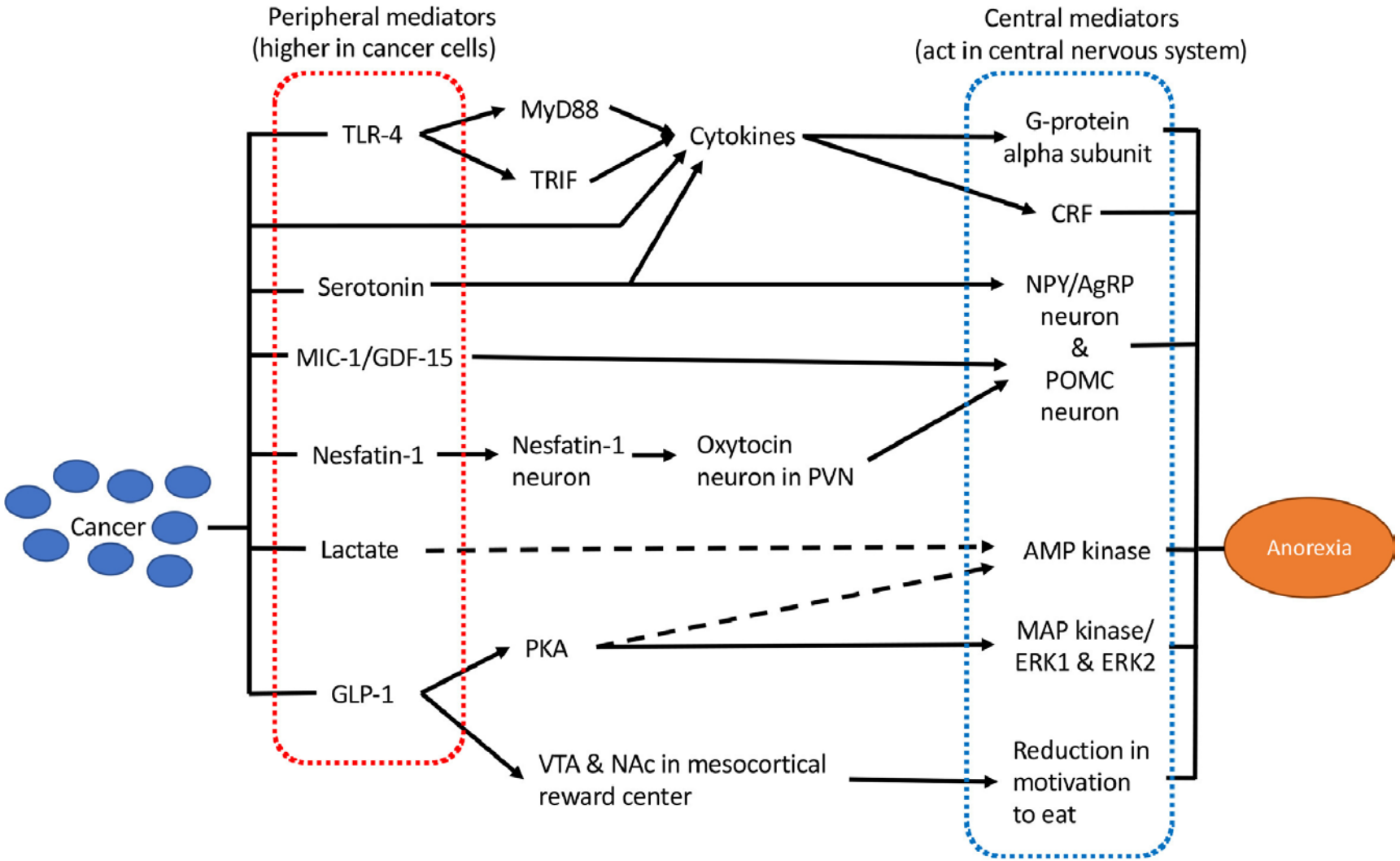


Peripheral Regulation: Glucagon-like peptide-1

- Produced by processing of proglucagon gene in gut and brain.
- Active form→ GLP-1(7–36) amide.
- Released into circulation after eating in proportion to amount of food consumed.
- Acts on pancreas to release insulin.
- Peripherally administered GLP-1 has been shown to exert anorexigenic effects, with other possible influences on food intake being linked to reduction in gastric emptying and suppression of gastric acid secretion.
- Both central and peripheral GLP-1 or GLP-1 receptor agonists enhance satiety, reduce food intake, and promote weight loss.

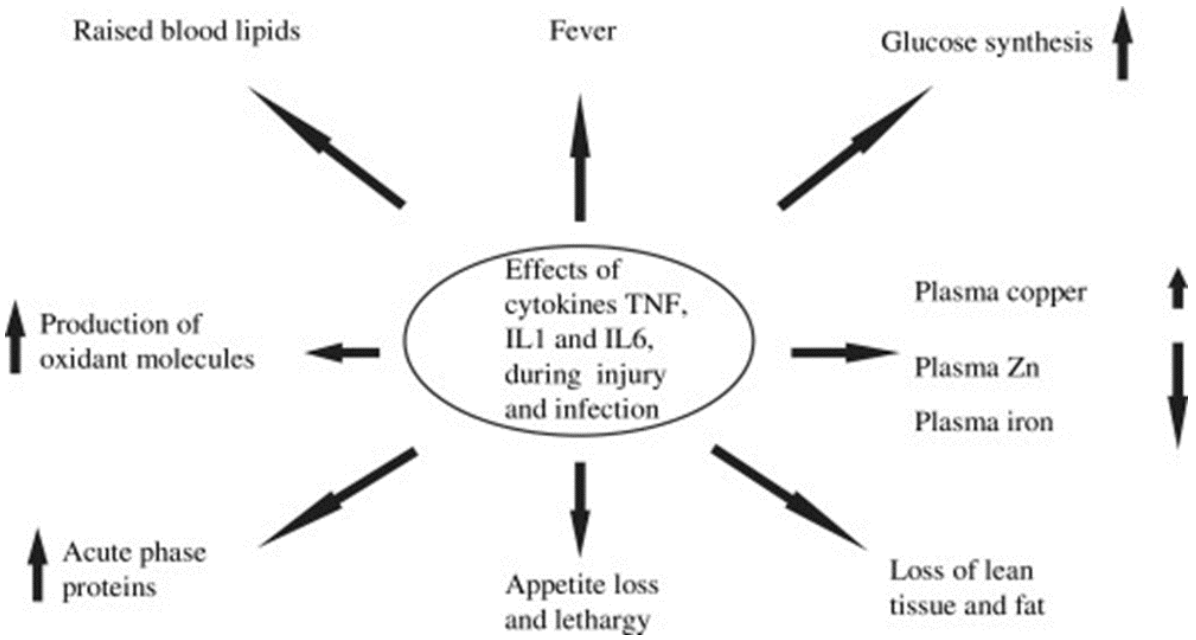


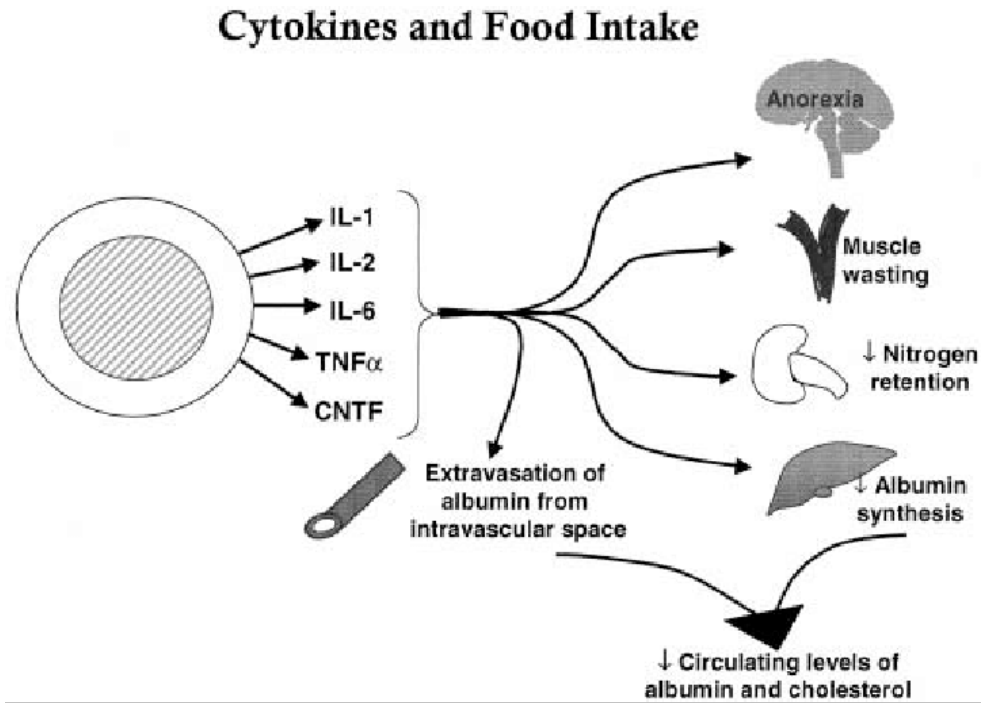
Pathophysiology of anorexia



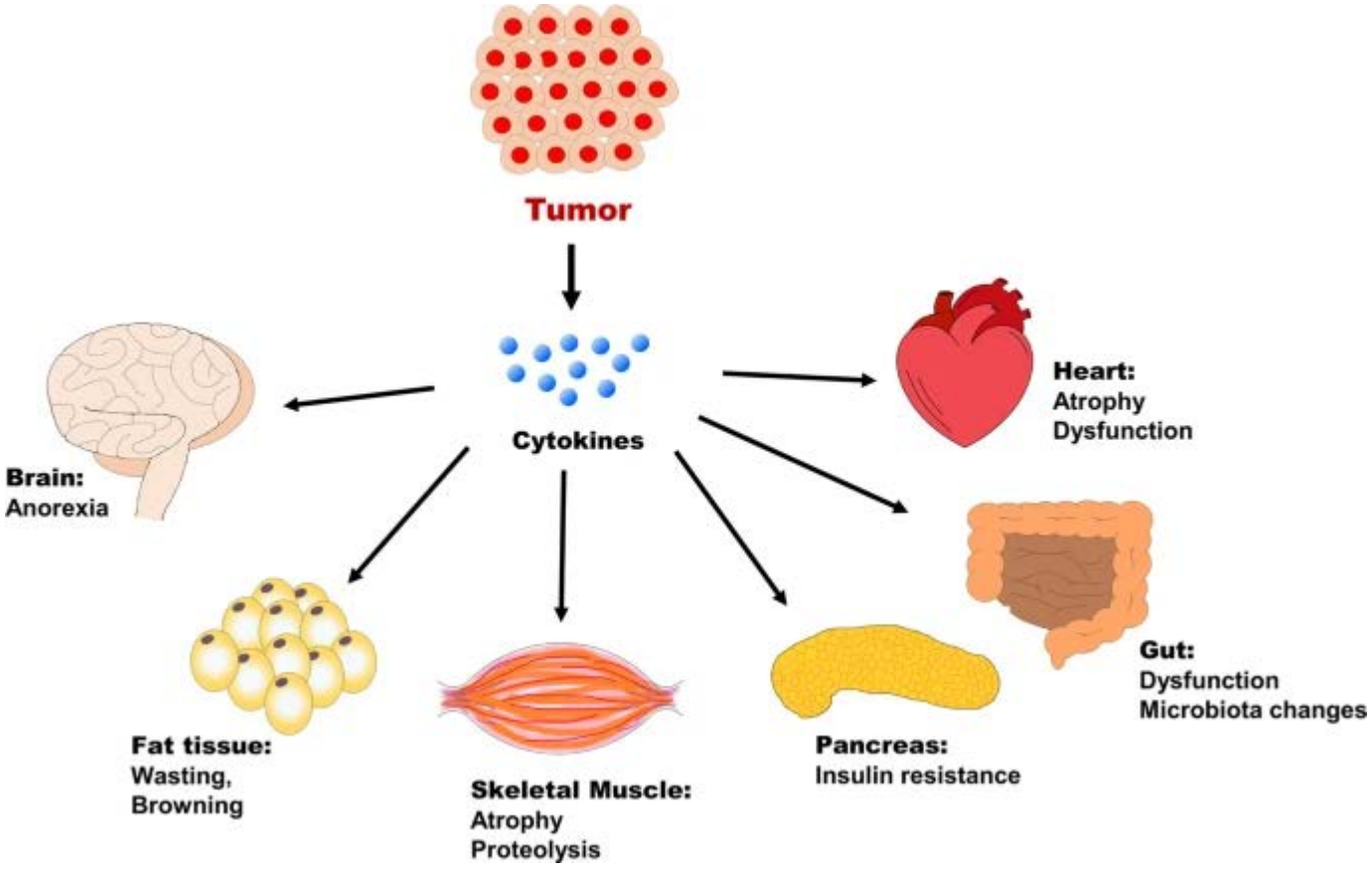
Note:
(dash line) = inhibiton
(continuous line) = stimulation

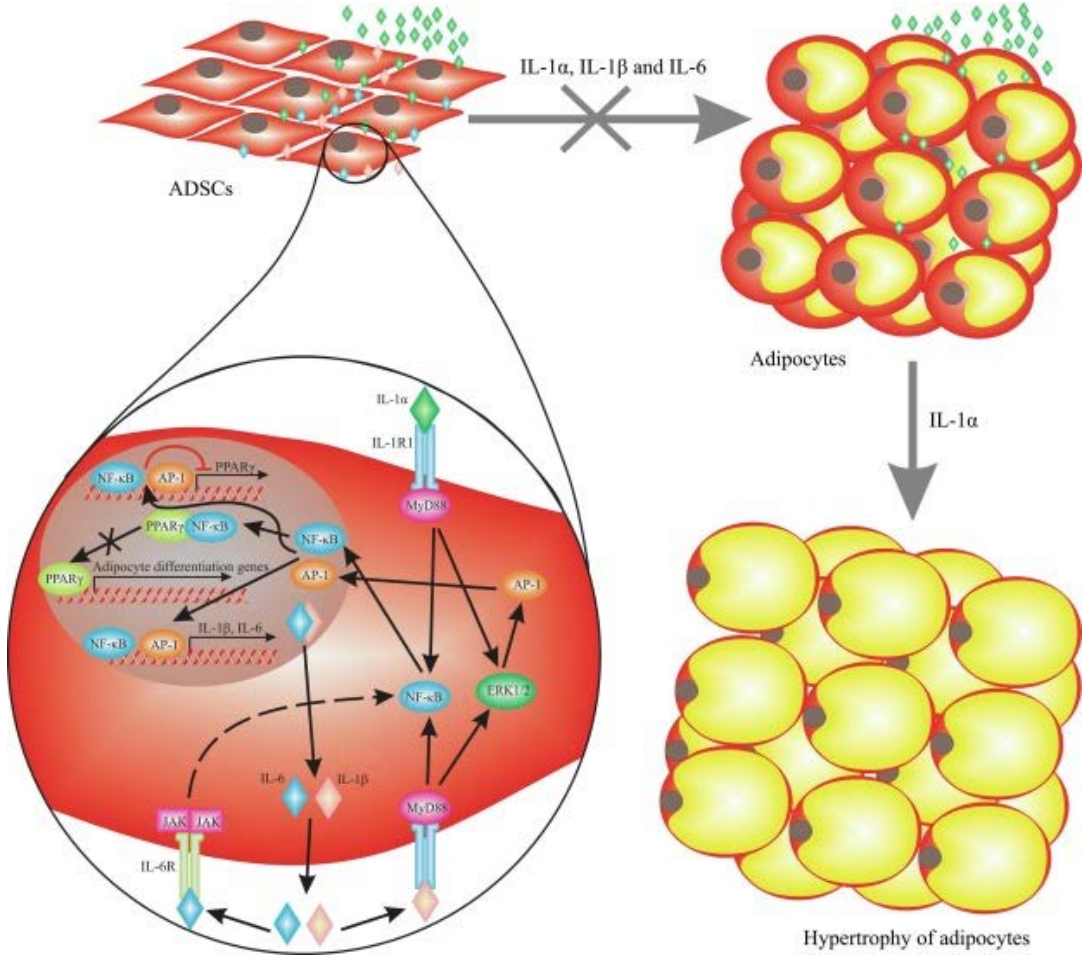
Cytokines


Raised blood lipids
Fever
Glucose synthesis
Effects of cytokines TNF, IL1 and IL6, during injury and infection
Production of oxidant molecules
Plasma copper
Plasma Zn
Plasma iron
Acute phase proteins
Appetite loss and lethargy
Loss of lean tissue and fat


Cytokines and Food Intake
Anorexia
IL-1
IL-2
IL-6
TNFα
CNTF
Muscle wasting
↓ Nitrogen retention
Extravasation of albumin from intravascular space
↓ Albumin synthesis
↓ Circulating levels of albumin and cholesterol

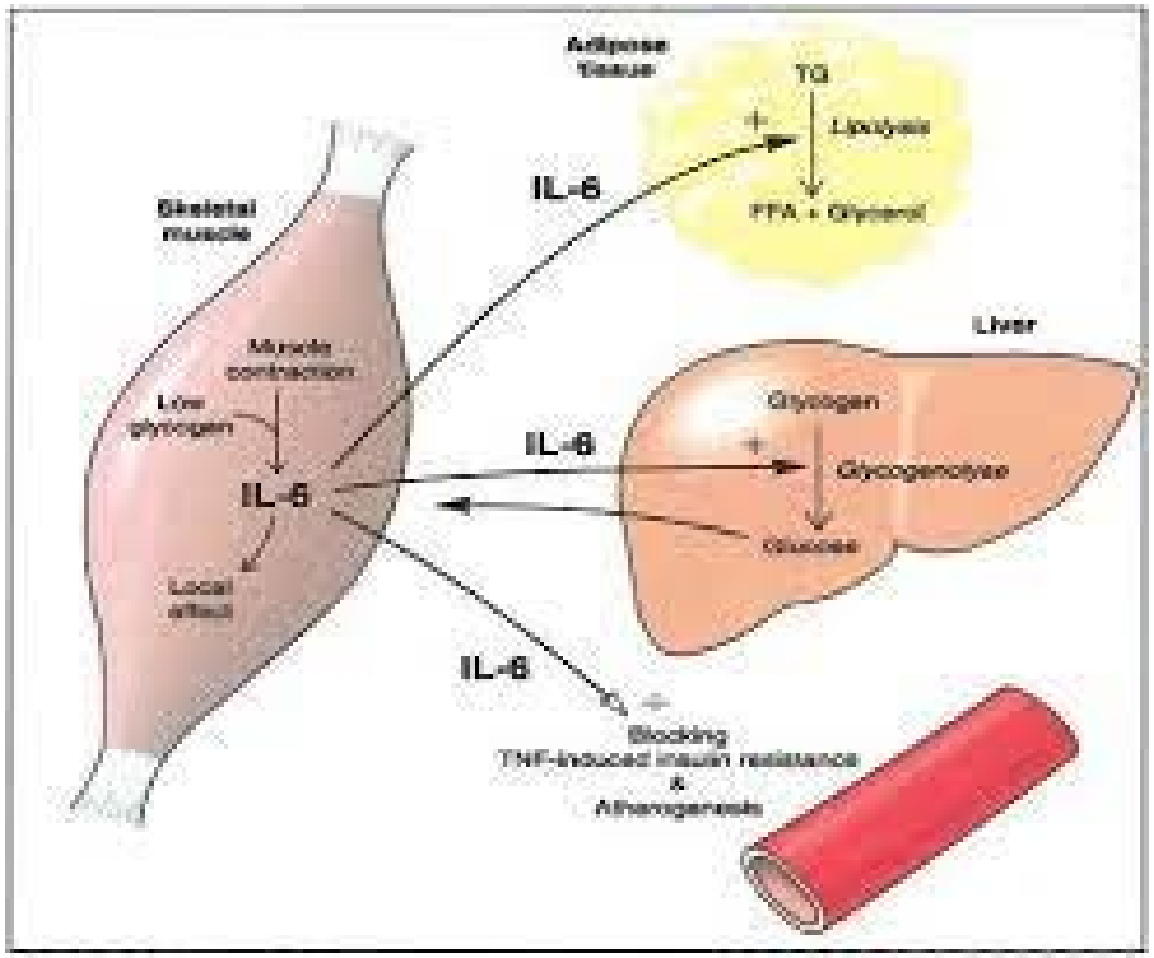
Cytokines: IL-1





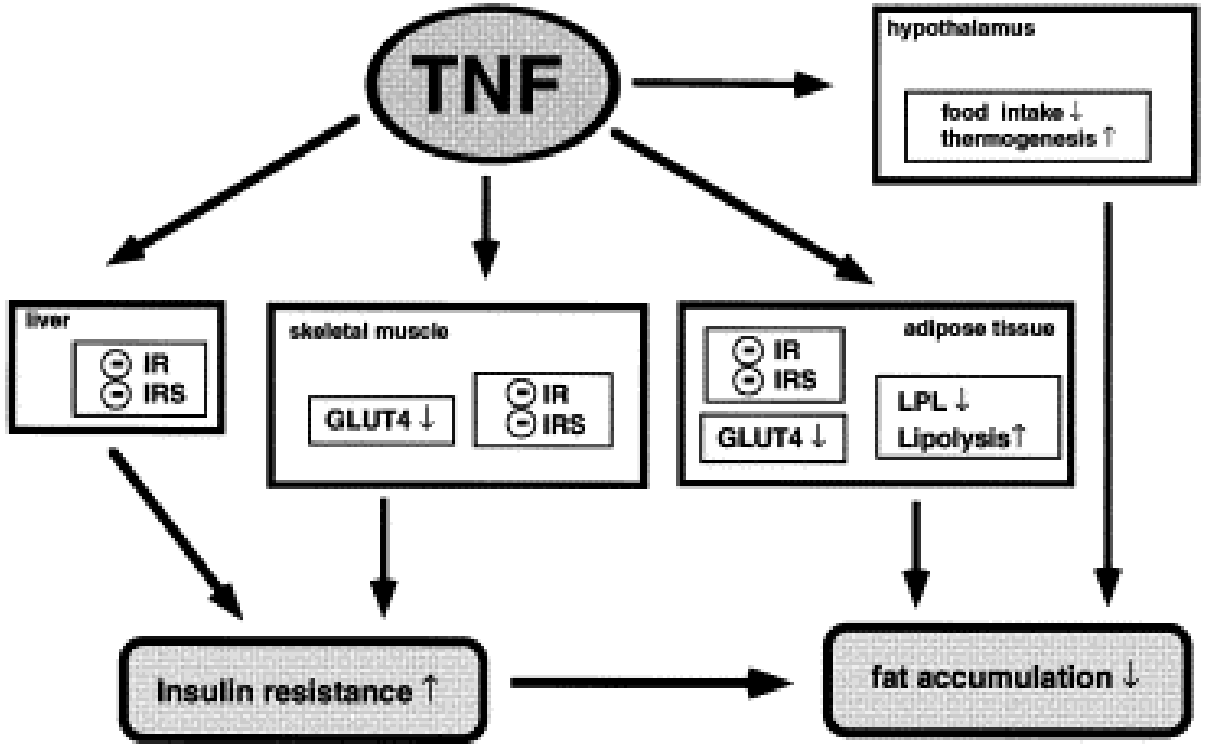
Cytokines: IL-6

- Contributes to development of cancer anorexia.
- Intraperitoneal injection led to reduction in both food intake and gastric emptying.
- Pharmacological disruption of CNS IL-6 biological activity associated with attenuation of anorexia and body weight loss.

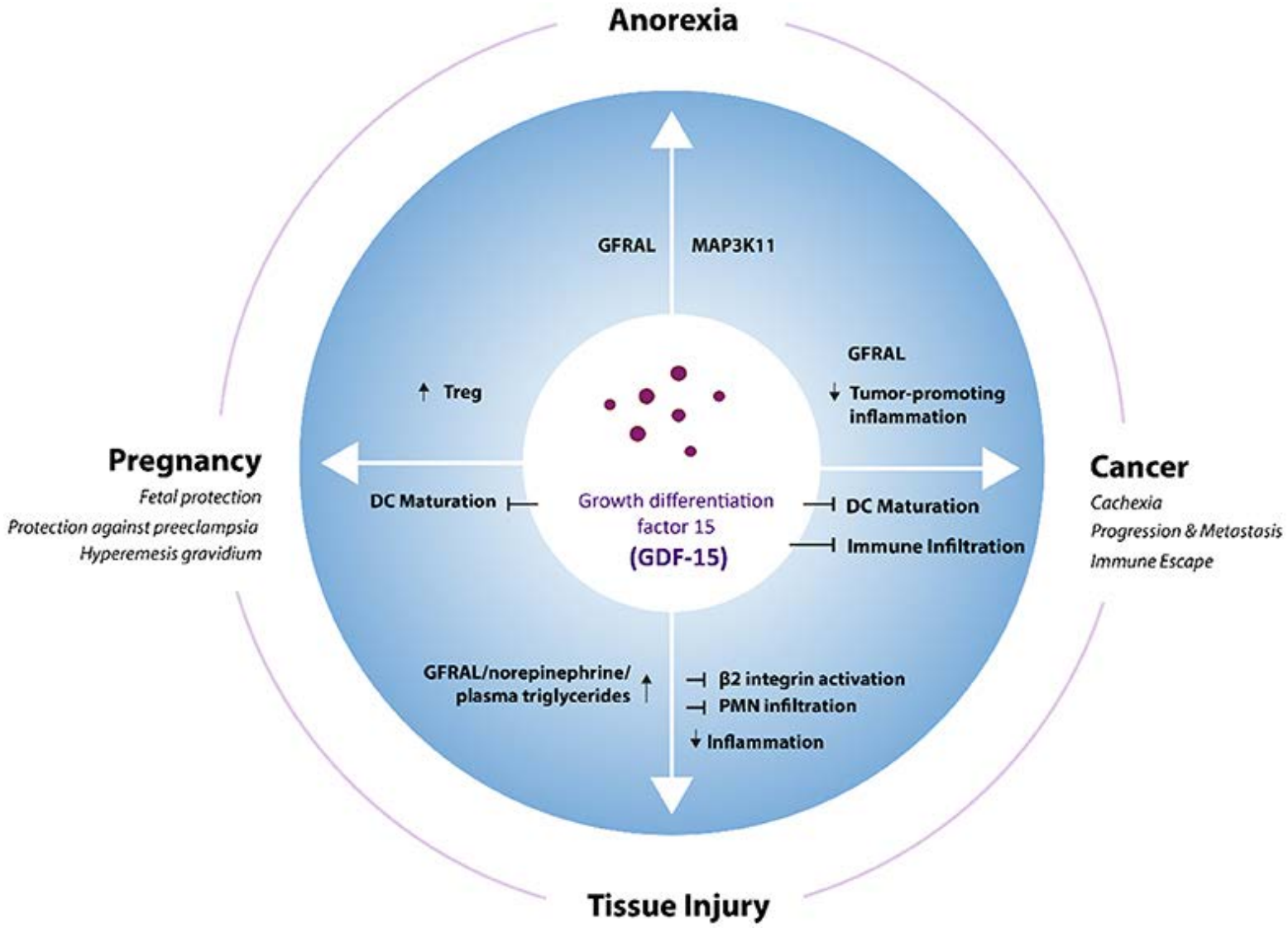


Cytokines: TNF-α

- Produced by monocyte, macrophages, and tumors.
- Reduction of food intake observed when TNF-α administered peripherally and centrally.
- TNF-α inhibitor injection→ shown to improve food intake in anorectic tumor-bearing rats.

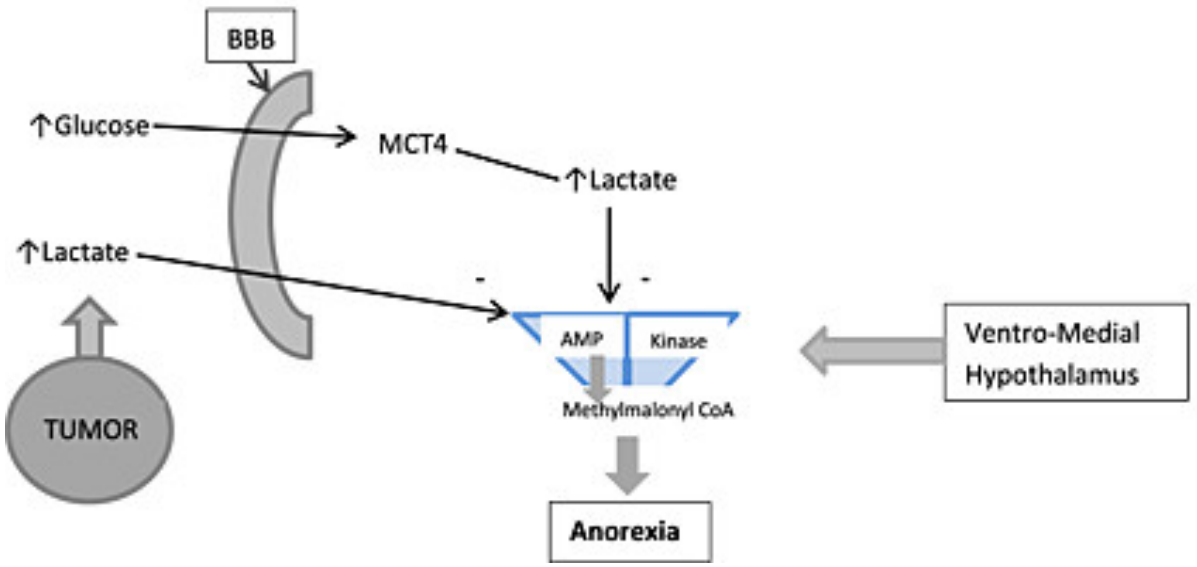


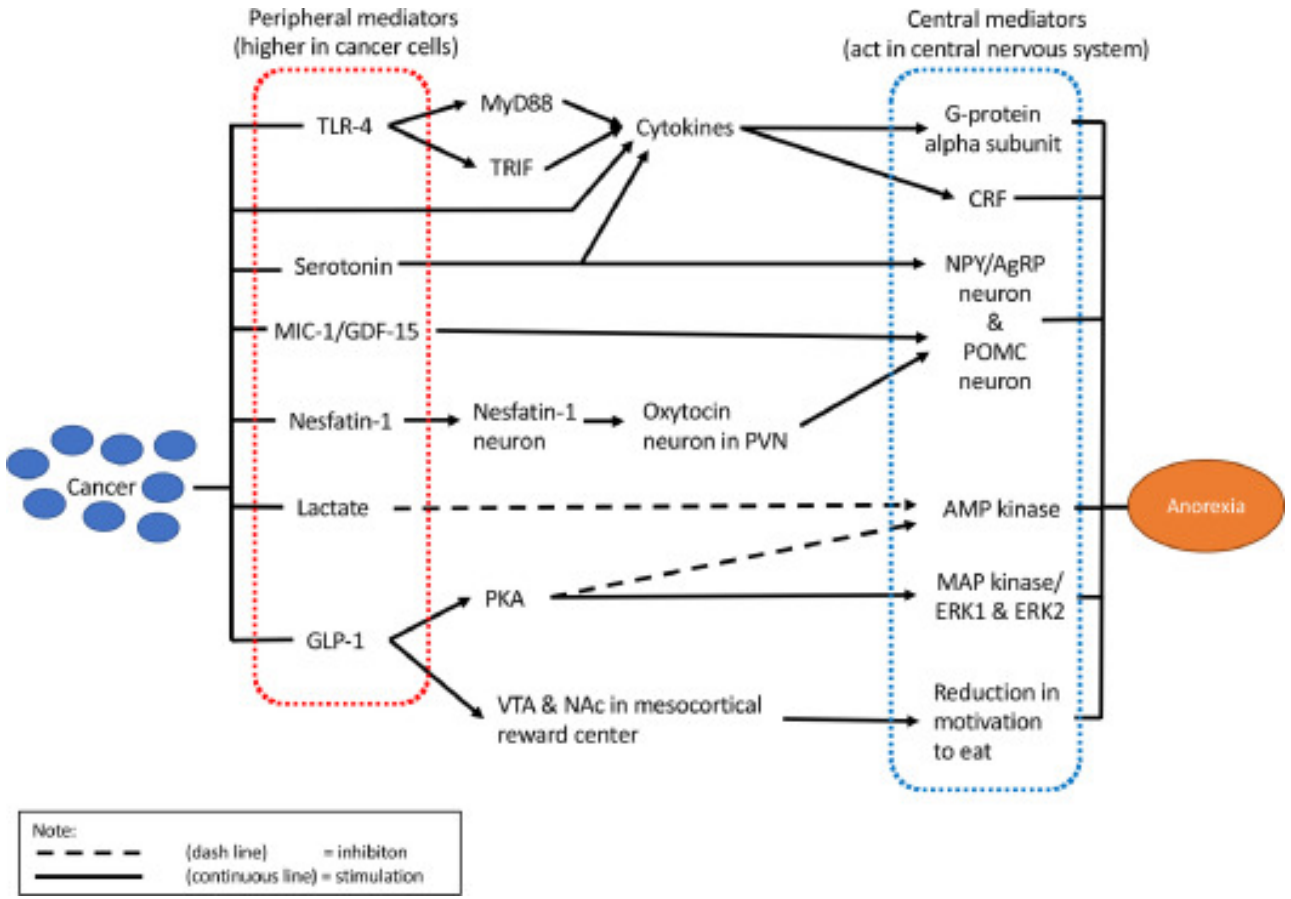
Macrophage inhibitory cytokine-1/growth and differentiation factor-15



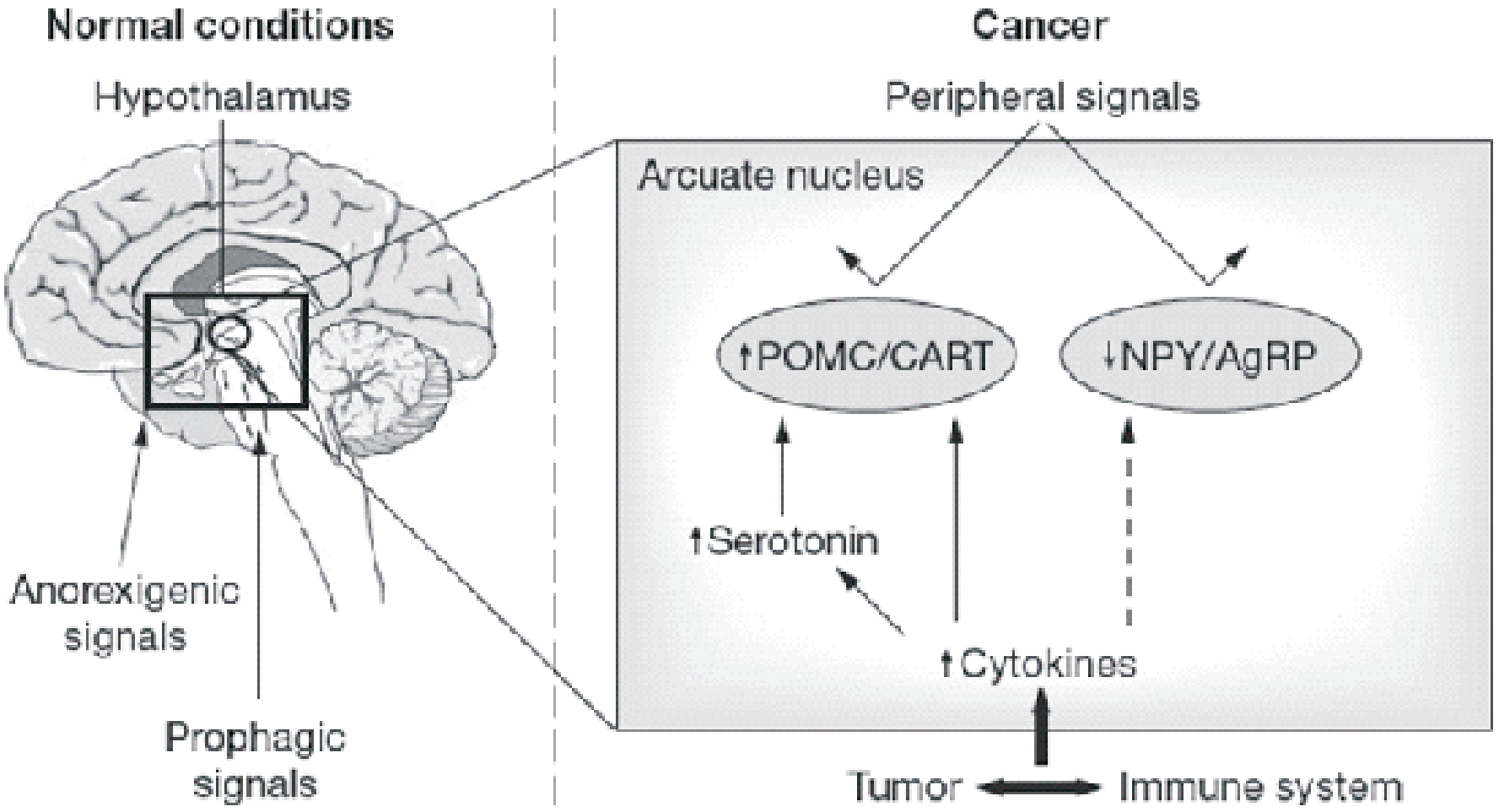
Lactate

↑ = Increased; - = inhibits; BBB = Blood Brain Barrier; MCT4 = Monocarboxylate transporter

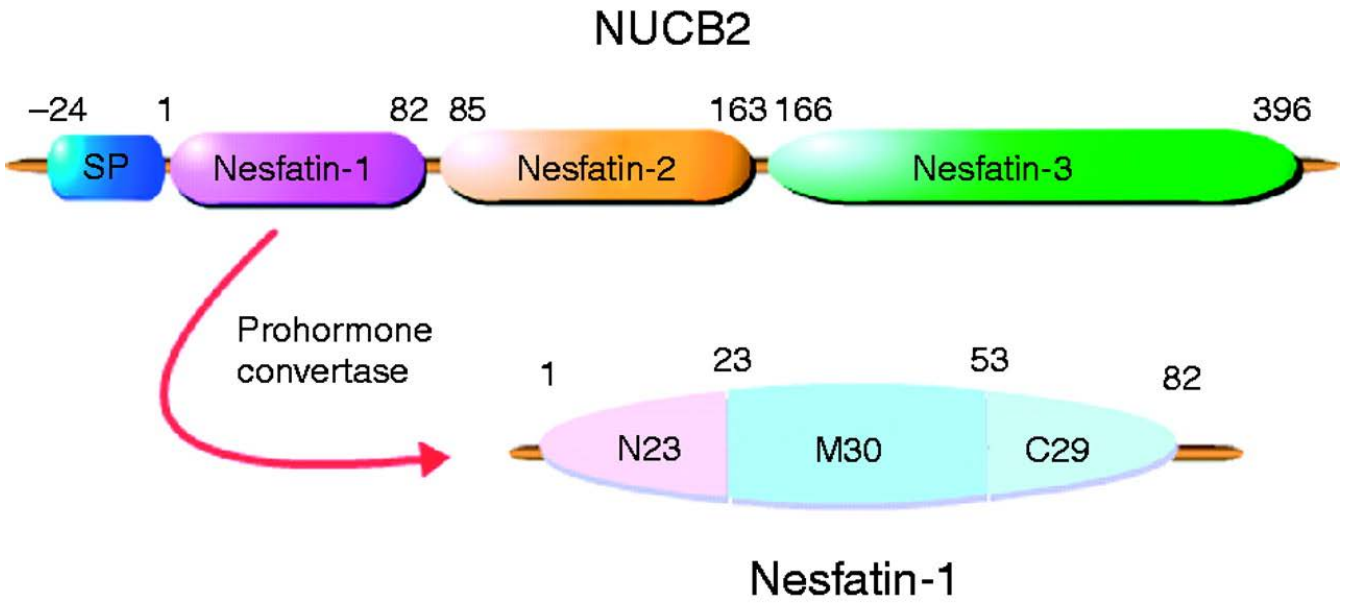




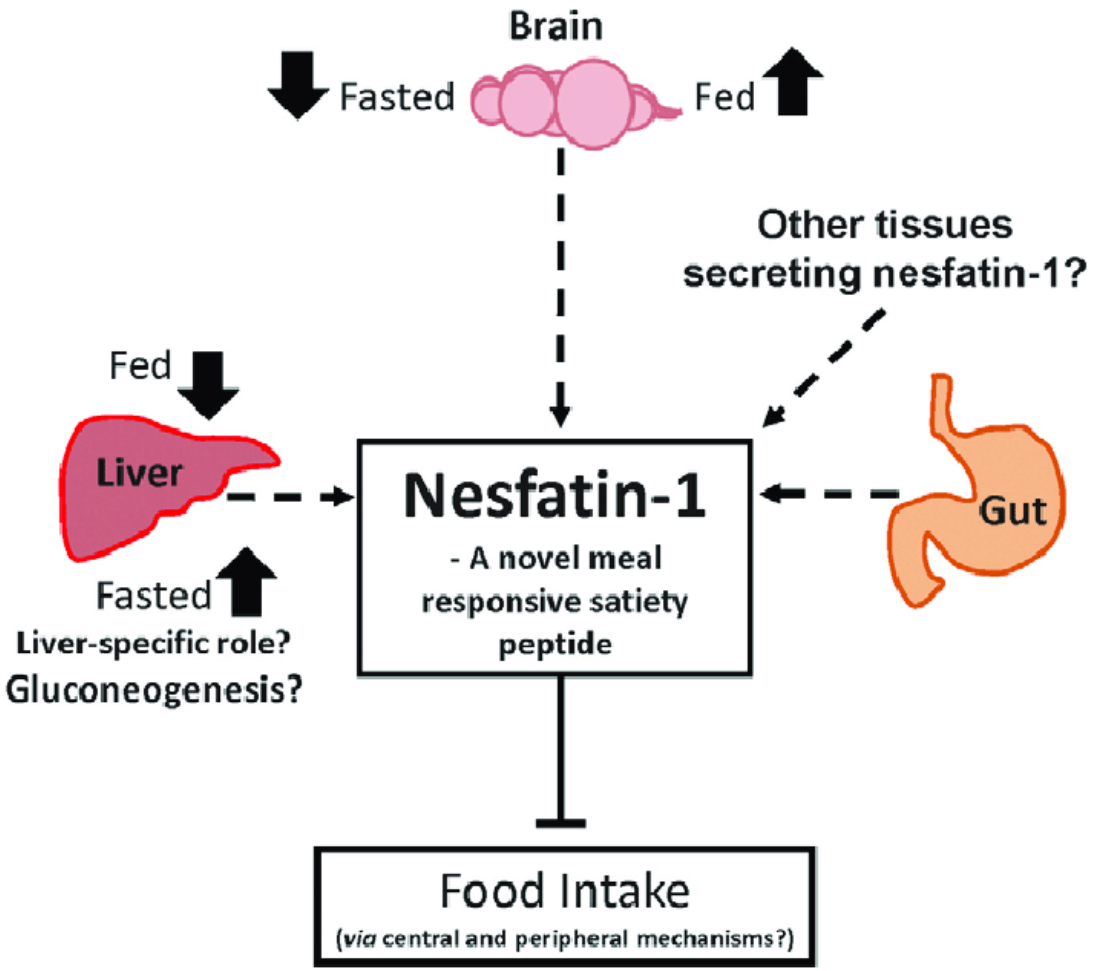
Serotonin


Normal conditions
Hypothalamus
Anorexigenic signals
Prophagic signals
Cancer
Peripheral signals
Arcuate nucleus
↑POMC/CART
↓NPY/AgRP
↑Serotonin
↑Cytokines
Tumor
Immune system

Nesfatin-1



Mid-segment (30 aa): PDTGLYYDEYLKQVIEVLEETDPHFREKLQK



Diagnosis

Table 1. Questionnaire commonly used to assess anorexia in cancer patients.

Questionnaire	Description	Study	Cut-off value
A/CS of FAACT	12-item of questions, which specifically measures the symptoms and concerns of patients with anorexia/cachexia. Each question is awarded with scoring system from 0 (not at all) to 4 (very much) and total possible score of 48.	Muscaritoli et al. [114] Buskermolen et al. [106] Turcott et al. [115]	≤24 ≤37 ≤32
VAS	100-mm line in which the extremities were anchored by "I had no appetite at all" (0mm) and "My appetite was very good" (100mm).	Buskermolen et al. [106]	≤70

Anorexia symptom scale of EORTC QLQ C-30	Consist of one item that assesses appetite "Have you lacked appetite?" The responses are scaled on a four-point Likert scale (1=not at all, 2=*a* little, 3=quite a bit, and 4=very much).	Buskermolen et al. [106]	≥2
Anorexia component of ESAS	Assesses the anorexia symptom and the severity is rated on a numerical scale of 0 (no suffering) to 10 (unbearable suffering).	Oldenmenger et al. [107]	≥4

A/CS=Anorexia/Cachexia Scale;.

FAACT=Functional Assessment of Anorexia/Cachexia Therapy;.

VAS=Visual Analog Scale;.

EORTC QLQ C-30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire;.

ESAS=Edmonton Symptoms Assessment Scale.

Treatment

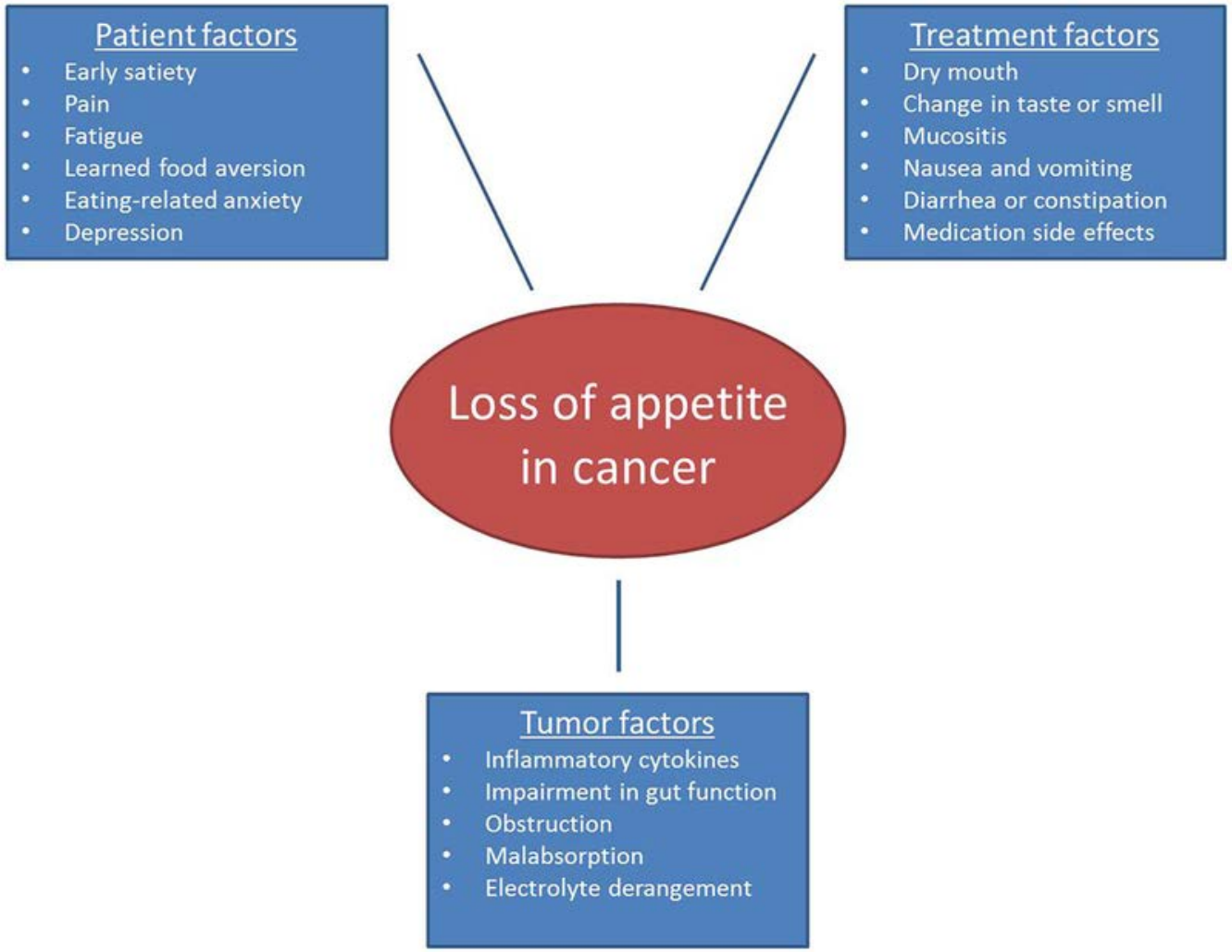
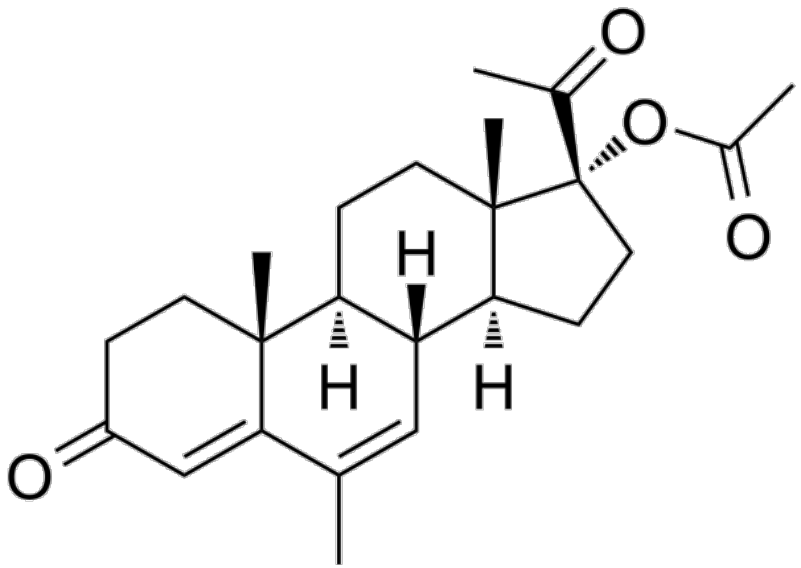
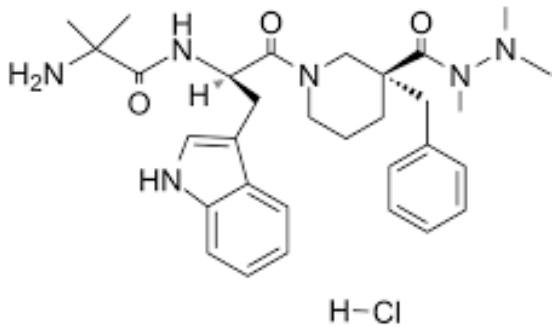
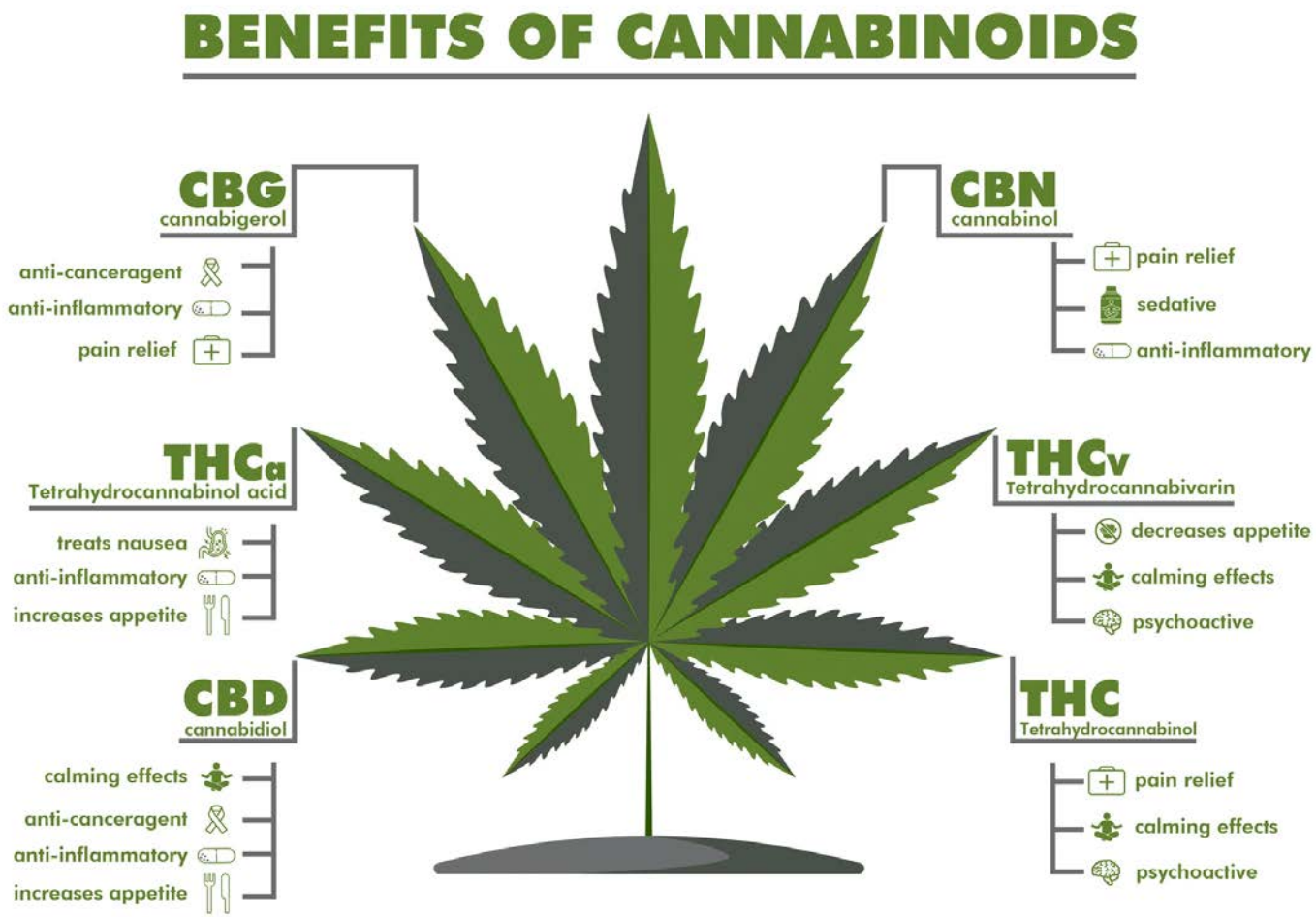

Patient factors
Early satiety
Pain
Fatigue
Learned food aversion
Eating-related anxiety
Depression
Treatment factors
Dry mouth
Change in taste or smell
Mucositis
Nausea and vomiting
Diarrhea or constipation
Medication side effects
Loss of appetite in cancer
Tumor factors
Inflammatory cytokines
Impairment in gut function
Obstruction
Malabsorption
Electrolyte derangement

Table 2. Summary of drugs which are currently under investigation to improve appetite in cancer patients.

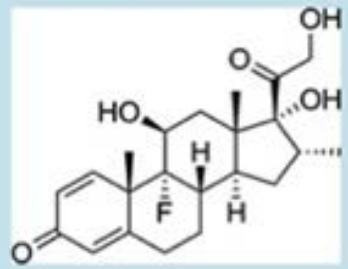
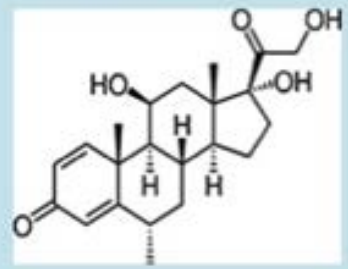
Drug	Mechanism of action	Dosage	Side effects
Megestrol Acetate 	Modulation of calcium channel in the satiety center of the ventromedial hypothalamus (VMH). Directly increase NPY levels in hypothalamus. Inhibit the activity of proinflammatory cytokines (IL-1, IL-6, TNF-α, and IFN-γ).	160 mg to 1600 mg/day.	Dyspnea, edema of extremities, impotence, thromboembolic phenomena, gastrointestinal intolerance.

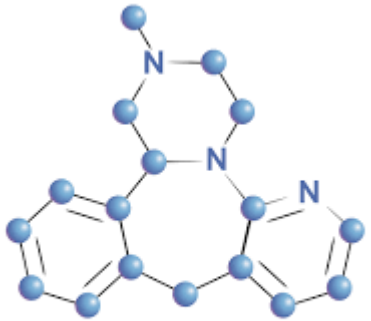
Anamorelin HCl  	Bind to and stimulate GHSR that stimulate NPY production. Decrease the production of proinflammatory cytokines (IL-6, TNF-α).	50mg to 100mg/day	GI disorder (nausea, diarrhea, vomiting), cardiac disorder (ischemia, cardiomyopathy), metabolic disorder (hyperglycemia, hypocalcemia), fatigue, rash.

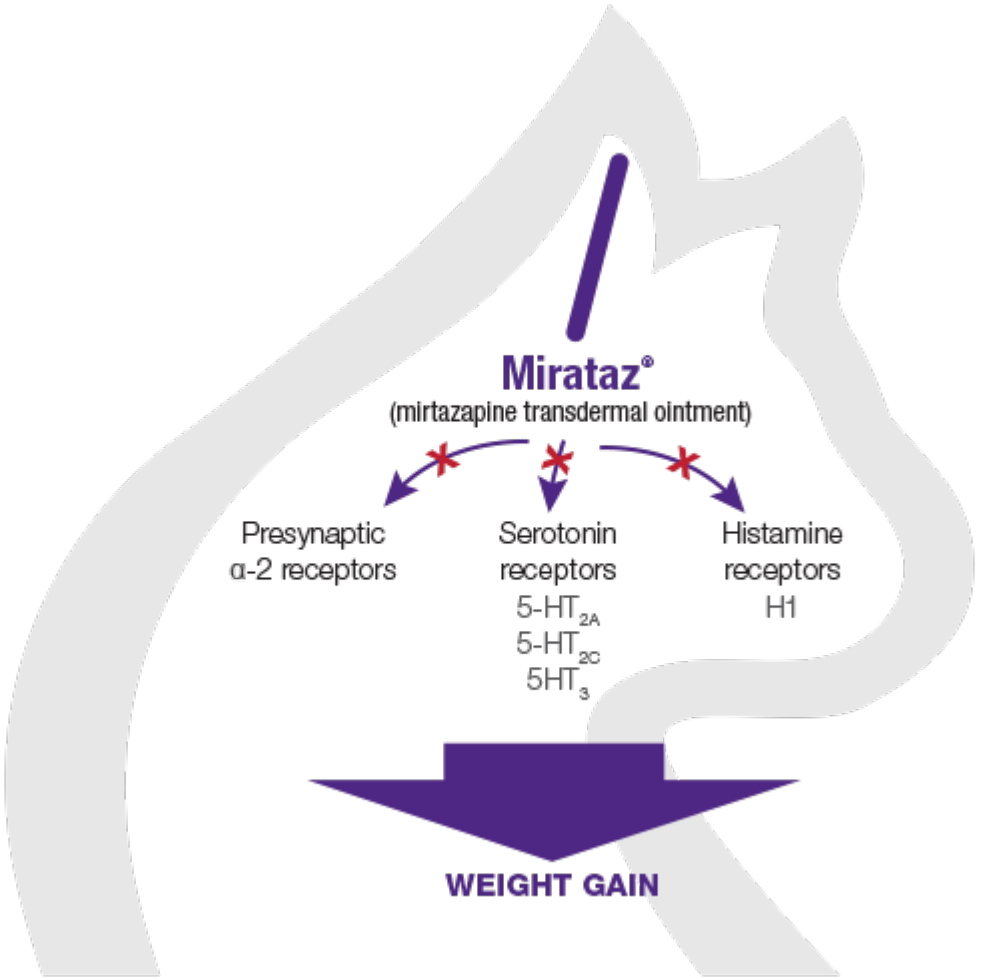
Cannabinoids	Work in the CB1 receptor in the hypothalamus to stimulate appetite. Stimulate the mesolimbic reward system. Inhibit proinflammatory cytokines (IL-1, IL-6, and TNF-α). Act in the vomiting center in the brain to prevent nausea and vomiting.	2.5 mg once daily to 5 mg twice daily.	Nausea, dizziness, headache, mood changes, impotence.



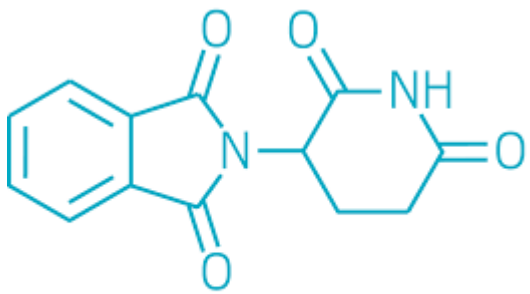
Corticosteroids	Inhibit the release of proinflammatory cytokines (TNF-α and IL-1). Enhance NPY levels in the hypothalamus via AMPK signaling.	Prednisolone 5 mg three times daily; dexamethasone 3–6 mg daily; methylprednisolone 125 mg daily.	Oral symptoms, restlessness, weakness, delirium, osteoporosis, immunosuppression.

	Dexamethasone	Methylprednisolone
		
Mechanism of Action	Although not clear, it is believed that corticosteroids exhibit their pharmacological activity through inhibition of prostaglandins, and inflammatory cytokines (tumor necrosis factors, and interleukin-1)	
Therapeutic Considerations	• Have not been demonstrated to increase weight • More beneficial for those with a short life expectancy • Effect is short: 3-4 weeks	

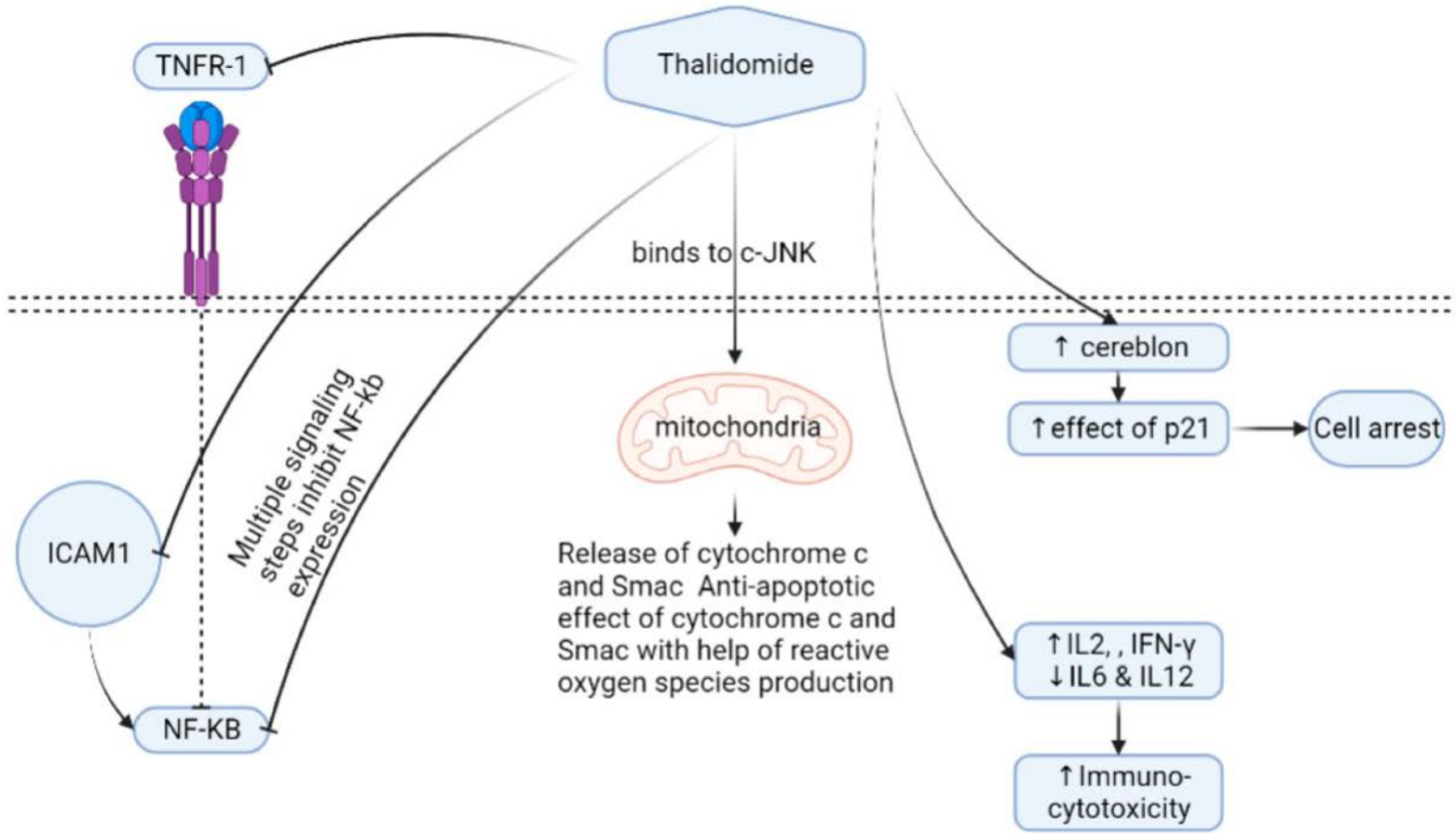
Mirtazapine  Mirtazapine	Inhibit 5-HT_3 receptor that mediates nausea and vomiting. Inhibit 5-HT_{2c} receptor which can help to increase in food intake.	7.5mg daily to 30mg daily.	Confusion, dizziness, blurred vision, dry mouth and drowsiness.



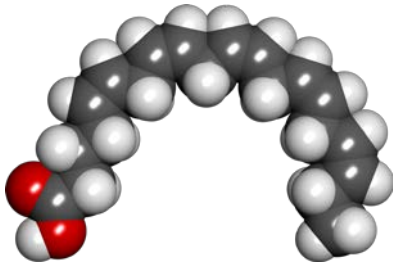
Thalidomide	Reduce the production of TNF-α and IL-1β.	50mg daily to 200mg daily.	Peripheral neuropathy, paresthesia, rash, daytime somnolence, VTE, diarrhea, headache, nausea.

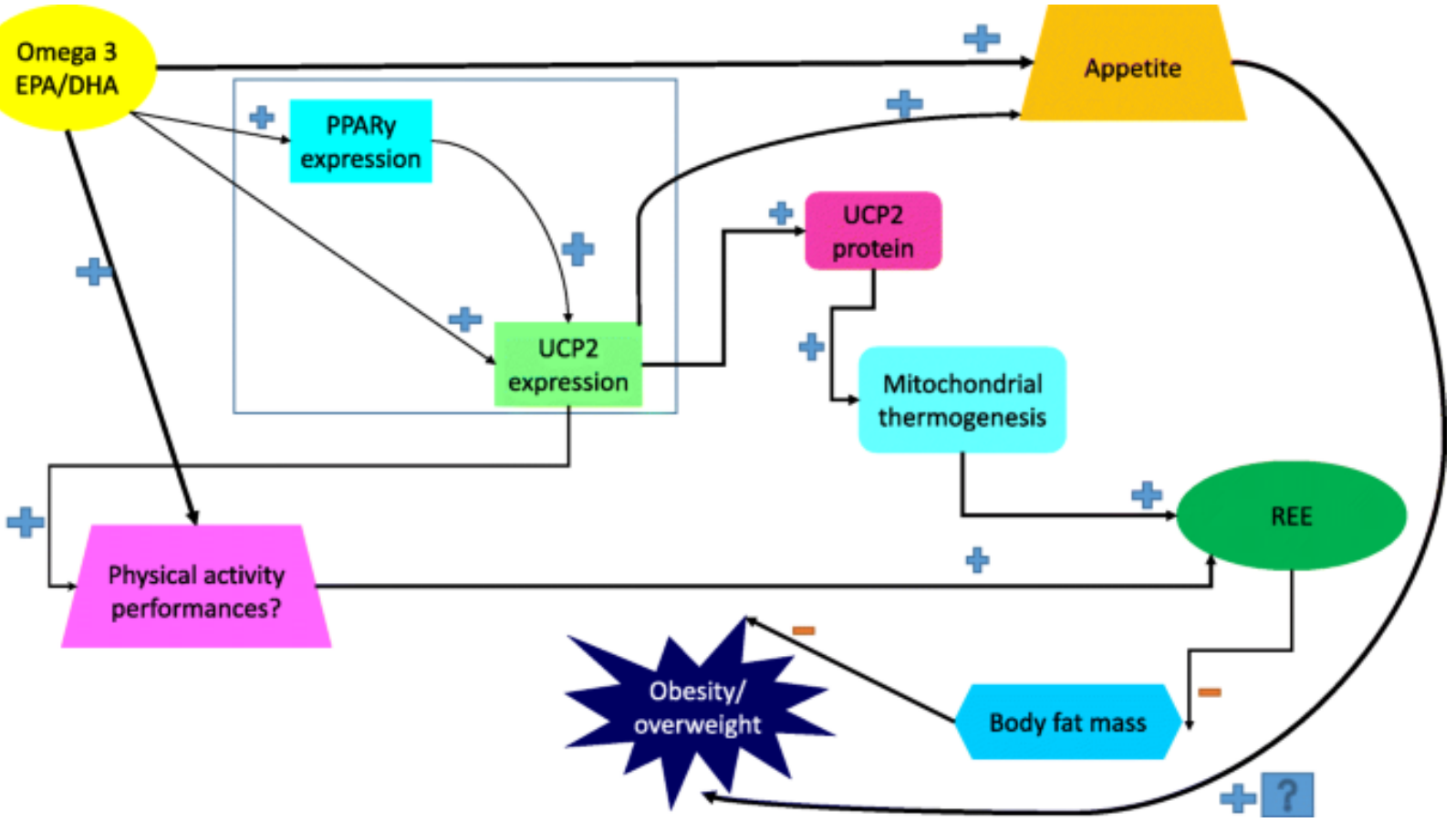


Thalidomide

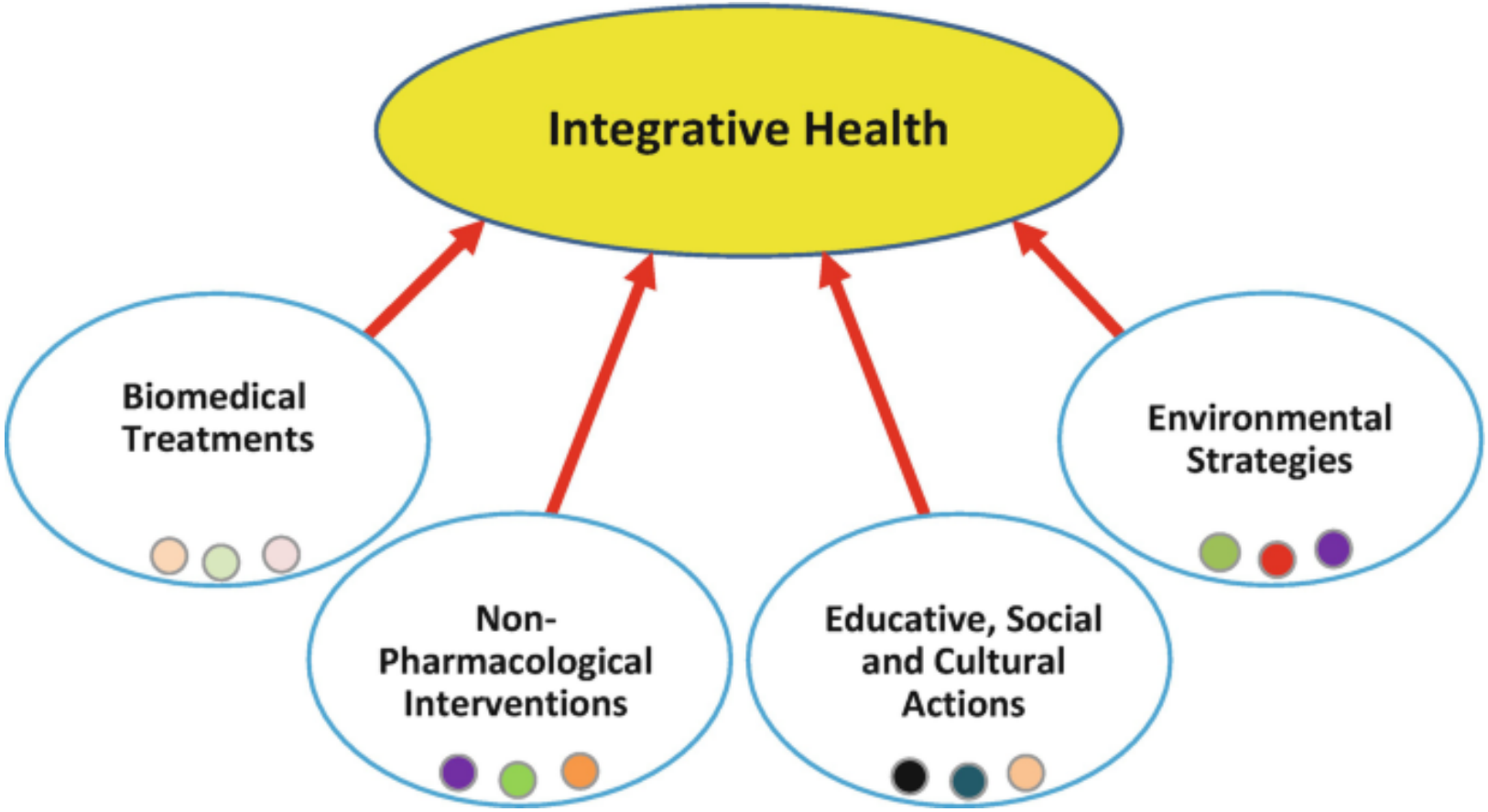


Eicosapentaenoic acid (EPA)	Downregulate CRP, IL-6 and TNF-α production. Inhibit the ubiquitin proteasome pathway. Increase insulin sensitivity.	1 g once daily to 1 g twice daily.	N/A

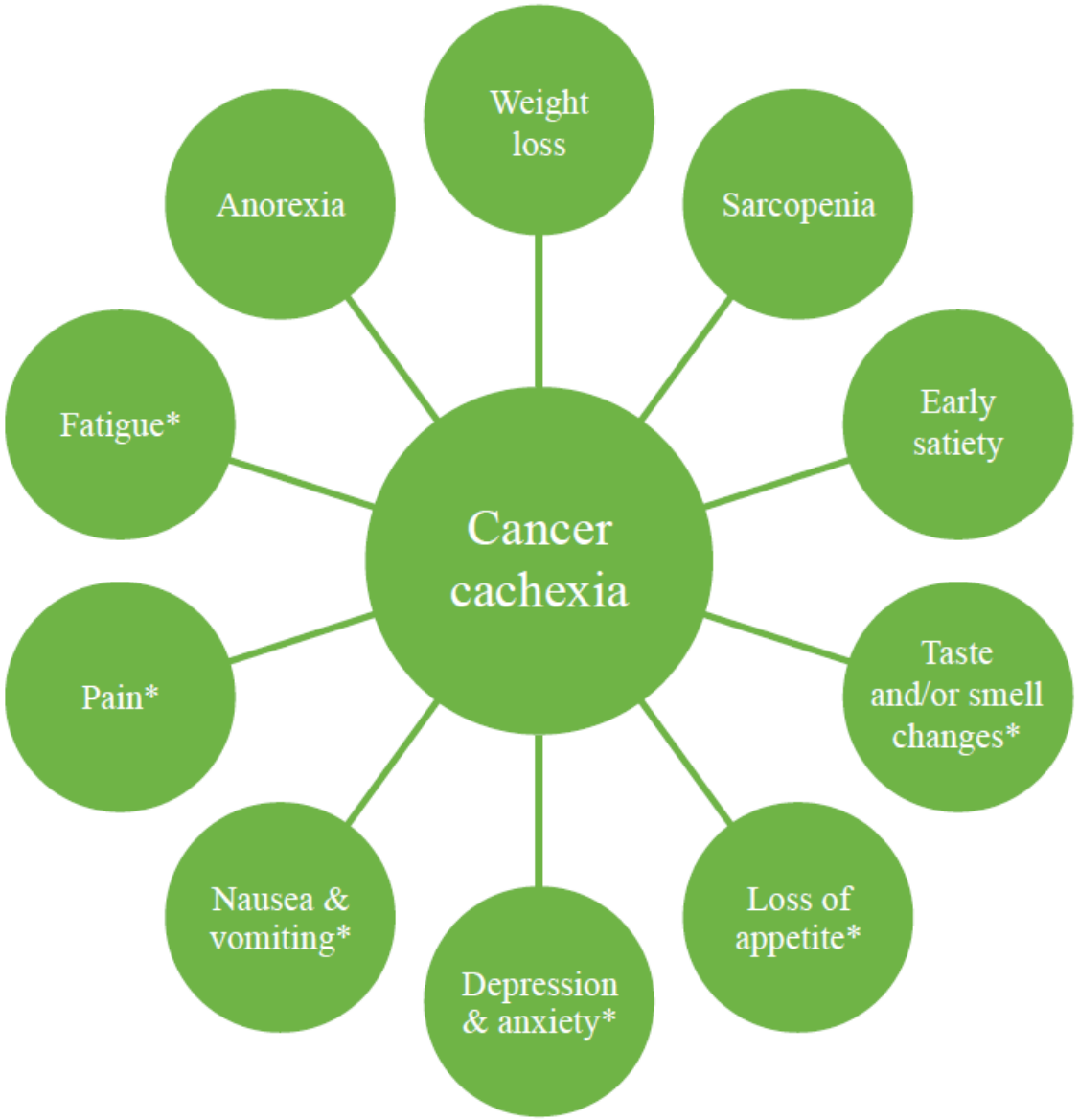




Non-pharmacological Interventions



Should loss of appetite be palliated?

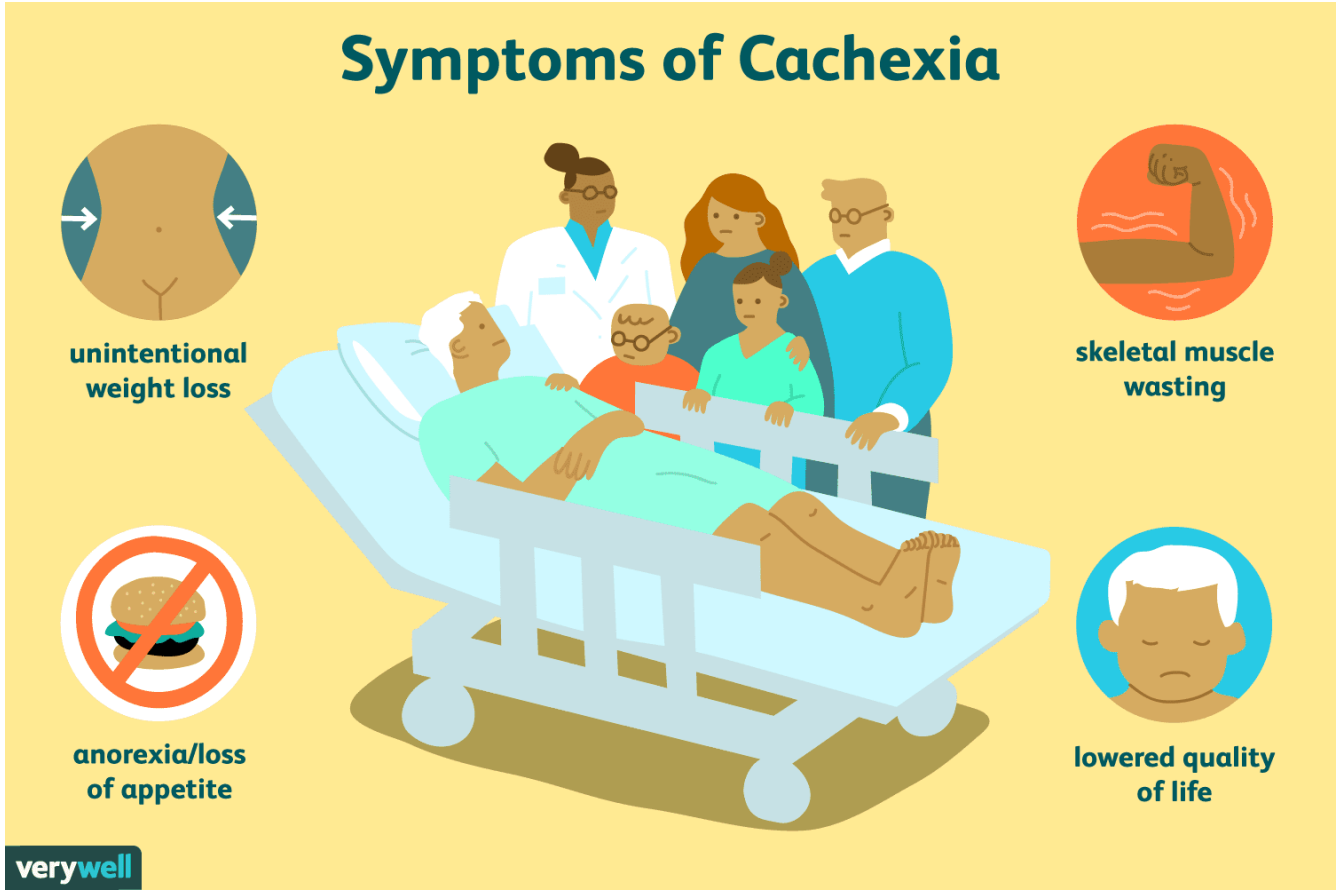


Dietary Counseling

- Systematic review: dietary counseling helps cancer patients with loss of appetite.
- Lack of granularity in methodology that provides healthcare providers sufficient detail on how best to implement.
- Suggested as a beneficial intervention.

Family Factor

- Loss of appetite and inability to participate in meals bothers family members.
- Extra time with and attention to family members necessary to help all involved understand loss of appetite, its implications, and that family members should not blame themselves for poor PO intake.



Case Example Revisited

- 63 M, metastatic pancreatic adenocarcinoma.
- Clinical Course: weight loss c/b gastric outlet obstruction, protein-calorie malnutrition.
  - s/p PEG-J. On FOLFOX.
- Weight loss: affected by clinical events, medical intervention, and surgical intervention.
- Potential correlations among growth of metastatic tumor burden and cachexia.
- Assessment: early satiety.
- Treatment: Dronabinol with improvement. Several weeks later, reported appetite reduced again. Increased dose of Marinol. Several weeks later, endorsed feelings of demoralization, possible depression iso intermittent insomnia.
- Considering addition of Mirtazapine.

Conclusion

- Several factors induce anorexia in cancer patients and the underlying mechanism is complex.
- Diagnosis of appetite problems in cancer patients assisted with use of questionnaires: FAACT, Visual Analog Scale (VAS), EORTC-QLQ30, and ESAS.
- Pharmacotherapy options: anamorelin, thalidomide, and mirtazapine
  - randomized phase 3 clinical trials needed to confirm findings.
- Loss of appetite should always be palliated [not necessarily with pharmacological interventions].

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Questions/Comments