

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

Palliative Care ECHO Session

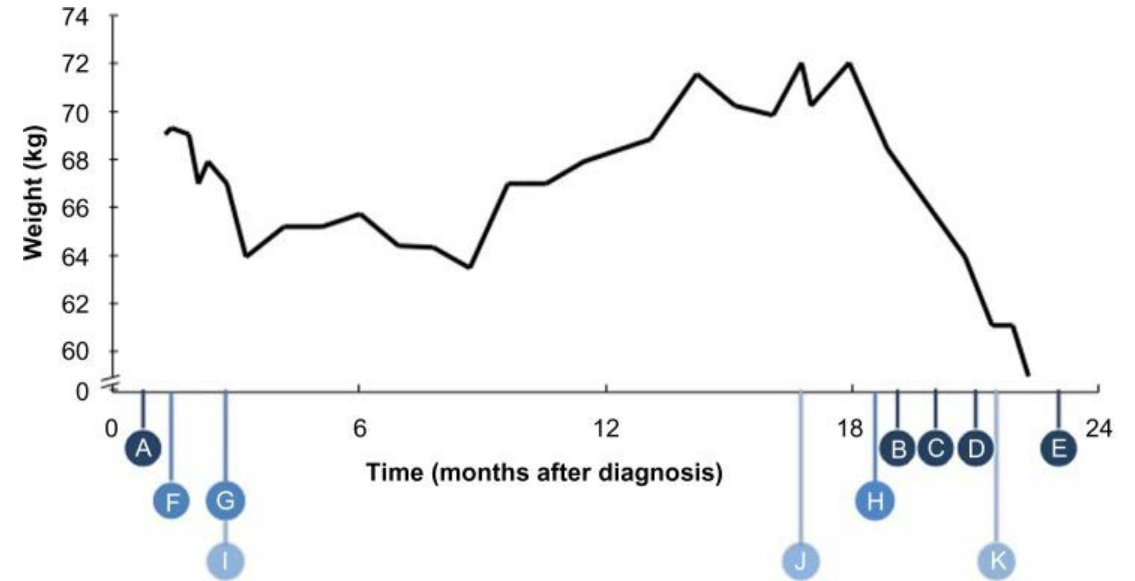
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# Learning Objectives

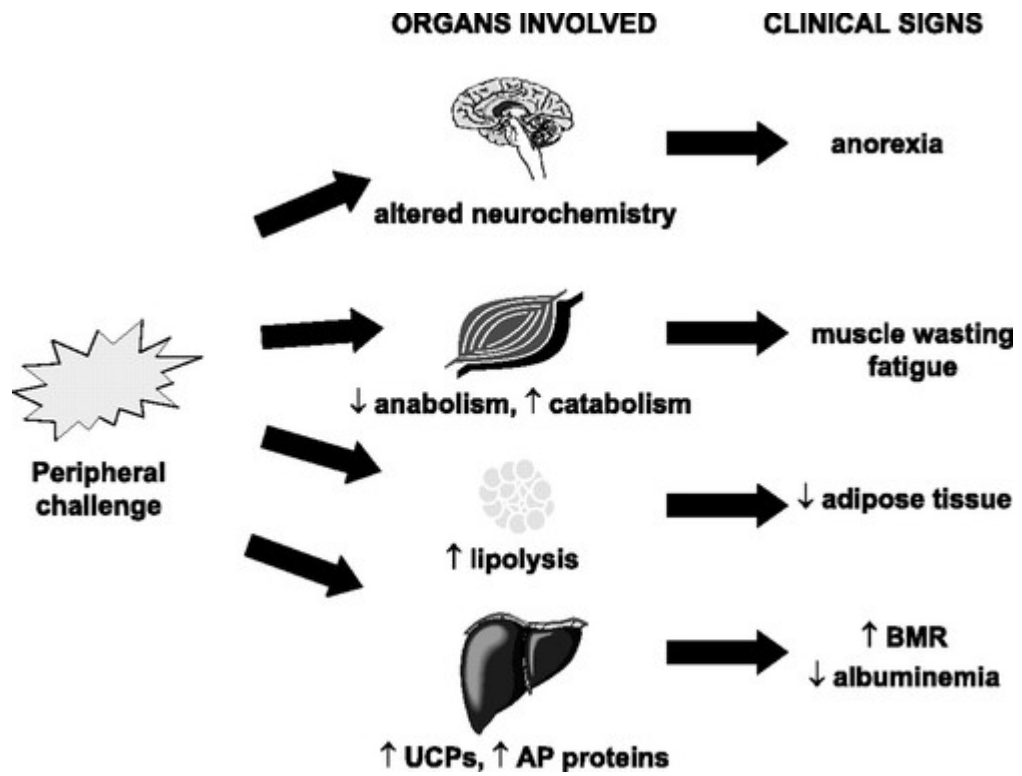
- Describe the pathophysiology of anorexia in cancer patients
- Employ tools and assessment scales for diagnosing cancer-associated anorexia/cachexia
- Understand and apply pharmacotherapy options for anorexia/cachexia in cancer patients
- Instruct on non-pharmacological interventions to address anorexia/cachexia.

# 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.

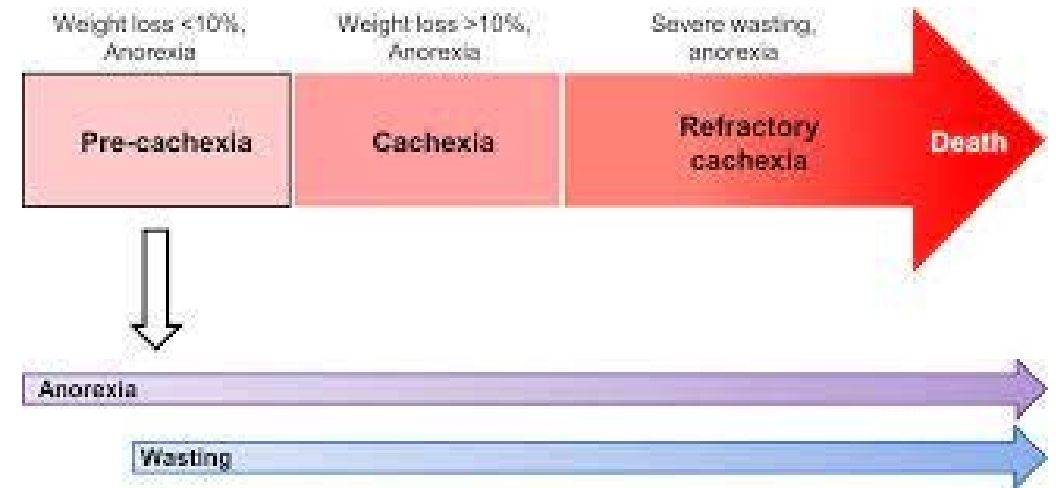


# Introduction



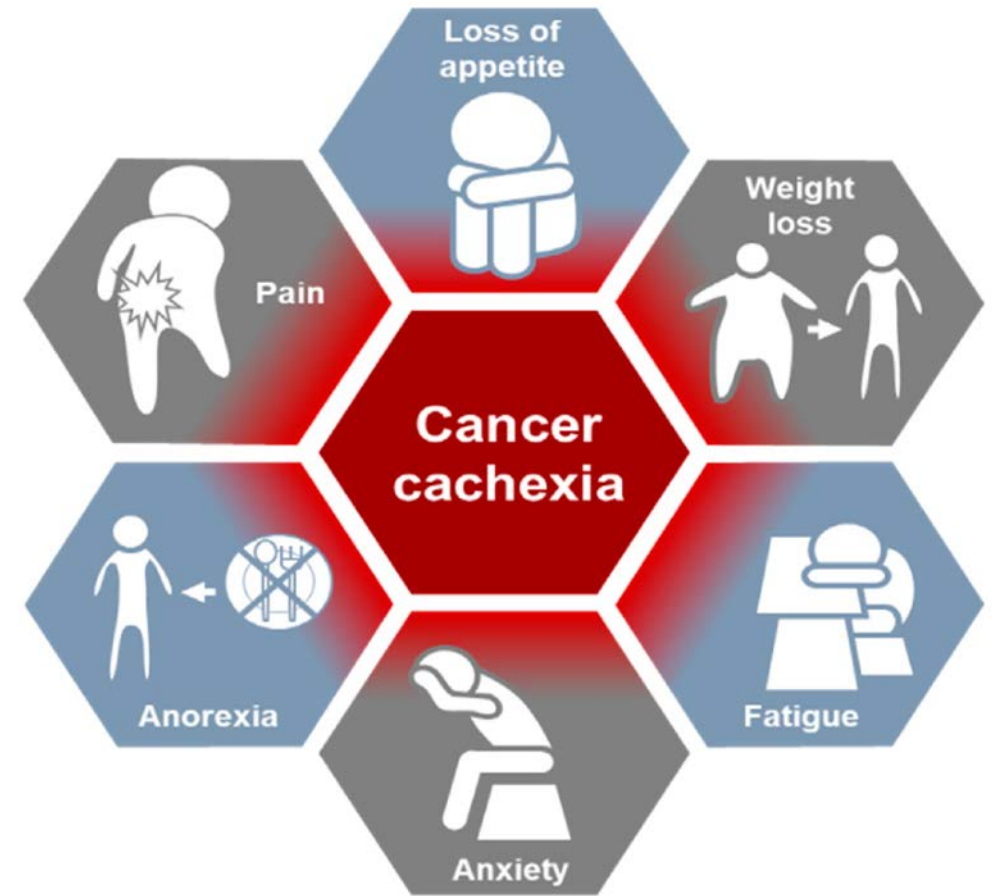
# Introduction

- **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.

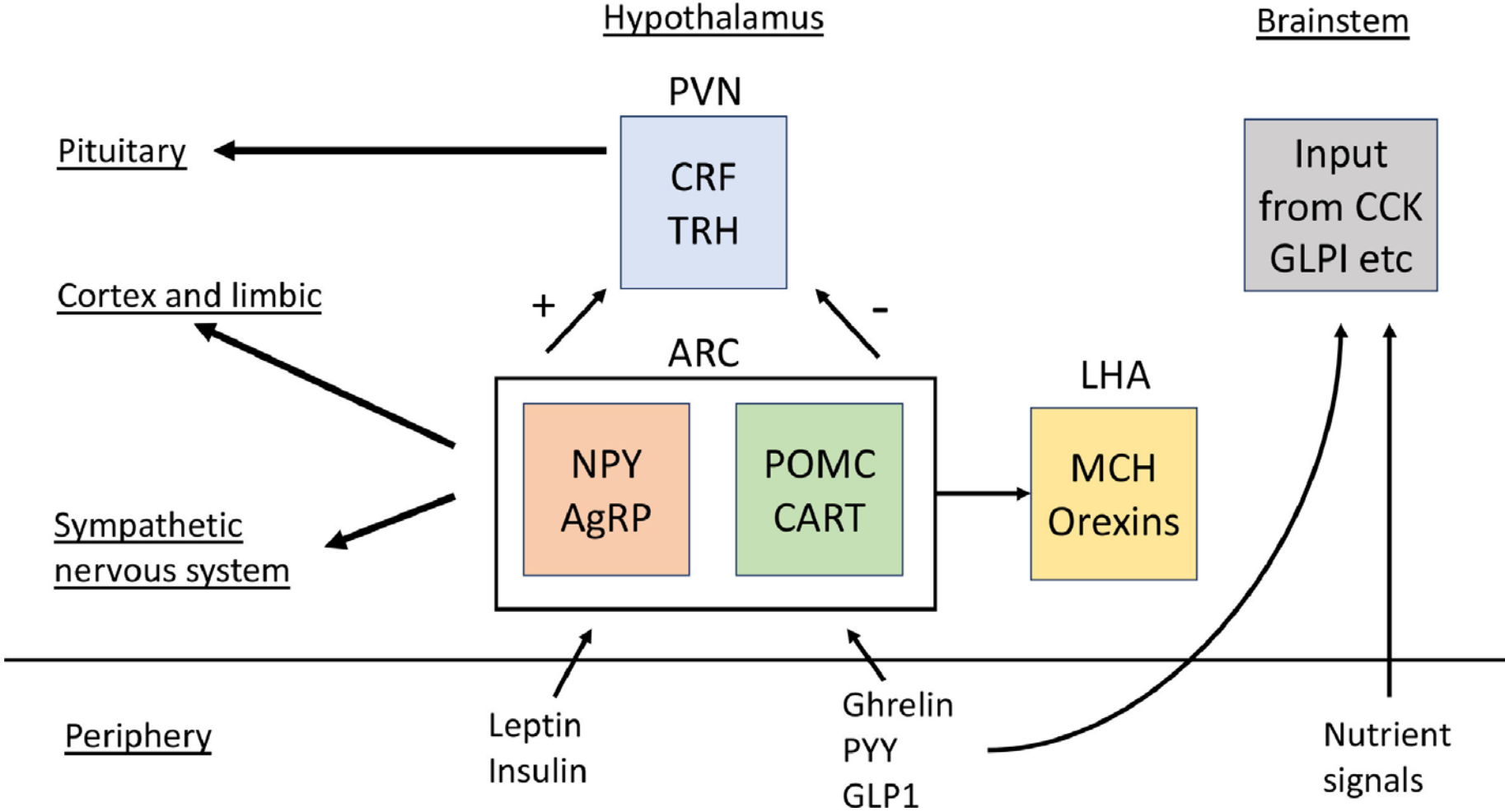


# Introduction

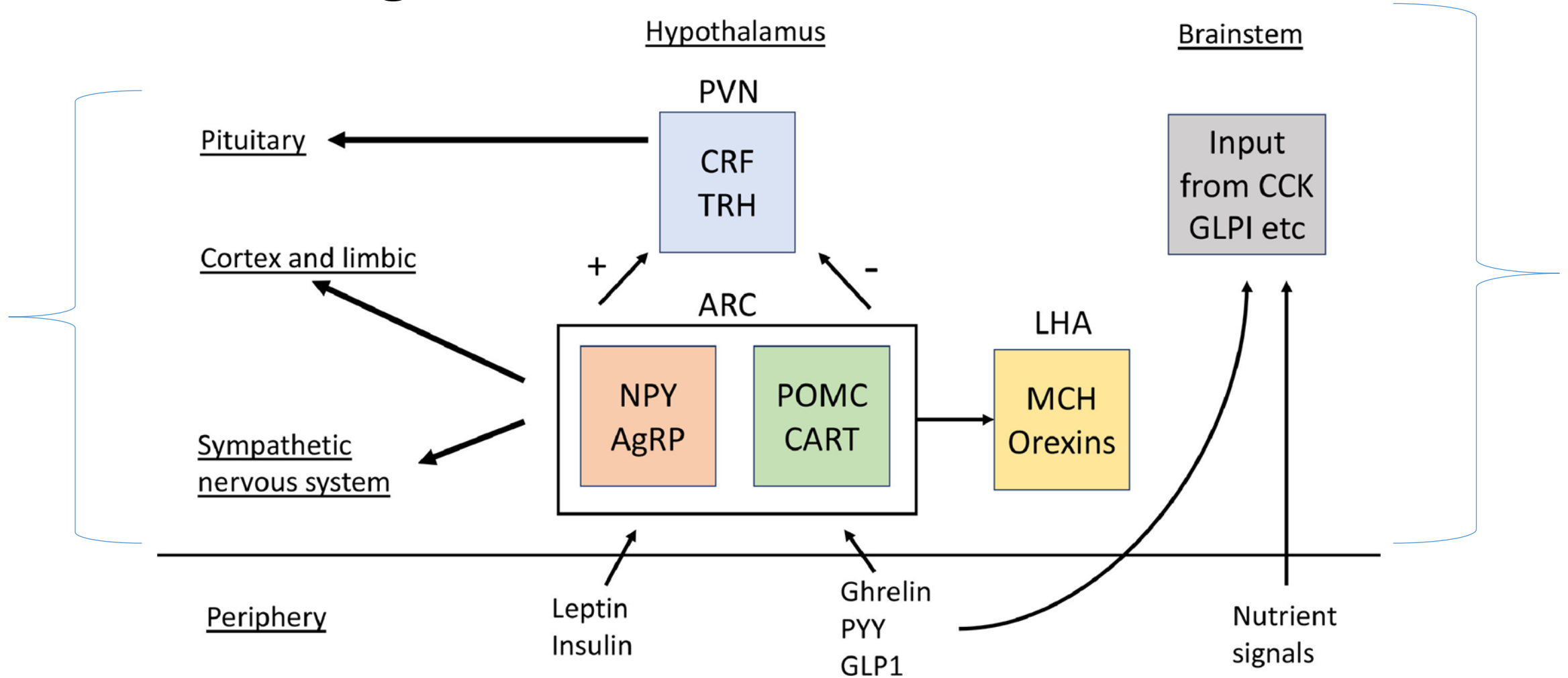
- Anorexia components: nausea, altered taste sensation, swallowing difficulties, or depression.
- Failure of nutritional supplementation to reverse weight loss → **cancer cachexia**.
- Loss of appetite reported to be most important factors in physical and psychological aspects of quality of life (QOL).
- 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

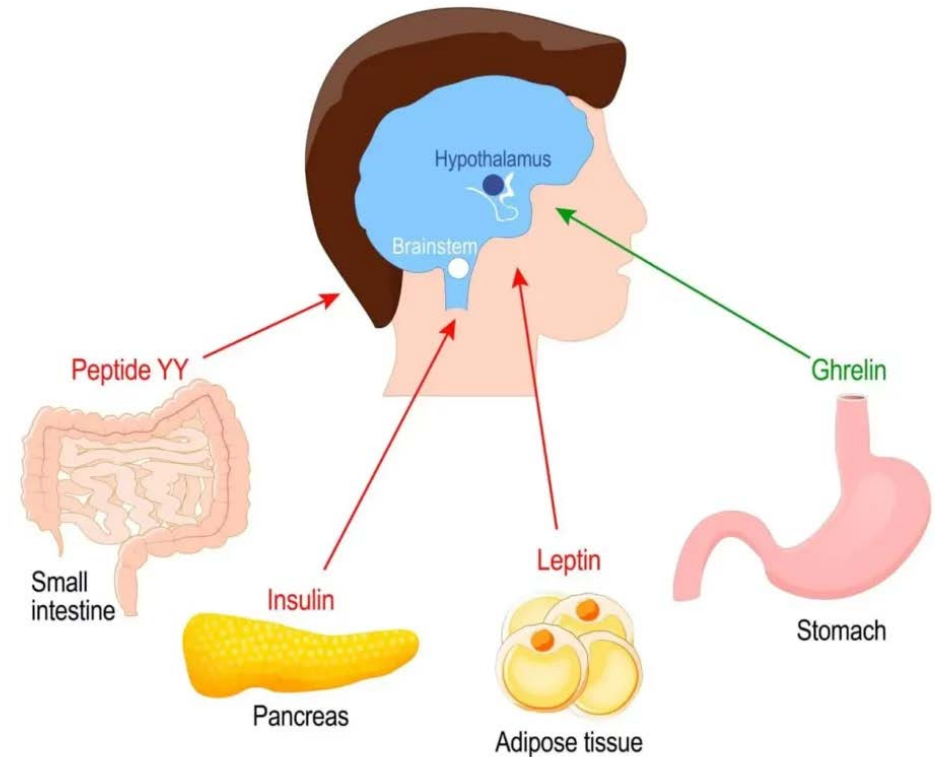
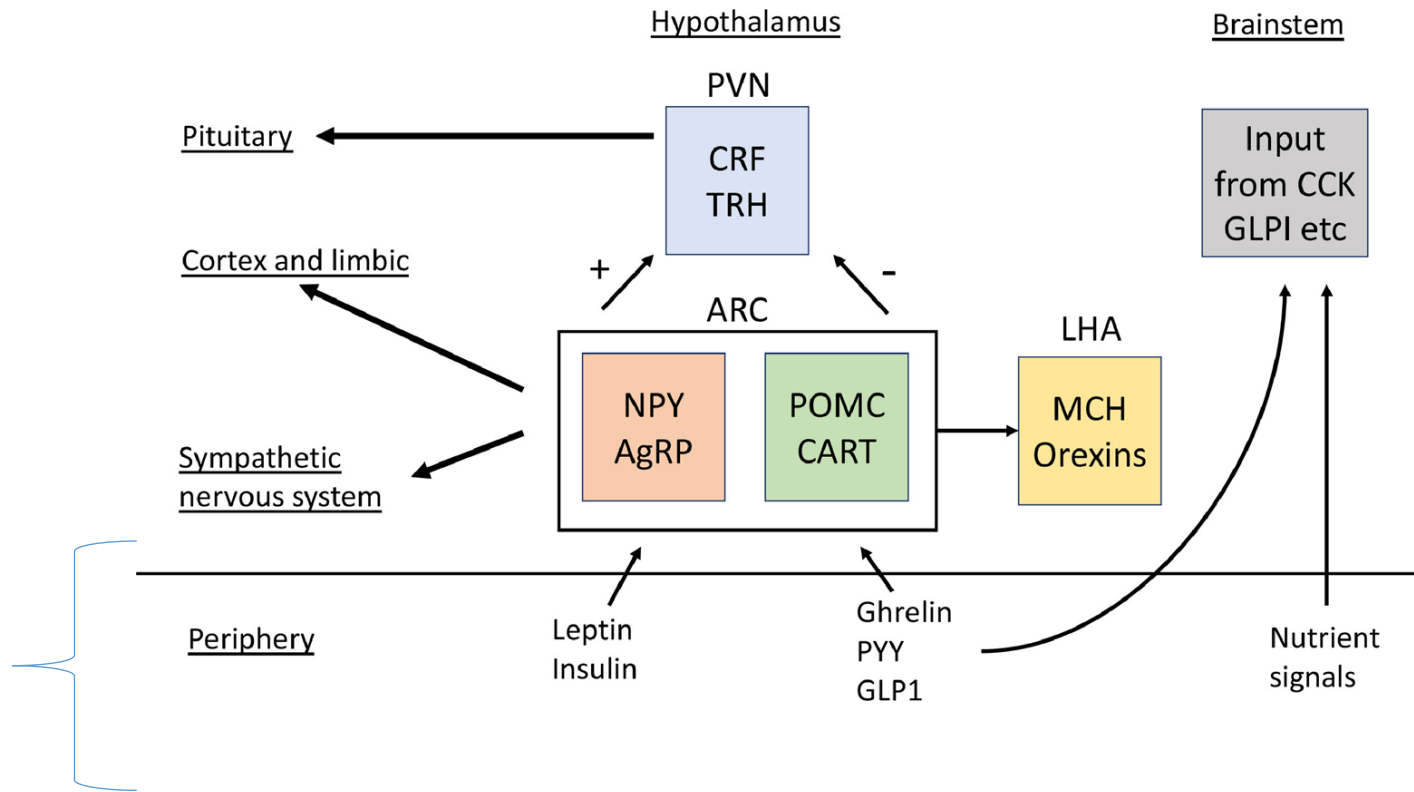


# Central Regulation

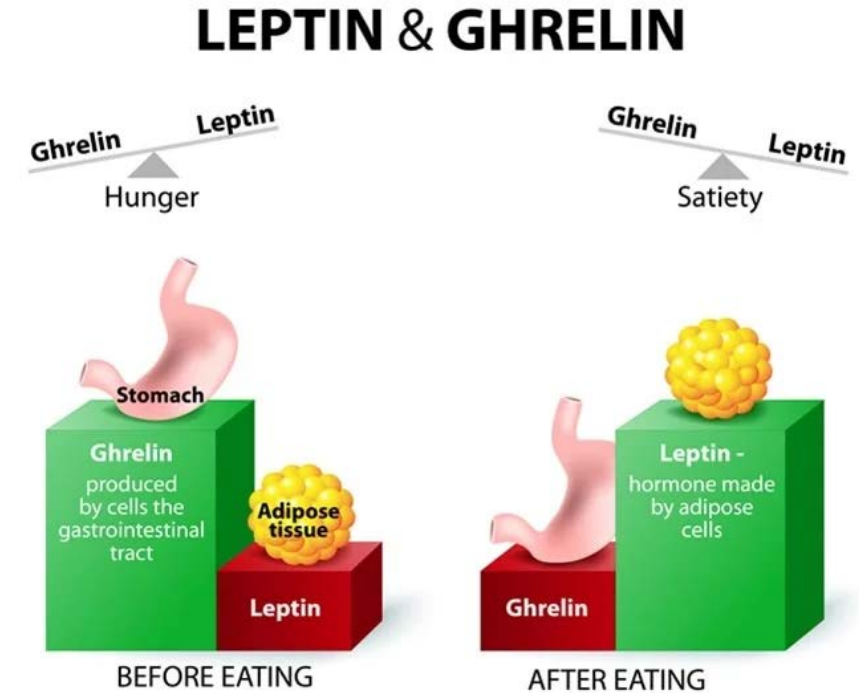
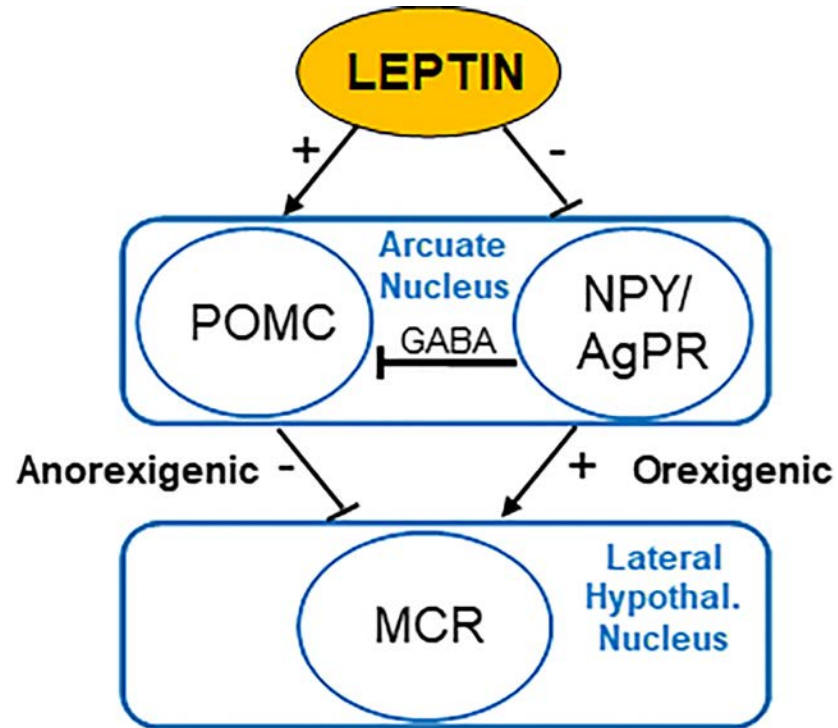
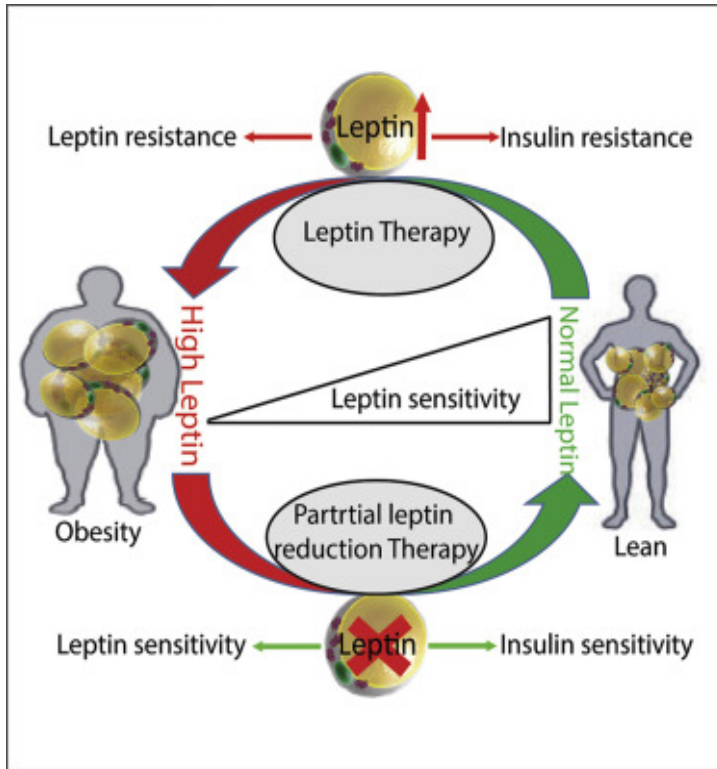




# Peripheral Regulation

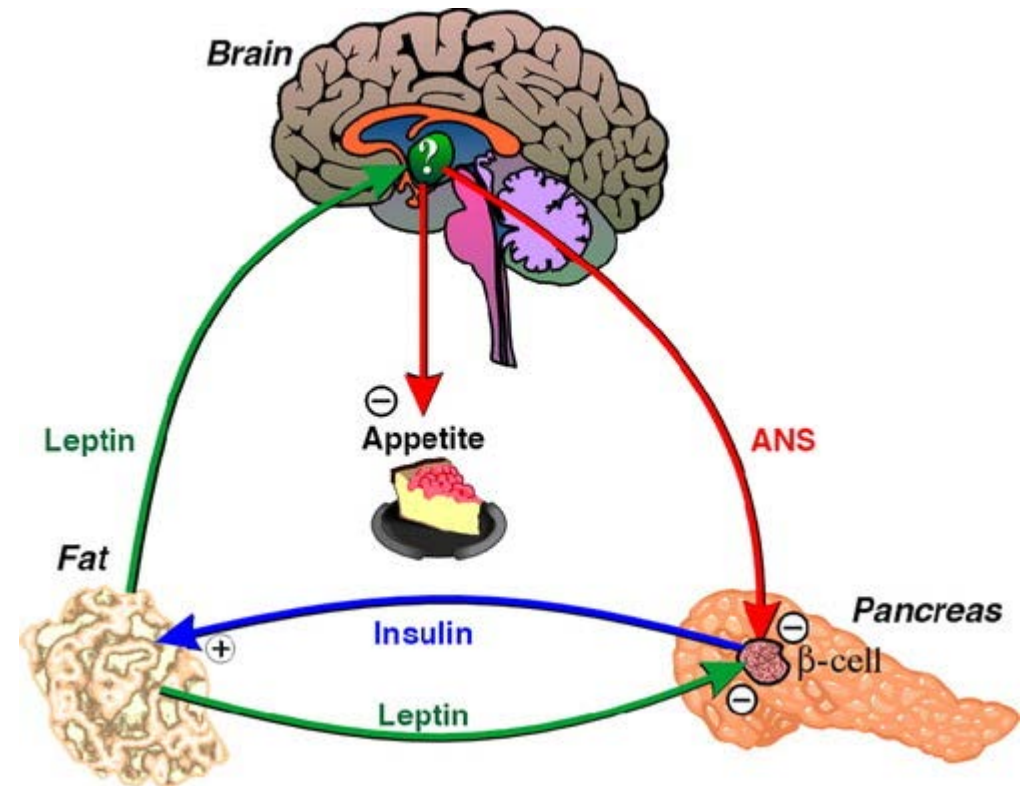


# Peripheral Regulation: Leptin



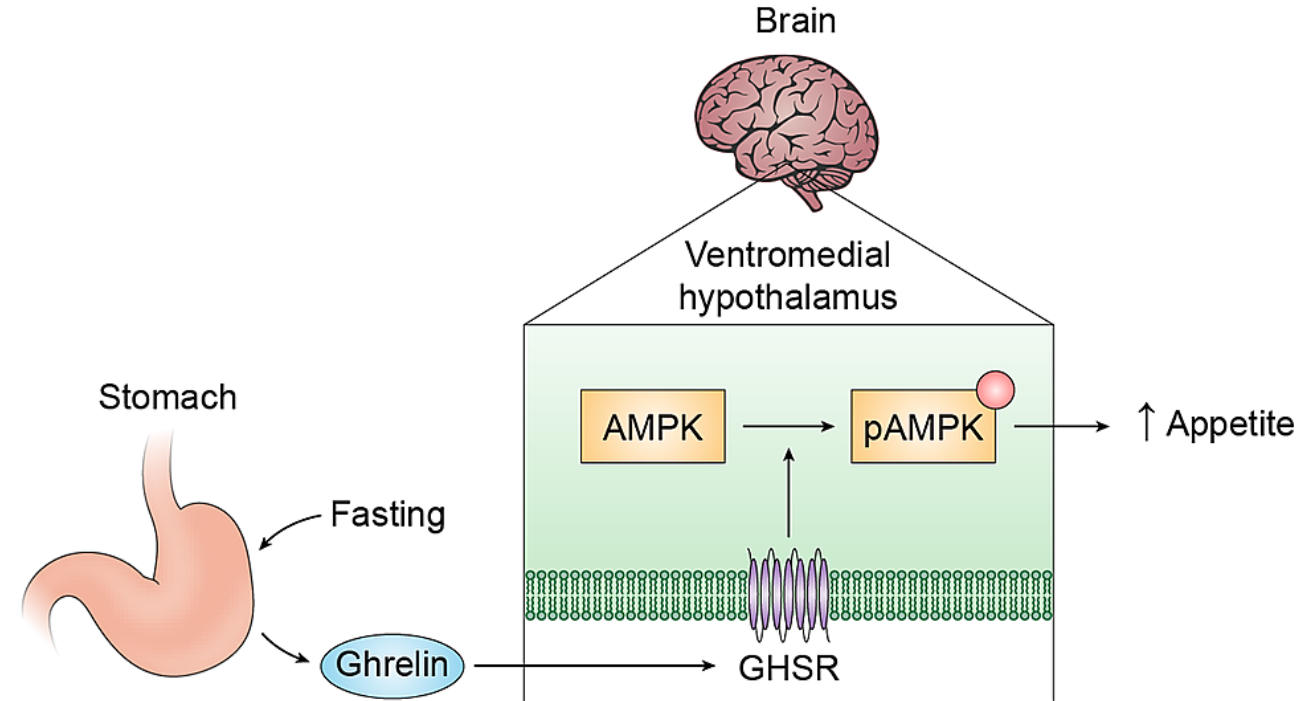
# Peripheral Regulation: Insulin

- 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**.



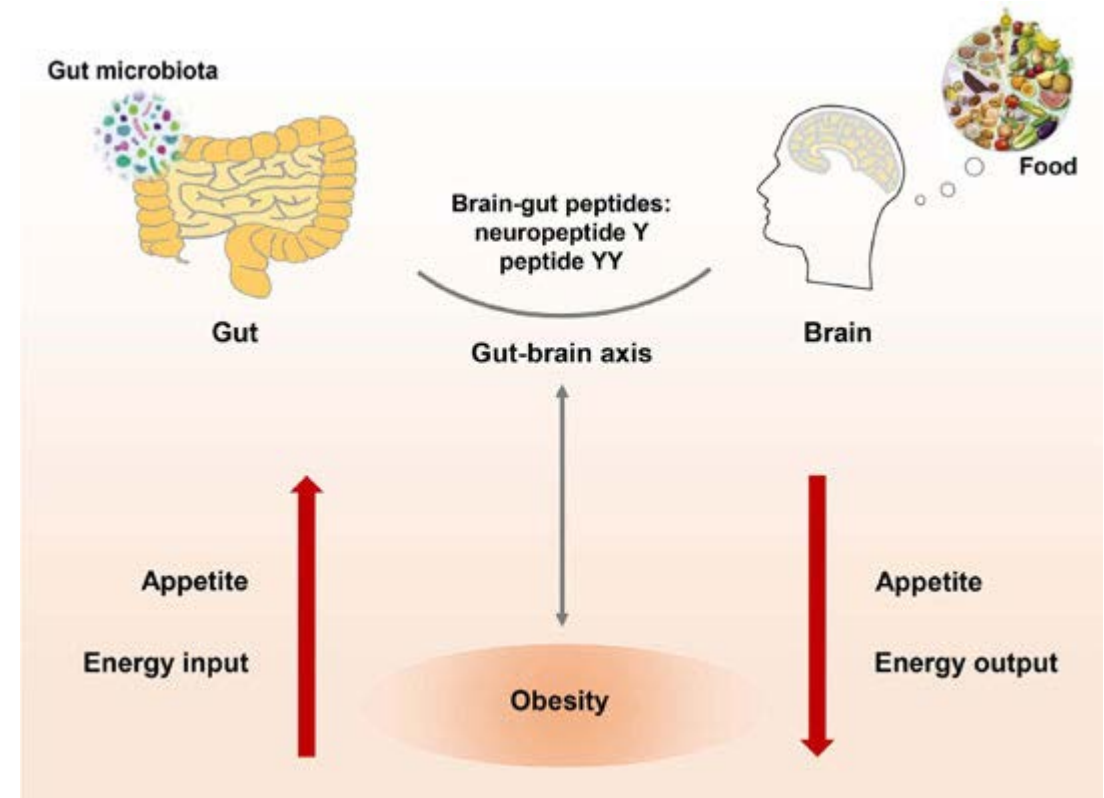
# Peripheral Regulation: Ghrelin

- 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.



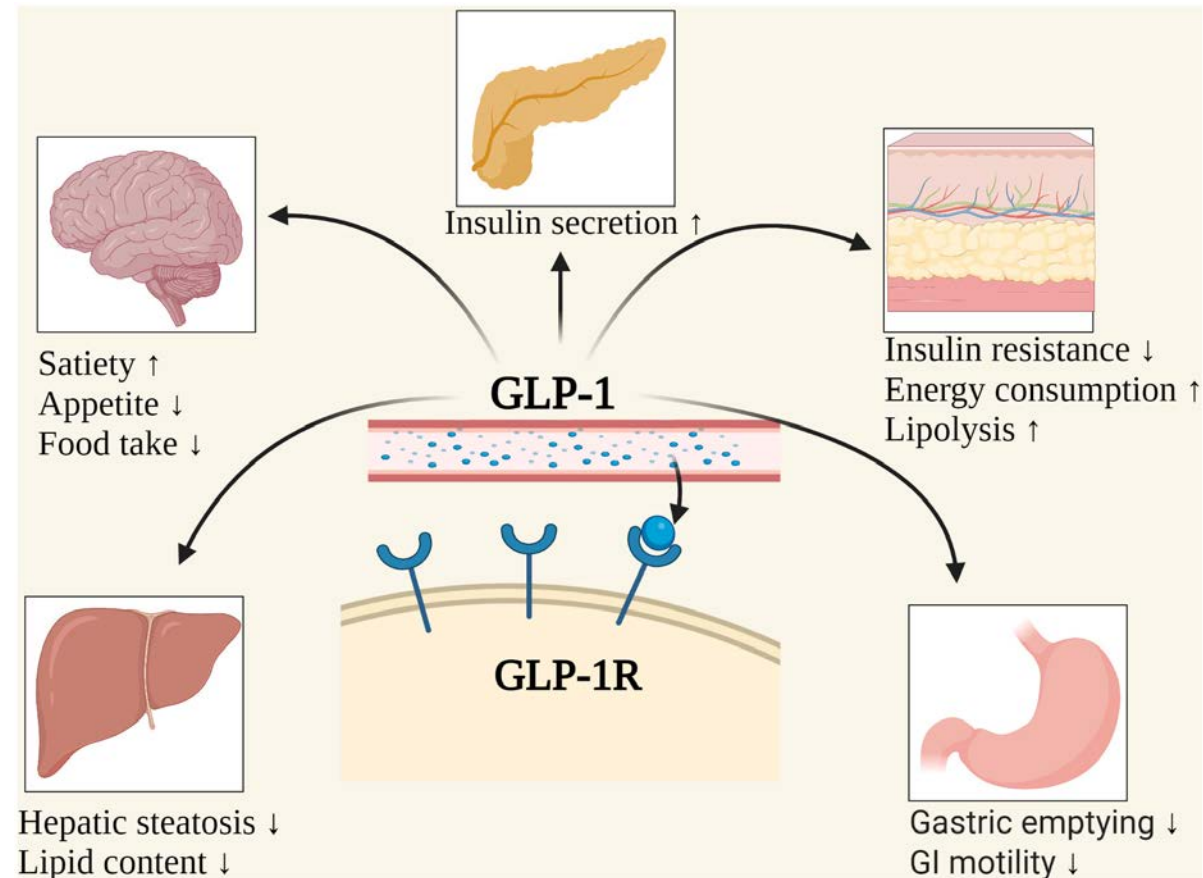
# Peripheral Regulation: Peptide YY

- Produced by I-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

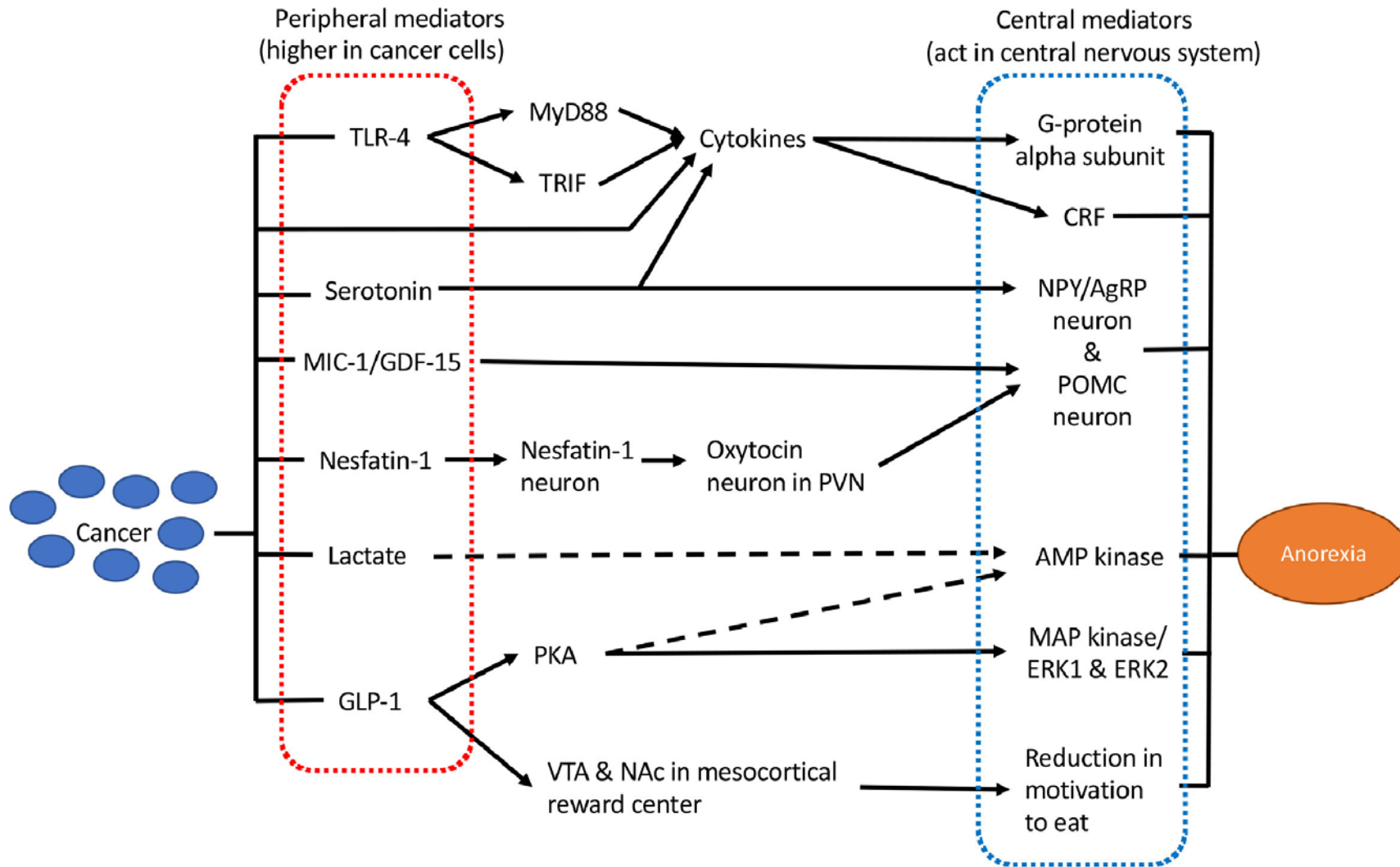


# Peripheral Regulation: Glucagon-like peptide-1

- 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.
- Acts on brain to increase satiety, decrease appetite, and decrease food intake.
- 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.

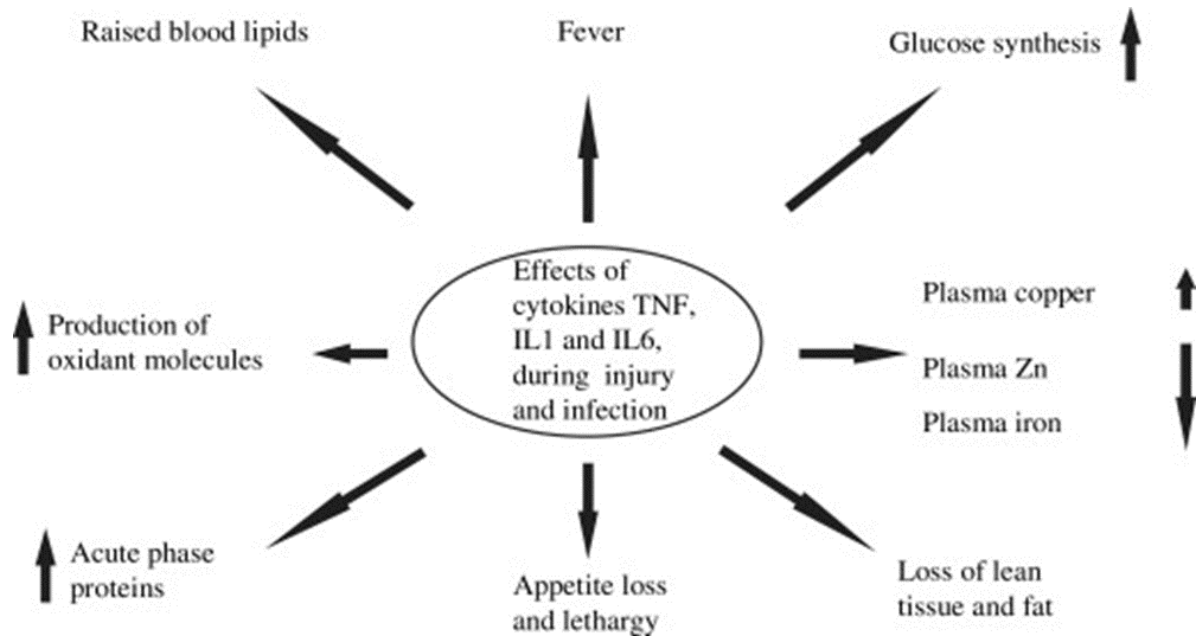


# Pathophysiology of anorexia

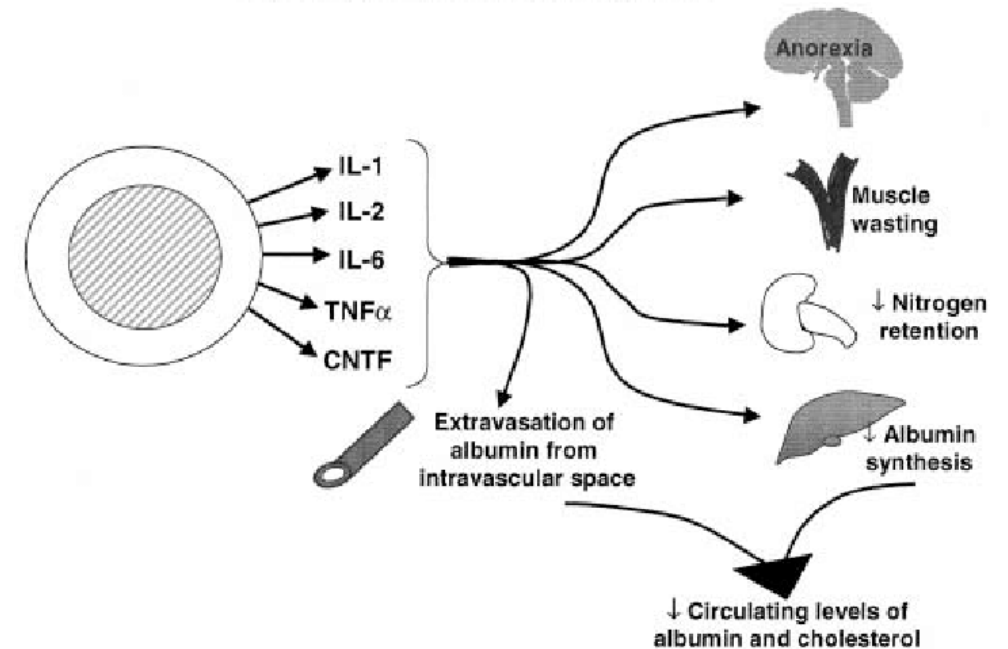


Note:  
- - - (dash line) = inhibition  
— (continuous line) = stimulation

# Cytokines

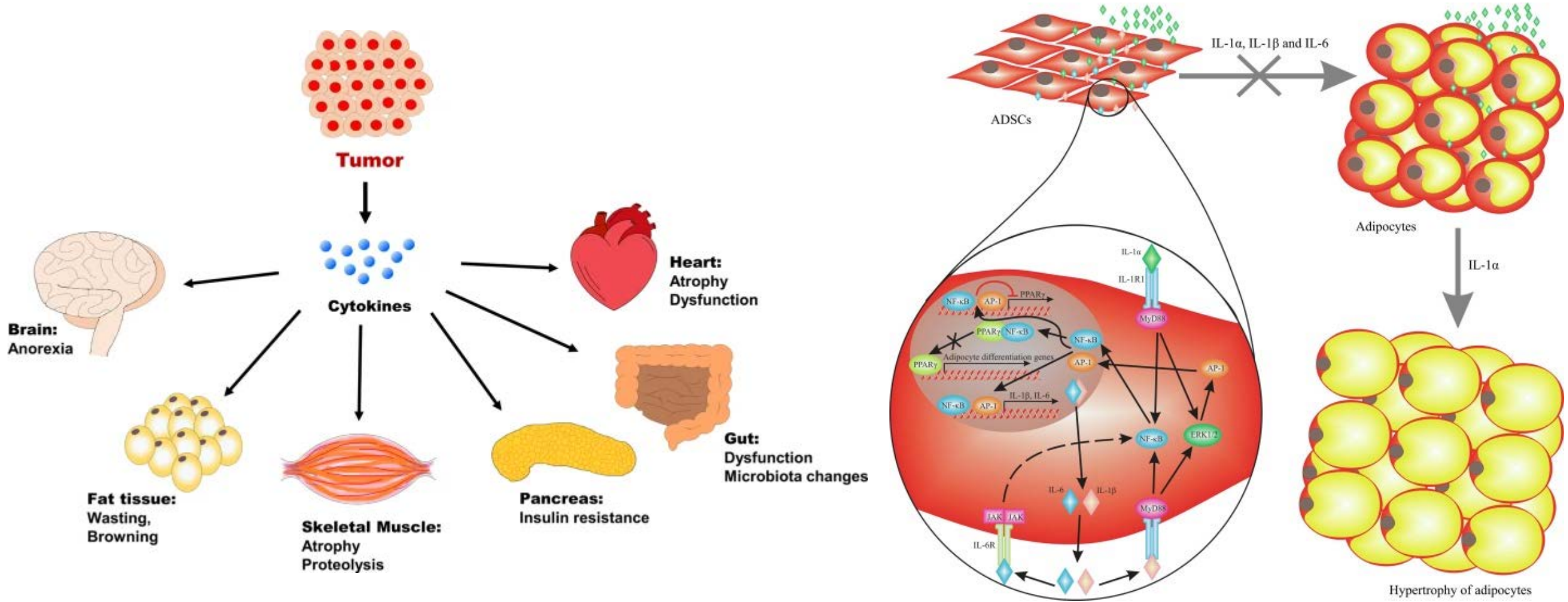


## Cytokines and Food Intake



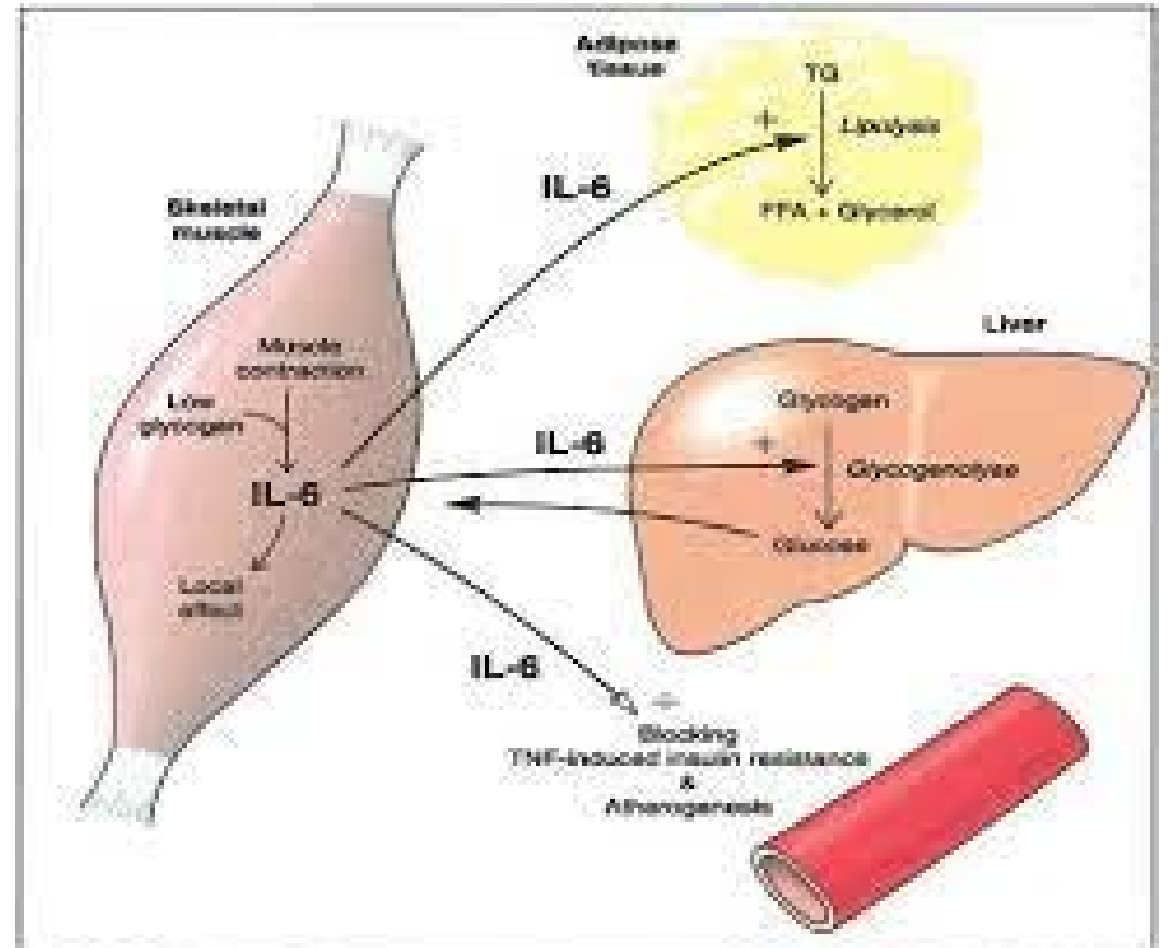


# Cytokines: IL-1



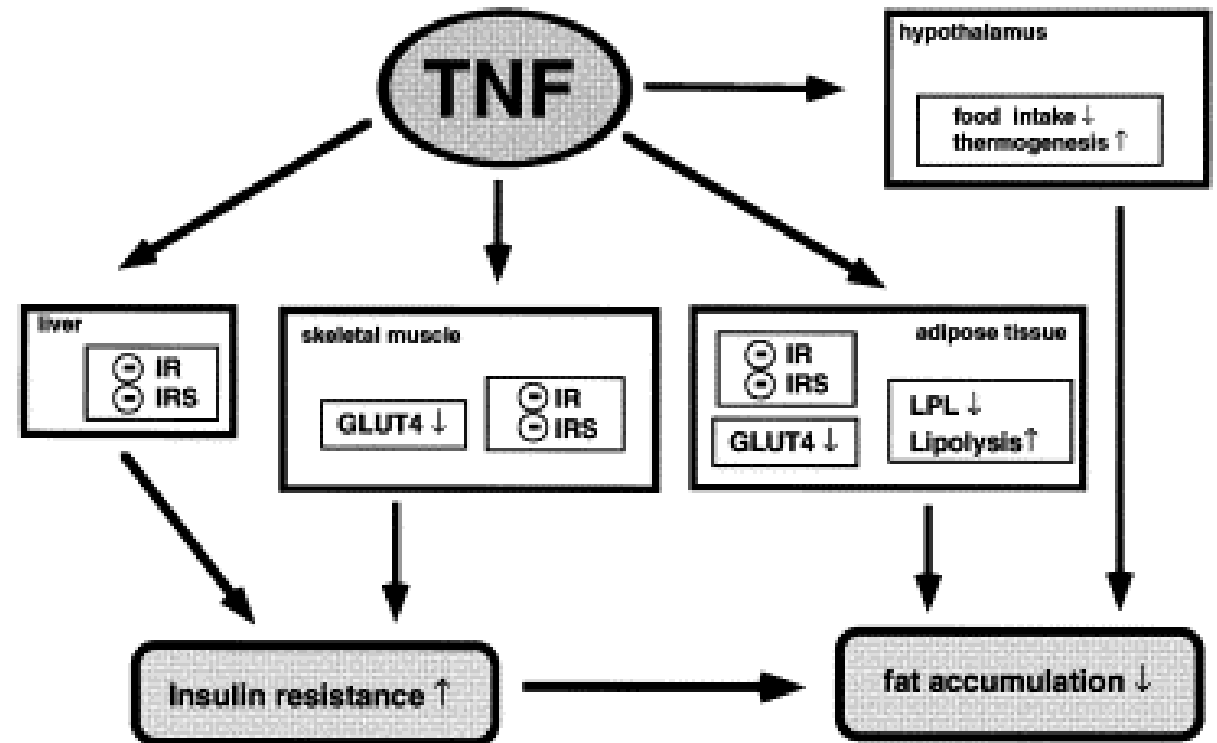
# Cytokines: IL-6

- 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.

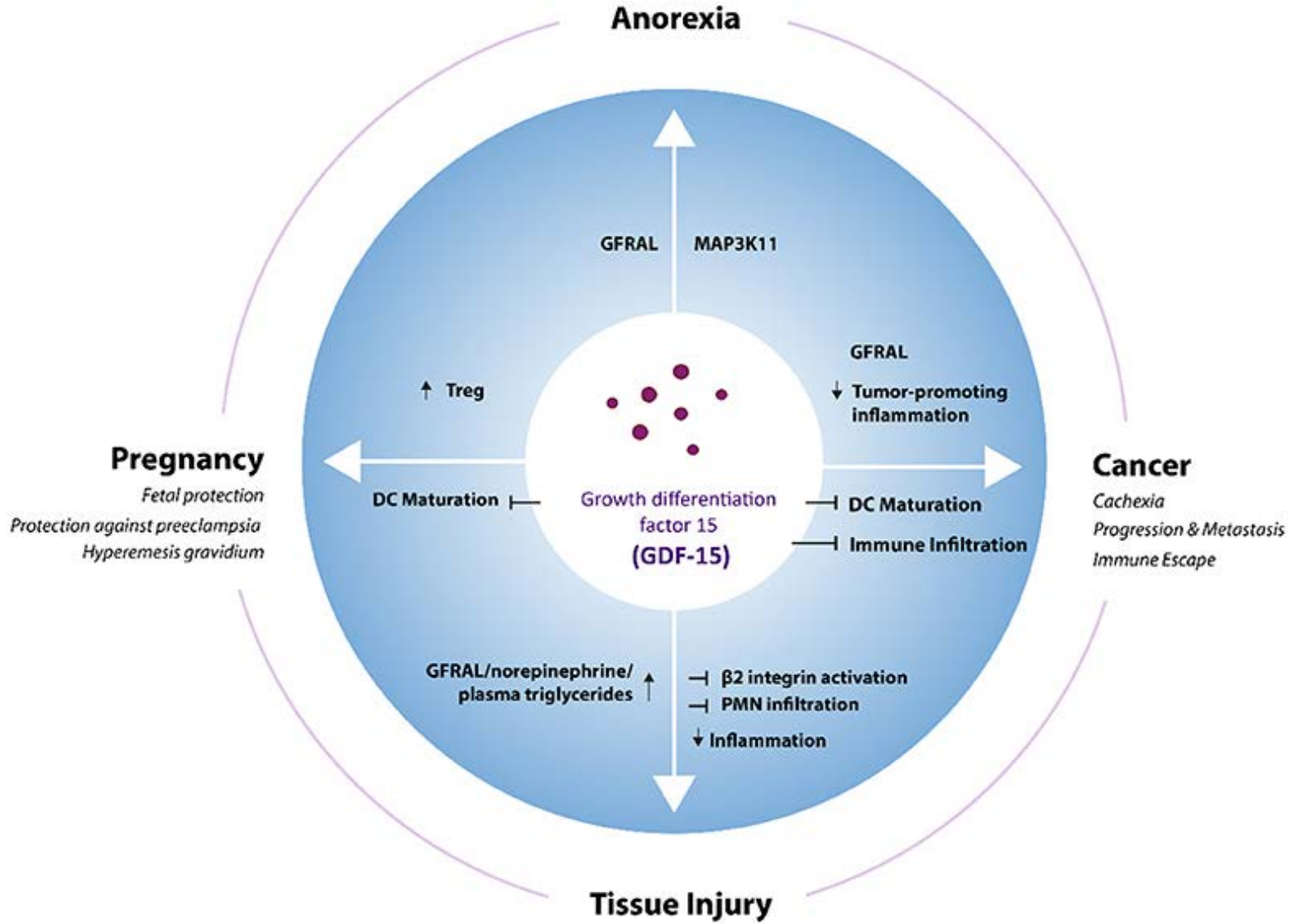


# Cytokines: TNF- $\alpha$

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

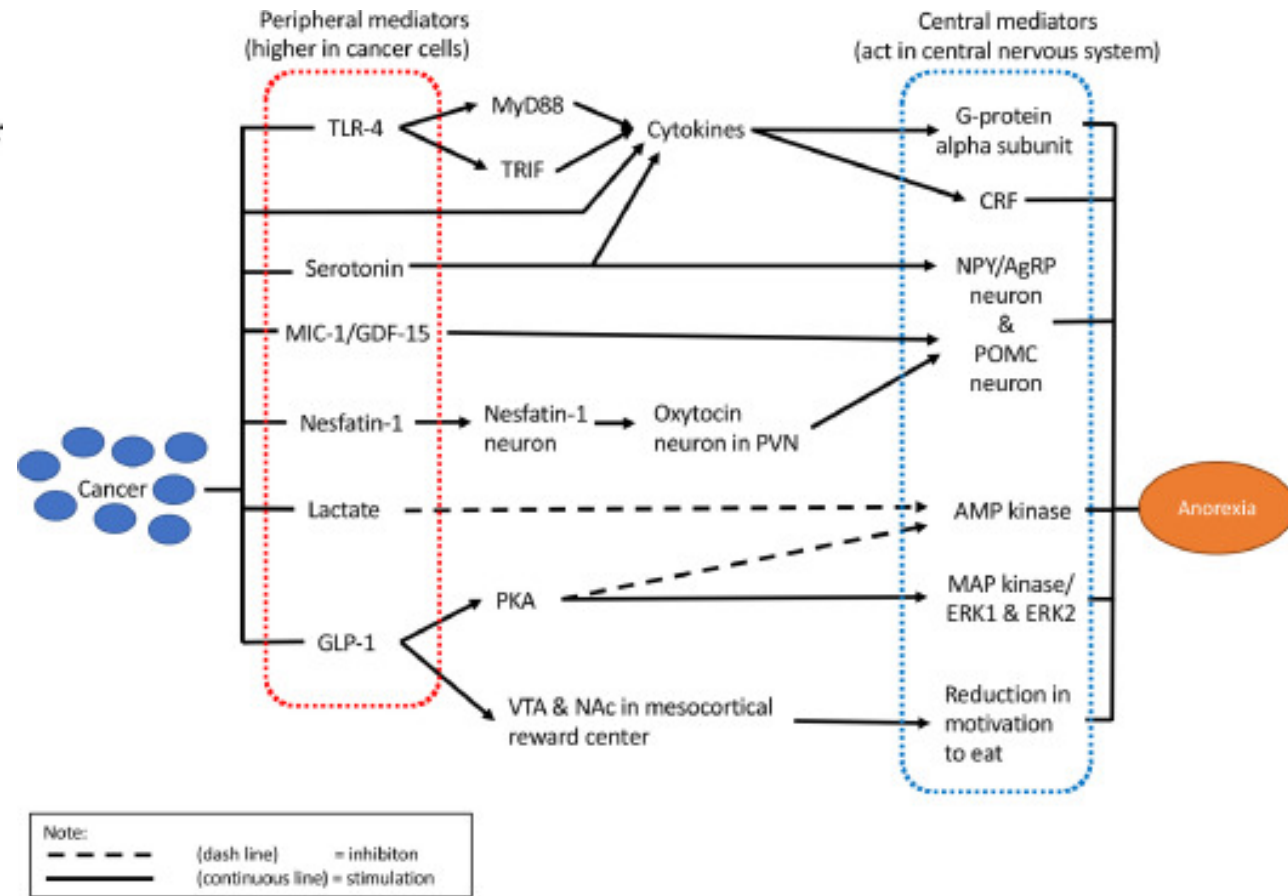
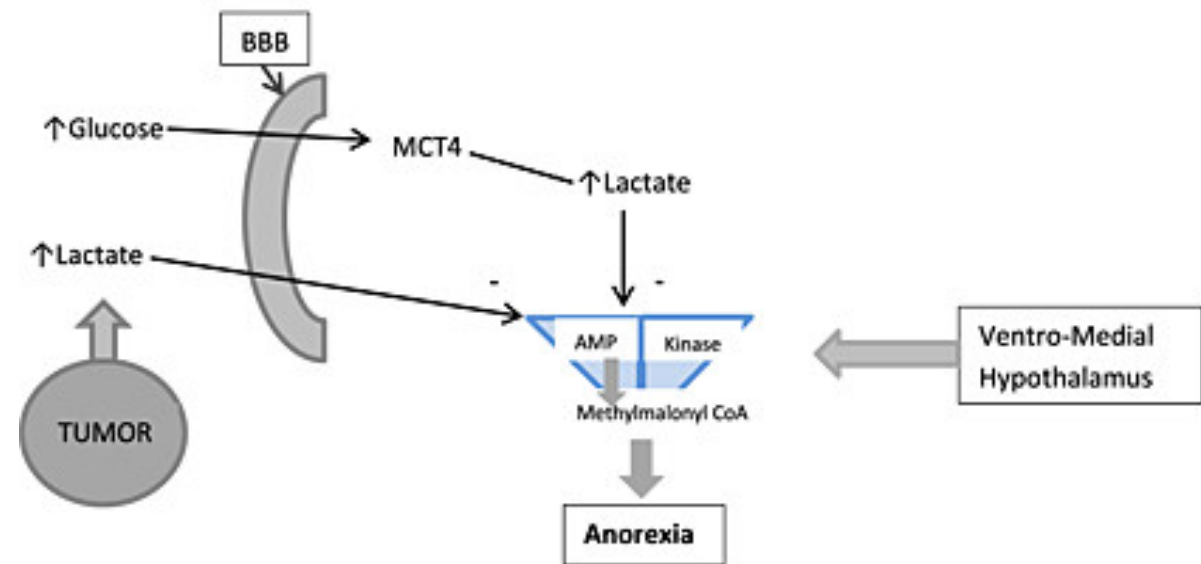


# Macrophage inhibitory cytokine-1/growth and differentiation factor-15

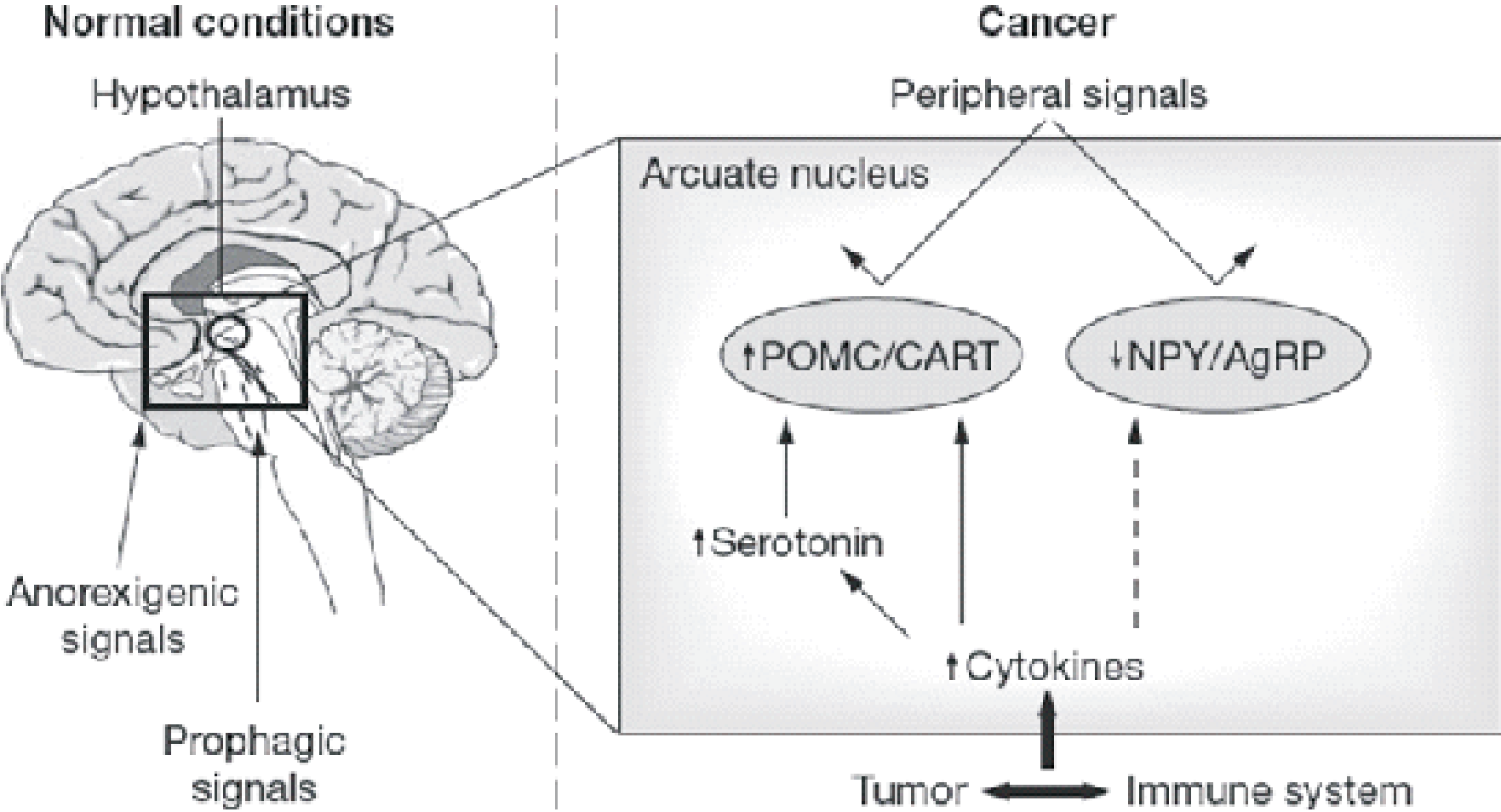


# Lactate

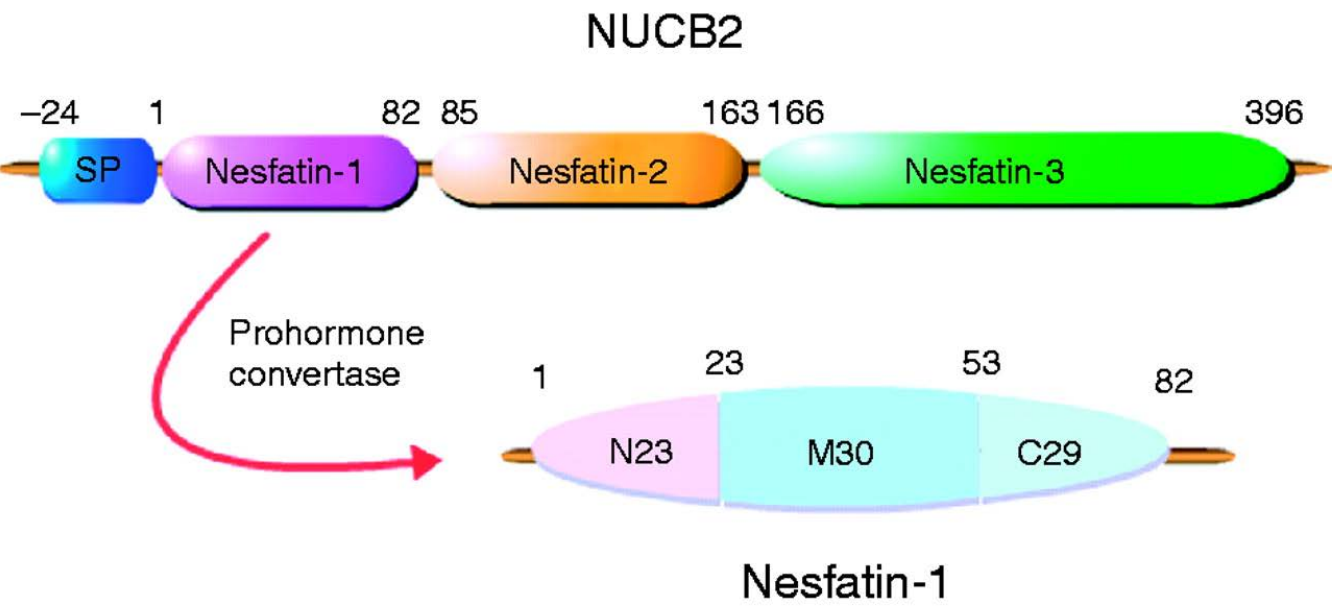
↑ = Increased; - = inhibits; BBB = Blood Brain Barrier; MCT4 = Monocarboxylate transporter



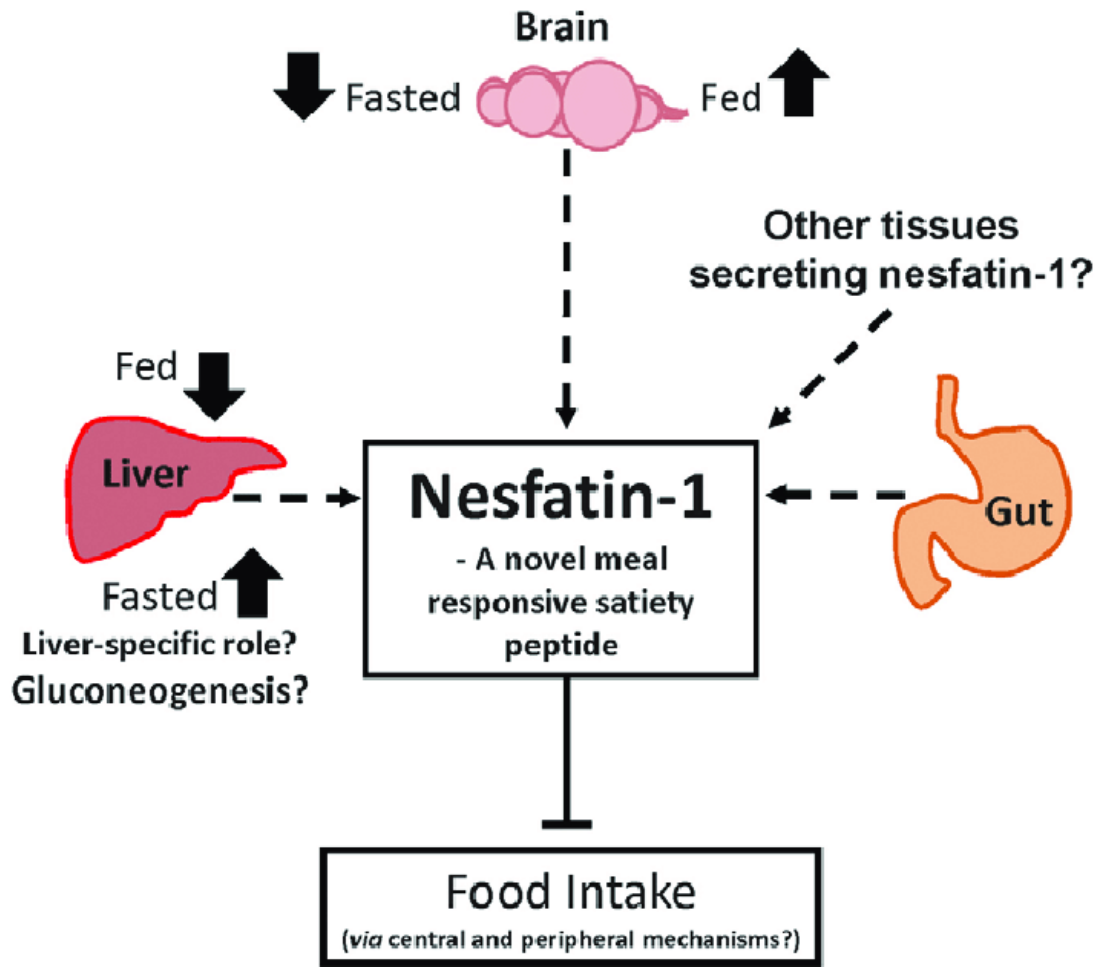
# Serotonin



# 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]	$\leq 24$ $\leq 37$ $\leq 32$
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]	$\leq 70$

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= <i>a</i> little, 3=quite a bit, and 4=very much).	Buskermolen etal. [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 etal. [107]	≥4

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A/CS=Anorexia/Cachexia Scale;.

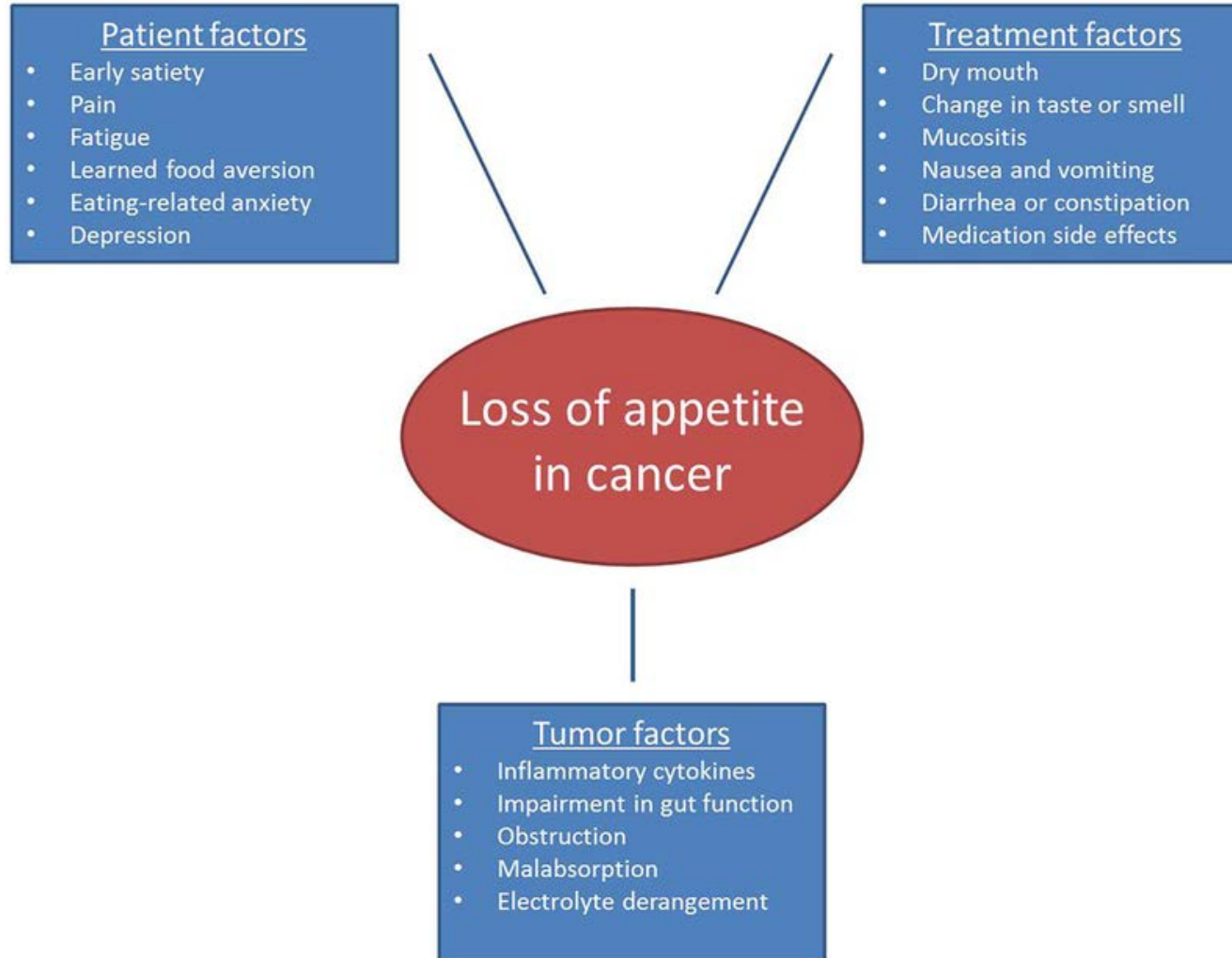
FAACT=Functional Assessment of Anorexia/Cachexia Therapy;.

VAS=Visual Analog Scale;.

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

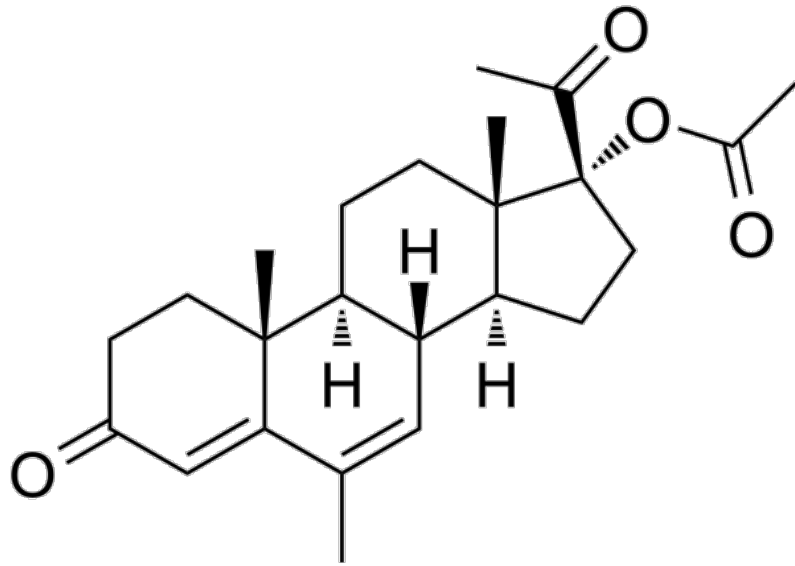
ESAS=Edmonton Symptoms Assessment Scale.

# Treatment



# 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	<p>Modulation of calcium channel in the satiety center of the ventromedial hypothalamus (VMH).</p> <p>Directly increase NPY levels in hypothalamus.</p> <p>Inhibit the activity of proinflammatory cytokines (IL-1, IL-6, TNF-<math>\alpha</math>, and IFN-<math>\gamma</math>).</p>	160mg to 1600mg/day.	Dyspnea, edema of extremities, impotence, thromboembolic phenomena, gastrointestinal intolerance.

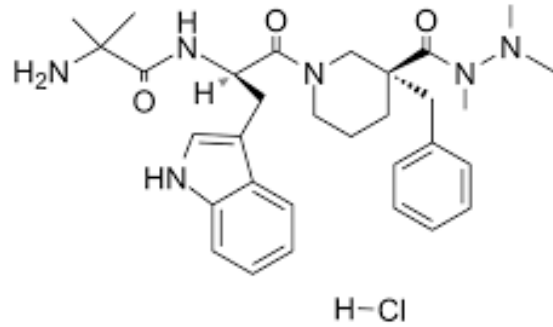


## Anamorelin HCl

Bind to and stimulate GHSR that stimulate NPY production.

50mg to 100mg/day

GI disorder (nausea, diarrhea, vomiting), cardiac disorder (ischemia, cardiomyopathy), metabolic disorder (hyperglycemia, hypocalcemia), fatigue, rash.



Decrease the production of proinflammatory cytokines (IL-6, TNF- $\alpha$ ).

## Cannabinoids

Work in the CB1 receptor in the hypothalamus to stimulate appetite.

Stimulate the mesolimbic reward system.

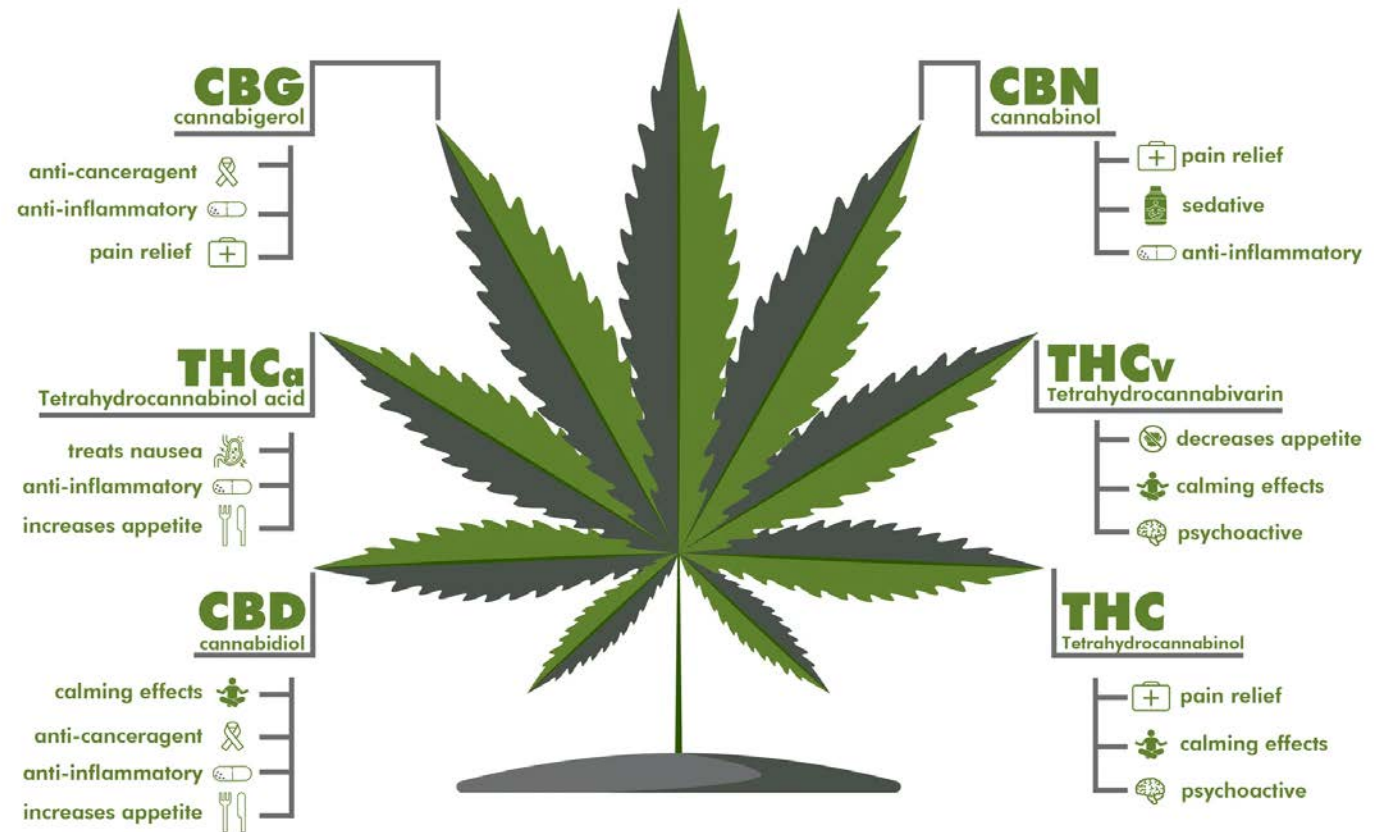
Inhibit proinflammatory cytokines (IL-1, IL-6, and TNF- $\alpha$ ).

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.

## BENEFITS OF CANNABINOIDS



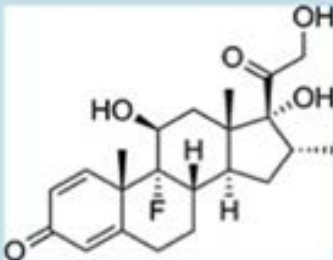
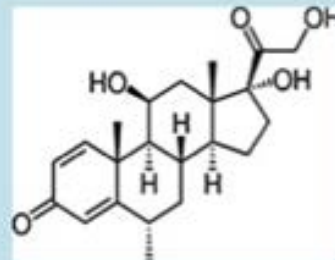
## Corticosteroids

Inhibit the release of proinflammatory cytokines (TNF- $\alpha$  and IL-1).

Enhance NPY levels in the hypothalamus via AMPK signaling.

Prednisolone 5mg three times daily;  
dexamethasone 3–6mg daily;  
methylprednisolone 125mg daily.

Oral symptoms, restlessness, weakness, delirium, osteoporosis, immunosuppression.

	Dexamethasone	Methylprednisolone
		
<b>Mechanism of Action</b>	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)	
<b>Therapeutic Considerations</b>	<ul style="list-style-type: none"><li>• Have not been demonstrated to increase weight</li><li>• More beneficial for those with a short life expectancy<ul style="list-style-type: none"><li>• Effect is short: 3-4 weeks</li></ul></li></ul>	

## Mirtazapine

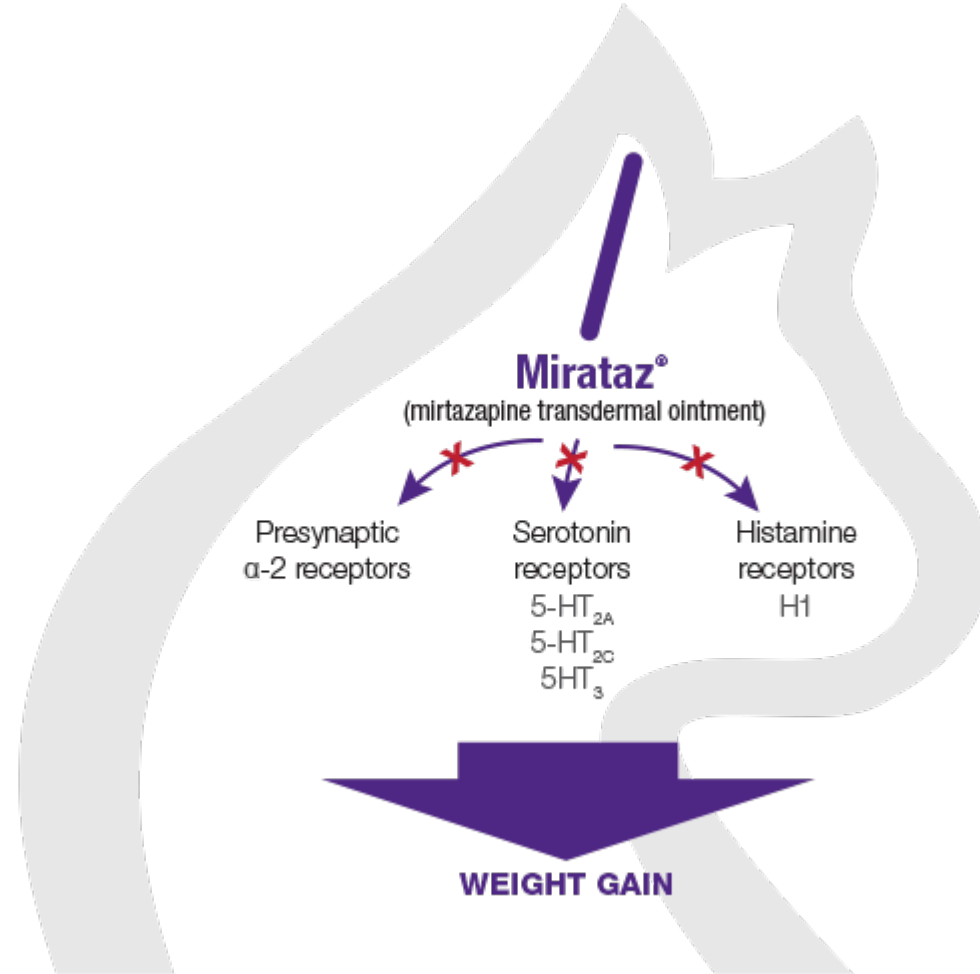


Mirtazapine

Inhibit 5-HT<sub>3</sub> receptor that mediates nausea and vomiting.

Inhibit 5-HT<sub>2c</sub> receptor which can help to increase in food intake.

7.5 mg daily to 30 mg daily. Confusion, dizziness, blurred vision, dry mouth and drowsiness.



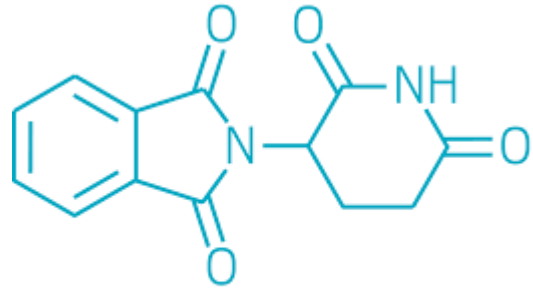


Thalidomide

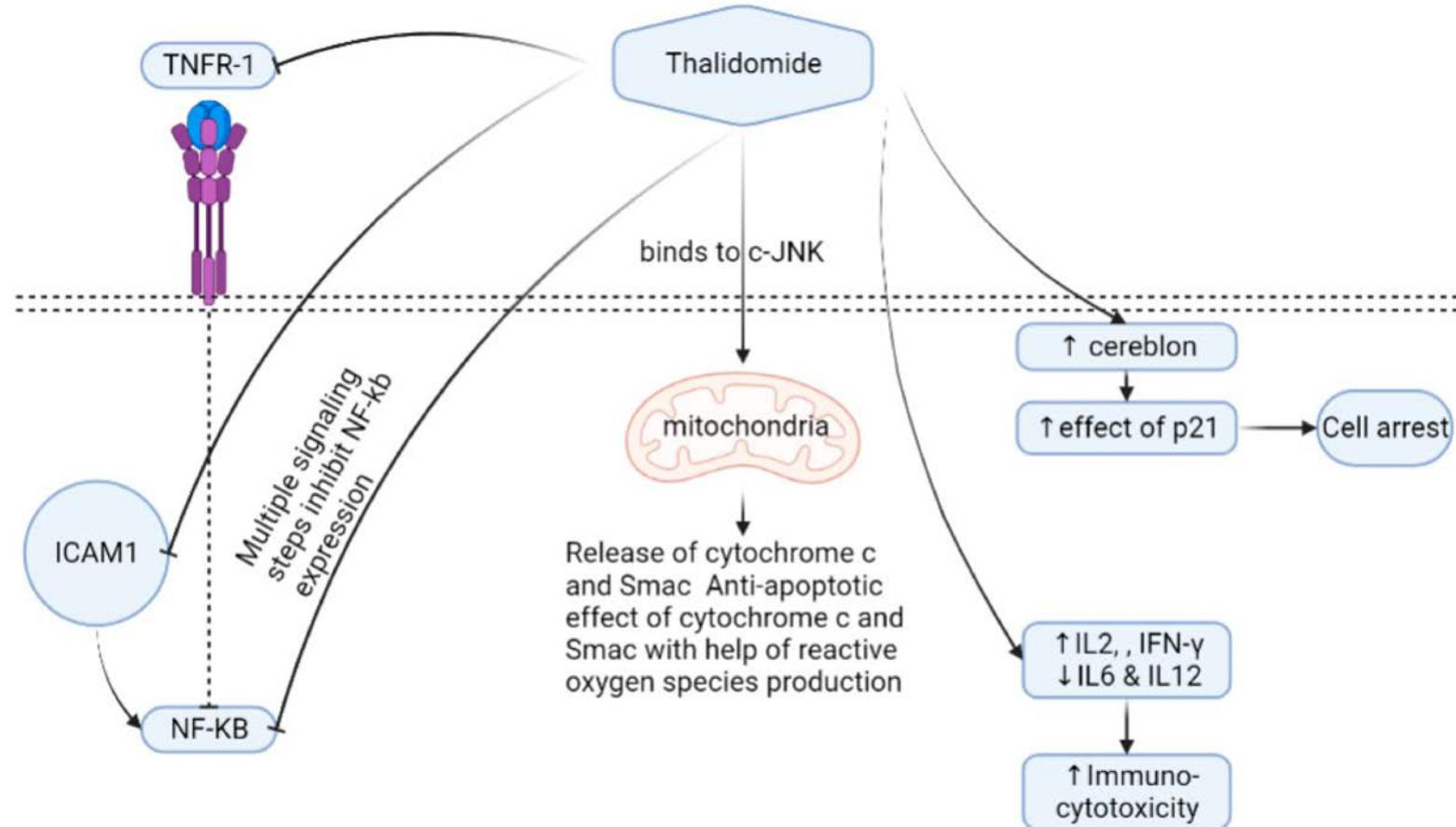
Reduce the production of TNF- $\alpha$  and IL-1 $\beta$ .

50mg daily to 200mg daily.

Peripheral neuropathy, paresthesia, rash, daytime somnolence, VTE, diarrhea, headache, nausea.



**Thalidomide**



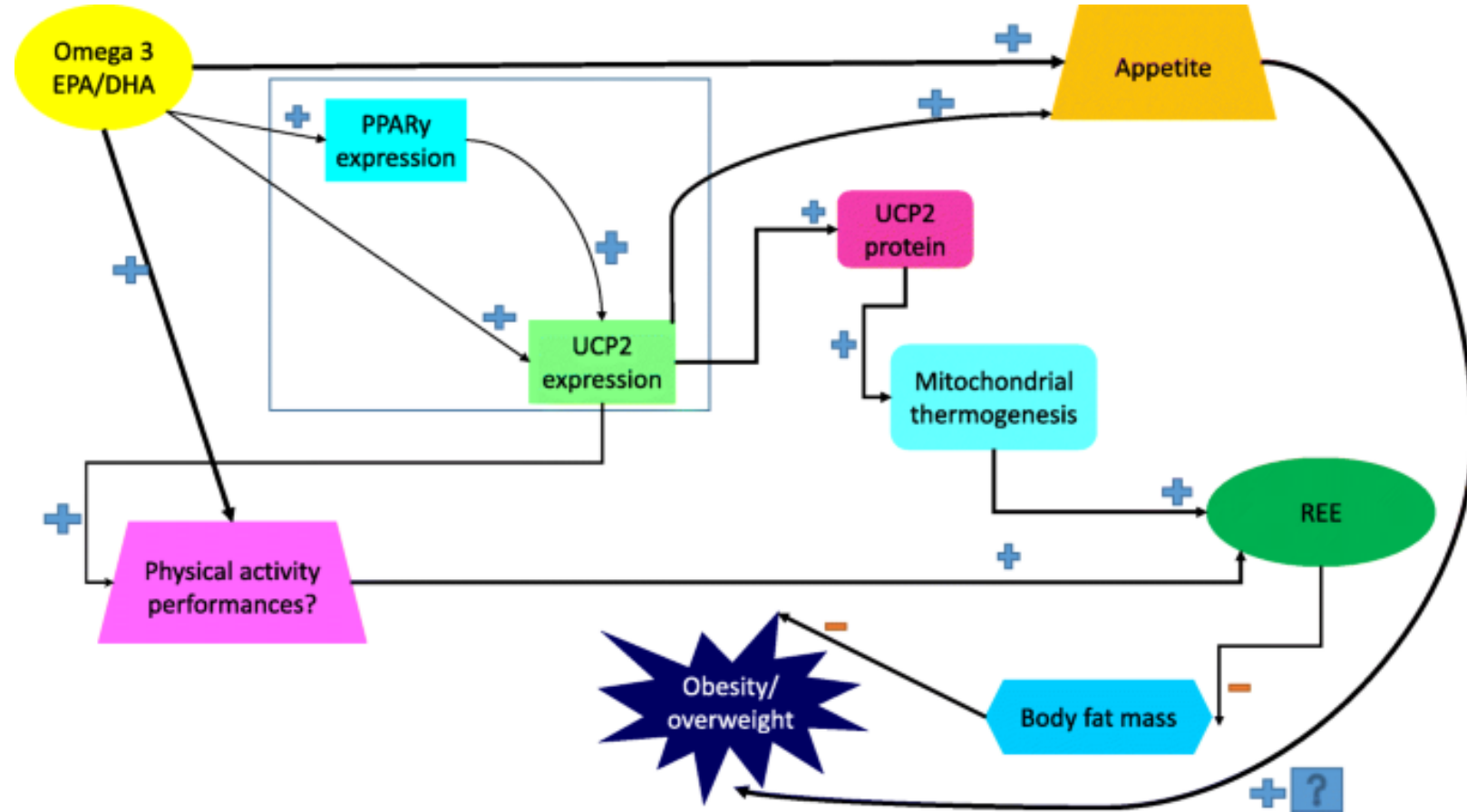
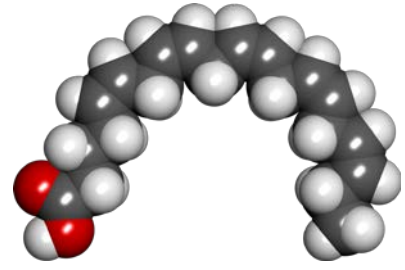
Eicosapentaenoic acid (EPA)

Downregulate CRP, IL-6 and TNF- $\alpha$  production.

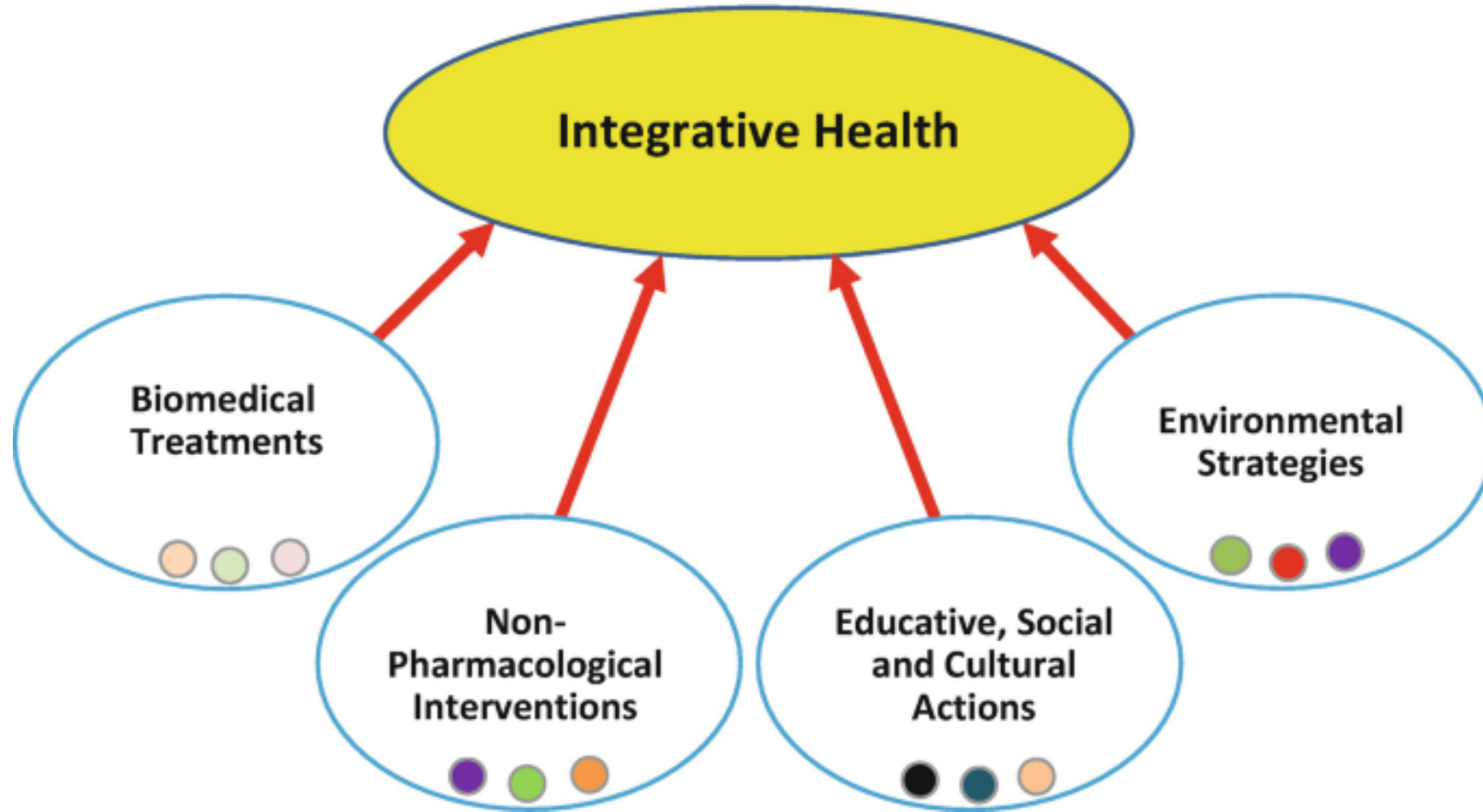
1 g once daily to 1 g twice daily. N/A

Inhibit the ubiquitin proteasome pathway.

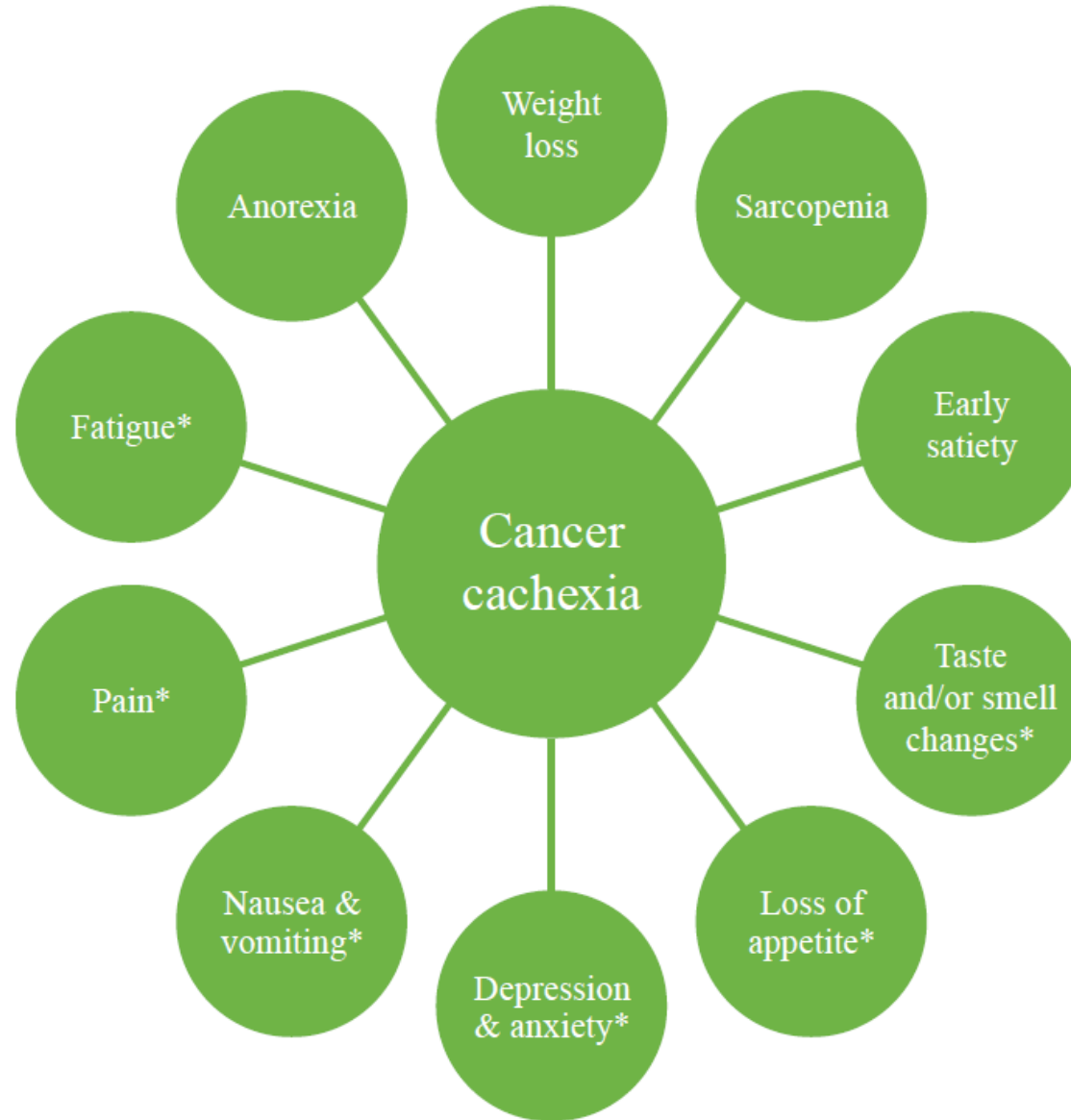
Increase insulin sensitivity.



# Non-pharmacological Interventions



# Should loss of appetite be palliated?



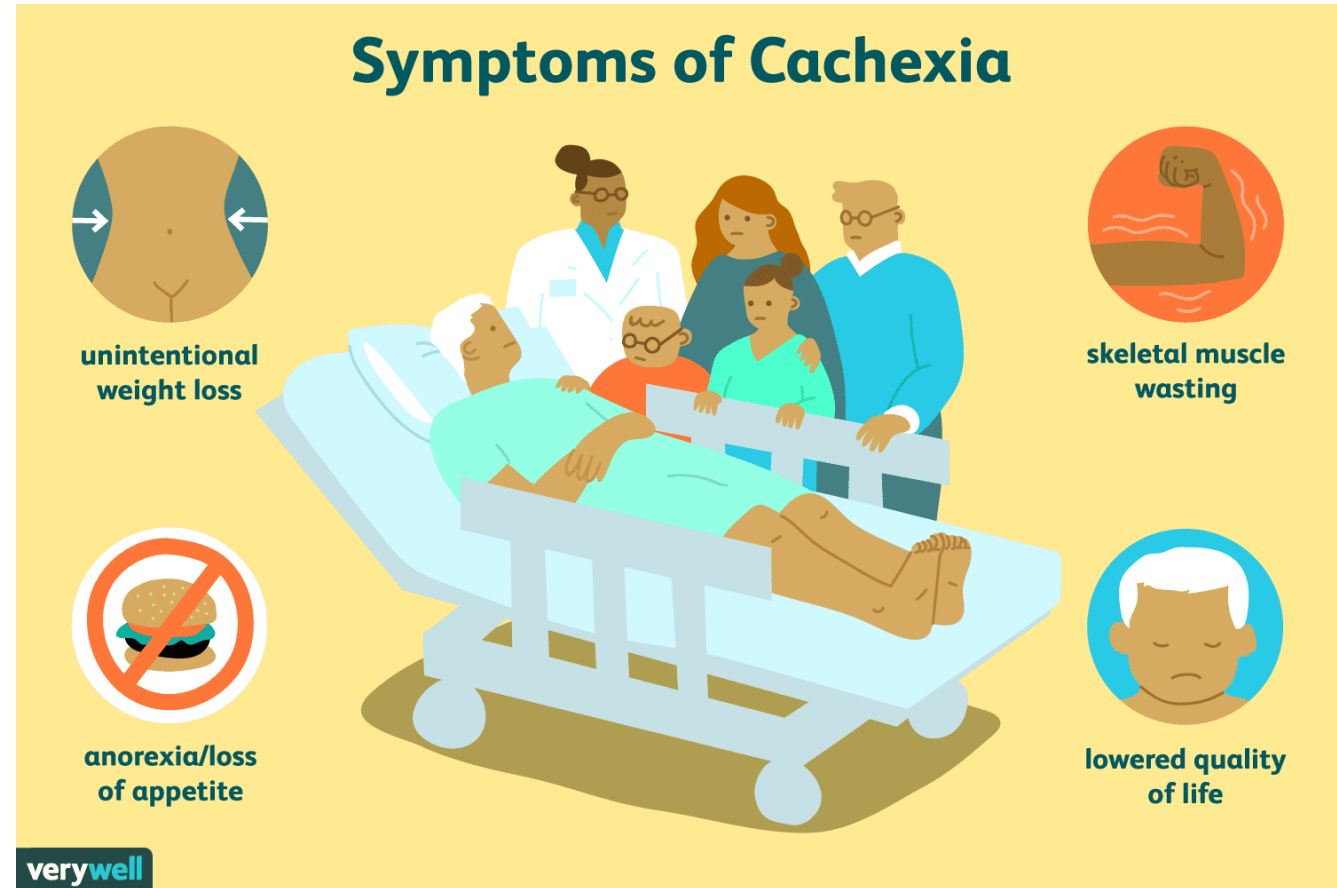
# Dietary Counseling

- 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].



# Sources

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Questions/Comments