Opening the fridge never been so difficult: Neuroendocrine pathways that regulates hunger and satiety. Identification of pharmacological targets against obesity.

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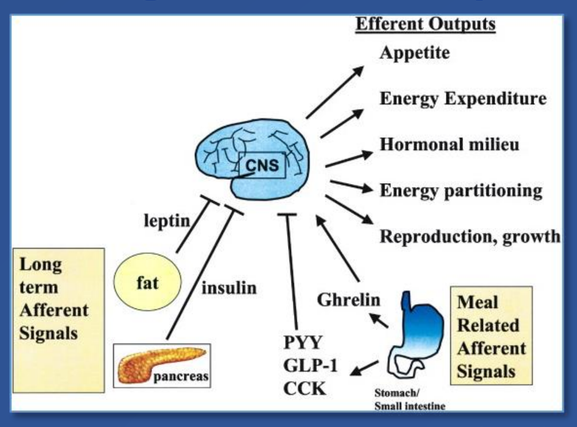
Have you ever wondered why you eat? Although hunger would be the omnipresent answer, we are closely attached to the conditions of our *Internal Milieu*. So the correct answer would be "I eat because my energetic deposits are low". Peripheral and CNS shares information thanks to the presence of neuropeptides and neurotransmitters. Energetic status, mechanical stomach-related information, nutrients availability and many more trigger several mechanisms and pathways that regulates hunger and satiety. The central integrator of all this information is the brain. Specifically hypothalamic and brain stem structures which are able to increase/reduce our food intake, increased/decrease of the energy expenditure. Paying special attention to our neurologic integrator, I explain the most important regulation tags and point out targets for the treatment of obesity.

Regulation duality



Adapted from Flyer, J. Cell 116, 337–350 (2004).

Long-term regulation

Leptin:

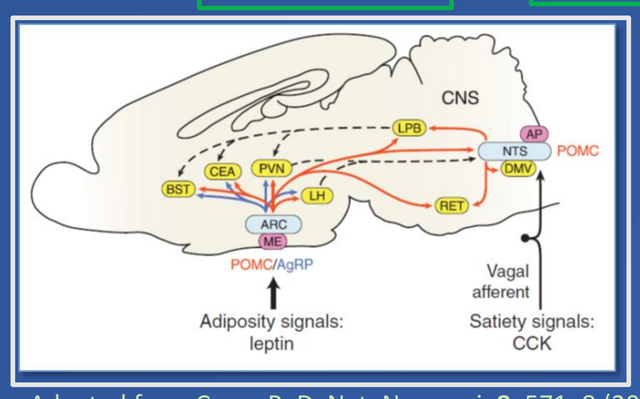
- A 165 aminoacid hormone which is mainly secreted in the lipids deposits.

High adipose deposits → Higher leptin secretion → Leptin as an adipose reporter

Insulin:

- Known as an metabolic modulator is produced on β-pancreatic cells.
- Glucemic reporter to the brain

High insulin and leptin concentrations → *Arcuate* nucleus / *Paraventricular nucleus* → *Reduce food intake and decrease energy expenditure*

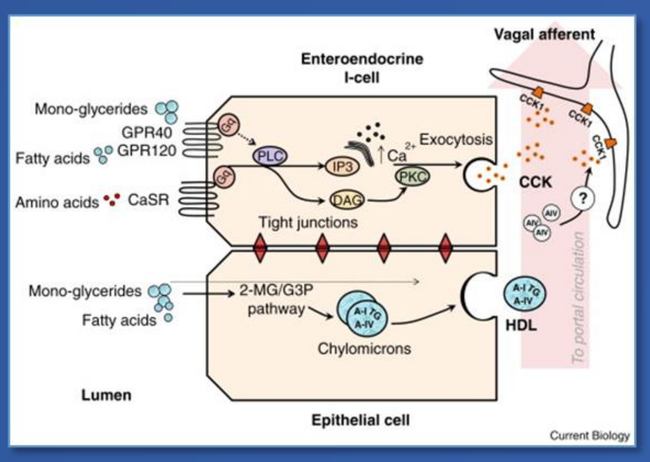


Adapted from Cone, R. D. Nat. Neurosci. **8,** 571–8 (2005).

Short-term regulation or meal related satiety signals

CCK(cholecystokinin):

- Anorexigenic neuropeptide
- L enteroendocrine cells secretion GPCR-dependent (40&120)
- High nutrients concentration triggers a vagal afference to the NTS.



Adapted from Murphy, K. G. & Bloom, S. R. Nature **444,** 854–9 (2006).

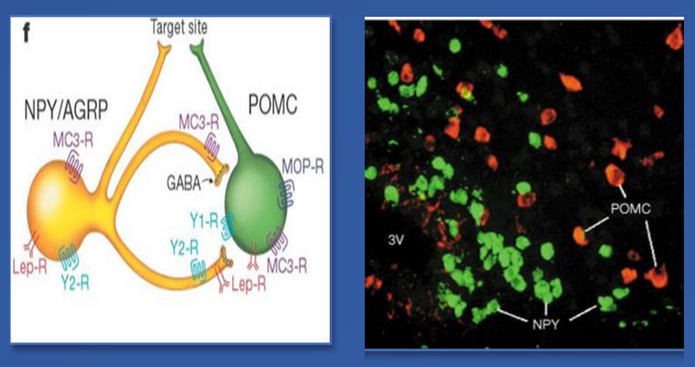
Although showed separately long and short term, its interaction is essential to maintain energetic homeostasis.

Hypothalamic regulation

Neuropeptides

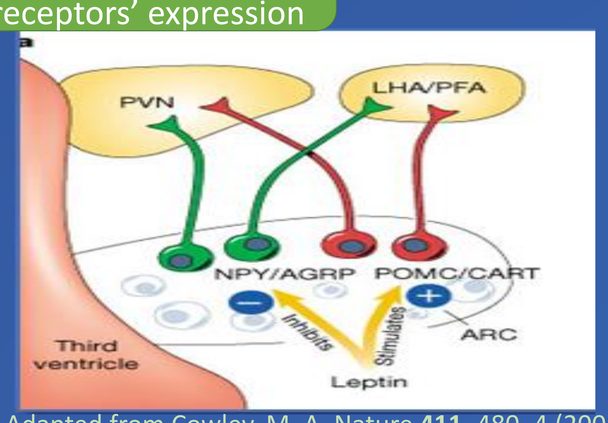
- Neurotransmitters and neuropeptides are important in food intake regulation
- Neuropeptide's secretion is attached to: high intracellular calcium molecules → not peptidic-like exocytosis (Large Density Secretion Vesicle)

Melanocortin system of the hypothalamus to regulate long-term hunger regulation.



Adapted from Chambers, A. P. Curr. Biol. **23,** R379–88 (2013).

NPY/AGRP Gabaergic POMC/CART inhibition + High leptin and others neuropeptides receptors' expression → Great importance in food intake regulation

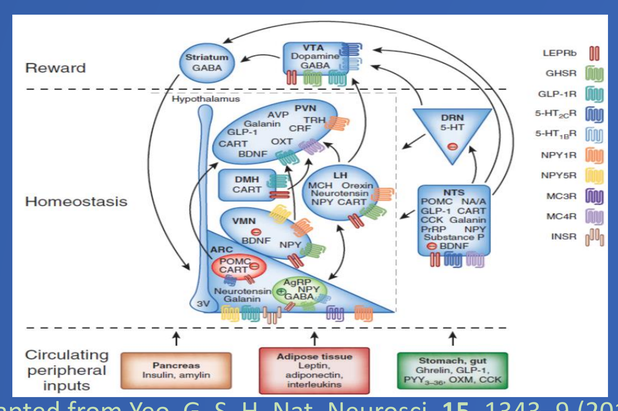


Adapted from Cowley, M. A. Nature **411,** 480–4 (2001).

1. High leptin concentration inhibits NPY neurons by hyperporalization (K+ channels opening)
2. Antagoniusly, leptin stimulates POMC neurons by desporalization (TRPC channels)
3. Paraventricular and Lateral hypothalamic nuclei are stimulated by NPY/AGRP and POMC/CART integrative responses

Several afferent innervations affect the melanocortin system:

Integrative responses from melanocortin system, nutrients availability, reward system trigger hunger regulation.



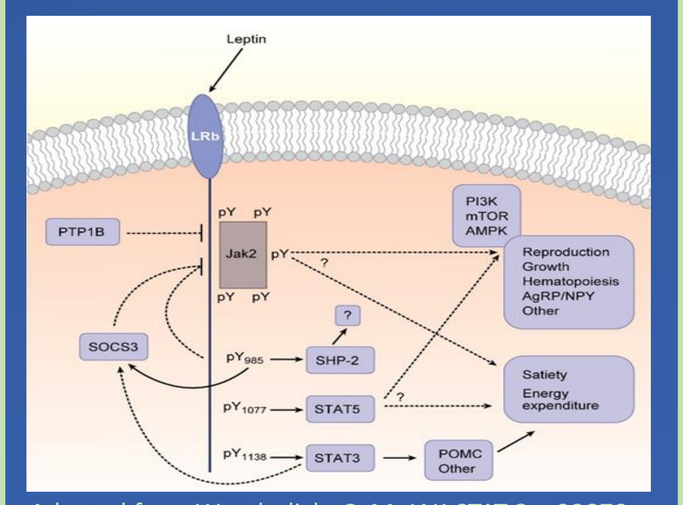
Adapted from Yeo, G. S. H. Nat. Neurosci. **15,** 1343–9 (2012).

Identification of pharmacological targets against obesity

Obesity is a pandemic disease affecting 1/3 of the First World.

Thanks to the identification of the important features of long-term food intake regulation we can approach pharmacological targets against obesity:

- Resistance to the Ob-R → a negative feedback through SOCS3 protein and long-term phosphorylations



Adapted from Wunderlich, C. M JAK-STAT **2,** e23878 (2013).

- Modification of the permeabilization to leptin trough tanicytes-independent transcytosis in the HEB.
- Differential stimulation of anorexigenic and orexigenic neuropeptides receptors:
  - Lorcaserin: 5-HT2C agonist
  - Venelperit: NPY5 antagonist

Regarded satiety meal-dependent responses reduces our food intake while we are eating, long-term regulation seems to offer a better response against obesity.

Conclusions

- Long and short term regulation are the biochemical pathways that inform our brain of our *Internal Milieu*
- Neuropeptides have a main character in hunger long-term regulation through stimulation and inhibition of hypothalamic nuclei
- There are several pharmacological targets to cure obesity but we aren't able to avoid off-targets.

References

- Coll, A. P., Farooqi, I. S. & O'Rahilly, S. The hormonal control of food intake. *Cell* **129,** 251–62 (2007).
- Cone, R. D. Anatomy and regulation of the central melanocortin system. *Nat. Neurosci.* **8,** 571–8 (2005).
- Wunderlich, C. M., integration. at Hövelmeyer, N. & Wunderlich, F. T. Mechanisms of chronic JAK-STAT3-SOCS3 signaling in obesity. *JAK-STAT* **2,** e23878 (2013).
- Cone, R. D. Anatomy and regulation of the central melanocortin system. *Nat. Neurosci.* **8,** 571–8 (2005).
- Berg, J. M., Tymoczko, J. L. & Stryer, L. Biochemistry. (2002). Chapter 15 Metabolism: basic concepts and