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

Long-term regulation
Leptin:
• A 165 aminoacid hormone which is mainly secreted in the lipids deposits.

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

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 concentration
• Reduce food intake and decrease energy expenditure


Short-term regulation or meal related satiety signals
CCK(cholecystokinin):
• Anorexigenic neuropeptide
• L enteroendocrine cells secretion GPCR-dependent (40,8,120)
• High nutrients concentration triggers a vagal afference to the NTS.


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 peptide-like excytosis (Large Density Secretion Vesicle)

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

NPY/AGRP Gabaergic POMC/CART inhibition
High leptin and others neuropeptides receptors’ expression


1. High leptin concentration inhibits NPY neurons by hyperpolarization (K+ channels opening)
2. Antagonistically, leptin stimulates POMC neurons by despolarization (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.


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
• Modification of the permeabilization to leptin trough tancytes-independent transcytosis in the HEB.
• Differential stimulation of anorexigenic and orexigenic neuropeptides receptors:
  • Lorcaserin: 5-HT2C agonist
  • Venlafex: 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
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