2022 비만대사증후군 연구회 춘계 연수강좌

식욕조절 기전과 관련 비만약물

2022. 5. 21

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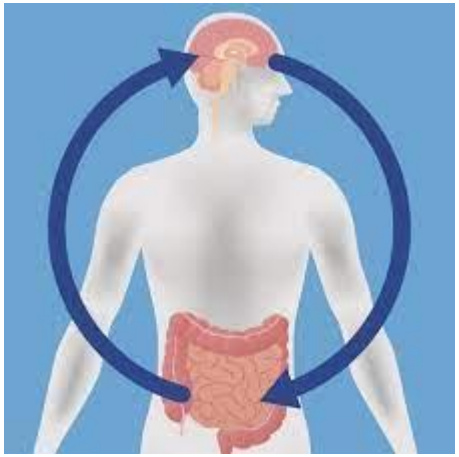
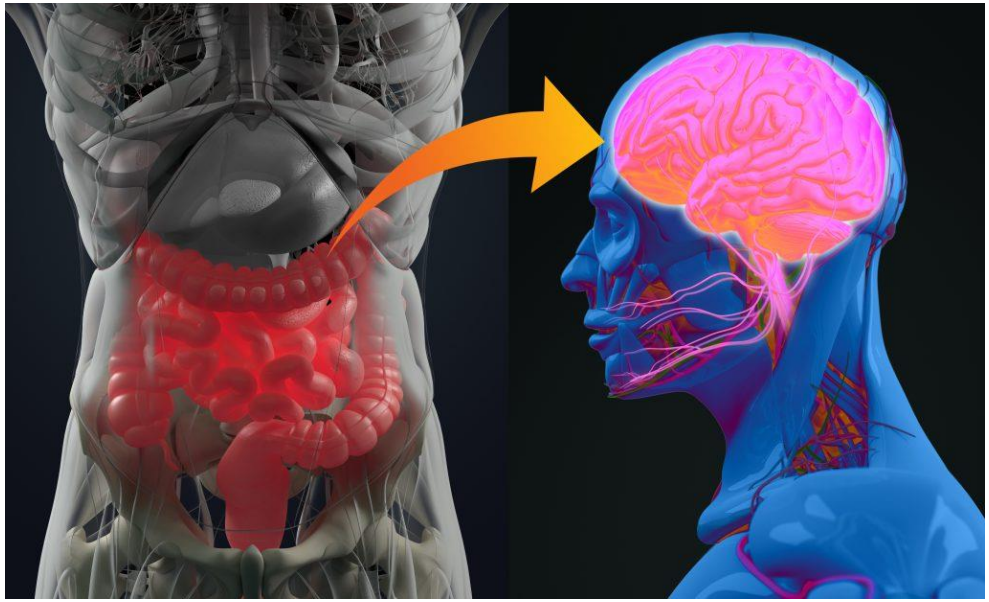
Regulation of appetite

- Key role in weight control
- Too complex
  - Brain
  - Gut
  - Adipose
  - Education
  - Environment

Physiologic(Homeostatic) appetite regulation





Gut Hormones

- Pancreatic Polypeptide-Fold Peptides
  - Peptide YY (PYY)
  - Pancreatic polypeptide (PP)
  - Neuropeptide Y (NPY)
- Proglucagon - Derived Peptides
  - Glucagon-Like-Peptide-1 (GLP-1)
  - Oxyntomodulin (OXM)
- Ghrelin
- Obestin
- Cholecystokinin (CCK)

Pancreatic Polypeptide-Fold Peptides

- **Peptide Tyrosine Tyrosine (PYY)** : PYY_{1-36}, PYY_{3-36}
  - **Appetite suppressing hormone**
  - Released from the L-cells of the distal gut (response to ingested nutrients)
  - Low concentration in Fasted states, peak at 1-2 hr after meal
  - Administration of PYY : reduce appetite and food intake (Animal)
  - Y2 Rc : cardiovascular effect (HTN)

Pancreatic Polypeptide-Fold Peptides

- **Pancreatic polypeptide (PP)**
  - **Appetite suppressing hormone**
  - Secreted from PP cell in the pancreatic islet of Langerhans in response to a meal
  - Act on Y4 Rc in brainstem and hypothalamus : area postrema (AP), nucleus of the tractus solitarius (NTS), dorsal motor nucleus of vagus (DVN), ARV, PVN
  - Delaying gastric emptying, decrease pancreatic exocrine secretion, inhibiting GB contraction
  - Diurnal variation : low in the morning, high in the evening
  - Increase after meal, remain up to postprandial 6 hrs

Proglucagon-Derived peptides

- **GLP-1, GLP-2, OXM, glucagon**

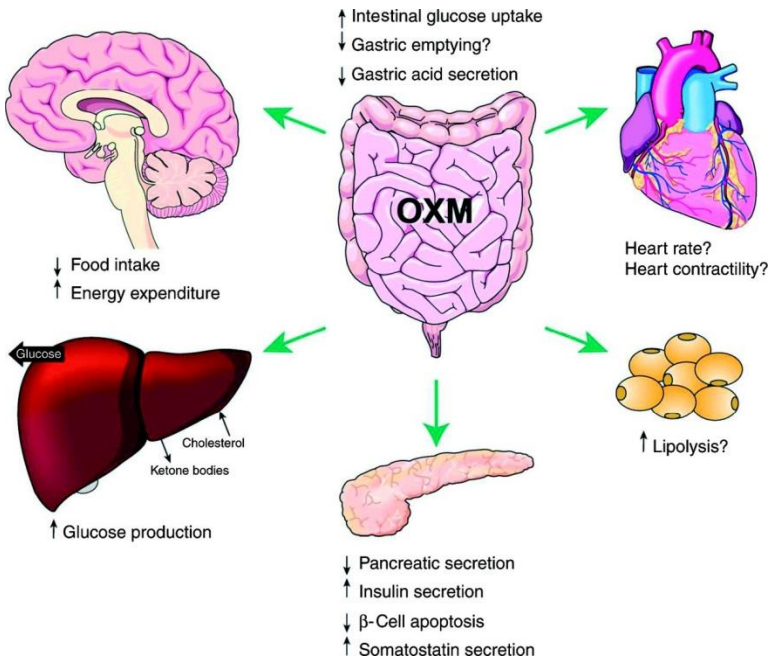
- **GLP-1 (Glucagon like peptide-1)**
  - **Anorectic effect**
  - Co-secreted with PYY from the L-cell in the intestine
  - GLP-1 in CNS (PVN, DMN, NTS, dorsal vagal complex(DVC), pituitary, thalamus)
  - GLP-1 Rc : widely distributed in brain, GI tract, pancreas
  - Increase after meal, fall in the fasting
  - Reduction of food intake, suppression of glucagon secretion, delaying gastric emptying
  - Incretin effect : stimulation of insulin secretion
  - Short half-life time (1-2 min, by DPP-VI)

Proglucagon-Derived peptides

- **Oxyntomodulin (OXM)**
  - Secreted by L-cells of the distal GI-tract with GLP-1, PYY in response to food intake
  - **Anorectic effect, incretin effect**
  - Reducing food intake, inhibition of gastric acid secretion, delaying gastric emptying
  - Administration of OXM (Animal)

    : decrease food intake,

    : increase energy expenditure
  - Inactivated by DPP-IV



Obstatin

- **Anorectic effect**
- Released from stomach

(originally derived from posttranslational cleavage of preproghrelin)

- Decreasing food intake, delaying gastric emptying
- Fail to demonstrate effects on food intake after administration (Animal)

Cholecystokinin (CCK)

- **Anorectic effect**
- Gastric emptying time increase
- Secreted postprandially by I-cell of the small intestine
- Short plasma half-life (a few minutes)
- Experimentally disappointing results (Human, Animal study)
- CCK + Leptin : synergistic effect

Amylin

- **Anorectic hormone**
- Co-released with insulin in response to meal ingestion
- Released from B-cell in pancreatic islet of Langerhans
- High level in obese subjects
- Anorectic effect by modulating activity of the serotonin, histamine, dopaminergic system (brain)
- Glycaemic control, satiety (delaying gastric emptying)
- Pramlintide : Synthetic analogue of human amylin

Ghrelin

- **Orexigenic gut hormone**
- Principally secreted from X/A-like cells within gastric oxyntic glands (80% ?)
- Increased by fasting decreased by feeding (not water)
- (Animal) administration(periph. & CNS) increase food intake and body Wt. / reduce fat utilization
- (Human) Negative correlation btw ghrelin and BMI
- Orexigenic action via stimulation of NPY/agouti-related peptide(AgRP) neurons in ARC of hypothalamus
- Brainstem, vagus N. contribute to orexigenic effect of Ghrelin

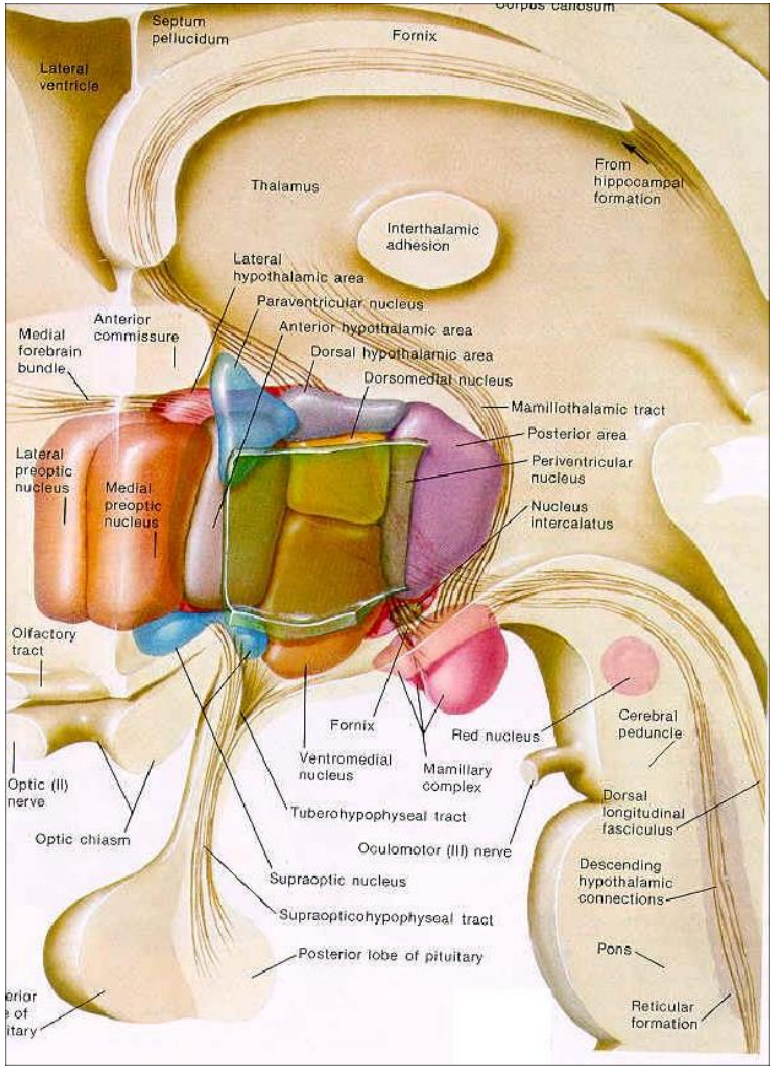
Adipose

- Adipocytokine : Leptin, adiponectin, resistin, visfatin etc.
- **Leptin**
  - Product of ob gene
  - **Anorectic effect** via ARC (NPY/AgRP, POMC/CART)
  - Reduced food intake, increased energy expenditure
  - Gut satiation signals (ex.CCK) can be amplified by Leptin
  - Exogenous leptin administration : ?? (resistance?)

Hypothalamus

- Control feeding by integrating peripheral hormonal signal with neural signal from brainstem

- Arcuate nucleus (ARC),
- Paraventricular nucleus (PVN),
- Ventromedial nucleus (VMN),
- Dorsomedial nucleus(DMN)
- Lateral hypothalamic area (LHA)



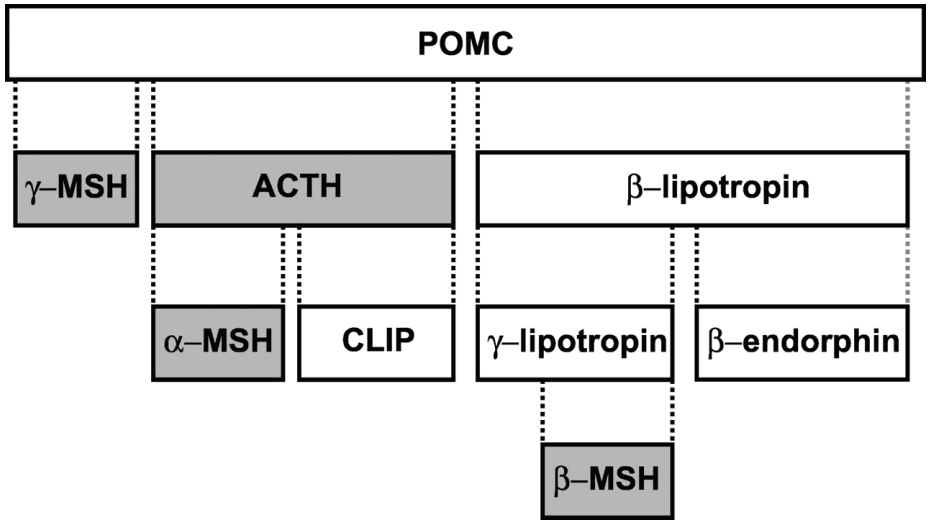
Arcuate nucleus (ARC)

- **Neuropeptide Y (NPY), agouti-related peptide (AgRP)**
  : Stimulate food intake

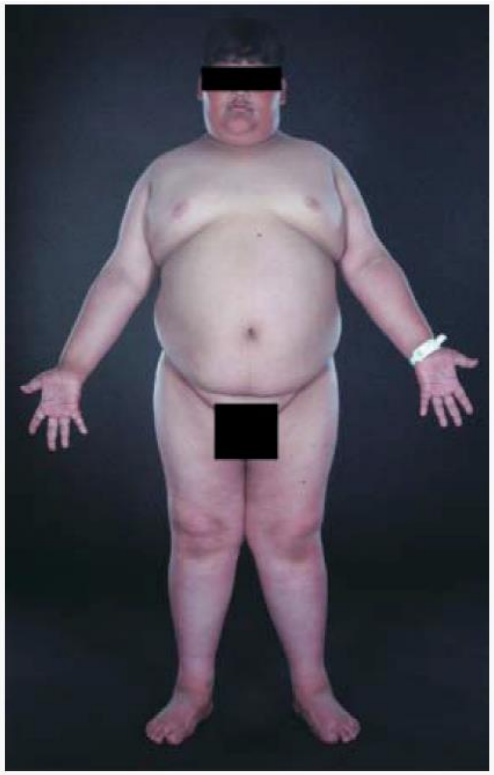
- **Pro-opiomelanocortin (POMC), cocaine- and amphetamine-related transcript (CART)**
  : Suppress food intake

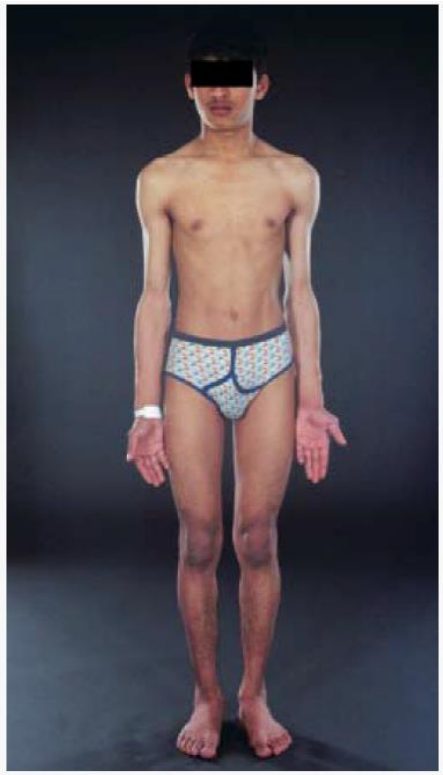
POMC

- Major role of anorectic stimulation
- POMC (cleavage of a precursor protein) produces ACTH, α-melanocyte-stimulating hormone (**α-MSH**), β-MSH, γ-MSH, β-endorphin,
- α-MSH binds to malnocortin-4 Rc. (**MC4R**), melanocortin-3 Rc. (MC3R),
- MC4R : highly express in the hypothalamus(**PVN**), major role in suppressing food intake



MC4R Mutation



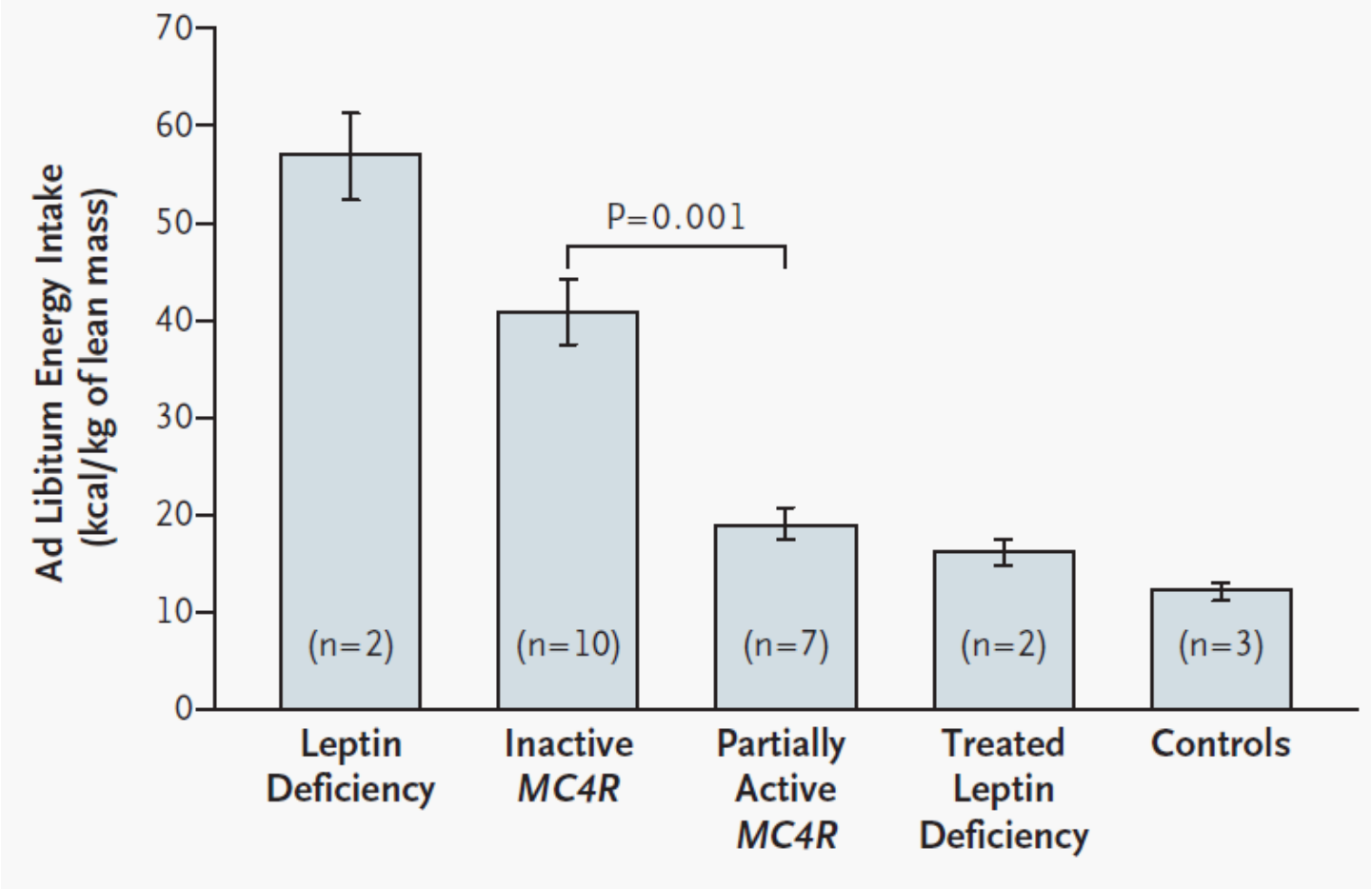


9-year-old boy homozygous for a mutation in MC4R

His 16-year-old brother

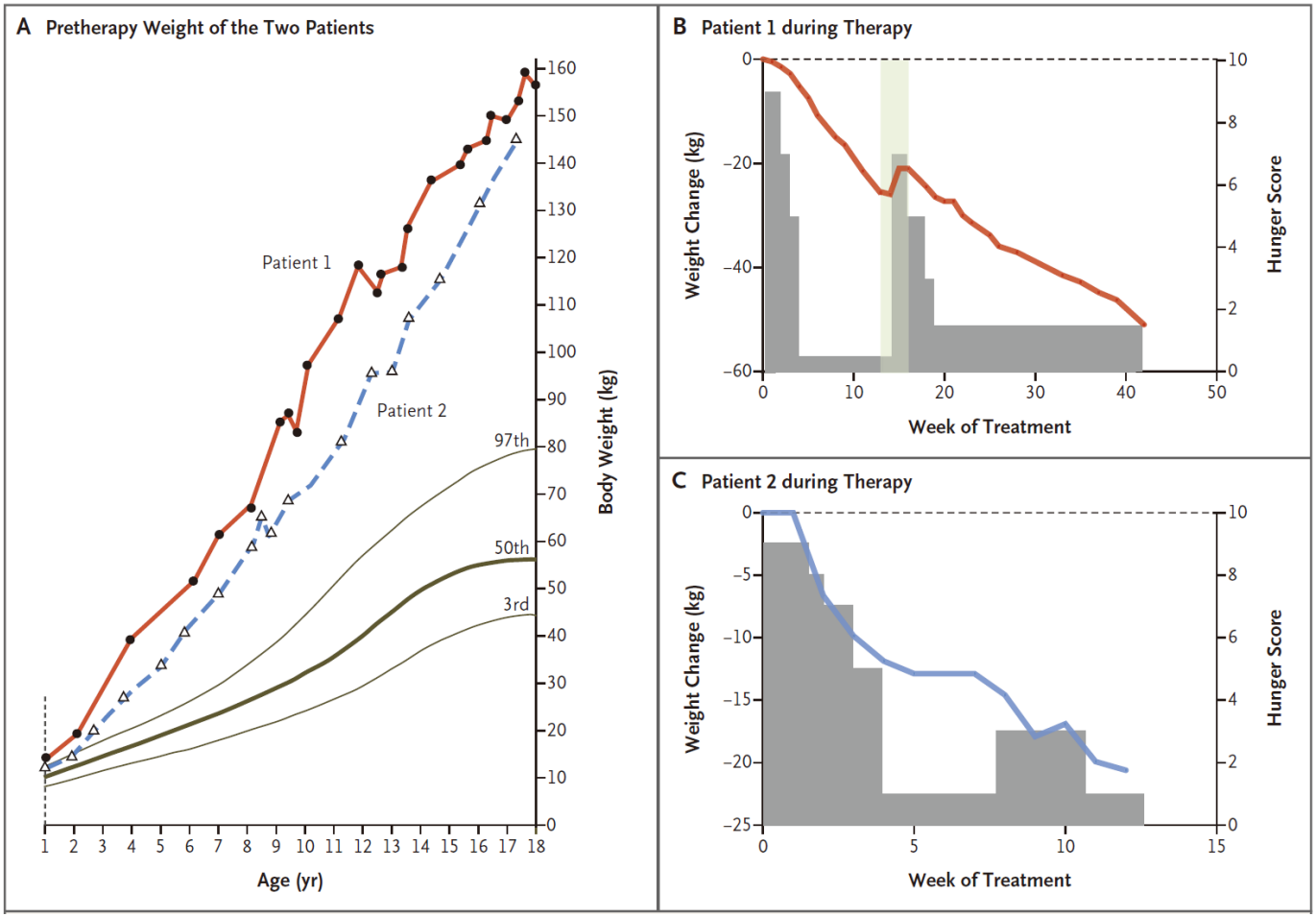
2003 NEJM Clinical Spectrum of Obesity and Mutations in the Melanocortin 4 Receptor Gene

Energy Intake in MC4R Deficiency and Leptin Deficiency



2003 NEJM Clinical Spectrum of Obesity and Mutations in the Melanocortin 4 Receptor Gene

MC4R Agonist for POMC Mutation Patient



2016 NEJM Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist

CART

- Relatively abundant transcript in hypothalamus
- Colocalized with POMC in the ARC
- Diverse effect on diet (depending on site)
  - Inj. CART in ICV : suppress feeding
  - Inj. CART in PVN or ARC directly : increase in feeding

NPY/AgRP

- **Orexigenic effect**
- NPY/AgRP neuron extensively project to the adjacent hypothalamic nuclei (ex. PVN, DMN, LHA etc.)
- NPY and AgRP colocalized in ARC
- (Animal) exogenous inj. Of NPY ICV : stimulate feeding
- NPY act via mediating by stimulation of hypothalaminc Y1, Y5 Rc.
- AgRP : potent-selective antagonist at the MC4R, MC3R

PVN

- Receive projection of POMC/CART, NPY/AgRP from ARC
- Thyrotropin- releasing H., corticotropin-releasing H.
- Diverse role in feeding through various substances
- Destruction of PVN : cause hyperphagia and obesity
  - Inhibitory role in food intake

LHA

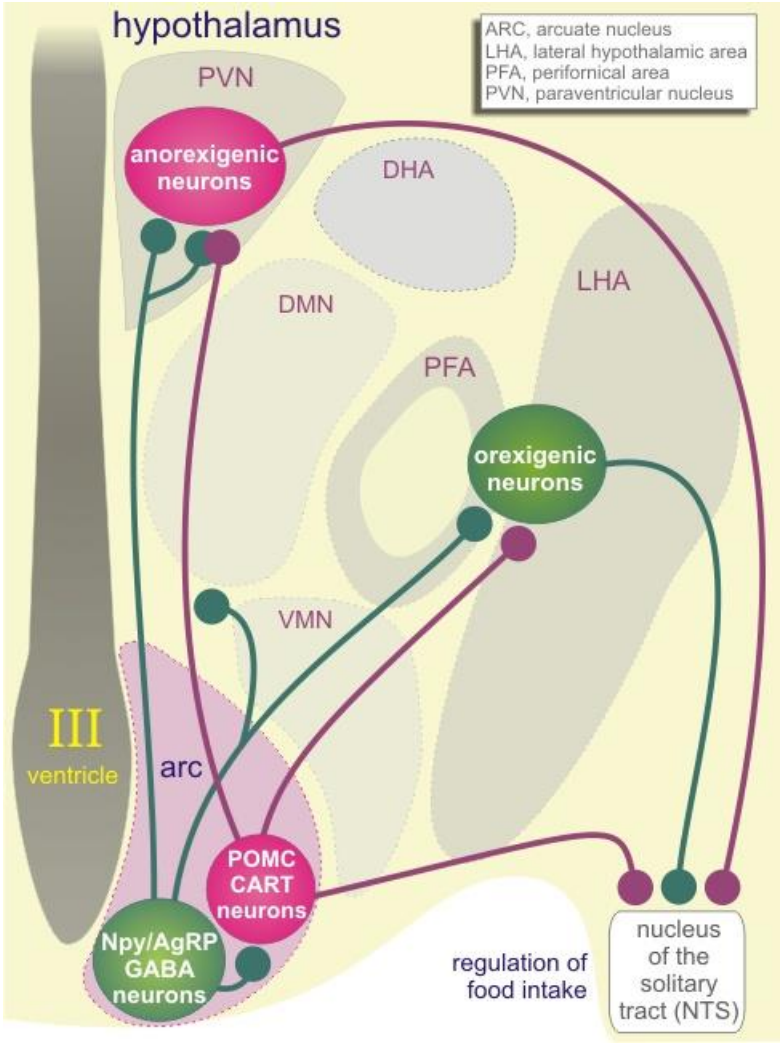
- Receive projection from the ARC
- Contains 2 orexigenic neuropeptide
  - **Melanin-concentrating hormone (MCH)**
    : MCH-R antagonist
  - **Orexin (hypocretin)**
    : variety physiologic effect (regulation of BP, neuroendocrine system, body temperature, sleep-waking cycle etc.)

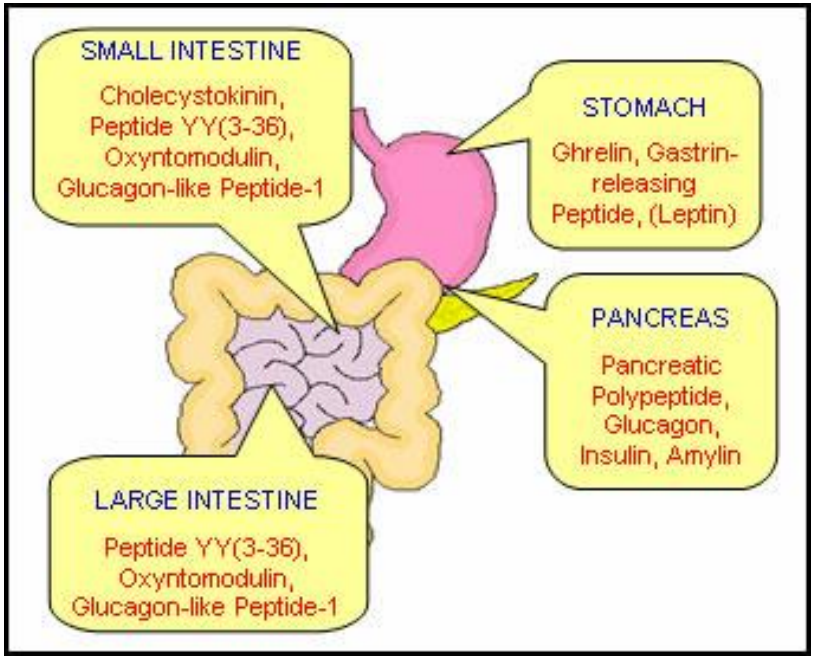
DMN, VMN

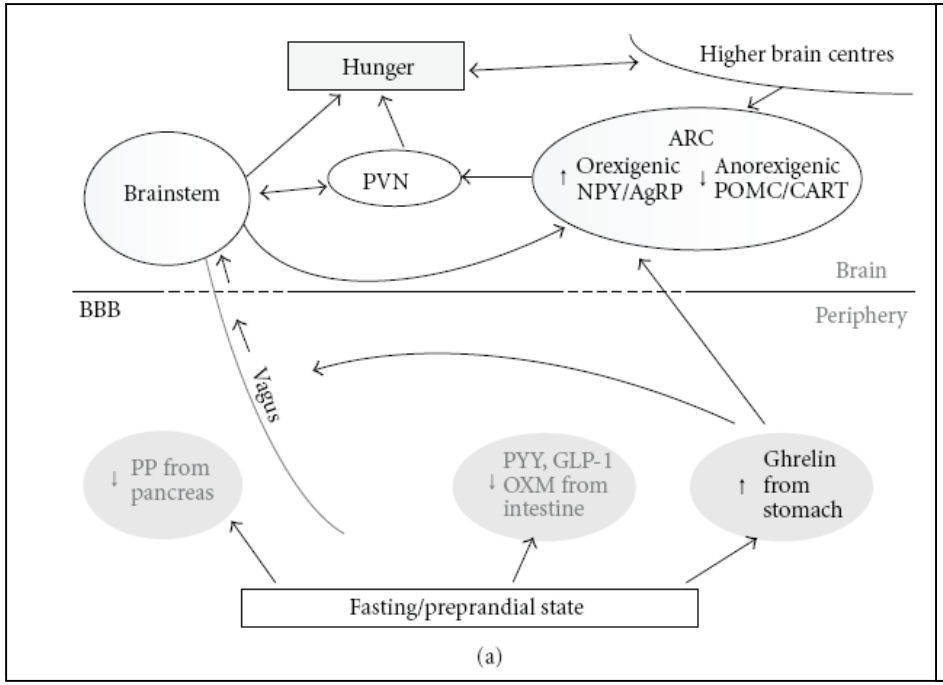
- Dorsomedial nucleus(DMN)
  - Receive NPY/AgRP projection from ARC
  - Project the a-MSH fiber to PVN
  - Suppressive role in appetite

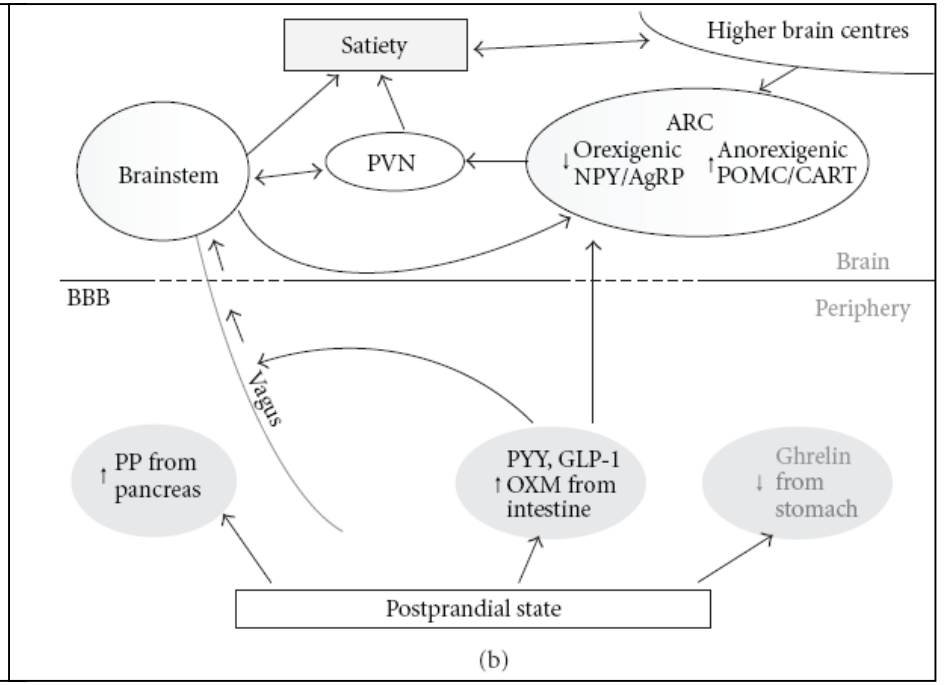
- VMN
  - high expression of Brain-derived neurotrophic factor (BDNF)
  - VMN BDNF neuron : suppress food intake through MC4R signaling

Appetite regulation in CNS

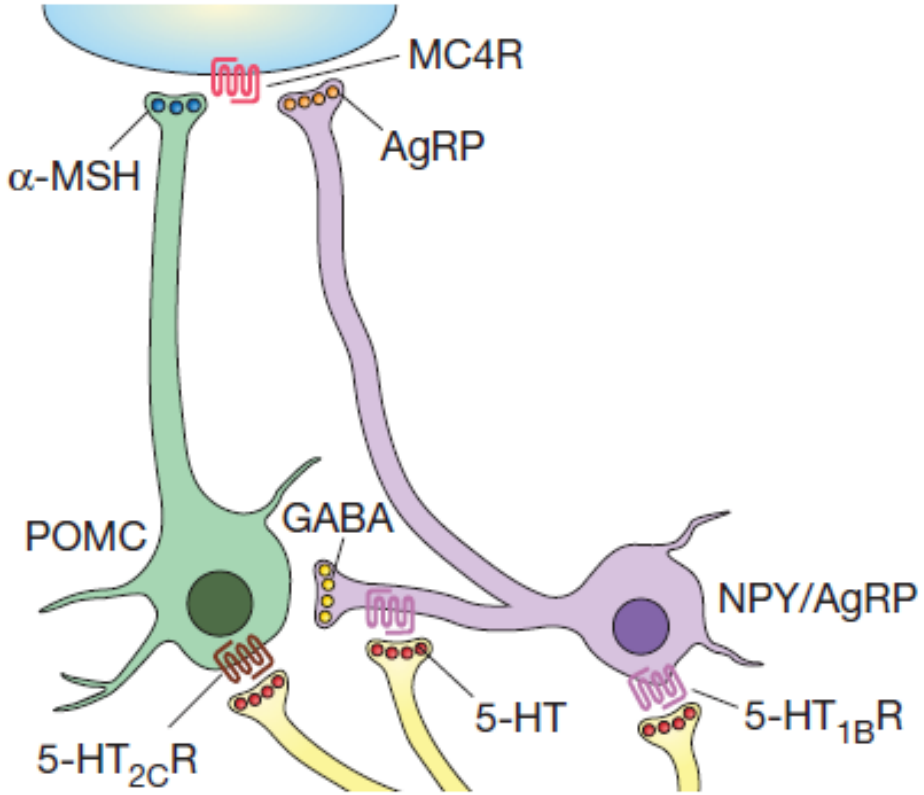








Appetite regulation via Serotonin in POMC

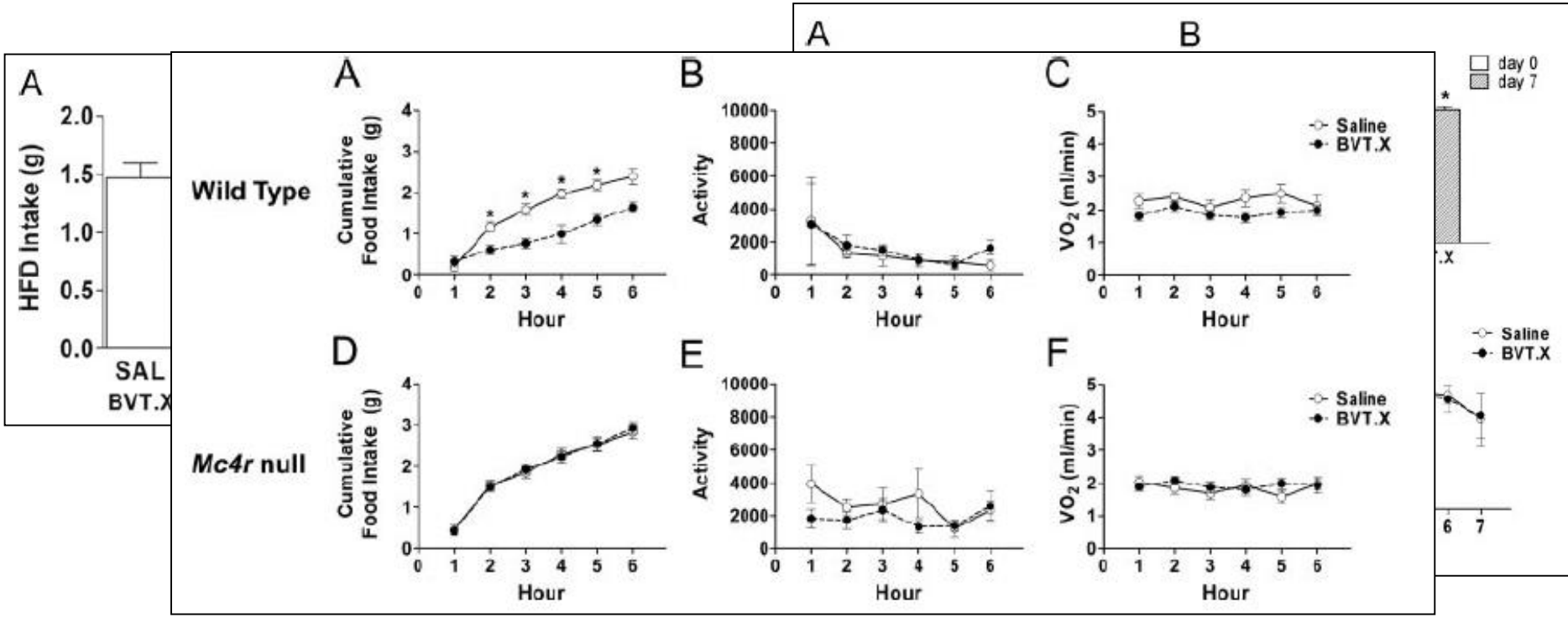


Serotonin anorexic effect via MC4Rc

Serotonin 5-HT$_{2C}$ Receptor Agonist Promotes Hypophagia via Downstream Activation of Melanocortin 4 Receptors

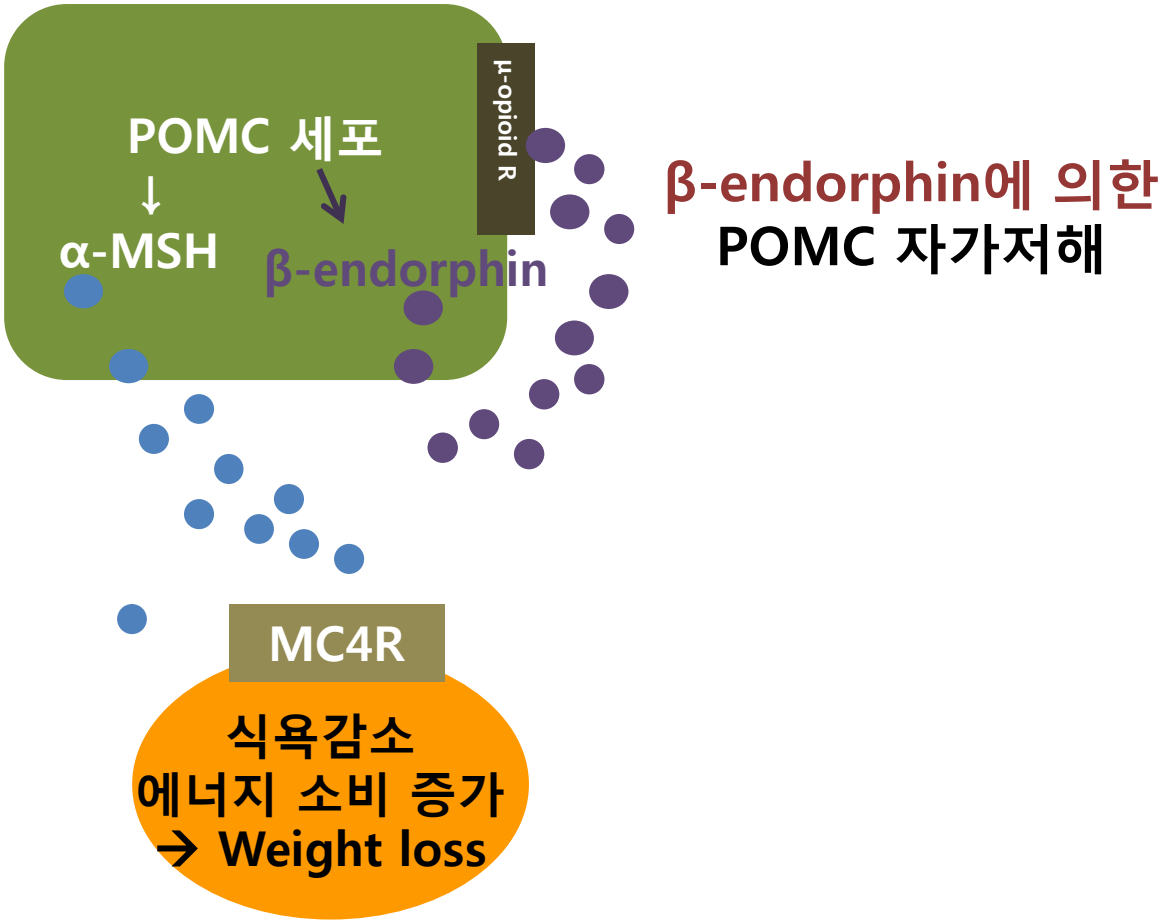
Daniel D. Lam, Magdalena J. Przydzial, Simon H. Ridley, Giles S. H. Yeo, Justin J. Rochford, Stephen O'Rahilly, and Lora K. Heisler

Department of Pharmacology (D.D.L., M.J.P., L.K.H.), University of Cambridge, Cambridge CB2 1PD, United Kingdom; and Department of Clinical Biochemistry (D.D.L., M.J.P., S.H.R., G.S.H.Y., J.J.R., S.O'R., L.K.H.), Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke's Hospital, University of Cambridge, Cambridge CB2 2QQ, United Kingdom



D.D. Lam et. Al. Endocrinology 149: 1323–1328, 2008

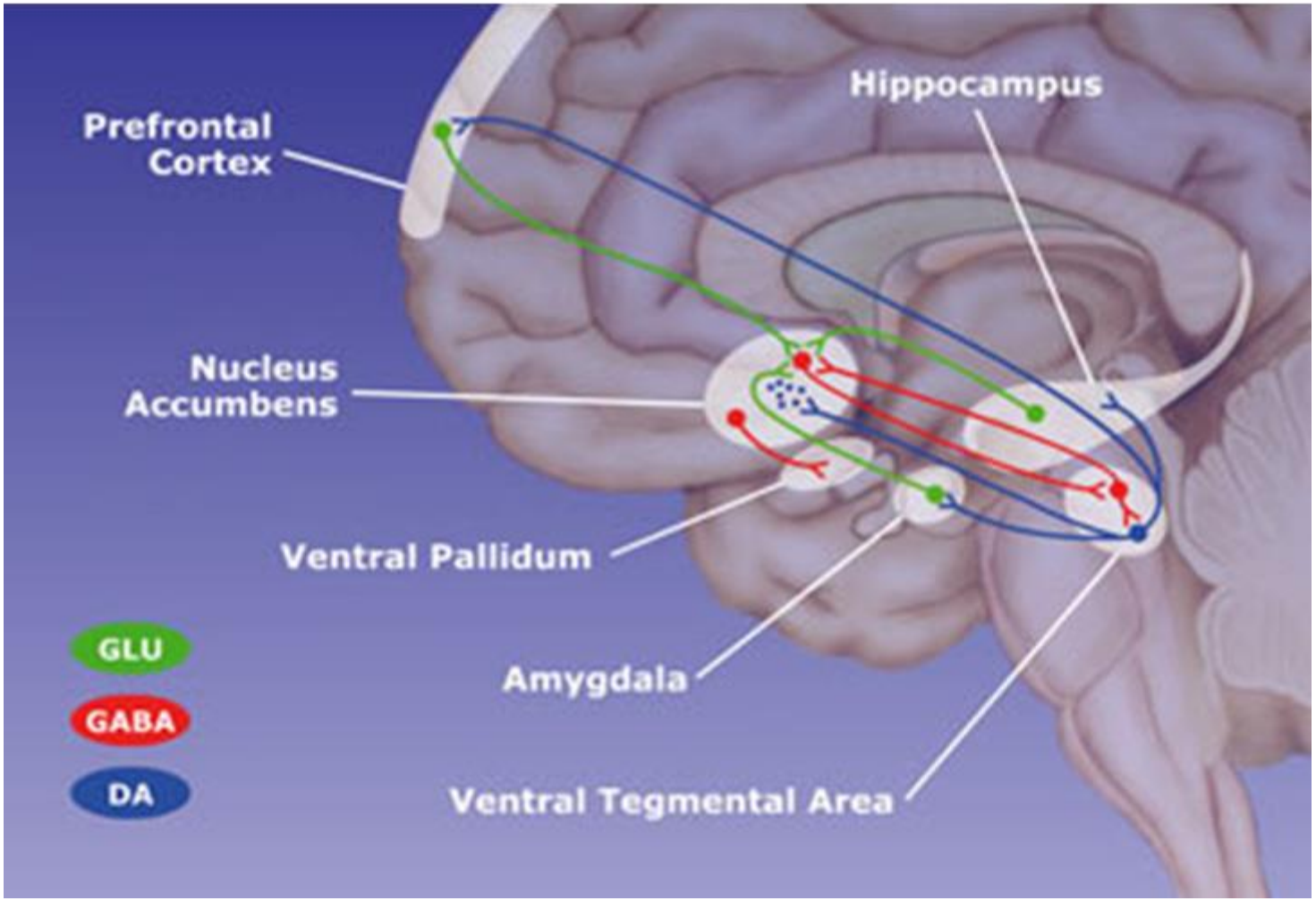
Limitation of POMC stimulation for appetite regulation



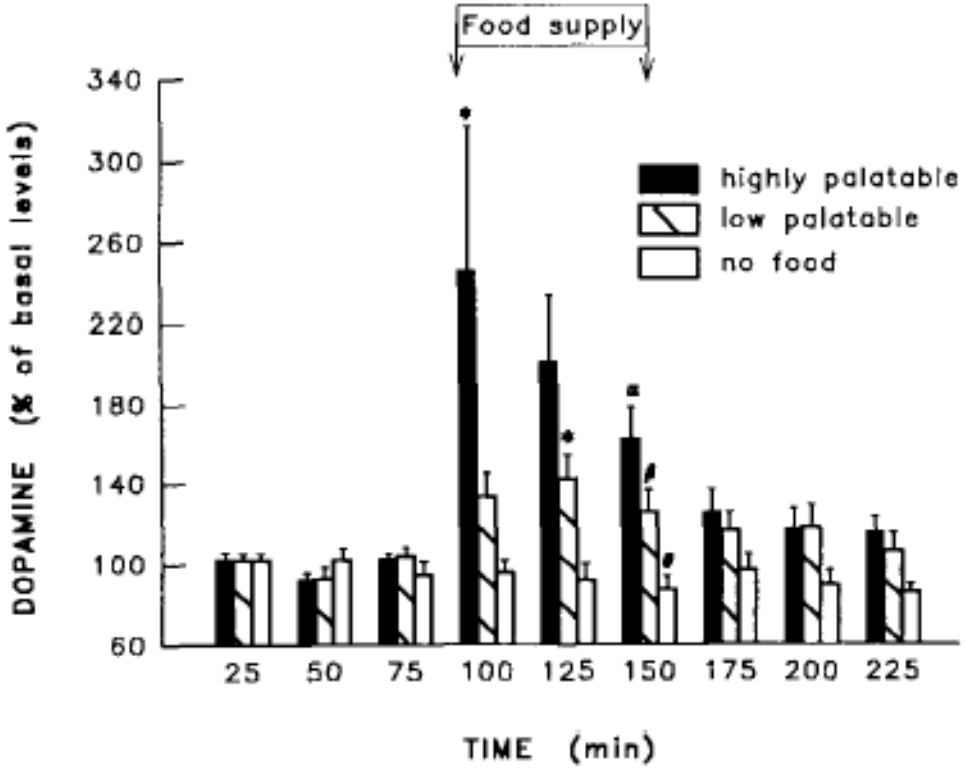
Craving

- Not Hunger!
- Want to eat!

The Reward Circuit



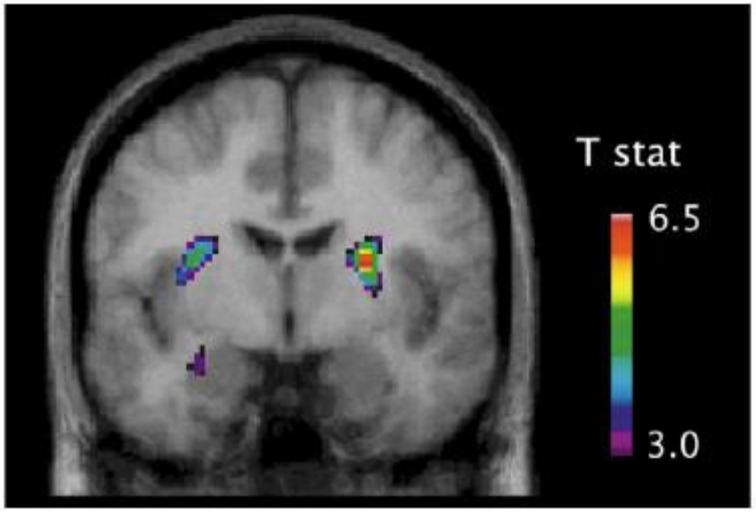
Feeding induced dopamine releasing



Pharmacology Biochemistry and Behavior, Vol. 53, No. 1, pp. 221-226, 1996

Pleasant after eating

1



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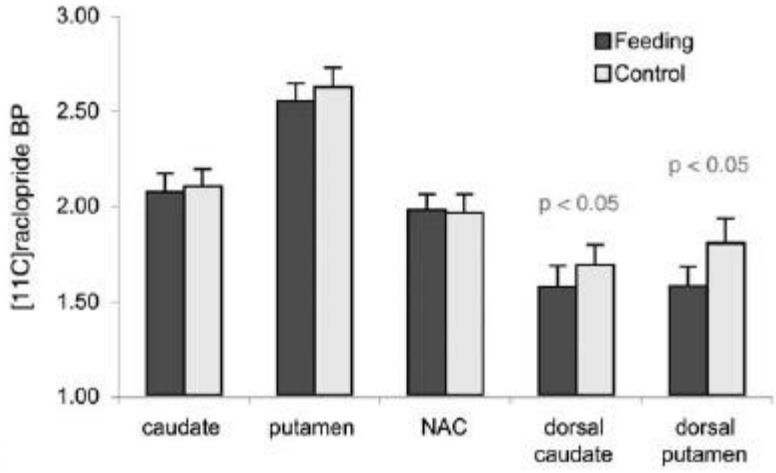
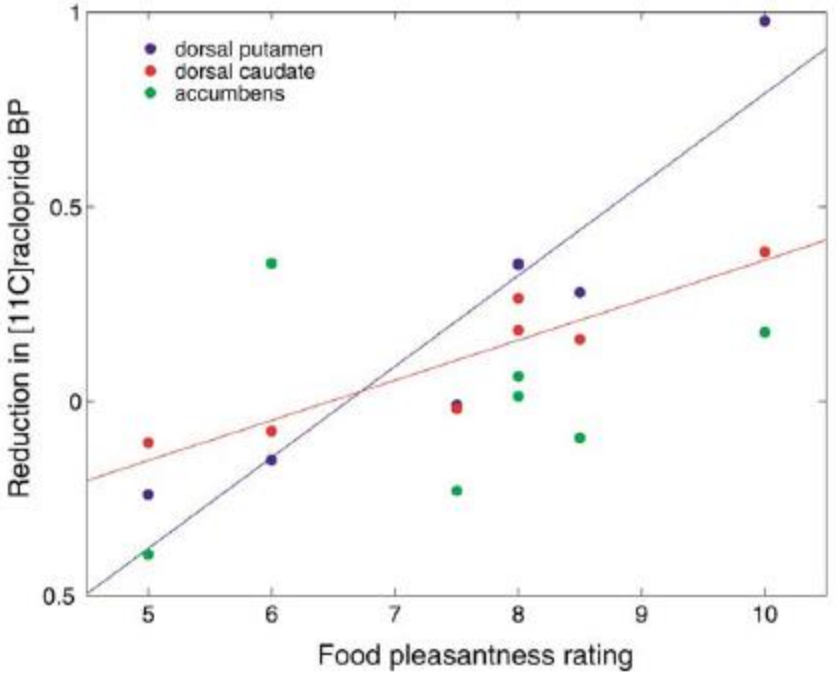




D.M. Small et al. NeuroImage 19 (2003) 1709–1715

Carbohydrate Addiction

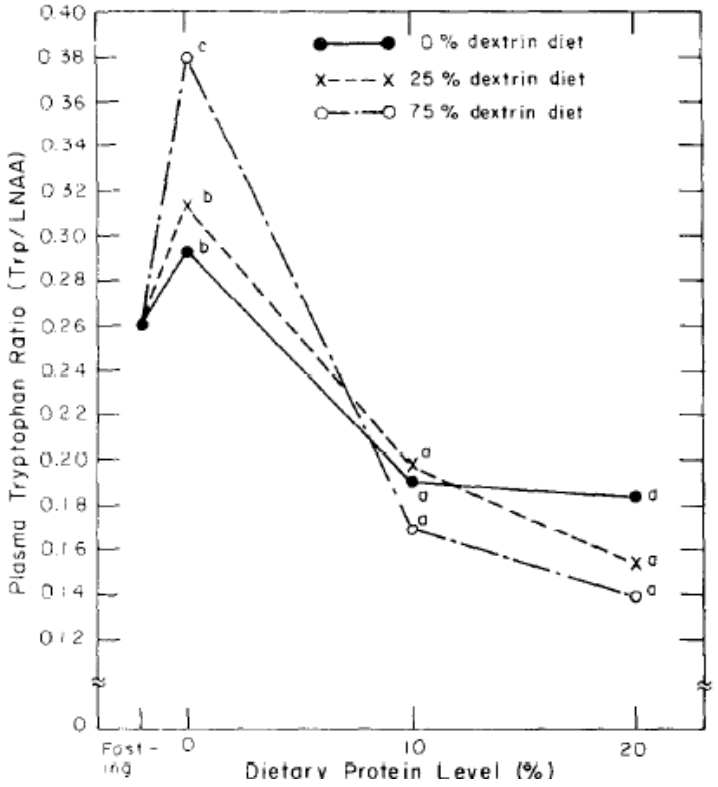
- Carbohydrate induce serotonin secretion

- OBESITY RESEARCH Vol. 3 Suppl. 4 Nov. 1995 477s-80s

- Comparison of Carbohydrate vs. Protein for serotonin secretion

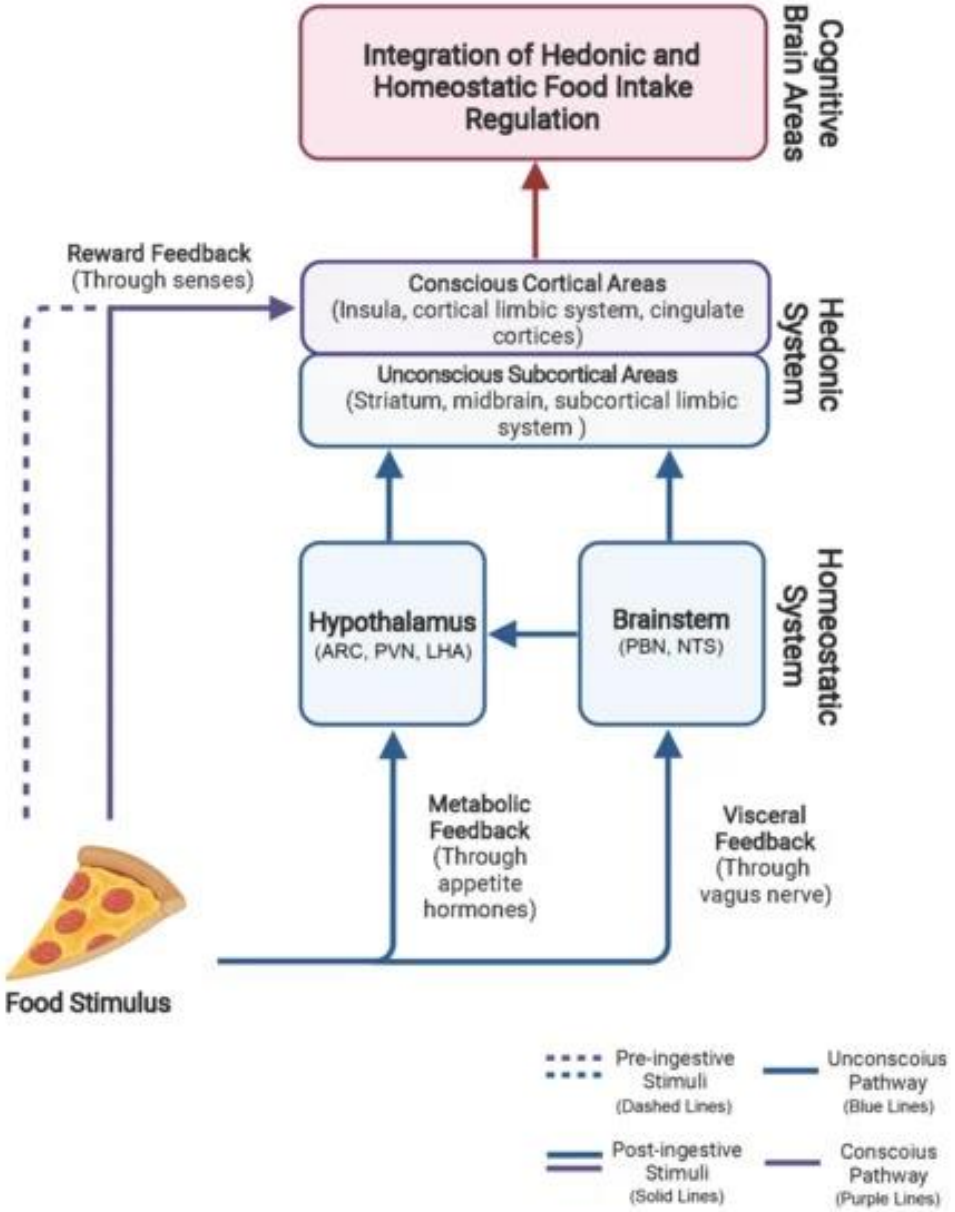
Table 2. Effect of Changes in Dietary Casein and Dex

Group	Diet	Food Intake for 2 h (g)	Tyrosine (nmol/mL)	Tryptophan (nmol/mL)
1	Fasting	—	37.3 ± 3.7[a]	70.8 ± 4.8[b]
2	0% Casein/ 0% Dextrin	2.9 ± 0.4	39.4 ± 5.5[a]	76.7 ± 10.5[bc]
3	0% Casein/ 25% Dextrin	3.9 ± 0.5	31.9 ± 5.7[a]	73.2 ± 0.9[b]
4	0% Casein/ 75% Dextrin	6.5 ± 1.3	22.4 ± 4.5[a]	51.3 ± 5.5[a]
5	10% Casein/ 0% Dextrin	5.8 ± 1.2	65.2 ± 9.4[b]	84.0 ± 10.3[bc]
6	10% Casein/ 25% Dextrin	7.1 ± 0.5	66.8 ± 5.0[b]	95.7 ± 1.5[c]
7	10% Casein/ 75% Dextrin	8.7 ± 0.9	90.0 ± 10.2[c]	81.1 ± 2.8[bc]
8	20% Casein/ 0% Dextrin	5.4 ± 0.5	91.3 ± 8.5[c]	128.2 ± 4.9[de]
9	20% Casein/ 25% Dextrin	7.5 ± 0.8	172.8 ± 9.9[e]	136.9 ± 3.4[e]
10	20% Casein/ 75% Dextrin	7.8 ± 0.4	144.7 ± 9.5[d]	115.6 ± 7.0[d]



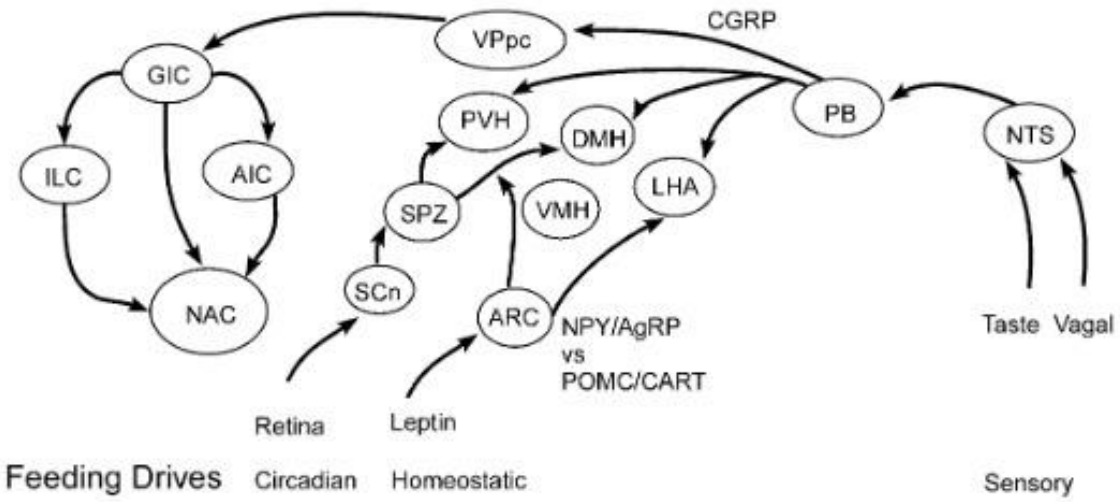
Metabolism, Vol 35, No 9 Eeptember), 1986: pp 837-842

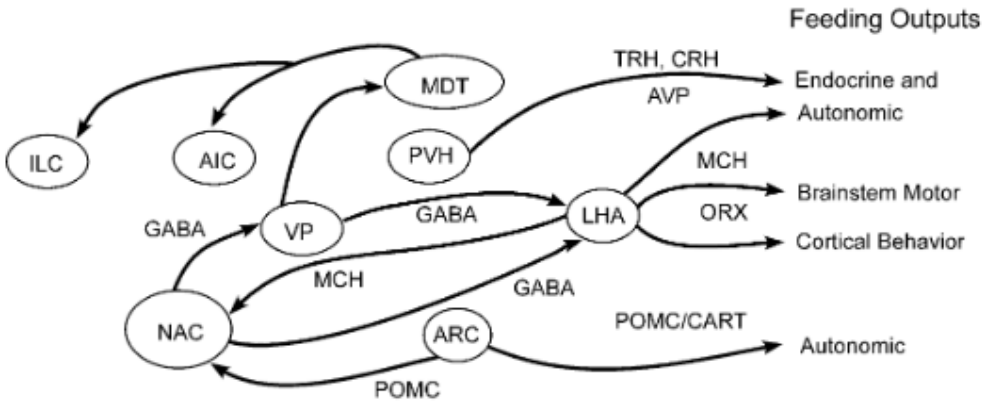
Homeostatic and hedonic control of eating



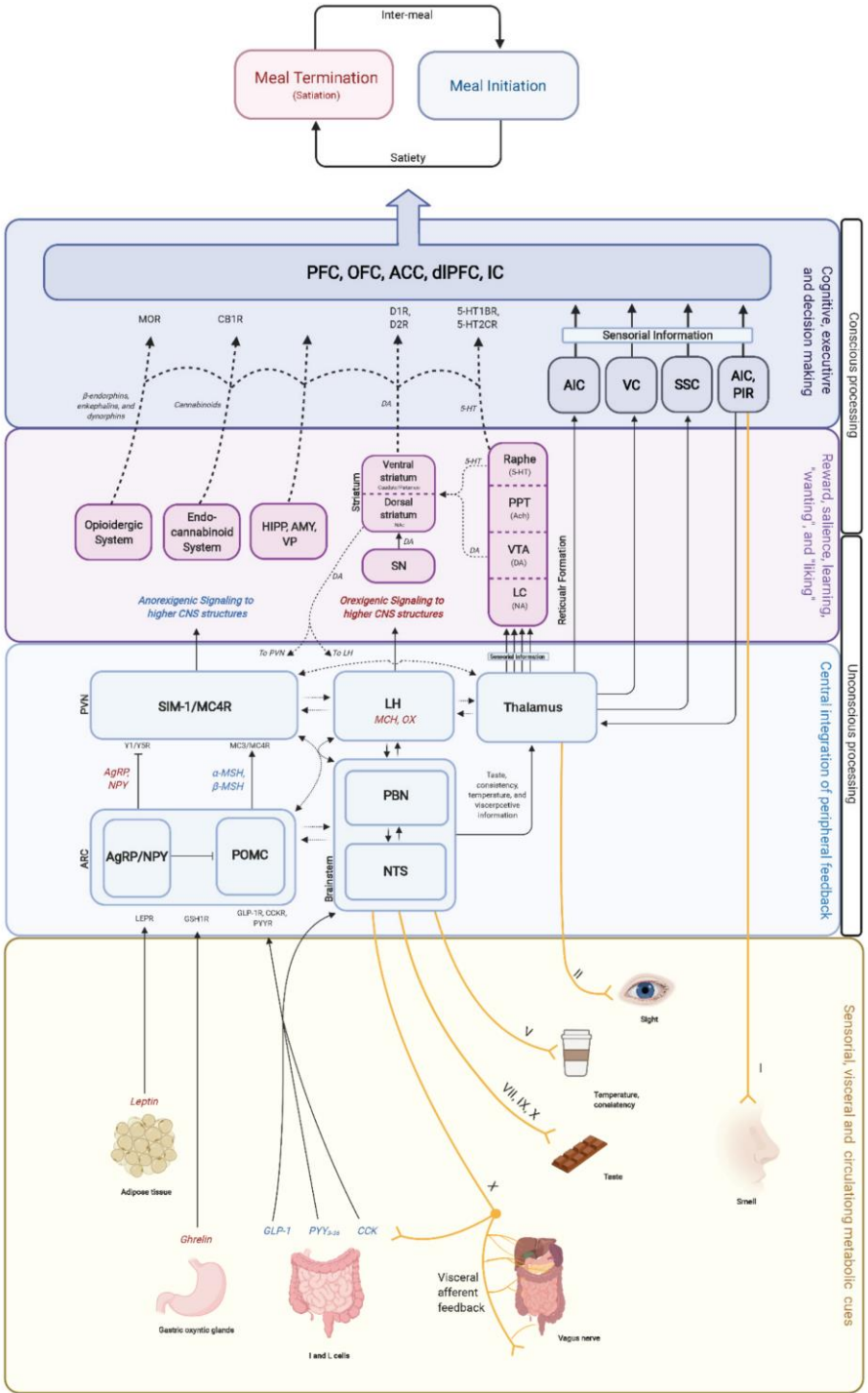
Brain Sci. 2022, 12(4), 431

Homeostatic and hedonic control of eating

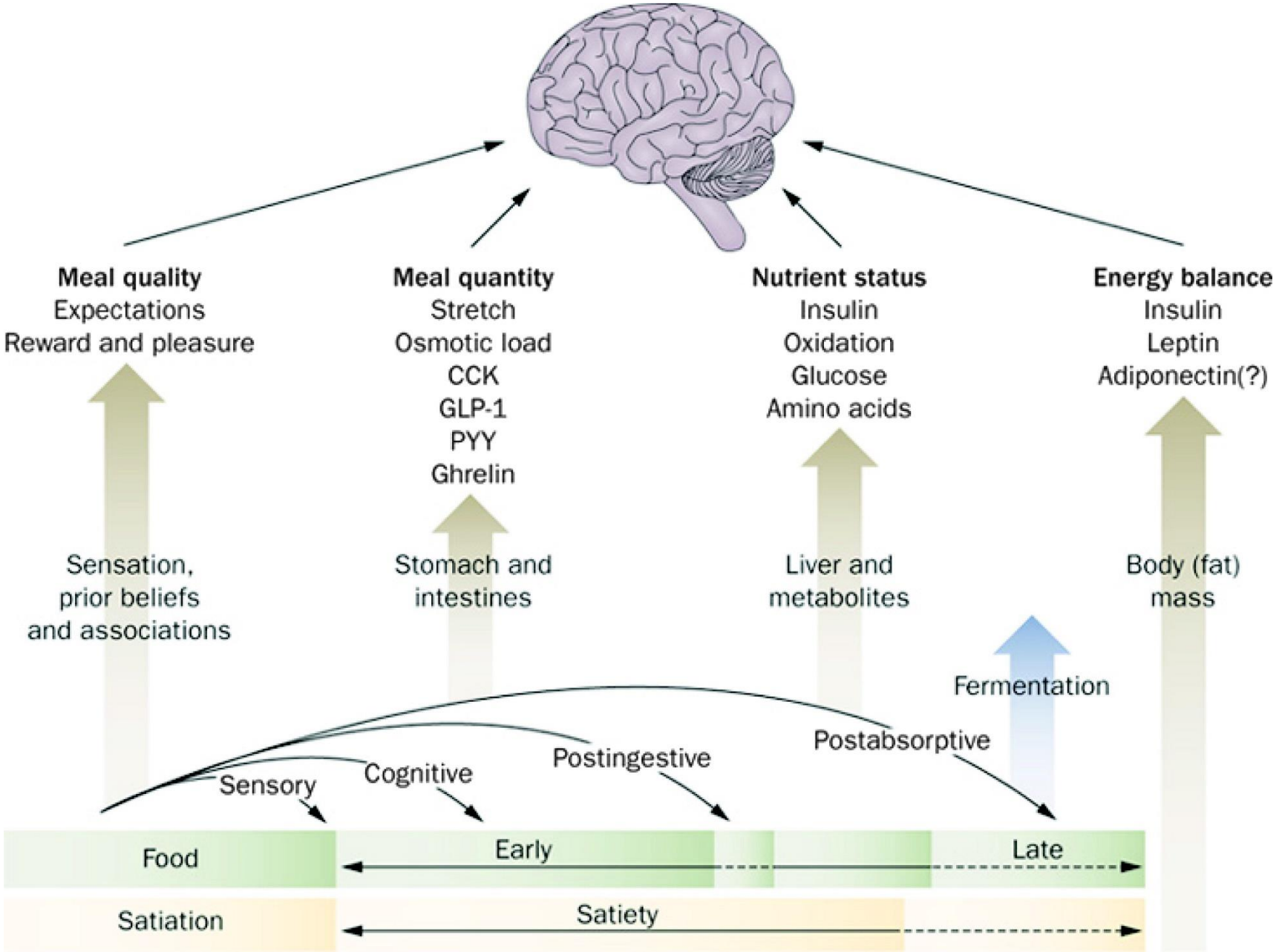




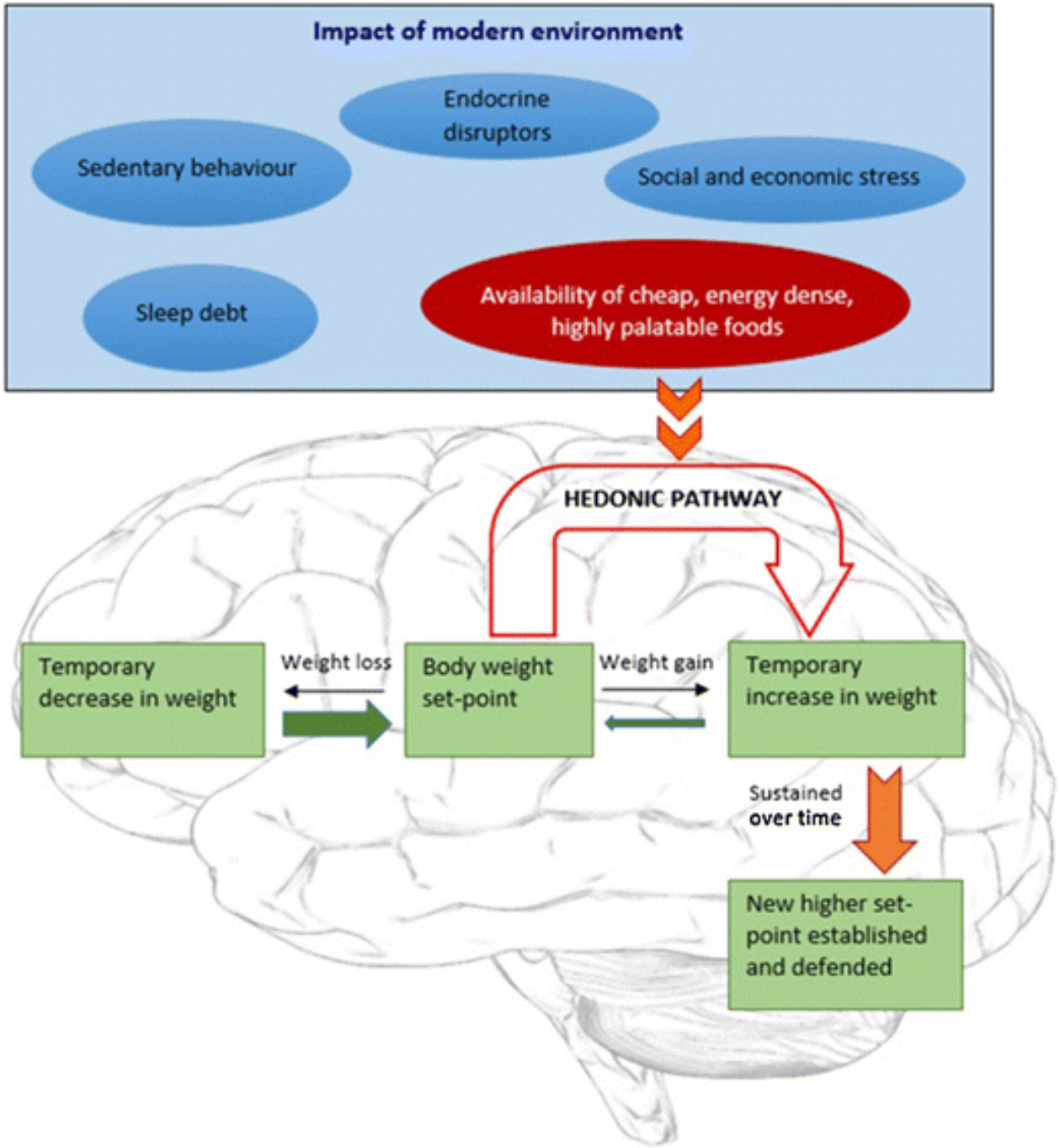
Neuron, Vol. 36, 199–211, October 10, 200



Brain Sci. 2022, 12(4), 431



Applied Physiology, Nutrition, and Metabolism. 40(10): 971-979.


Impact of modern environment
Endocrine disruptors
Sedentary behaviour
Social and economic stress
Sleep debt
Availability of cheap, energy dense, highly palatable foods
HEDONIC PATHWAY
Temporary decrease in weight
Weight loss
Body weight set-point
Weight gain
Temporary increase in weight
Sustained over time
New higher set-point established and defended

Conclusion

- Physiologic(Homeostatic) regulation
  - Peripheral signal – CNS reaction
- CNS (Hypothalamus – Arcuate N.)
  - POMC/CART (Anoretic) vs NPY/AgRP (Orexigenic)
  - POMC : α-MSH via MC4R

- Hedonic regulation
  - For pleasure, not hunger sense
  - More potent than physiologic regulation

Thank you for attention