Why Can’t I Just Take a Pill to Lose Weight?

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Topics

1. What is leptin?
2. How does leptin regulate weight homeostasis?
3. Why can leptin work in mice?
4. Why can’t leptin work in human?
5. Some other proteins about weight control.
6. Other methods about losing weight.

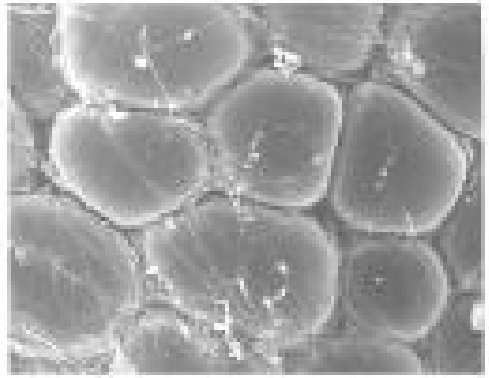
What is leptin?

Obesity

- Occurs due to an imbalance between energy intake and expenditure, resulting in a net increase in the storage of body energy primarily as fat.

- Often associated with other various diseases and risks, such as diabetes, articular problems and increased surgical risk.

Adipocytes



- The traditional role attributed to adipose tissue is energy storage, fatty acid being released when fuel is required.
- Adipose tissue performs complex metabolic and endocrine functions.
- The hormone derived from adipocytes: leptin and adiponectin.

Leptin

- The product of *ob* gene. from the Greek word λ ε π τ ο σ, *leptos*, meaning thin
- 167 a.a protein, 16 KDa
- 1950, a genetic defect that proceeds in massive obesity was identified in inbred obese mice. Ingalls *et al*.

Leptin

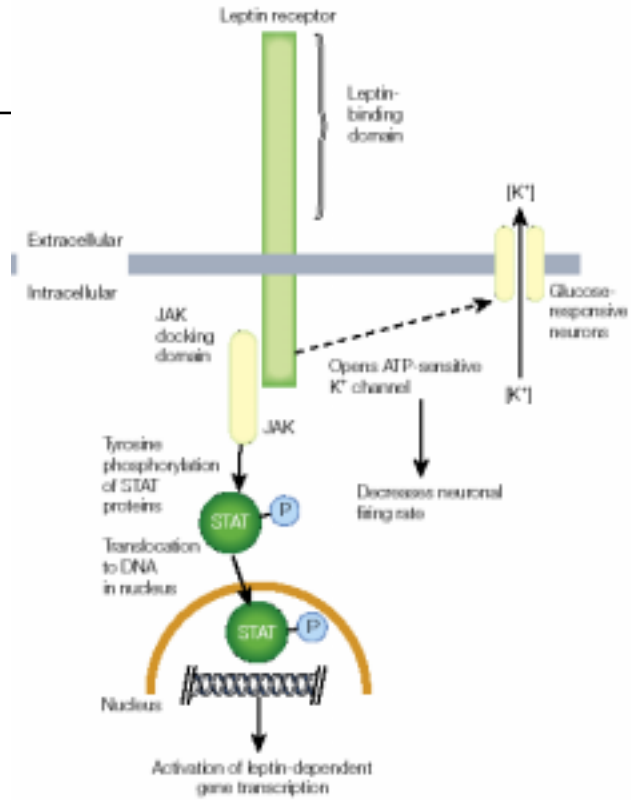
- 1973, parabiosis experiments: cross-circulation. *Diabetologia* 1973; 9: 294-298.
- 1994, cloning of the mouse *ob* gene and its human homologue. *Nature* 1994; 372: 425-432.
- 1996, identified leptin defective receptor of the *db/db* mouse. *Lee et al.*

Leptin

- Concentrations are higher in women when compared with men. (Caro *et al.* 1996).
- Slowly declines during aging. The reduction is higher in women than in men. (Isidori *et al.* 2000)

Leptin receptor

- single-transmembrane-domain receptor.
- leptin receptors are found not only in the brain.
- Three forms: long, short, and very short.

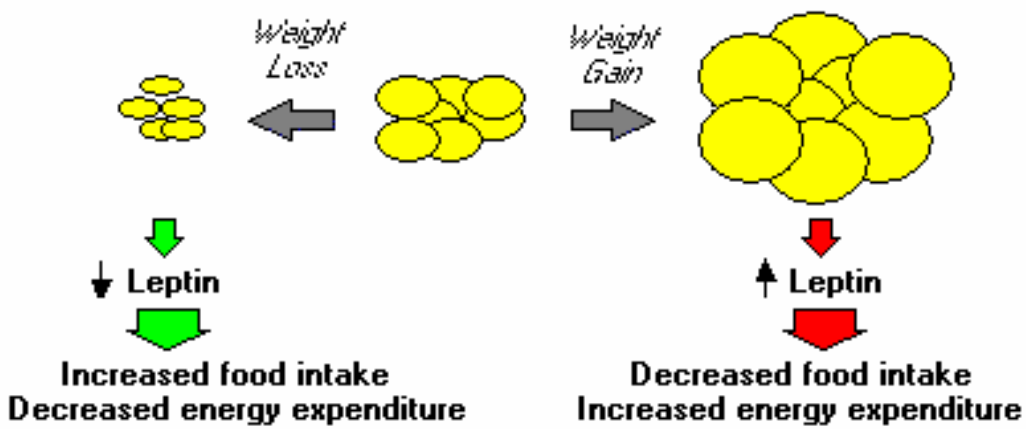


Signal transduction

BBB

Leptin

- Provide the brain with the information about fat storage of body.
- Feedback mechanism can function as a lipostat.



How does leptin regulate weight homeostasis?

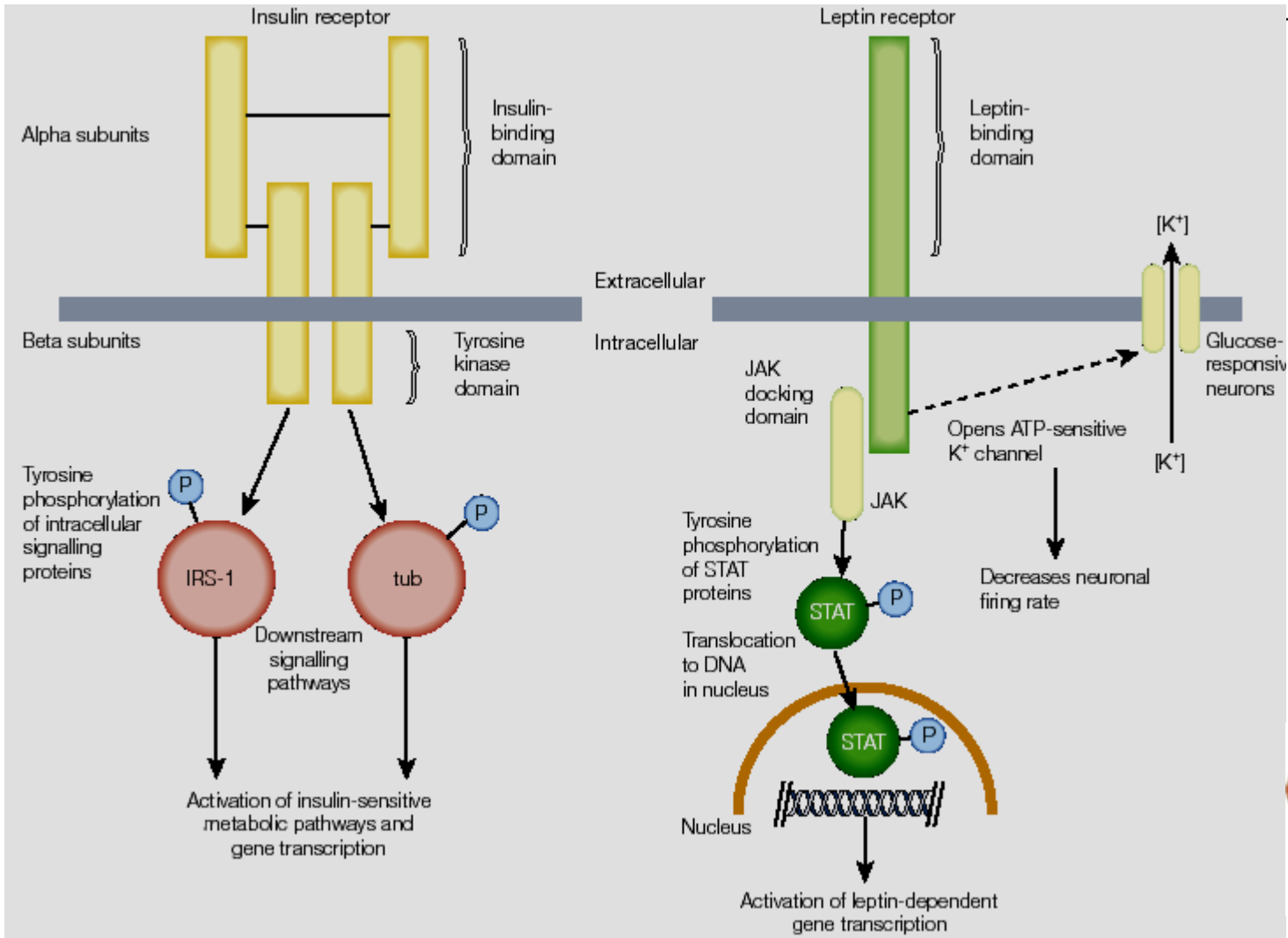
Leptin v.s Insulin

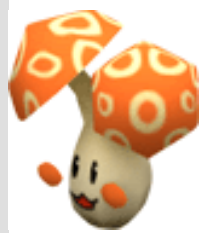
Round 1

- Leptin:
  1. Regulation of food intake
  2. Energy balance
  3. Inhibition of insulin secretion
  4. Stimulation of lipolysis in adipocytes
  5. Increasing of fatty acids synthesis in liver
- Insulin:
  1. Enhance glucose diposal
  2. Storage and oxidation in glucose homeostasis
  3. Be an anabolic hormone

Leptin v.s Insulin

Round 2

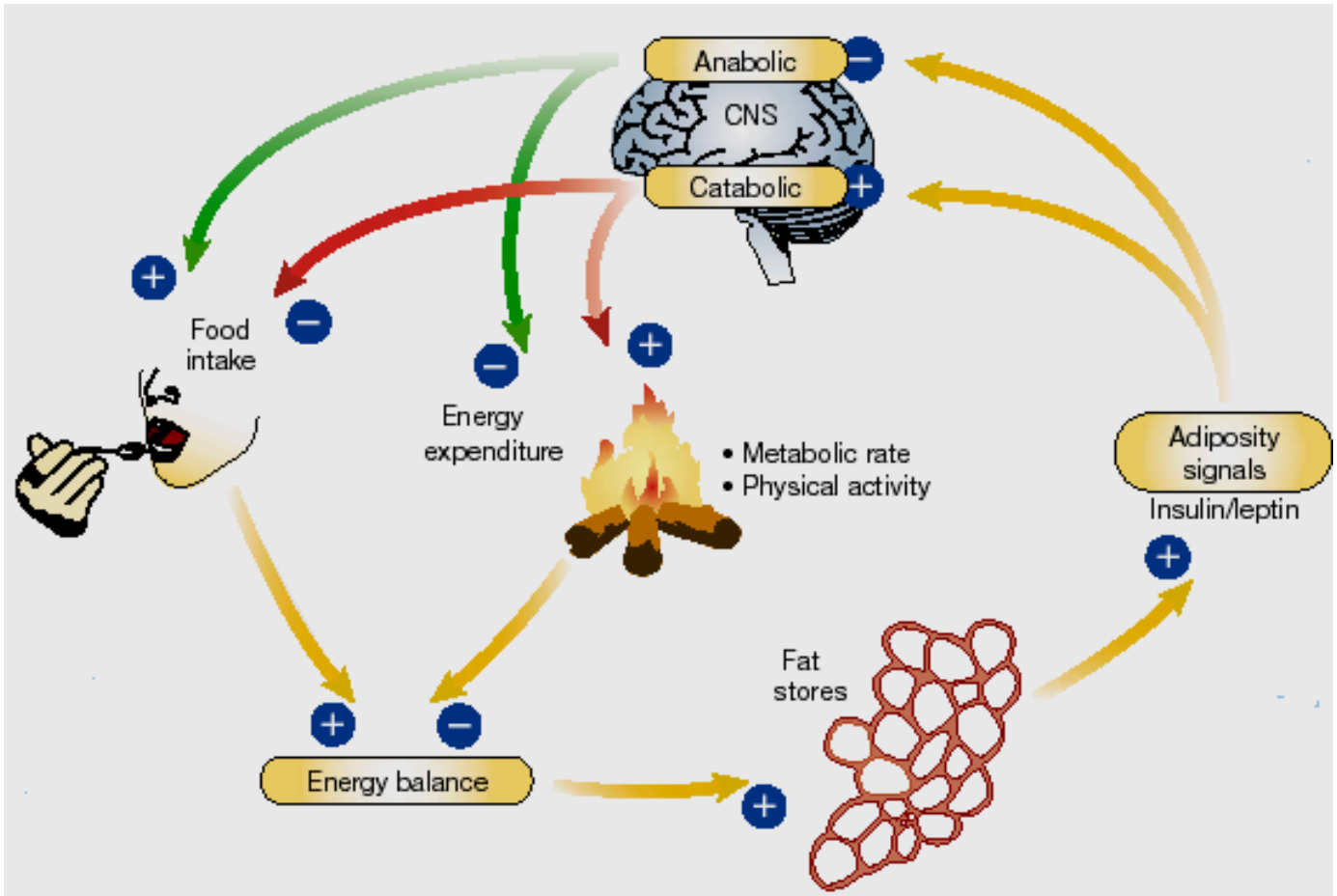




Nature 404, 661 - 671 (06 Apr 2000) Insight

Leptin v.s Mechanism

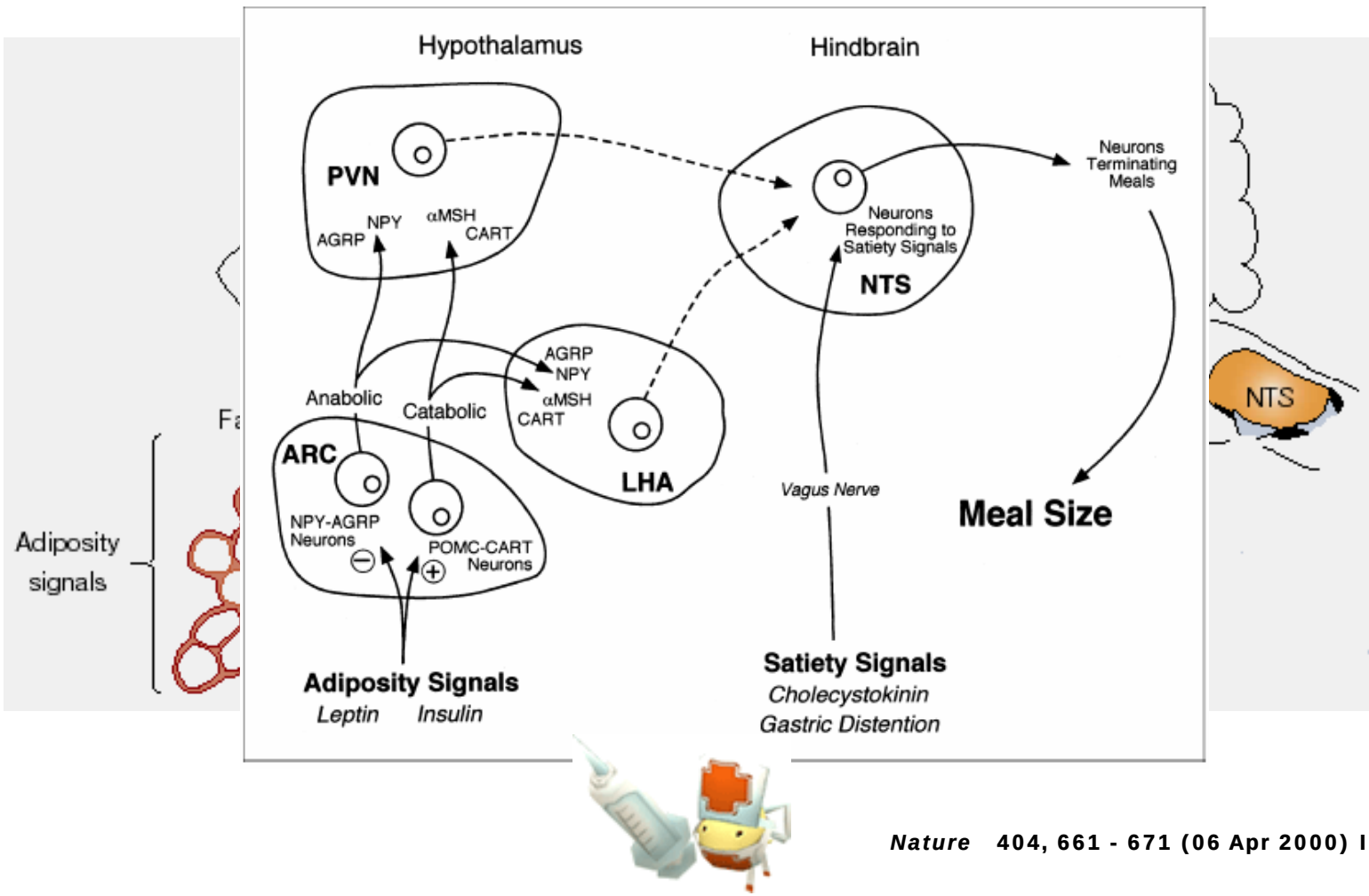
Round 3



Nature 404, 661 - 671 (06 Apr 2000) Insight

Leptin v.s CNS

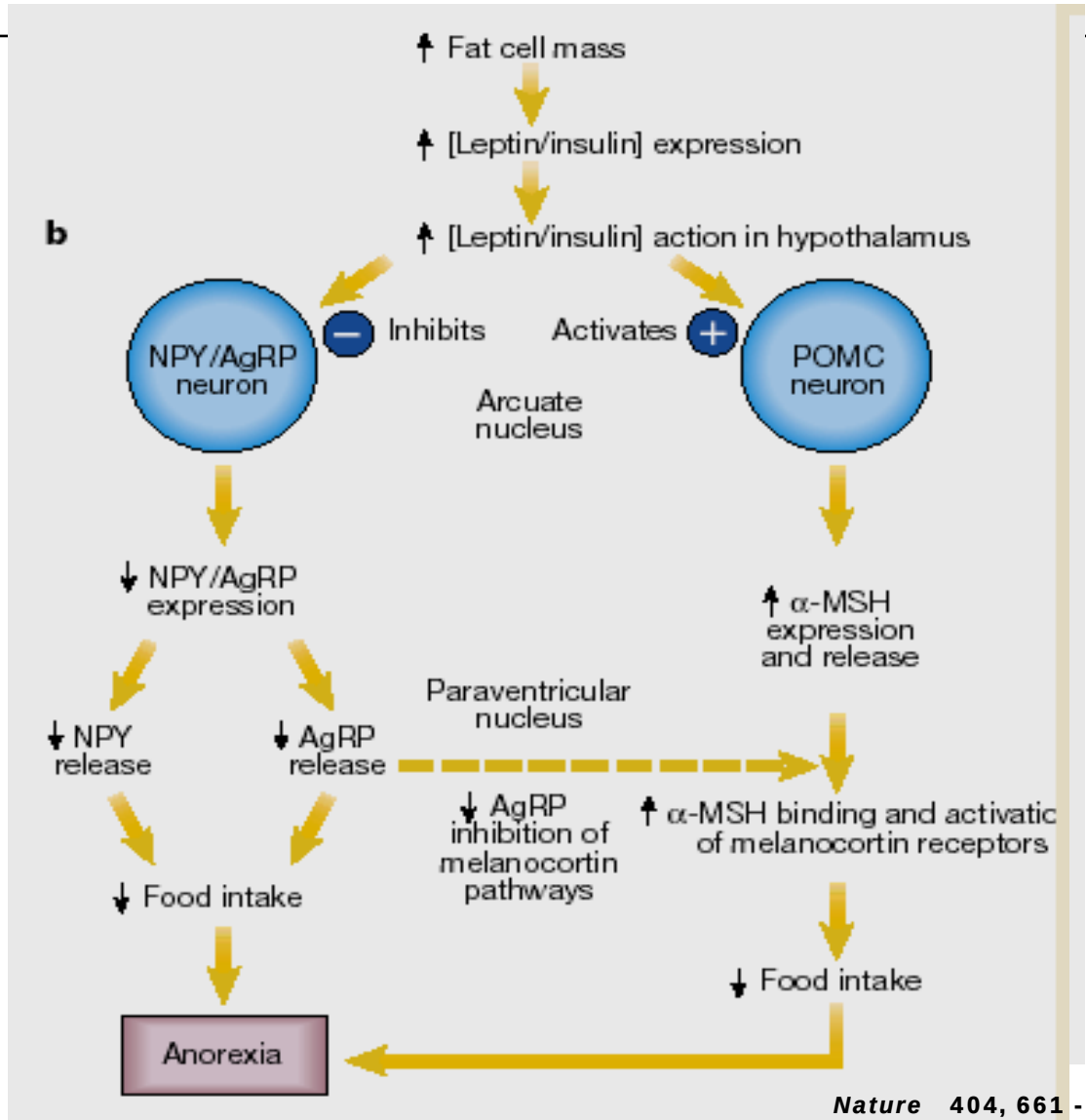
Round 4



Nature 404, 661 - 671 (06 Apr 2000) Insight

Leptin v.s Signal transduction

Final Round

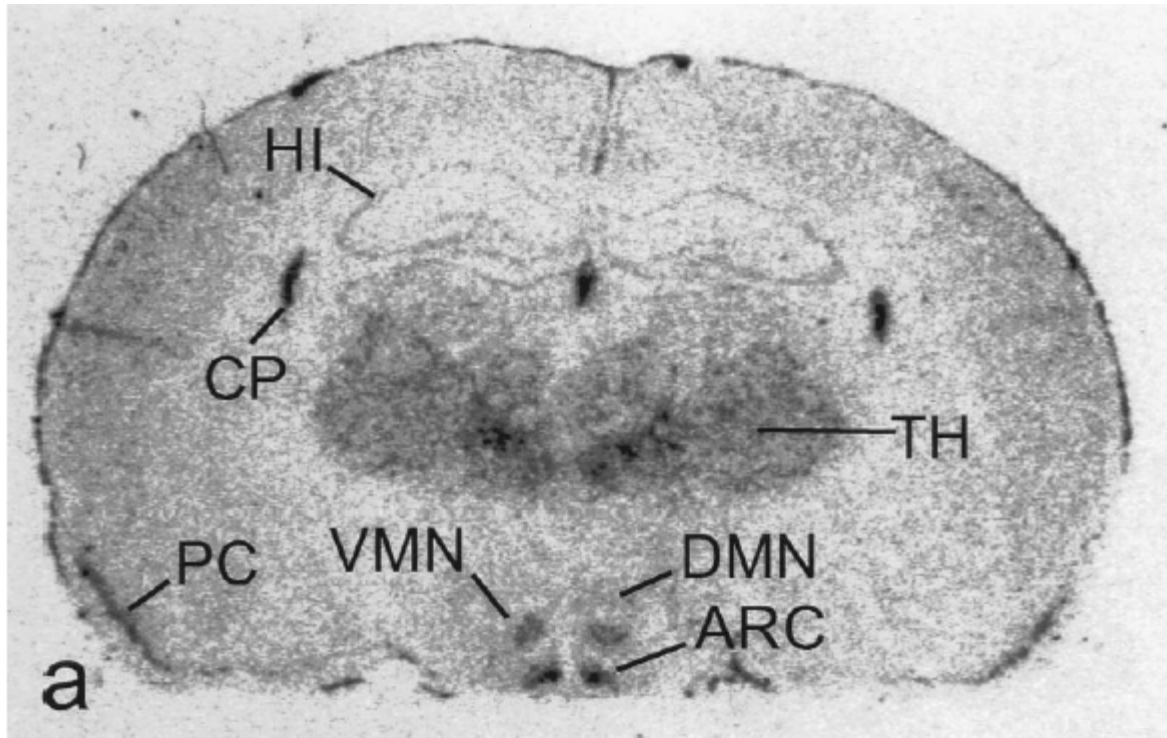


Nature 404, 661 - 671 (06 Apr 2000) Insight

Why can leptin work in mice?

Leptin在老鼠的作用機制

- Leptin receptor (LR), a single membrane-spanning receptor
- Gene expression for LR was strong in the arcuate nucleus (ARC), ventromedial nucleus (VMH or VMN) dorsomedial, paraventricular and ventral premammilary nuclei of the hypothalamus and moderate in the lateral hypothalamus (LH).



- The VMH, one of the largest nuclei of the hypothalamus, was long considered to be a "satiety center"

- Stimulation of the VMH inhibits feeding, whereas a lesion in this region causes overeating and weight gain.

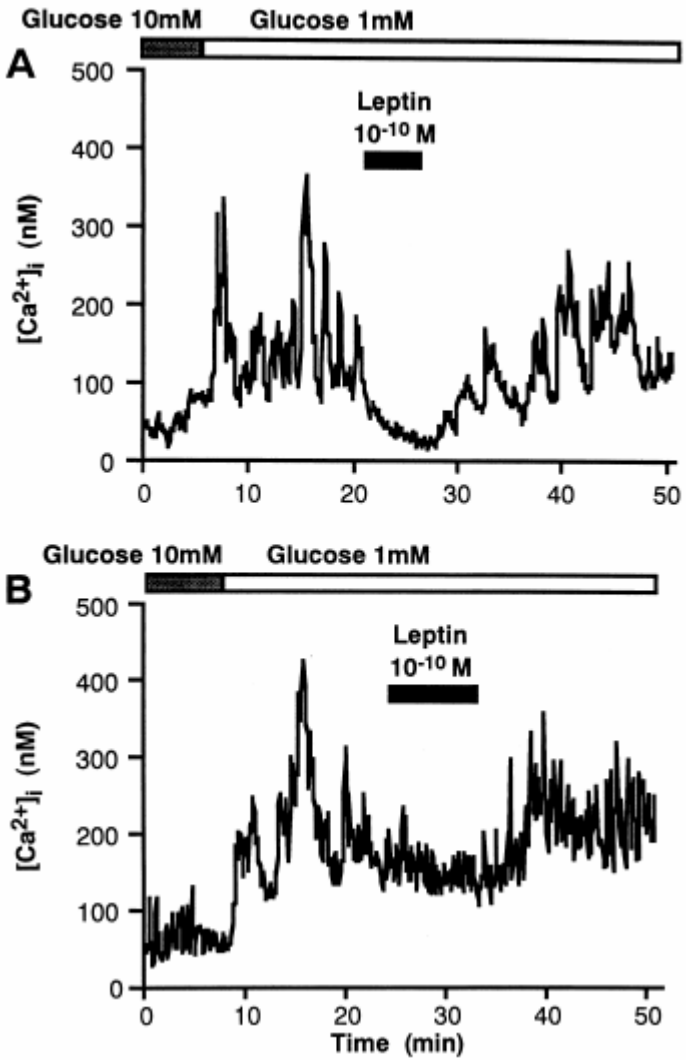
- Recent studies have shown high abundance of leptin receptors (long form: Ob-Rb) in neurones of the VMH, and evidence indicates that this region may be an important target for circulating leptin.

- The ARC and LH are feeding centers

- the ARC contains numerous neuropeptide Y (NPY)-containing neurons and fibers. NPY is involved in the stimulation of food intake and the regulation of energy balance.

- Leptin exerts its anorexic effects via a coordinated response that combines inhibition of NPY with stimulation of CRH-producing neurons.

- The present study first demonstrates that leptin inhibits Lg induced increase in $[Ca^{2+}]^i$ in the neurons of the feeding centers, ARC and LH, and increases $[Ca^{2+}]^i$ in the neurons of the satiety center, VMH.



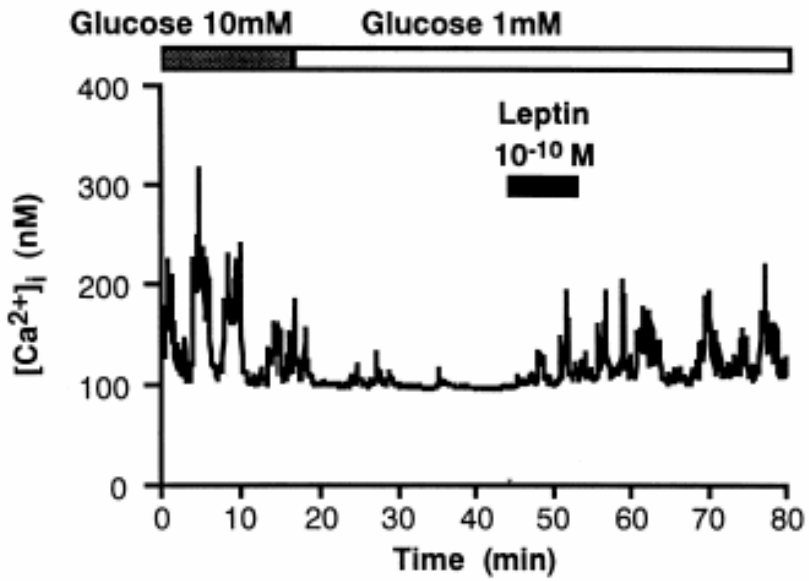
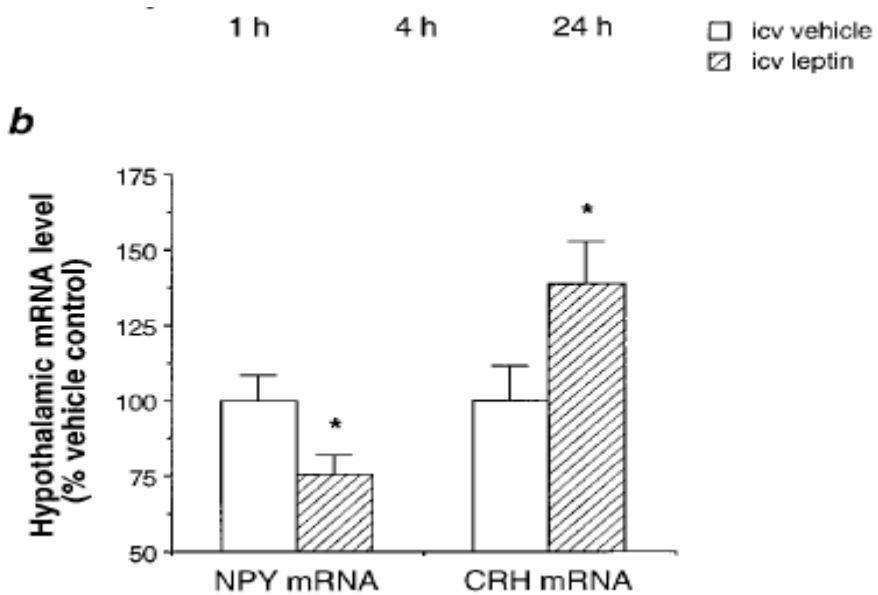


Fig. 3. High glucose- and leptin-induced $[Ca^{2+}]_i$ increases in VMH neurons. $[Ca^{2+}]_i$ in a single VMH neuron increased with 10 mM glucose and decreased with 1 mM glucose. In the presence of 1 mM glucose, leptin at 10^{-10} M also increased $[Ca^{2+}]_i$. The results shown are representative of 27 cells.

- Leptin administration directly into the brain of fasted rats should increase hypothalamic expression of CRH and decrease expression of NPY, leading to an attenuated feeding response. Since CRH acts in this brain area to inhibit food intake and to increase energy expenditure.



- Leptin therefore appears to stimulate the POMC neurones, with the increase in POMC expression presumably resulting in elevated α-MSH production and release and thus reduced food intake.
- Leptin also increases CART expression and leads to reduce food intake

- *Corticotropin-releasing hormone* (CRH):

PVN

decreases food intake and body weight; increases sympathetic nervous system activity, thereby increasing thermogenesis; energy expenditure, and lipolysis.

- *Cocaine- and amphetamine-regulated transcript* (CART):

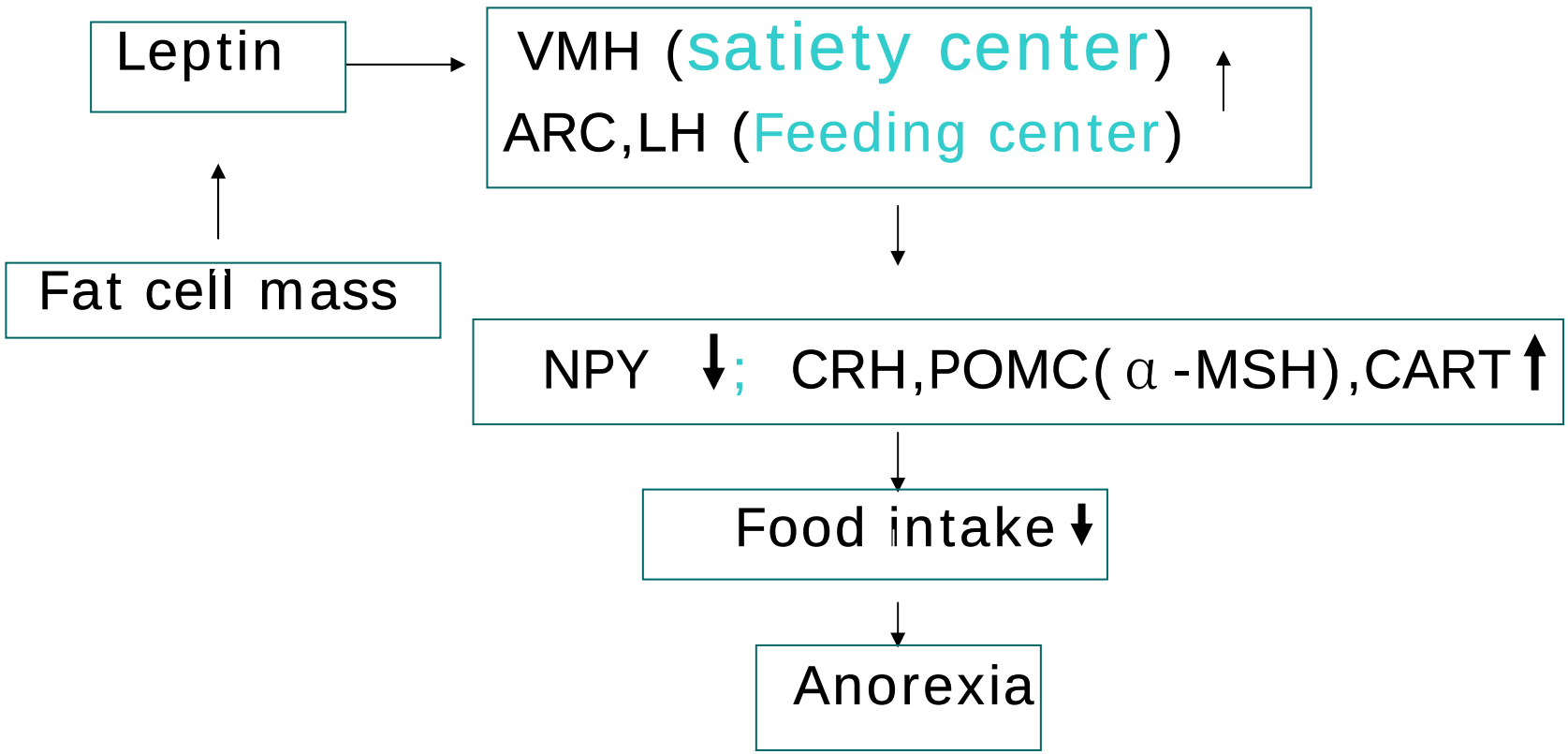
ARC, PVN, DMH, LHA

decreases food intake and body weight

Pro-opiomelanocortin (POMC ➤ ACTH & α-MSH)

ARC, pituitary gland, NTS

lipolysis ; decreases food intake and body weight ;immune function ; pigment formation ; nervous system function


Leptin
VMH (satiety center)
ARC,LH (Feeding center)
Fat cell mass
NPY ↓; CRH,POMC(α-MSH),CART ↑
Food intake ↓
Anorexia

Why can't leptin work in human?

何謂肥胖

- 肥胖已是全球重視的健康問題，許多研究指出肥胖與健康有密切的關係，如何定義肥胖?

- 世界衛生組織(WHO)、美國、歐洲及International Obesity Task Force分別對西方人及亞太地區人做出過重及肥胖的定義

造成肥胖的原因

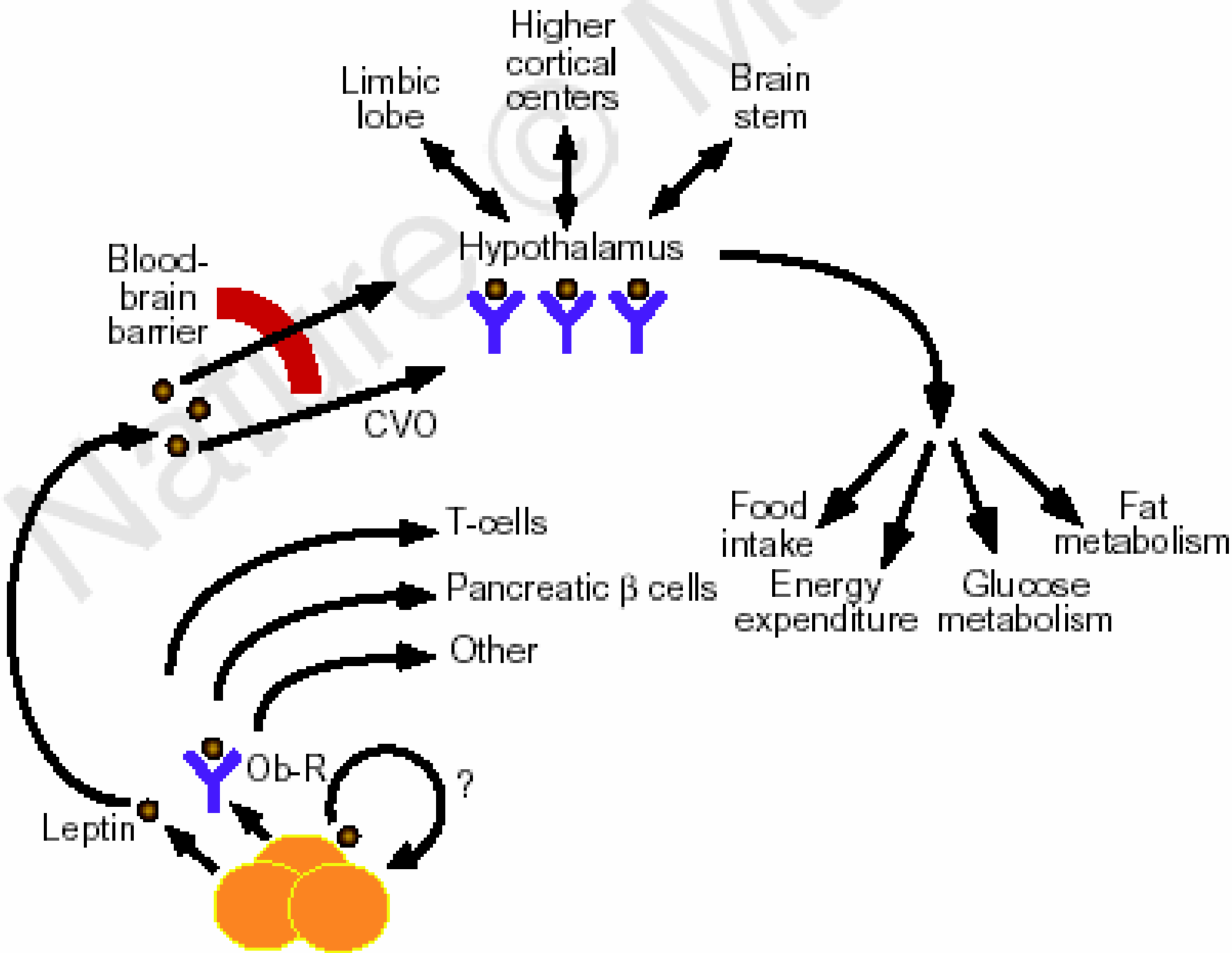
- 遺傳:1995 OB gene的發現提供最佳的佐證
- 環境:環境因子則包括了生活型態及飲食行為
- 心理:情緒因子 佔30%肥胖患者
- 其他:藥物 疾病

	罹病率	BMI值
體重過輕		<18.5
正常體重		18.5~24.9
體重過重	risk↑	25~29.9
肥胖(at risk)		>30
1級肥胖	mild	30~34.9
2級肥胖	severe	35~39.9
3級肥胖		>40

Human leptin

- Humans fat cells also manufacture a leptin (a protein of 167 amino acids)

- Mutations in the gene for leptin, or in its receptor, are rarely found in obese people.


Higher
cortical
centers
Limbic
lobe
Brain
stem
Hypothalamus
Blood-
brain
barrier
CVO
T-cells
Pancreatic β cells
Other
Food
intake
Energy
expenditure
Glucose
metabolism
Fat
metabolism
Ob-R
?
Leptin

The rare cases

- homozygous for mutations (frameshift in one family, missense in the other) in their **leptin** gene. ~ **ob/ob** mice
- homozygous for mutations in their **leptin receptor** gene . ~**db/db** mice
- heterozygous (one mutant and one normal) for their leptin genes.

Recombinant Human Leptin

- 1999, a year-long trial of **recombinant leptin** in a 9-year-old girl who is homozygous for a frameshift mutation in her leptin genes

The findings

- She began the trial weighing 208 pounds (94.4 kg), of which 123 lbs (55.9 kg) was fat.
- She had lost 36 lbs (16.4 kg), most of it fat.
- Her appetite and thus food intake had decreased.
- Her immune system made antileptin antibodies.

人體試驗

- 1999年10/27 Journal of American Medical Association發表Leptin 的人體試驗
- 在73個受試的肥胖者中，只有每天注射最高量的人能夠得到普通的效果
- 實驗中最好成果有兩人於24周內減去35磅，一人反而增加20磅，大部份的受試者都效果平平。

Leptin - Can Obese Mice Lead to Lean People?

- 人類肥胖者Leptin濃度比較高，且Leptin的量與體脂肪量成正相關，因此人類的肥胖症與db/db老鼠類似
- 因為腦部的瘦身蛋白接受器 (receptor) 異常，所以無法接受到leptin的刺激，或是對體內leptin敏感度很差，而不是缺少leptin所造成的影響

Result

- leptin治療肥胖效果有限,唯有在OB gene 發生mutant的病患可以產生效果
- 肥胖因素很多，牽涉到心理及環境，要能找出有效治療肥胖的方法並不容易
- 現在最有效的方法，還是吃少一點，並多運動，有研究指出持續且規律的運動可以幫助體內的leptin濃度正常化，以減輕體重

Some other proteins about weight control

Cholecystokinin(CCK)

- Produced by I-cell
- Pancreatic enzyme secretion
- Bile secretion and contraction of gall bladder
- Inhibition of gastric emptying
- Inhibition of food intake

Cholecystokinin(CCK)

- **Daily CCK injection enhances reduction of body weight by chronic intracerebroventricular leptin infusion**.

  Ebenezer IS. Eur J Pharmacol 2002 Apr 19;441(1-2):79-82

Neuropeptide Y(NPY)

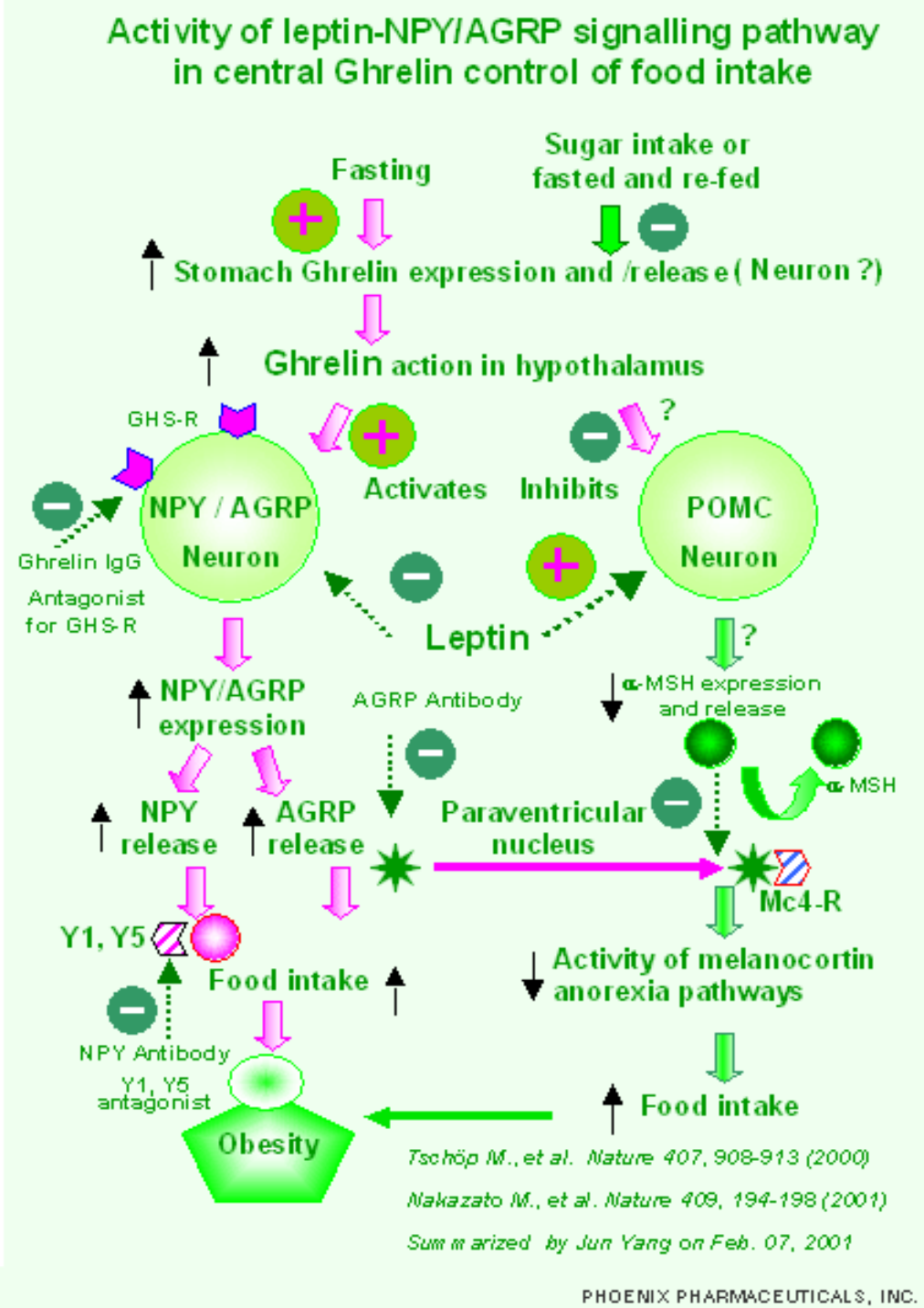
- secretion of the NPY peptide in the hypothalamus
- increas during active depletion of body fat stores and /or reduced leptin/insulin signalling to the brain
- Injection of NPY into the hypothalamus increases food intake
- High NPY levels are correlated with Leptin
- NPY-knockout can reduce obesity in leptin deficient mice.

Proopiomelanocortin (POMC) Precursor

- generated in neurons of the hypothalamus
- activation melanocortin-4 receptor (MC4R)

Ghrelin

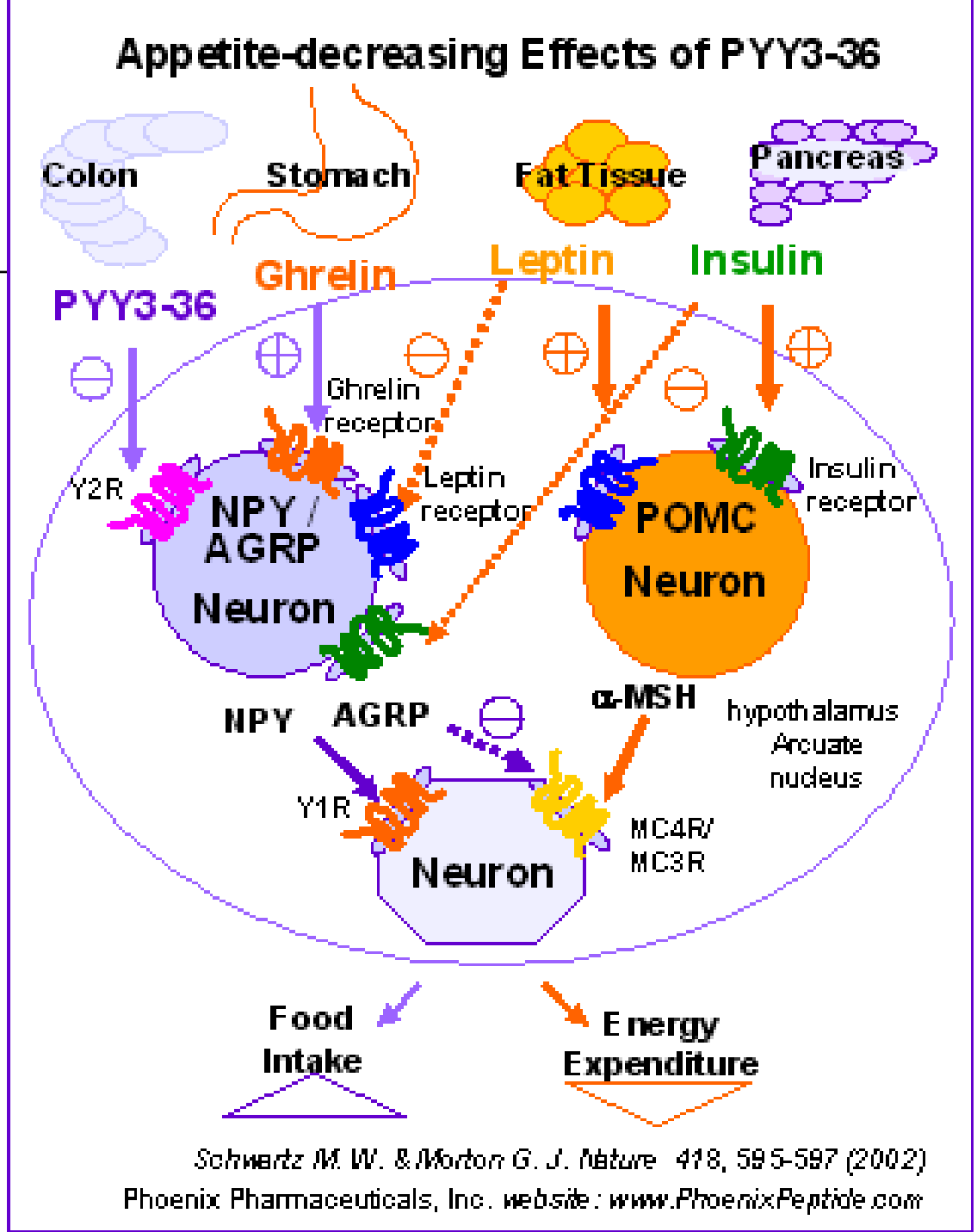
- made by stomach cells
- endogenous ligand for growth hormone seretagogue receptor (GHS-Rs)
- regulation of food intake and body weight


Activity of leptin-NPY/AGRP signalling pathway in central Ghrelin control of food intake
Fasting
Sugar intake or fasted and re-fed
Stomach Ghrelin expression and /release (Neuron ?)
Ghrelin action in hypothalamus
GHS-R
Activates
Inhibits
?
NPY / AGRP Neuron
POMC Neuron
Ghrelin IgG Antagonist for GHS-R
Leptin
NPY/AGRP expression
AGRP Antibody
α-MSH expression and release
α-MSH
NPY release
AGRP release
Paraventricular nucleus
Mc4-R
Y1, Y5
Food intake
Activity of melanocortin anorexia pathways
NPY Antibody
Y1, Y5 antagonist
Obesity
Food intake
Tschöp M., et al. Nature 407, 908-913 (2000)
Nakazato M., et al. Nature 409, 194-198 (2001)
Summarized by Jun Yang on Feb. 07, 2001
PHOENIX PHARMACEUTICALS, INC.

Peptide YY(PYY)

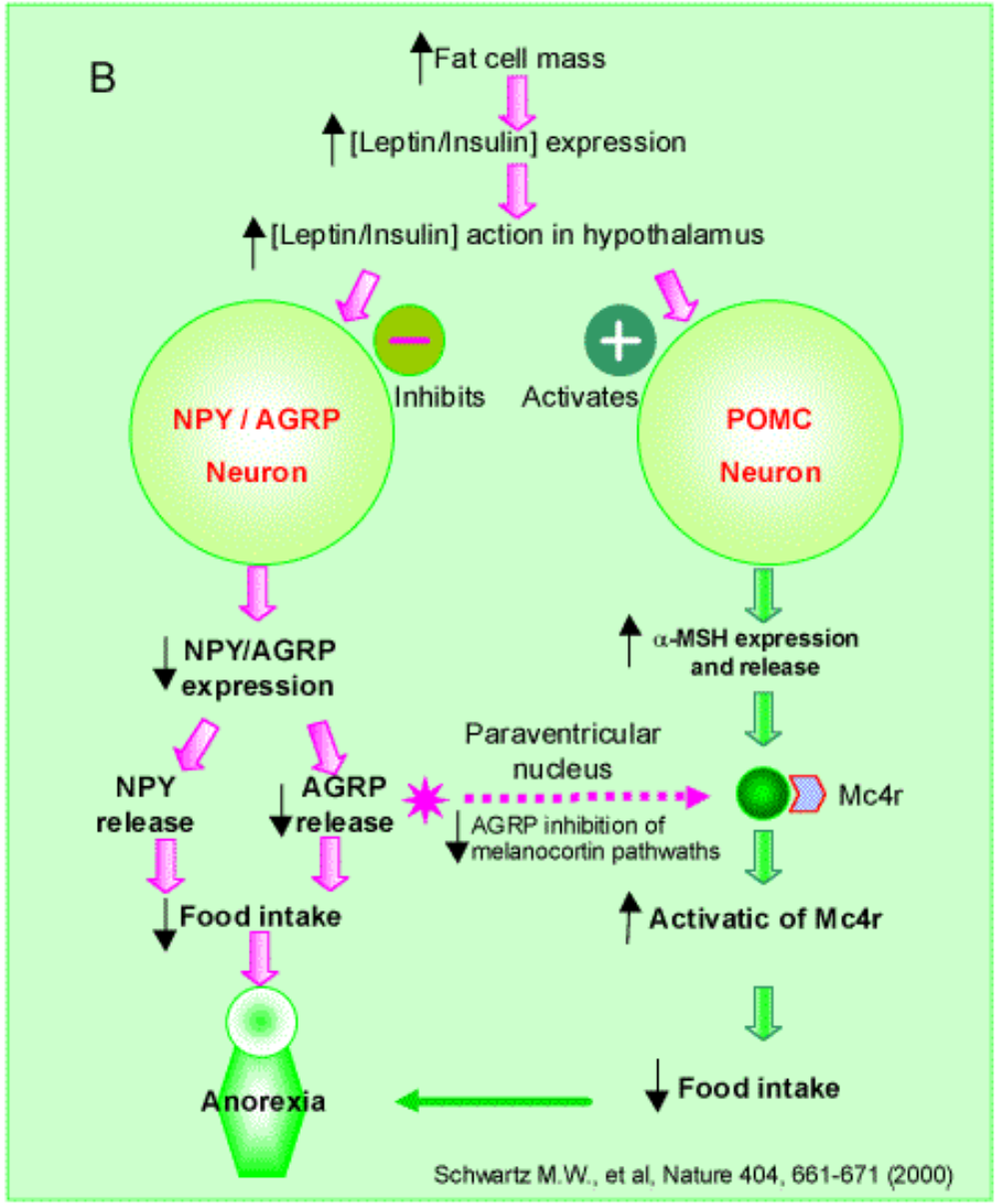
- distal gut hormone
- feedback inhibition of gastric acid secretion, gastrointestinal motility, and pancreatic enzyme output
- In humans, infusion of normal postprandial concentrations of PYY(3-36) significantly decreases appetite and reduces food intake by 33% over 24 h.

PYY


Appetite-decreasing Effects of PYY3-36
Colon
Stomach
Fat Tissue
Pancreas
Ghrelin
Leptin
Insulin
PYY3-36
Ghrelin receptor
Y2R
Leptin receptor
NPY / AGRP Neuron
POMC Neuron
Insulin receptor
α-MSH
NPY
AGRP
hypothalamus Arcuate nucleus
Y1R
MC4R/ MC3R
Neuron
Food Intake
Energy Expenditure
Schwartz M. W. & Morton G. J. Nature 418, 595-597 (2002)
Phoenix Pharmaceuticals, Inc. website: www.PhoenixPeptide.com

Agouti-Related Protein (AGRP)

- Present in the hypothalamus
- potent antagonist of MC3-R and MC4-R
- regulate feeding behavior and body weight



B Increased action of leptin/Insulin in arcuate nucleus inhibits the NPY/AGRP anabolic pathway and stimulates the POMC catabolic pathway, resulting in reduced food intake and anorexia

Peptide YY 3-36 (PYY)

- released from the gastrointestinal tract tract postprandially in proportion to the calorie content of a meal
- inhibits electrical activity of NPY nerve terminals activating adjacent pro-opiomelanocortin (POMC) neurons

Insulin

- Secretion from islet β cells of the endocrine pancreas.

- insulin has peripheral anabolic effects that increase lipid synthesis and storage. A misconception that insulin causes weight gain and obesity has evolved.

Insulin in CNS

- CNS neurons do not produce insulin.
- transported into the brain by a receptor-mediated mechanism.
- occurring over a period of hours after circulating insulin concentrations increase.
- insulin is the long-term regulation of body adiposity rather than as a short-term satiety signal.

Insulin suppress food intake

- 1979, Woods, Porte and colleagues:

  infusion of insulin into the cerebral ventricles → inhibition of food intake and body weight loss.

- 1995, Sipols AJ, Baskin DG, Schwartz MW:

  insulin-deficient diabetic rats (marked increase of food intake) → diabetic hyperphagia was reduced by 50%

- In addition to inhibiting food intake, insulin increases sympathetic neural activity and energy expenditure.

  Vollenweider P, J Clin Invest **93:**2365– 2371, 1994. & Diamond P, LeBlanc J. Am J Physiol **254:**E625–E632, 1988.

- Thus, insulin can modulate energy balance by inhibiting food intake and by increasing thermogenesis.

Other methods about losing weight

- 飲食減肥法
- 藥物治療
- 外科手術

飲食減肥法

（1）節食法：

吃很少的食物 → 沒有足夠的熱量 → 保存脂肪，消耗瘦肌肉 → 基礎代謝率越來越低，脂肪所佔比例越來越高（“溜溜球效應”(yo-yo effect)）容易罹患飲食障礙及憂鬱症等。

（2）低卡代餐包：

可減少熱量攝取而不會引起營養不良，但不繼續吃體重又會回昇，可以在一天中搭配一餐或兩餐食用，每天大概可減少300-600卡的熱量。缺點是價格昂貴、單調，以至於無法長時間進行。

(http://www.wedar.com/library4/yesdiet/yes000802.htm)

飲食減肥法

（3）吃肉減肥法 (高蛋白減肥法)：

可抑制促進脂肪吸收的荷爾蒙分泌，避免贅肉；由於蛋白質所需消化的時間長，因此不容易感到飢餓；有利於體內鹽分排出，消除水腫。但前提是不能攝取到任何醣類食物，否則會胖得更快。

由於醣類攝取量極低，造成脂肪燃燒不完全，使身體產生大量酮體。此法對心臟病、高血壓、痛風、肝、腎或腦血管病變者不適宜，且會增加肝臟氮代謝負擔，可能影響腎臟機能。長期食用會造成營養不均衡、骨質疏鬆、酸中毒、抽筋及破壞腎臟功能等現象。

(http://www.wedar.com/library4/yesdiet/yes000802.htm)

(http://104beauty.com/)

飲食減肥法

（4）喝水減肥法：

根據研究顯示，水分攝取減少會導致脂肪的堆積，相反的，如果增加水分的攝取，則可以有效減少水分的堆積，加上多喝水可以有效抑制食慾，並且幫忙代謝脂肪，所以簡單的多喝水，是減重不可不備的靈藥。

- 肝臟作用無法完全發揮會讓減重變慢：

  腎臟的作用是代謝，而腎臟只有在水分充足的情況下可以發揮作用。當腎臟因為水分不足無法有效進行工作的時候，相關運作便會轉移到肝臟去負責。肝臟主要的功能之一是幫助脂肪的代謝，讓儲存的脂肪轉為可運用的體力。如果肝臟需要幫忙負荷腎臟的工作，肝臟便無法全面發揮代謝脂肪的功能，最後的結果會造成肝臟所代謝掉的脂肪減少，一但儲存於身體的脂肪增加，減重的效果便會停滯。

(http://104beauty.com/)

藥物治療

（1）睡眠減肥法－胺基酸減肥法 ：

主要的方式就是在睡覺前補充氨基酸來達到促進人體基礎代謝的作用。科學家證實，補充多種"複合氨基酸"可提供體內合成生長激素的原料，提供人體腦下垂體足夠的刺激，分泌足夠的生長激素使身體維持年輕時的水準，促進人類生長激素的釋放，如L-精氨酸 (L-Arginine)、L-麩醯氨酸 (L-Glutamine)、L-離氨酸 (L-Lysine)等氨基酸。

使用複合氨基酸的方法跟一般營養補充品不同，由於人體分泌生長激素的時間主要在晚上11點到凌晨1點之間，所以在睡前使用是最佳時機。在入睡前補充高濃度的複合氨基酸，可以促進成年人HGH生長激素的分泌增加，即可燃燒體內多餘的脂肪，因此在睡眠中就能恢復健美身材。

(http://104beauty.com/)

藥物治療

（2）美體新寵－藤黃果 ：

1.含有大量HCA（即為：hydroxycitric acid，氫氧化檸檬酸），此脂肪的合成，阻礙葡萄糖在體內合成脂肪
2.結構與檸檬酸相似，會抑制酵素ATP-Citrate lyase的活性，阻礙醣類轉換成為體內多餘的脂肪
3.促進體內脂肪燃燒，將多餘的能量轉化為易於消耗的肝糖
4.能調節人體內脂肪代謝，將過多未被身體當作熱量消耗掉的營養成份轉以肝醣的形式儲存在肌肉及肝臟內
5.增加肝臟和肌肉儲存肝醣的能力，減少脂肪的製造量
6.若體內肝醣的儲存增加，當人體在運動時，能立即供應能量，而因血糖下降產生饑餓的自然反應情況也會減少，因此具有抑制食慾的功效，使碳水化合物和蛋白質的製造過程減慢
7.具產熱性，能燃燒脂肪，刺激身體的機能，將脂肪釋出
8.研究證實，HCA能於餐後8至12小時內減低40%以上的脂肪形成
＊服用：服用HCA產品，在飯前30分鐘效果最好

(http://104beauty.com/)

藥物治療

（3）啤酒酵母妙用多：

由於減肥的人大多會節食，而啤酒酵母富含的維生素便可以補充能量，此外，提高基礎代謝率後人體能消耗的能量也越多。啤酒酵母也含大量的膳食纖維，有助於腸胃蠕動，所以卡在腸胃絨毛上宿便也較易清出，因此對改善長期便秘也十分有效。若在飯前配合大量的水食用，會提供飽食感，用餐量也會減少，長期下來體重自然就變輕。

不過要注意的是，啤酒酵母只能提高妳消耗能量的能力，並不會主動消耗脂肪，所以如果要減肥，還是要配合熱量計算和運動才是不二法門。

(http://104beauty.com/)

藥物治療

（3）雞尾酒減肥法 ：

營養師所認定的雞尾酒減重法應該是一種綜合的減重方法，其中包含有飲食的控制、運動習慣的養成等兩種合併實施 。

雞尾酒減重裏所可能使用的合法藥物包含一些過敏性藥物的另類療法，它可用來提高基本代謝率；另外還有抑制油脂及澱粉質吸收的藥； 所謂的過敏性藥物它可提昇基礎代謝率，降低食慾，加速熱量的消耗；抑制脂肪或澱粉質吸收的藥，則是針對油脂或米飯、麵食、甜食等含醣量多的食物攝取量偏高的人而言有較好的效果。

除此之外，飲食習慣未更改而只是單純依靠藥物者，則更容易加重藥物的副作用產生，例如脂溶性維生素A、D、E的吸收障礙、腹瀉、脹氣等現象。

(http://www.webhospital.org.tw/health/10.html)

藥物治療

（4）減肥藥物 ：

目前國內只有兩種合法減肥藥，一是PPA，一是Orlistat。不過由於PPA的副作用不小，美國食品暨藥物管理局（FDA）已宣布禁用PPA，而即將上市的減肥藥Sibutramine因安全性較高，其重要性應可望取代PPA。

根據衛生署所公佈的標準減肥速度，是平均每周減0.5-1公斤，當減肥速度太快時，輕則可能誘發急性痛風及膽結石，重則可能導致死亡，更重要的是會有復胖率極高的Yo-Yo球效應，並容易罹患飲食障礙及憂鬱症等。

(http://www.webhospital.org.tw/health/10.html)

藥物治療

(5)「MG基因」的發現，多吃少動不發胖，指日可待！

２０００年７月，英國劍橋大學宣佈培育出「轉基因實驗鼠」，即使讓牠們終日暴飲暴食，體內也不會聚積過多脂肪。此外，美國麻省研究者最近也宣佈，在鼠身上找到一種具有抑制肥胖症，又能調節熱量消耗的基因—「MG基因」，這是被發現與肥胖有關的第六個基因，卻是第一個被發現與代謝和能量消耗有關的基因。這批攜帶突變「MG基因」的鼠，不論吃高脂或低脂的食物，都不會增加體重，研究者相信，「MG基因」在人身上也應扮演同樣的角色。

(http://www.webhospital.org.tw/health/10.html)

不可不知的減肥須知

＊西瓜是減肥的理想水果

因為西瓜利尿，又可以消除血液中的廢物，藉著尿液排出體外，減肥者不可不知。

＊用餐前先喝流質來抑制食慾

三餐之前，可先喝一大杯開水或檸檬水，可以降低食慾，避免吃得過多。

＊運動後洗熱水澡幫助減肥

運動後如能洗個熱水澡，不但可以消除疲勞，也有減肥的功效。

＊不要過度抑制食慾

減肥時，很多人都靠意志力來抵抗高熱量的食物誘惑，然而完全的禁食，有時反而會引起更大的食慾，倒不如想吃的時候吃一點點，這樣對減肥計劃才有幫助。

(http://104beauty.com/)

不可不知的減肥須知

＊喝茶可以去油減肥

茶具有去油的功效，當攝取過多的油膩食品後，可喝杯濃茶來洗去過多的油份。

＊食用蒸煮的食物

油炸的食物是致胖的大敵，如果能把食物改成用蒸的，熱量可以減少三分之一以上。

＊冬季易發胖

冬天時人的食慾會變好，所以別忘了吃飯前先喝一杯熱開水，可既暖自己的胃又可降低食慾。

＊冰塊在果汁之前

當您想喝果汁時，在杯子裡先加滿半杯的冰水（冰塊），再倒進果汁，就可以減少一半的量。

(http://104beauty.com/)

不可不知的減肥須知

＊改掉吃宵夜的習慣

吃宵夜的習慣會讓人熱量全部累積在體內，叫肥胖無所遁形。

＊辛辣食物會刺激食慾

請改掉吃辛辣食物的習慣，辛辣的口味會刺激食慾讓人胃口大開。

(http://104beauty.com/)