Why Do Onions Make You Cry?

By Anne Marie Helmenstine, Ph.D., About.com Guide

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Question: Why Do Onions Make You Cry?

Answer: Unless you've avoided cooking, you've probably cut up an onion and experienced the burning and tearing you get from the vapors. When you cut an onion, you break cells, releasing their contents. Amino acid sulfoxides form sulfenic acids. Enzymes that were kept separate now are free to mix with the sulfenic acids to produce propanethiol S-oxide, a volatile sulfur compound that wafts upward toward your eyes. This gas reacts with the water in your tears to form sulfuric acid. The sulfuric acid burns, stimulating your eyes to release more tears to wash the irritant away.

No more tears? Try chilling your onion before cutting it.

Marcelo Brito Filho

Cooking the onion inactivates the enzyme, so while the smell of cooked onions may be strong, it doesn't burn your eyes. Aside from wearing safety googles or running a fan, you can keep from crying by refrigerating your onion before cutting it (slows reactions and changes the chemistry inside the onion) or by cutting the onion under water.

The sulfur-containing compounds also leave a characteristic odor on your fingers. You may be able to remove or reduce some of the smell by wiping your fingers on a stainless steel odor eater.

Lab note

Ultrastructural Organization of Human Corneal Nerves

Linda J. Müller, Liesbeth Pels, and Gijs F. J. M. Vrensen

Purpose. Although the human cornea is densely innervated, observations of the nerve fiber distribution and ultrastructure are scarce. This study aimed to provide a detailed electron microscopic analysis of nerve fibers in the central and peripheral human cornea.

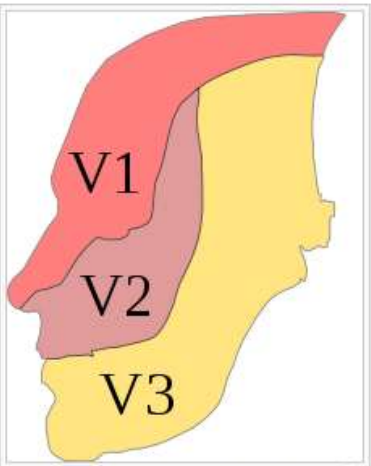
Methods. Samples from seven fresh corneas, obtained from eyes of persons with melanoma, were processed for light and electron microscopic examinations. Both frontal and cross-sections were studied. Furthermore, serial ultrathin sections from the mid-epithelium to the anterior stroma were used.

Results. Unmyelinated nerve fiber bundles (as many as 30 nerve fibers and cross-section as large as 20 μm) run parallel to the stromal collagen fibers. Nerve fibers contain clear, dense cored and dense vesicles and are ensheathed by thin rims of Schwann cell protrusions and amorphic matrix. Some nerve fibers invaginate the cytoplasm of keratocytes. After passing through Bowman's membrane, bundles of straight fibers (cross-section 0.1 to 0.5 μm) and single-beaded nerve fibers, which both lack Schwann cell ensheathment, run parallel in an alternating manner. Beaded nerve fibers, containing many mitochondria and glycogen (cross-section as large as 2 μm), turn upward and invaginate both basal and wing cells. Except for the presence of myelinated nerve fibers in the peripheral stroma, no differences in the central cornea were observed.

Conclusions. Nerve fibers invaginating epithelial cells and keratocytes suggest that both cell types are directly innervated. The presence of vesicles, mitochondria, and glycogen in stromal and epithelial nerve fibers suggest that classical and peptidergic transmitters, probably of sensory origin, innervate the human cornea. Peptidergic transmitters in nerve fibers may be involved in neuroimmunomodulation of the cornea. Invest Ophthalmol Vis Sci. 1996;37:476–488.

The human cornea is a densely innervated structure.[1–6] Most of the corneal nerve fibers are of sensory origin, derived from the trigeminal nerve.[1,7] These sensory nerve fibers respond to mechanical, thermal, and chemical stimulation of the cornea.[8–10] Antibodies after immunohistochemical staining with cholinergic,[4,20,21] adrenergic,[5,22,23] and peptidergic[4,24–26] antibodies. These stainings reflect the nerve fiber distribution and provide evidence that corneal nerve fibers contain classical and peptidergic neurotransmitters.

Sensory branches of the trigeminal nerve [edit]



Dermatome Distribution of the Trigeminal Nerve

The ophthalmic, maxillary and mandibular branches leave the skull through three separate foramina: the superior orbital fissure, the foramen rotundum and the foramen ovale. The mnemonic *standing room only* can be used to remember that V_1 passes through the superior orbital fissure, V_2 through the foramen rotundum, and V_3 through the foramen ovale. [1]

- The **ophthalmic** nerve carries sensory information from the scalp and forehead, the upper eyelid, the conjunctiva and cornea of the eye, the nose (including the tip of the nose, except alae nasi), the nasal mucosa, the frontal sinuses, and parts of the meninges (the dura and blood vessels).
- The **maxillary** nerve carries sensory information from the lower eyelid and cheek, the nares and upper lip, the upper teeth and gums, the nasal mucosa, the palate and roof of the pharynx, the maxillary, ethmoid and sphenoid sinuses, and parts of the meninges.
- The **mandibular** nerve carries sensory information from the lower lip, the lower teeth and gums, the chin and jaw (except the angle of the jaw, which is supplied by C2-C3), parts of the external ear, and parts of the meninges.
- The mandibular nerve carries **touch/position** and **pain/temperature** sensation from the mouth. It does not carry **taste** sensation (chorda tympani is responsible for taste), but one of its branches, the lingual nerve carries multiple types of nerve fibers that do not originate in the mandibular nerve.

Exp Eye Res. 2010 Mar 23. [Epub ahead of print]

TRPV channels mediate temperature-sensing in human corneal endothelial cells.

Mergler S, Valtink M, Coulson-Thomas VJ, Lindemann D, Reinach PS, Engelmann K, Pleyer U.

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Abstract

The physiology and transparency of the cornea are dependent on corneal endothelial function. The role of temperature sensitive ion channels in maintaining such activity is unknown. This study was undertaken to probe for the functional expression of such pathways in human corneal endothelial cells (HCEC). We used HCEC-12, an immortalized population derived from whole corneal endothelium, and two morphologically distinct clonal cell lines derived from HCEC-12 (HCEC-H9C1, HCEC-B4G12) to probe for gene expression and function of transient receptor potential (TRP) channels of the vanilloid (V) isoform subfamily (i.e. TRPV1-3) in these cell types. Expression of TRPV isotypes 1, 2 and 3 were detected by RT-PCR. Protein expression of TRPV1 in situ was confirmed by immunostaining of corneoscleral remnants after keratoplasty. TRPV1-3 functional activity was evident based on capsaicin-induced Ca(2+) transients and induction of these responses through rises in ambient temperature from 25 degrees C to over 40 degrees C. The currents underlying Ca(2+) transients were characterized with a novel high throughput patch-clamp system. The TRPV1 selective agonist, capsaicin (CAP) (10-20 muM) increased non-selective cation whole-cell currents resulting in calcium increases that were fully blocked by either the TRPV1 antagonist capsazepine (CPZ) or removal of extracellular calcium. Similarly, heating from room temperature to over 40 degrees C increased the same currents resulting in calcium increases that were significantly reduced by the TRP channel blockers lanthanum chloride (La(3+)) (100 muM) and ruthenium-red (RuR) (10 muM), respectively. Moreover, application of the TRPV channel opener 2-aminoethoxydiphenyl borate (2-APB) (400 muM) led to a reversible increase in intracellular Ca(2+) indicating putative TRPV1-3 channel activity. Taken together, TRPV activity modulation by temperature underlies essential homeostatic mechanisms contributing to the support of corneal endothelial function under different ambient conditions.

http://video.pbs.org/video/995676319/

70-80% genetic, second only to height in genetic influence

Leptin = Greek for 'Thin'

Would you have rather won the lottery or found out about MC4

Leptin hormone k/o mice are obese because of *appetite*

Disruptions in other arms of the complex leptin signaling pathway also causes obesity

~1 in 1,000 people estimated to have an MC4 receptor mutation and are obese

But however influential genetics is, obesity is not possible without a permissive environment:
US obesity map: http://www.cdc.gov/obesity/data/trends.html

Obesity genes with mongenetic effects mapped to chromosomes

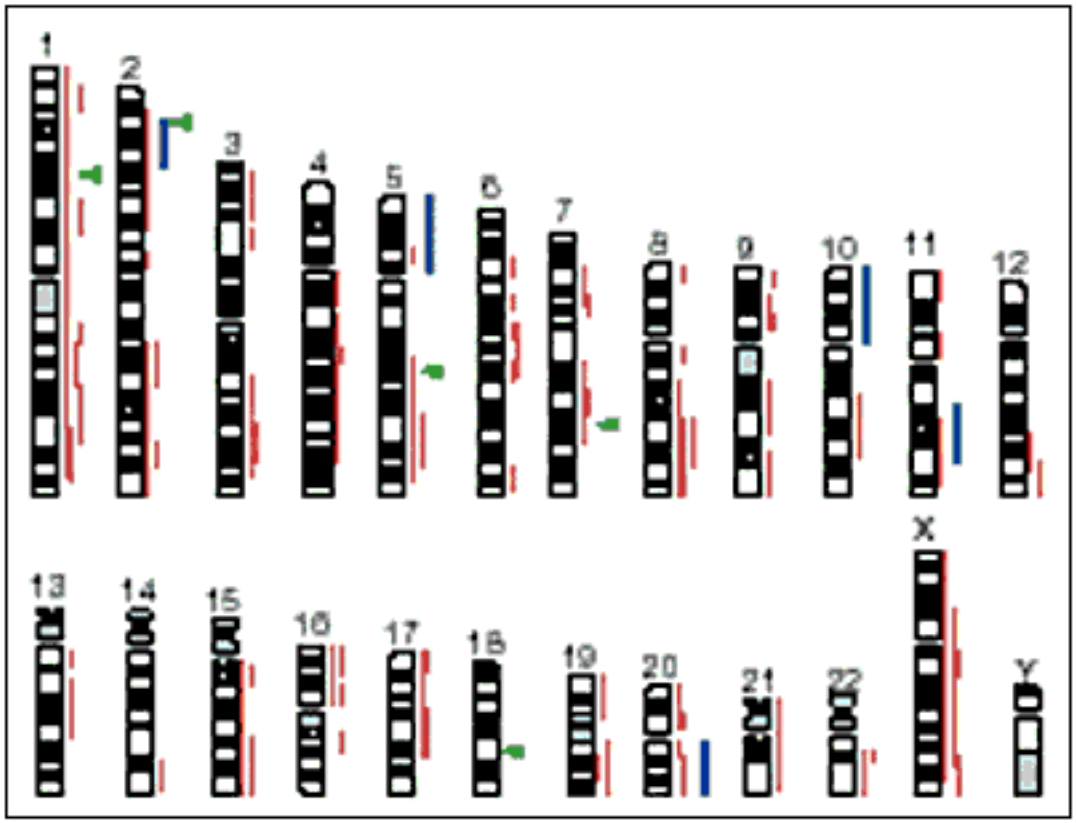


Figure 2. Chromosomal location of obesity genes. Ideogram of human karyotype with human monogenic mutations indicated in green, human loci identifed by genome-wide linkage scans indicated in blue, and the potential location of one or more mouse QTLs (based on conserved homology) indicated in red. From [416].

Our paper focused on monogenetic effects, but if you understand what was presented about these pathways, you would know that polygene effects are also likely in explaining obesity

http://www.endotext.org/obesity/obesity6/obesity6.htm

obesity reviews doi: 10.1111/j.1467-789X.2007.00378.x

Appetite Regulatory Peptides

The leptin melanocortin pathway and the control of body weight: lessons from human and murine genetics

A. Oswal and G. S. H. Yeo

correlations of monozygotic, dizygotic, biological and adopted siblings reveal that body weight may be hereditary in up to between 30% and 70% of cases (5–7).

LEPTIN FACTS:

- Discovered 1994 as product of mouse ‘obese’ mutation- leptin was missing in this mouse

- Linked to human obesity in a few families in 1997 paper

- Mapped to hypothalamus and other limbic (emotional) structures

- Leptin is classified as a hormone. Why? What kind of hormone is it?

- Mouse and human leptin deficiency causes post-weaning obesity (birth weight is normal) and general endocrine dysregulation

- Theory of Adaptive function of leptin: maintain fat stores during starvation– evolutionarily more plausible than a ‘weight loss’ function

The leptin receptor

The *diabetes* (*db*) mice are almost phenotypically identical to the *obese* strain (21) and parabiosis experiments suggested that *obese* mice were lacking an adipostatic hormone, whereas the *diabetes* strain lacked the receptor for the hormone (30,31).

parabiosis

Also found in: Medical, Encyclopedia

par·a·bi·o·sis (pă'r'ə-bī-ō'sĭs)

n. pl. **par·a·bi·o·ses** (-sēz)

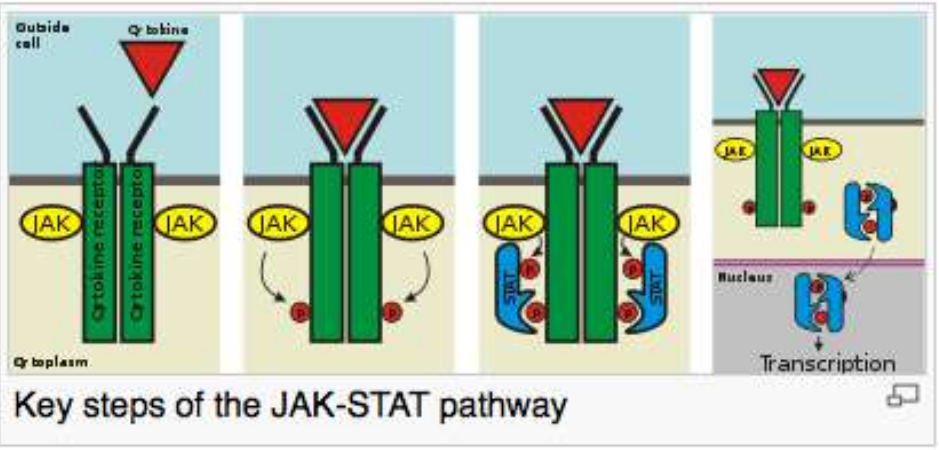
1. The natural or surgical union of anatomical parts of two organisms, usually involving exchange of blood, as in the development of Siamese twins or in certain transplant operations.

2. A temporary suspension of conductivity or excitability in a nerve.

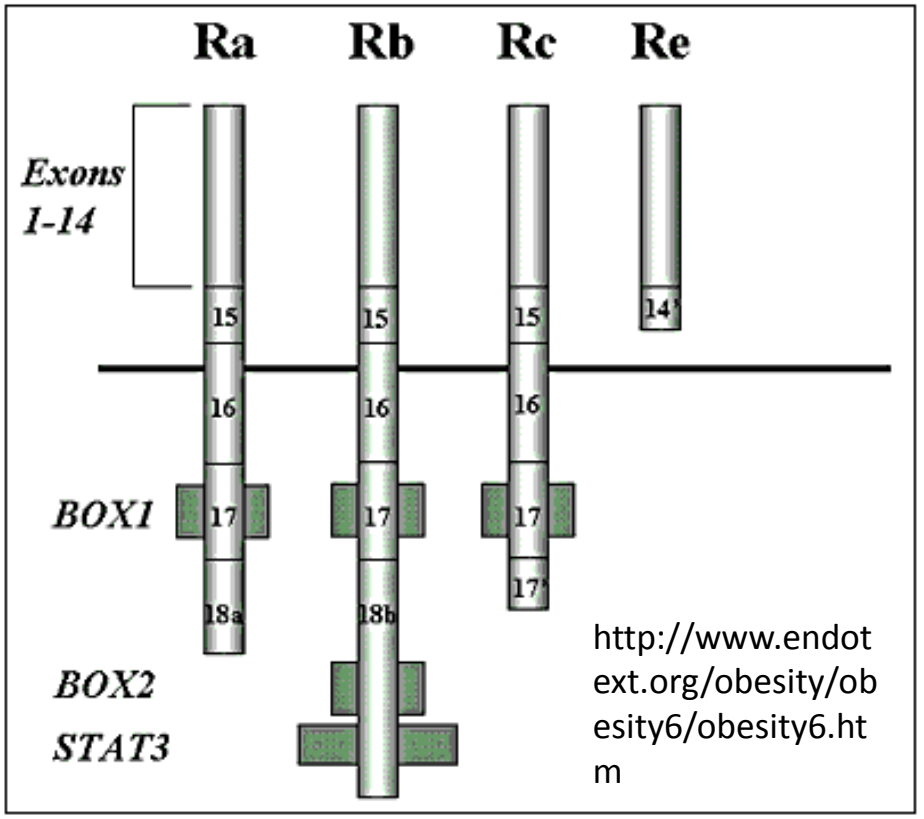
Leptin receptors: in the class 1 cytokine receptor superfamily

Uses JAK/STAT, not G-protein. (Janus kinase / signal transducer and activator of transcription) . Regulates gene transcript and ion channels

receptor (32–34). The leptin receptor is a single membrane spanning protein which shows structural similarity to the class 1 cytokine receptor family (32,35). Several different alternatively spliced isoforms of the leptin receptor (OB-R) exist (35), each with a characteristic intracellular domain. Depending upon the length of the intracellular domain, the isoforms are classified as either short or long. The short isoforms (ObRa, ObRc, ObRd, ObRe and ObRf) have limited signalling capacity, while the long isoform ObRb is believed to be the primary signalling form of the receptor (35–37). The ObRa and ObRc are expressed at high levels in the cerebral microvessels which constitute the blood–brain barrier and are believed to play important roles in leptin transport into the central nervous system (CNS) (38). Defective transport of leptin across the blood–brain barrier



Key steps of the JAK-STAT pathway



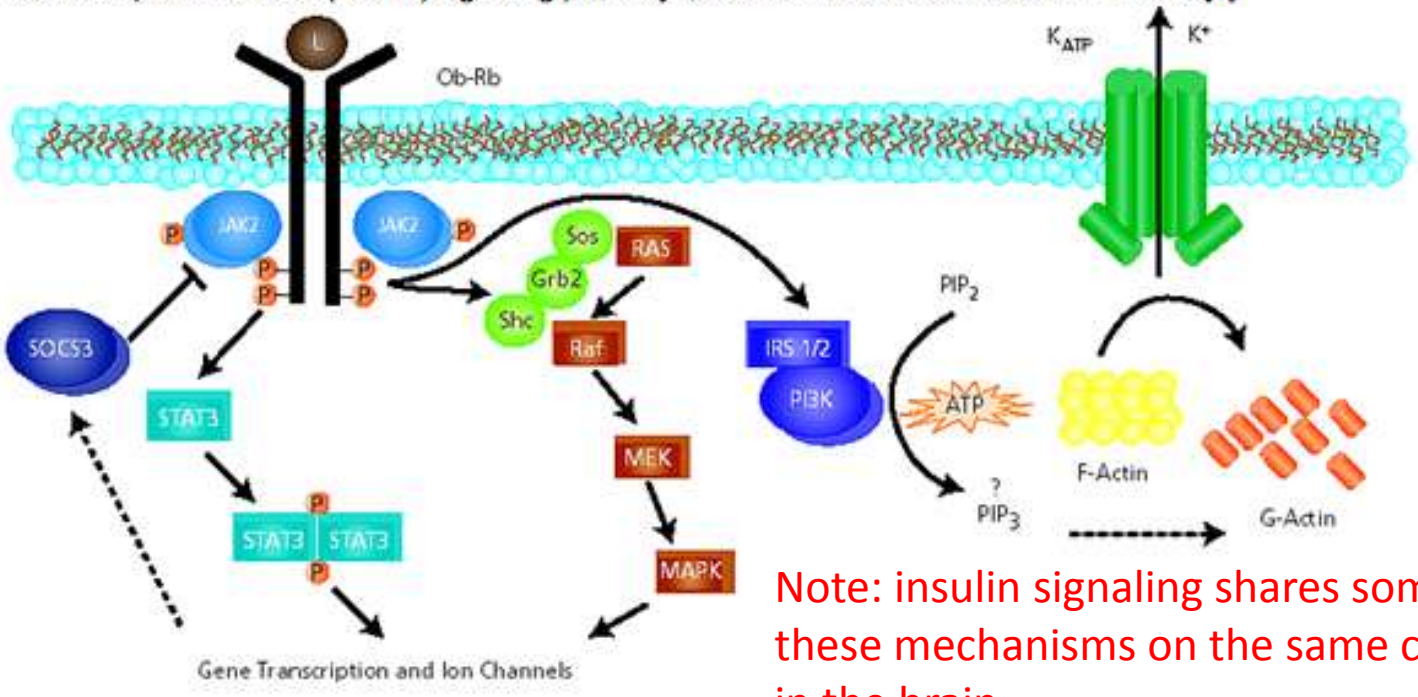
http://www.endotext.org/obesity/obesity6/obesity6.htm

Figure 1A. Leptin receptor isoforms. Lepr-a (Ra) encodes the short form of the leptin receptor, and Lepr-b (Rb), encodes the long form. Exon 17 contains a Jak docking site (BOX1) common to Ra, Rb and Rc, while exon 18b contains additional motifs (BOX2 and STAT) required for STAT3 signaling. Soluble LEPR isoform Re lacks a transmembrane domain.

Leptin signlaing activates intracellular pathways. Genetic defects in parts of the pathway (IRS-2) can mimic leptin deficiency, while defects in intracellular suppressors of the pathway (SOCS3) cause opposite phenotype. Intracellular signaling info critical for linking different mutations

Leptin

Leptin (L4146) is the product of the obese (*ob*) gene and is produced predominantly in white adipose tissue [1]. The leptin receptor (Ob-R), isolated by expression cloning, is encoded by the diabetes (*db*) gene and alternate splicing of the *db* gene generates six leptin receptor (Ob-Ra-f) isoforms [1]. The Ob-Rb isoform, the long isoform, plays a vital role in regulating obesity and high levels of the isoform exist in the hypothalamus, the main site of leptin action [1]. The absence of this isoform results in the obese phenotype in *db/db* mice [1]. The leptin receptor is a member of the class I cytokine receptor superfamily. Like other family members, leptin receptor activation stimulates STAT1, STAT3 and STAT5 tyrosine phosphorylation *in vitro* and STAT3 tyrosine phosphorylation *in vivo* [1]. Indeed, the Ob-Rb isoform acts as a potent JAK/STAT signaling activator and the ability of leptin to activate STAT3 is decreased in the hypothalamus when mice are subjected to high fat diets [2]. Leptin deficiency occurs through two mechanisms, either by a defect in leptin transport across the blood brain barrier or by suppression of leptin signaling [2]. Leptin signaling is blocked by suppressors of cytokine signaling-3 (SOCS-3) and by dephosphorylation by protein tyrosine phosphatase 1B (PTP-1B, Product Code P6244). SOCS-3 and PTP-1B deficient mice exhibit increased sensitivity to leptin and resistance to obesity [2]. In addition, leptin receptor activation stimulates both the phosphotidylinositol 3-kinase (PI3K) and Ras-mitogen activated protein kinase (MAPK) signaling pathways, both of which are downstream of JAK [1].



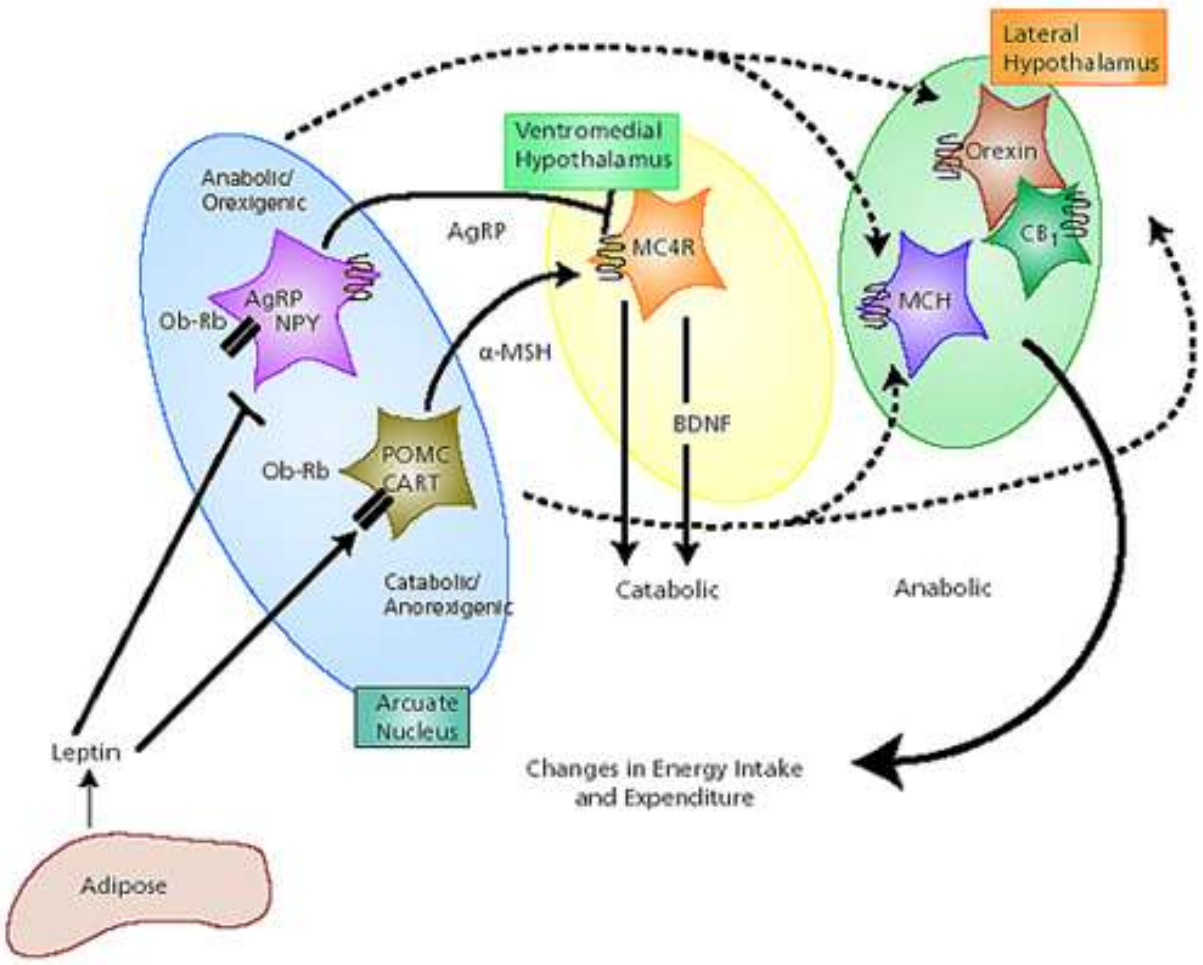
Note: insulin signaling shares some of these mechanisms on the same cells in the brain

http://www.sigmaaldrich.com/life-science/cell-biology/obesity-research/learning-center/effects-of-peptides.html

Figure 1: Leptin receptor signaling. Adapted from Harvey and Ashford, *Neuropharmacology*, **44**, 947-849 (2003)

WHERE ARE THESE LEPTIN RECEPTORS? Think of the "four F's" of hypothalamic function….

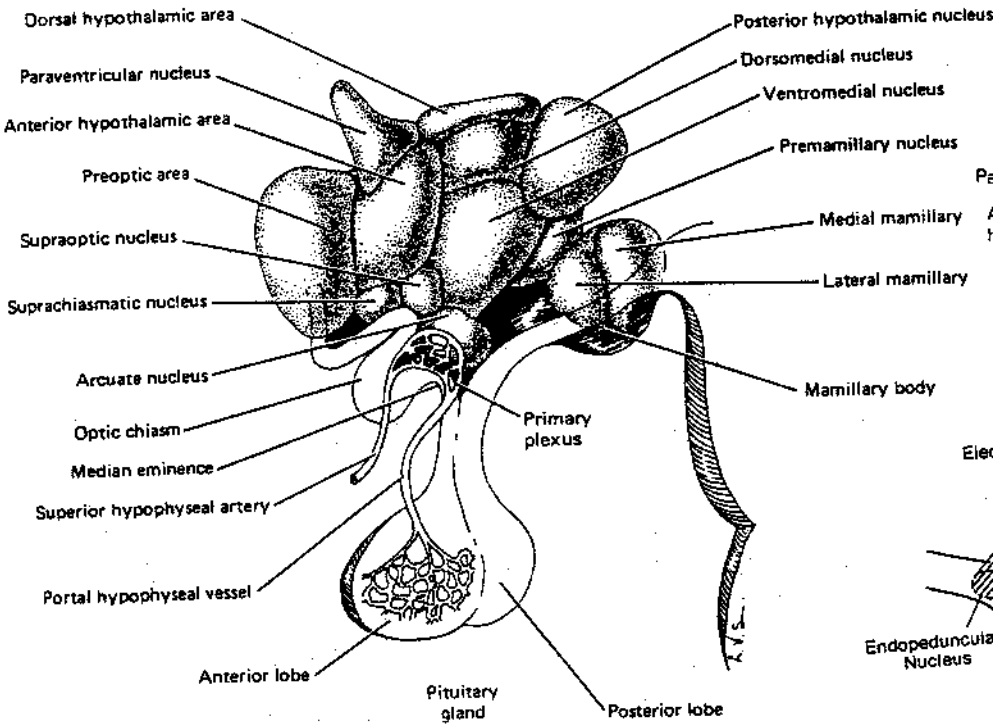
Considering the four F's, it's not surprising that ObRb gene defects can lead to infertility and general endocrine dysfunction (leptin defects don't though… what does that suggest?)



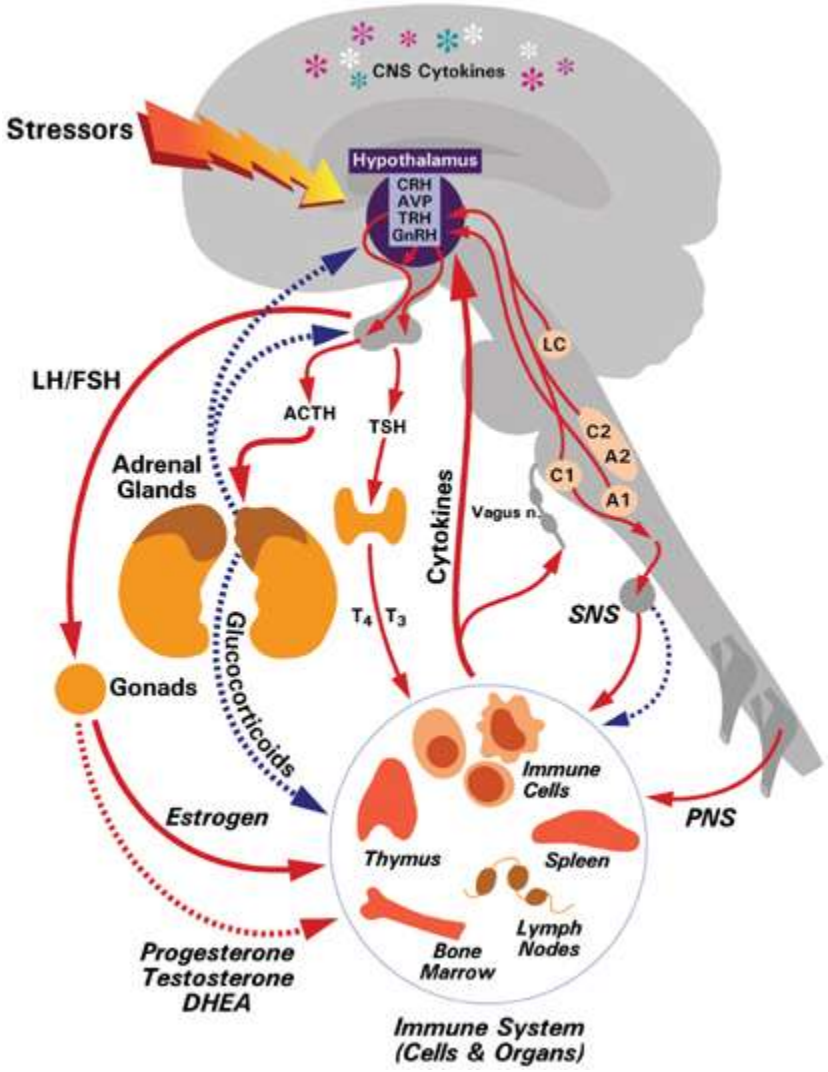
http://www.sigmaaldrich.com/life-science/cell-biology/obesity-research/learning-center/effects-of-peptides.html

Figure 2: Leptin actions and downstream effects in the arcuate nucleus, ventromedial hypothalamus (VH) and lateral hypothalamus. Adapted from Flier, *Cell*, **116**, 342 (2004).

THE HYPOTHALAMUS IS A SYSTEM A MULTIPLE NUCLEI- GENERALLY, THEY ARE INVOLVED IN NEUROENDOCRINE CONTROL, HOMEOSTASIS / EMOTION



http://www.benbest.com/science/anatmind/FigVII19.gif



http://www.nature.com/mp/journal/v10/n3/fig_tab/4001643f1.html

What is POMC?

Any evidence of a role in obesity?

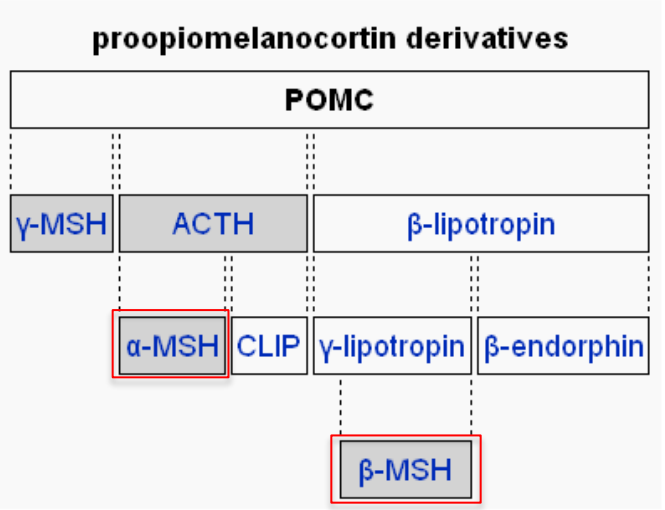
Why would it be related to obesity?

Genetic POMC deficiency described in 6 obese individuals to date (paper)

Derivatives [edit]

The large molecule of POMC is the source of several important biologically active substances. POMC can be cleaved enzymatically into the following peptides:

- Adrenocorticotropic hormone (ACTH) and β-LPH in the anterior pituitary gland
- CLIP, γ-LPH, α-MSH and β-endorphin in the intermediate lobe
  - γ-MSH
  - β-MSH



241 AA long

Although the N-terminal 5 amino acids of beta-endorphin are identical to the sequence of Met-enkephalin, it is not generally thought that beta-endorphin is converted into Met-enkephalin. Instead, Met-enkephalin is produced from its own precursor, proenkephalin.

The production of β-MSH occurs in humans but not in mice or rats due to the absence of the enzymatic processing site in the rodent POMC.

Mutations that disrupt POMC processing (eg, POMC→PC1→γ/a MSH) can cause more specific phenotypes, including obesity

Function [edit]

Each of these peptides is packaged in large dense-core vesicles that are released from the cells by exocytosis in response to appropriate stimulation.:

- α-MSH produced by neurons in the arcuate nucleus has important roles in the regulation of appetite and sexual behavior, while α-MSH secreted from the intermediate lobe of the pituitary regulates the production of melanin.
- ACTH is a peptide hormone that regulates the secretion of glucocorticoids from the adrenal cortex.
- β-endorphin and met-enkephalin are endogenous opioid peptides with widespread actions in the brain.

Signaling through the leptin receptor can activate POMC production and cleavage to MSH's.
So what are the receptors for POMC products in the hypothalamus involved in eating control?
Any evidence that either of these receptors is involved in human obesity?

In 1998, we and another group independently reported heterozygous mutations in MC4R in humans that were associated with dominantly inherited obesity (121,122). Since then, a large number of pathogenic mutations in MC4R have been reported in obese humans from various ethnic groups (123–126), accounting for anywhere between 0.5% and 6% of all severe cases of early-onset obesity, making this the most common monogenic obesity disorder in humans described to date (123). Recent studies have reported that in UK and European populations, 1–2.5% of people with a BMI greater than 30 kg m^{-2} harbour pathogenic mutations in MC4R (127), providing an amazing indication of the true population prevalence of this disorder and placing it among the most common of genetic diseases, with a higher prevalence than more familiar diseases such as cystic fibrosis (8).

Effects of MC3R defects are less clear. Some evidence of human familial obesity related to MC3R mutation, but not as clear as MC4R

HET MC4R mutants have intermediate phenotypes and elevated obesity risk.

Haploinsufficiency?
Dominant negative effects?
Or..
Mut/WT dimerization?

Receptor dimerization comes up a lot these days!

Agouti! And AgRP

Agouti refers to a number of species of rodents as well as a number of genes affecting coat coloration in several different animals. Agouti fur contains a pattern of pigmentation in which individual hairs have several bands of light and dark pigment with black tips.

What is AgRP?

Where is it produced and where does it act in the brain?

What receptors does it bind to?

What effect does it have on those receptors?

Is the effect of AgRP binding to its receptor orexigenic or anorexic?

Does this fit with the effects of MC4R k/o, POMC k/o, and leptin k/o? How?

"The Model"

Many questions remain:
-MC3R signaling effects
-Appetite regulation vs metabolism regulation effects of leptin
-Independent functions of leptin vs MCR pathways
-Intracellular mediators of signaling through MC3/4R

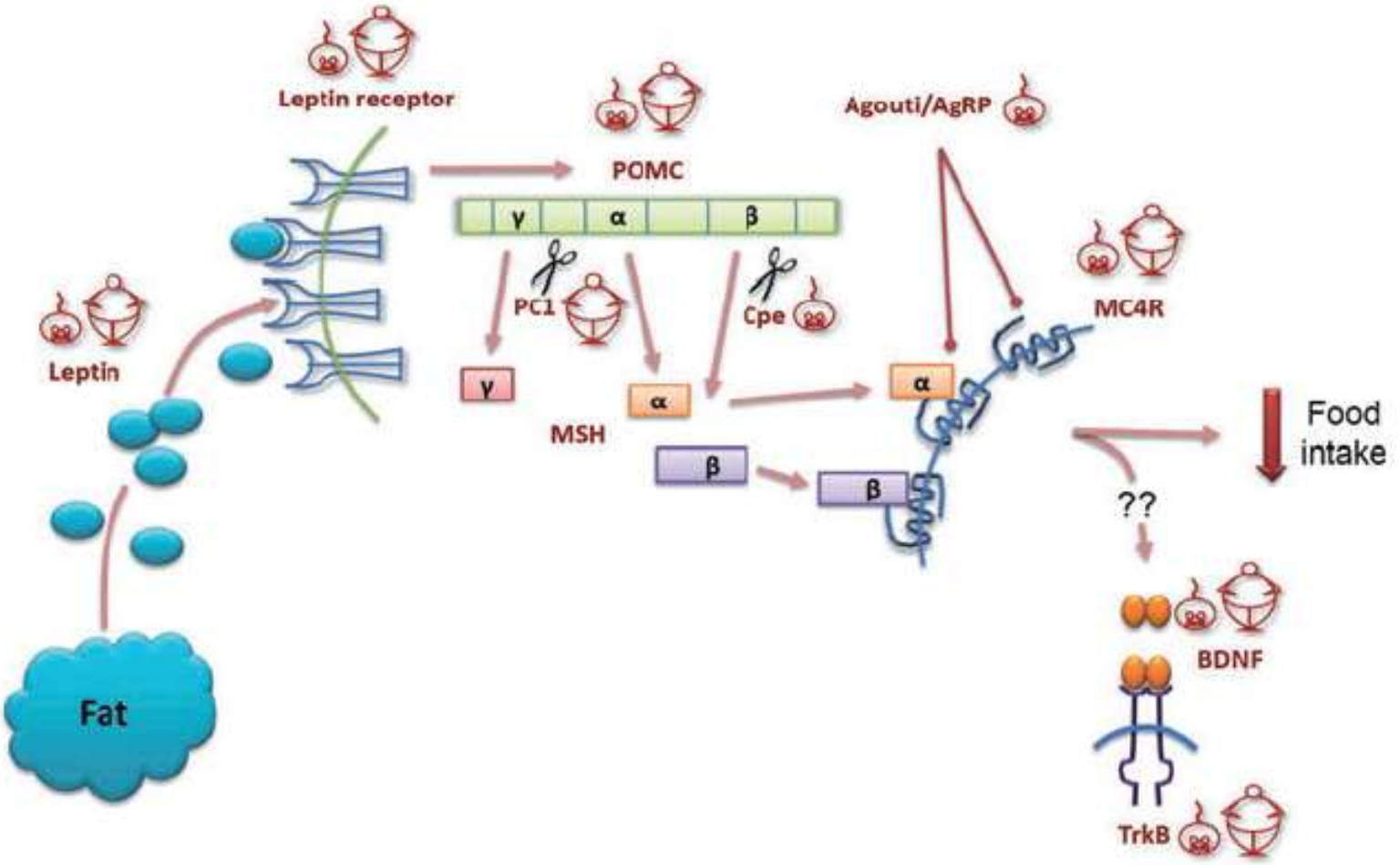


Figure 1 Disruption of the leptin melanocortin pathway results in severe obesity in humans and mice. Existence of a human monogenic obesity syndrome or an obese mouse model is illustrated with a 'fat man' or a 'fat mouse'. α, β or γ MSH, α, β or γ melanocyte stimulating hormone; AgRP, agouti-related peptide; BDNF, brain-derived neurotrophic factor; Cpe, carboxypeptidase E; MC4R, melanocortin 4 receptor; PC1, prohormone convertase 1; POMC, pro-opiomelanocortin.

Cellular Neuroscience is hard work!

A glance downstream of melanocortin 4 receptor signalling: brain-derived neurotrophic factor (BDNF) and TrkB?

Many 'scientist hours' continue to be invested in working out the details of how the leptin and melanocortin pathways interact, as well as understanding the physiological roles they play in a myriad of other biological systems and pathways. One of the key questions which many groups are focusing on is: 'What happens downstream of MC4R signalling?' Despite the collective brain-power that has been focused on this question to date, the specific mechanisms that mediate MC4R signalling still remain a 'black-box'.

But without knowledge of intracellular signaling mechanisms, the relationships among different mutations would not be apparent, and strategies for replacement therapy– already used successfully in some monogenetic obesity disorders– would not be clear.