Anorexia, Bulimia
&
The Skinny on Fat

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Faculty Disclosure
for
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Speaker's Bureau: Boehringer-Ingelheim (Pradaxa)

BMI = 24

Definition of Alcoholism/Addiction

"Alcoholism is a primary, chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. The disease is often progressive and fatal. It is characterized by continuous or periodic: Impaired control over drinking, preoccupation with the drug alcohol, use of alcohol despite adverse consequences, and distortions in thinking, most notably denial."

American Society of Addiction Medicine/NCADD (1992)

Definition of Alcoholism/Addiction
continued

- Additional characteristics:
  - Tolerance (physical and behavioral)
  - Escalating usage
  - Withdrawal upon abstinence
  - Craving and obsession

True or False Pre-Test

- All eating disorders are addictions
- Bulimia is the same as Anorexia
- Obesity is an addiction
- All eating disorders respond to therapy
- All eating disorders respond to 12 Steps
- All eating disorders belong in the same room

Prevalence of Eating Disorders

- lifetime prevalence estimates are:
  - 0.6% for anorexia nervosa
  - 1.0% for bulimia nervosa
  - 2.8% for binge-eating disorder
  - Risk is up to 3 times higher in women vs men
  - Median age of onset is 18 to 21 years.

- *Am Fam Physician*. 2008;77:187-195, 196-197.

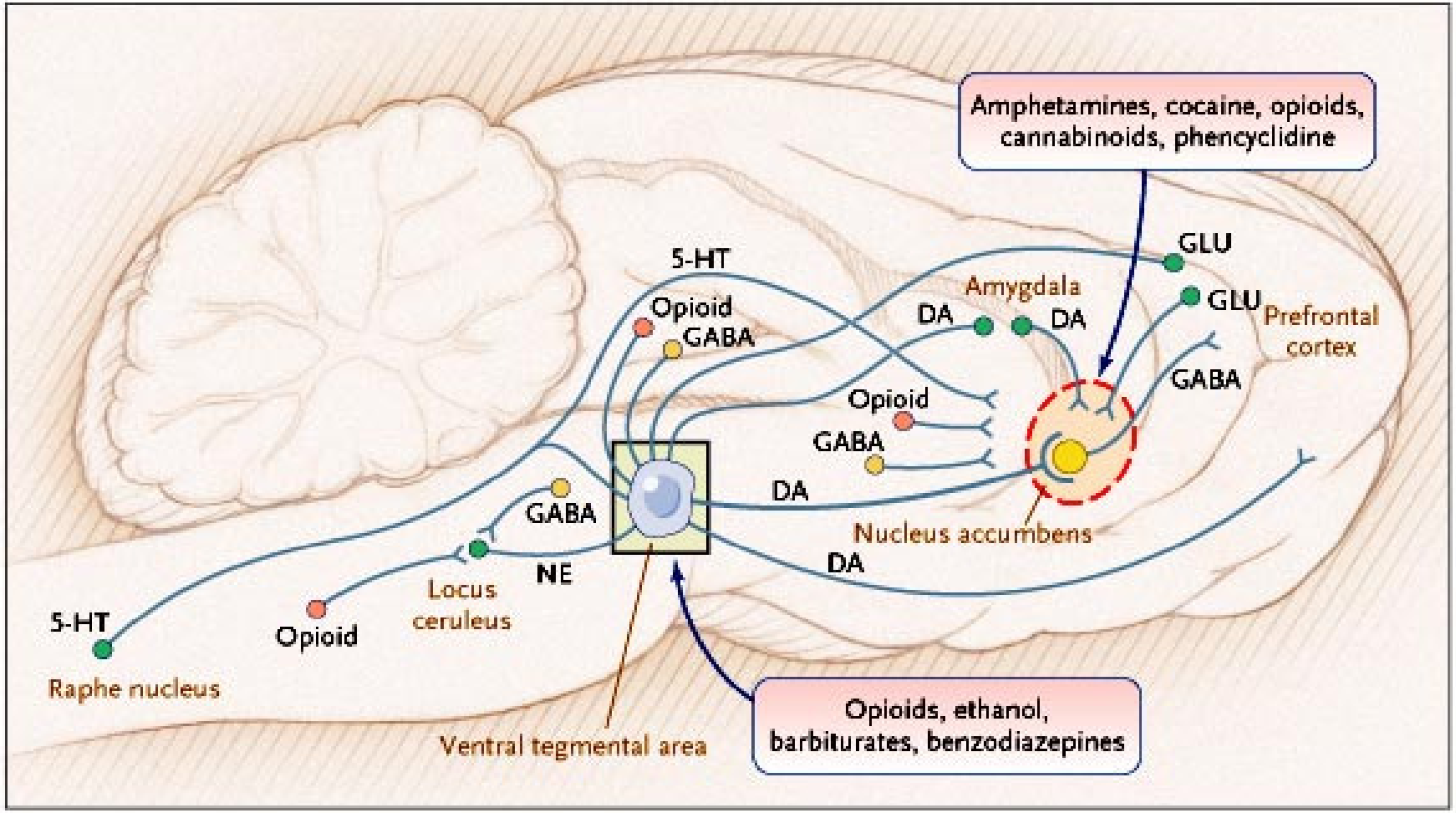
Anorexia & Bulimia:
Similarities & Differences to Alcoholism

- Similarities:
  - Inherited
  - High mortality
- Differences:
  - Prodromal psychiatric components
  - Begin in adolescence, trigger at puberty, favor females
  - Not related to chemical (food) exposure
  - Avoidance rather than consumption
  - Residual psychiatric components

Anorexia & Bulimia:
Similarities & Differences to Each Other

- Similarities
  - Inheritable patterns
  - Both have food component
  - Shared other behavioral/psychiatric components
  - Serotonin system
- Differences
  - Abstinence patterns
  - Within Serotonin system

Neural Reward Circuits Important in the Reinforcing Effects of Drugs of Abuse



Camí, J. et al. N Engl J Med 2003;349:975-986

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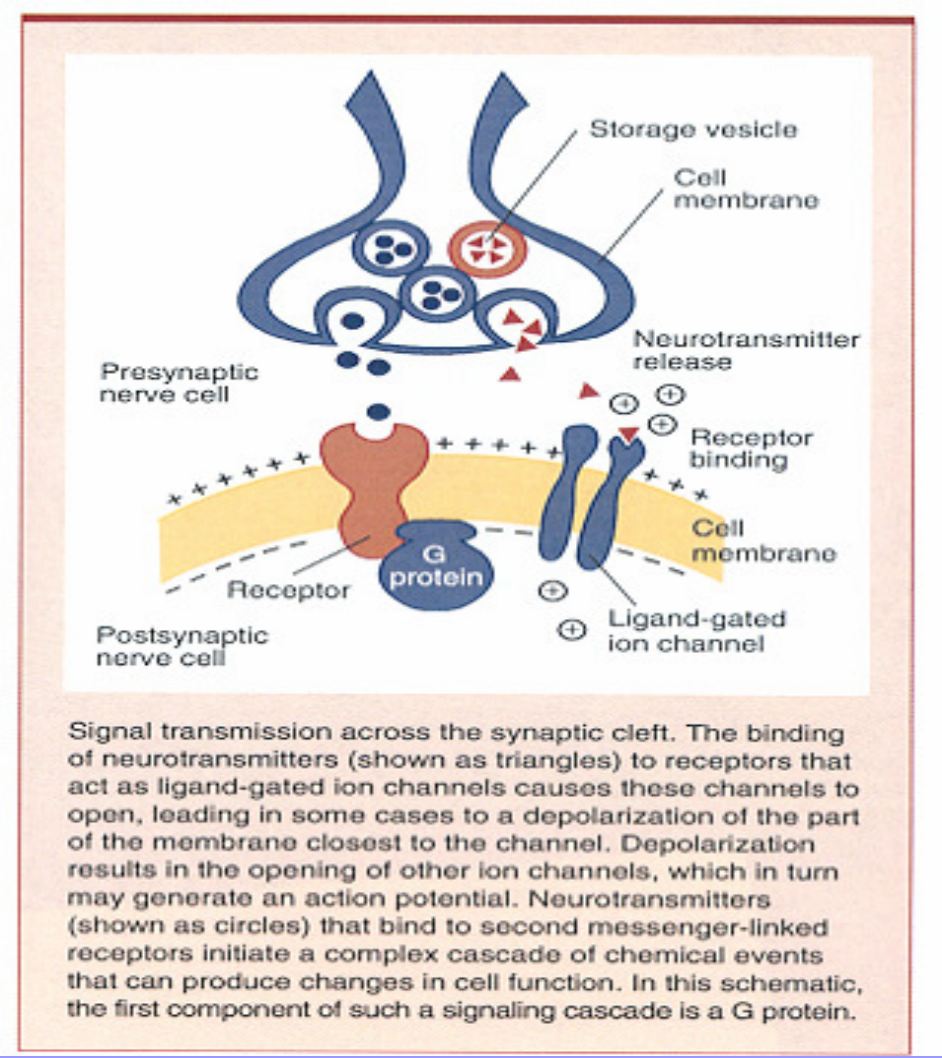
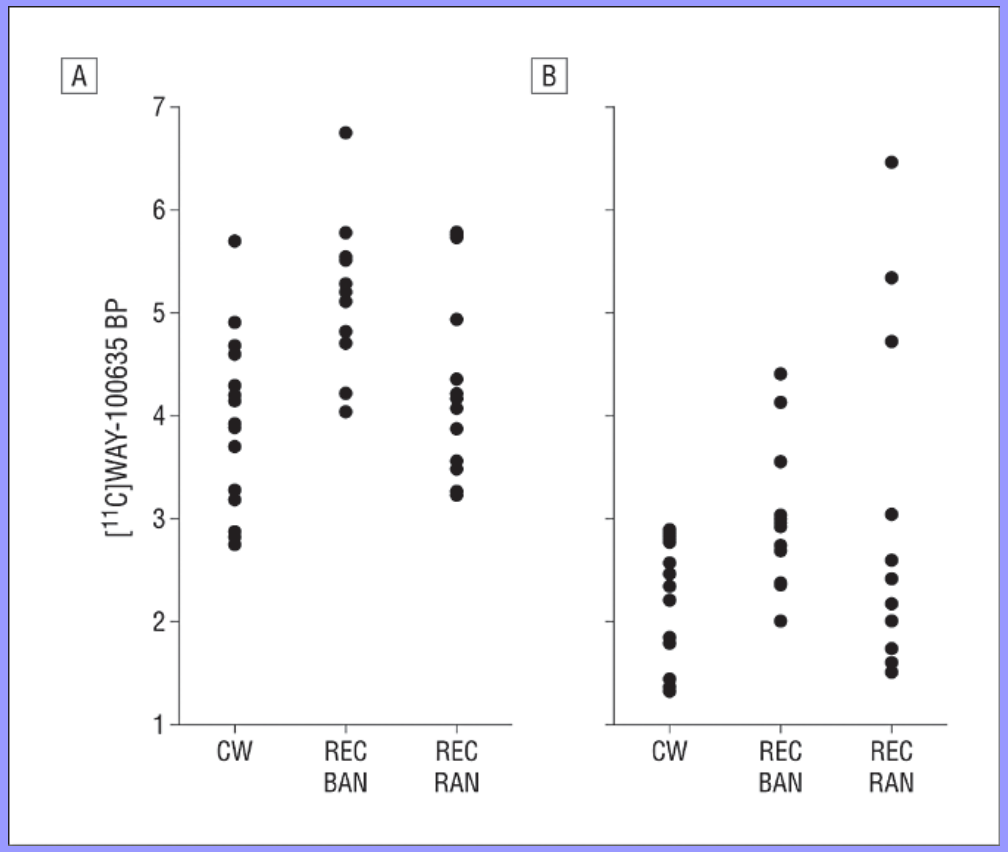
The Architecture: The Synapse



Signal transmission across the synaptic cleft. The binding of neurotransmitters (shown as triangles) to receptors that act as ligand-gated ion channels causes these channels to open, leading in some cases to a depolarization of the part of the membrane closest to the channel. Depolarization results in the opening of other ion channels, which in turn may generate an action potential. Neurotransmitters (shown as circles) that bind to second messenger-linked receptors initiate a complex cascade of chemical events that can produce changes in cell function. In this schematic, the first component of such a signaling cascade is a G protein.

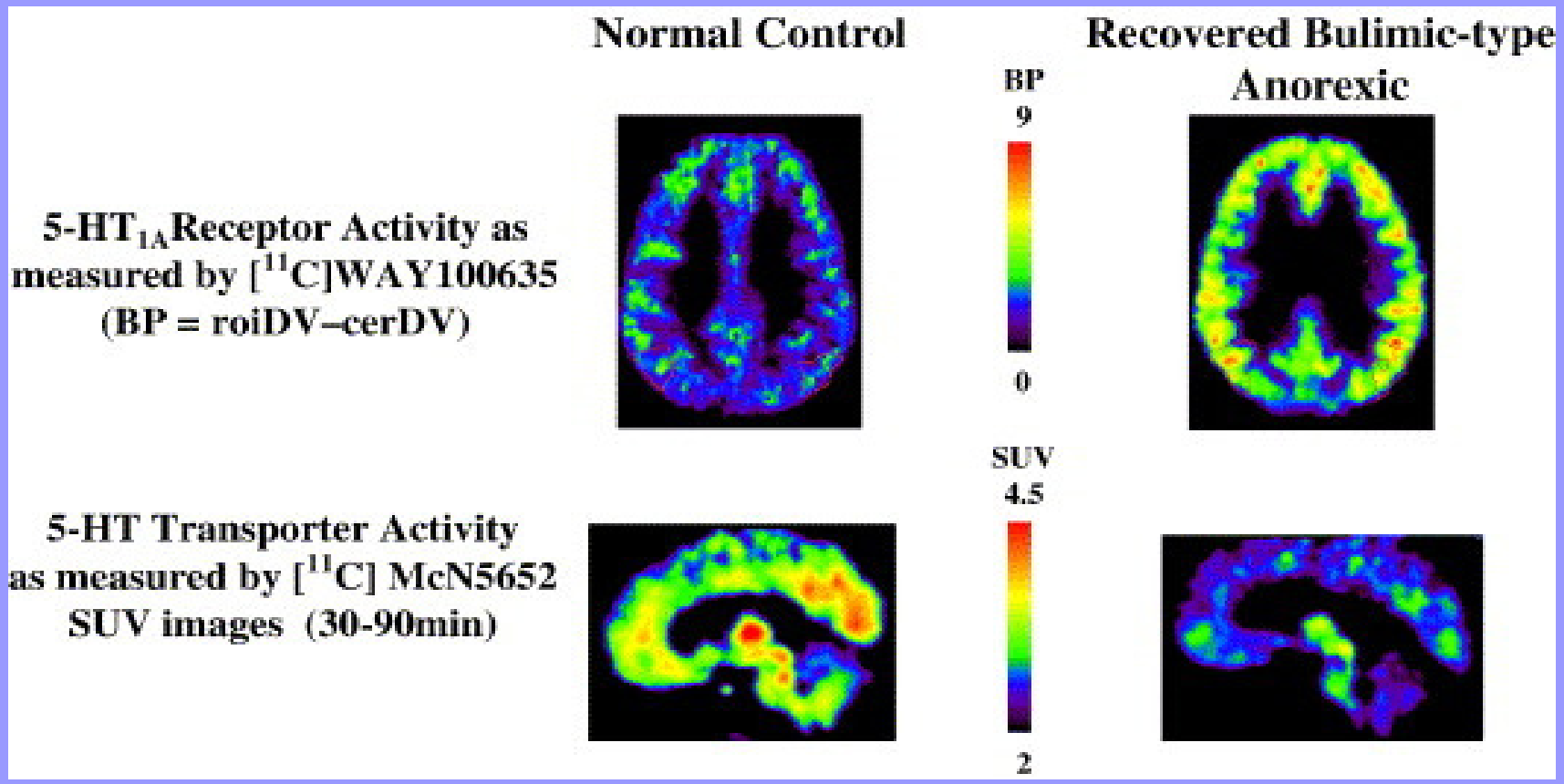
- *from Mihic & Harris, 1997*

Differences between Anorexia and Bulimia in 5HT1A receptor binding



- A: Frontal Cortex B: Dorsal Raphe
- Bailer et al., 2005 Arch. Gen. Psychiatry, 62: 1032-1041

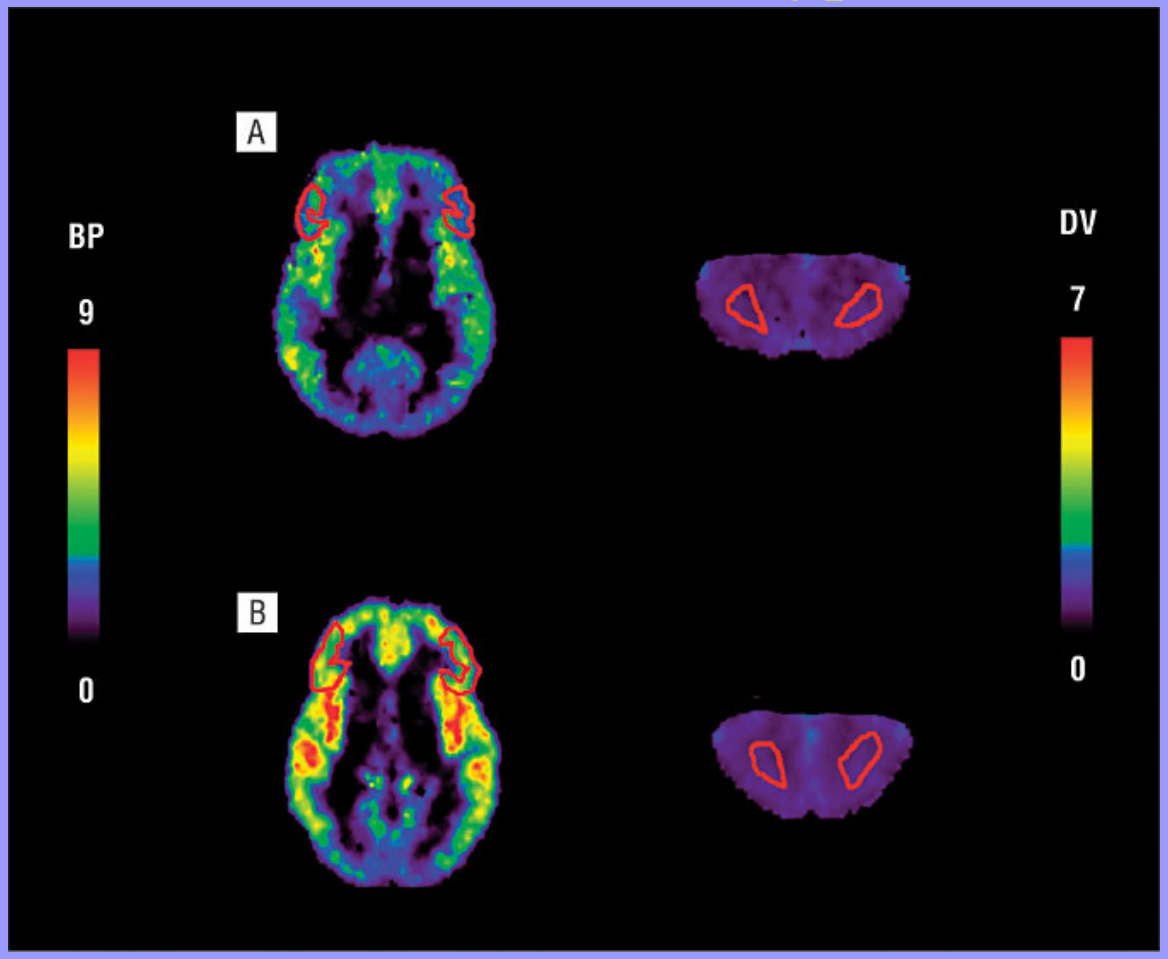
Normal *vs* Recovered Bulimia-type Anorexia Nervosa



Representational comparison of PET 5-HT radioligand findings in a woman recovered from BAN and a CW.

Kaye et al.,2005 Physiology & Behavior, 85: 73-81

Binding to 5HT1A receptors
Normal *vs* Recovered Bulimia-type Anorexia Nervosa



- A: Normal Control Female B: Recovered Bulimia-type Anorexia Nervosa
- Bailer et al., 2005 Arch. Gen. Psychiatry, 62: 1032-1041

Prodromal Components

Anorexia

- Anxious, obsessional, and perfectionistic in childhood
- Inexplicable fear of weight gain
- Unrelenting obsession with fatness
- Paradoxical harm avoidance
- High anxiety

Bulimia

- Anxious, obsessional, and perfectionistic in childhood
- Usually emerges after a period of dieting, which may not have been associated with weight loss
- Impulsivity and behavioral dyscontrol

Shared Residual Components

- Perfectionism
- Inflexible thinking
- Restraint in emotional expression
- Social introversion
- Body image disturbances
- Obsessions related to symmetry, exactness and order

Take home points

- Anorexia
  - Serotonin storm
  - Don't give SSRIs
- Bulimia
  - Underpowered serotonin system
  - May respond to SSRIs

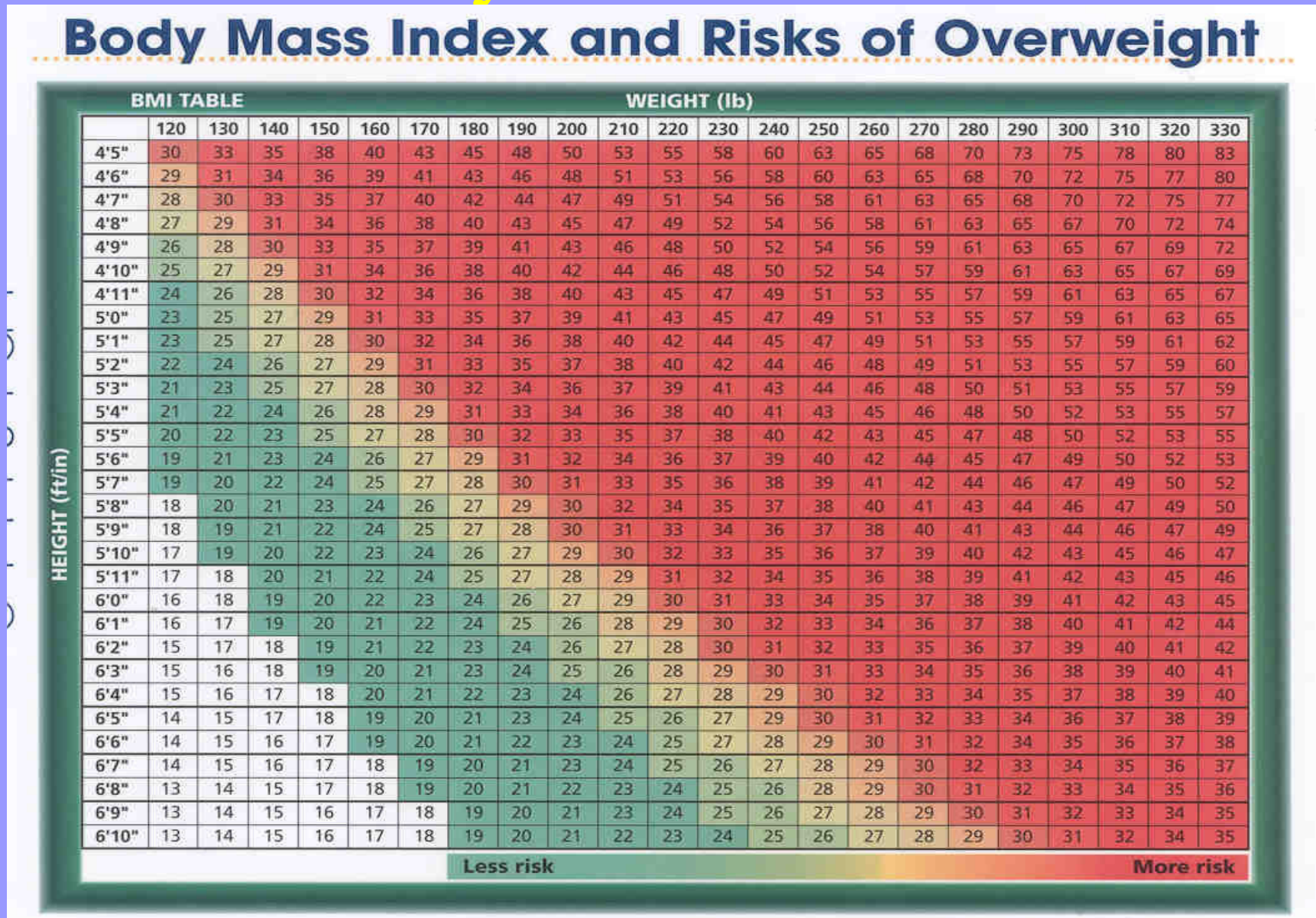
The “Larger” Problem

- Prevalence of adult obesity (BMI >30) has increased from 23% to 31%
- Prevalence of adult overweight (BMI >25) is 66%
- 33% of children today are overweight
- BMI predicts higher mortality

Breaking news, July 2008

- *The American Academy of Pediatrics announces……..*
  - More children will now die of complications of obesity than will die of starvation
  - Never before, in the history of Western Man, has this problem existed

Body Mass Index



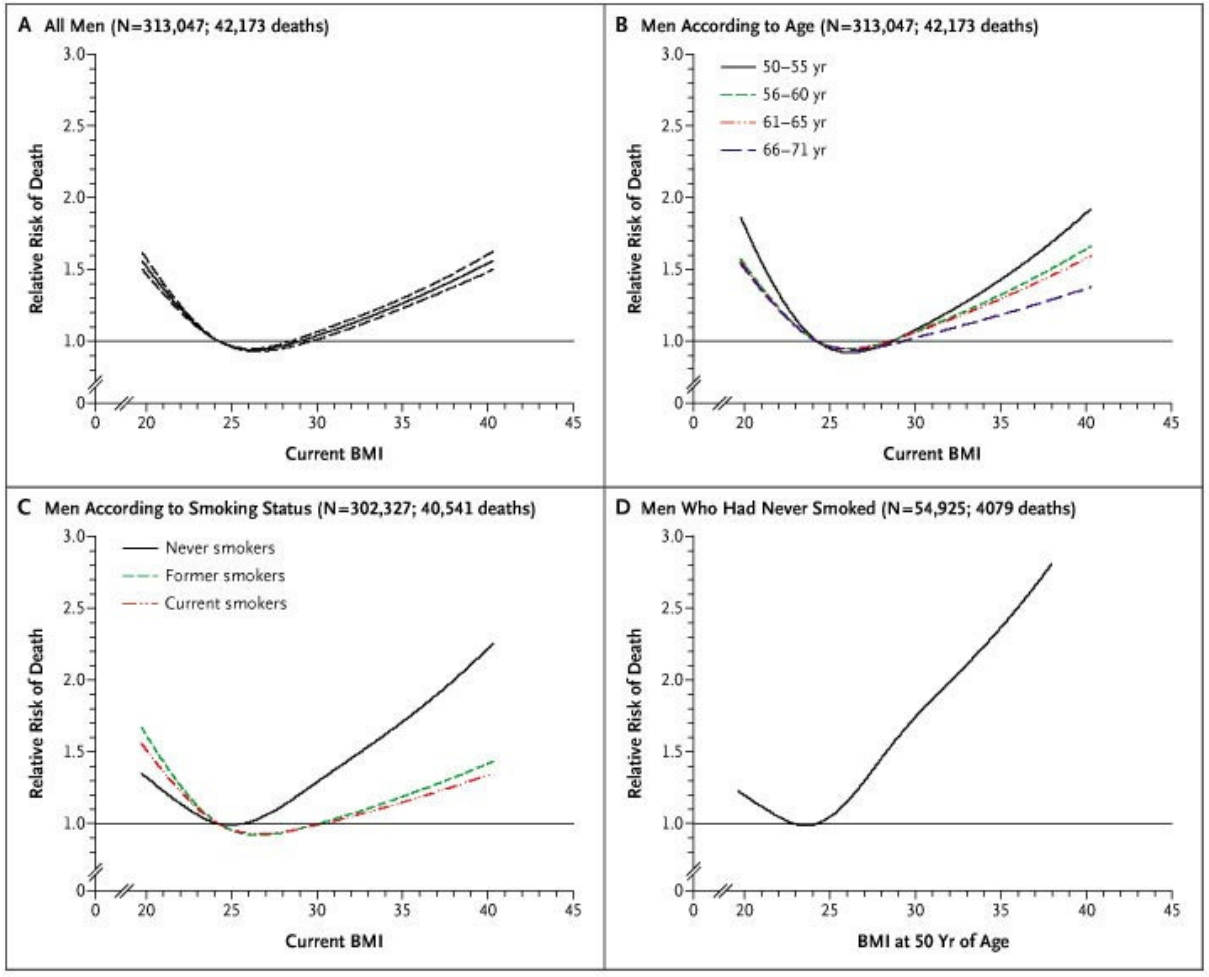
Body Mass Index and Risks of Overweight

BMI TABLE

HEIGHT (ft/in) \ WEIGHT (lb)	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300	310	320	330
4'5"	30	33	35	38	40	43	45	48	50	53	55	58	60	63	65	68	70	73	75	78	80	83
4'6"	29	31	34	36	39	41	43	46	48	51	53	56	58	60	63	65	68	70	72	75	77	80
4'7"	28	30	33	35	37	40	42	44	47	49	51	54	56	58	61	63	65	68	70	72	75	77
4'8"	27	29	31	34	36	38	40	43	45	47	49	52	54	56	58	61	63	65	67	70	72	74
4'9"	26	28	30	33	35	37	39	41	43	46	48	50	52	54	56	59	61	63	65	67	69	72
4'10"	25	27	29	31	34	36	38	40	42	44	46	48	50	52	54	57	59	61	63	65	67	69
4'11"	24	26	28	30	32	34	36	38	40	43	45	47	49	51	53	55	57	59	61	63	65	67
5'0"	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57	59	61	63	65
5'1"	23	25	27	28	30	32	34	36	38	40	42	44	45	47	49	51	53	55	57	59	61	62
5'2"	22	24	26	27	29	31	33	35	37	38	40	42	44	46	48	49	51	53	55	57	59	60
5'3"	21	23	25	27	28	30	32	34	36	37	39	41	43	44	46	48	50	51	53	55	57	59
5'4"	21	22	24	26	28	29	31	33	34	36	38	40	41	43	45	46	48	50	52	53	55	57
5'5"	20	22	23	25	27	28	30	32	33	35	37	38	40	42	43	45	47	48	50	52	53	55
5'6"	19	21	23	24	26	27	29	31	32	34	36	37	39	40	42	44	45	47	49	50	52	53
5'7"	19	20	22	24	25	27	28	30	31	33	35	36	38	39	41	42	44	46	47	49	50	52
5'8"	18	20	21	23	24	26	27	29	30	32	34	35	37	38	40	41	43	44	46	47	49	50
5'9"	18	19	21	22	24	25	27	28	30	31	33	34	36	37	38	40	41	43	44	46	47	49
5'10"	17	19	20	22	23	24	26	27	29	30	32	33	35	36	37	39	40	42	43	45	46	47
5'11"	17	18	20	21	22	24	25	27	28	29	31	32	34	35	36	38	39	41	42	43	45	46
6'0"	16	18	19	20	22	23	24	26	27	29	30	31	33	34	35	37	38	39	41	42	43	45
6'1"	16	17	19	20	21	22	24	25	26	28	29	30	32	33	34	36	37	38	40	41	42	44
6'2"	15	17	18	19	21	22	23	24	26	27	28	30	31	32	33	35	36	37	39	40	41	42
6'3"	15	16	18	19	20	21	23	24	25	26	28	29	30	31	33	34	35	36	38	39	40	41
6'4"	15	16	17	18	20	21	22	23	24	26	27	28	29	30	32	33	34	35	37	38	39	40
6'5"	14	15	17	18	19	20	21	23	24	25	26	27	29	30	31	32	33	34	36	37	38	39
6'6"	14	15	16	17	19	20	21	22	23	24	25	27	28	29	30	31	32	34	35	36	37	38
6'7"	14	15	16	17	18	19	20	21	23	24	25	26	27	28	29	30	32	33	34	35	36	37
6'8"	13	14	15	17	18	19	20	21	22	23	24	25	26	28	29	30	31	32	33	34	35	36
6'9"	13	14	15	16	17	18	19	20	21	23	24	25	26	27	28	29	30	31	32	33	34	35
6'10"	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	34	35

Less risk — More risk

Multivariate Relative Risks of Death in Relation to BMI among Men



Adams K et al. N Engl J Med 2006;355:763-778

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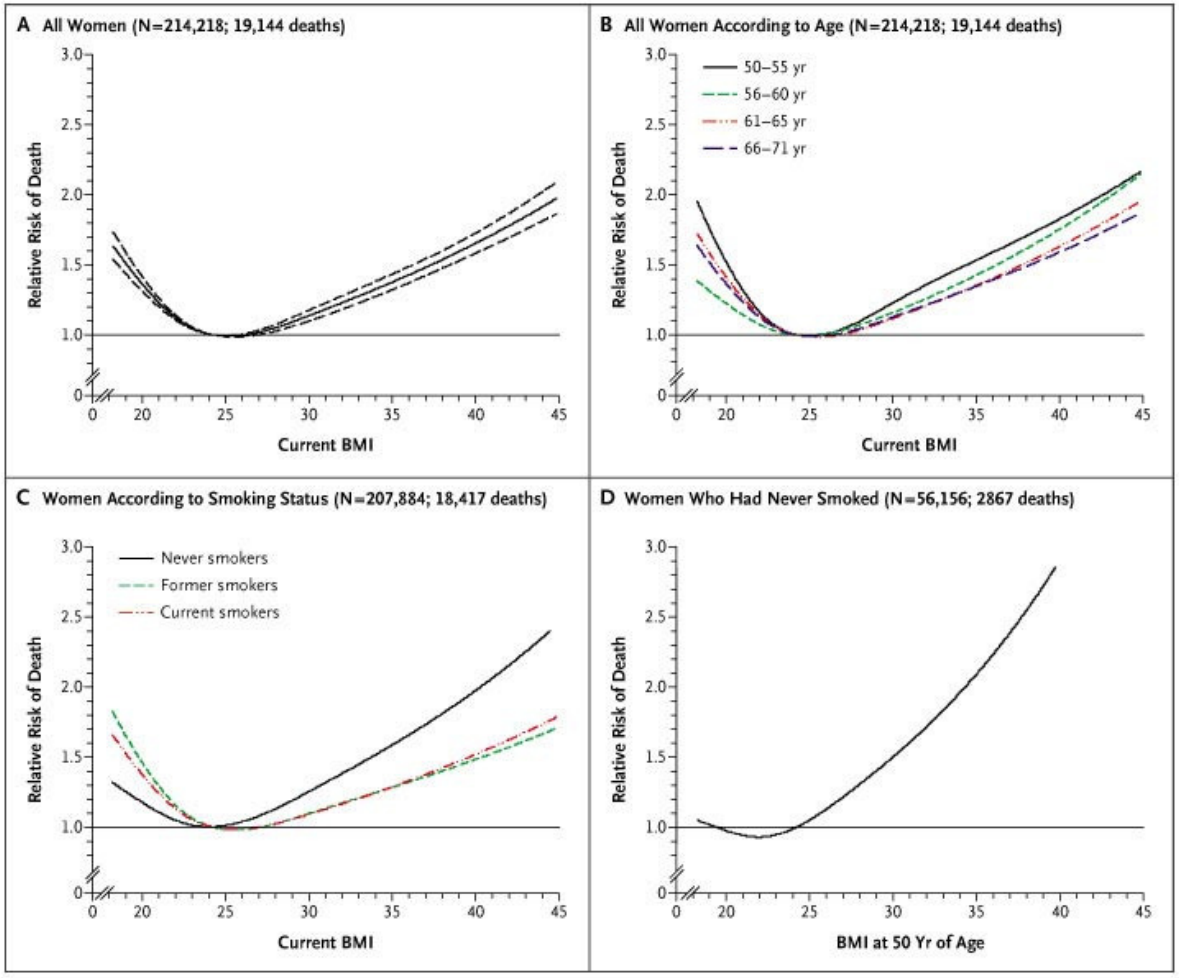
Multivariate Relative Risks of Death in Relation to BMI among Women



Adams K et al. N Engl J Med 2006;355:763-778

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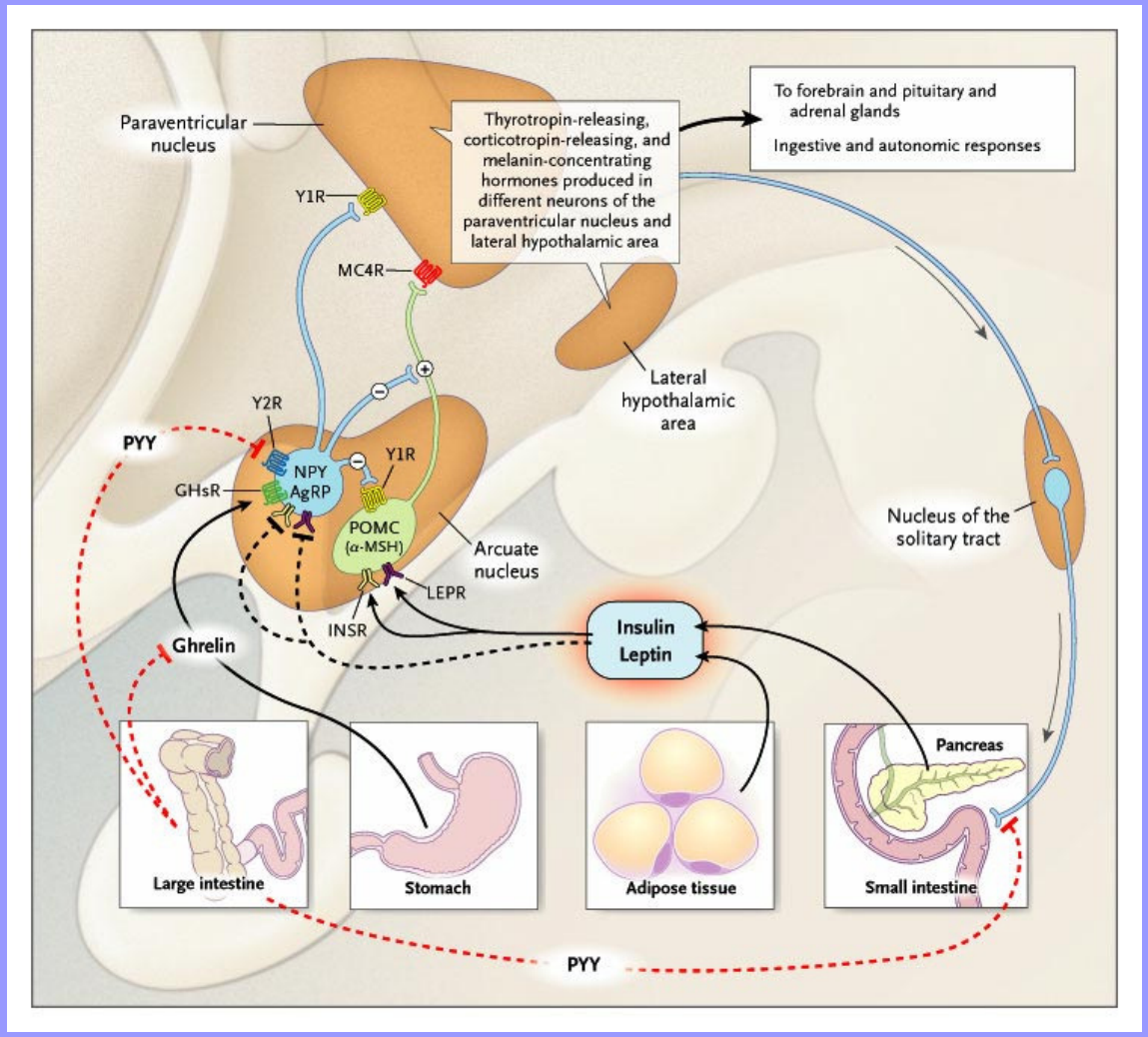
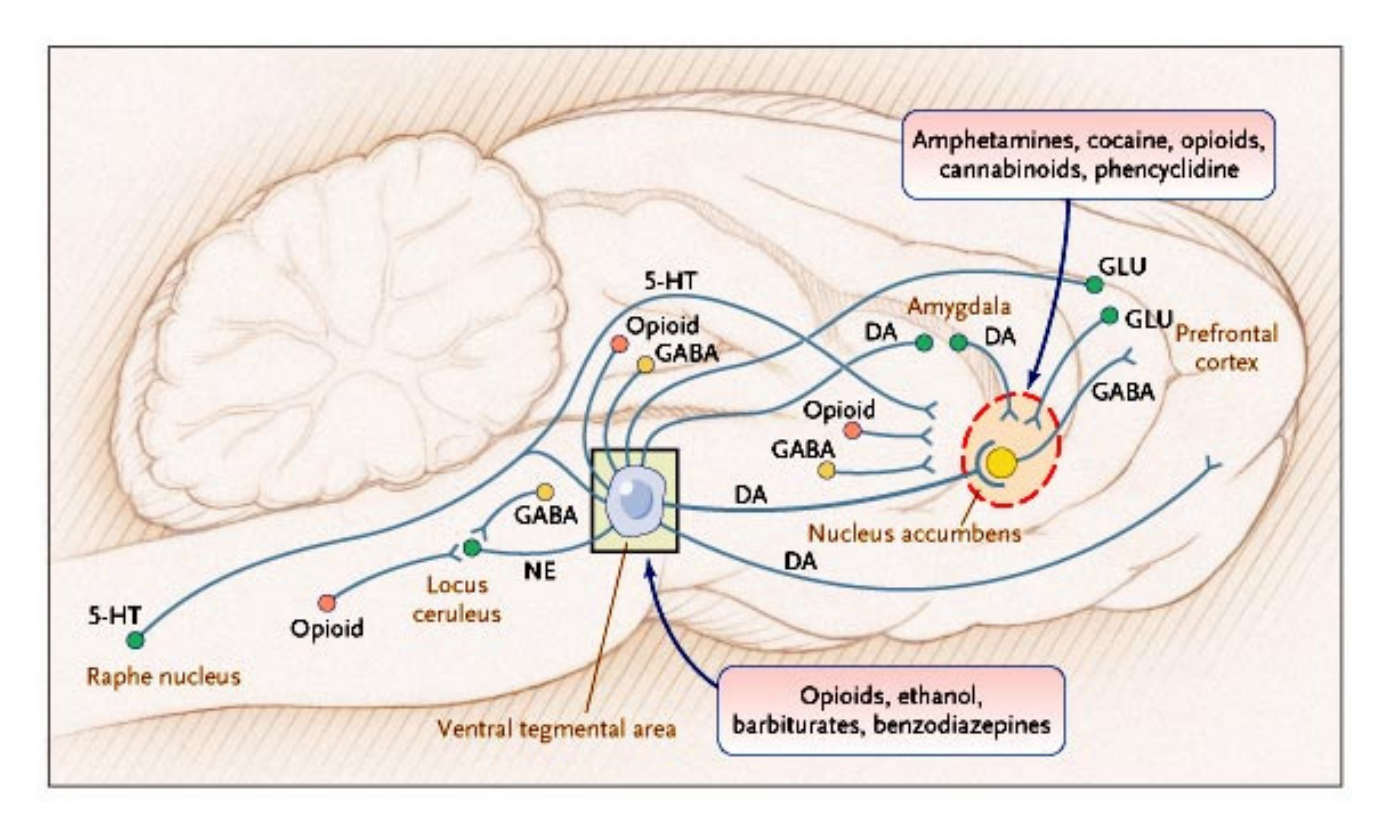
Interactions among Hormonal and Neural Pathways That Regulate Food Intake and Body-Fat Mass



Korner J and Leibel R. N Engl J Med 2003;349:926-928

Interactions among Hormonal and Neural Pathways That Regulate Food Intake and Body-Fat Mass. In this schematic diagram of the brain, the dashed lines indicate hormonal inhibitory effects, and the solid lines stimulatory effects. The paraventricular and arcuate nuclei each contain neurons that are capable of stimulating or inhibiting food intake. Y1R and Y2R denote the Y1 and Y2 subtypes of the neuropeptide Y (NPY) receptor, MC4R melanocortin 4 receptor, PYY peptide YY3-36, GHsR growth hormone secretagogue receptor, AgRP agouti-related protein, POMC proopiomelanocortin, {alpha}-MSH {alpha}-melanocyte-stimulating protein, LEPR leptin receptor, and INSR insulin receptor.

Neural Reward Circuits Important in the Reinforcing Effects of Drugs of Abuse



Camí, J. et al. N Engl J Med 2003;349:975-986

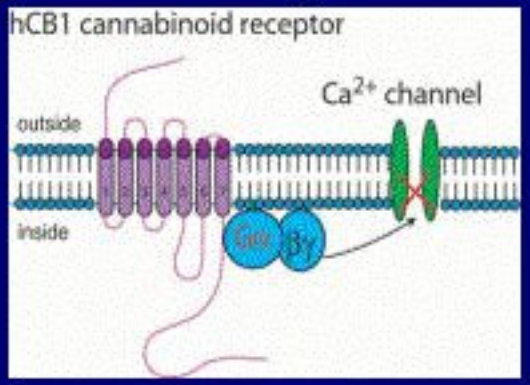
History of the Endocannabinoid System

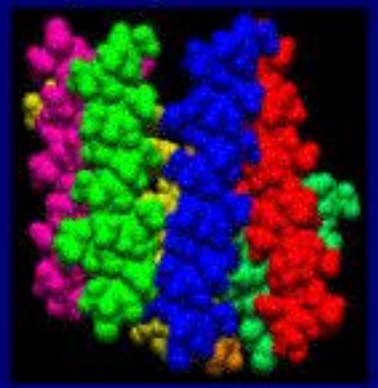
1964 – Isolation of Δ9-THC, the active constituent of *Cannabis sativa*

1988 – High-affinity cannabinoid binding sites were discovered in rat brain[2]

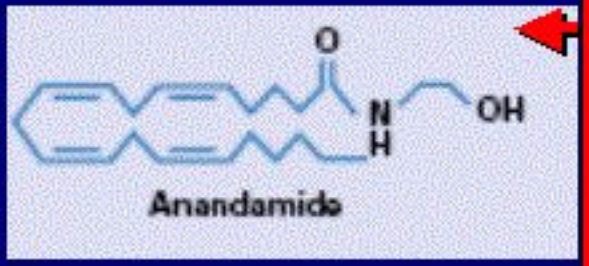
1990 – Cloning of the rat G-protein coupled cannabinoid receptor type 1 (CB_1) receptor[3]

1991 – Cloning of the human CB_1 receptor[4]





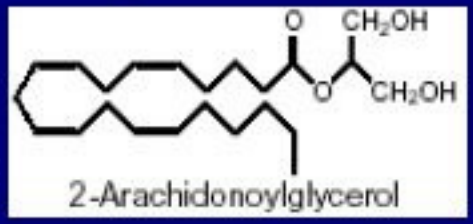
1992 – Discovery of anandamide, the first endogenous cannabinoid[5]



1993 – Cloning of the peripheral CB_2 receptor[6]

1994 – Characterisation of the first CB_1 receptor blocker[7]

1995 – Isolation of a second endocannabinoid, 2-AG (from gut and brain)[8]



2000s –
- Identification of new endocannabinoids
- Wide tissue distribution of CB_1 receptors
- Role of the endocannabinoid system in obesity

1. Gaoni Y et al. *J Am Chem Soc*. 1964;86:1646-1647.
2. Devane WA et al. *Mol Pharmacol*. 1988;34:605-613.
3. Matsuda LA et al. *Nature*. 1990;346:561-564.
4. Gerard CM et al. *Biochem J*. 1991;279:129-134.
5. Devane WA et al. *Science*. 1992;258:1946-1949.
6. Munro S et al. *Nature*. 1993;365:61-65.
7. Rinaldi-Carmona M et al. *FEBS Lett*. 1994;350:240-244.
8. Sugiura T et al. *Biochem Biophys Res Commun*. 1995;215:89-97.
9. Di Marzo V et al. *Nat Rev Drug Discov*. 2004;3:771-784.

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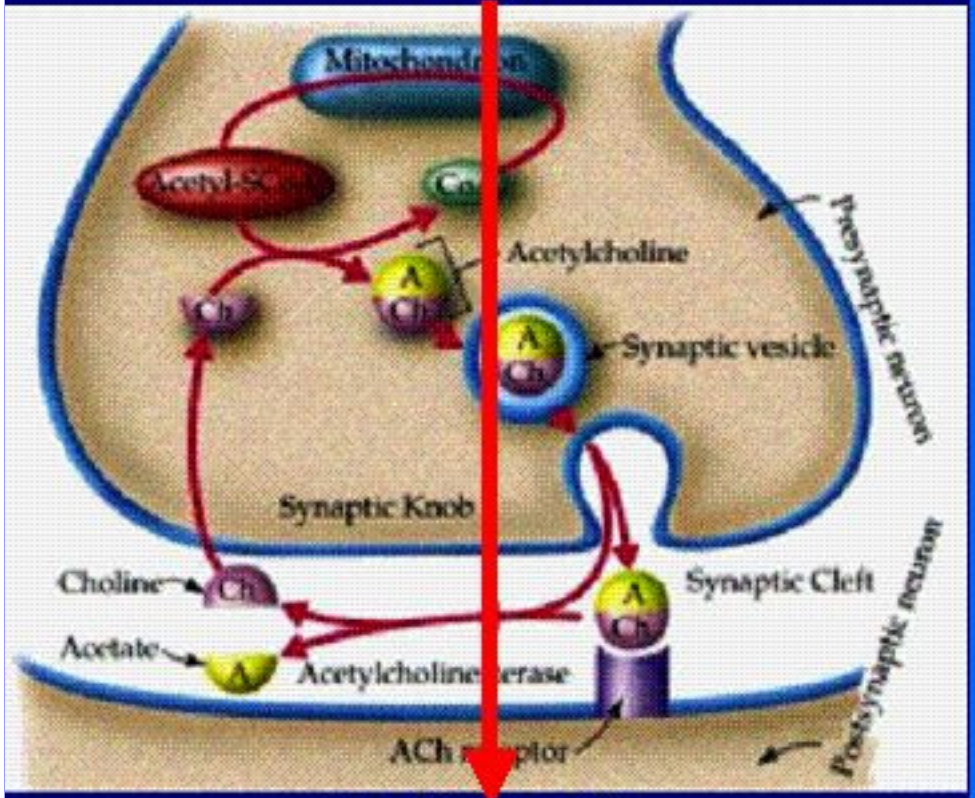
Contrast Between Classic Neurotransmission and the Endocannabinoid System

Classic Neurotransmitter: Acetylcholine (ACh)

Presynaptic



Postsynaptic

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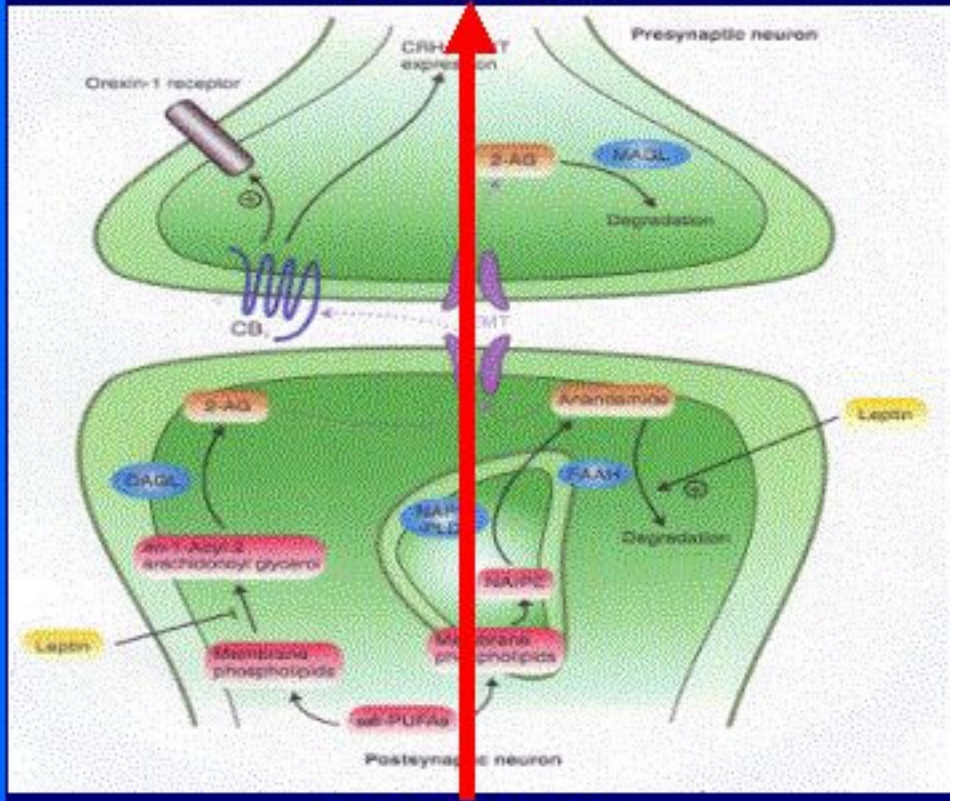
EC System

Presynaptic



Postsynaptic

Di Marzo V et al. *Nat Neurosci*. 2005;8:585-589.

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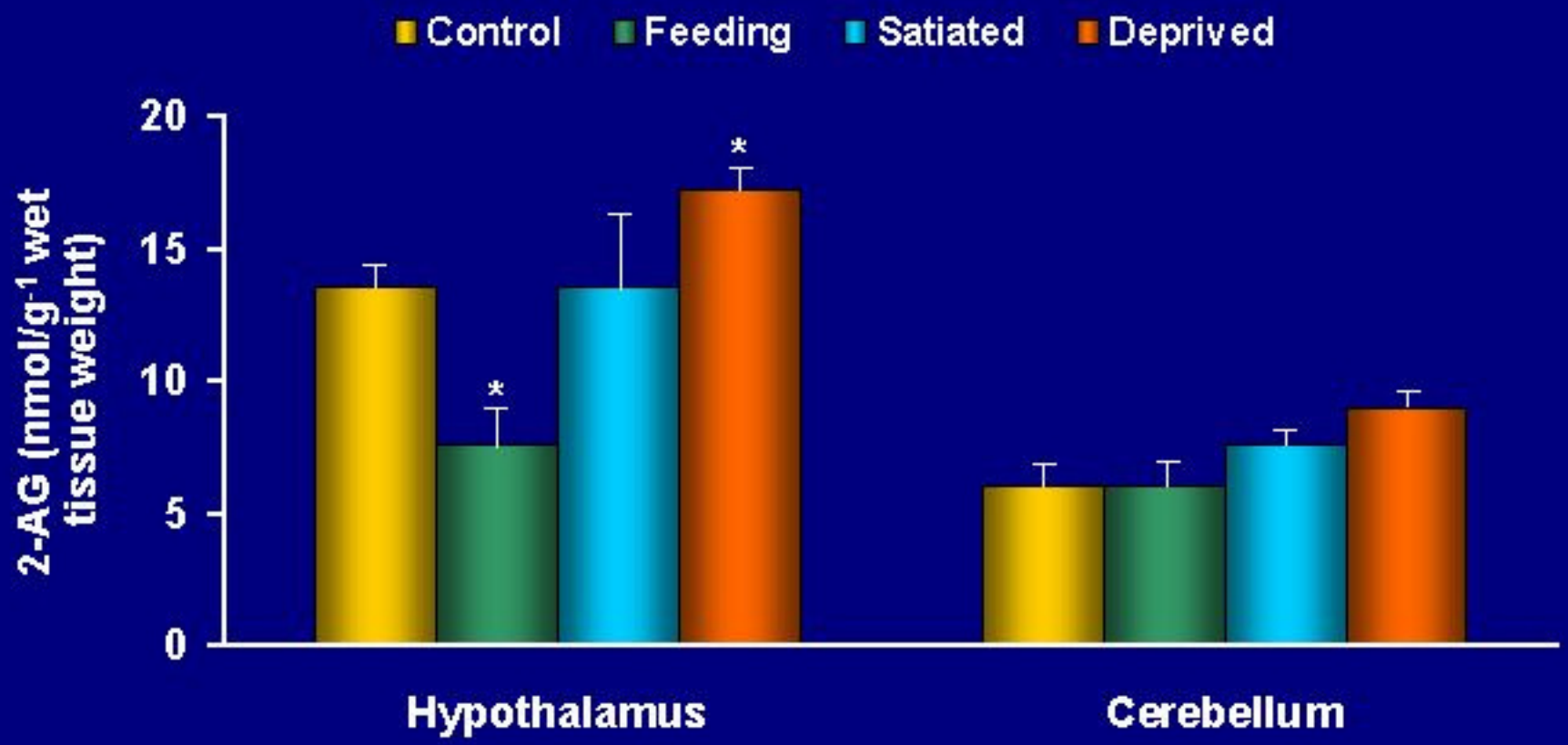
Physiologic Effects of the Endocannabinoid System

- Affect a number of physiologic processes[1-4]
  - Increased feeding behavior
  - Antinociception
  - Motor control
  - Memory and learning
  - Immune and inflammatory responses
  - Neuroprotection
- Summary of effects: "Relax, eat, sleep, forget, and protect"[3]

1. Di Marzo V et al. *Nat Neurosci.* 2005;8:585-589. 2. Di Marzo V et al. *Nat Rev Drug Discov.* 2004;3:771-784. 3. Di Marzo V et al. *Trends Neurosci.* 1998;21:521-528. 4. Di Marzo V et al. *Nat Rev Drug Discov.* 2004;3:771-784.

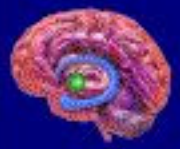
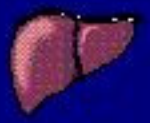
Hypothalamic Endocannabinoid Levels in Relation to Fasting and Eating



*$P<0.05$.
Values are means ± SEM.

Adapted with permission from Kirkham TC et al. *Br J Pharmacol.* 2002;136:550-557.

Endocannabinoid System: Effects of CB_1 Antagonism

	Site of Action	Mechanism(s)	Clinical Implications
	Hypothalamus/ nucleus accumbens	↓ Food intake	↓ Body weight ↓ Waist circumference
	Adipose tissue	↑ Adiponectin ↓ Lipogenesis	↓ Visceral fat ↓ Dyslipidemia ↓ Insulin resistance
	Muscle	↑ Glucose uptake ↑ O_2 consumption	↓ Insulin resistance
	Liver	↓ Lipogenesis	↓ Dyslipidemia ↓ Insulin resistance
	GI tract	↑ Satiety signals	↓ Body weight
	Pancreas	Potential effect on insulin secretion	Potential effect on glucose/insulin metabolism

Adapted with permission from Woods SC. *Am J Med.* 2007;120:S19-S25. Juan-Pico P et al. *Cell Calcium.* 2006;39:155-162.

The Endocannabinoid System and Obesity

- EC system activation is associated with both central mechanisms (increased appetite) and peripheral effects (stimulation of lipogenesis and fat accumulation)
- Overactive EC system in tissues controlling energy balance may contribute to development of obesity and associated cardiovascular and metabolic risk factors
  - May be caused by high-fat diet
  - May be sustained by leptin resistance associated with obesity
- Peripheral EC system overactivity may explain why CB_1 blockade may affect peripheral tissues, such as adipose tissue

Di Marzo V et al. *Nat Neurosci.* 2005;8:585-589.

Summary of Basic Endocannabinoid Biology

- The EC system is overactivated in human obesity and in animal models of genetic and diet-induced obesity
- EC system stimulation centrally and peripherally favors metabolic processes that lead to:
  - Weight gain, lipogenesis, insulin resistance, dyslipidemia, and impaired glucose homeostasis
  - CB_1 blockade reverses or ameliorates these effects in preclinical models
- Central and peripheral EC system dysfunction provides a biological basis for therapeutic CB_1 receptor blockade

So, some people are *genetically* as well as behaviorally predisposed for *accelerated* weight gain when exposed to high fat diet

Is there a "magic bullet"?

Drugs Prescribed for Weight Loss

Table 1. Drugs Prescribed for Weight Loss.*

Drug	FDA-Approved for Weight Loss	Schedule IV Controlled Substance	Mechanism	Dose	Approximate Weight Loss beyond That with Placebo	Side Effects	Comments
					%		
Diethylpropion (Tenuate, Sanofi-Aventis)	Yes	Yes	Sympathomimetic mechanism	25 mg 3 times a day or 75 mg controlled-release daily	3	Dry mouth, insomnia, dizziness, mild increase in blood pressure and heart rate	Has minimal effect, excreted by kidneys, pregnancy category B, requires monitoring of blood pressure
Orlistat (Xenical, Roche; Alli, GlaxoSmithKline)	Yes	No	Lipase inhibition in gastrointestinal tract	120 mg 3 times a day (Xenical) or 60 mg 3 times a day, available over the counter (Alli)	3	Oily spotting, flatus with discharge, fecal urgency	Side effects decrease with time; may work better when fat remains in diet, but this results in increased side effects; decreases LDL cholesterol, pregnancy category B
Phentermine (e.g., Adipex-P, Gate; Fastin, Hi-Tech; Ionamin, Celltech)	Yes	Yes	Sympathomimetic mechanism	15, 30, or 37.5 mg daily	4	Dry mouth, insomnia, dizziness, mild increase in blood pressure (rarely more severe) and heart rate	Insufficient data from RCTs, increased risk of pulmonary hypertension probably not a concern, pregnancy category C, available as generic, requires monitoring of blood pressure
Sibutramine (Meridia, Abbott)	Yes	No	Inhibition of norepinephrine and serotonin reuptake	5, 10, or 15 mg daily	5	Mild increase in blood pressure and heart rate (rarely more severe), palpitations	Pregnancy category C, requires monitoring of blood pressure
Rimonabant (Acomplia, Sanofi-Aventis)	No	NA	Inhibition of cannabinoid receptor CB1	5 or 20 mg daily	5	Nausea, diarrhea, anxiety, depression	Prototype in a new class of prescription drugs

* LDL cholesterol denotes low-density lipoprotein cholesterol, NA not applicable, and RCTs randomized controlled trials.

Eckel R. N Engl J Med 2008;358:1941-1950

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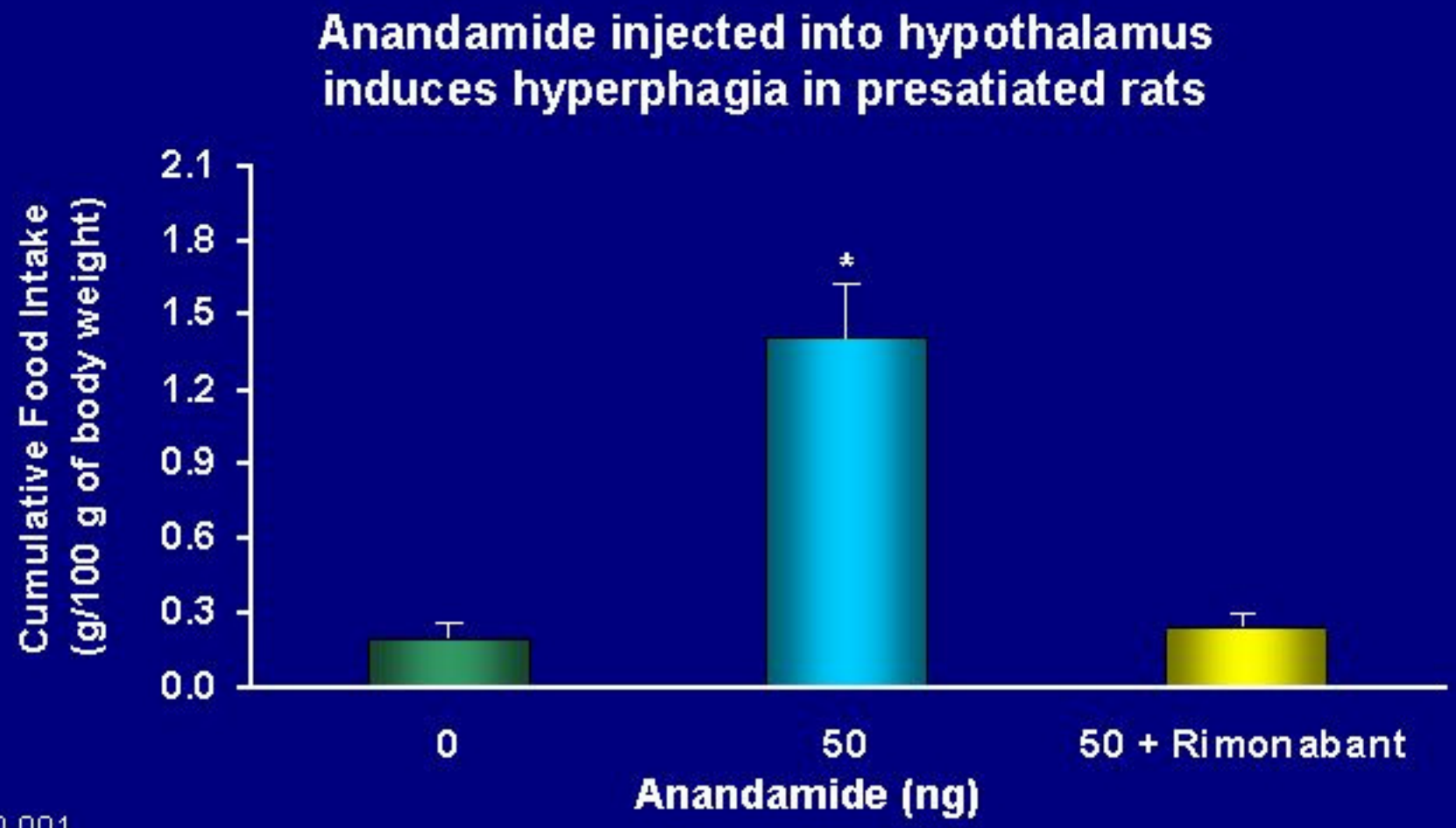
Hypothalamic CB_1 Receptor Activation by Endocannabinoids Stimulates Food Intake

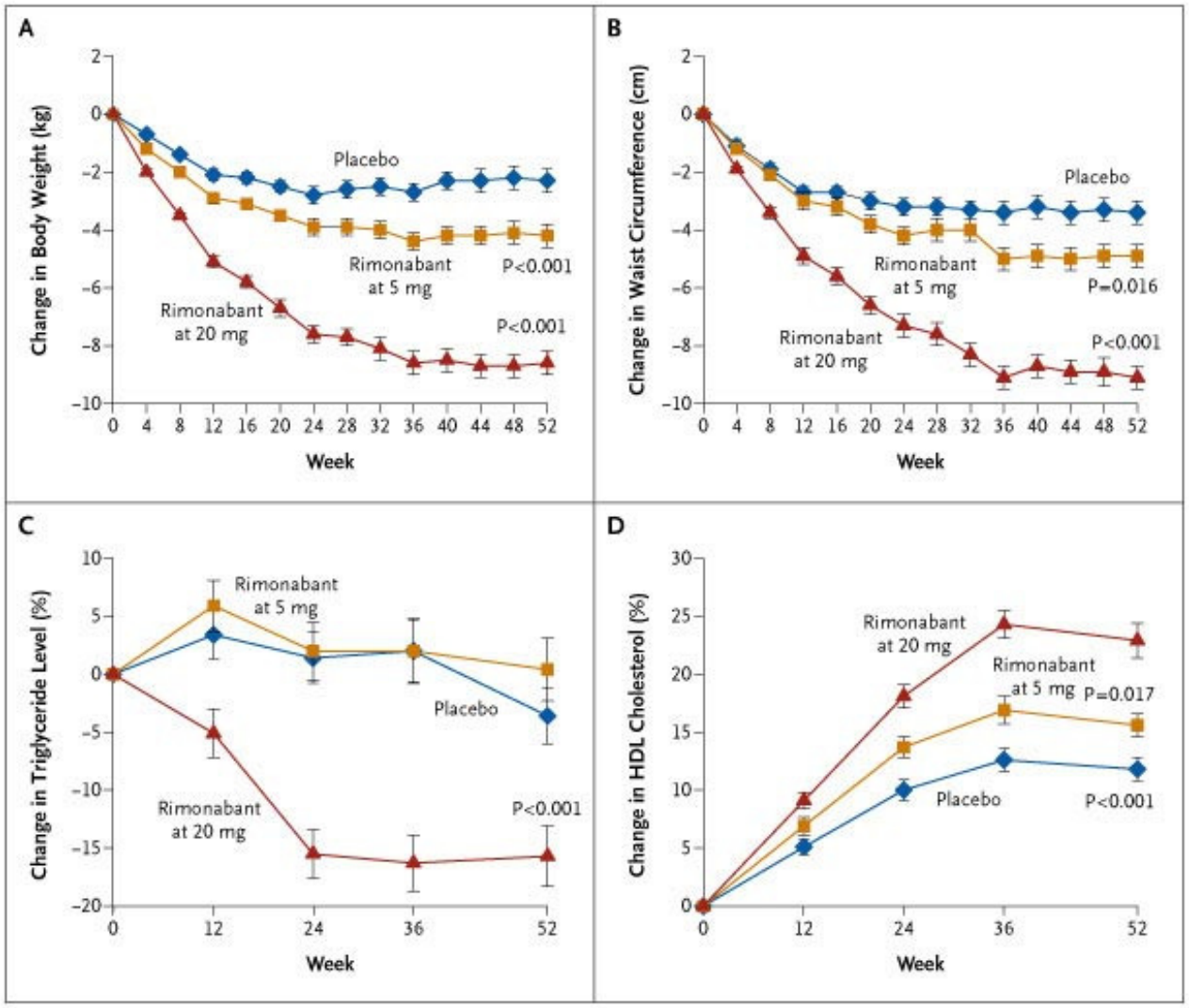


*P<0.001.

Values are means ± SEM.

Adapted with permission from Jamshidi N et al. *Br J Pharmacol.* 2001;134:1151-1154.

Effect of Placebo or Rimonabant for 52 Weeks on Body Weight, Waist Circumference, Plasma Triglyceride Levels, and High-Density Lipoprotein (HDL) Cholesterol Levels



Despres J et al. N Engl J Med 2005;353:2121-2134

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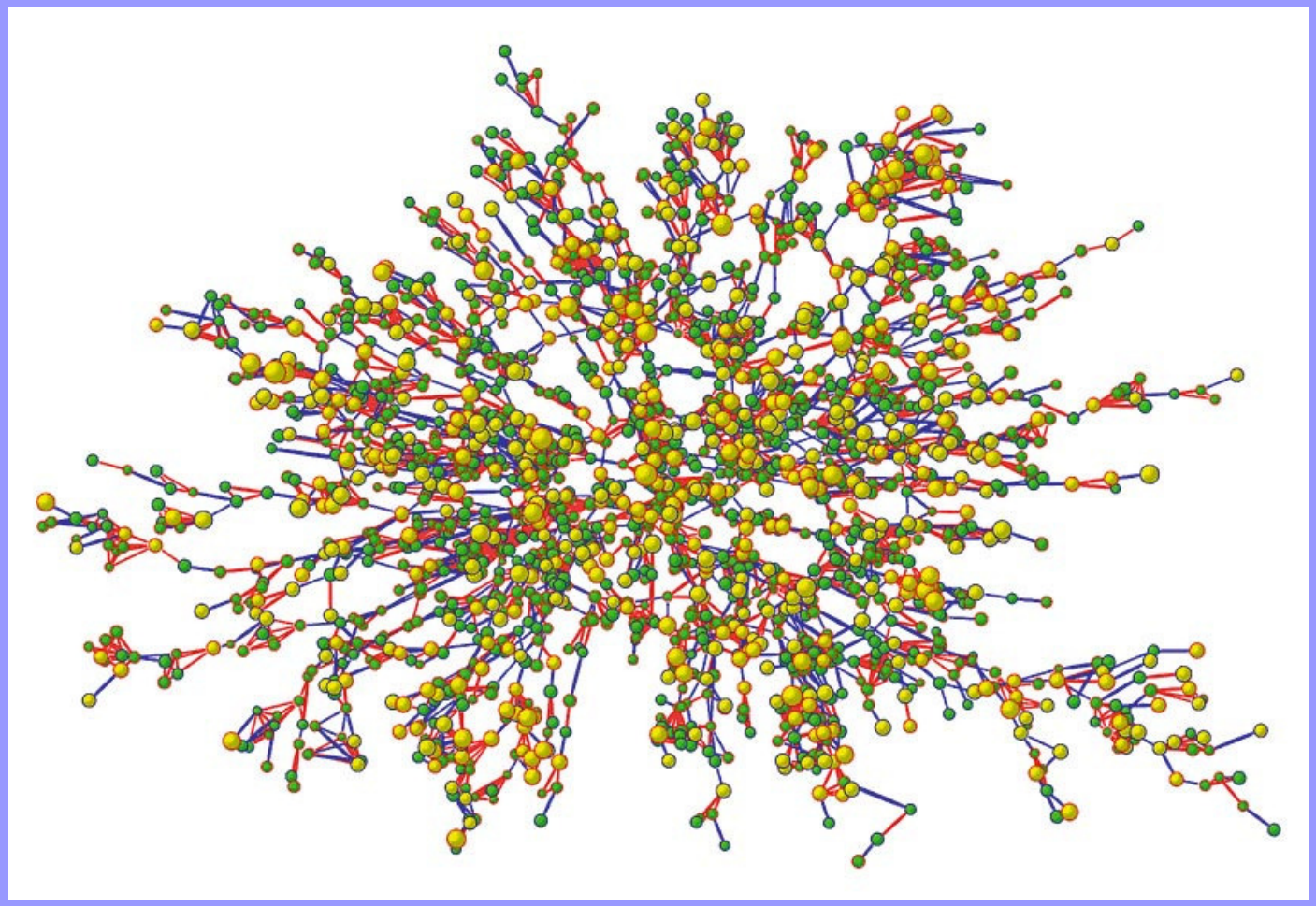
Now you understand……..

The "munchies"

Is Obesity Contagious?

Ask 38,611 residents of Framingham, Massachusetts, related to 5,124 people who were the focus of study!

Largest Connected Subcomponent of the Social Network in the Framingham Heart Study in the Year 2000



Christakis N and Fowler J. N Engl J Med 2007;357:370-379

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Lessons from Framingham

-A person's chances of becoming obese increased by 57% if he or she had a friend who became obese in a given interval.
- Among pairs of adult siblings, if one sibling became obese, the chance that the other would become obese increased by 40%
-If one spouse became obese, the likelihood that the other spouse would become obese increased by 37%.
-These effects were not seen among neighbors in the immediate geographic location.
-Persons of the same sex had relatively greater influence on each other than those of the opposite sex.
-The spread of smoking cessation did not account for the spread of obesity in the network

Surgical Intervention

- Gastric bypass surgery (GBP) results in important and sustained weight loss and remarkable improvement of Type 2 diabetes. The favorable change in the incretin gut hormones is thought to be responsible, in part, for diabetes remission after GBP, independent of weight loss. However, the relative role of the change in incretins and of weight loss is difficult to differentiate. After GBP, the plasma concentrations of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide increase postprandially by three- to fivefold.

  - **Diabetes remission after bariatric surgery: is it just the incretins?**
  - **Int J Obes (Lond). 2011; 35 Suppl 3:S22-5**

Weight-Loss Treatment Guidelines from the National Heart, Lung, and Blood Institute

Table 2. Weight-Loss Treatment Guidelines from the National Heart, Lung, and Blood Institute.*

Treatment	BMI				
	25.0–26.9	27.0–29.9	30.0–34.9	35.0–39.9	>40.0
Diet, physical activity, behavioral therapy, or all three	Yes	Yes	Yes	Yes	Yes
Pharmacotherapy†		In patients with obesity-related disease	Yes	Yes	Yes
Surgery‡				In patients with obesity-related disease	Yes

* Data are from www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm. These guidelines are generally consistent with those from the American Heart Association, the American Medical Association, the American Dietetic Association, the Obesity Society (Practical Guide), the American Diabetes Association, the American Academy of Family Physicians, the American College of Sports Medicine, and the American Cancer Society. BMI denotes body-mass index, calculated as the weight in kilograms divided by the square of the height in meters.

† Pharmacotherapy should be considered only in patients who are not able to achieve adequate weight loss with available conventional lifestyle modifications and who have no absolute contraindications for drug therapy.

‡ Bariatric surgery should be considered only in patients who are unable to lose weight with available conventional therapy and who have no absolute contraindications for surgery.

Eckel R. N Engl J Med 2008;358:1941-1950

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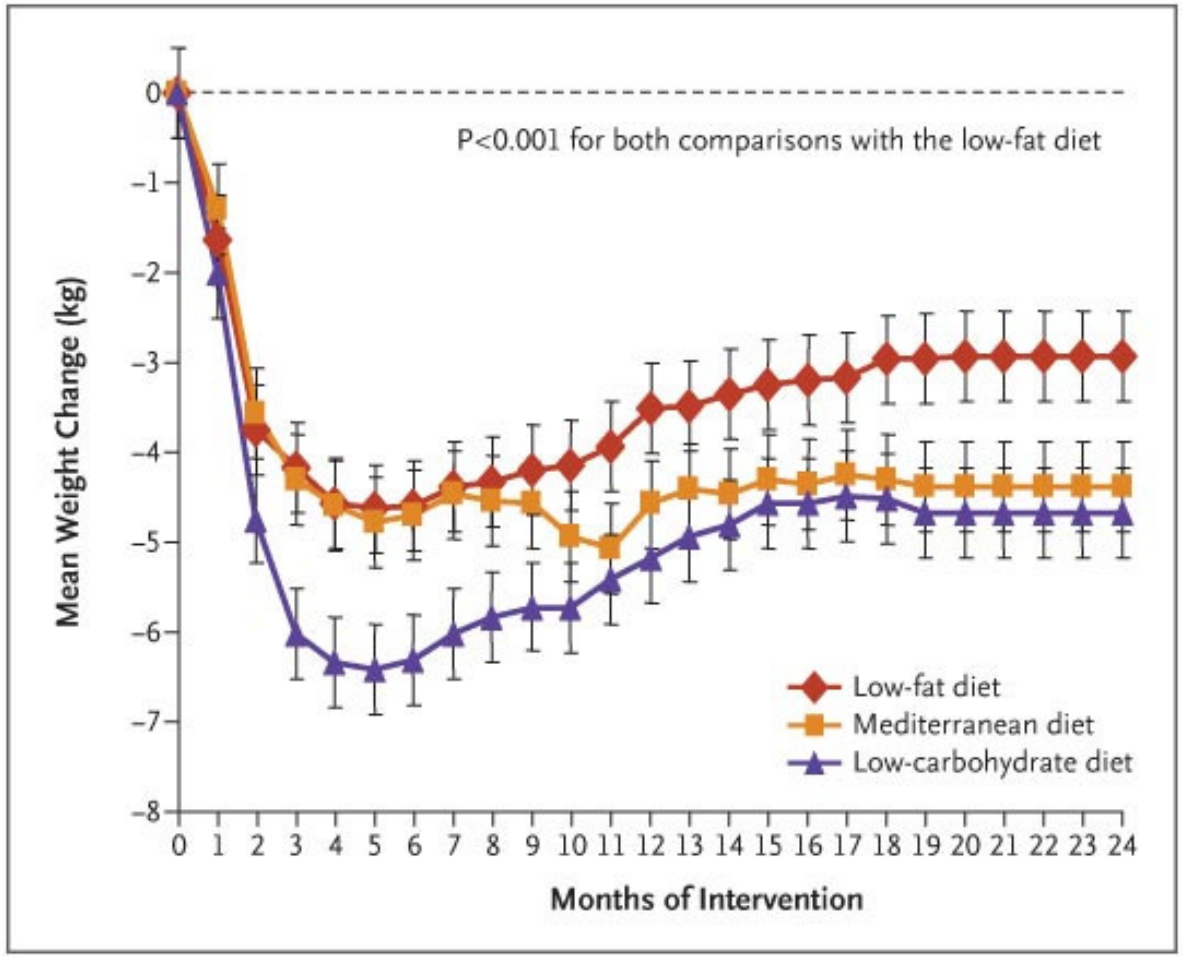
So, Dr. Adair, how do we lose weight?

- Slowly
- Over a prolonged period
- Steadily
- Without daily or periodic dietary swings
- With first goal being stability or disappearance of "withdrawal" and cravings
- And by keeping good company!

Weight Changes during 2 Years According to Diet Group



Shai I et al. N Engl J Med 2008;359:229-241

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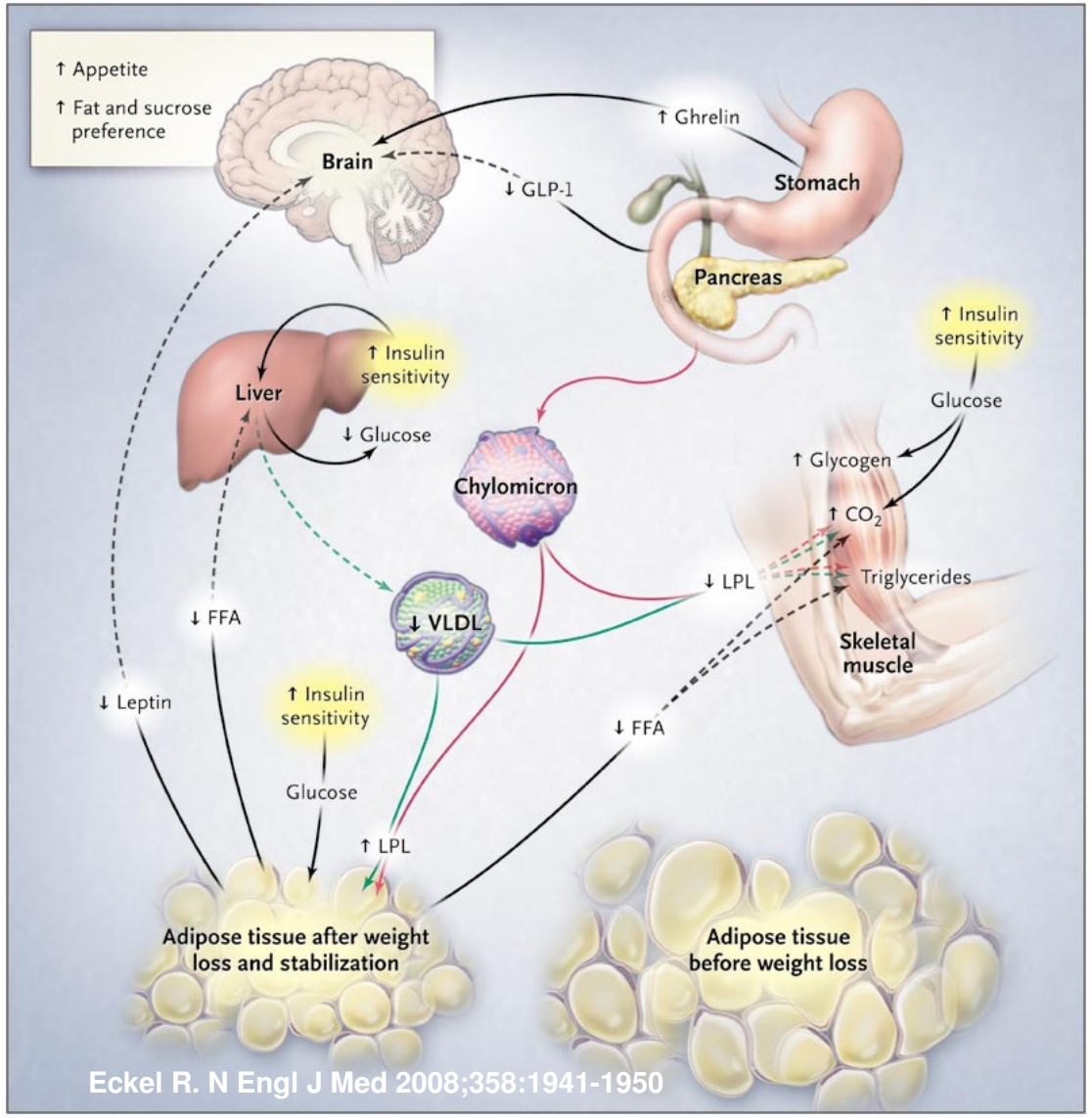
So, which diets work?

- All
  - If they become a *lifestyle change*
  - It's caloric arithmetic
- None
  - If not followed for minimum 1-2 years
  - *Remember that dopamine reward system, endocannabanoid withdrawal thing!!!*
- Best
  - All are good, Atkins is better
  - *If followed for 2 years!!!!!!!*
  - *(……and the entire rest of your life!!!!!!)*

Biologic Mechanisms Protecting Adipose Tissue Mass



Eckel R. N Engl J Med 2008;358:1941-1950

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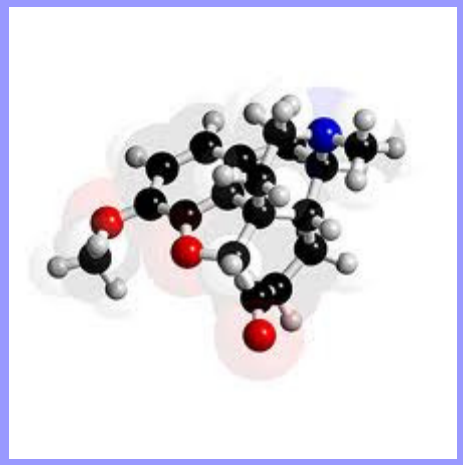
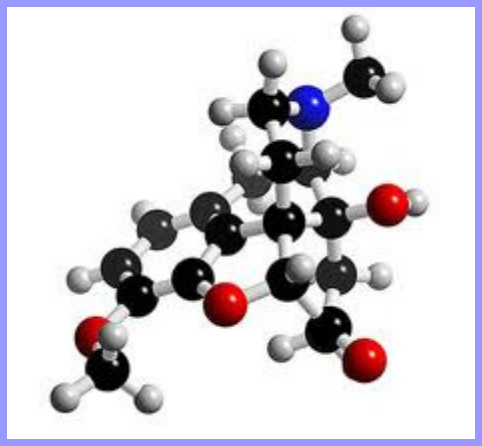
- Biologic Mechanisms Protecting Adipose Tissue Mass. Pathways of metabolic regulation before and after stabilized weight reduction are shown. After stabilized weight reduction, there is a reduction in adipocyte size and in circulating levels of leptin. Increases in ghrelin and reductions in glucagon-like peptide 1 (GLP-1) also stimulate signals in the brain to increase caloric intake. With maintenance of weight reduction, increased insulin sensitivity results in decreased lipolysis of triglyceride stores and free fatty acids (FFAs) in adipose tissue, increased insulin-mediated glucose uptake and storage in adipose tissue and skeletal muscle, and reduced hepatic glucose production. After weight reduction and stabilization, the synthesis and secretion of very-low-density lipoproteins (VLDLs) by the liver are reduced. There is also reduced uptake of FFAs from triglyceride-rich lipoproteins (chylomicrons and VLDLs) in skeletal muscle because of relative decreases in skeletal-muscle lipoprotein lipase (LPL). The increased action of insulin in adipose tissue also results in increased adipose-tissue LPL. Overall, fat calories are more likely to be partitioned in adipose tissue for storage than to be oxidized in skeletal muscle. With close monitoring of caloric intake and energy expenditure, these changes can be overcome, and weight loss sustained.

Should we as addiction professionals be involved in obesity treatment?

Yes! Because……





Should we as addiction professionals be involved in obesity treatment?

Yes! Because……

- It's treatable as an addiction
- It responds to the 12 Steps
- It leads to other substance dependences, especially opioid addiction
- It's predicts a premature, miserable death if not treated
- It's an equal-opportunity destroyer

True or False Post-Test

- All eating disorders are addictions

  False: Anorexia and Bulimia are profound disruptions of the serotonin system

- Bulimia is the same as Anorexia

  False:

  Anorexia is reduced 5HT2A *receptor* activity, possibly increased 5HT *transporter* activity

  Bulimia is increased 5HT1A *receptor* activity

- Obesity is an addiction

  True: Meets addiction criteria for *exposure, tolerance, withdrawal, & craving*, and is mediated by the same neurophysiological system that mediates alcohol addiction and tolerance, plus a host of others!

True or False Post-Test

- All eating disorders respond to therapy

  True: both counseling and pharmacotherapy, anorexia less so

- All eating disorders respond to 12 Steps

  True: proven history

- All eating disorders belong in the same room

  Probably not, given residual issues

We all get heavier as we get older because there's a lot more information in our heads. So I'm not fat, I'm just really intelligent and my head couldn't hold any more so it started filling up the rest of me!

That's my story and I'm sticking to it!

Thank you!!!