Obesity Research And Relationship to Type 2 Diabetes

Jeffrey S. Flier, M.D.

Beth Israel Deaconess Medical Center

Boston

The Rising Tide of Diabetes Worldwide

Diabetes Mellitus

Definition- group of syndromes with hyperglycemia (plus)

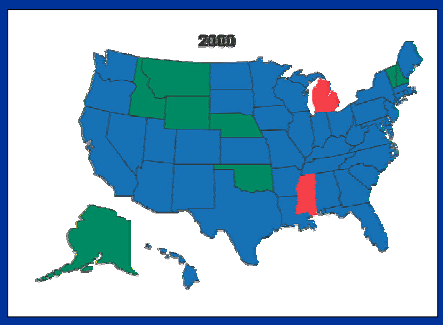
Type I, Type II, others (pancreatic etc)

Link to complications – specific (eye, kidney, nerves)
+ general (athero)

Diagnostics

Blood glucose – normal (<110 mg/dl), IFG (110-125)
Diabetes (>125 fasting); role of IGT
Hemaglobin A1C

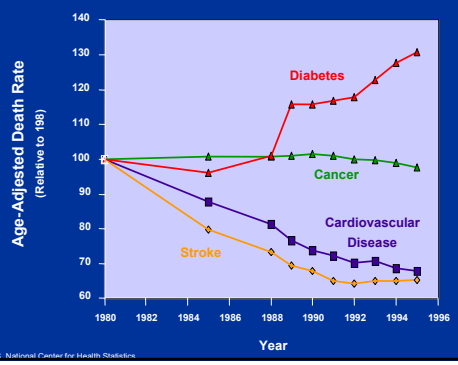
Epidemic of Diabetes in the U.S.



Percentage of Population Over 18 with Diabetes

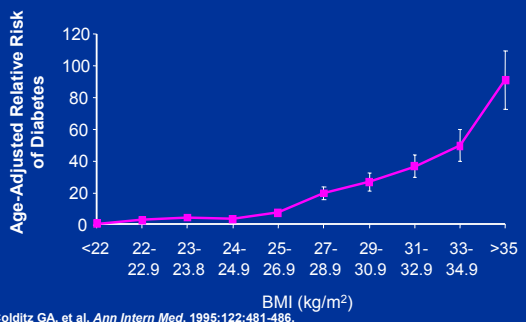
No data available | Less than 4% | 4% - 6% | Above 6% | Above 8%

Increasing Deaths Due to Diabetes



Source: U.S. National Center for Health Statistics

Link Between Obesity and Type 2 Diabetes: Nurses' Health Study



Colditz GA, et al. *Ann Intern Med*. 1995;122:481-486.

Obesity: Definition

Excess mass of adipose tissue

Defined medically via linkage to morbidity

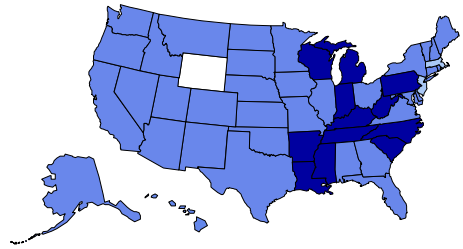
Fat mass measured directly or indirectly

- BMI most widely used – wt (kg)/ht (M2)
- Obesity – BMI > 30 (morbid obesity >40, or 100 lbs excess)
- Overweight – BMI 25 – 29.9

Obesity Trends* Among U.S. Adults

BRFSS, 1993

(*BMI ≥ 30, or ~ 30 lbs overweight for 5'4" woman)

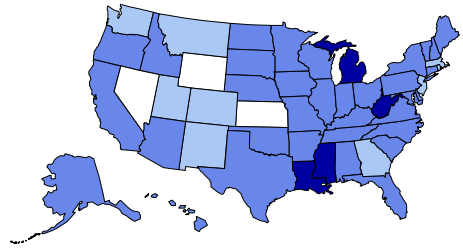


No Data | <10% | 10%-14% | 5-19% | 0% | >20%

Obesity Trends* Among U.S. Adults

BRFSS, 1991

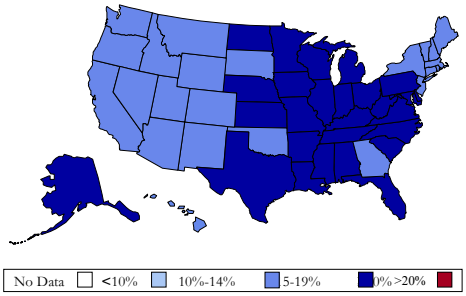
(*BMI ≥ 30, or ~ 30 lbs overweight for 5'4" woman)



No Data | <10% | 10%-14% | 5-19% | 0% | >20%

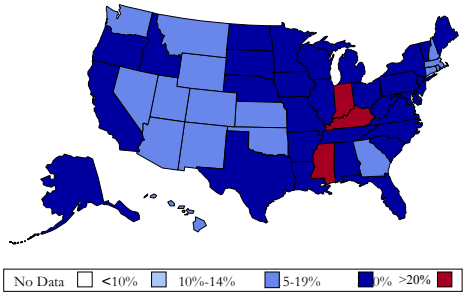
Obesity Trends* Among U.S. Adults
BRFSS, 1995

(*BMI ≥ 30, or ~ 30 lbs overweight for 5'4" woman)



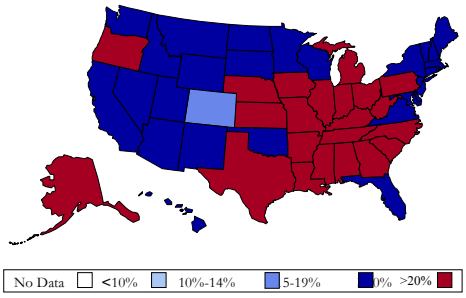
Obesity Trends* Among U.S. Adults
BRFSS, 1997

(*BMI ≥ 30, or ~ 30 lbs overweight for 5'4" woman)

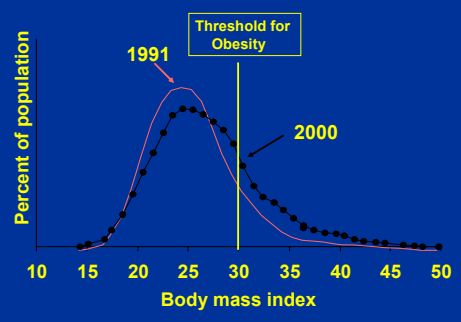


Obesity Trends* Among U.S. Adults
BRFSS, 2000

(*BMI ≥ 30, or ~ 30 lbs overweight for 5'4" woman)



BMI OF MEN (20-39) 1991 VS 2000



SOURCE: Katherine Flegal CDC/NCHS

Obesity epidemic: A Worldwide Event

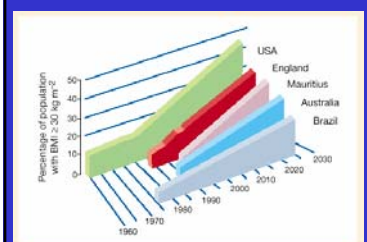


Figure 2 Historic, current and projected obesity prevalence rates (BMI ≥ 30 kg m^{-2}) for the United States, England and Wales, Mauritius, Australia and Brazil from 1960 to 2025. Courtesy of the International Obesity Task Force.

Kopelman PG, 2000

Morbidity

Diabetes
HTN
Dyslipidemia
Atherosclerosis
Repro. dysfunction
Cancer
Sleep apnea
Cholelithiasis
Arthritis

***Increased mortality**

Pathogenesis of Obesity

Genes

Monogenic ⟷ **Polygenic (susceptibility)**

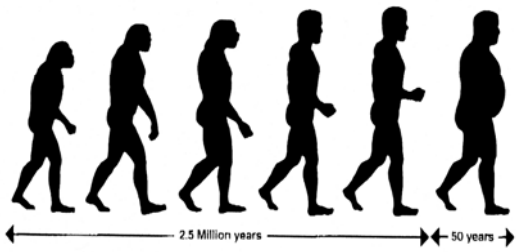
Obesity vs leanness

Diet (availability; composition)

Physical activity (energy expenditure)

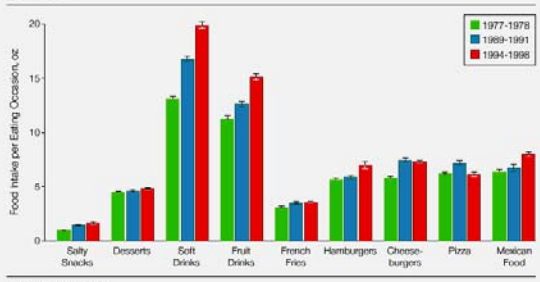
Environment

Obesity: Genetics and Environment



Increasing Portion Size of Foods

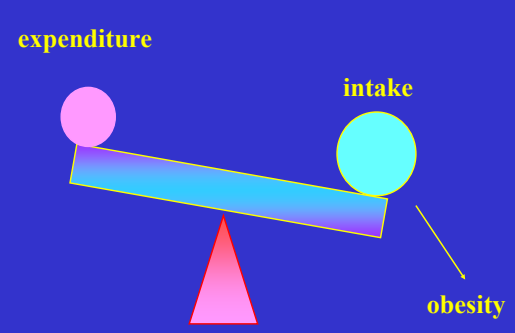
Figure 1. Portion Sizes for Selected Key Food Items for Americans Aged 2 Years and Older, 1977-1996



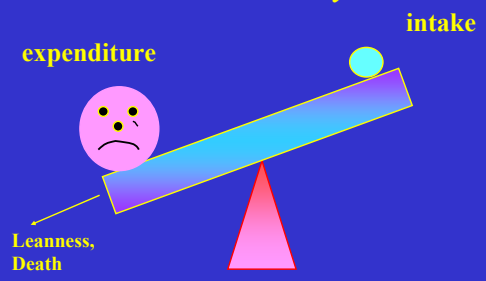
Error bars indicate SE.

JAMA, Jan 29, 2003

Obesity is a Disorder of Energy Balance

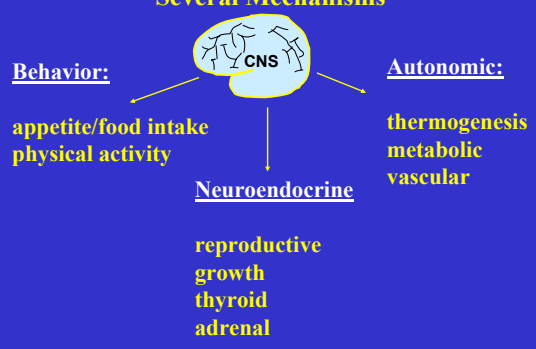


Leanness is a Greater Threat to Survival than Obesity

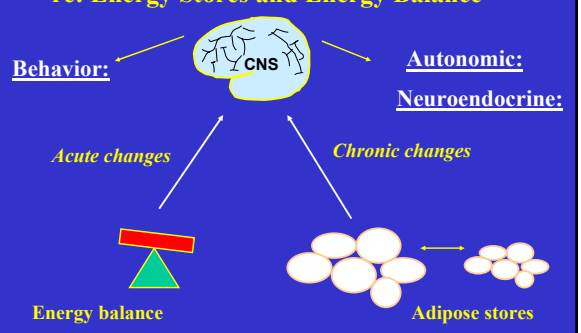


Evolution Favored Energy Storage and Avoidance of Starvation! That was then, and this is now!

The Brain Affects Energy Balance through Several Mechanisms



Feedback Signals to the Brain re: Energy Stores and Energy Balance



2 cousins with Complete leptin Deficiency (ob/ob)

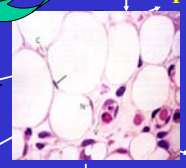
Montague et al Nature, 1997

The effects of recombinant Leptin in Leptin deficient Child.

Farooqi et al, JCI, 2002

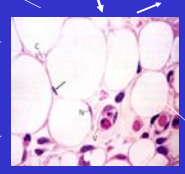
Massive obesity as an Inborn error of Metabolism, cured By replacement therapy

The Adipocyte as an Endocrine Cell



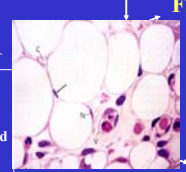
cortisone
11 beta HSD-1
cortisol
Leptin
FFA
FFA → fuel
FFA → signal
androstenedione
estrone
Complement factors
adipsin/D
angiotensinogen
PAI-1
TNF- α
IL-6
MCP-1
Resistin
adiponectin

The Adipose Endocrine Organ: Likely Downstream Targets

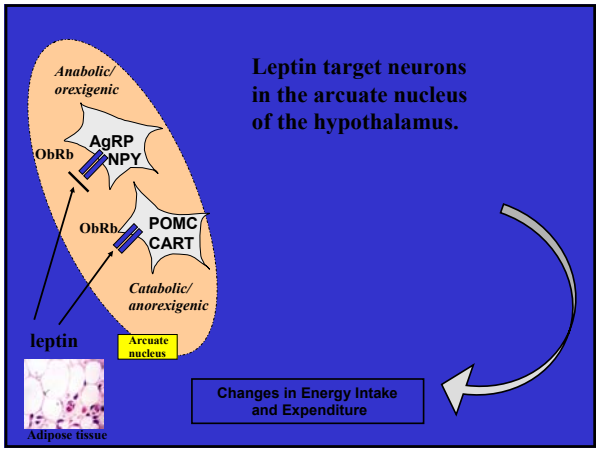


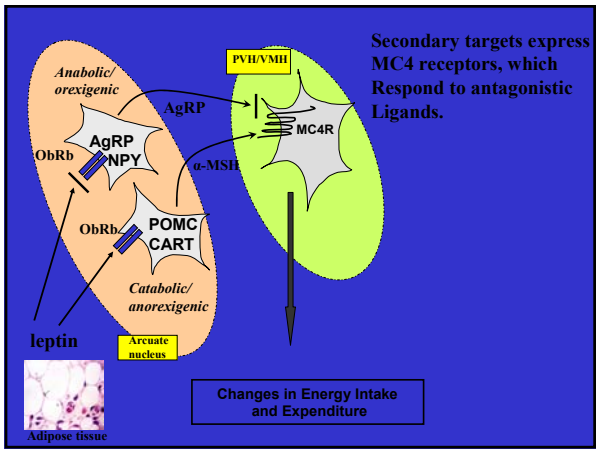
Neural development
FFA
FFA → fuel
FFA → signal
Neuroendocrine function
Sex Steroid and Glucocorticoid action
Autonomic activity
Inflammation/Immunity: Complement/cytokines
Appetite
Thrombosis
Vascular tone
Glucose and Lipid metabolism

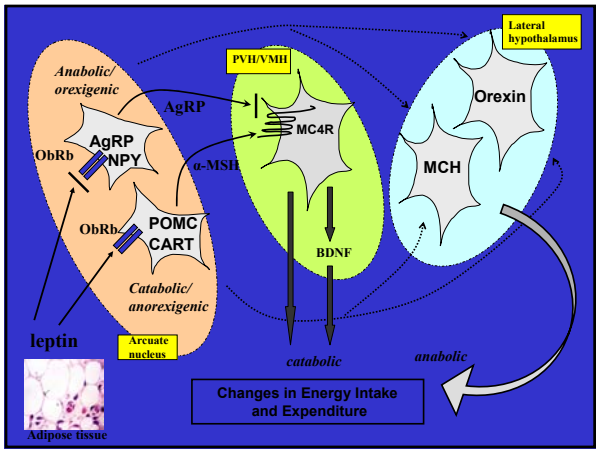
The Adipocyte as an Endocrine Cell

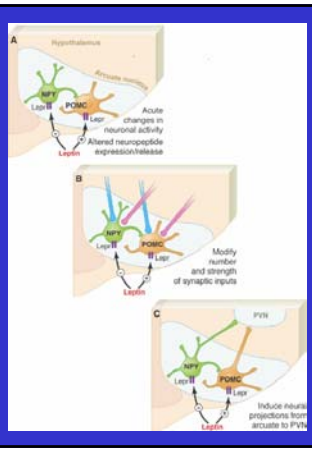


Adipokines
Resistin
Adiponectin
Insulin sensitivity
Lipid oxidation
Vascular protection
CNS target/energy expend
Novel receptors –AMPK
Reg by TZD drugs
FFA
FFA → fuel
FFA → signal
androstenedione
estrone
Complement factors
adipsin/D
Vascular factors
angiotensinogen
PAI-1
Cytokines
TNF
IL-6


Leptin target neurons in the arcuate nucleus of the hypothalamus.
Anabolic/ orexigenic
AgRP
NPY
ObRb
ObRb
POMC
CART
Catabolic/ anorexigenic
leptin
Arcuate nucleus
Adipose tissue
Changes in Energy Intake and Expenditure


Secondary targets express MC4 receptors, which Respond to antagonistic Ligands.
PVH/VMH
Anabolic/ orexigenic
AgRP
MC4R
AgRP
NPY
ObRb
α-MSH
ObRb
POMC
CART
Catabolic/ anorexigenic
leptin
Arcuate nucleus
Adipose tissue
Changes in Energy Intake and Expenditure

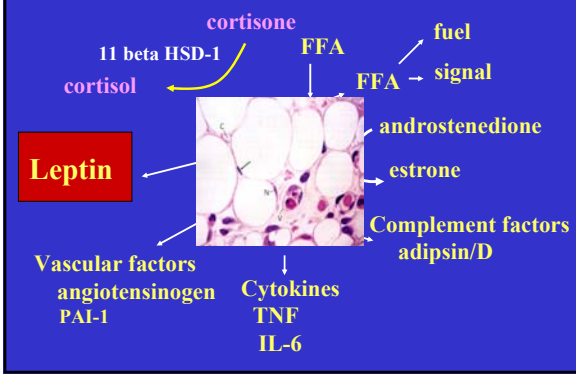

Lateral hypothalamus
PVH/VMH
Anabolic/ orexigenic
AgRP
Orexin
MC4R
AgRP
NPY
ObRb
α-MSH
MCH
ObRb
POMC
CART
BDNF
Catabolic/ anorexigenic
leptin
Arcuate nucleus
catabolic
anabolic
Adipose tissue
Changes in Energy Intake and Expenditure



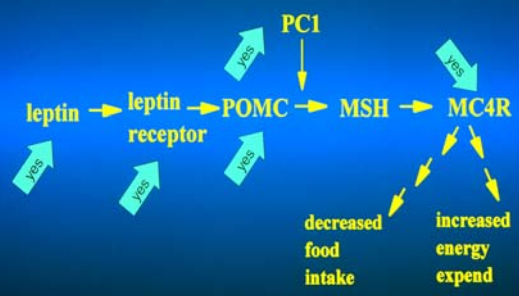
Leptin can influence Arcuate circuits by at Least 3 mechanisms:

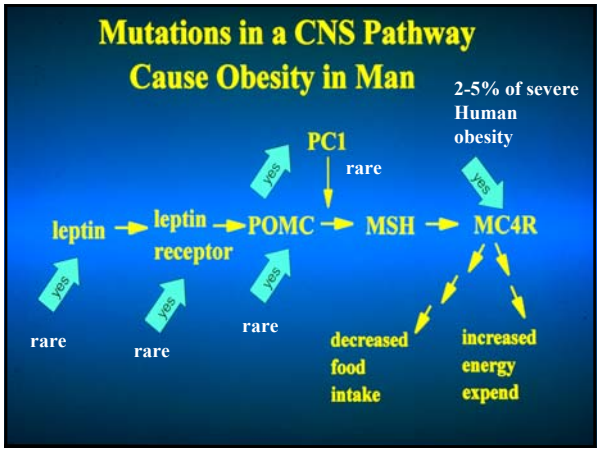
1. Neural activity/neuro-Peptide expression
2. Synaptic inputs
3. Neural projections

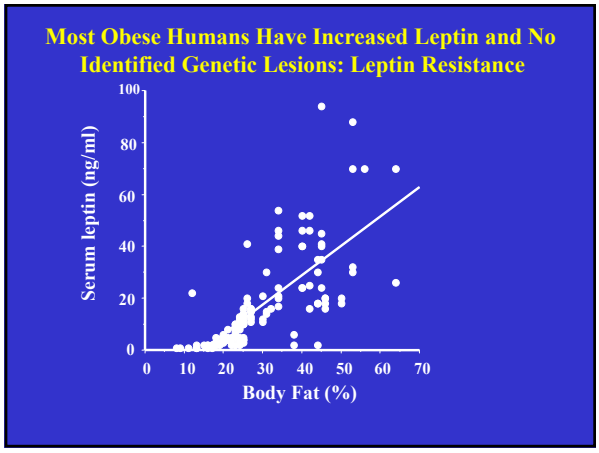
The Adipocyte as an Endocrine Cell

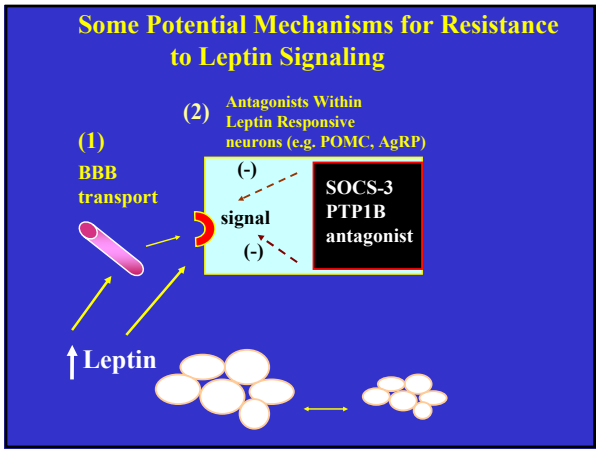


Mutations in a CNS Pathway Cause Obesity in Man

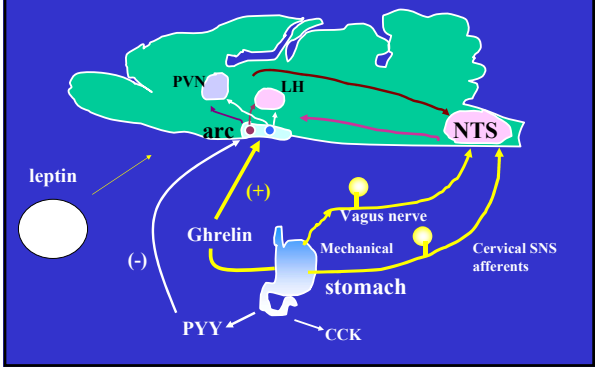



Mutations in a CNS Pathway
Cause Obesity in Man
2-5% of severe
Human
obesity
PC1
rare
yes
yes
leptin
leptin
receptor
POMC
MSH
MC4R
yes
yes
yes
rare
rare
rare
decreased
food
intake
increased
energy
expend


Most Obese Humans Have Increased Leptin and No
Identified Genetic Lesions: Leptin Resistance
Serum leptin (ng/ml)
100
80
60
40
20
0
0
10
20
30
40
50
60
70
Body Fat (%)


Some Potential Mechanisms for Resistance
to Leptin Signaling
(1)
BBB
transport
(2)
Antagonists Within
Leptin Responsive
neurons (e.g. POMC, AgRP)
(-)
signal
(-)
SOCS-3
PTP1B
antagonist
Leptin

Leptin actions are integrated with Signals Regulating Meal Size: Recent Insights



46 year old male

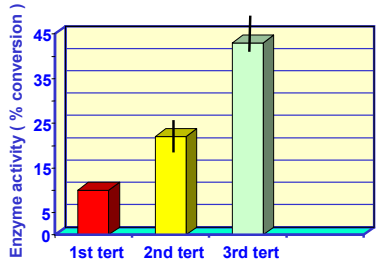
Central obesity
Hypertension
Glucose intolerance
(no weakness, plethora etc)

Normal dexamethasone suppression
Normal Cortisol levels
Normal urinary free cortisol

i.e. No Cushings syndrome

Might there be a disorder of Intracellular Cortisol Metabolism?

11β HSD-1 Activity In Subcutaneous Fat Biopsies of Humans Stratified By Body Weight



Average BMI	22.9	26.4	31.7

Modified from E. Rask *et al.*
J. Clin. Endocrinol.Metab. 86, 1418 (2001).

Key Features in 11 beta HSD-1 Mice

- ❑ Local cortisol excess in fat - initiating event
- ❑ Obesity, especially visceral
- ❑ Hyperphagia
- ❑ Glucose intolerance/diabetes, insulin resistance
- ❑ High triglycerides, FFA
- ❑ Altered adipocyte-derived circulating factors
- ❑Hypertension, fatty liver

Implications of 11 beta HSD-1 Story

Local Glucocorticoid reactivation in fat can cause visceral obesity and its complications.

Obese humans may have such a phenomenon.

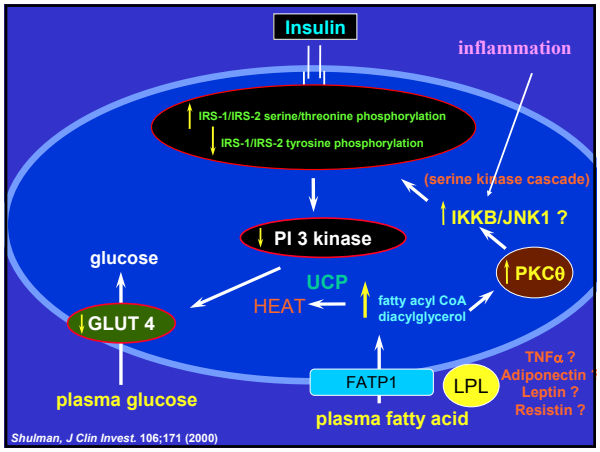
Inhibition of this enzyme may have beneficial effects on obesity and metabolic/vascular complications.

Another Frontier in Pathogenesis of Diabetes and Obesity: Inflammation

Inflammatory Markers in both States

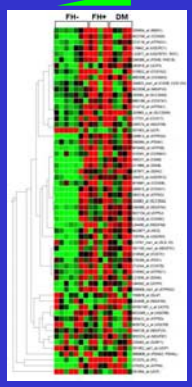
Increasingly linked to pathogenesis and complications

- e.g. cytokines in pathogenesis of insulin resistance
- production in fat cells, macrophage infiltration
- possible role of SOCS 3



Expression of Mitochondrial Oxidative Metabolism Genes is Reduced in Humans with Insulin Resistance and DM

Increasing Insulin Resistance



1st degree relatives: Patti et al (2003)
Insulin resistant Pima: Yang et al (2002)
(NADH dehydrogenase, ATP5C1)
IGT: Mootha et al (2003)
Uncontrolled DM: Sreekumar R et al (2002)

Patti et al, PNAS, 2003

Available Obesity Therapies: 2003

Diet – calories, composition, fads
Exercise
Behavior Modification

Drugs
- Meridia (sibutramine)
- Xenical (orlistat)
- OTC

Surgery – gastric bypass or limitation

Ongoing Debate re: Therapeutic Approach

Position # 1:
Since the major increase in obesity recently is surely caused by environment (i.e. diet, exercise) not change in genes, we should treat obesity by attacking the environment.

Position # 2:
That would be nice, but we don't know how to do it, so if we are interested in public health, we should develop safe and effective medications.

Trials to Prevent/Delay Progression from IGT to Type 2 Diabetes

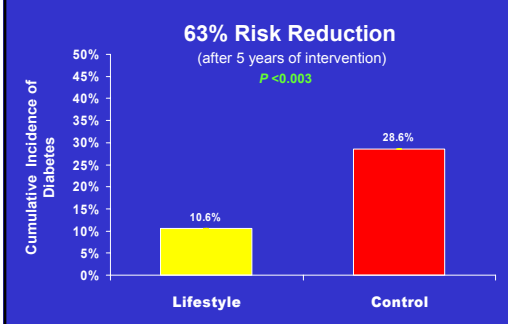
LIFESTYLE CHANGES

- MALMO STUDY
- DA QING STUDY
- FINNISH DIABETES PREVENTION STUDY
- DIABETES PREVENTION PROGRAM

MEDICATIONS

- DIABETES PREVENTION PROGRAM: **metformin, (troglitazone)**
- TRIPOD: **troglitazone**
- STOP-NIDDM: **acarbose**
- NAVIGATOR: **nateglinide and valsartan**
- DREAM: **rosiglitazone and ramapril**
- XENDOS: **orlistat**

Cumulative Incidence of Type 2 DM in the Malmo Study



Eriksson KF, Lindgarde F. Diabetologia 1991, 34(12):891-8

Future Obesity Therapies: What is in the Pipeline?

Leptin – can a responsive subset or new mode of administration be found? Leptin sensitivity enhancers?

Axokine (CNTF) – neurocytokine, failure for ALS, ? leptin mimic, ? overcomes leptin resistance – problem with antibodies, ? reason for prolonged effect

Melanocortin 4 receptor agonist – feeding and metabolic effects

Beta 3 adrenergic agonists – increase thermogenesis, work well in rodents, ? human efficacy

Future Obesity Therapies: What is in the Pipeline?

Other central pathways – e.g. MCHR1 antagonist; endocannabinoid receptor CB1 antagonist; serotonin receptors, other GPCR's

Gut Peptides – Ghrelin antagonists, PYY agonists, GLP-1 pathway, CCK; alternative gut approaches

Inhibitor of 11 beta HSD-1 – efficacy for diabetes, obesity

DGAT 1, ACC2, FATP1 antagonists – fatty acid metabolism

Inflammatory pathways – JNK, JNK related

Nuclear receptors – e.g. PPAR delta agonists

Possibility of combination therapies

Final Thoughts

The obesity epidemic (and associated diabetes, CVD etc) represents a major and increasing unmet medical need.

Modifications of the "environment" are worthy, and Should be pursued, but are unlikely to reverse the epidemic anytime soon.

New insights into the molecular basis for regulation of energy balance in brain and periphery offer exciting targets for Drug development. Goal would be to enable everyone to tolerate the effects of the environment as well as some, because of their genes, are able to do without treatment!