

# **The Skinny on Endocrine Mediated Weight Gain**

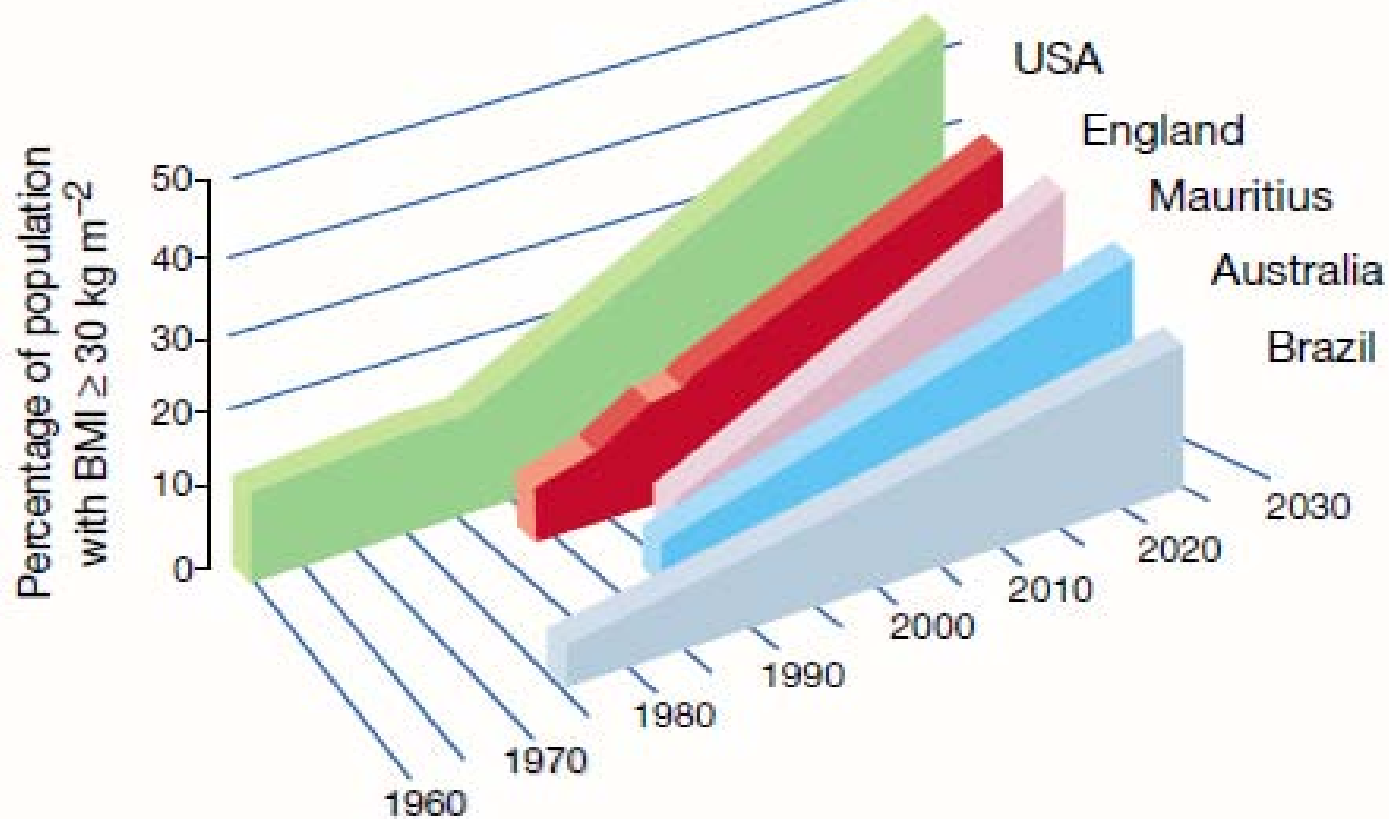
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Diabetes and Metabolism  
Ohio University College of Osteopathic Medicine  
and Feedback Consulting, LLC**



# BMI Trend Predictions

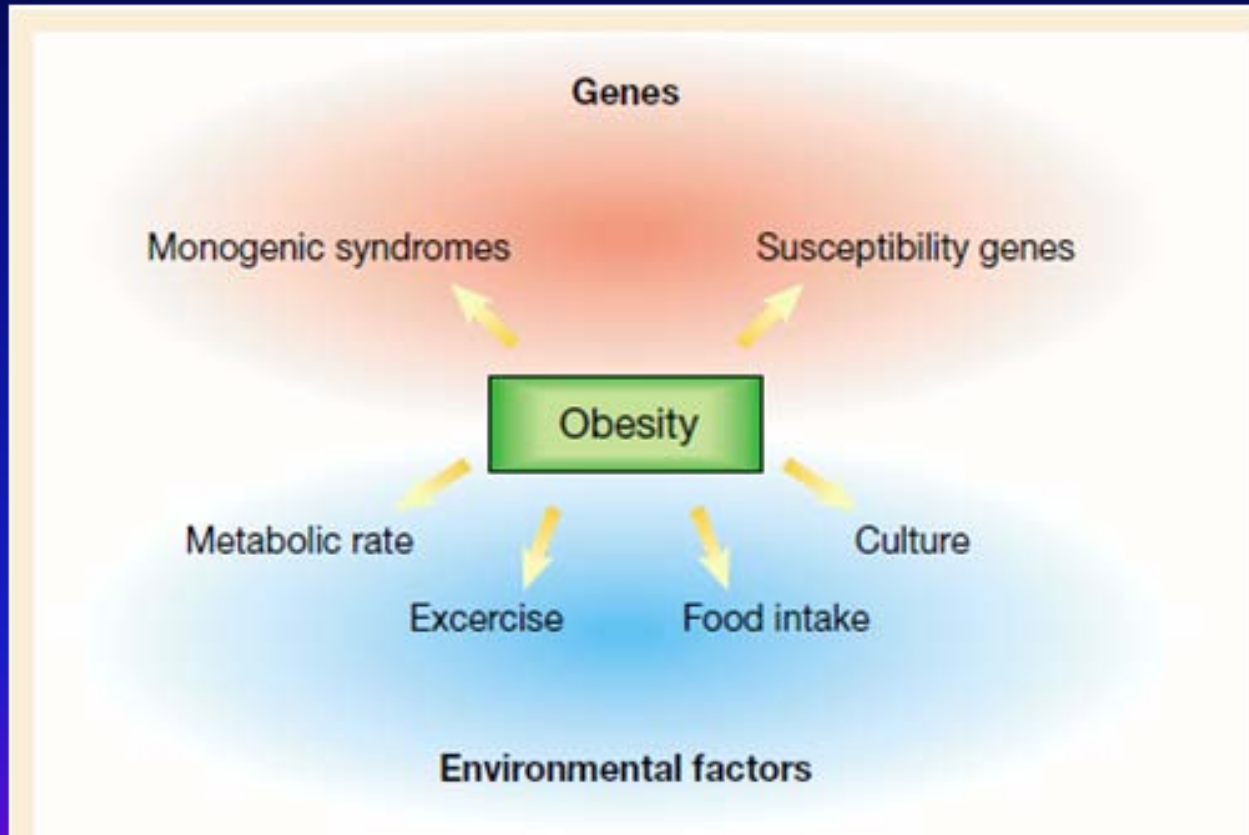
\$66 Billion/year by  
2030

50% (164 million) of US  
population by 2030  
*Lancet 2011*



*Nature, Vol 404, 2000.*

# Factors Influencing Obesity

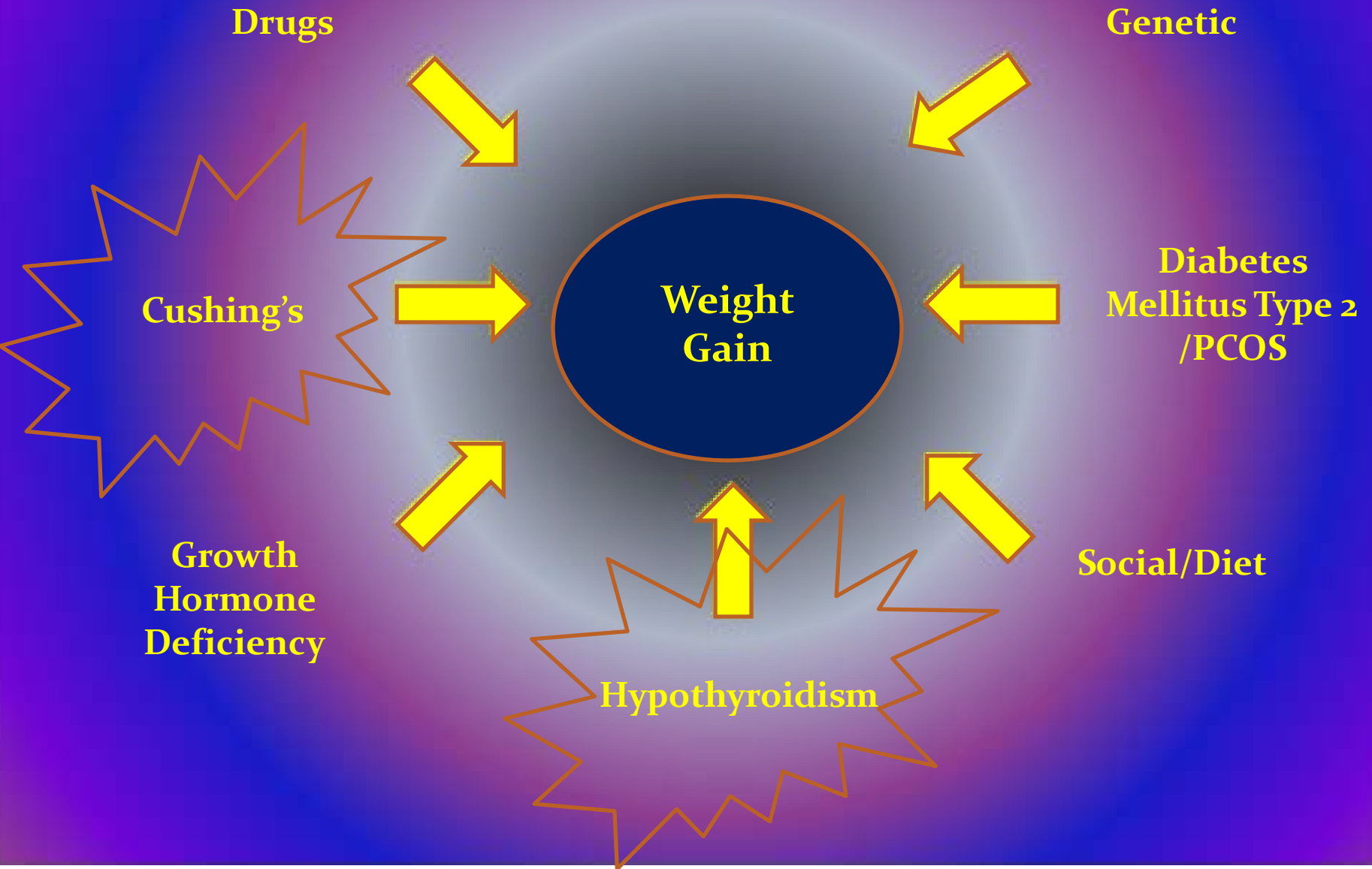


*Nature, Vol 404, 2000.*

# Point

- **Our clinical understanding of obesity is constantly challenged by our molecular/in vitro understanding of endocrinology**
  - **Endocrine and paracrine signaling of endocrine hormones /energy signaling**
  - **Integrated sensors of metabolism require further understanding and allows for targeted therapies**
  - **Adapted/maladapted counterregulatory responses re-define a broader perspective of endocrine mediated weight gain**

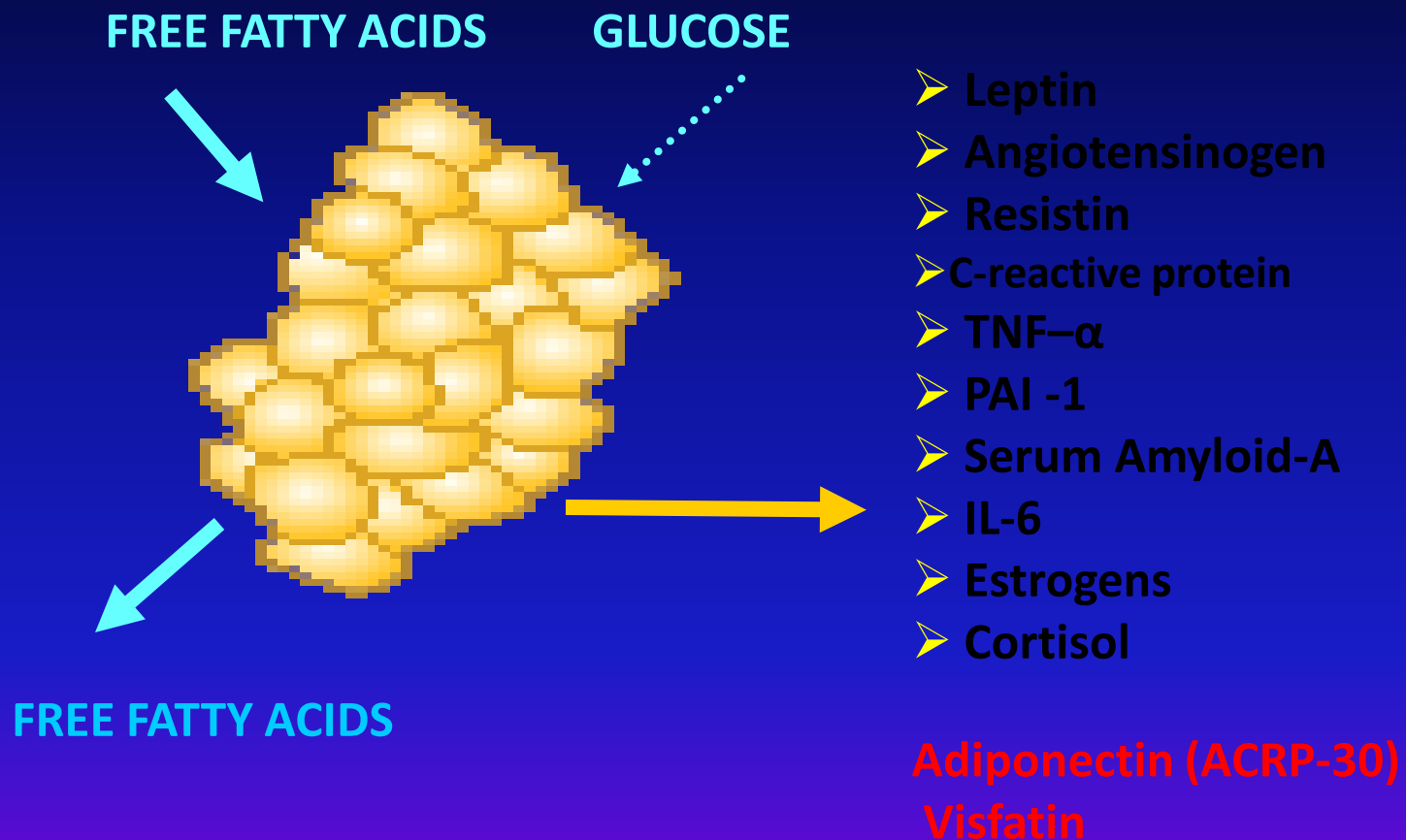
# Common Clinical Endocrinopathies



# Regulation of Metabolic Processes

Anabolic ↑ I:G	Metabolic Process	Catabolic ↓ I:G
↑	Glycogen synthesis (liver and muscle)	↓
↓	Glycogen breakdown	↑
↓	Gluconeogenesis	↑
↑	Fatty acid synthesis and triglycerides (hepatocytes and adipose tissue)	↓
↑	Muscle protein synthesis	↓
↑	Lipogenesis and triglyceride formation	↓
↓	Lipolysis	↑
↓	Free fatty acid oxidation	↑
↓	Ketone body formation	↑
↓	Muscle proteolysis	↑

# Adipocyte: Integrated Energy Model



Modified from: Kahn B & Flier J, JCI 106:473-481, 2000



# Does this patient have an endocrinopathy?

Amy is a 32 year old female.

CC: weight gain  
Tempo: 35 pounds in 4 months

PMHx: Major Depression

SocHx: no exercise, specific diet, works 9 hours a day, single mother  
Drinks 3 beers per week

FMHx: Autoimmune thyroid disease

Twin sister

Meds: health food store stuff

“Will I gain more weight”

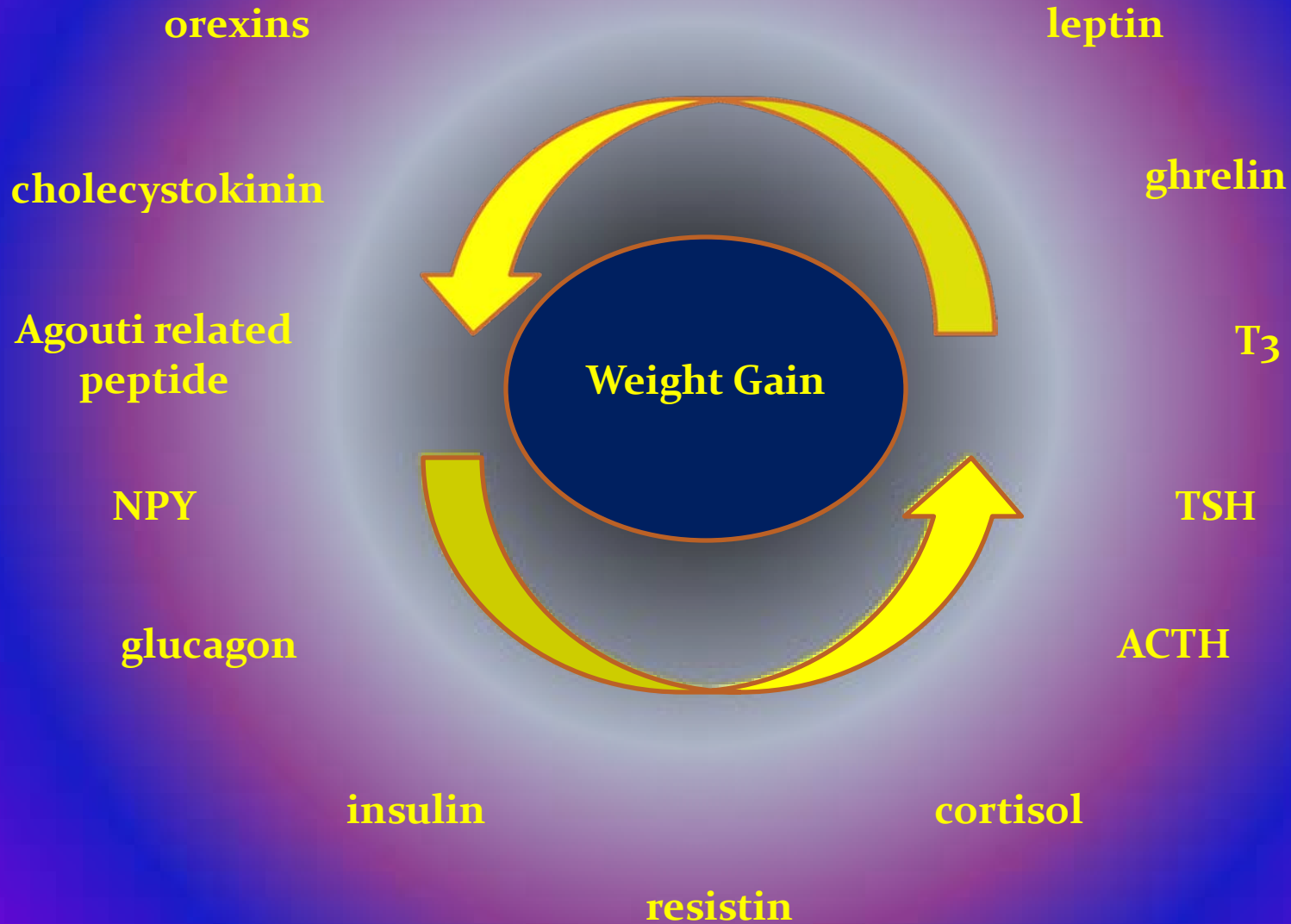
“I know/I think it is my thyroid”

“I don’t eat that much”

“Is there a pill for me”

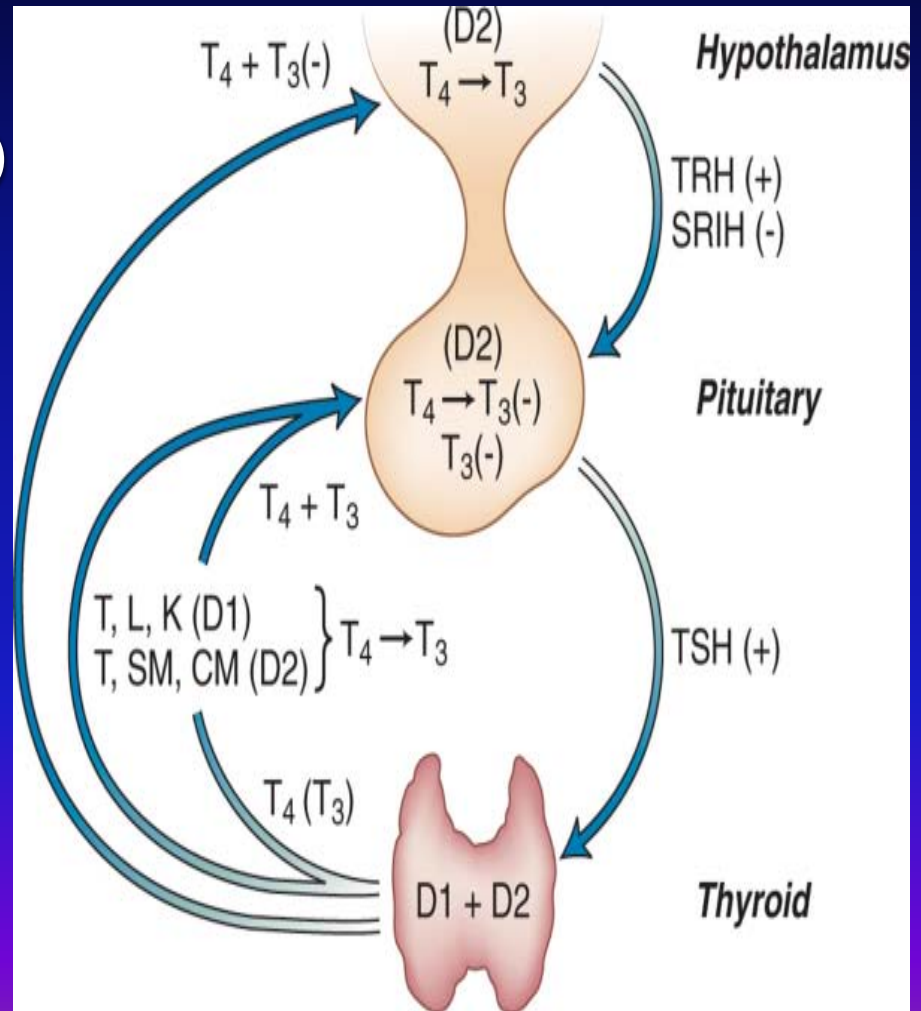


# Clinical Rethinking of Weight Gain

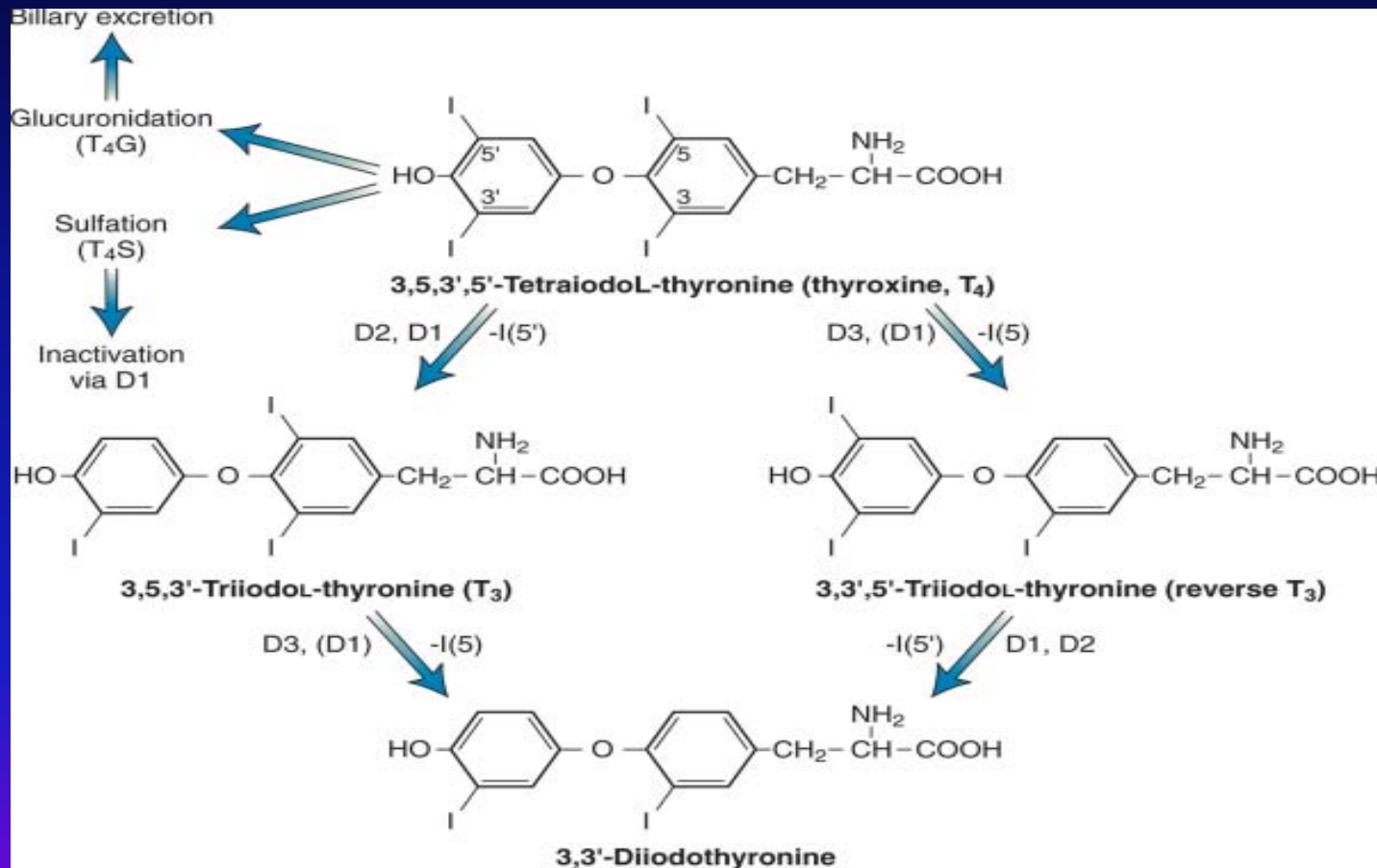


# Clinical Disorders of Hypothyroidism

- **Primary**
  - Overt (AI, RAI, etc)
    - TSH >10
  - Mild (MTF)
    - TSH 5-10
- **Secondary**
  - Pituitary
    - Free t<sub>4</sub> and T<sub>3</sub>
- **Central**
  - Hypothalamic



# Thyroid Hormone Metabolism



**It has been clear for some time  
that thyroid function is not  
grossly impaired in most patients  
with obesity**

- TSH “mildly elevated” in <20% of obese individuals

Emerson, Thyroid 2010  
Kaptein et al., JCEM 2009  
Michalaki, Thyroid, 2006

# Biochemical Hypothyroidism

## Assertion of disease/therapy

- Causes excessive weight gain
- Weight gain will increase TSH
- T<sub>3</sub> therapy in single or combination is needed
- Continued symptoms with “normal” labs means continued hypothyroidism

## Reality

- Minimal : 5-7% of TBW
- Maybe: is this disease or compensation?
- Clinical trials demonstrate poor outcomes
- No (mostly), yes (maybe)

# Is Obesity an Anthropometric Thyroidopathy?

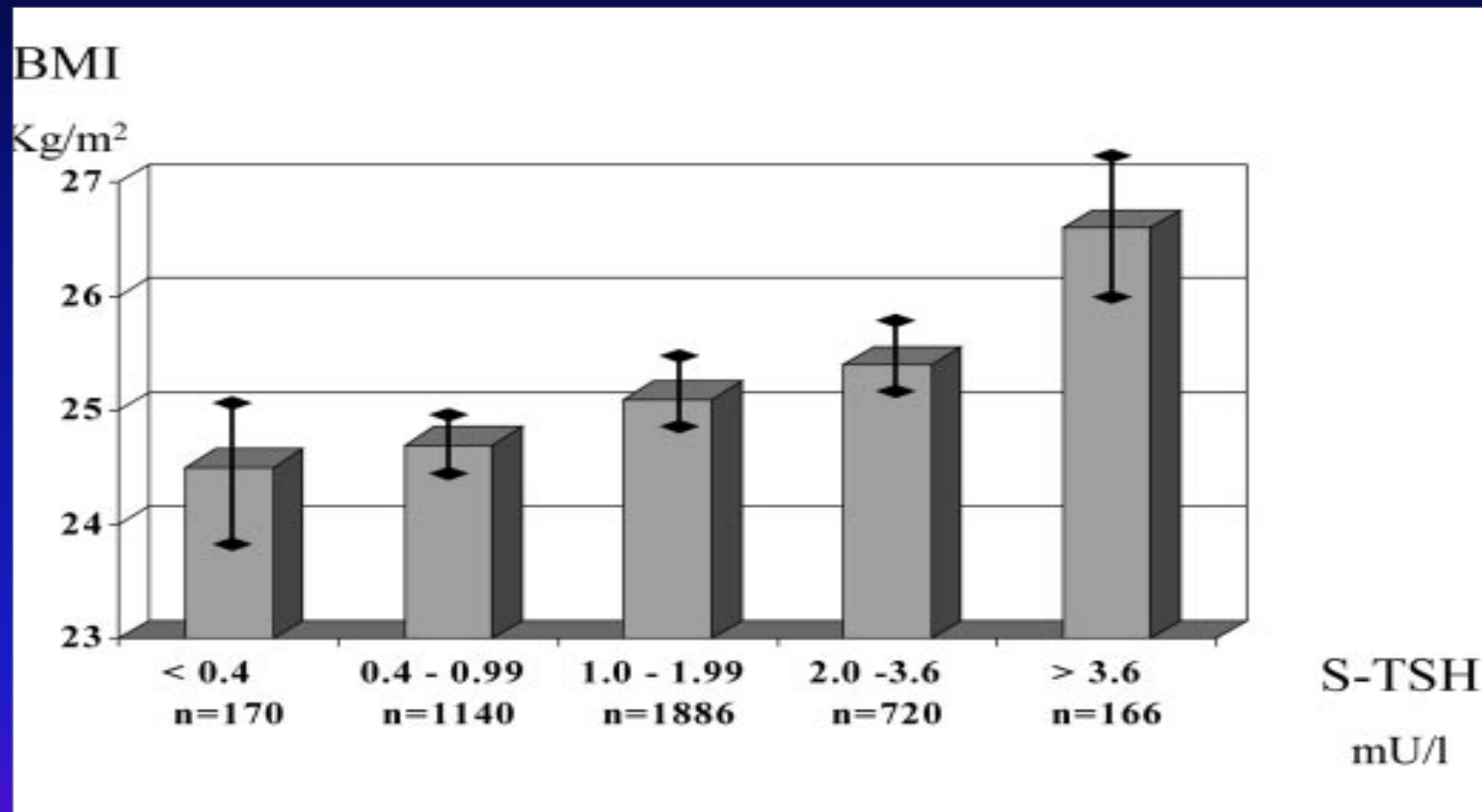
Mild Thyroid Failure ?

Versus

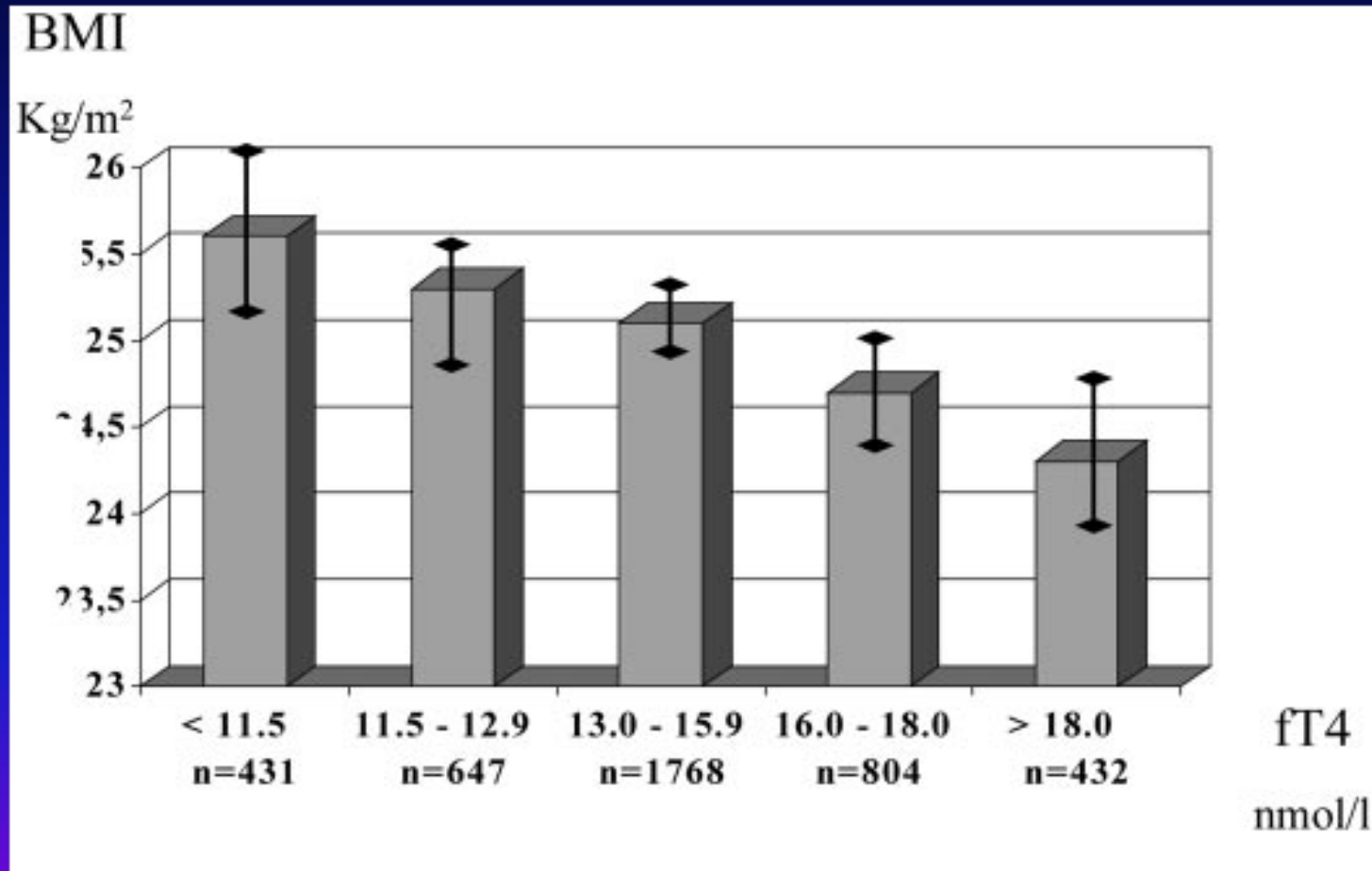
Inappropriate TSH secretion?

Emerson, Thyroid 2010  
Kaptein et al., JCEM 2009

# Relationship of BMI to TSH in MTF



# Relationship of BMI to Free T<sub>4</sub> in MTF

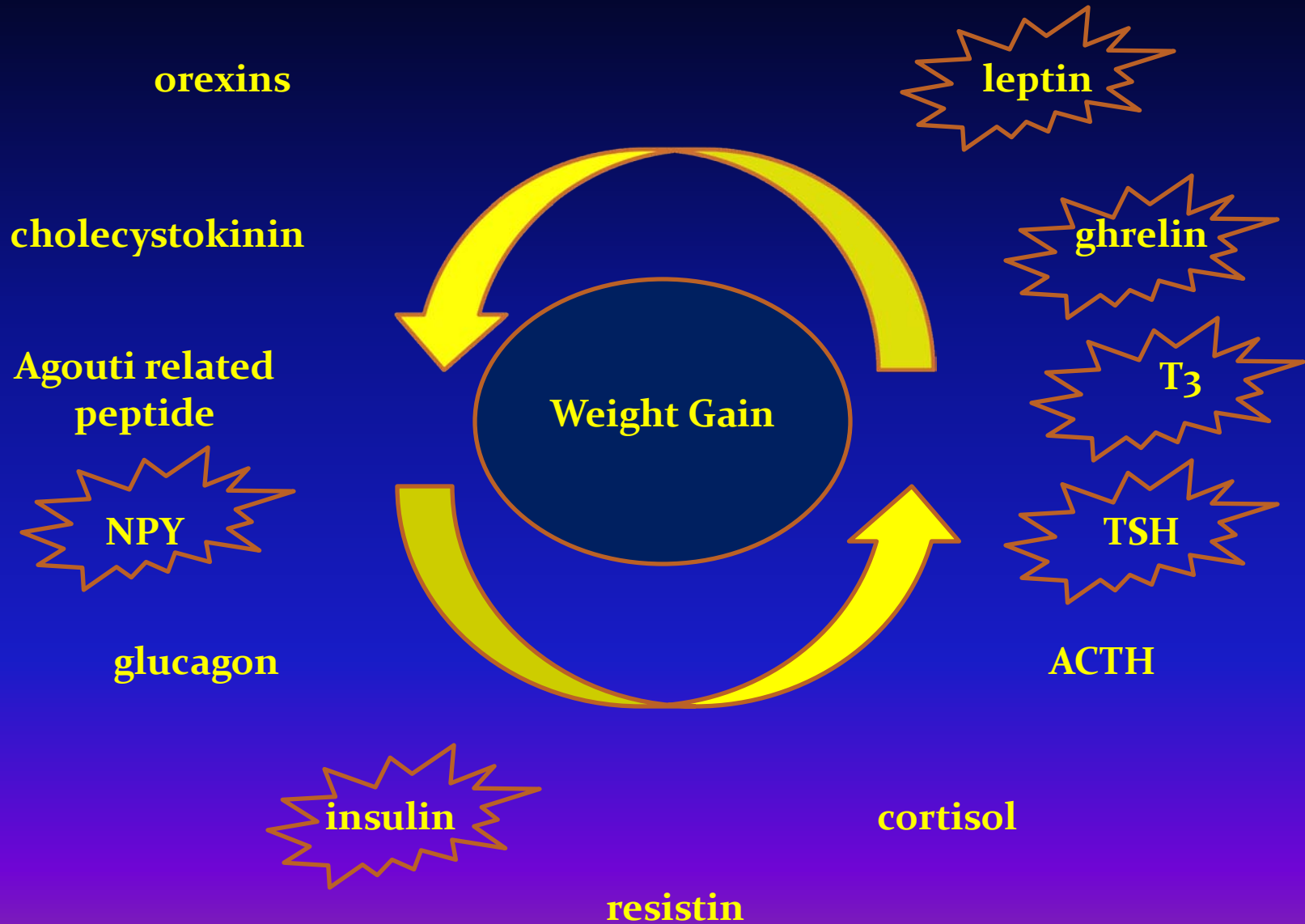


# Mild Thyroid Failure

- Modest increases in TSH have been associated with modest weight gain in adults (The DanTHyr Study)
- Framingham Offspring Study also demonstrated this phenomenon
- Treatment of MTF does not appear to be associated with weight loss

Knudsen, et al. JCEM 2005  
Fox et al. Arch Intern Med 2008

# Thyroid Disease as an Endocrinopathy



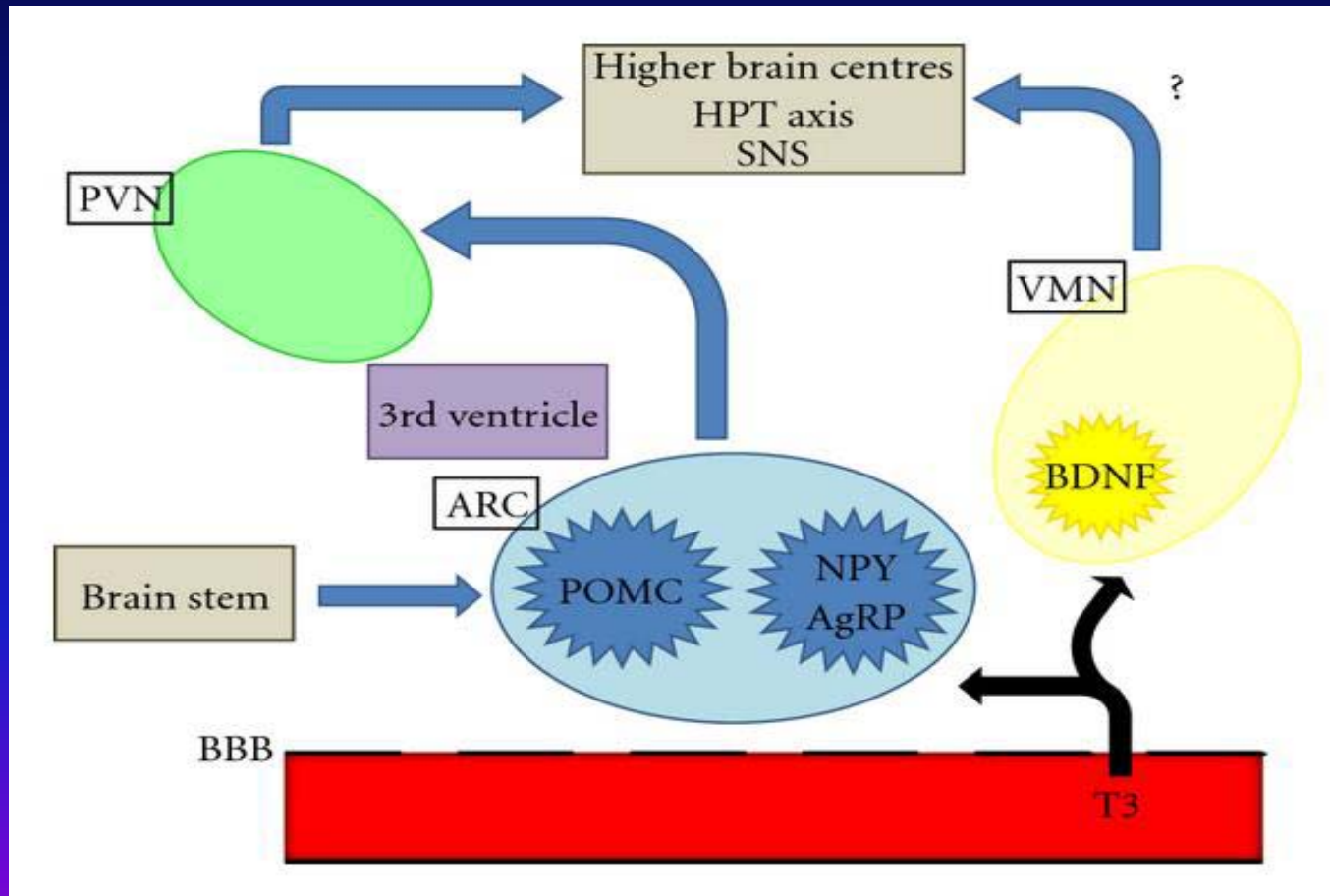
# Serum T<sub>3</sub> and Caloric Intake

- Fasting and caloric restriction
  - reduces free and total T<sub>3</sub>
  - rT<sub>3</sub> levels remain the same
- Overfeeding normal weight or obese subjects
  - Increases free T<sub>3</sub> levels
- T<sub>3</sub> levels may be lower in dieting obese
- T<sub>3</sub> levels may be elevated in non-dieting obese due to energy needed to maintain weight
- Conclusion: Food intake must be considered with interpretation of lab data

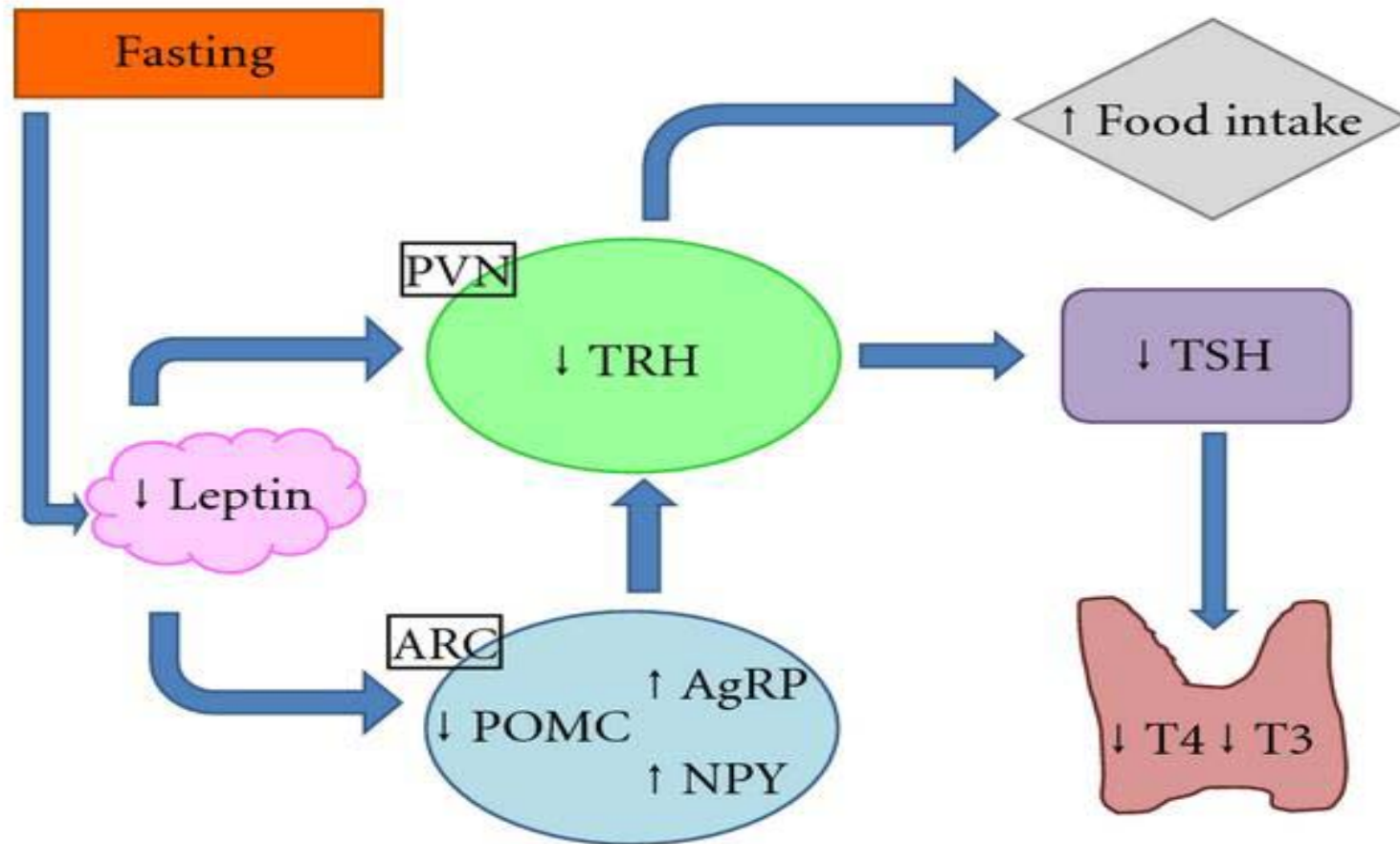
# Thyroid Hormone and Appetite Regulation

- **TH resistance/Thyrotoxicosis:**  
**associated with hyperphagic behavior**
  - cocaine and amphetamine related transcripts (CART: reduce food intake)
  - NPY (neuropeptide Y) increases in hyperthyroidism, increases appetite
  - Antagonism of NPY regulated by 5' adenosine monophosphate-activated protein kinase (AMPK)

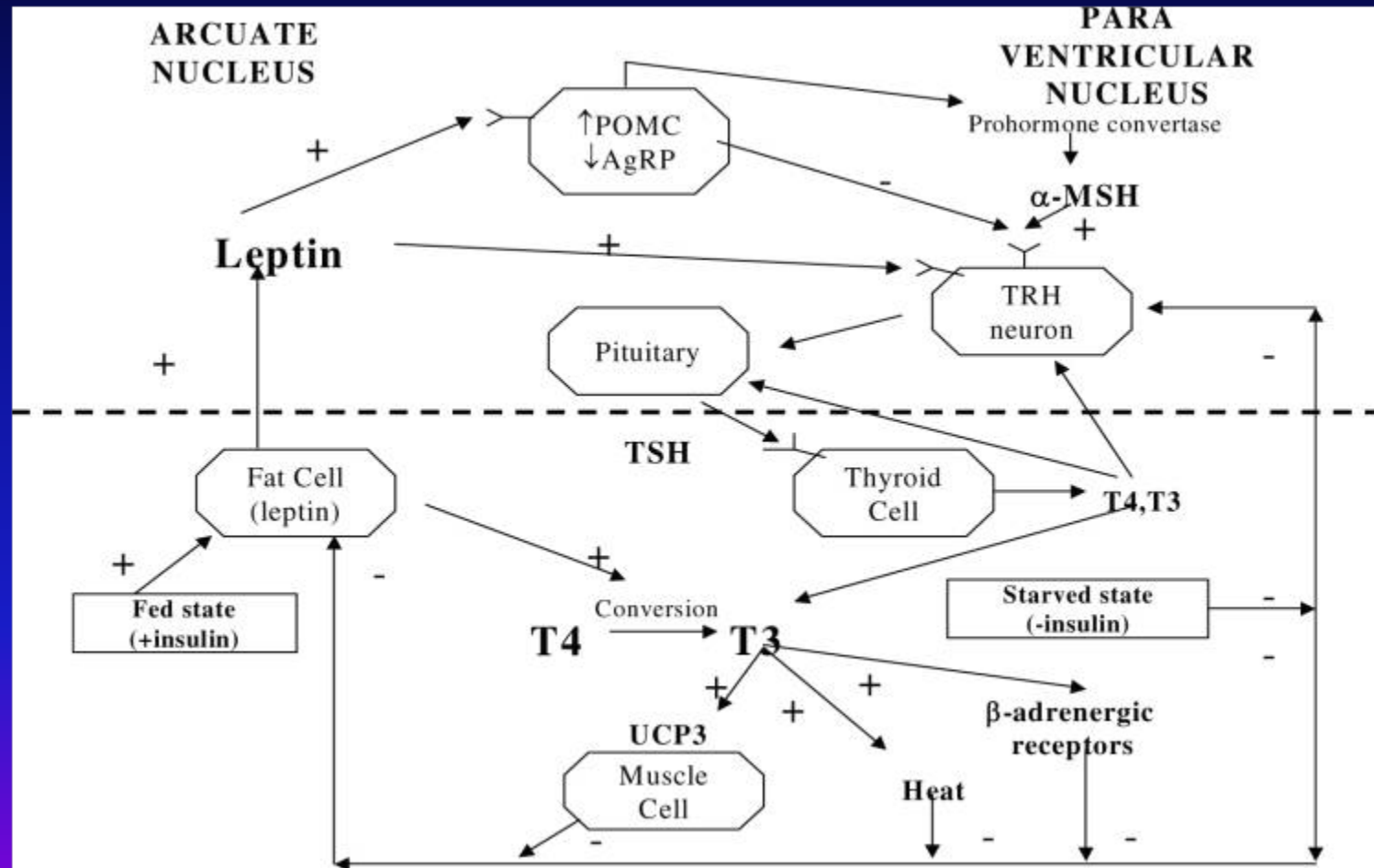
# Thyroid Hormone and Appetite Regulation



# Thyroid Hormone and Appetite Regulation--Fasting



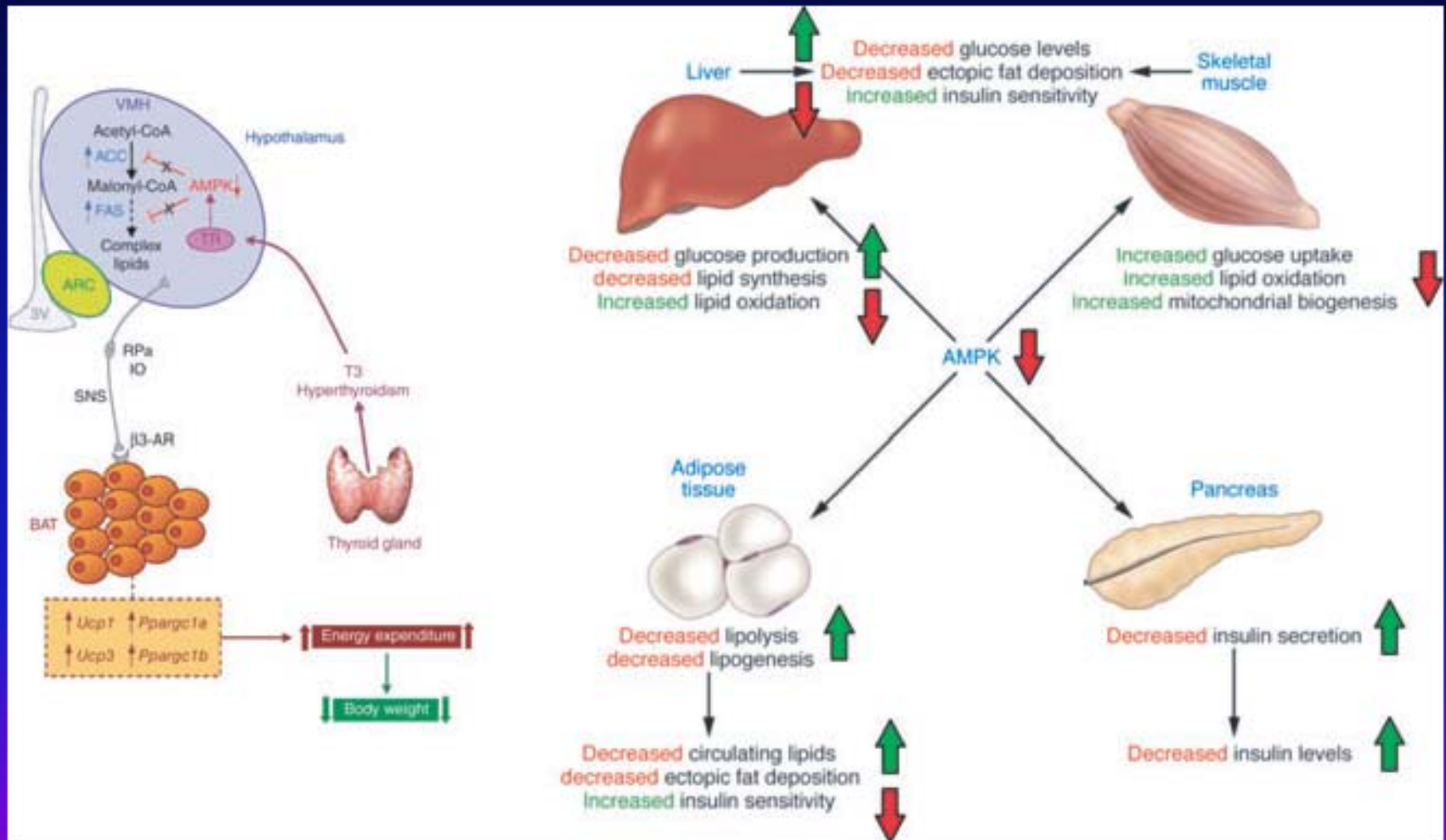
# Thyroid and Leptin



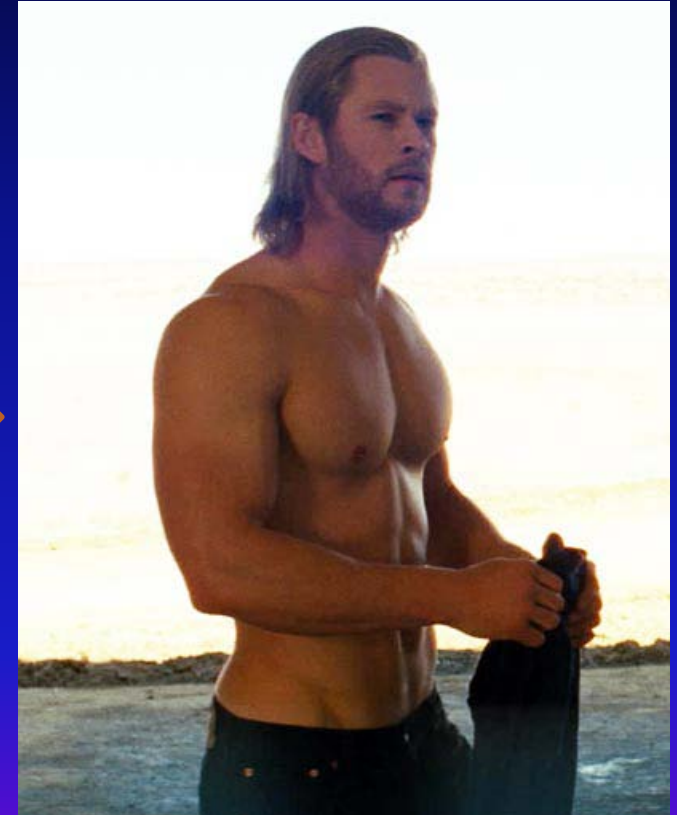
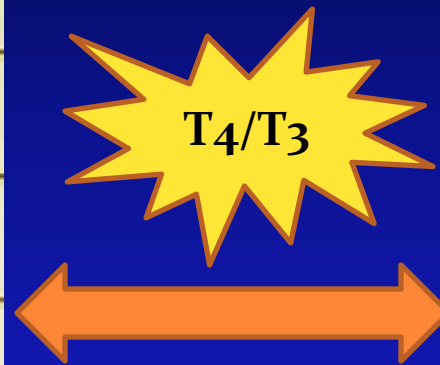
# Thyroid Hormone and Ghrelin

- Ghrelin (unacetylated): Anti-leptin action
  - Levels are low in obese state
  - Stimulates food intake and adiposity via activation of NPY and Agouti Related Peptide
  - Stimulates GH release
  - Levels are inversely related to T<sub>3</sub> levels
  - Modulates insulin sensitivity
  - Effects islet cell survival and proliferation

# AMPK: Cellular Energy Sensor



# Thyroid: Miracle Cure or Scapegoat?



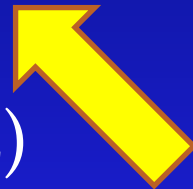
# Thyroid: Miracle Cure or Scapegoat?



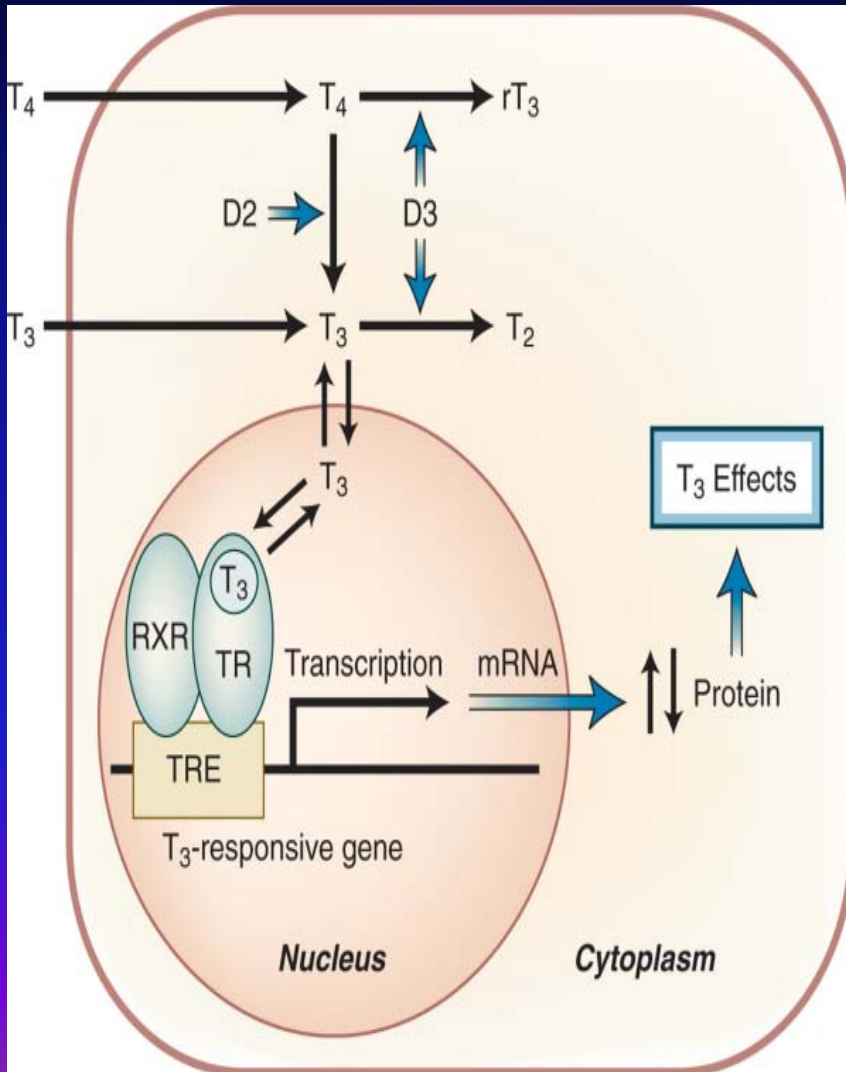
however . . .

# (over)Simplified Clinical Tools

TSH  
(0.5-5.0 mU/L)



# Thyroid Hormone Actions/Targets

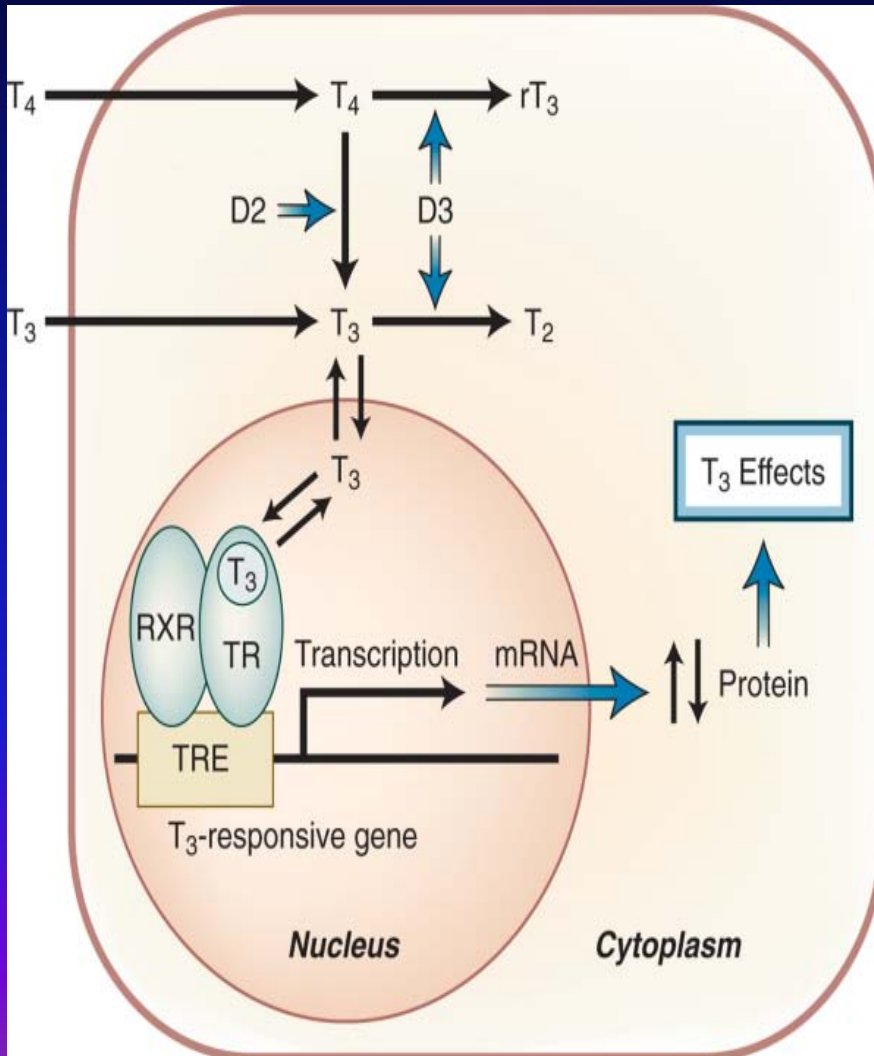


- Obesity-thermogenic
- Hypercholesterolemia
- Heart failure
- Impaired cognition
- Thyroid cancer
- Affective disorders

Ribeiro, Thyroid 2008

Williams Textbook of Endocrinology, 11<sup>th</sup> ed

# Thyroid Hormone Actions/Targets



- Bone
- Heart
- Liver
- Muscle
- Brain
- No FDA approved targeted therapies (yet): TR $\alpha$ /TR $\beta$  receptor

# Thyroid Mimetics

- TR $\alpha$ /TR $\beta$  effects
  - Triatrol and 3,5-diiodothyropropionic acid (DIPTA)—worsened heart failure (increased HR and bone turnover)
- TR $\beta$  specific effects
  - Primary lipid lowering
  - Calorigenic effects

# Thyroid Mimetics

- **TR $\beta$  specific effects**
  - **Primary lipid lowering**
    - **Sobetrome** –phase 1 22% reduction LDL-C
    - **Eprotrome**
      - LDL-C and Lp(a) reduction
      - Combo with statin in heterozygous FH
      - Combination with ezetimibe
      - Phase 3 trials under way soon. . .

# Can we answer these questions?

Amy is a 32 year old female.

CC: weight gain  
Tempo: 35 pounds in 4 months

PMHx: Major Depression

SocHx: no exercise, specific diet, works 9 hours a day, single mother  
Drinks 3 beers per week

FMHx: Autoimmune thyroid disease

Twin sister

Meds: health food store stuff

“Will I gain more weight” maybe

“I know/I think it is my thyroid” maybe

“I don’t think I eat too much” maybe

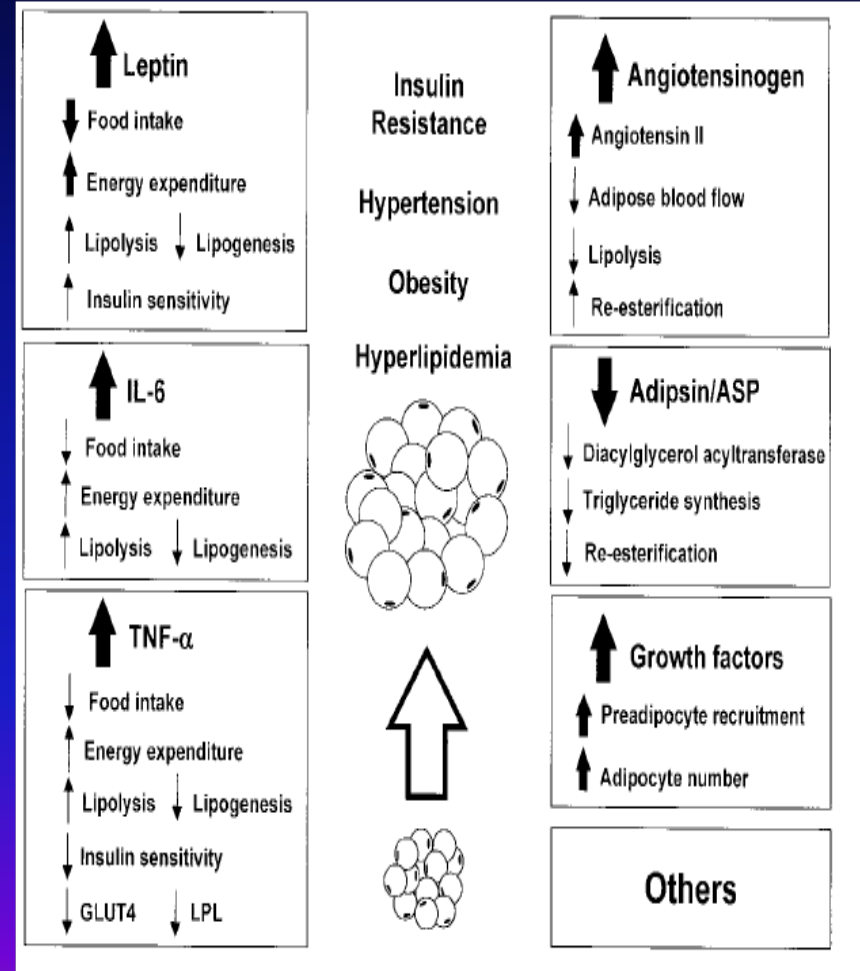
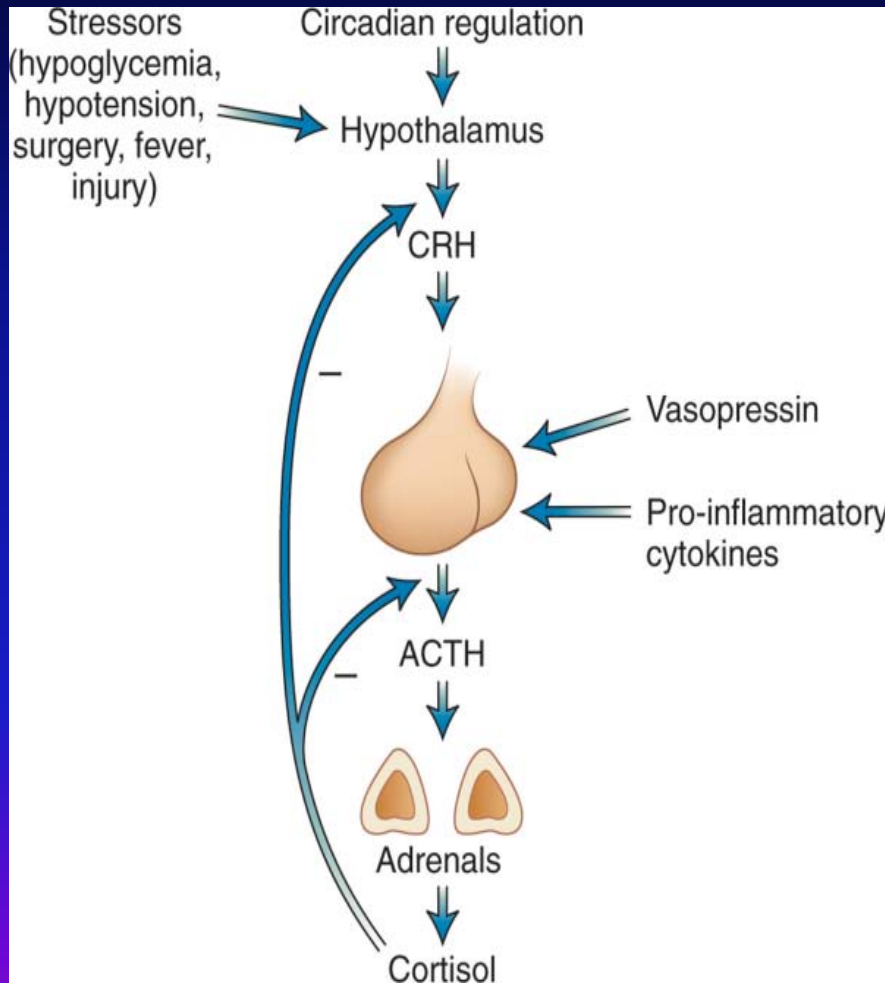
“Is there a pill for me” maybe/not yet



# Clinical Disorders of Hypercortisolism

- **Cushing's Syndrome**
  - ACTH dependent
    - Pituitary
    - Ectopic ACTH/CRH
    - Macronodular adrenal hyperplasia
  - ACTH independent
    - Adrenal adenoma or carcinoma
    - PPNAH/Carney's
    - iatrogenic
- **Pseudo-Cushing's**
  - Alcoholism
  - Depression
  - Obesity

# Clinical Disorders of Hypercortisolism



# Cushing's or Pseudo-Cushing's

- Central adiposity
- Supraclavicular fat pad
- Proximal muscle weakness
- Fatigue
- Hypertension
- Glucose intolerance
- Acne
- Hirsutism
- Menstrual irregularity



# Cushing's or Pseudo-Cushing's

**Amy is a 32 year old female.**

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**SocHx: no exercise, no specific diet, works 9 hours a day, single mother**

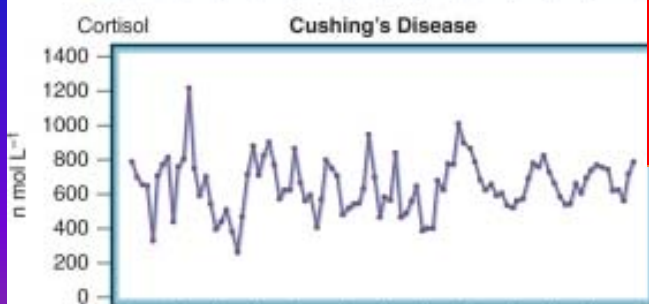
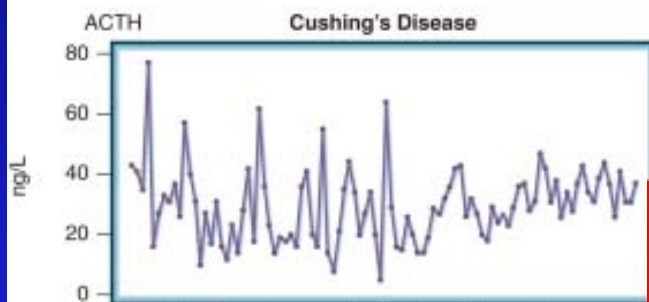
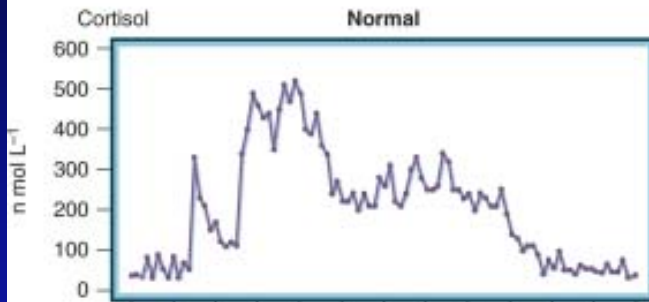
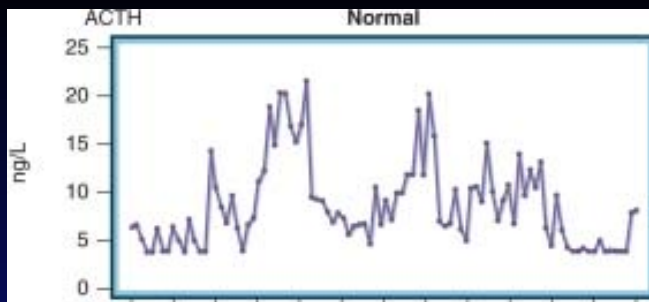
**Drinks 6 beers per week (report)—actual is 17**

**FMHx: Autoimmune hypothyroidism**

**Twin sister**

**Meds: health food store stuff (when asked directly)**





**Normal ACTH and cortisol dynamics**

**Increased pulse frequency and pulse amplitude in Cushing's disease**

**Non-suppressability of cortisol**

# Cortisol Metabolism in Obesity

**Cortisone  
(inactive)**

**11  $\beta$  hydroxysteroid  
dehydrogenase type 1**

**Cortisol  
(active)**

- Cortisol levels are normal or reduced in obesity

- Cortisol levels determine fat distribution, especially visceral fat

- 11  $\beta$  HSD-1 is impaired in obesity

- No known interaction with thyroid hormone or insulin function

**Assumption: with increased cortisol activity, to maintain normal levels, then cortisol should have an increased net metabolic clearance rate**

Stewart, JCEM, 1999

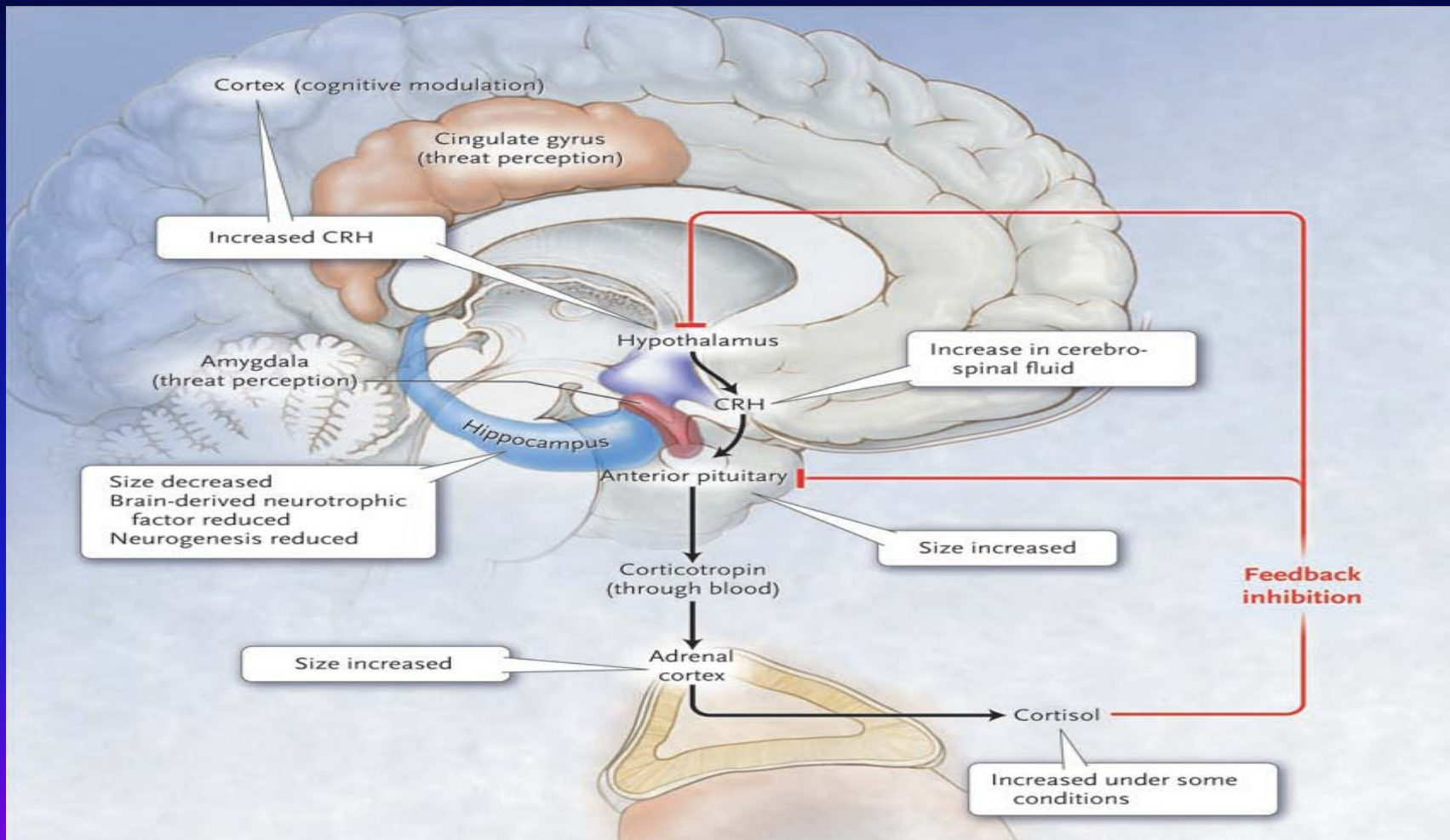
Tomlinson, JCEM, 2004

Yaniv, Intern J Obesity 2003

# HPA Axis: Alcohol

- Alcohol influence on HPA axis based upon duration of intake with exact mechanism unknown
- Malnutrition and associated depression stimulate HPA axis simultaneously
- No direct stimulus to adrenal glands
- Appears to be related to hypersecretion of CRF with pituitary non-responsiveness

# HPA Axis: Depression



# HPA Axis: Depression

- Mild elevations of cortisol and ACTH are present
- ACTH and cortisol levels are significantly higher in those depressed patients who have not lost weight
- DST is not diagnostic, but non-suppression of cortisol post therapy for depression predicts poor prognosis
  - Suppression of neurogenesis
  - Hippocampal atrophy

Pfohl, et al. Biol Psychiatry 1985

Ribeiro , Am J Psychiatry. 1993

# Cushing's Screening

- **Screening**

- 1 mg or 3mg overnight dexamethasone suppression test

- Cutoff  $<1.8$  mcg/dl preferred due to sensitivity
    - Anticonvulsants can cause false positive (accelerate hepatic metabolism of dexamethasone)
    - Testing measures suppression of autonomous adrenal function

# Cushing's Screening/Confirmatory Testing

- **Confirmatory**
  - 24 hour urinary free cortisol
  - Midnight salivary cortisol measurement
  - Serum ACTH and cortisol
  - 2 day 2mg dexamethasone suppression
  - Dexamethasone-CRH testing
  
  - Rec: 3.9: Repeat if needed . . .

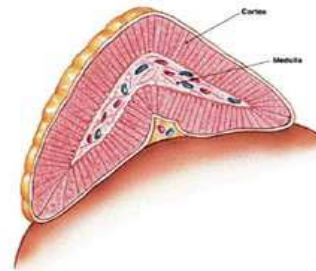
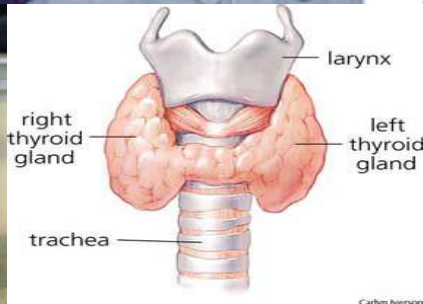
# Diagnosis: Cushing's Disease



\*\*\*\*\*NOTE\*\*\*\*\*

Case is not typical, but illustrates complexity of clinical obesity:

- Genetics
- Endocrine impact
- Lifestyle
- Medications/Alcohol
- Psychiatric Health
  - Diagnosis
  - Therapy



Carlym Iverson



# Clinical Take Home Points

- Continue to leverage therapeutic lifestyle changes
  - We don't get paid for it, but we are paying for it!
- Optimize thyroid hormone therapy
  - TSH (0.5-2.5 OR 1-2.5 mU/L based on age)
  - Use with empty stomach, water only
  - Am use or HS 2 hours post meal
- Consider concerns of potential mild thyroid failure
- Be aware of your limitations clinically—avoid inappropriate “over-therapy”

# Clinical Take Home Points

- Obesity phenotypes are difficult to distinguish from Cushing's disease and Pseudo-Cushing's
  - Muscular atrophy
  - Purple striae
- Correction of underlying confounders and patience with biochemical investigation, though extensive, can potentially be clinically rewarding (but slow)

# Conclusions

- **Weight gain is a greatly endocrine mediated condition, but not thyroid exclusively**
- **Complex milieu of interactions influencing the energy metabolism equation that exceed most clinical tools we have currently**
- **Thyroid hormone therapy is not the panacea of energy metabolism, but . . . an important part of it (and increasingly investigated)**

# Conclusions

- Our clinical understanding of obesity is constantly challenged by our molecular/in vivo understanding of endocrinology
  - Endocrine and paracrine signaling of endocrine hormones /energy signaling
  - Integrated sensors of metabolism require further understanding
  - Adapted/maladapted counterregulatory responses re-define a broader perspective of endocrine mediated weight gain