Leptin & Glucose Metabolism

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Overview

- IA CNS Control of Glucose Homeostasis
- IB Adiposity Signals: Insulin & Leptin
- IIA JakSTAT Pathway
- IIB IRS-PI3K Pathway
- IIIA Leptin & Glucose Metabolism
- IIIB CNS Sites & Mechanisms of Leptin Action
- IIIC Role of Hypothalamic PI3K→ review from insulin lecture
- IIID CNS Nutrient Sensing
- IIIE Leptin-Sensitive Neuronal Subsets
- IIIF Effect of CNS Leptin on Glucose Metabolism
- IIIG Neurocircuits for Leptin Reg of Insulin Sensitivity
- IIIH Indirect Effects of CNS Leptin on Glucose Metabolism
- VA Leptin Resistance
- VB Physiological Relevance
- VI Conclusions

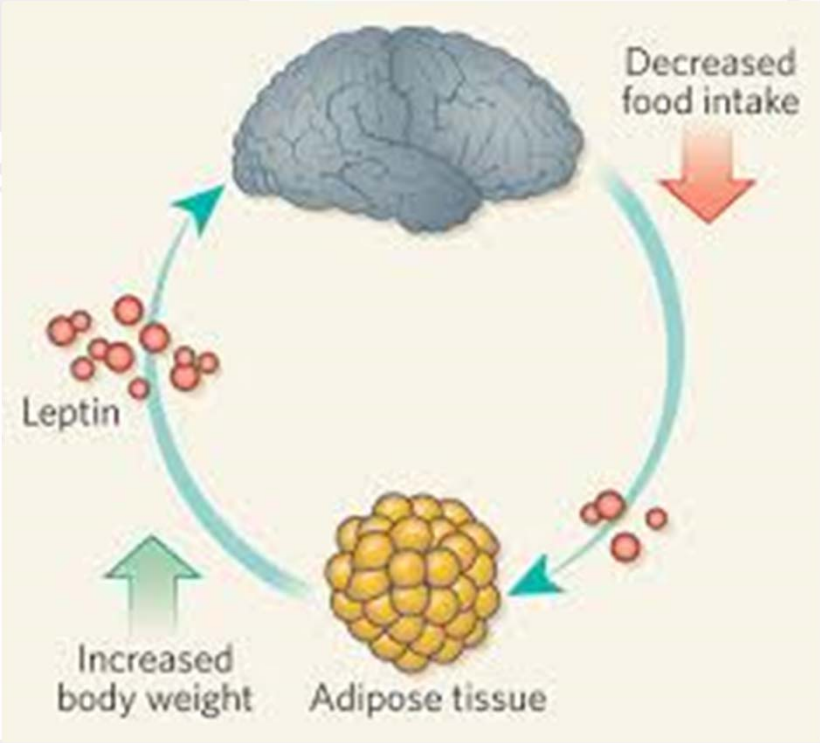
Leptin Basics

-Maintains the body's normal energy balance

-Increased leptin will decrease food intake and increase energy expenditure

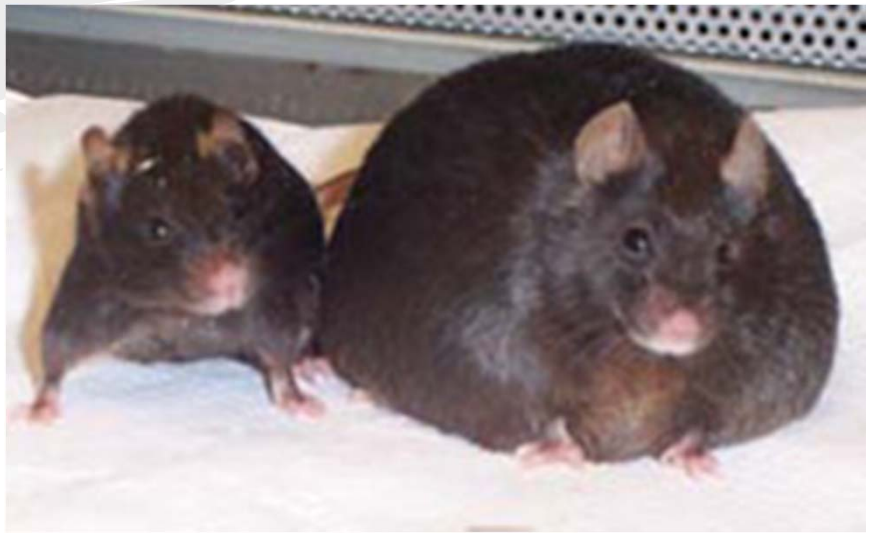
-Levels are proportional to body fat (adipose tissue)

-Can act to increase OR decrease plasma glucose depending on body's needs



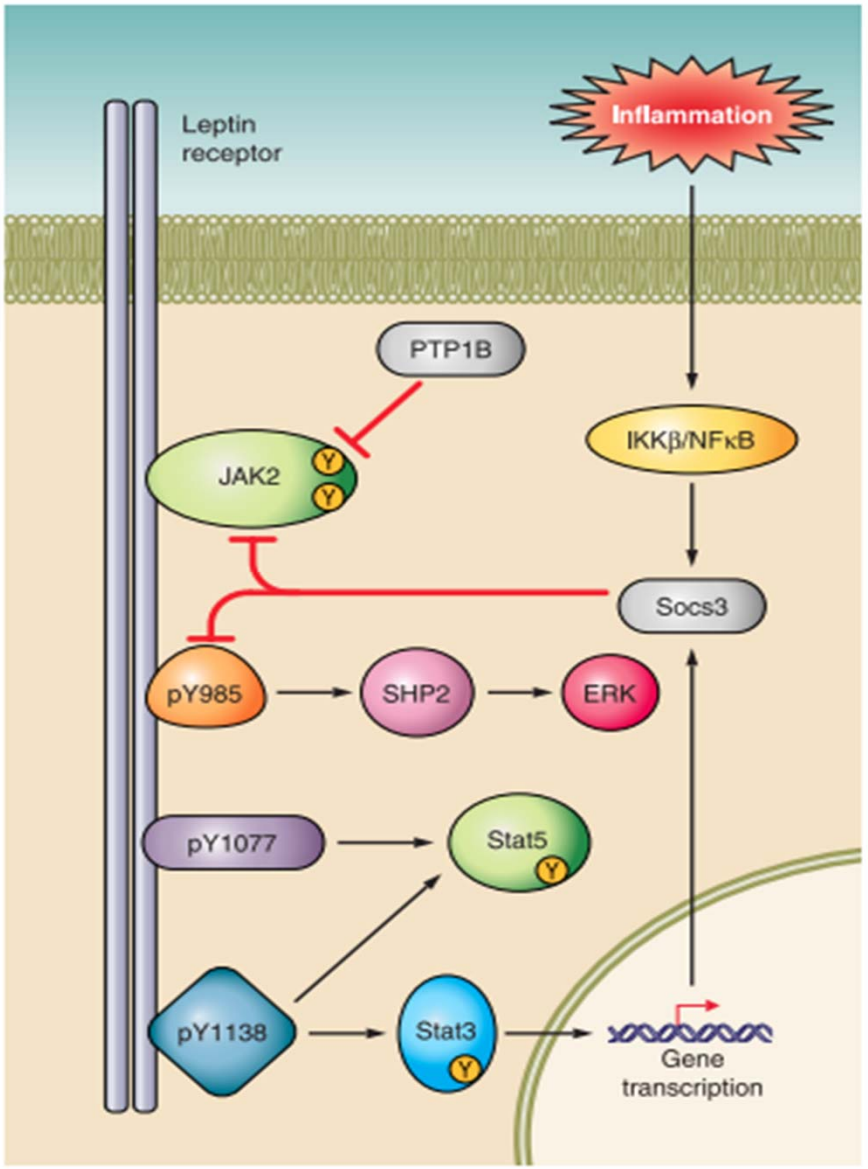
IA /IB: Insulin and Leptin: CNS Control of Glucose Metabolism

- Insulin and Leptin give info to CNS about long term energy stores
- Ob gene: in adipose: encodes leptin
  - –Ob/ob mice have obesity, leptin administration in CSF= reduced food intake and body weight
  - –In humans subjected to weight loss, admin of leptin blocks reduction of SNS (encourages weight gain)



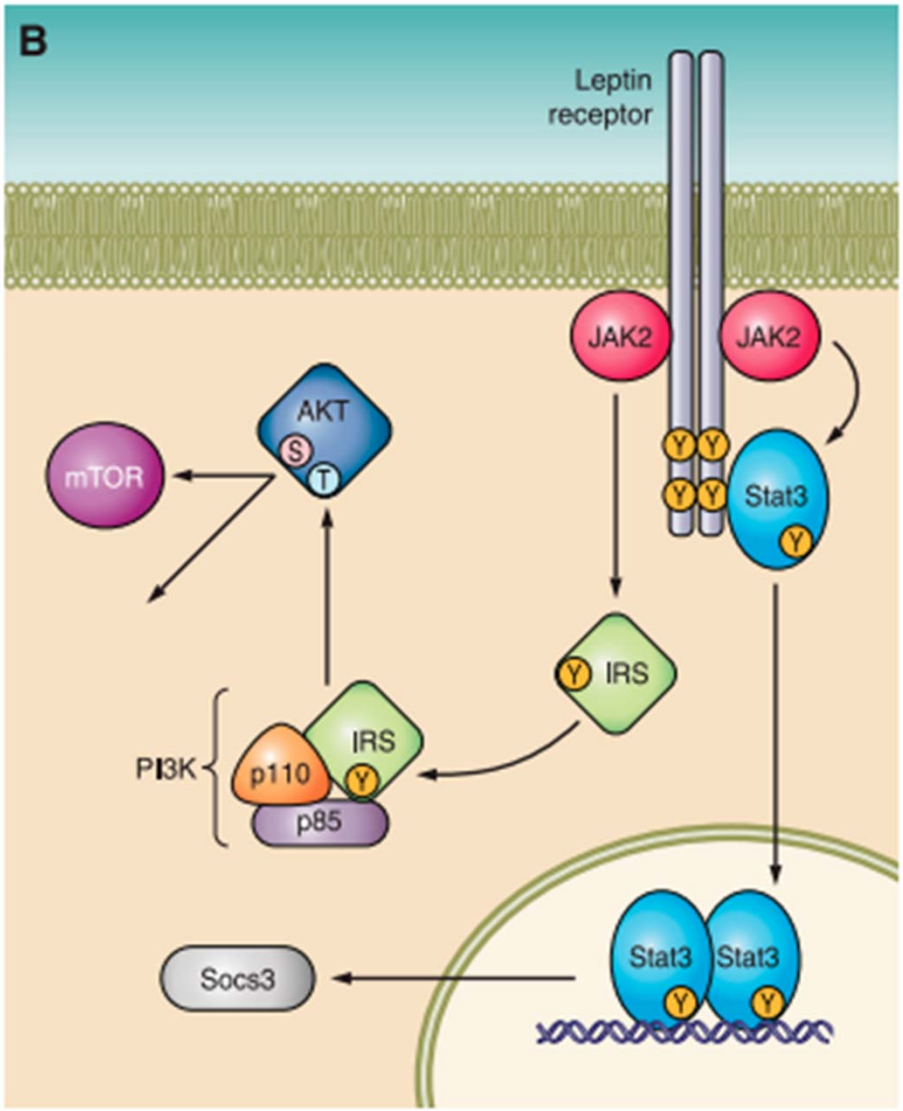
IIA- JakSTAT pathway

- Leptin Receptor=LepRb
- If you replace Tyrosine with serine:
  - –985→ Decrease food intake, decrease adiposity, increase leptin sensitivity (no SOCS binding.
  - –1077→Never tried! But we know STAT5 is important
  - –1138→ no STAT3= hyperphagia, Decrease energy expen.
- JAK phos-Independent pathway: truncate LepRb: we see delayed diabetes progression but all else remains the same



IIB: IRS PI3K Pathway

- Convergence of leptin and insulin?
  - –inhibition of PI3K= inhibition of leptin and insulin action on hypothalamus
- Both AFFECT glucose responsive neurons in ARC via kATP (there are different subsets with diff responses)
- SH2B1: facilitates Jak2 mediated IRS phosphorylation in response to LepRb activation
  - SH2B1 has been ID'd as obesity risk allele in humans



IIIA: Leptin and Glucose Metabolism

- At least two distinct ways leptin helps glucose regulation:
  1) Energy balance (food intake, expenditure)
  2) direct action on tissues/ genes
  - Leptin administration fixes hyperglycemia and hyperinsulinemia even when diffs in food intake are controlled

  Model: lipodystrophy= low leptin
  - Leptin therapy seems to preferentially help insulin signaling in liver (not other tissues) so it alone cannot normalize glucose
  - Glucagon (enzyme for gluconeogenesis) signaling is required for hyperglycemia and leptin is involved in decrease of blood glucagon

IIIB: CNS Sites and Mechs of Leptin Action

What Leptin does:

- suppresses hepatic glycogenolysis
- inhibits hepatic gluconeogenesis
- Enhances insulin prevention of glucose production without affecting (and sometimes even improving) insulin dependent glucose uptake
- Can do this even in the face of severe insulin deficiency

Where Leptin is found:

-ARC, VMH, DMN

-Block all receptors, then selectively reactivate→ ARC is the big player for leptin signaling effect on glucose independent of energy management

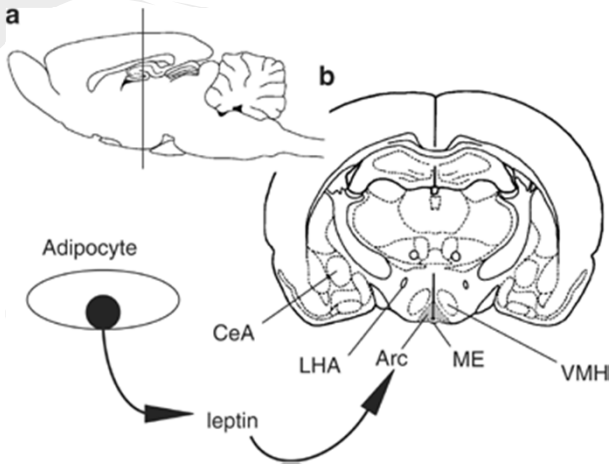
-if we inhibit PI3K ARC loses its effects

IIIE: Leptin-Sensitive Neurons

Arcuate nucleus (ARC):

1) NPY expressing: Stimulate food intake and inhibit energy expenditure (inhibited by leptin and insulin)
2) POMC: inhibit food intake, increase energy expenditure (stimulated by leptin, insulin mixed effects)

- Contradictory effects- possible subpopulations for insulin vs leptin



Ventromedial Hypothalamus (VMH):

- Leptin increases firing of steroidogenic factor (SF-1)→ promotes glucose uptake in tissues via SNS
- VMH is also implicated in glucagon secretion (we established ins section IIIA that leptin is involved in glucagon signaling)

IIIF: Effect of CNS Leptin on Glucose Metabolism

- **Leptin affects gluconeogenesis** through melanocortin pathway (MSH, also involved with insulin signaling) and **inhibits glycogenolysis** through a separate, melanocortin-independent pathway.
- **Influences hepatic genes and insulin** to reduce glucose production and increase glucose use
  - Inhibits SCD1 (lipogenesis) → alters insulin sensitivity
  - Upregulates IGFB2 (reduces blood glucose through increased insulin sensitivity)

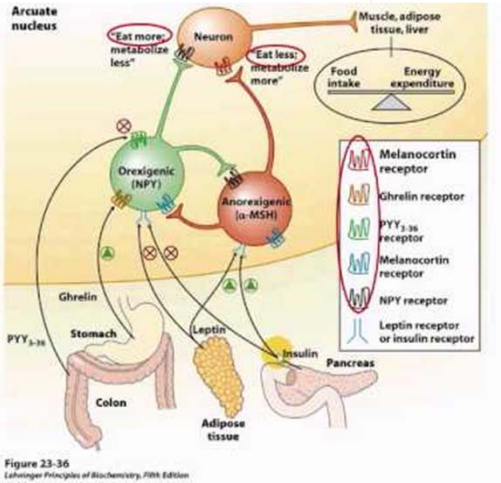


Figure 23-36

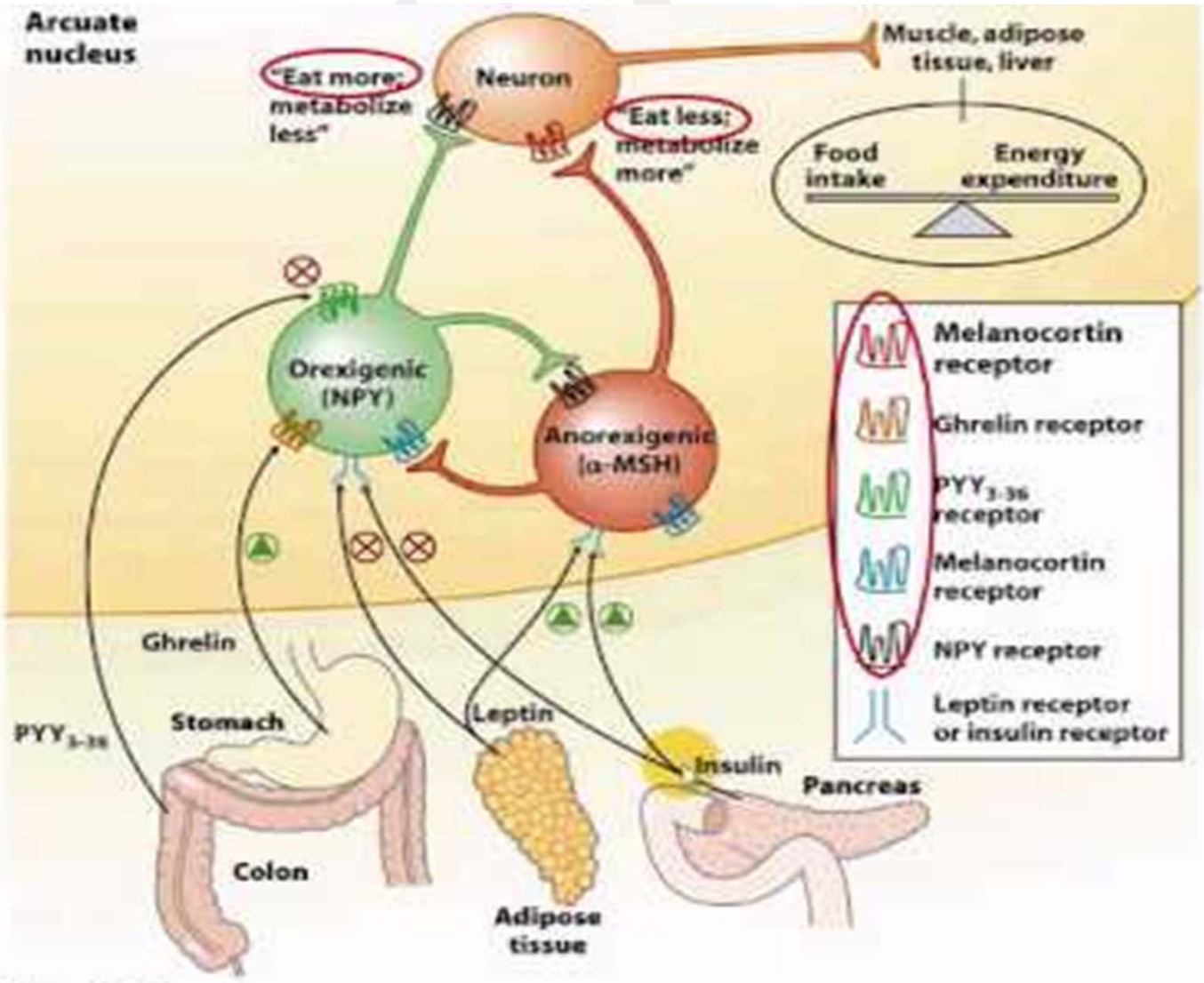
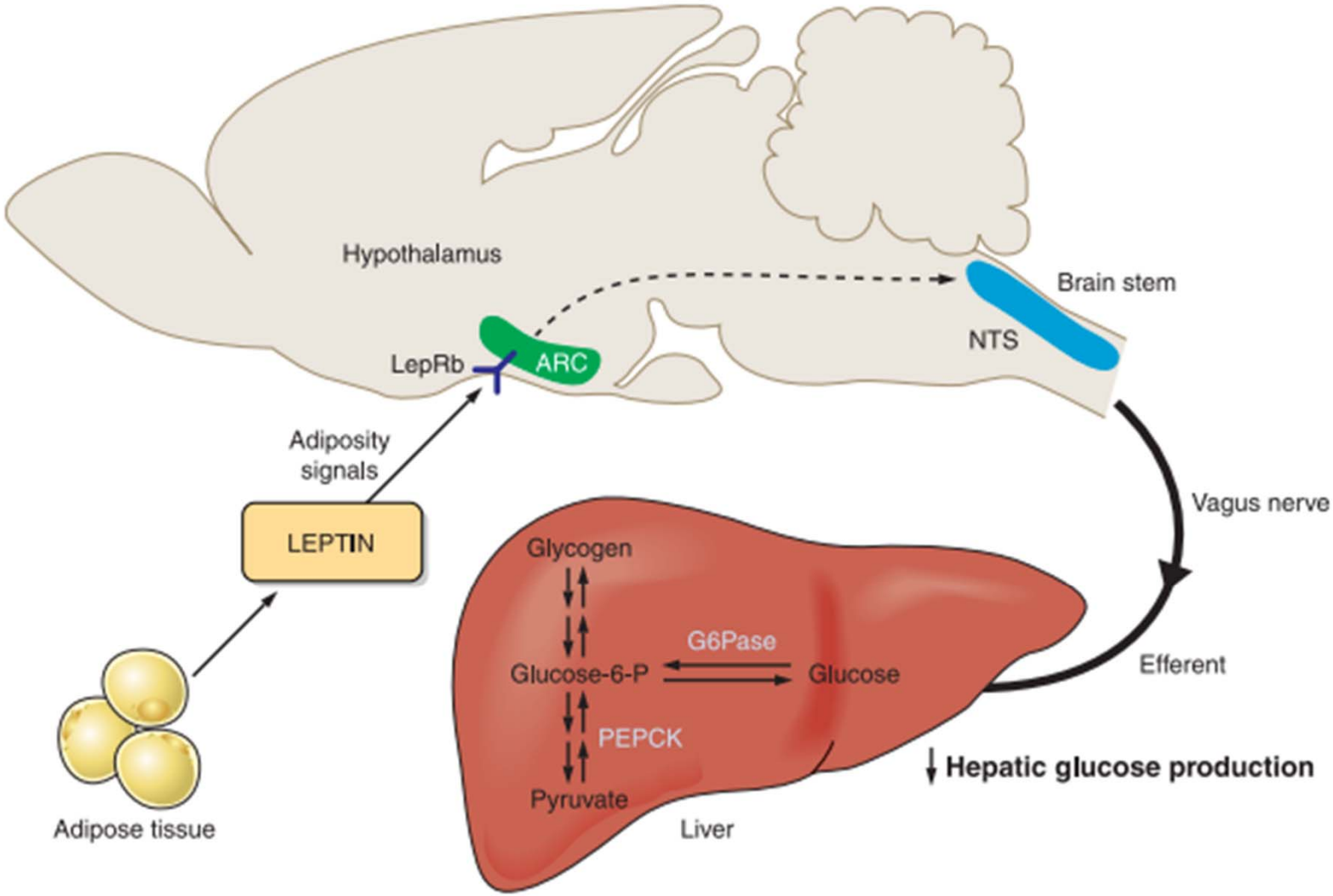


Figure 23-36
Lehninger Principles of Biochemistry, Fifth Edition

IIIG: Neurocircuits for Leptin Reg of Insulin Sensitivity

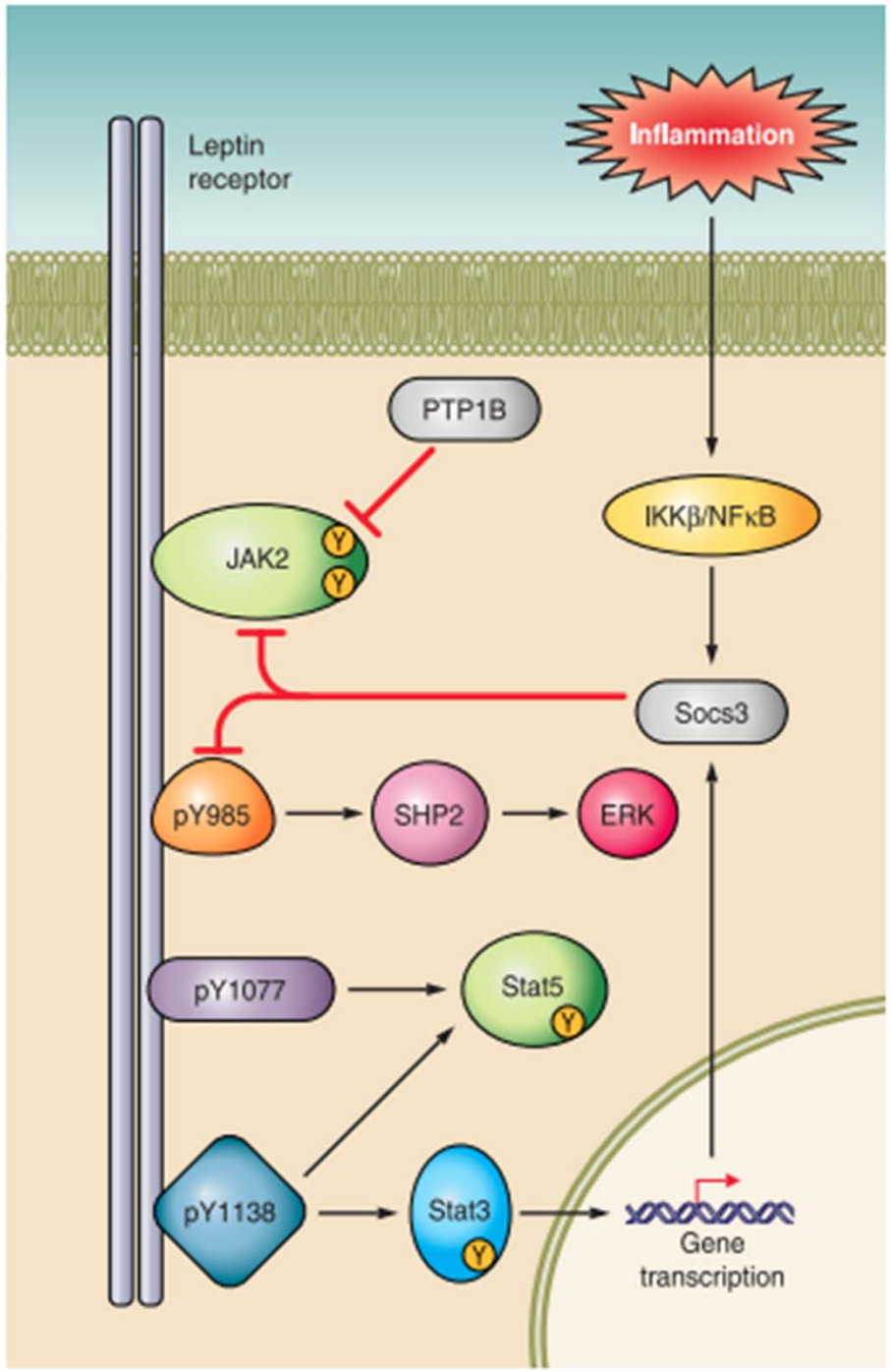


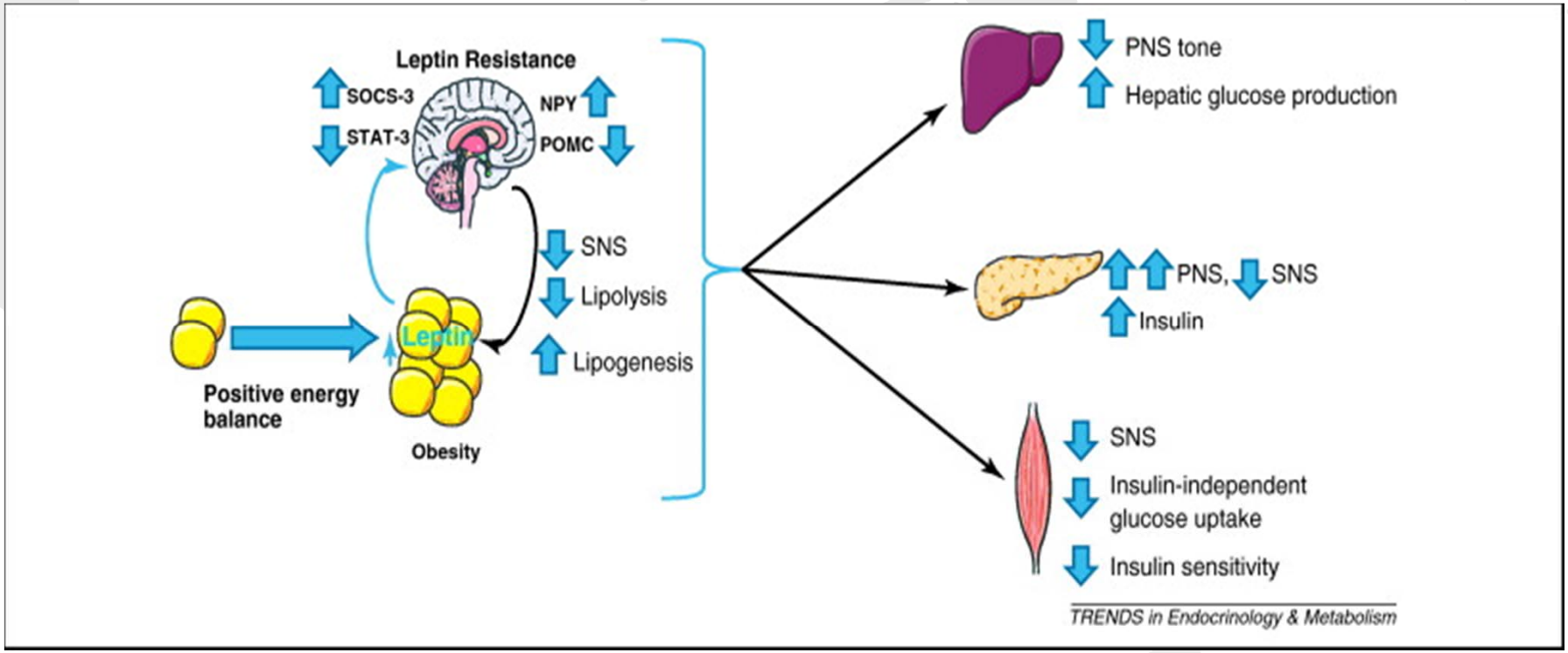
IIIH: Indirect Effects

Weight loss as little as 5-10% improves insulin sensitivity

Leptin Effect	**Mechanism**
-Regulate food intake -Glucose metabolism -Reproductive function	STAT3 signaling
-Adipose tissue metabolism -Energy regulation	Hypothalamic PI3K and SNS outflow

Leptin resistance can develop much the same as insulin resistance (Peter and the wolf)




Leptin Resistance
SOCS-3
STAT-3
NPY
POMC
SNS
Lipolysis
Lipogenesis
Leptin
Positive energy balance
Obesity
PNS tone
Hepatic glucose production
PNS, SNS
Insulin
SNS
Insulin-independent glucose uptake
Insulin sensitivity
TRENDS in Endocrinology & Metabolism

Conclusions

- Leptin and insulin have overlapping effects and may involve similar mechanisms (IRS PI3K signaling) but they act on different subsets of neurons and have varying effects based on physiological context
- Leptin influences glucose production (often by effects on insulin and hepatic gene expression) more than glucose uptake
- Leptin has effects on energy maintenance and glucose metabolism through separate and distinct mechanisms, most of which require further study to be fully understood