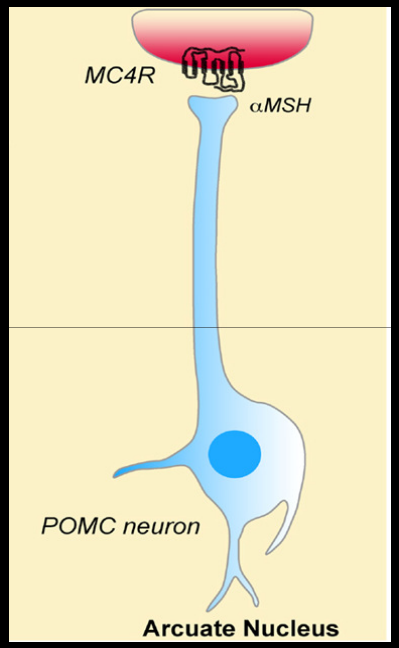
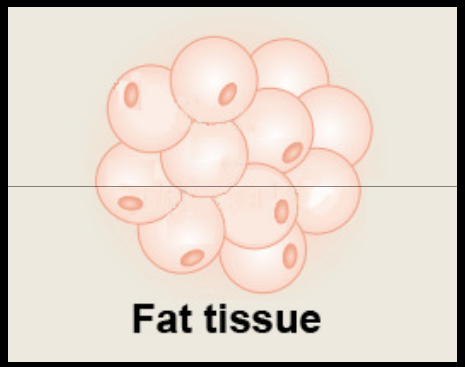
Melanocortin neurons and metabolic syndrome-associated sexual dysfunction



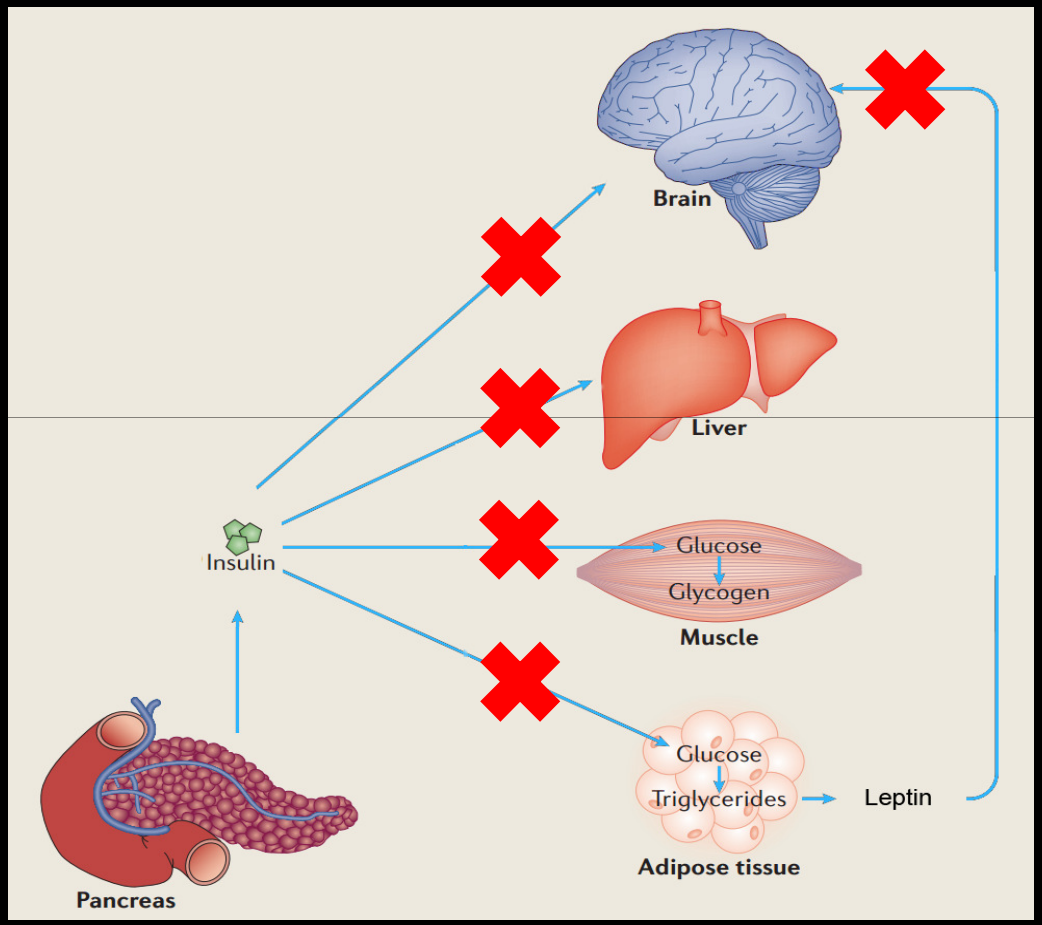
Jennifer W. Hill
Department of Physiology
University of Toledo

The metabolic syndrome consists of five risk factors for type 2 diabetes and heart disease



1. Abdominal obesity
2. High triglyceride levels
3. Low HDL cholesterol
4. High blood pressure
5. High fasting blood sugar

Obesity is a state of insulin and leptin resistance



Source: Leto and Saltiel, 2012

Obesity in men is associated with infertility



40% increased chance
of infertility

60% increased chance
of erectile dysfunction

Source: Saigal et al. 2006; Nguyen et al. 2007

Type 2 diabetes in men is associated with infertility



3 times more likely to
need fertility treatment

Three out of four men with T2D
develop erectile dysfunction

Source: Malavige et al., *2014; Mulholland et al. 2011*

Metabolic syndrome-associated sexual dysfunction



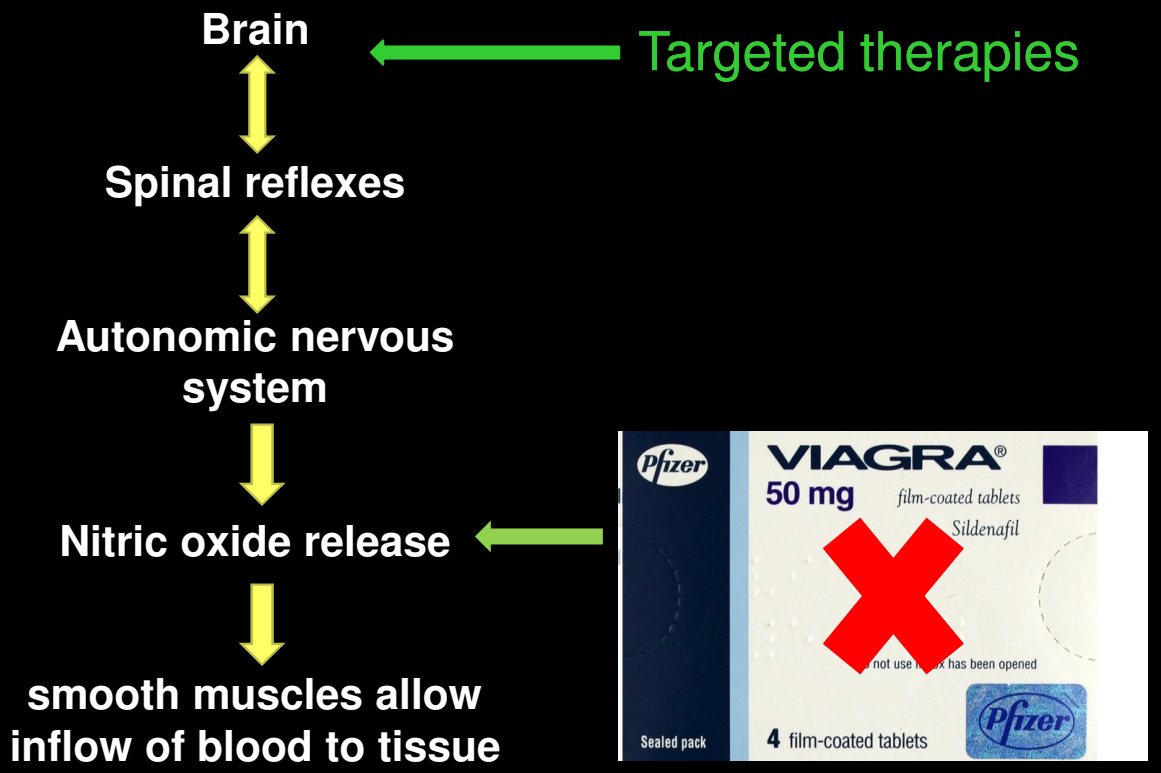
Why do obesity and T2D lead to infertility?

Half of men with type 2 diabetes do not respond to Viagra





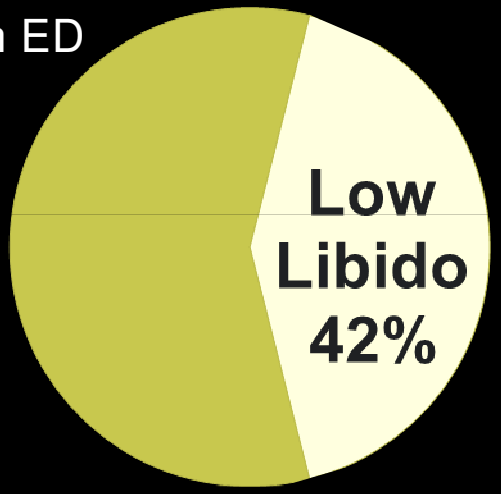
Erectile function starts in the brain



Men with ED often have decreased libido

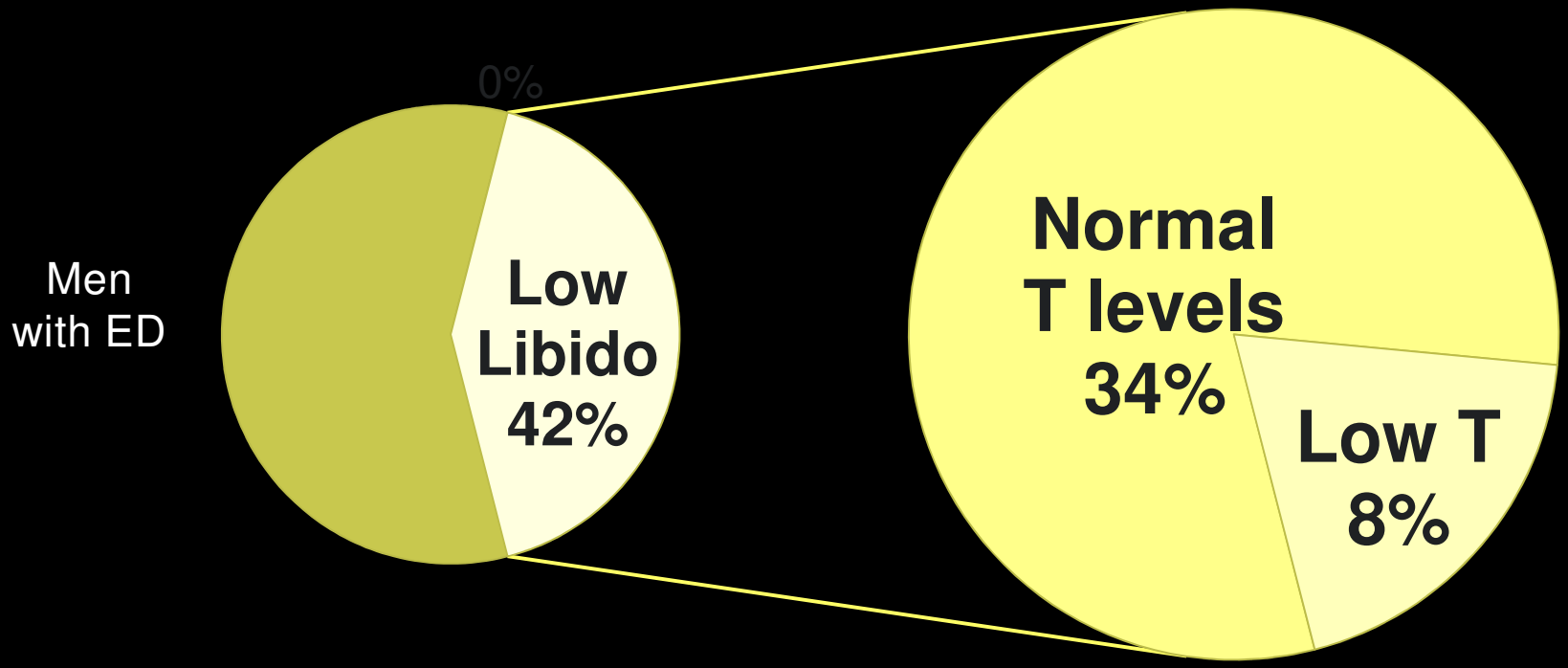


Men with ED



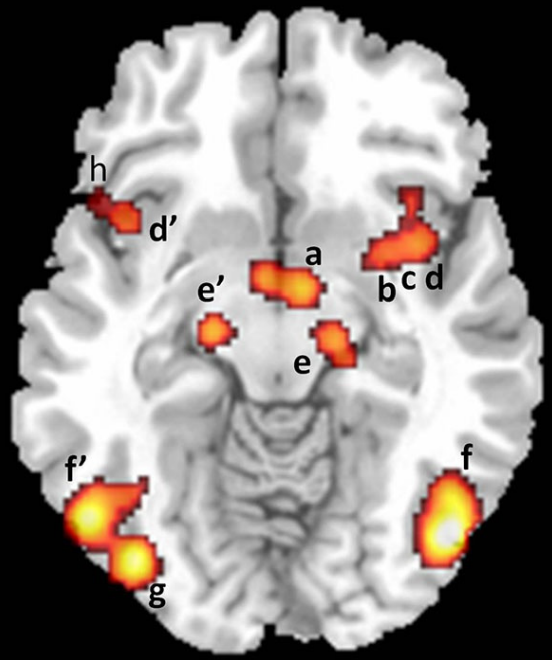
Source: Muezzinoglu et al 2007

Low libido is not usually due to low testosterone levels



Source: Muezzinoglu et al 2007

Libido may originate in the hypothalamus



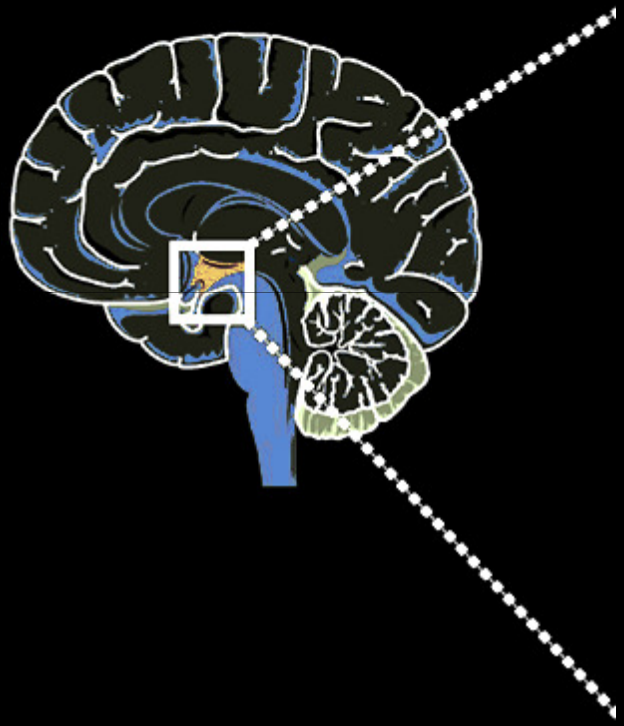
After viewing erotic stimuli, the hypothalamus is active

This activity is abnormal in patients with unexplained ED

- Premotor cortex = initiating behaviors
- Basal ganglia = anticipation of reward

Source: Stoléru et al., 2014; Montorsi 2003

The hypothalamus produces melanocortins



POMC

↓

ACTH

↓

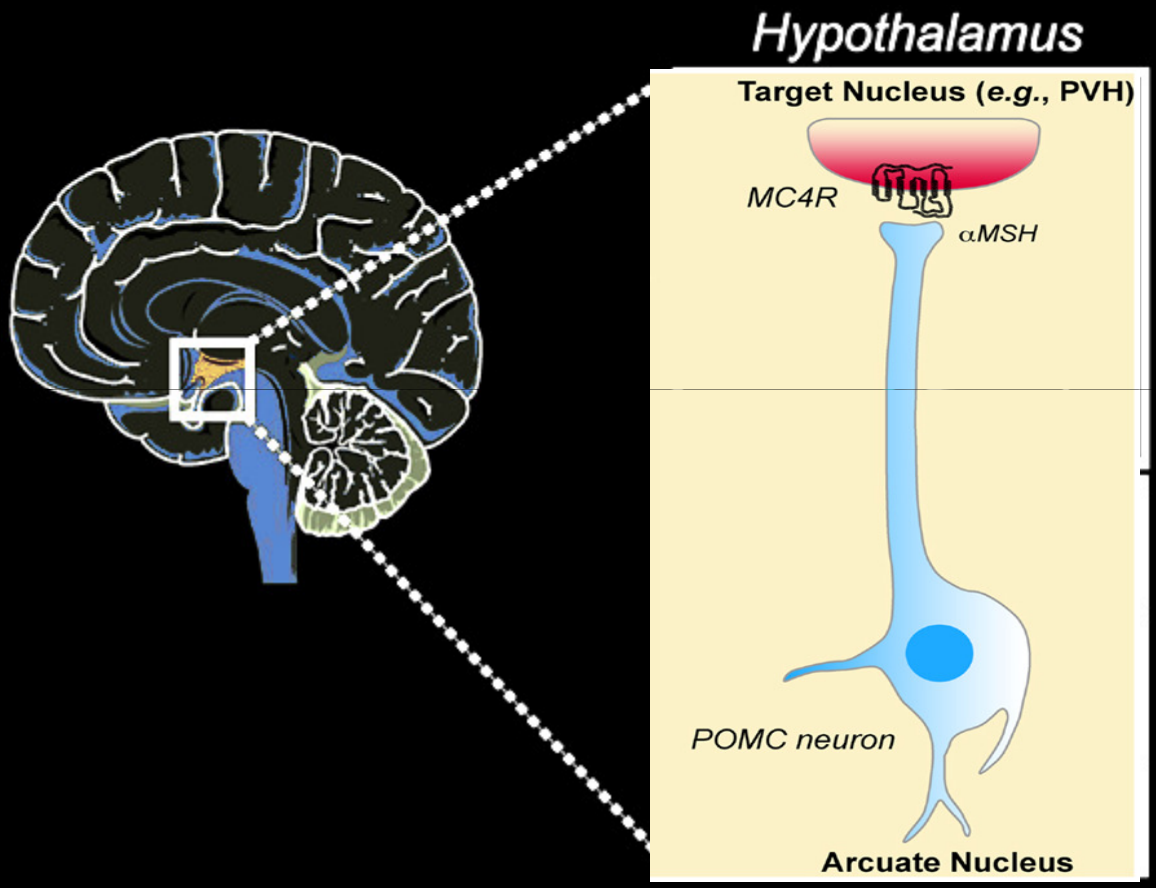
$ACTH_{1-17}$

↓

α-MSH

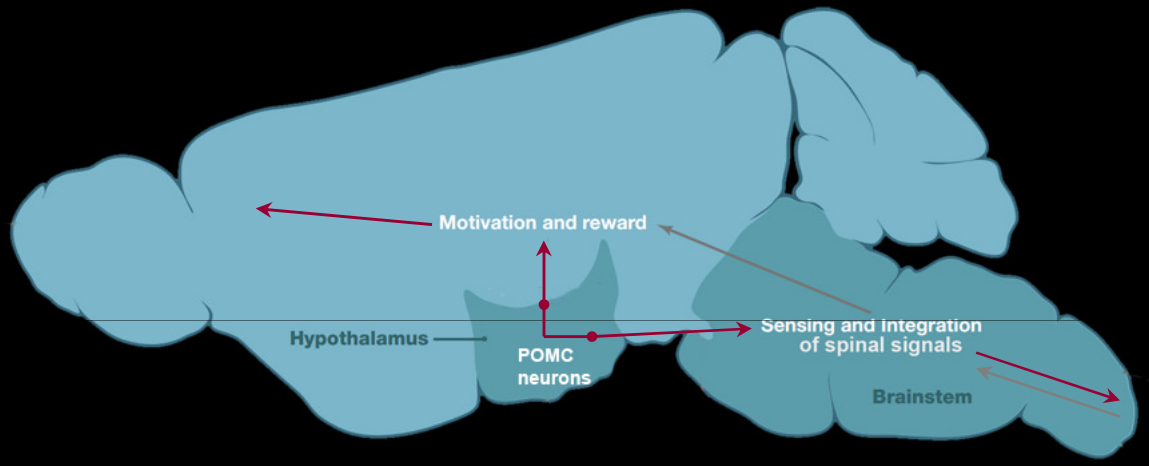
Source: Coupe and Bouret, 2013

α-MSH is detected in regions of the brain with MC3 and MC4 receptors



Source: Coupe and Bouret, 2013

A network of neurons respond to melanocortins



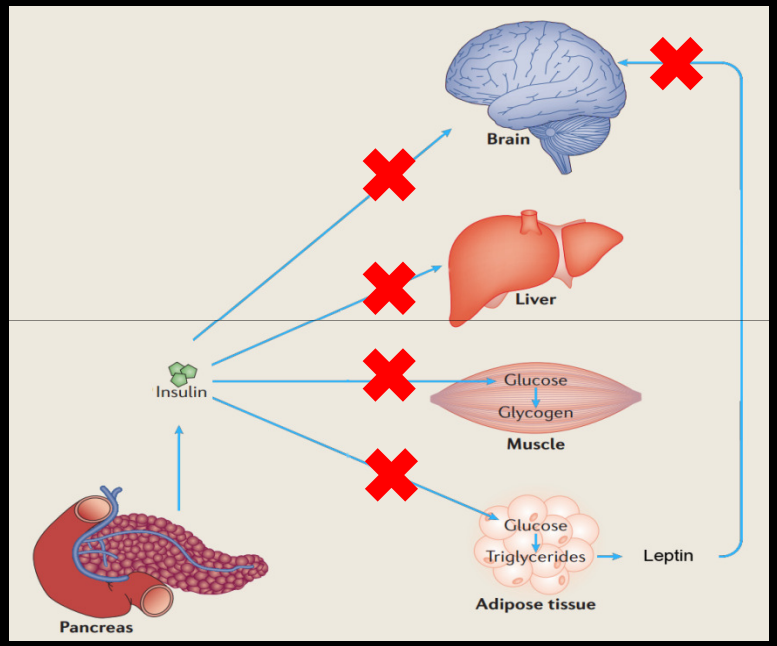
Mouse brain

Source: Myers and Olson 2014

α-MSH is involved in many functions

- Blood pressure
- Food intake
- Blood glucose levels
- Penile erection
- Libido
- Other behaviors

α-MSH



Hypothesis:

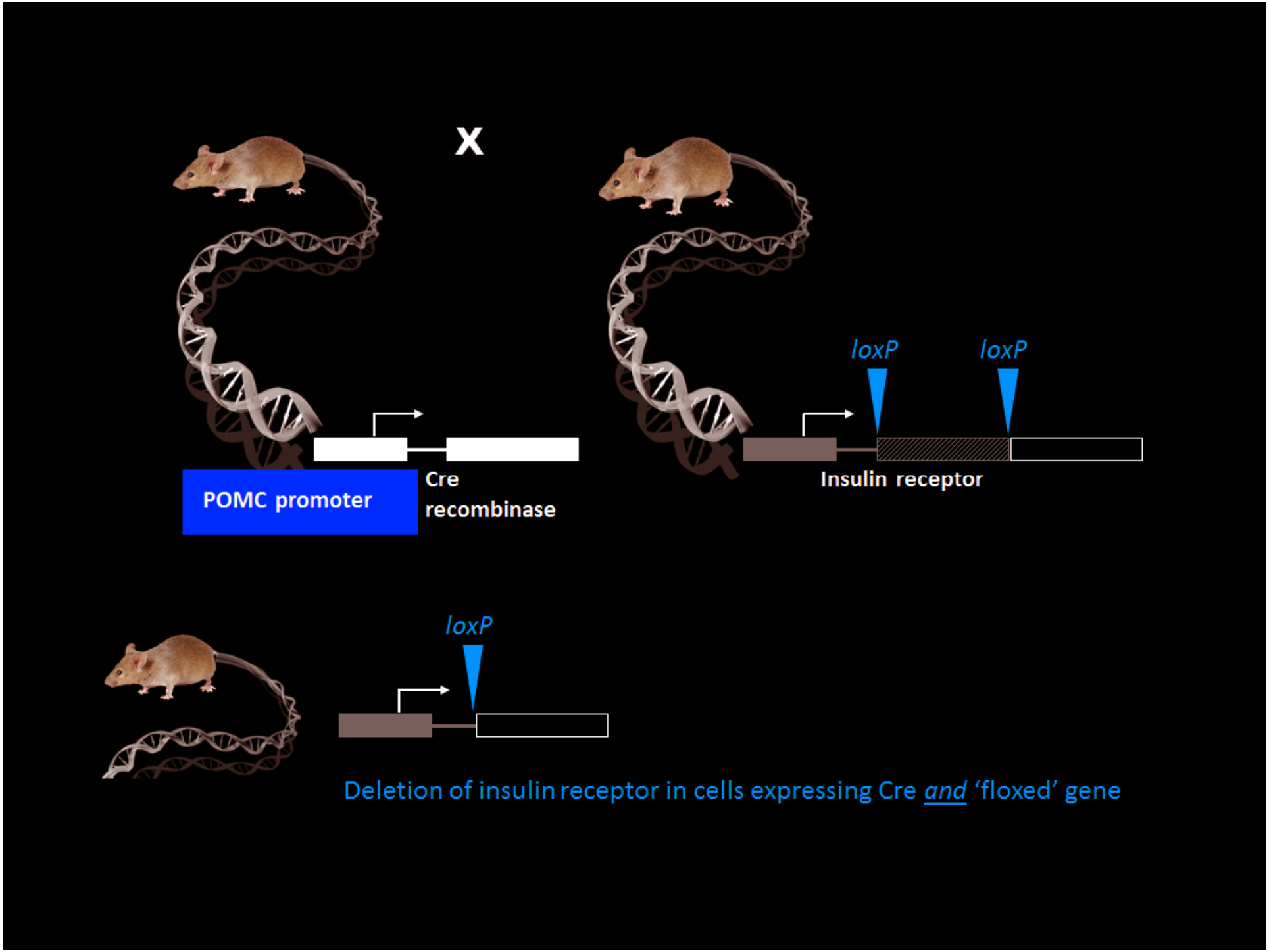
POMC leptin and insulin resistance
in obesity and T2D
impairs libido and erectile function

Creating a model of insulin and leptin resistance in POMC neurons





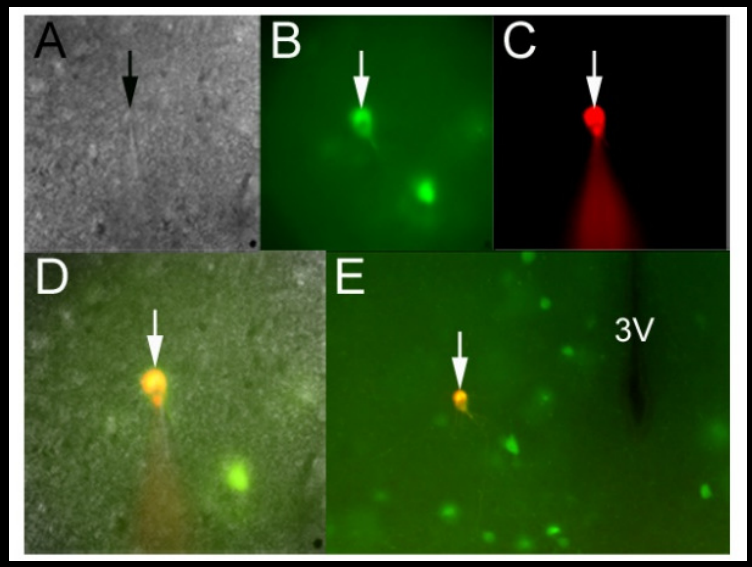
LepR/IR^{POMC} mice


x
loxP
loxP
POMC promoter
Cre
recombinase
insulin receptor
loxP
Deletion of insulin receptor in cells expressing Cre and 'floxed' gene

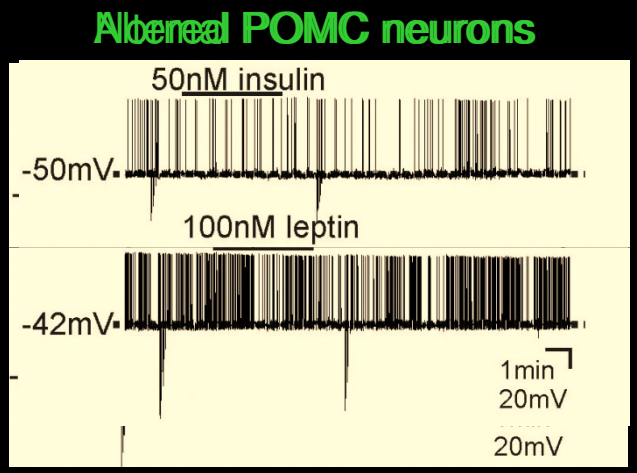
The activity of POMC neurons can be recorded

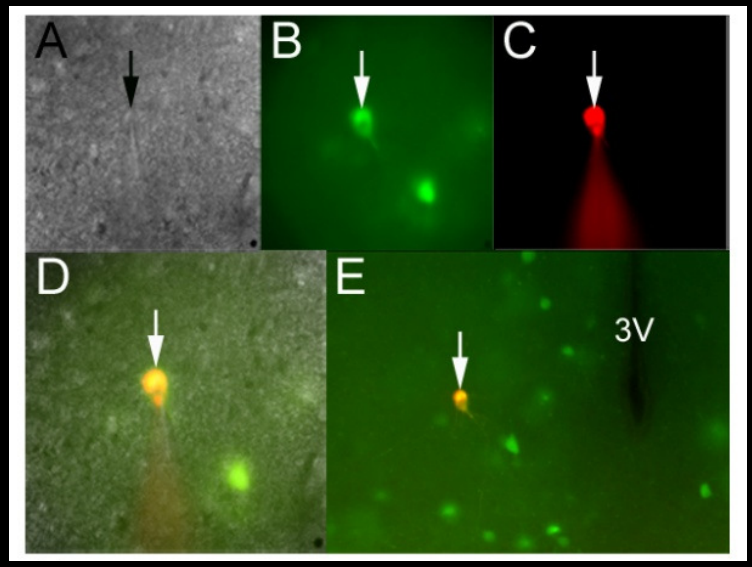


LepR/IR^{POMC} mice

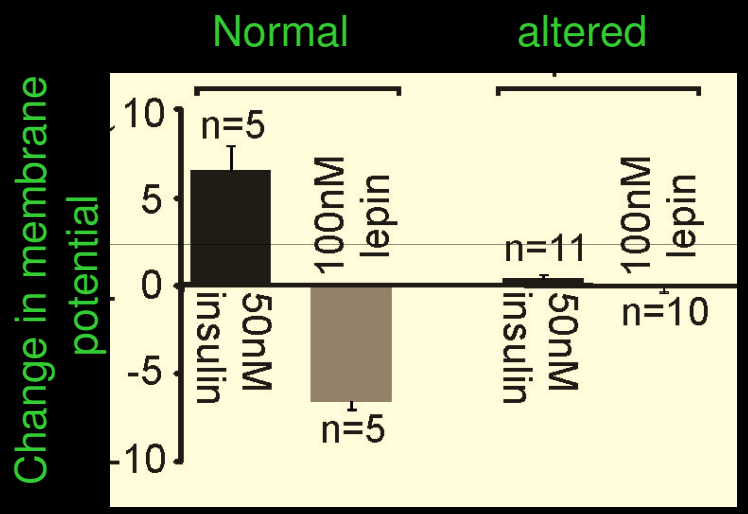


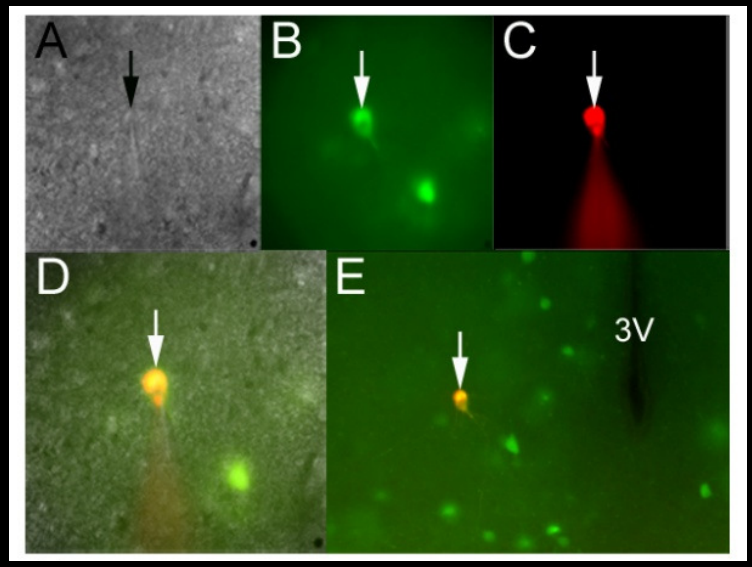
The activity of POMC neurons is changed





The activity of POMC neurons is changed

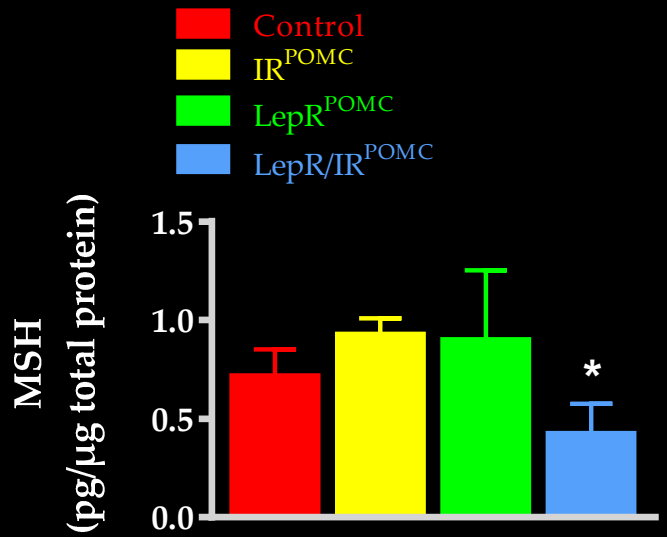




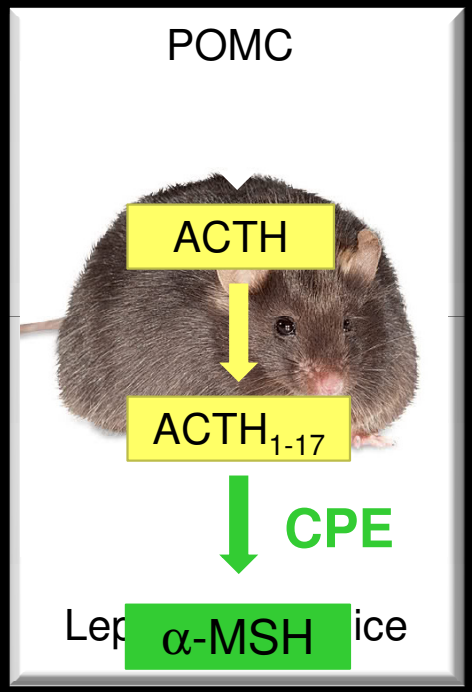
These mice produce less αMSH

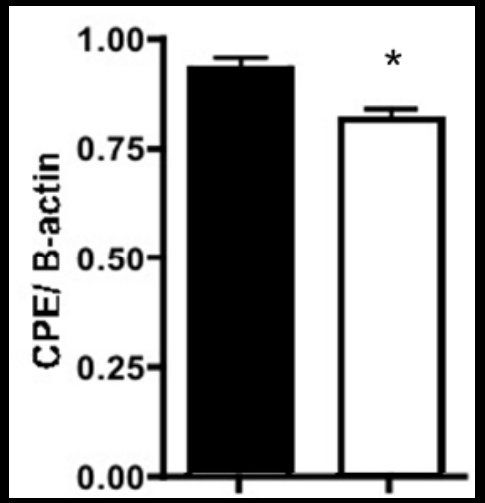


LepR/IR^{POMC} mice



These mice produce less of the enzyme Carboxypeptidase E



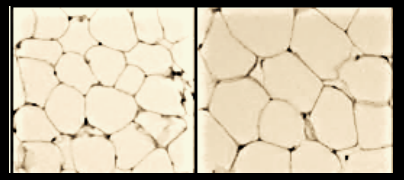


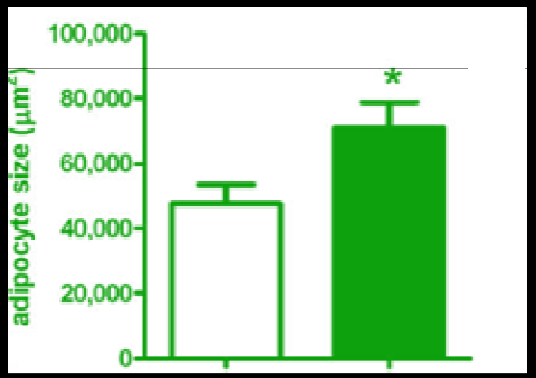
LepR/IR^{POMC} mice are fat



LepR/IR^{POMC} mice

Abdominal fat





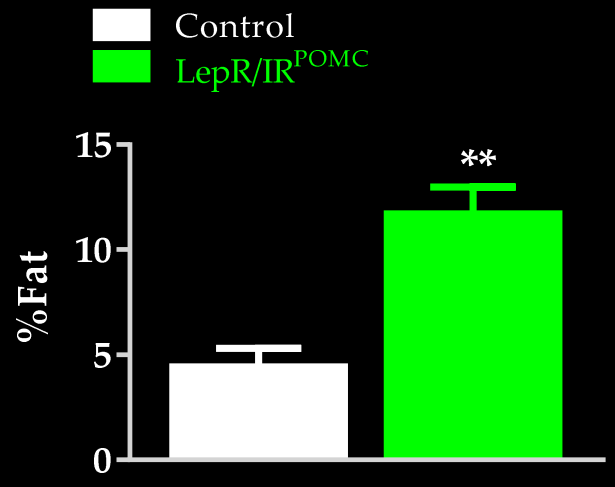
Normal LepR/IR^{POMC}

Source: Marino….Hill, 2012

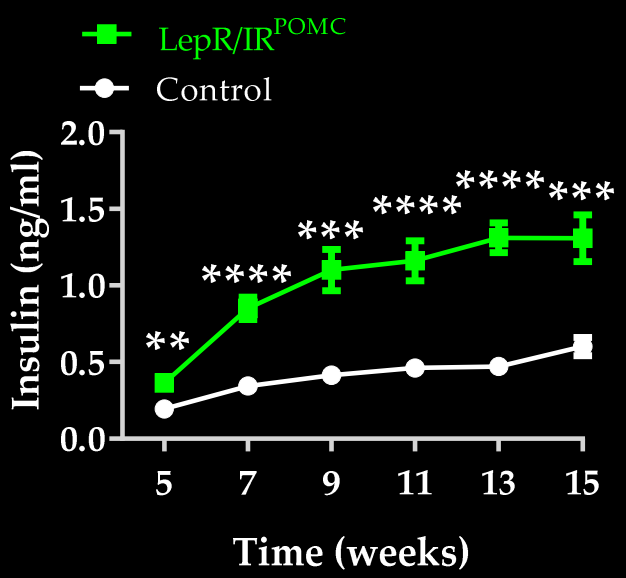
LepR/IR^{POMC} mice are fat

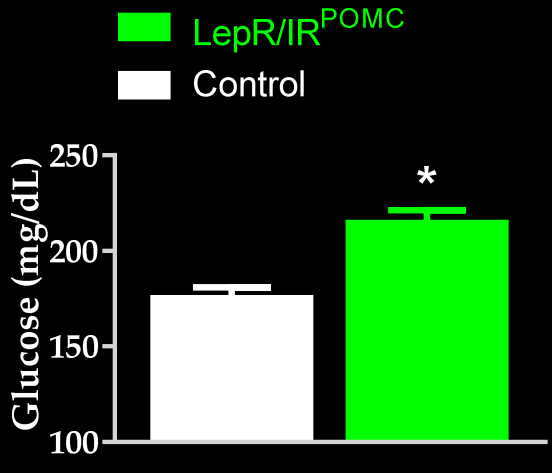


LepR/IR^{POMC} mice

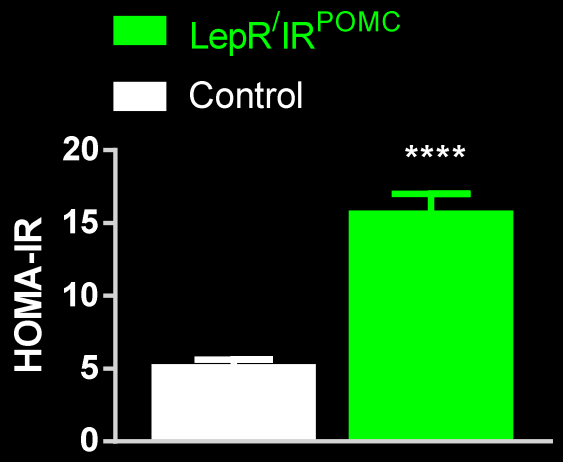


LepR/IR^{POMC} mice are hyperglycemic and insulin resistant





LepR/IR^{POMC} mice are hyperglycemic and insulin resistant



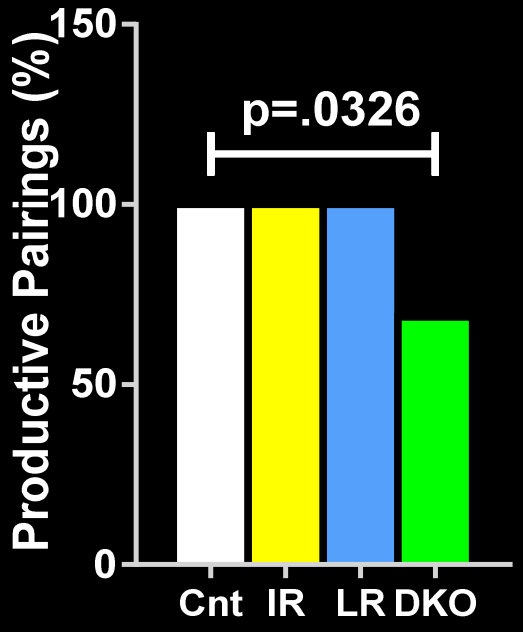
Are LepR/IR^{POMC} mice a model of metabolic syndrome-associated infertility?



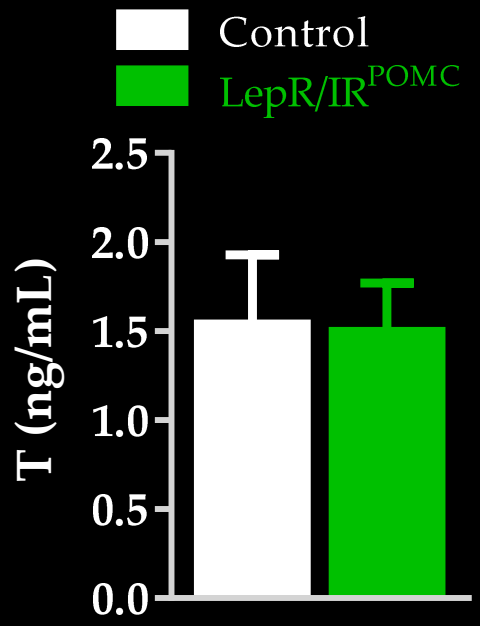
LepR/IR^{POMC} mice

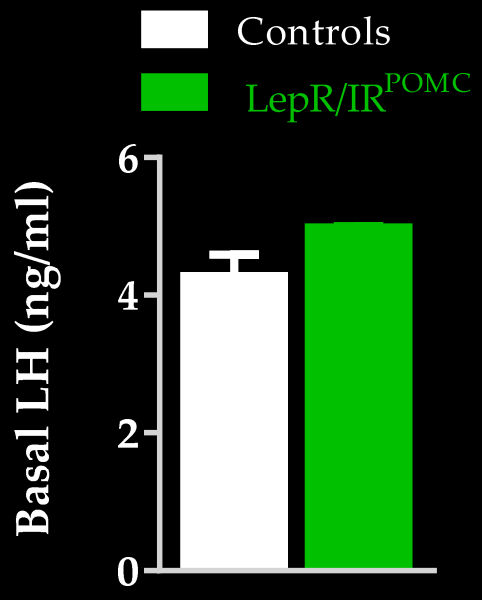
- POMC neurons have altered activity and αMSH production
- Obese
- Have “pre-diabetes”

LepR/IR^{POMC} mice have reduced fertility without low testosterone levels

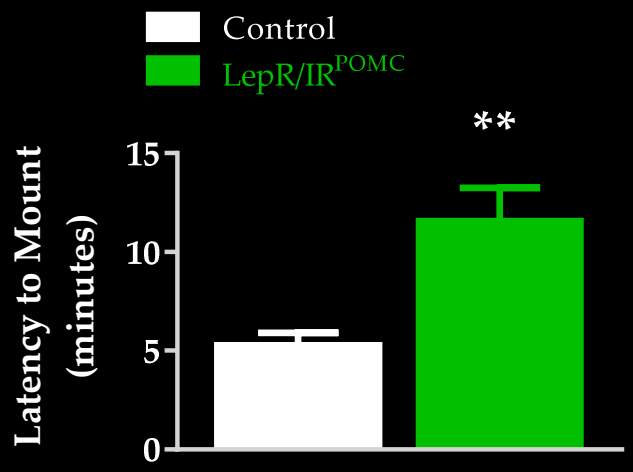


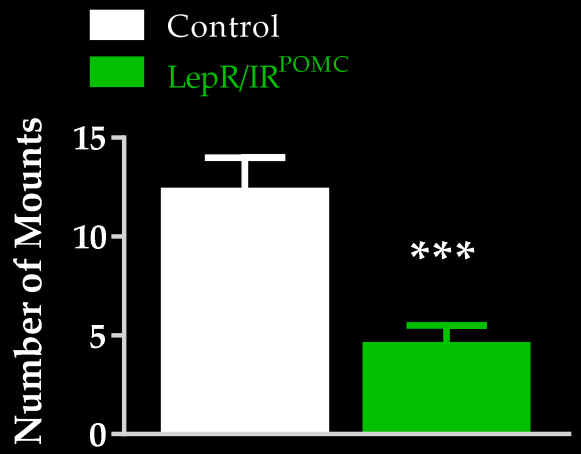
LepR/IR^{POMC} mice have reduced fertility without low testosterone levels



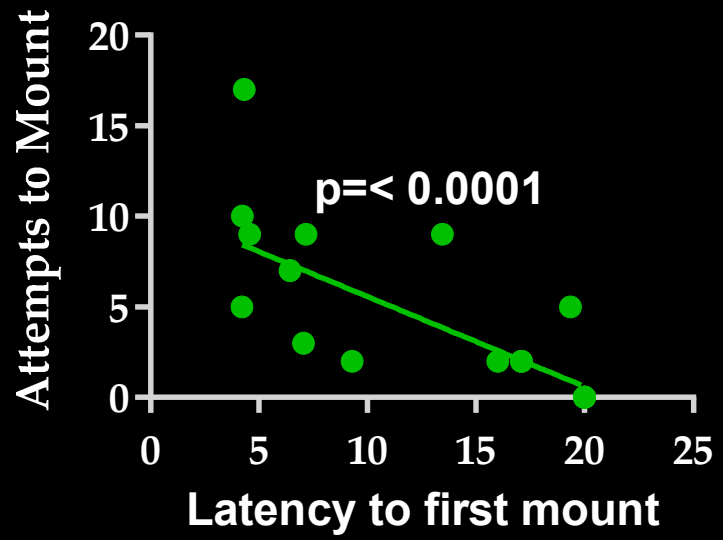


LepR/IR^{POMC} mice have low libido





LepR/IR^{POMC} mice have low libido



LepR/IR^{POMC} mice are a model of metabolic syndrome-associated infertility

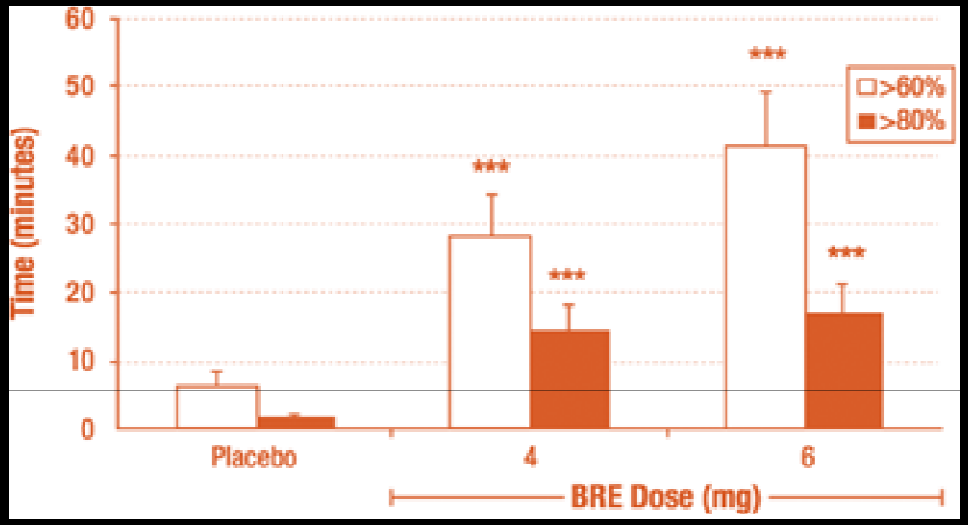


LepR/IR^{POMC} mice

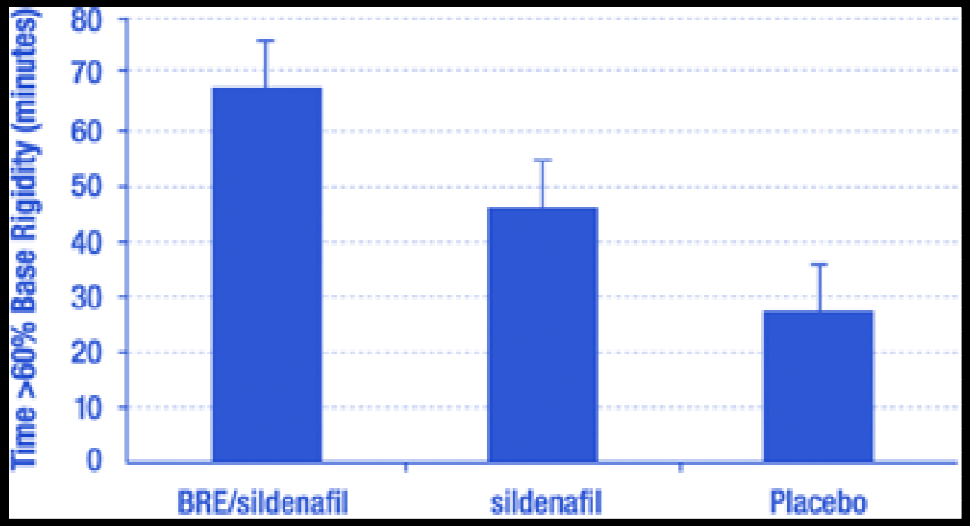
- POMC neurons have altered activity and αMSH production
- Obese
- Have “pre-diabetes”
- Have low libido
- Erectile dysfunction?

MC4R agonists are being developed as a treatment for erectile dysfunction

Bremelanotide is an MC4 agonist



-rigidity



Source: Hedlund, 2007

Side effects of α-MSH agonists

Raise blood pressure

Suppress food intake

Lower blood glucose levels

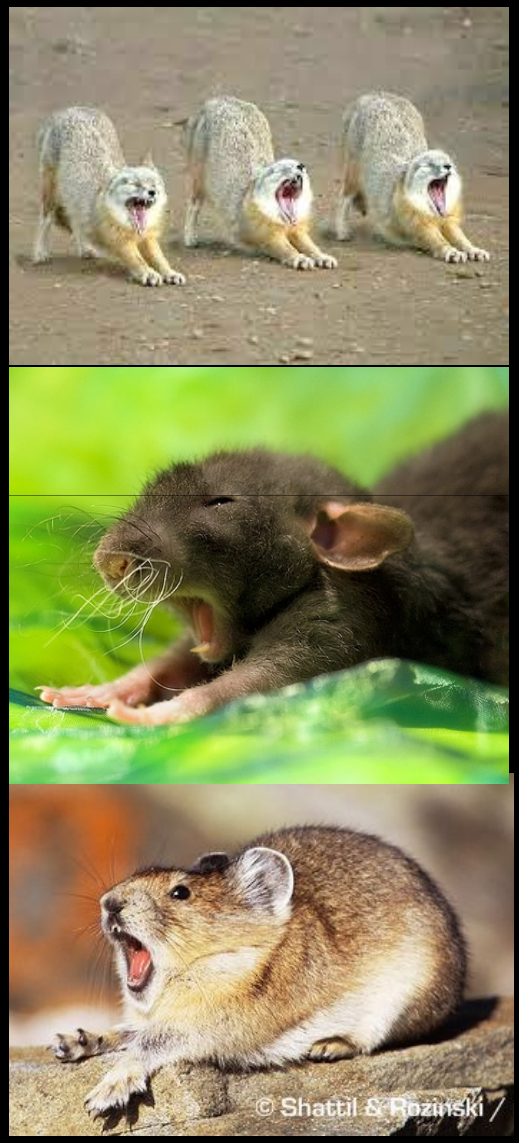
Induce penile erection

Increase libido

Other behaviors

α-MSH

α-MSH causes other behavioral effects

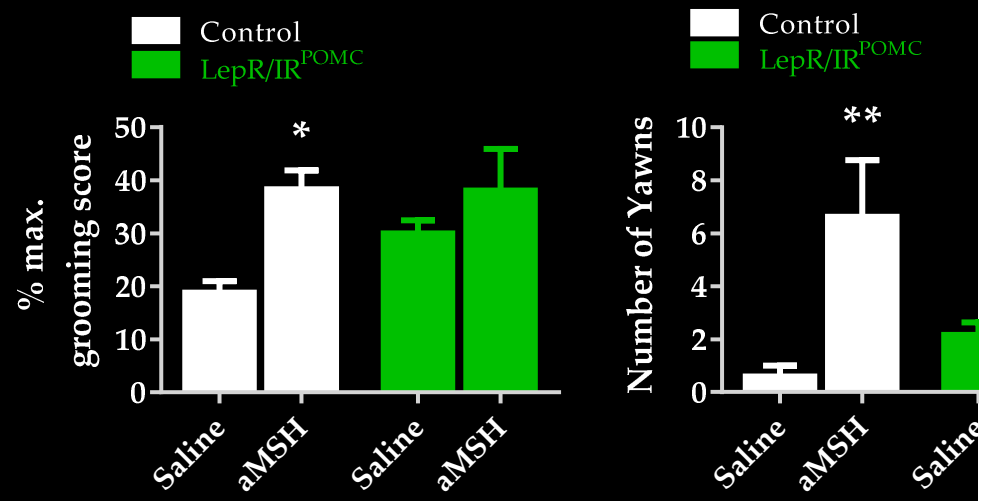


α-MSH Induces yawning, stretching, and grooming

Low α-MSH production may lead to insensitivity to α–MSH



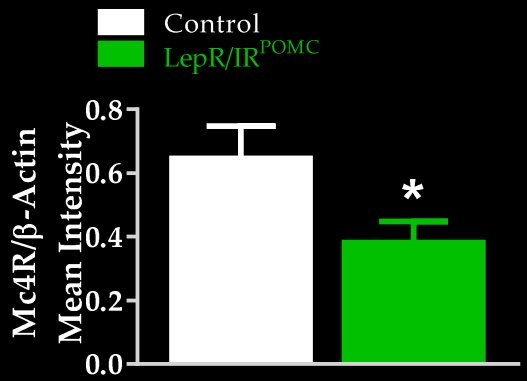
LepR/IR^{POMC} mice



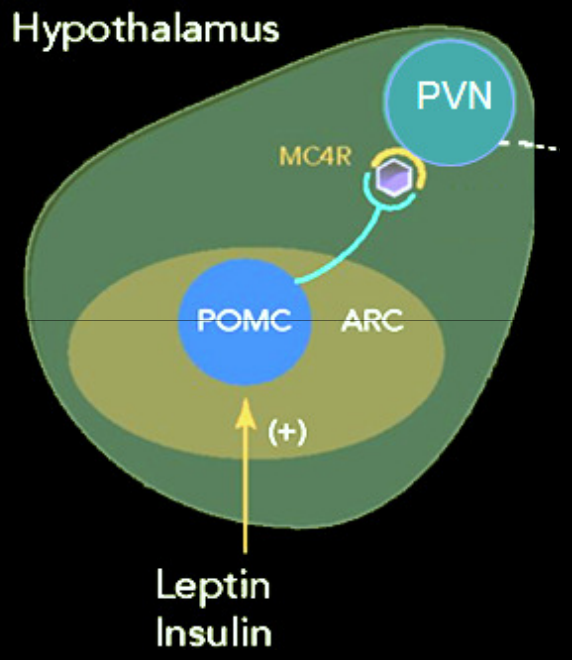
Low α-MSH production may lead to insensitivity to α–MSH



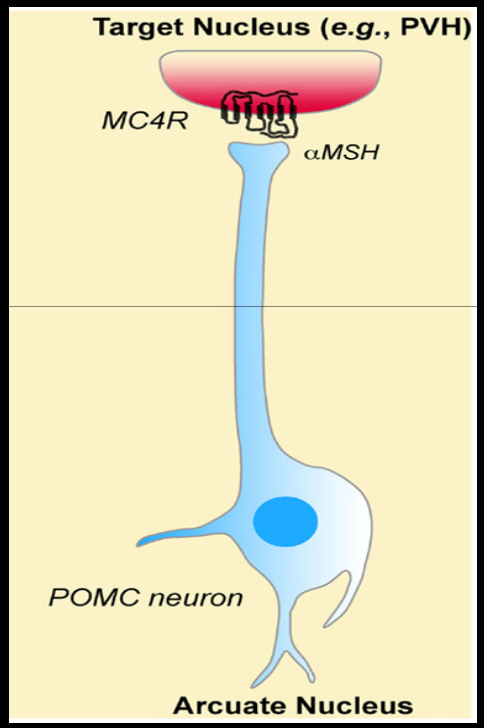
LepR/IR^{POMC} mice



Can we avoid side effects in ED drugs (or sexual side effects in obesity drugs) by targeting downstream neurons?



To sum up, genetically-induced POMC leptin and insulin resistance impairs libido and/or erectile function in mice



Obesity/Diabetes

↓

Leptin and insulin resistance

↓

αMSH

↓

2nd order neuron

↓

Sexual impairment

Source: Coupe and Bouret, 2013

Future directions



Do men with the metabolic syndrome also have less a-MSH and fewer MC4Rs?

Acknowledgements



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Kevin Williams, PhD (UT Southwestern)

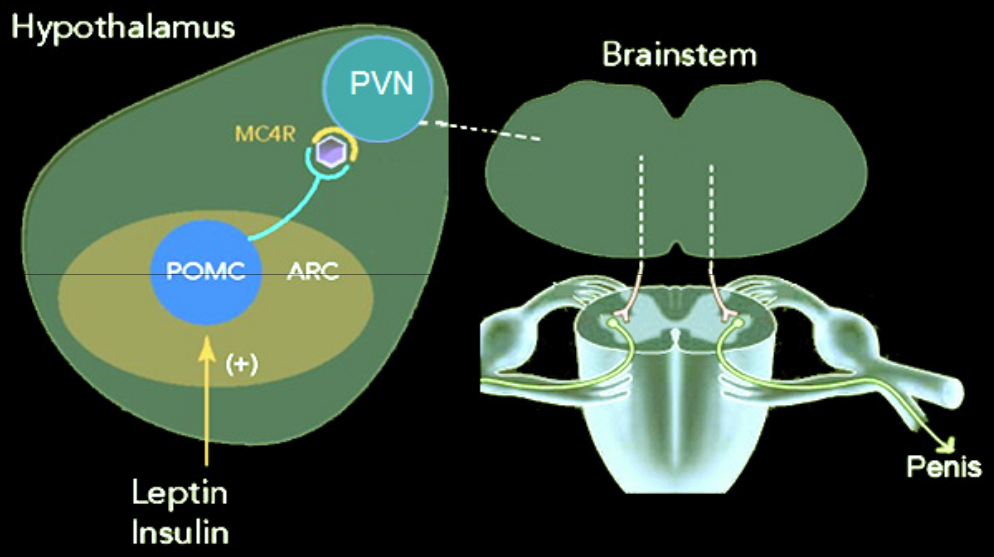
Center for Diabetes and Endocrine Research (CeDER) members
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Oregon Nat'l Primate Research Center Endocrine Technology Support Core Lab

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The deArce-Koch Fund

THANK YOU


Hypothalamus
PVN
MC4R
POMC
ARC
(+)
Leptin
Insulin
Brainstem
Penis