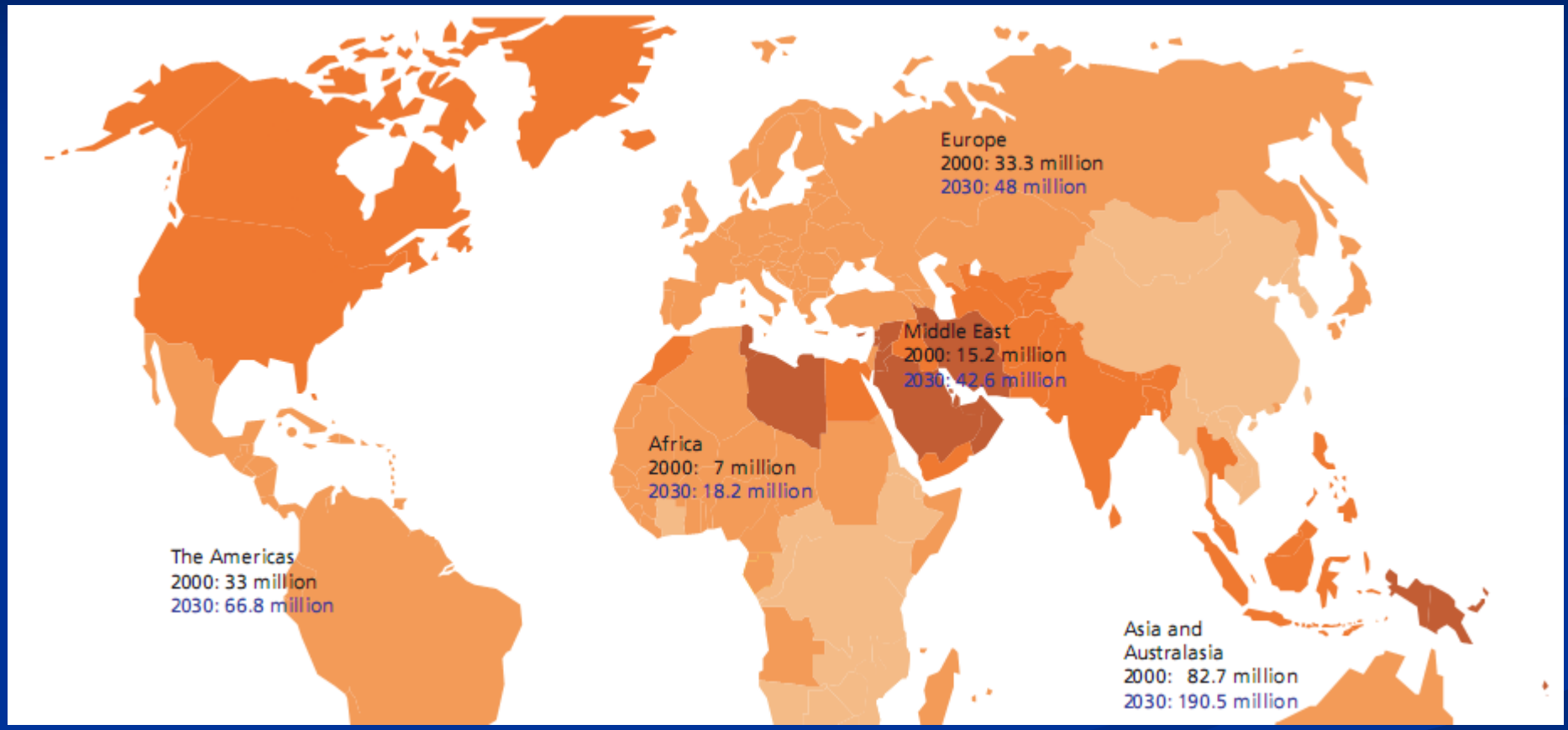
Mechanisms for Improved Insulin Sensitivity by Branched-chain Amino Acids Deprivation

Reporter : Fei Xiao, PhD

Shanghai Institute for Nutritional Sciences,
Chinese Academia of Sciences

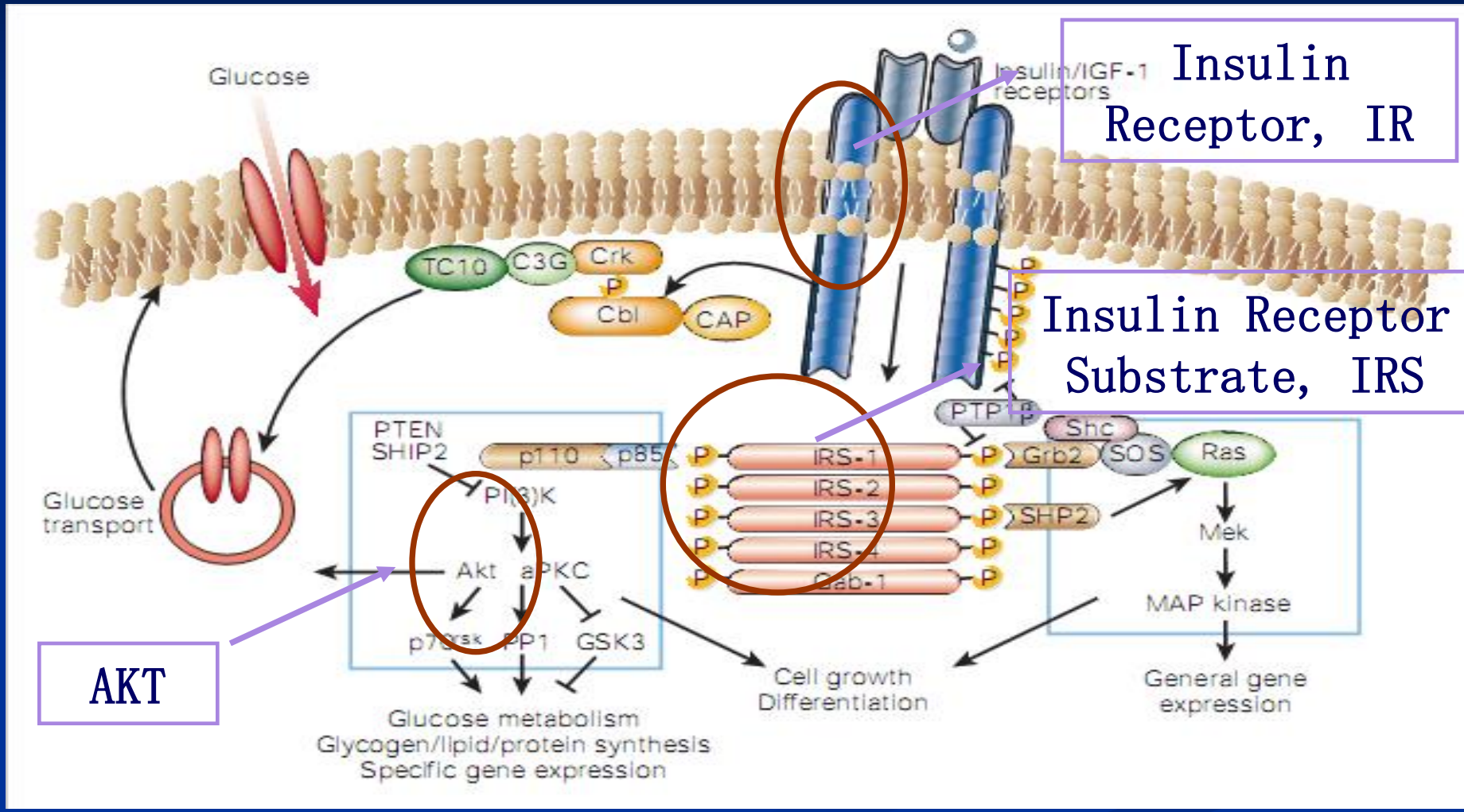
Background

Prevalence of diabetes



World Health Organization

Insulin signaling



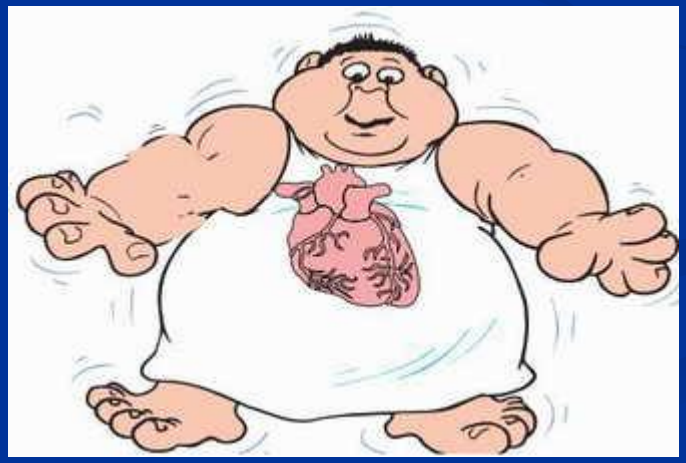
Nature. 2001, 414:799-806

Background

Insulin resistance:

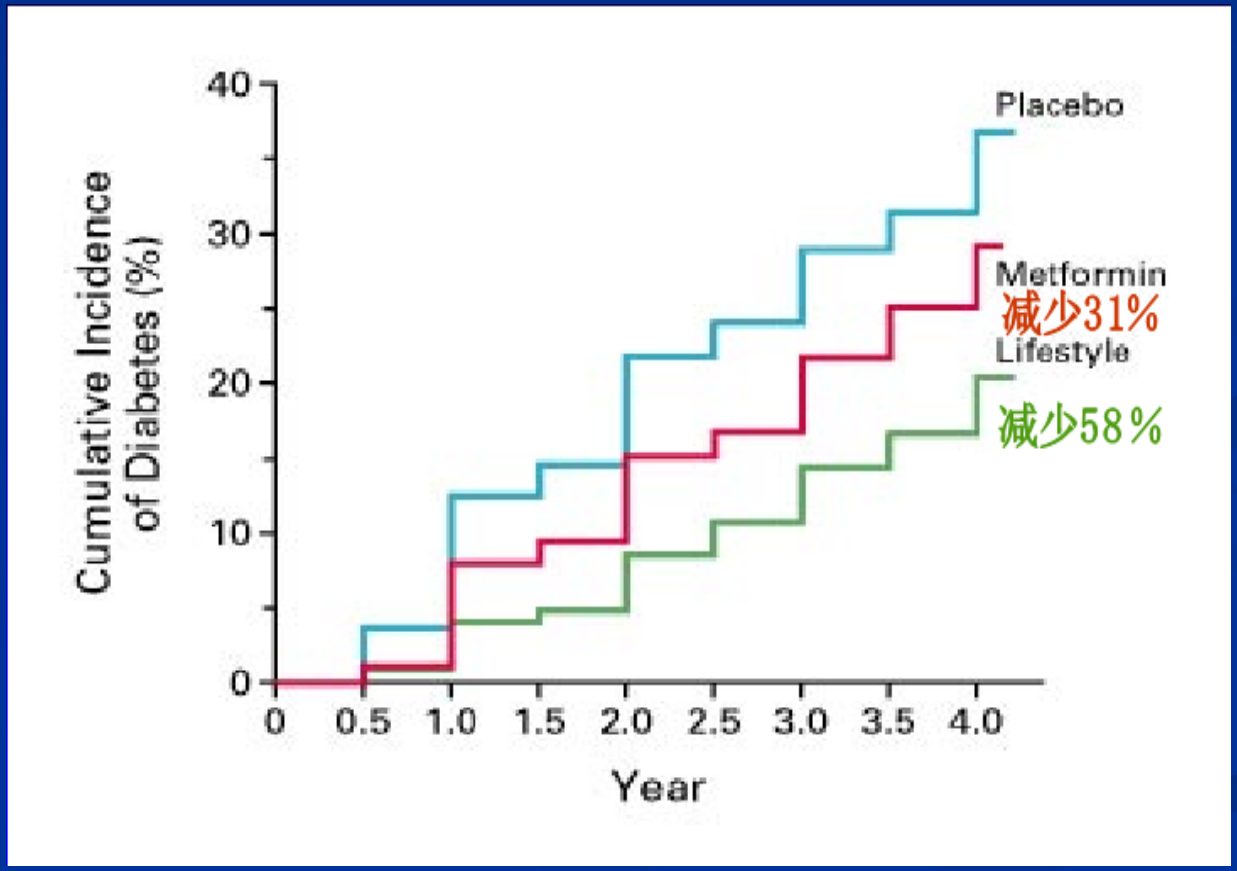
a physiological condition where insulin becomes less effective at lowering blood glucose

a common feature of many metabolic diseases



Background

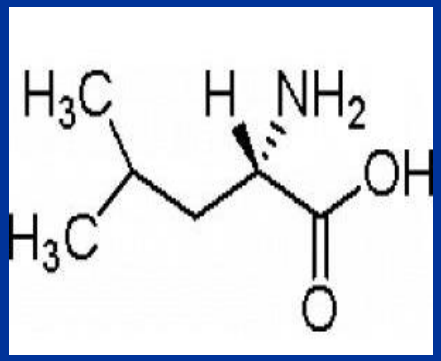
Various strategies to treat insulin resistance



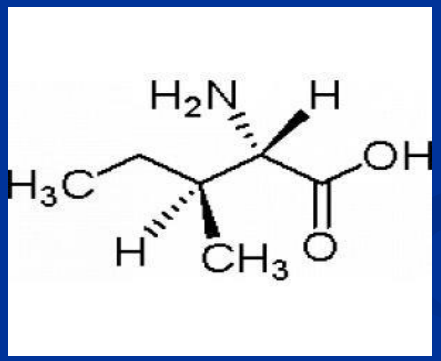
The DPP Research Group, NEJM,2002

Background

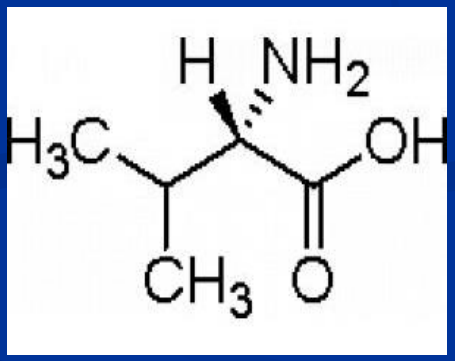
Branched-chain amino acids (BCAAs)



L-leucine



L-isoleucine



L-valine

The role of leucine in insulin sensitivity

Increased serum leucine level:

* Improves the whole body glucose metabolism

Diabetes 56:1647-1654, 2007

* Does not alter susceptibility to diet-Induced obesity

J. Nutr. 139: 715–719, 2009.

* Increases insulin resistance in models of obesity

?

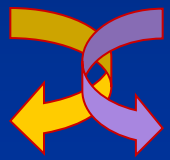
Cell Metab 9:311-326, 2009

Diabetes 54:2674-2684, 2005

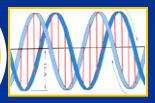
Research interest of our work



Nutrient (BCAAs)



Genetic factors



sensing

Metabolism regulation

Metabolic diseases
(insulin sensitivity/glucose metabolism)

Outline

Part Ⅰ The role of leucine deprivation in insulin sensitivity

Part Ⅱ Effects of individual BCAAs on insulin sensitivity and glucose metabolism in mice

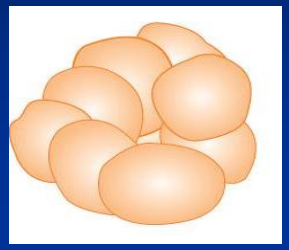
Part Ⅲ Looking for new genes regulating insulin sensitivity by leucine deprivation model

Part Ⅰ

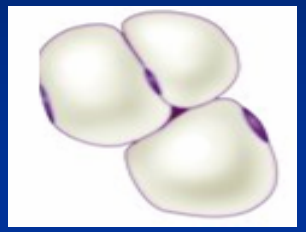
The role of leucine deprivation in insulin sensitivity

In Our Lab

Fat mass

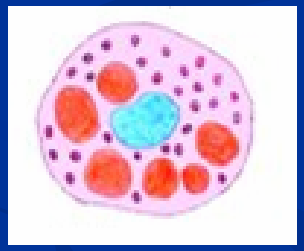


Lipolysis in WAT



Leucine deprivation

UCP1 in BAT



CNS food intake



Serum Insulin

Blood Glucose Normal

Cell Metab 5:103-114, 2007

Diabetes 59:17-25

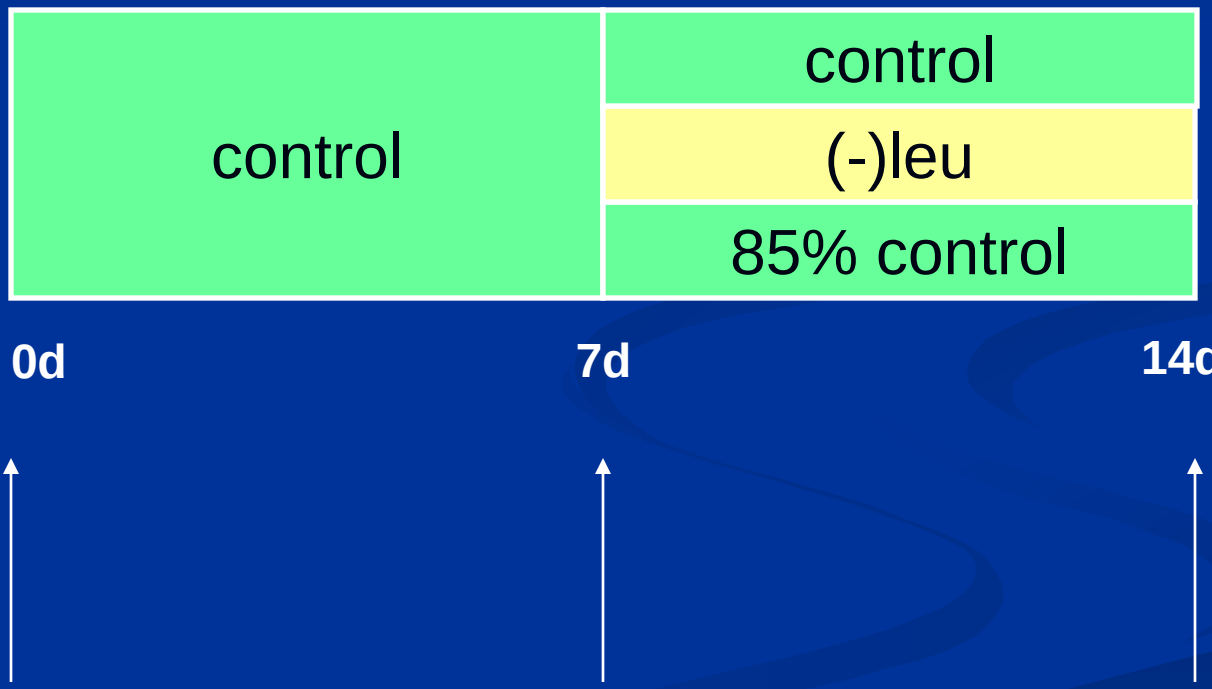
Hypothesis

Leucine deprivation may improve insulin sensitivity



Experimental Design

- Control
- (-)leu
- Pair-fed

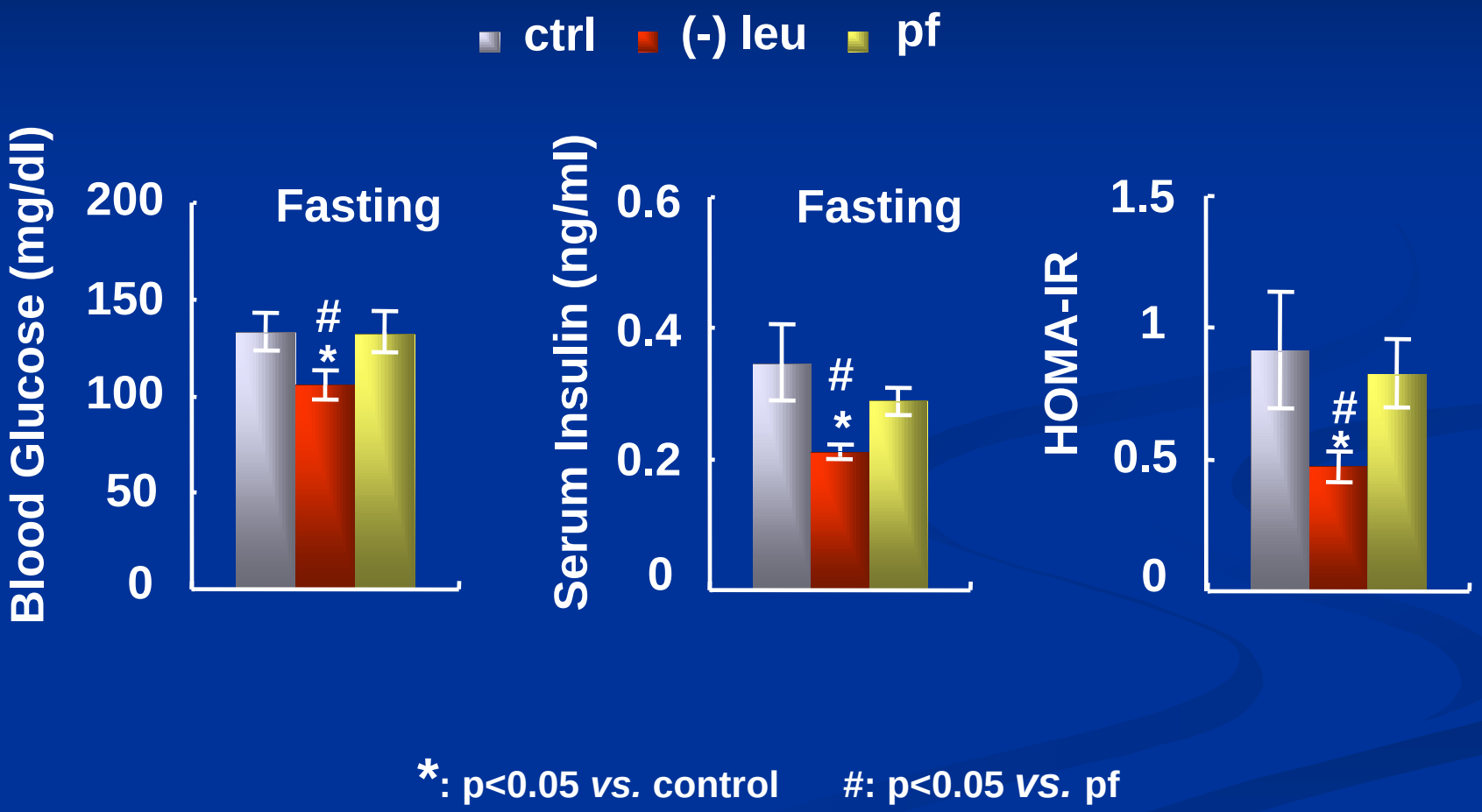


Mice were acclimated to control diet for 7 days

Change different diets

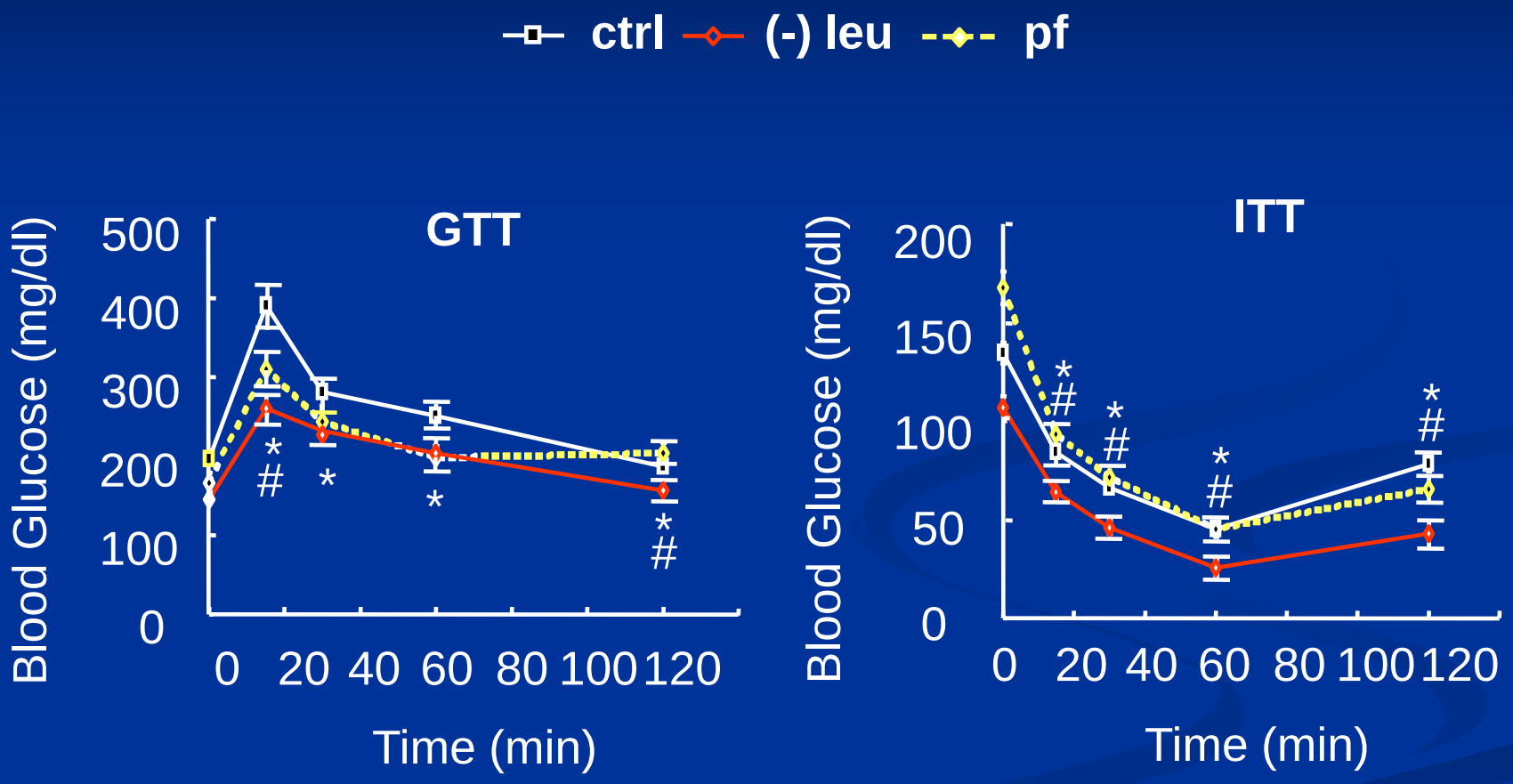
Collect tissues

Result 1: (-) leu improves insulin sensitivity *in vivo*



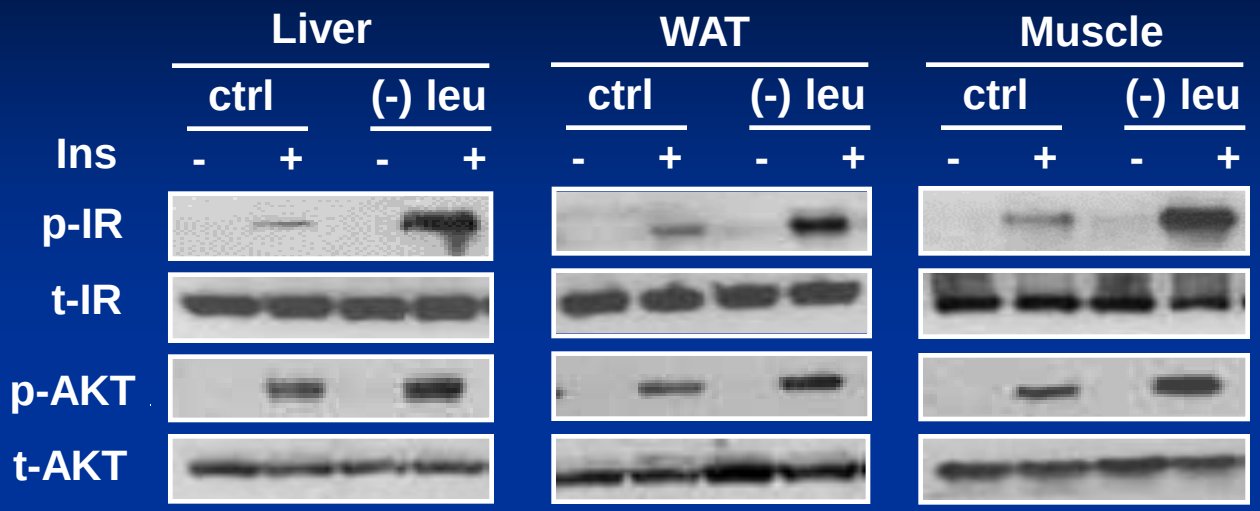
*: p<0.05 *vs.* control #: p<0.05 *vs.* pf

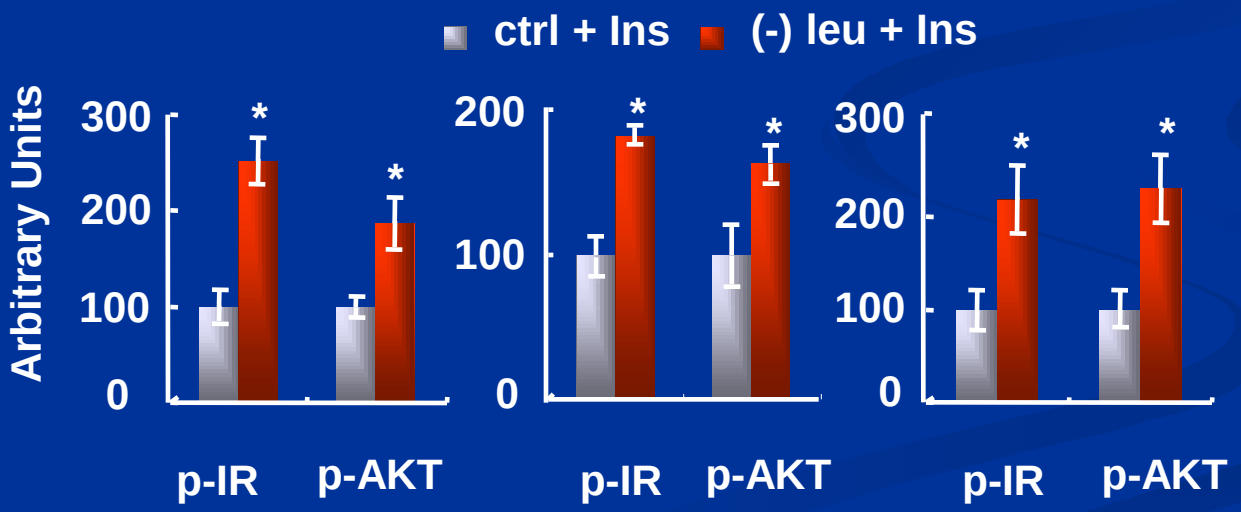
Result 2: (-) leu improves insulin sensitivity *in vivo*



*: p<0.05 *vs.* control #: p<0.05 *vs.* pf

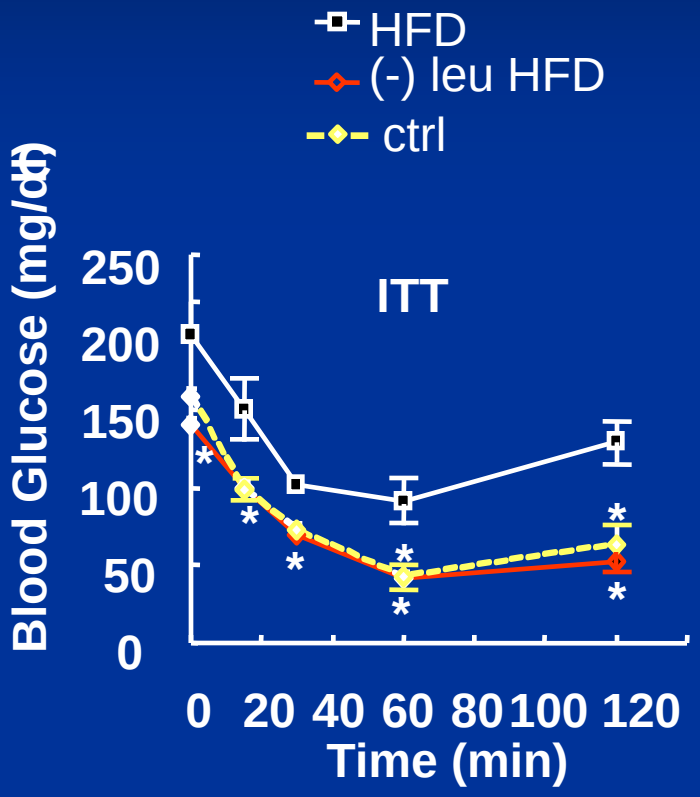
Result 3: (-) leu improves insulin sensitivity *in vivo*



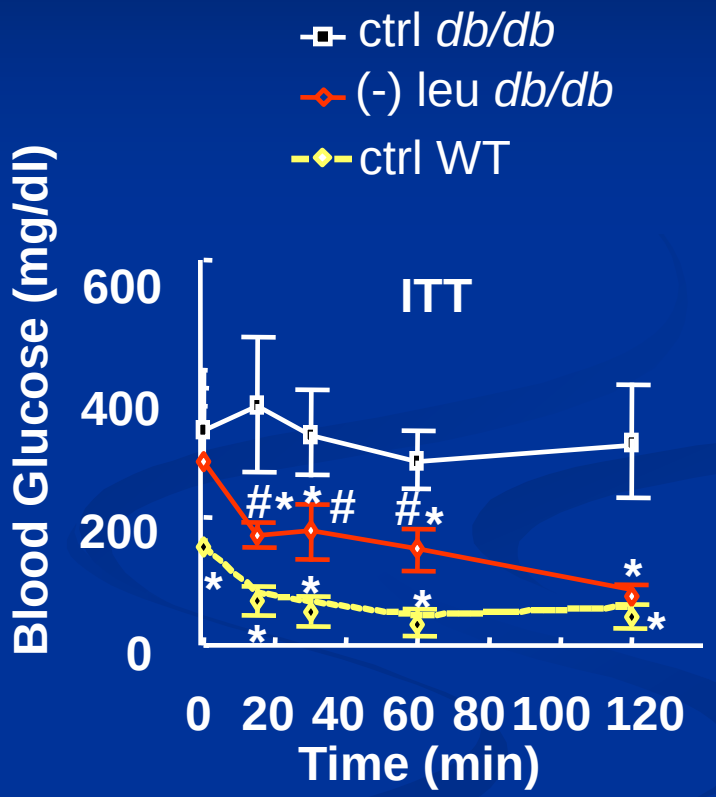


*: p<0.05 *vs.* control

Results 4 :(-) leu improves insulin sensitivity under insulin-resistance conditions



*: p<0.05 *vs.* HFD
#: p<0.05 *vs.* ctrl



*: p<0.05 *vs.* ctrl *db/db*
#: p<0.05 *vs.* ctrl WT

Summary 1

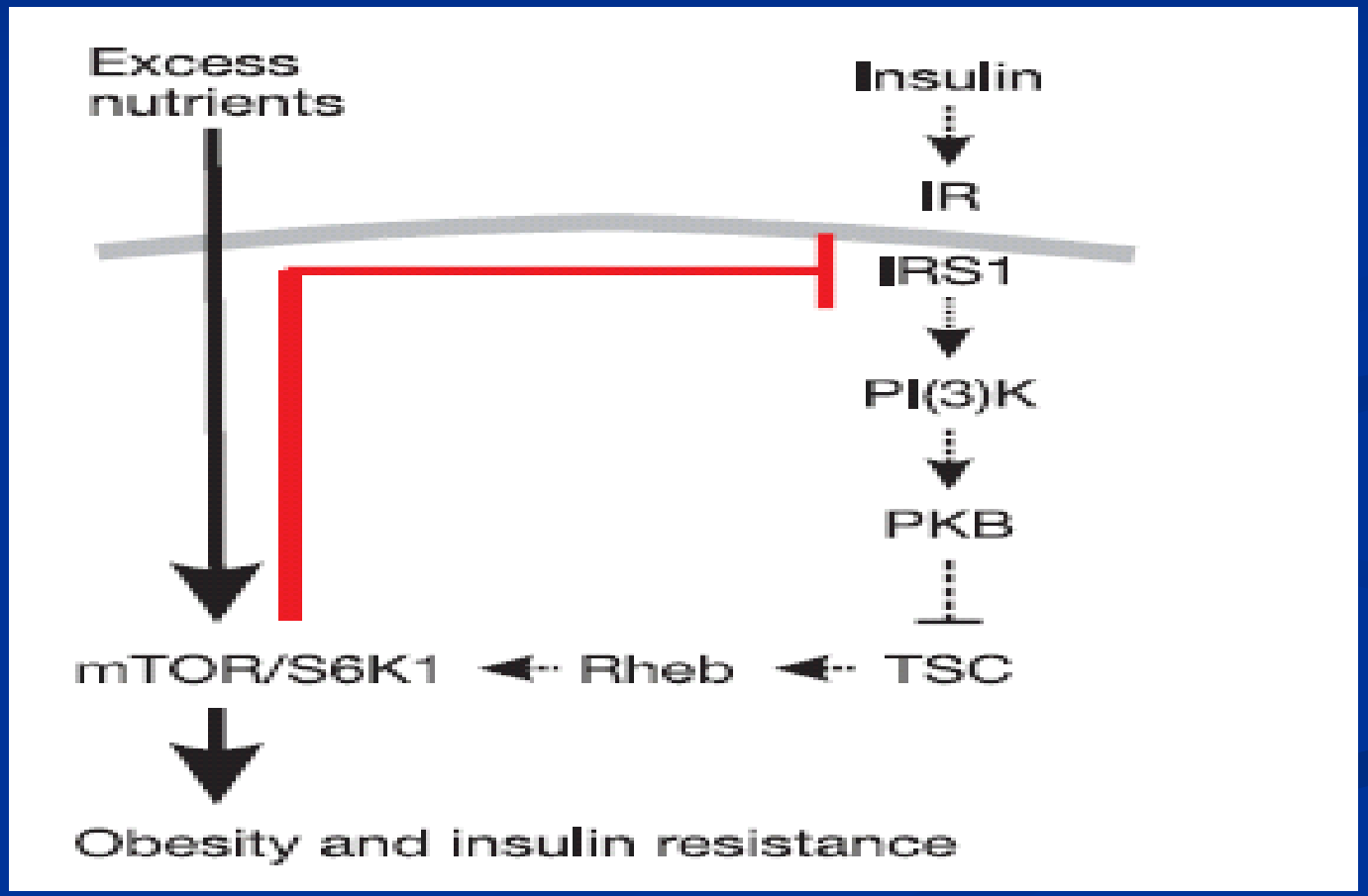
leucine deprivation improves insulin sensitivity under normal and insulin-resistant conditon

Mechanisms ?

Role of mTOR/S6K1 signaling in insulin sensitivity

mTOR: mammalian target of rapamycin

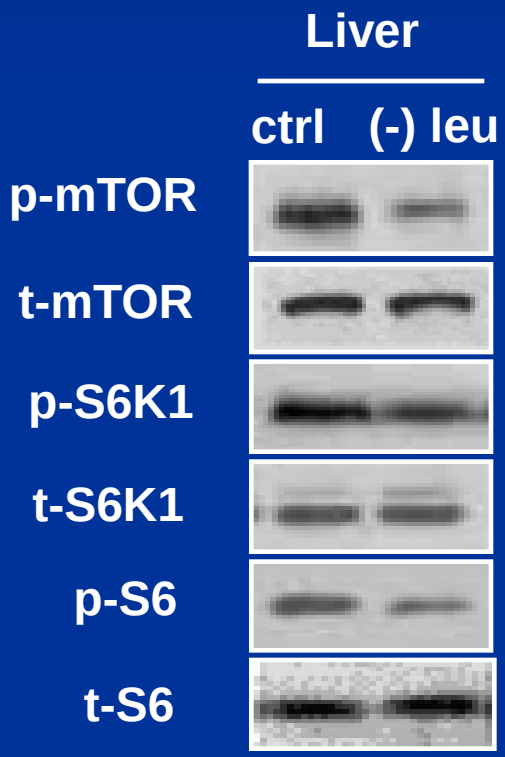
S6K1: ribosomal protein S6 kinase 1



Nature 431:200-205, 2004

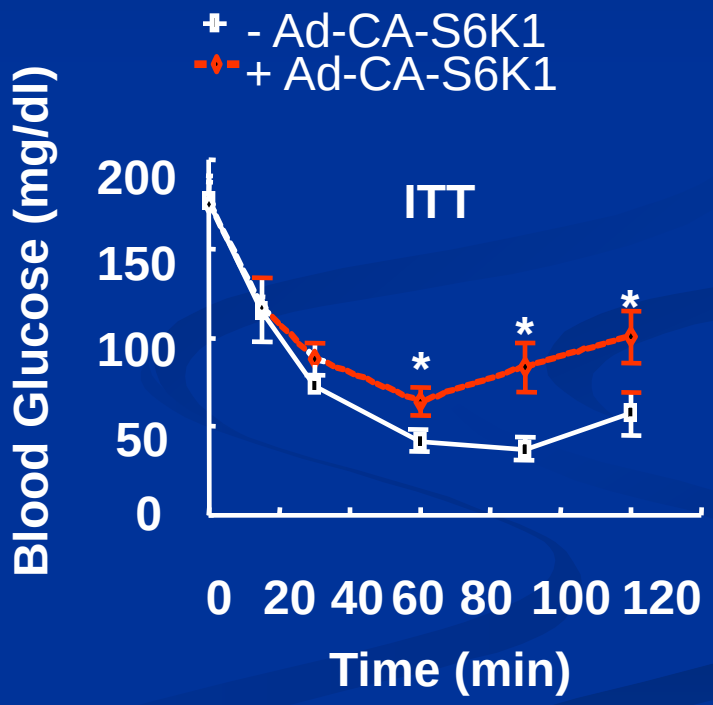
Results 5 :(-) leu increases insulin sensitivity by decreasing mTOR/S6K1 signaling *in vivo*

A



B

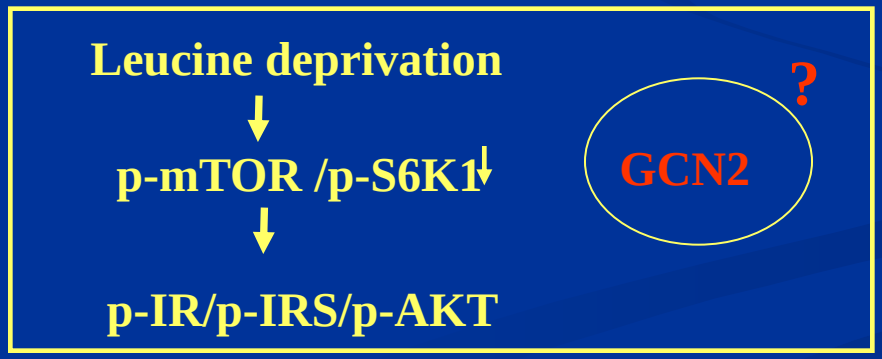
On a leucine-deficient diet



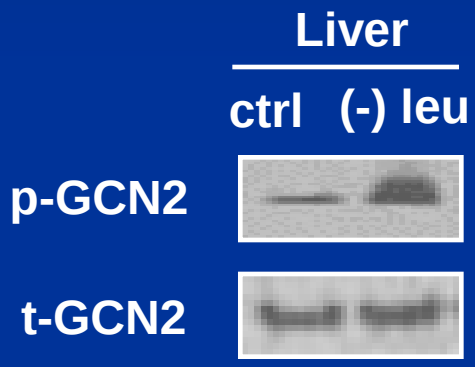
*: p<0.05 *vs.* control

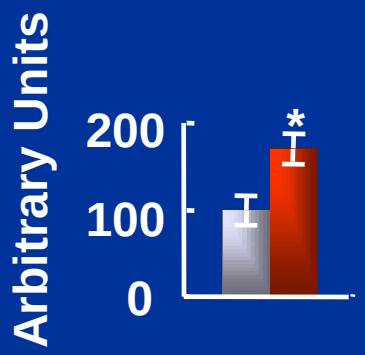
GCN2

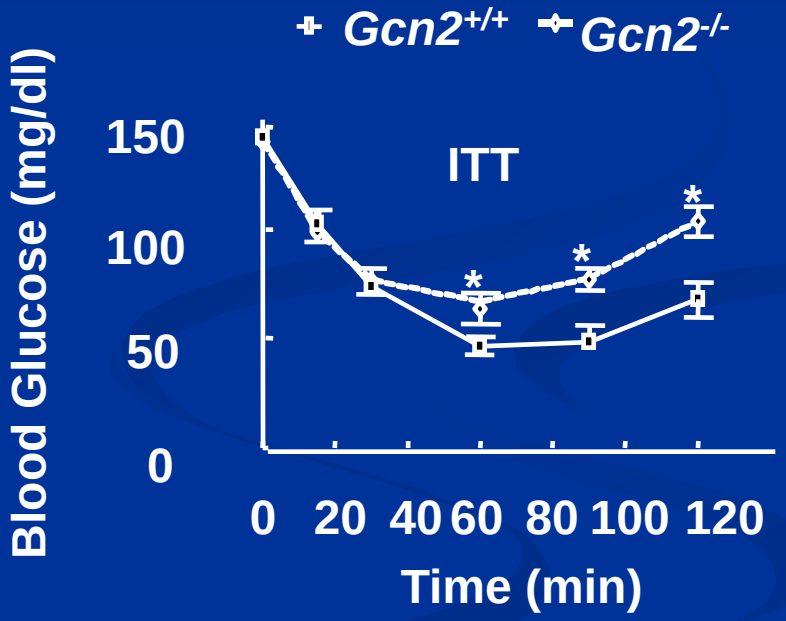
- General control nonderepressible (GCN)2
- A serine protein kinase
- Function as a sensor for amino acid deprivation



Results 6:(-) leu increases insulin sensitivity by activation of GCN2



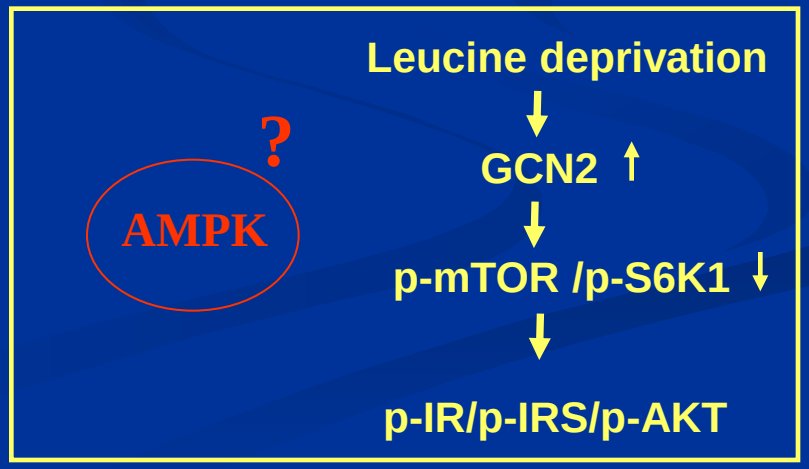




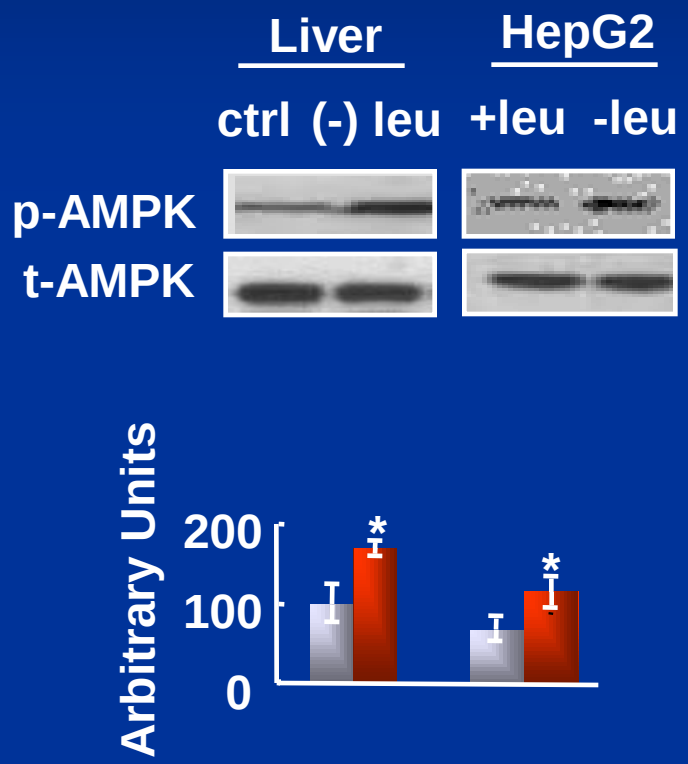
*: p<0.05 *vs.* control

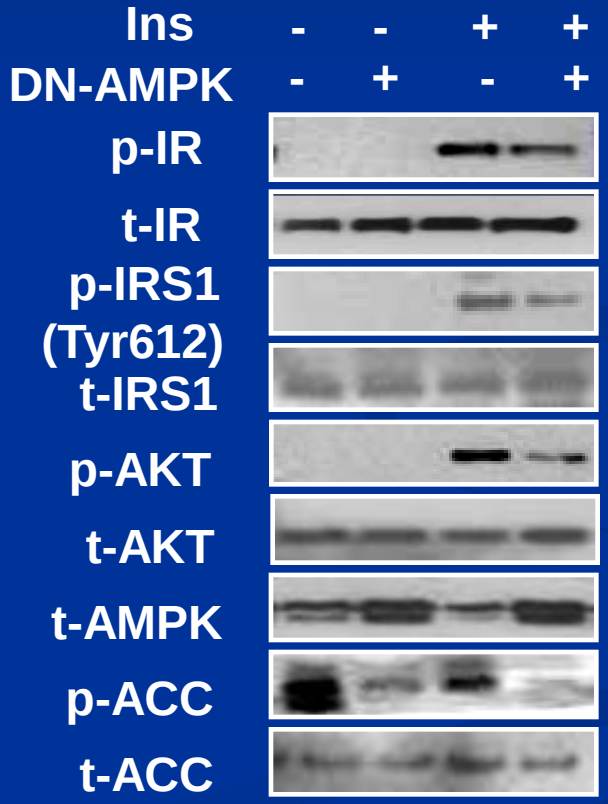
AMPK

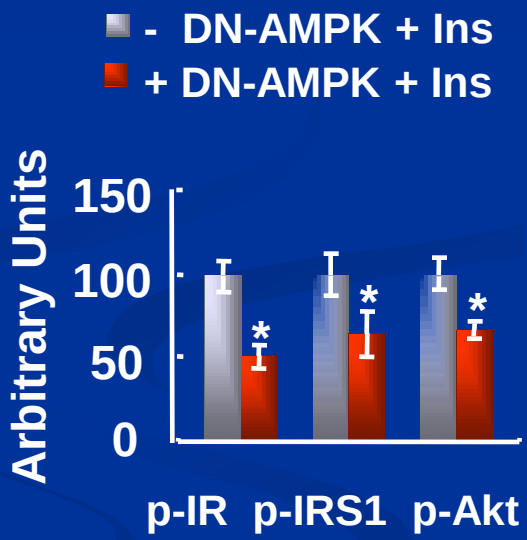
- AMP-activated protein kinase
- Energy sensor
- Target of many drugs



Results 7 :(-)leu improves insulin sensitivity via activation of AMPK





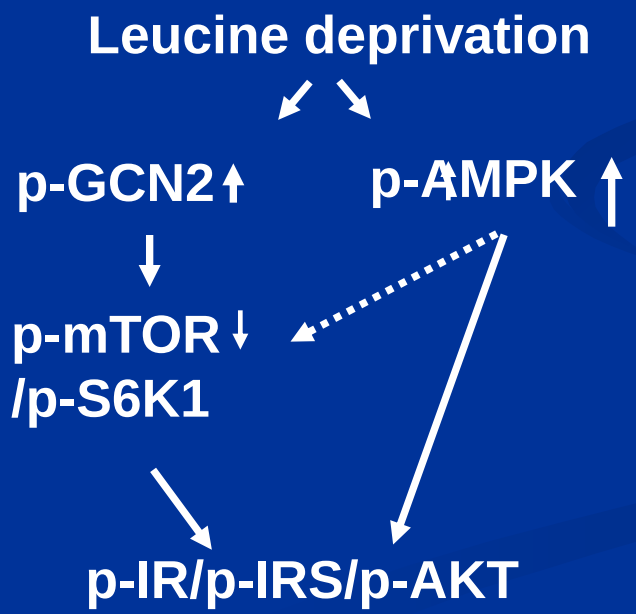


*: $p<0.05$ *vs.* control

Summary2

Leucine deprivation increases hepatic insulin sensitivity via GCN2/mTOR/S6K1 and AMPK pathways

model



Conclusion One

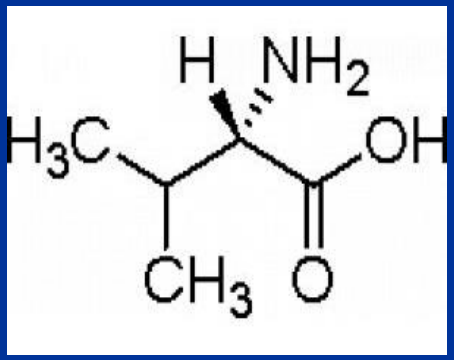
- Elucidate the mechanisms underlying increased insulin sensitivity by leucine deprivation

  GCN2/mTOR/S6K1 and AMPK pathways

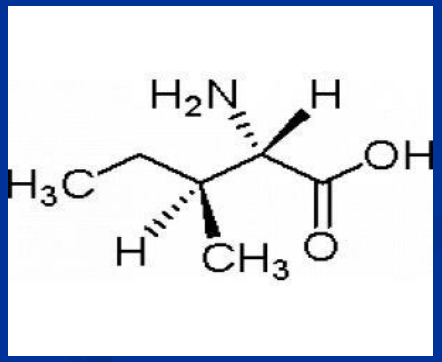
- Demonstrate a novel function for GCN2 in the regulation of insulin sensitivity

The paper titled “leucine deprivation increases hepatic insulin sensitivity via GCN2/mTOR/S6K1 And AMPK pathways” was published in ***Diabetes***, 60:746-756,2011.

How about the other two branched-chain amino acids ?



L-valine (val)



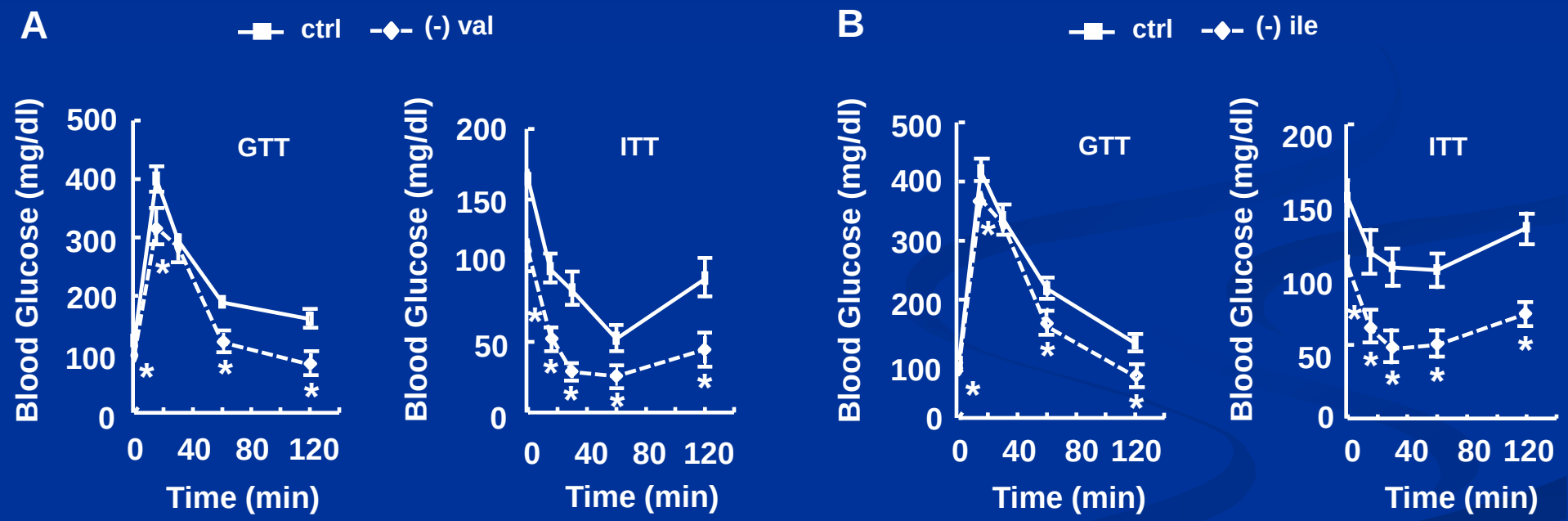
L-isoleucine (ile)



Part Ⅱ

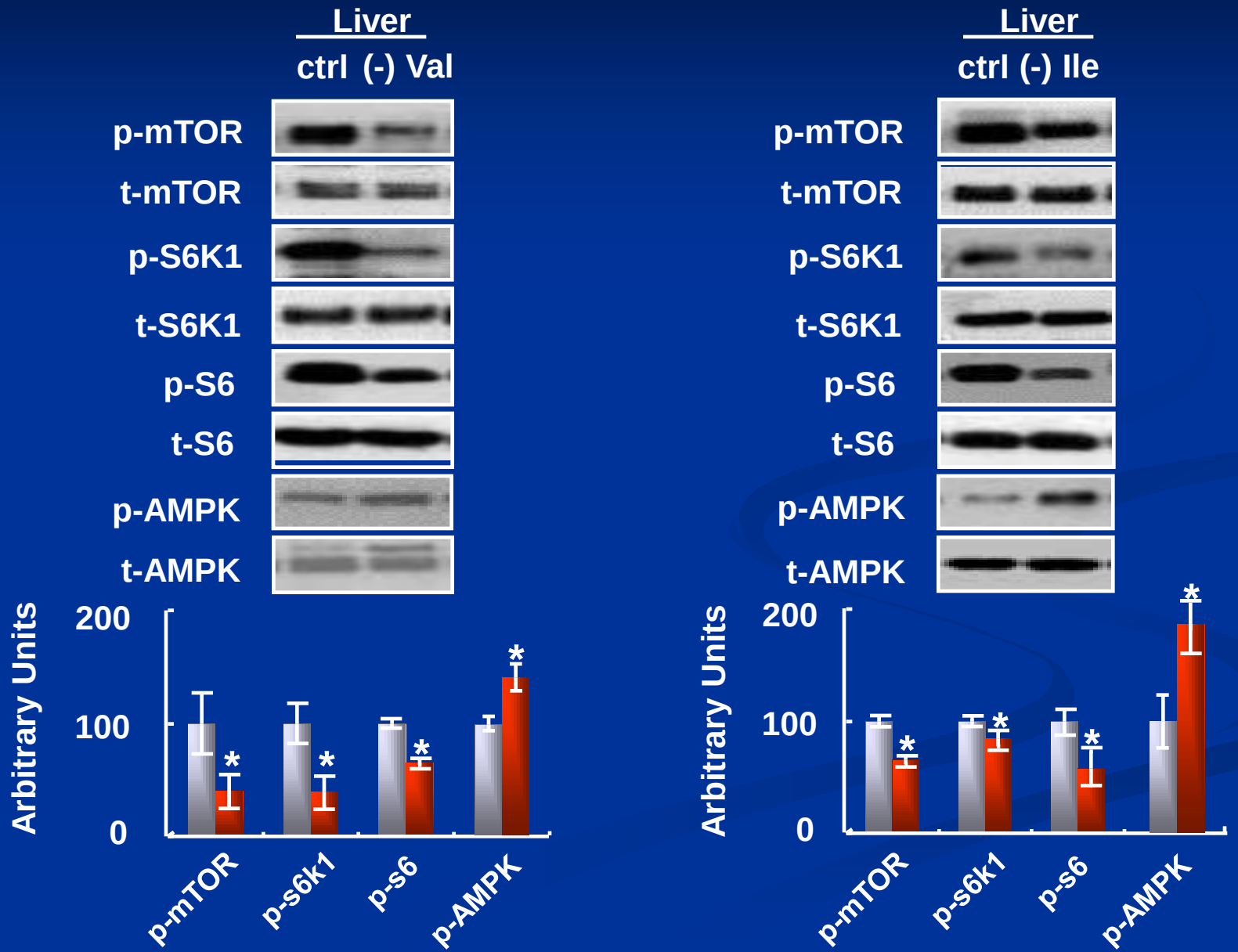
Effects of individual branched-chain amino acids on insulin sensitivity and glucose metabolism in mice

Results 8: (-)val and (-)ile improves insulin sensitivity in vivo

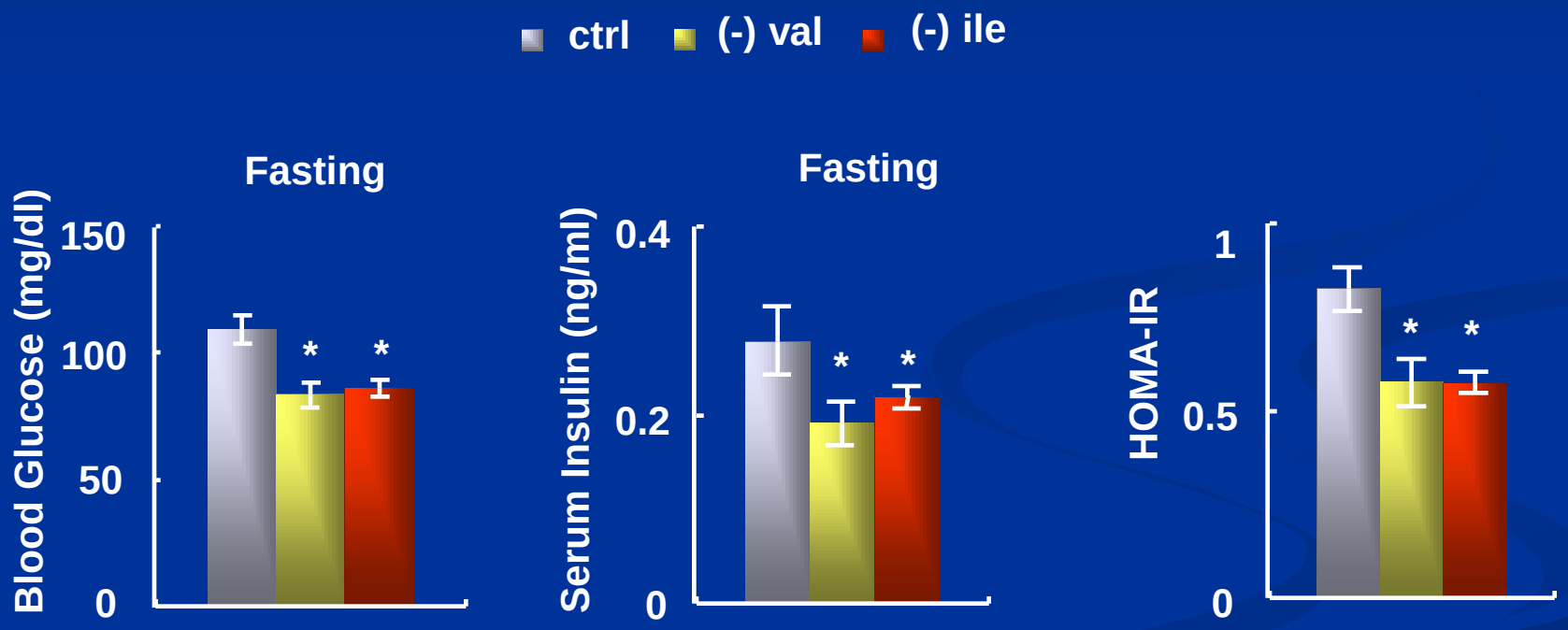


Part II

Result 9: (-)val and (-)ile decrease mTOR/S6K1 and increase AMPK signaling

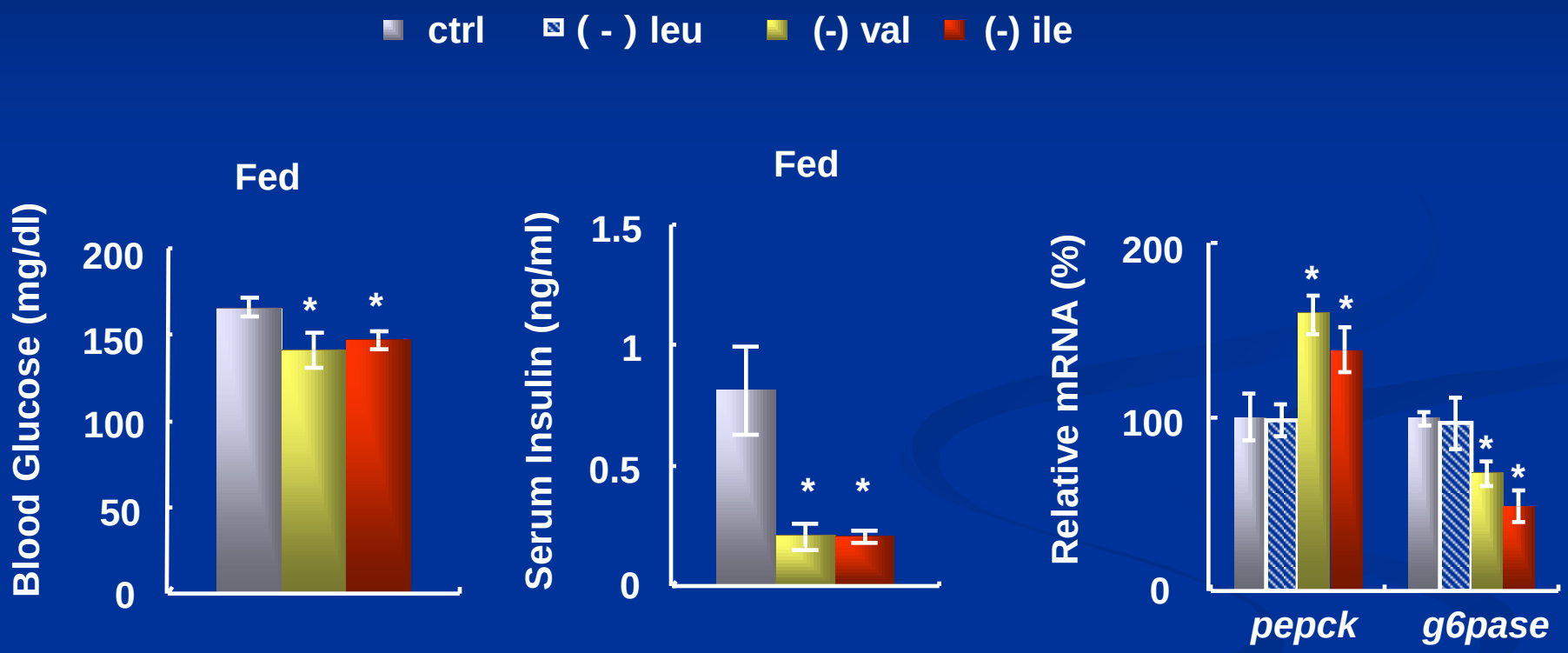


Results 10: Effects of individual BCAA deficiency on glucose metabolism



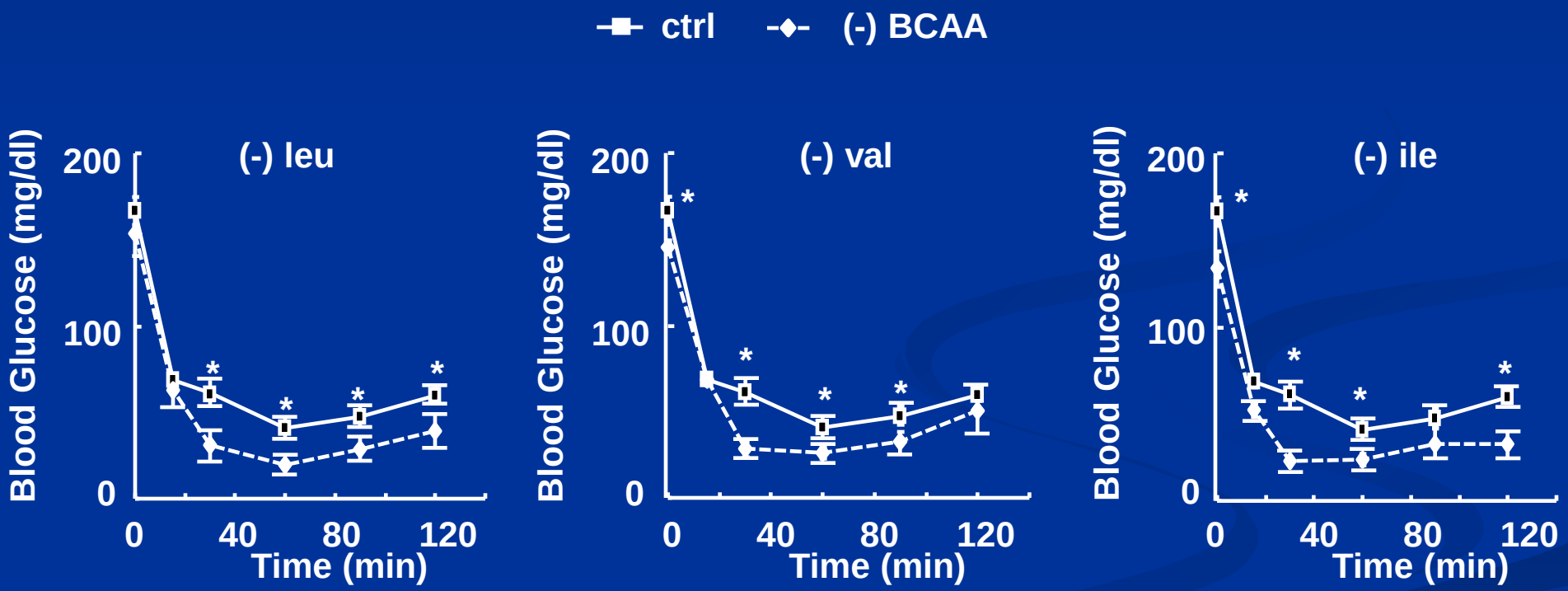
*: $p<0.05$ *vs.* control

Results 11: Effects of individual BCAA deficiency on glucose metabolism



*: $p<0.05$ *vs.* control

Results 12: BCAA deprivation for 1 day improves whole body insulin sensitivity



*: $p<0.05$ *vs.* control

Conclusion Two

- **Leucine deprivation represents a general effect of BCAAs on regulation of insulin sensitivity**

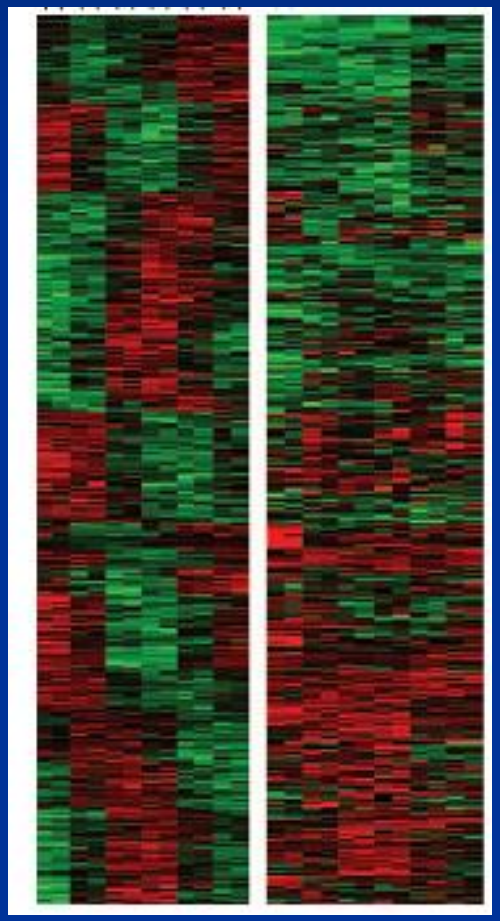
- **The effect of BCAAs deprivation differs in glucose metabolism**

The paper titled “Effects of individual branched-chain amino acids deprivation on insulin sensitivity and glucose metabolism in mice ” was published in ***Metabolism***, 2014.

Part Ⅲ

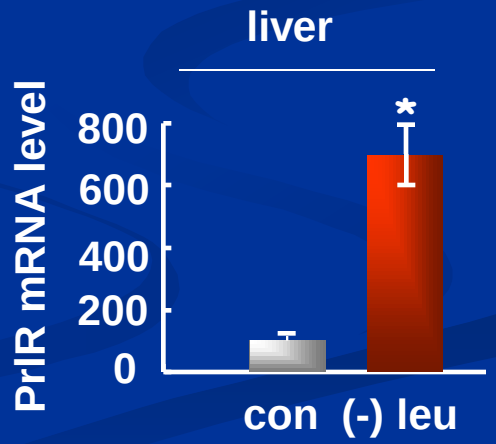
Looking for new genes regulating insulin sensitivity by leucine deprivation model (gene chip)

Hepatic Gene Chip of lecine-deprived male mice



(-) leu/con	Gene number
Upregulate more than twice	984
Downregulate more than twice	1163

Prolactin receptor (PRLR)



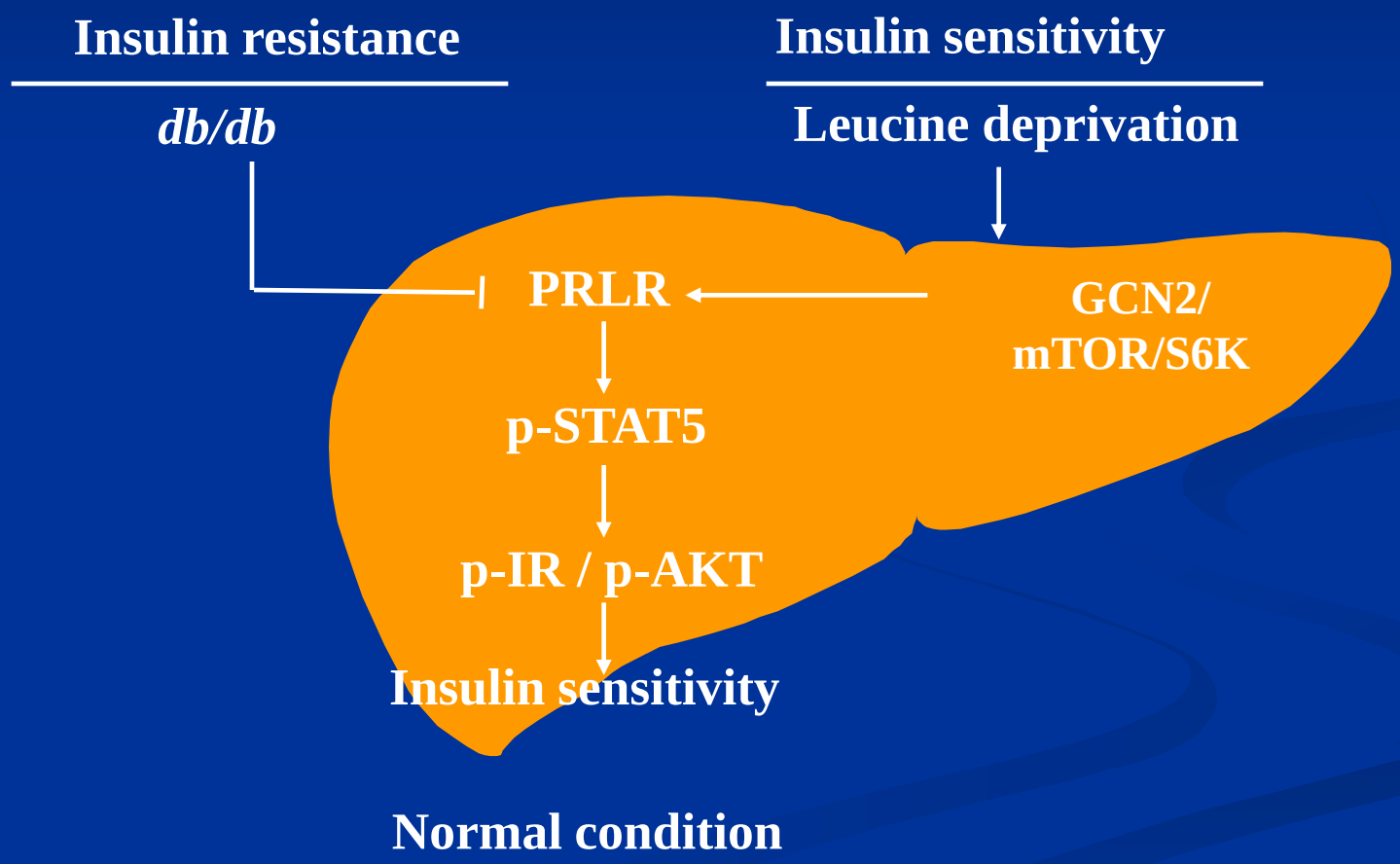
Prolactin Receptor (PRLR)

Prolactin： A hormone best known for its role in lactation.

PRLR: Present in nearly all organs and tissues.
Numerous biological functions of PRLR have been identified.
(Regulates glucose levels by modulating the secretion of insulin）

a direct effect on
insulin sensitivity
?

working model



Conclusion Three

- **Identify a novel function for hepatic PRLR in the regulation of insulin sensitivity**

- **Provide important insights in the nutritional regulation of PRLR expression**

The paper titled “PRLR Regulates Hepatic Insulin Sensitivity in Mice via STAT5” was published in ***Diabetes***, 62:3103-3113,2013.

Acknowledgments

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Shanghai Chen
Kai Li
Hao Liu
Yajie Guo
Jiali Deng
Yuzhong Xiao
Yalan Deng



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Qingshu Meng
Zhiying Huang
Bin Liu

Houkai Li, PhD
Ziquan Li, Ph.D

Douglas cavener (Penn State Univ)
Brad lowell (Harvard Med School)
Xiang Gao (Nanjing Univ)
Yong Liu (INS, CAS)
Hongguang Sheng (CAS clinical center)