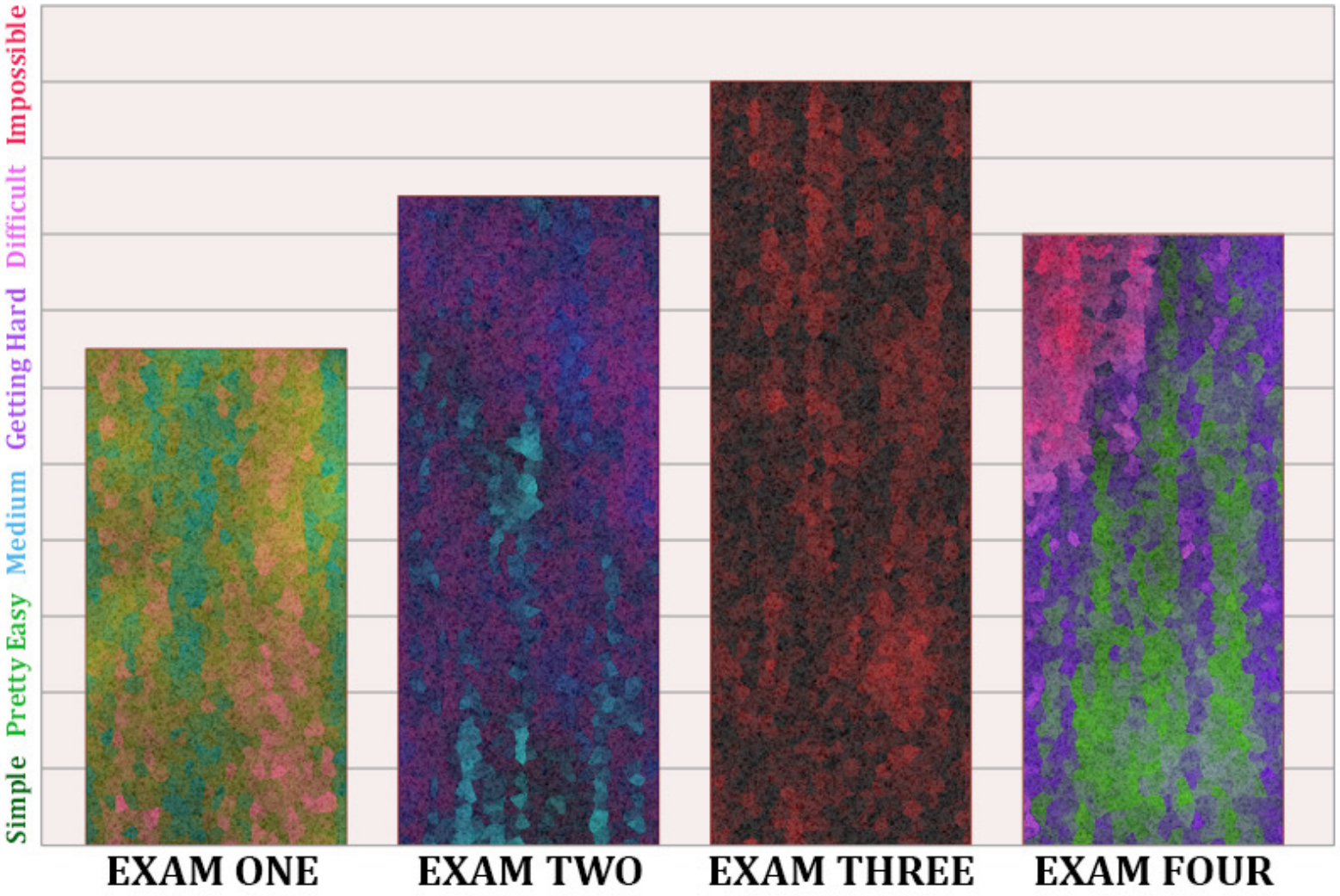
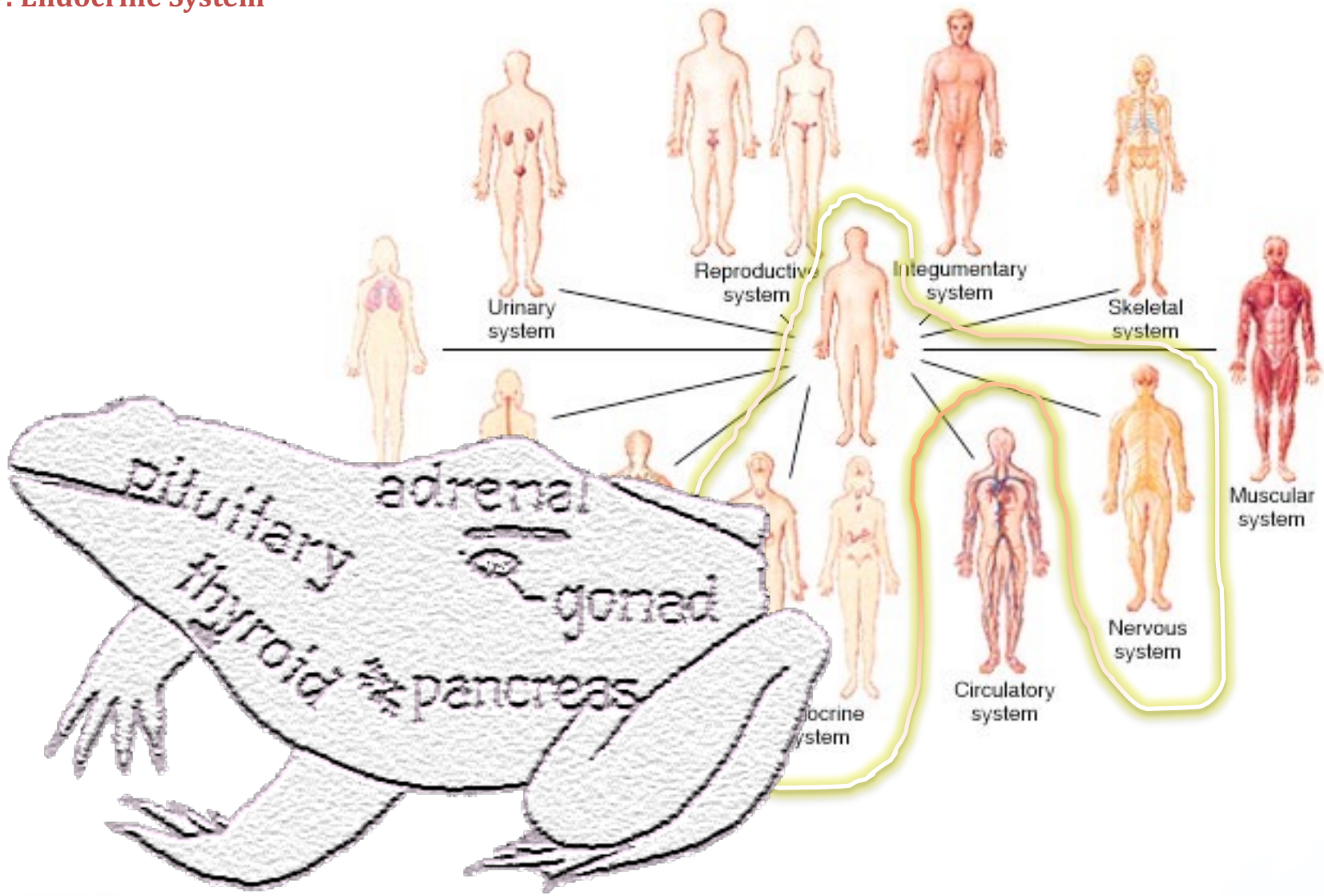
# HESP 147

## Review for Exam 3

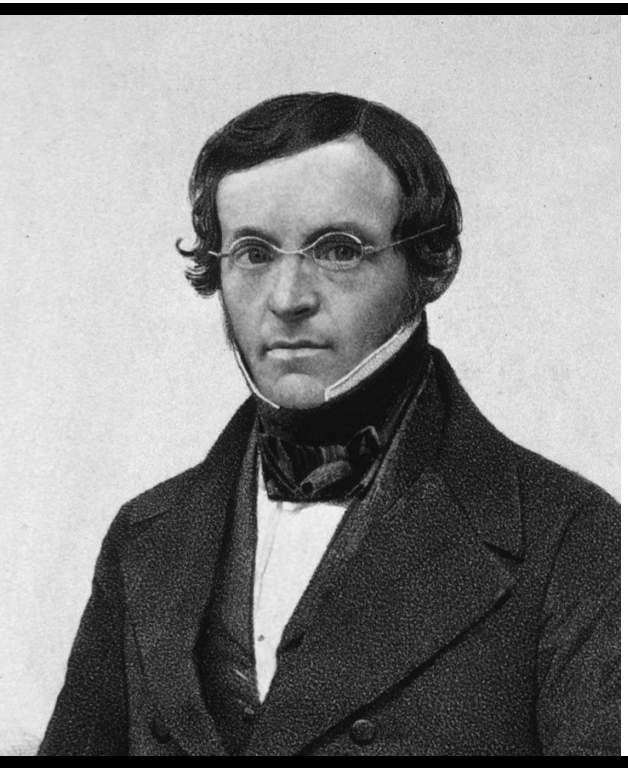
## Hormones, Enzymes, & Cell Signaling

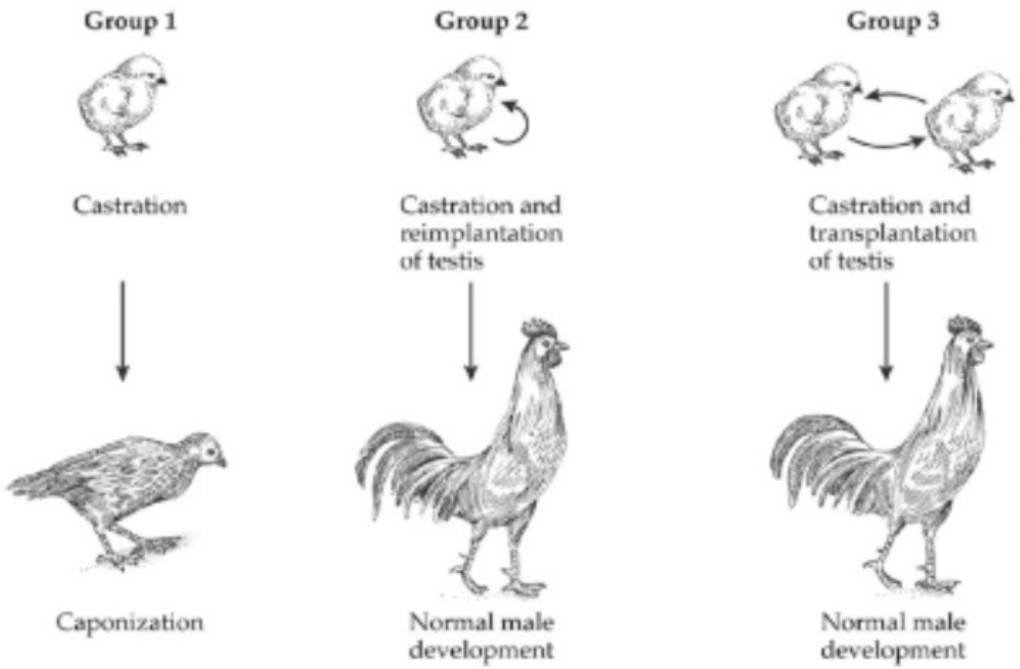

Simple
Pretty Easy
Medium
Getting Hard
Difficult
Impossible
EXAM ONE
EXAM TWO
EXAM THREE
EXAM FOUR

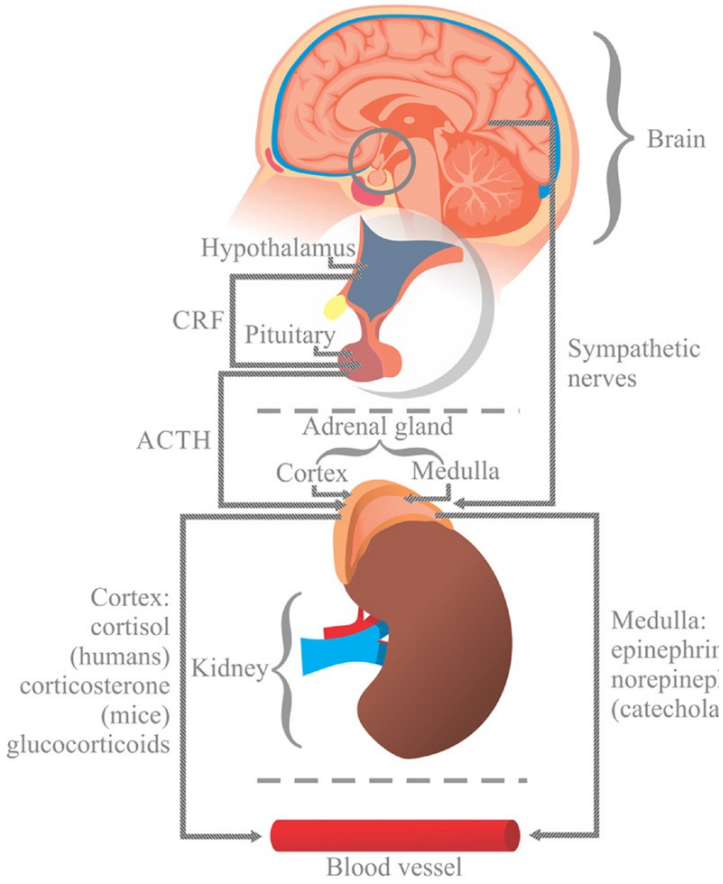
## REVIEW: Endocrine System

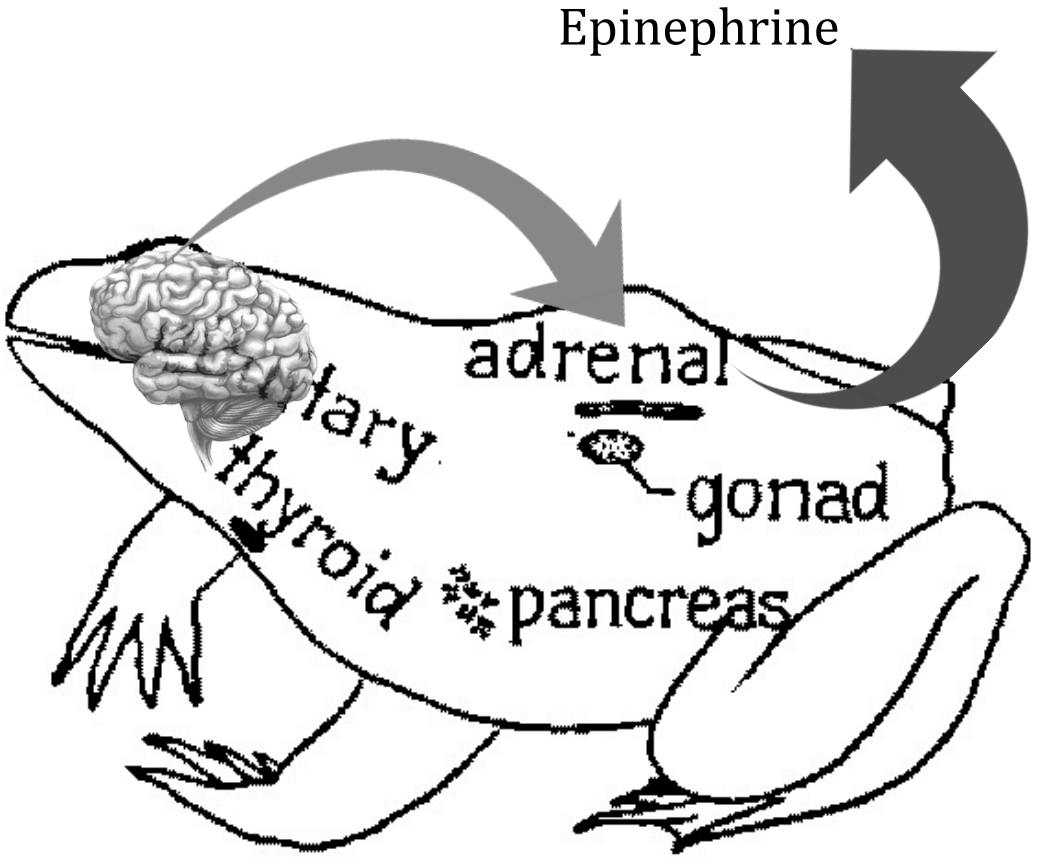


# When (and how) did the study of endocrinology begin?





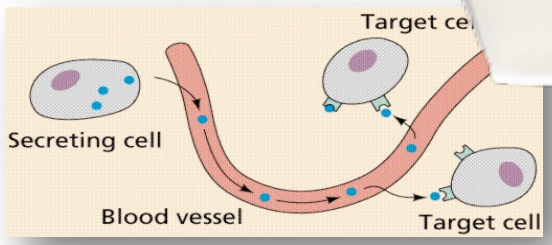



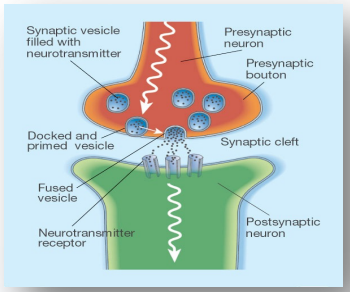

What regulates X?

# Short range vs. long range

**Chemical messenger:** compound that transmits a message.




**Hormones** are long range communication.

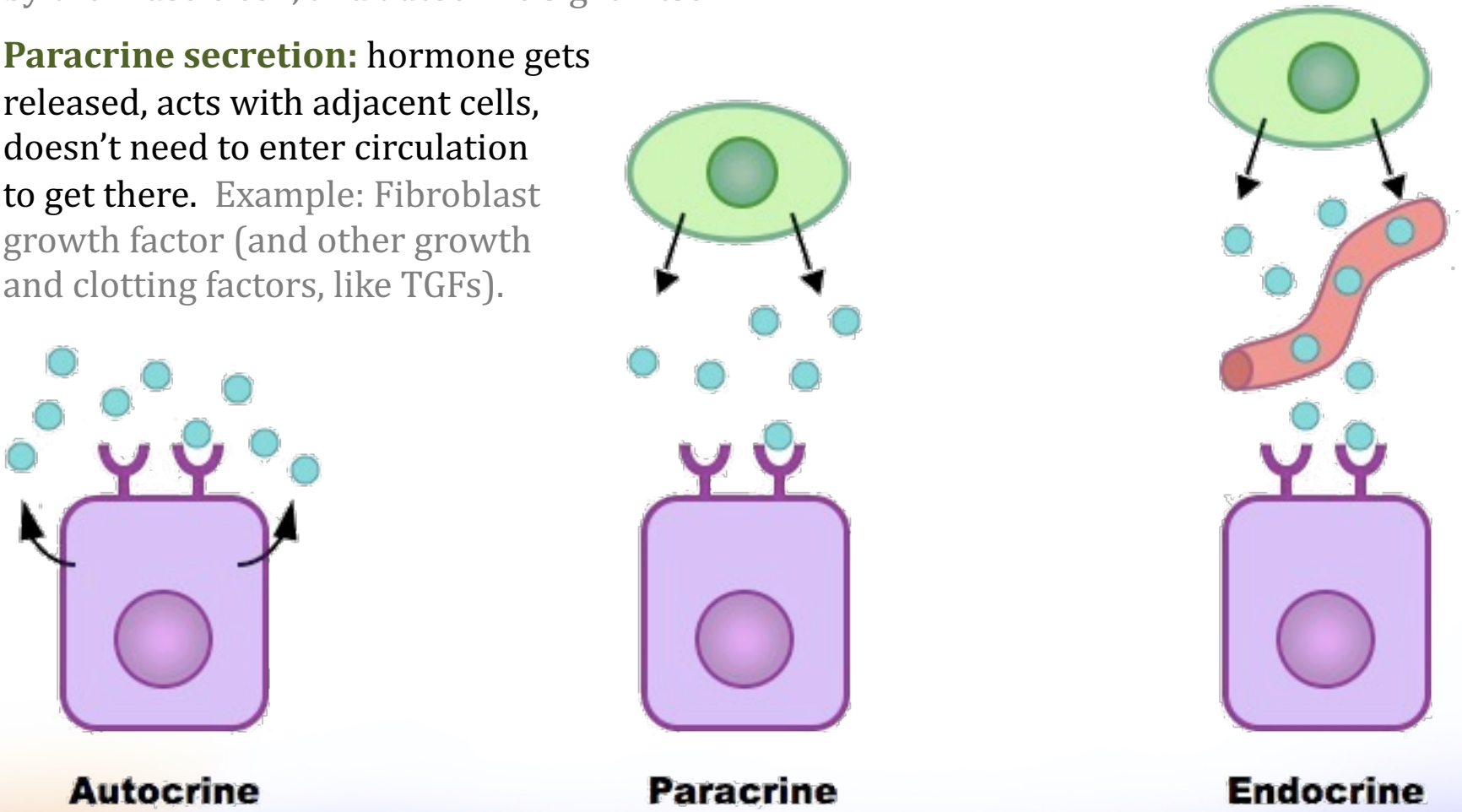



**Neurotransmitters** are communication to adjacent cells.

# Different types of secretion and transportation

**Autocrine secretion:** cell releases a hormone that binds to itself. It never really leaves home. MGF can be stimulated by muscle activity, be released by the muscle cell, and autocrine signal itself.

**Paracrine secretion:** hormone gets released, acts with adjacent cells, doesn't need to enter circulation to get there. Example: Fibroblast growth factor (and other growth and clotting factors, like TGFs).



# Different types of secretion and transportation

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**Paracrine secretion:** hormone gets released, acts with adjacent cells, doesn't need to enter circulation to get there. Example: Fibroblast growth factor (and other growth and clotting factors, like TGFs).

**Endocrine secretion:** almost every hormone you think of: insulin, glucagon, hGH, leptin, ghrelin, androgens, estrogens, epinephrine, etc.

**Some hormones have multiple actions. Myostatin is classically thought of as autocrine, but:**

J Appl Physiol 2016 Mar 15; 120(6): 592–598.

**Paracrine and endocrine modes of myostatin action**

Yun-Sil Lee[1], Thanh V. Huynh[1], Se-Jin Lee[1]

# Peptide

- Made in cells from amino acids (just like all peptides/proteins)
- Water soluble (so they can't diffuse across sarcolemma)
- Usually act through second messenger on cell surface
- Fast initiation, temporary action

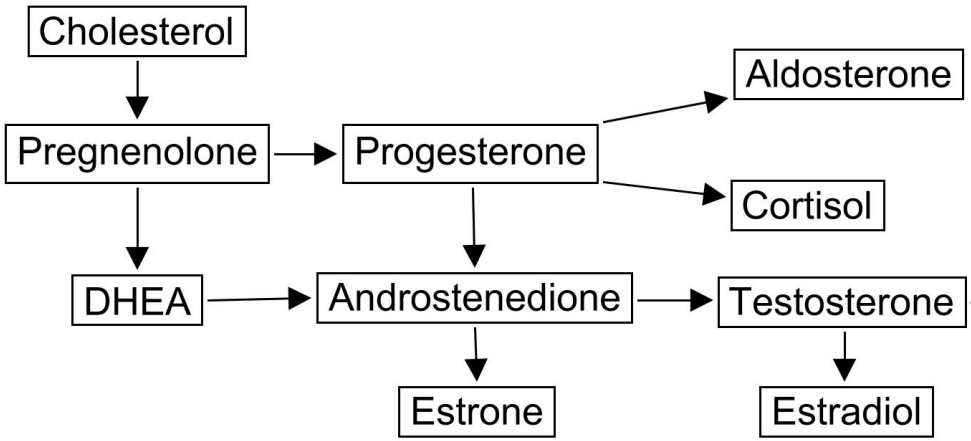
Anterior pituitary: ACTH and growth hormone. Posterior pituitary: vasopressin and oxytocin. Heart: atrial-natriuretic peptide. Pancreas: glucagon, insulin, and somatostatin. Adipose tissue: leptin.

# Steroid

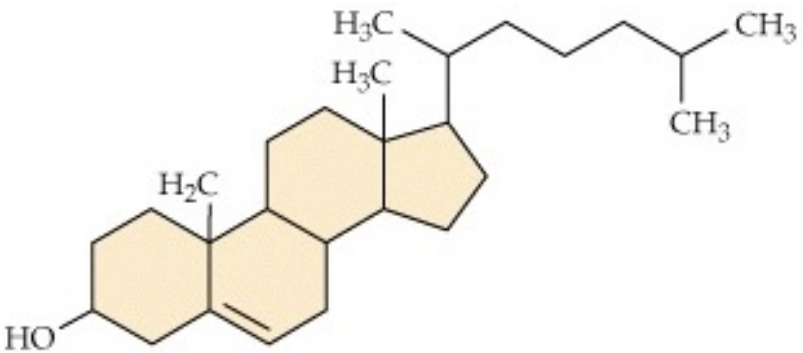
- Made from cholesterol
- Fat soluble (so they can diffuse across sarcolemma)
- Adrenal cortex, testes, ovaries
- Nuclear or cytosolic receptors
- Slow initiation, long action

Different types (based on different types of receptors they bind to): glucocorticoids, mineralocorticoids, androgens, estrogens, and progestogens.

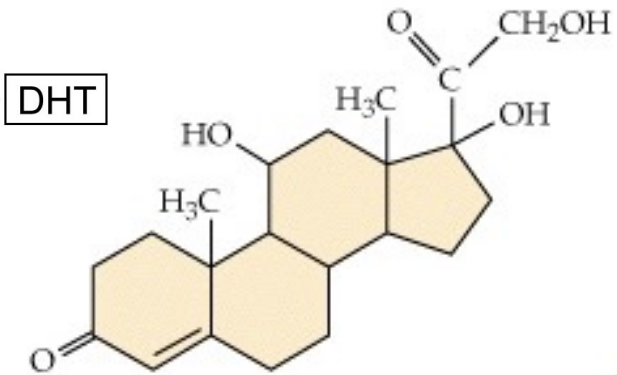
# REVIEW: Steroid Hormones



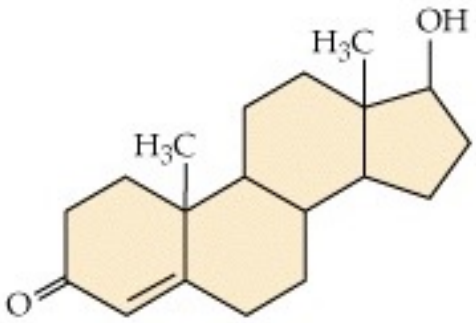

Steroid hormones are synthesized from cholesterol and are fat soluble.



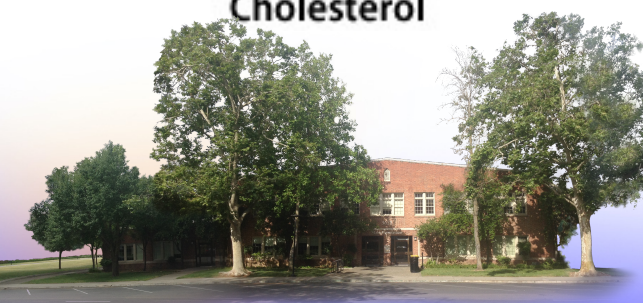

Cholesterol



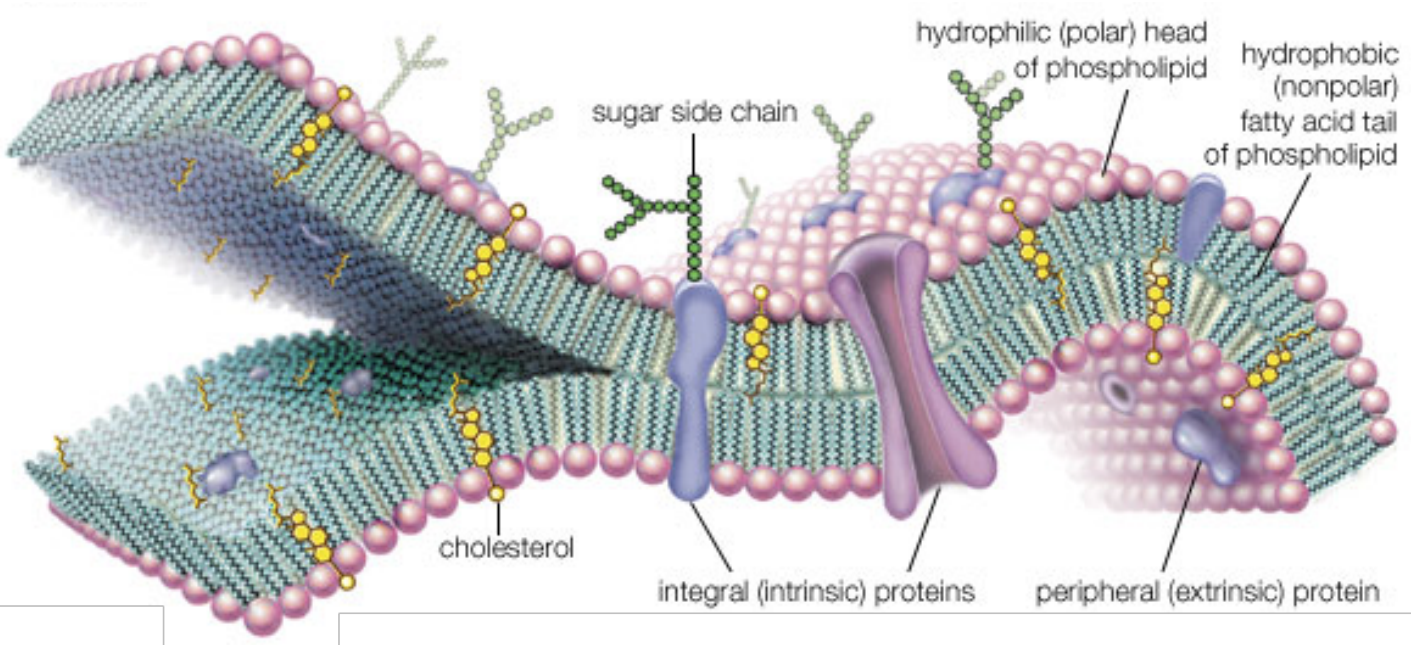

Cortisol

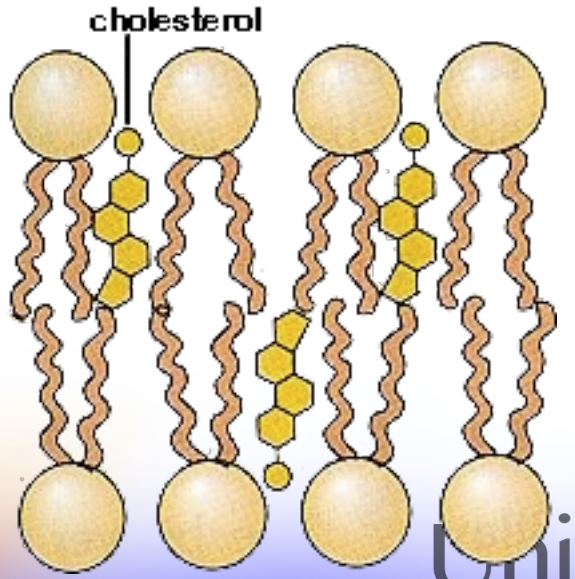



Testosterone



## REVIEW: Steroid Hormones

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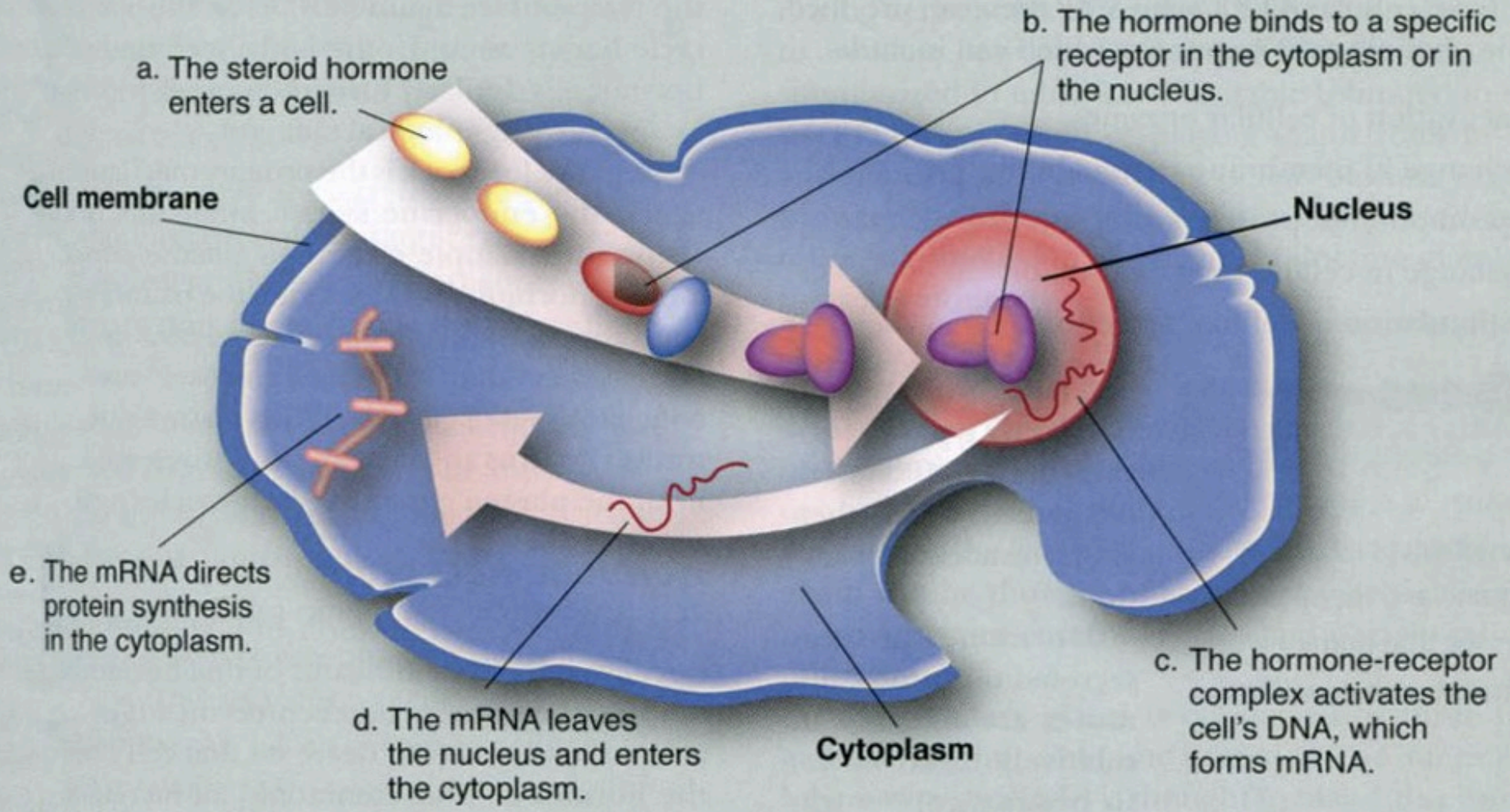
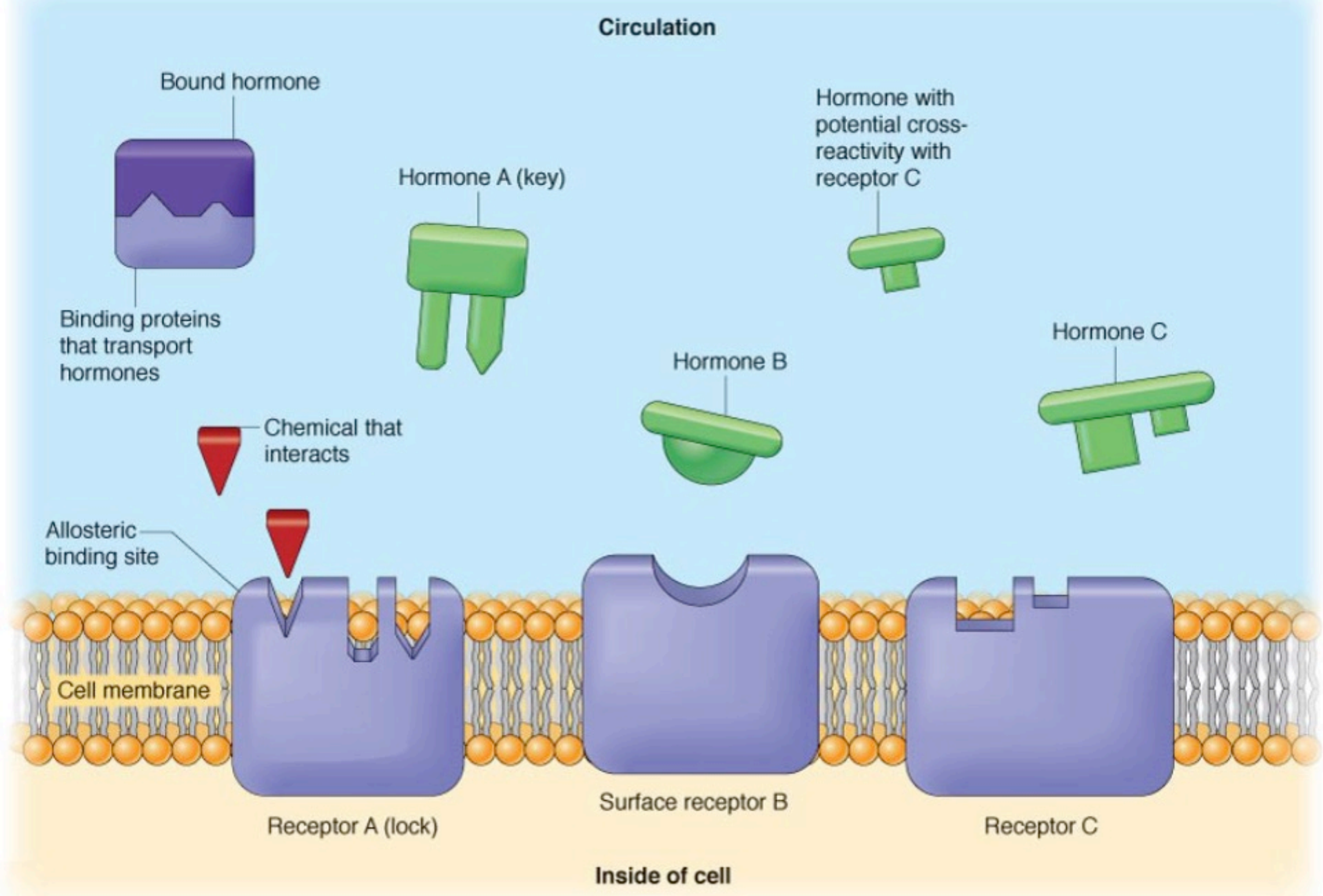
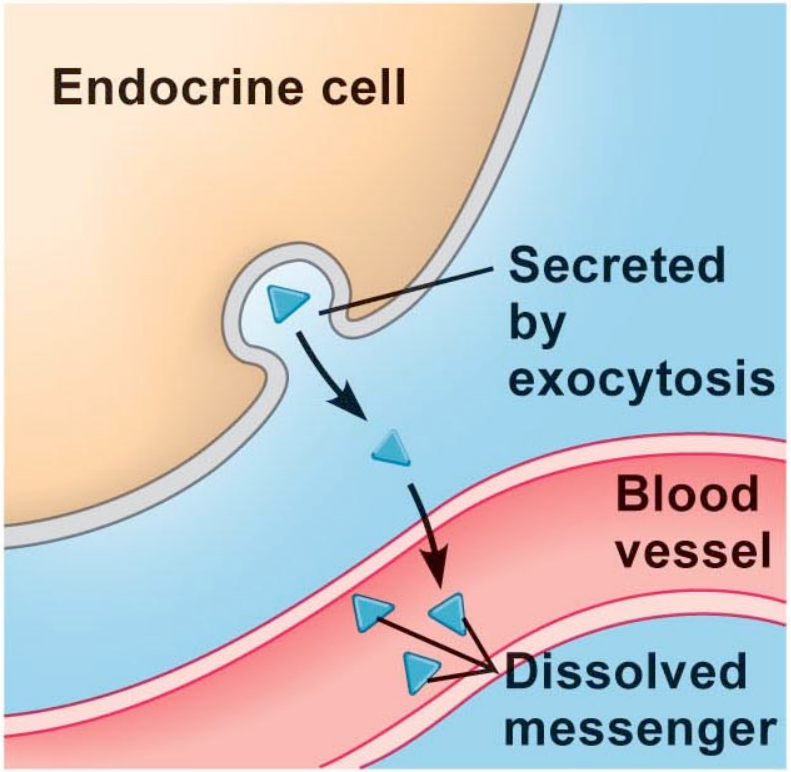
# REVIEW: Steroid Hormones



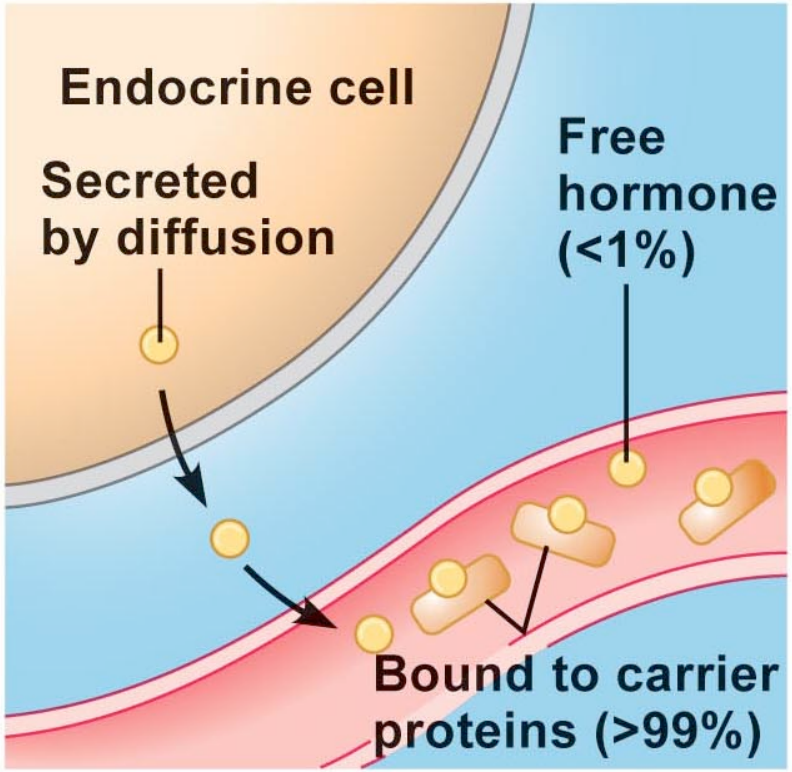
# REVIEW: Polypeptide Hormones



**Binding proteins:** These carry hormones through circulation, prolonging the (otherwise brief) half-life of the hormone. Major role in endocrine function.

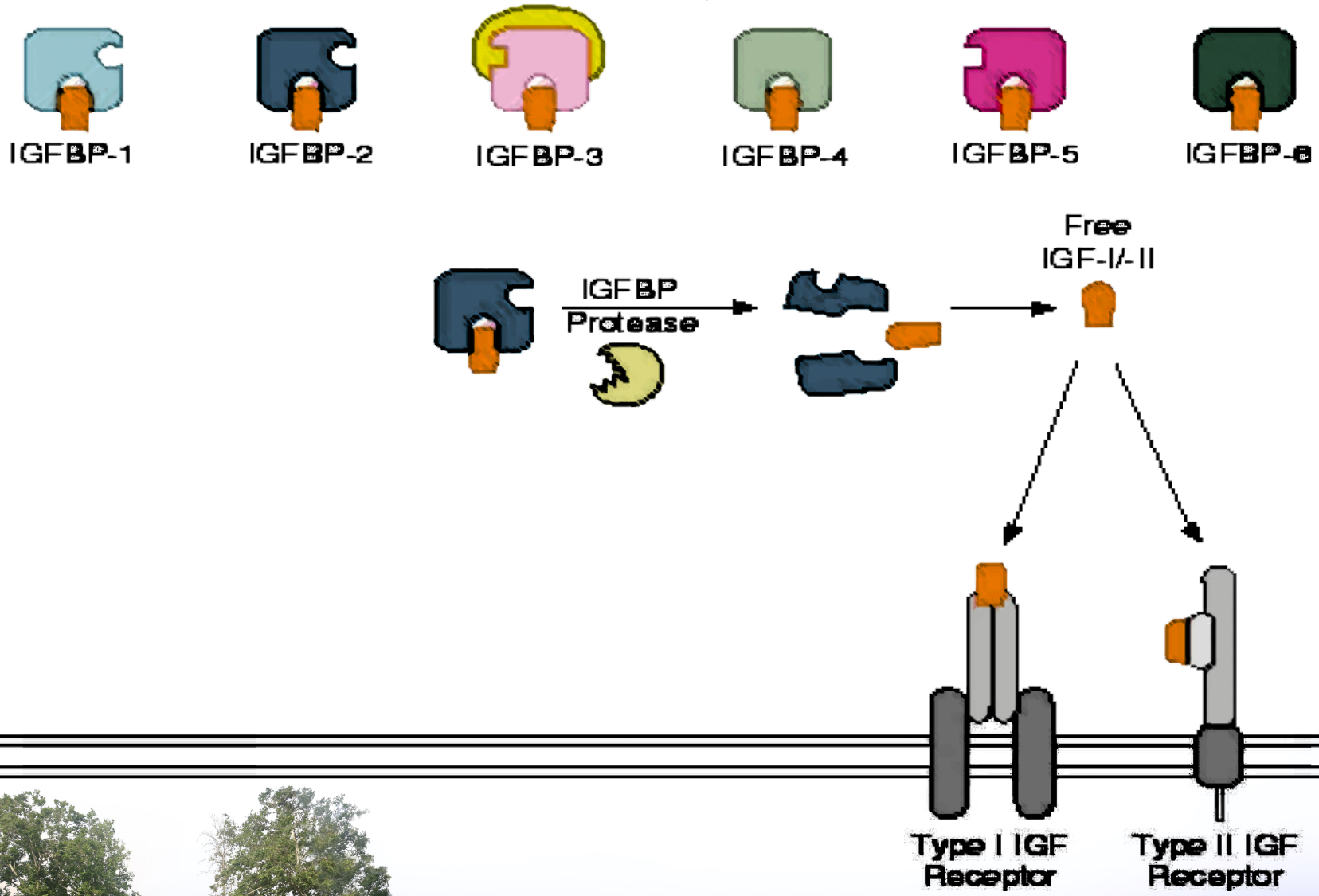



Hydrophilic messenger



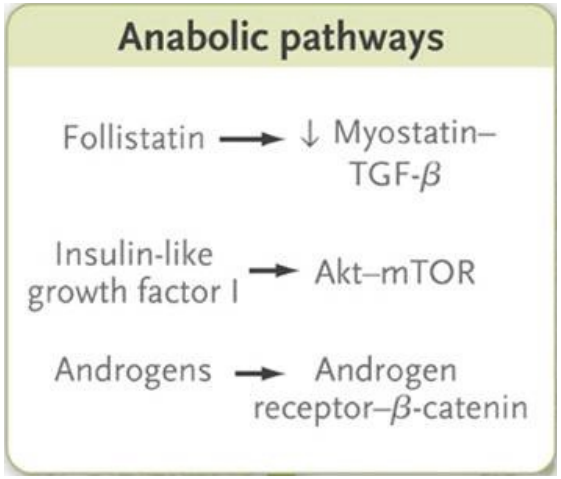

Hydrophobic messenger

# REVIEW: IGF Binding Proteins

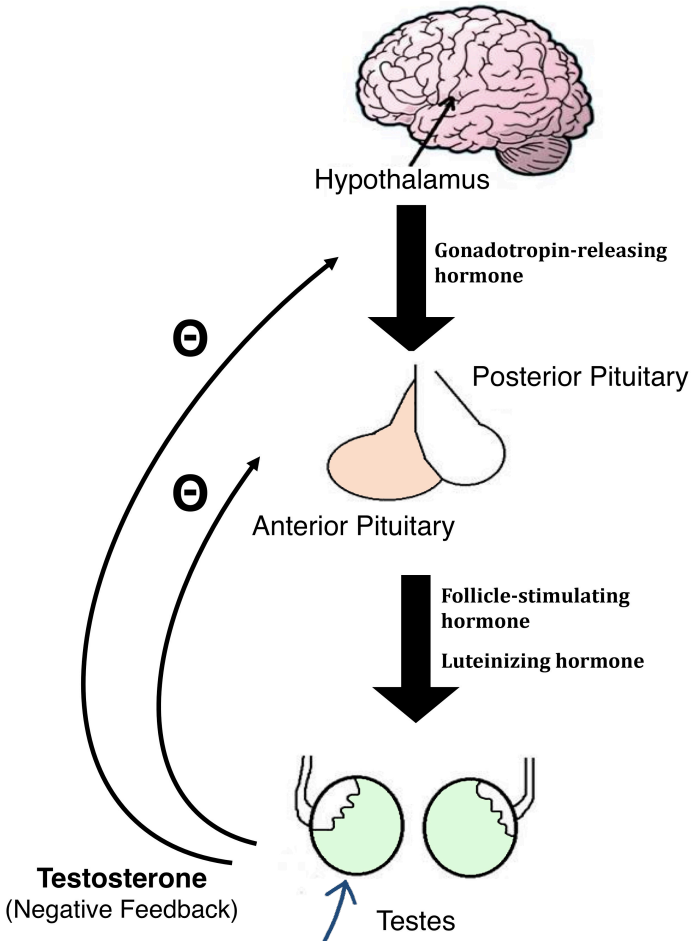



# Androgens

Steroid hormones that bind to androgen receptors, e.g., testosterone, dihydrotest., and androstenedione.




Testosterone is the primary androgen interacting with skeletal muscle.




Witnesses (that testify to, provide testimony for, or write a testament about) a man's virility.

# Androgens

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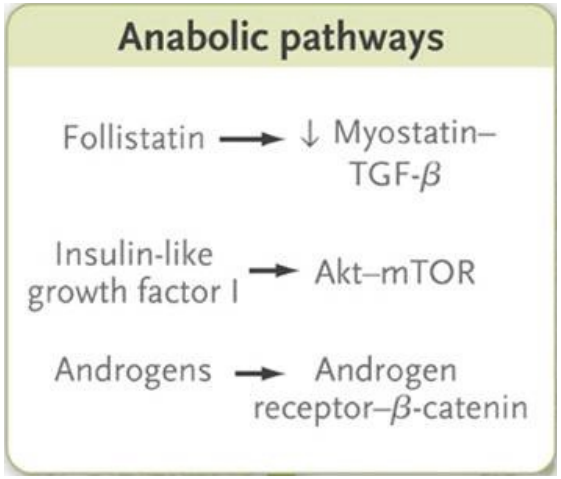
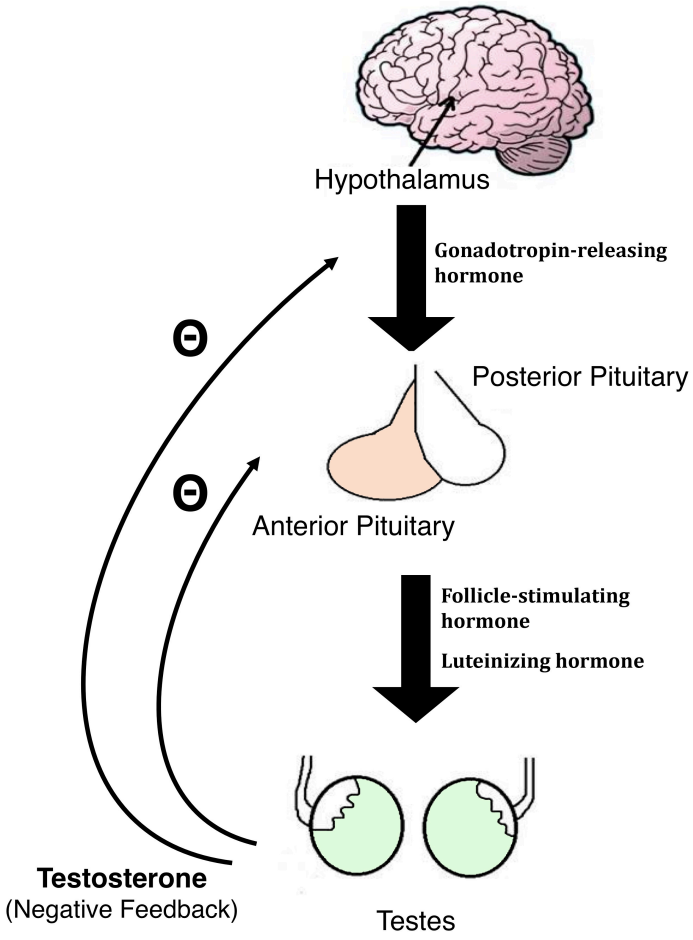


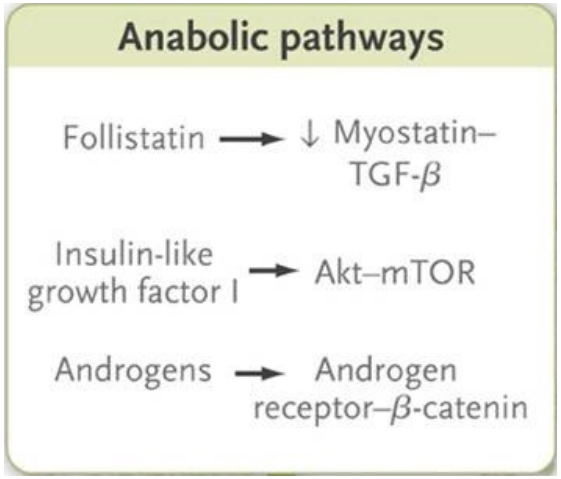

Testosterone is the primary androgen interacting with skeletal muscle.

Men have much higher levels than women (15-20x); women's serum concentrations don't vary much throughout the day.


In men, LH stimulates testosterone production; in women, LH triggers ovulation.

# Follistatin

Glycoprotein (binding protein) that binds to TGF-β proteins (transforming growth factor).




Myostatin is a myokine (little protein) produced by muscle cells that acts locally.

It inhibits Akt (PKB), inhibiting protein synthesis through the mTOR signaling cascade, *and* binds to the activin II receptor, which initiates a cell signaling cascade that prevents myoblasts from differentiating into mature muscle fibers.

## REVIEW: Follistatin

Biochemical and Biophysical Research Communications 431 (2013) 309–314

Myostatin acts as an autocrine/paracrine negative regulator in myoblast differentiation from human induced pluripotent stem cells

Fei Gao [a,1], Tsunao Kishida [a,1], Akika Ejima [a], Satoshi Gojo [b], Osam Mazda [a,*]

J Appl Physiol 2016 Mar 15; 120(6): 592–598.

**Paracrine and endocrine modes of myostatin action**

Yun-Sil Lee[1], Thanh V. Huynh[1], Se-Jin Lee[1]

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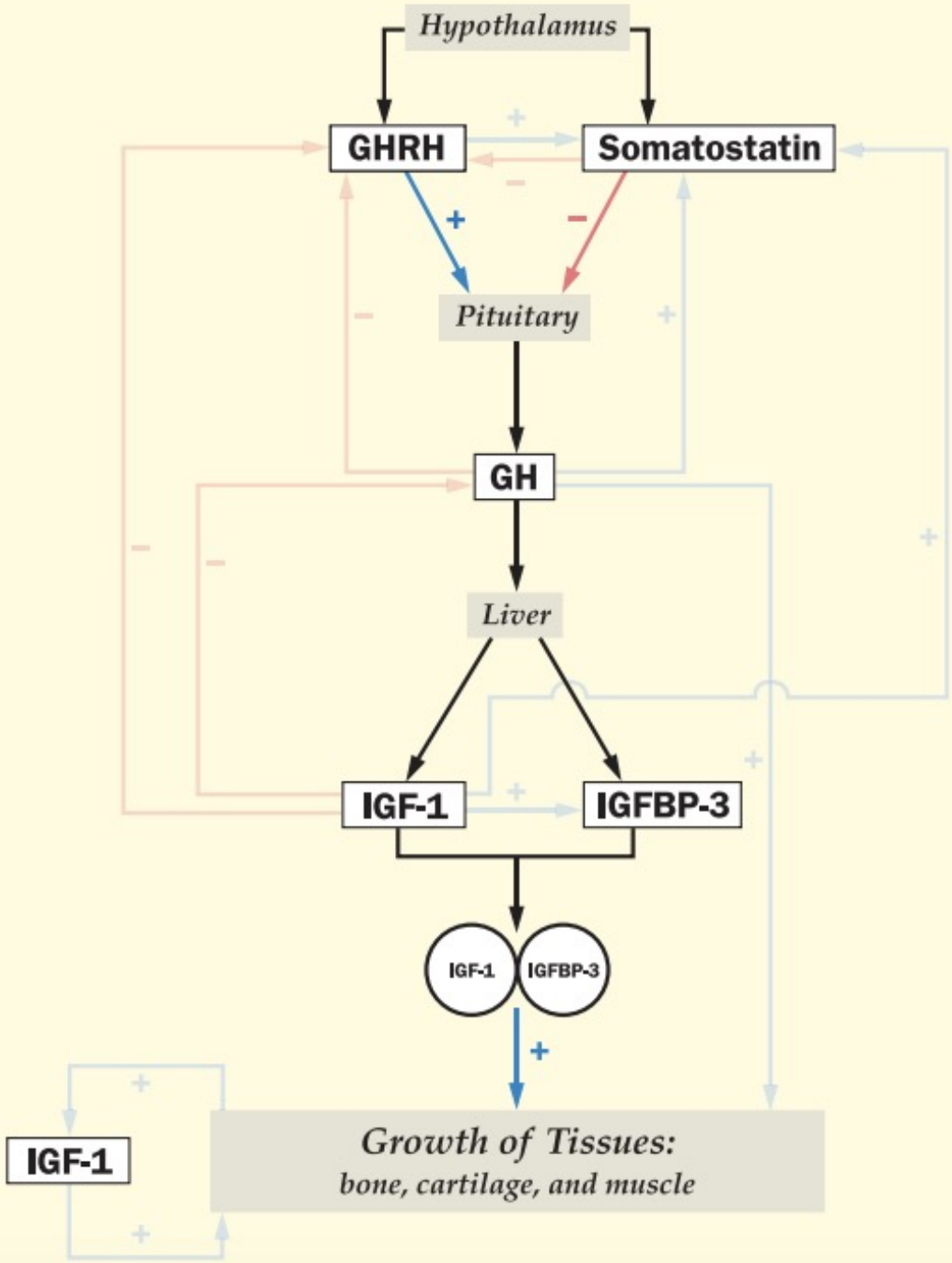
## REVIEW: hGH

Growth Hormone release is initiated by the hypothalamus.

Growth hormone-releasing hormone stimulates the anterior pituitary to release GH.

GH stimulates the liver to produce both IGF-1 and IGFBP-3.

Much of the anabolic effect of GH is mediated through IGF-1.

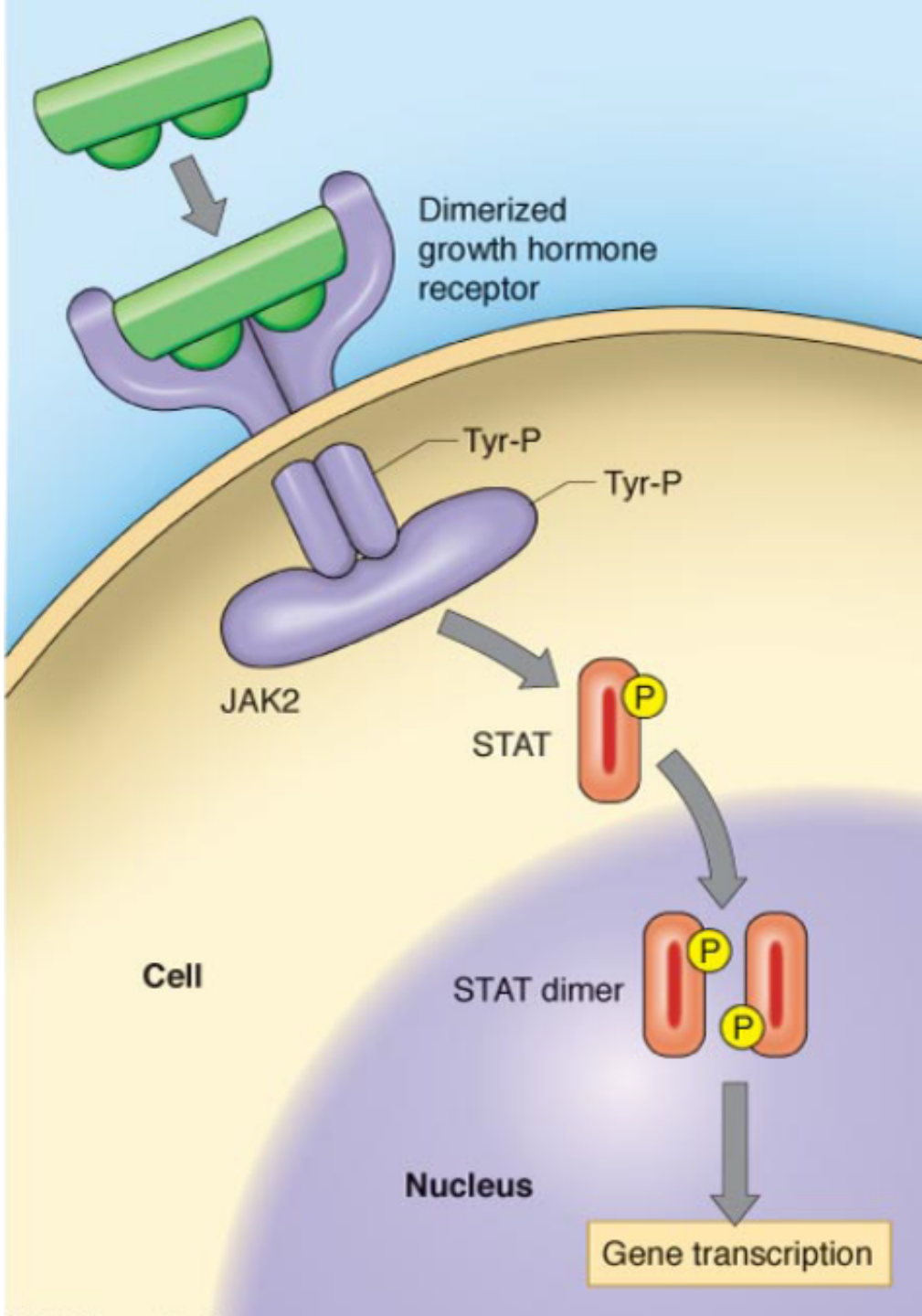


## REVIEW: hGH

Growth Hormone does not *just* stimulate IGF-1 production.

It also facilitates gene transcription via the JAK/STAT signaling pathway.

GH binds to external receptor and uses a secondary messenger (STAT) to enter the cell's nucleus, where it promotes transcription.




* JAK = Janus kinase

* STAT = Signal Transducer and Activator of Transcription

# GH does a lot:

- Preservation of glycogen stores
- Increase lipolysis and use of fatty acids
- Decreased amino acid degradation
- Increase amino acid transport across cell membranes
- Increase protein synthesis (and muscle mass)
- Increase collagen synthesis
- Cartilage growth, bone growth
- Enhance immune cell function

… but pharmacological GH doesn't seem to be very effective. It's certainly not predictable (in terms of muscle properties).

jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY

# Thyroid Hormone Stimulates Protein Synthesis in the Cardiomyocyte by Activating the Akt-mTOR and p70$^{S6K}$ Pathways*

**Agnes Kenessey**[‡] **and Kaie Ojamaa**[‡§1]

*From* [‡]*The Feinstein Institute for Medical Research, North Shore-Long Island Jewish Health System, Manhasset, New York 11030 and the* [§]*Departments of Cell Biology and Medicine, New York University School of Medicine, New York, New York 10016*

# What is an ergogenic aid?

## What is a hormone?

## What is a steroid?

A thing that helps an athlete perform better.

Three classes:

Mechanical Aids – Better cleats, pre-bent fiberglass vaulting pole, alloy bat
Psychological Aids – Positive self talk, hypnosis, cheering, music
Physiological Aids – Tylenol, caffeine, steroids, creatine, water, vitamins

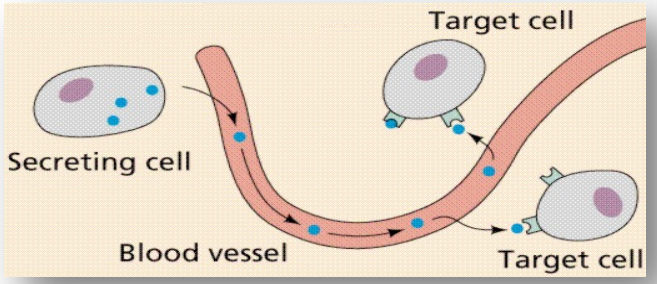
* Nutritional aids and performance-enhancing drugs are sometimes regarded as separate classes of aids. They aren't.

What is an ergogenic aid?

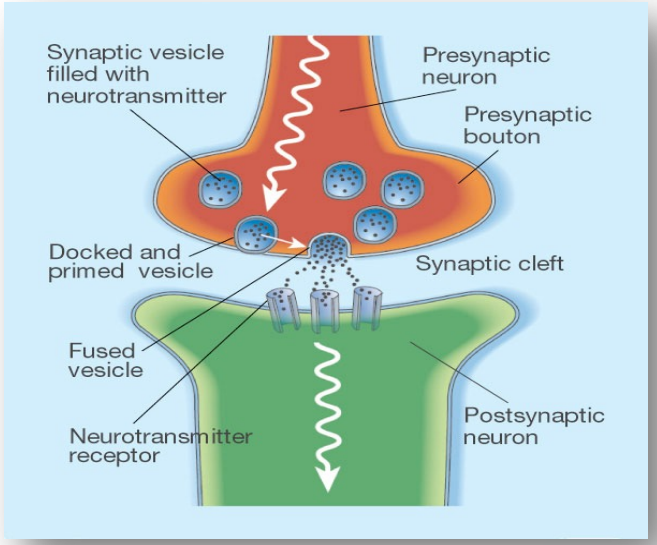
What is a hormone?

What is a steroid?

## Chemical Messengers




## Neurotransmitters




A chemical messenger is a compound that transmits a message.

**Hormones** = long range communication.

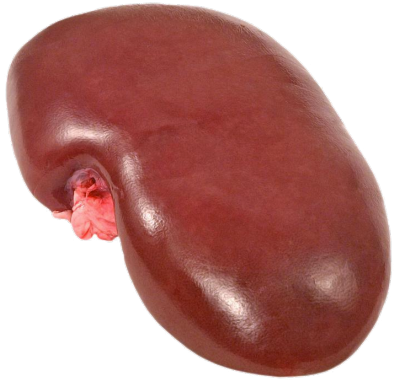
**Neurotransmitters** = communication to adjacent cells.

What is an ergogenic aid?

What is a hormone?

What is a steroid?

A bunch of things.



**Aldosterone** is a steroid (*mineralocorticoid*)

**Cortisol** is a *corticosteroid* (hydrocortisone)


"Steroids" usually refers to "anabolic-androgenic steroids".

Androgens. What are androgens?

# The arguments:

**1:** The athlete's health.

**2:** Unnecessary risk for harm, undue social coercion.

**3:** Steroids are unfair.

**4:** Steroids strip the soul from the sport.

**5:** Natural vs. unnatural.

**6:** Rules.

**7:** Harm to other people.

**8:** The purported effects are unproven.

**9:** Paying one's dues: Steroid users are getting something for nothing.

# Physiological effect: Increasing myonuclei.

## Testosterone-induced increase in muscle size in healthy young men is associated with muscle fiber hypertrophy

INDRANI SINHA-HIKIM,[1] JORGE ARTAZA,[1] LINDA WOODHOUSE,[1]
NESTOR GONZALEZ-CADAVID,[1] ATAM B. SINGH,[1] MARTIN I. LEE,[1] THOMAS W. STORER,[1]
RICHARD CASABURI,[2] RUOQUING SHEN,[1] AND SHALENDER BHASIN[1]
[1]*Division of Endocrinology, Metabolism, and Molecular Medicine, Charles R. Drew University of Medicine and Science, Los Angeles, 90059; and* [2]*Division of Respiratory and Critical Care Physiology and Medicine, Harbor-University of California at Los Angeles Medical Center, Torrance, California 90509*

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*Am J Physiol Endocrinol Metab* 283: E154–E164, 2002.
First published March 12, 2002; 10.1152/ajpendo.00502.2001.

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Review Article

## ADDITION OF NEW MYONUCLEI IS A PRE-REQUISITE FOR SKELETAL MUSCLE GROWTH

Muhammad Mustafa Qamar*[1], Ayesha Basharat[2]

[1]*Department of Exercise Physiology and Sports Medicine, Orebro University, Sweden;* [2]*Department of Physiotherapy, University of Sargodha, Pakistan*

*Corresponding author: Muhammad Mustafa Qamar (*dearqamar@hotmail.com*), Department of Exercise Physiology and Sports Medicine, Orebro University, Sweden.

PNAS PNAS PNAS PNAS

## Myonuclei acquired by overload exercise precede hypertrophy and are not lost on detraining

J. C. Bruusgaard, I. B. Johansen, I. M. Egner, Z. A. Rana, and K. Gundersen[1]

Department of Molecular Biosciences, University of Oslo, 0371 Oslo, Norway

Edited by Gerald D. Fischbach, The Simons Foundation, New York, NY, and approved July 16, 2010 (received for review December 4, 2009)

Author contributions: J.C.B. and K.G. designed research; J.C.B., I.B.J., I.M.E., Z.A.R., and K.G. performed research; J.C.B., I.B.J., I.M.E., and K.G. analyzed data; and J.C.B., I.B.J., I.M.E., and K.G. wrote the paper.

www.pnas.org/cgi/doi/10.1073/pnas.0913935107

PNAS Early Edition

## Myonuclear number and myosin heavy chain expression in rat soleus single muscle fibers after spaceflight

D. L. ALLEN, W. YASUI, T. TANAKA, Y. OHIRA, S. NAGAOKA,
C. SEKIGUCHI, W. E. HINDS, R. R. ROY, AND V. R. EDGERTON
*Department of Physiological Science, University of California, Los Angeles 90095-1527; Brain Research Institute, University of California, Los Angeles 90095-1726; Space Life Science Payload Office, National Aeronautics and Space Administration Ames Research Center, Moffett Field, California 94035-1000; Department of Physiology and Biomechanics, National Institute of Fitness and Sports, Kanoya City, Kagoshima 891-23; and Space Experiment Group, National Space Development Agency of Japan, Tsukuba City 305, Japan*

*J Appl Physiol. (1996). 81: 145-151.*

# REVIEW: Anabolic Steroids

ADULT UROLOGY

ELSEVIER

## EFFICACY AND SAFETY OF A DUAL INHIBITOR OF 5-ALPHA-REDUCTASE TYPES 1 AND 2 (DUTASTERIDE) IN MEN WITH BENIGN PROSTATIC HYPERPLASIA

CLAUS G. ROEHRBORN, PETER BOYLE, J. CURTIS NICKEL, KLAUS HOEFNER, AND GERALD ANDRIOLE, ON BEHALF OF THE ARIA3001, ARIA3002, AND ARIA3003 STUDY INVESTIGATORS

UROLOGY 60: 434–441, 2002.




## Androgens and estrogens in benign prostatic hyperplasia: past, present and future

Tristan M. Nicholson and William A. Ricke

Androgens and estrogens in benign prostatic hyperplasia: past, present and future
Differentiation. 2011 Nov-Dec; 82(4-5): 184–189.

0022-5347/04/1724-1399/0
THE JOURNAL OF UROLOGY®


Vol. 172, 1399–1403, October 2004
*Printed in U.S.A.*
**DOI: 10.1097/01.ju.0000139539.94828.29**

## DIHYDROTESTOSTERONE AND THE PROSTATE: THE SCIENTIFIC RATIONALE FOR 5α-REDUCTASE INHIBITORS IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

GERALD ANDRIOLE,*† NICHOLAS BRUCHOVSKY, LELAND W. K. CHUNG, ALVIN M. MATSUMOTO, ROGER RITTMASTER,‡ CLAUS ROEHRBORN, DAVID RUSSELL AND DONALD TINDALL‡

*From the Washington University in St. Louis (GA), St. Louis, Missouri, British Columbia Cancer Agency (NB), Vancouver, British Columbia, Canada, Winship Cancer Institute, Emory University (LWKC), Atlanta, Georgia, University of Washington School of Medicine and Geriatric Research, Education and Clinical Center, Veterans Affairs Puget Sound Health Care System (AMM), Seattle, Washington, GlaxoSmithKline, (RR), Research Triangle Park, North Carolina, University of Texas Southwestern Medical Center at Dallas (CR, DR), Dallas, Texas, and Mayo Clinic College of Medicine (DT), Rochester, Minnesota*

*"Oral administration of stanozolol reduced HDL-cholesterol concentrations 33% after only one week of treatment. Testosterone, in contrast, induced comparably little change."*

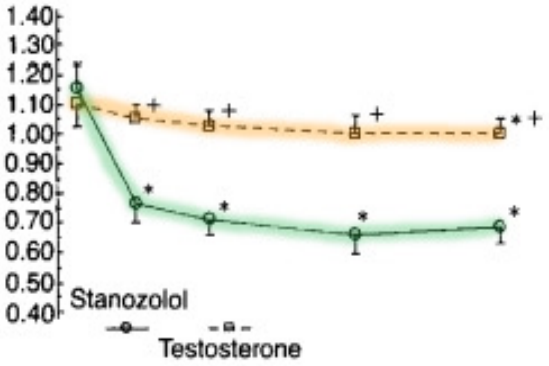
# Contrasting Effects of Testosterone and Stanozolol on Serum Lipoprotein Levels

Paul D. Thompson, MD; Eileen M. Cullinane; Stanley P. Sady, PhD; Claire Chenevert; Ann L. Saritelli; Mina A. Sady; Peter N. Herbert, MD

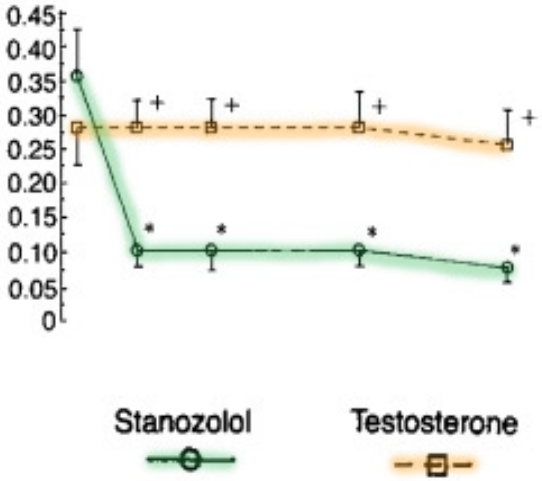
Oral anabolic steroids produce striking reductions in serum concentrations of high-density lipoprotein (HDL) cholesterol. We hypothesized that this effect related to their route of administration and was unrelated to their androgenic potency. We administered oral stanozolol (6 mg/d) or supraphysiological doses of intramuscular testosterone enanthate (200 mg/wk) to 11 male weight lifters for six weeks in a crossover design. Stanozolol reduced HDL-cholesterol and the $HDL_2$ subfraction by 33% and 71%, respectively. In contrast, testosterone decreased HDL-cholesterol concentration by only 9% and the decrease was in the $HDL_3$ subfraction. Apolipoprotein A-I level decreased 40% during stanozolol but only 8% during testosterone treatment. The low-density lipoprotein cholesterol concentration increased 29% with stanozolol and decreased 16% with testosterone treatment. Stanozolol, moreover, increased postheparin hepatic triglyceride lipase activity by 123%, whereas the maximum change during testosterone therapy (+25%) was not significant. Weight gain was similar with both drugs, but testosterone was more effective in suppressing gonadotropic hormones. We conclude that the undesirable lipoprotein effects of 17-α-alkylated steroids given orally are different from those of parenteral testosterone and that the latter may be preferable in many clinical situations.

(*JAMA*. 1989;261:1165-1168)

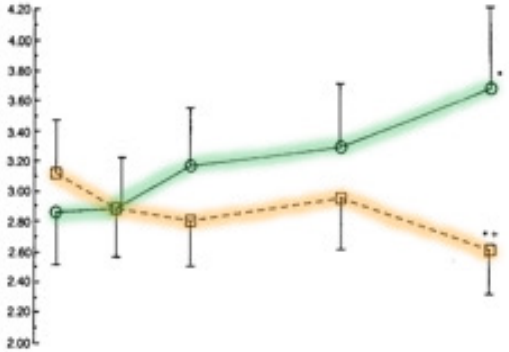
*HDL Cholesterol Level, mmol/L*




*HDL-2 Cholesterol Level, mmol/L*




*LDL Cholesterol Level, mmol/L*



Surgical Practice

doi:10.1111/j.1744-1633.2010.00501.x Case report

**Massive hepatic haemorrhage caused by anabolic steroid-induced peliosis hepatis: Successful treatment by radiofrequency ablation**

Fabio Garofalo,[1] Riccardo E. Vandoni,[4*] Adriano Guerra,[1] Mario Alerci,[2] Stefano Crippa[3] and Philippe Gertsch[1]

*Departments of [1]Surgery and [2]Radiology, Ospedale San Giovanni, Bellinzona, [3]Istituto Cantonale di Patologia, Locarno and [4]Department of Surgery, Hôpital du Jura Bernois, Moutier, Switzerland*

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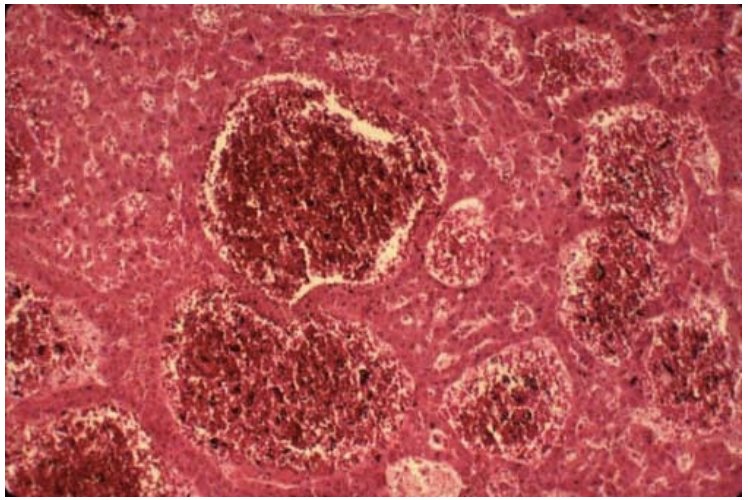
Email: riccardo.vandoni@bluewin.ch
Received 3 September 2009; accepted 15 January 2010.

*Surgical Practice* (2010) **14**, 111–115 

Blood-filled cysts can form; if they rupture, you bleed into your gut. If you bleed into your muscle, the muscle will compress the bleed and ultimately stop it. You don't have that safety net in your gut.



*Just remember: Tylenol is worse.*

LIVER FAILURE AND LIVER DISEASE
LIVER FAILURE

## Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study

Anne M. Larson,[1] Julie Polson,[2] Robert J. Fontana,[3] Timothy J. Davern,[4] Ezmina Lalani,[2] Linda S. Hynan,[5] Joan S. Reisch,[5] Frank V. Schiødt,[2] George Ostapowicz,[2] A. Obaid Shakil,[6] William M. Lee,[2] and the Acute Liver Failure Study Group

HEPATOLOGY, Vol. 42, No. 6, 2005

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2006; **15**: 398–405
Published online 18 November 2005 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pds.1191

ORIGINAL REPORT

## Estimates of Acetaminophen (Paracetamol)-associated overdoses in the United States

Parivash Nourjah PhD*, Syed Rizwanuddin Ahmad MD, MPH, Claudia Karwoski Pharm D and Mary Willy PhD

*Office of Drug Safety, Division of Drug Risk Evaluation, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA*

*Correspondence to: Dr P. Nourjah, Food and Drug Administration (FDA), 10903 New Hampshire Avenue, 3414 Building 22, Silver Spring, MD 20993. E-mail: NOURJAHP@CDER.FDA.GOV

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ISSN 0002-9270
doi: 10.1111/j.1572-0241.2007.01388.x

## Population-Based Surveillance for Acute Liver Failure

William A. Bower, M.D.,[1] Matthew Johns, M.P.H.,[2] Harold S. Margolis, M.D.,[1] Ian T. Williams, Ph.D.,[1] and Beth P. Bell, M.D.[1]

[1]*Centers for Disease Control and Prevention, Atlanta, Georgia; and* [2]*Georgia Emerging Infections Program, Atlanta, Georgia*

(Am J Gastroenterol 2007;102:2459–2463)

JACC Vol. 19, No. 2
February 1992:278–82

# Left Ventricular Function Is Not Impaired in Weight-Lifters Who Use Anabolic Steroids

PAUL D. THOMPSON, MD, FACC, ARA SADANIANTZ, MD, FACC,
EILEEN M. CULLINANE, MS, KURT S. BODZIONY, MS,* DON H. CATLIN, MD,†
GEORGE TOREK-BOTH, PHD,† PAMELA S. DOUGLAS, MD, FACC‡
*Providence and Kingston, Rhode Island; Los Angeles, California; Boston, Massachusetts*

**Recent reports suggest that anabolic steroid use might deleteriously affect left ventricular function. To examine this possibility, the present study measured left ventricular size and function with use of Doppler echocardiographic techniques in 23 weight lifters: 12 who were currently using anabolic steroids and 11 who reported that they had never used these drugs. Drug users had administered anabolic steroids to themselves for at least three cycles over the past year. All studies were interpreted by blind review and group assignment was confirmed by urine testing. Average age, years of exercise training and body weight, as well as heart rate and blood pressure at rest were similar in both groups.**

**Cardiac dimensions (mean ± SD) including left ventricular diastolic cavity diameter (57 ± 3 vs. 56 ± 5 mm), septal thickness (10 ± 2 vs. 9 ± 1 mm), posterior wall thickness (8 ± 1 vs. 8 ± 1 mm) and myocardial mass (149 ± 27 vs. 135 ± 21 g) did not differ between the anabolic steroid users and nonusers, respectively. Left ventricular systolic and diastolic function at rest were also similar in the users and nonusers: left ventricular fractional shortening (38 ± 5% vs. 41 ± 5%); peak rate of wall thickening (4.3 ± 1.1 vs. 4 ± 1.1 $s^{-1}$) and thinning (−5.9 ± 1.6 vs. − 5.6 ± 2.1 $s^{-1}$); left ventricular filling rate (3.1 ± 0.6 vs. 3.3 ± 0.5 $s^{-1}$), as well as early (81 ± 12 vs. 83 ± 12 cm/s) and atrial maximal inflow velocities (41 ± 6 vs. 41 ± 9 cm/s) and their ratio (2.01 ± 0.49 vs. 2.16 ± 0.67) were not different between groups.**

**These results suggest that anabolic steroid use was not associated with left ventricular hypertrophy or clinically detectable systolic and diastolic dysfunction in a small sample of weight lifters who were using these drugs.**

***(J Am Coll Cardiol 1992;19:278–82)***

0195-9131/85/1706-0701$2.00/0
MEDICINE AND SCIENCE IN SPORTS AND EXERCISE

Vol. 17, No. 6
Printed in U.S.A.

# Left ventricular size and function in body builders using anabolic steroids

RICHARD C. SALKE, THOMAS W. ROWLAND, and EDMUND J. BURKE

*Department of Movement Science, Springfield College, and the Department of Pediatrics, Baystate Medical Center, Springfield, MA 01199*

## Methods:

*"The total amount of anabolic steroids reportedly used by the athletes was very large, amounting to 10 to 20 times that which would be normally recommended by a pharmaceutical manufacturer."*

**Results:** They didn't find any differences in cardiac function. No meaningful differences of any kind relative to controls.

# REVIEW: Anabolic Steroids

Asian Journal of Sports Medicine
Tehran University of Medical Sciences

Echocardiographic Findings in Power Athletes Abusing Anabolic Androgenic Steroids

Behzad Hajimoradi, MD and Hashem Kazerani, MD

Asian J Sports Med. 2013 March; 4(1): 10–14.

**Other studies with similar outcomes:**

Urhausen A, Holpes R, Kindermann W. (1989). One- and two-dimensional echocardiography in bodybuilders using anabolic steroids. European Journal of Applied Physiology and Occupational Physiology, 58(6): 633-640.

Palatini P, Giada F, Garavelli G, Sinisi F, Mario L, Michieletto M, Baldo-Enze G. (1996). Cardiovascular effects of anabolic steroids in weight-trained subjects. Journal of Clinical Pharmacology, 36(12): 1132-1140.

**It's unlikely that steroids are ruining hearts…**

## Same basic study, 18 years later, same findings. A quotation from the discussion:

*"In the current study there was not any statistically significant difference in LV systolic and diastolic dimensions between cases and control groups. Systolic and diastolic function in all groups was relatively similar and it is suggestive of no effect, or minimal effect of chronic anabolic steroid abuse on size, function and stiffness of the heart."*

Original Articles

## Long-Term Anabolic-Androgenic Steroid Use Is Associated With Left Ventricular Dysfunction

Aaron L. Baggish, MD; Rory B. Weiner, MD; Gen Kanayama, MD, PhD; James I. Hudson, MD, ScD; Michael H. Picard, MD; Adolph M. Hutter, Jr, MD; Harrison G. Pope, Jr, MD

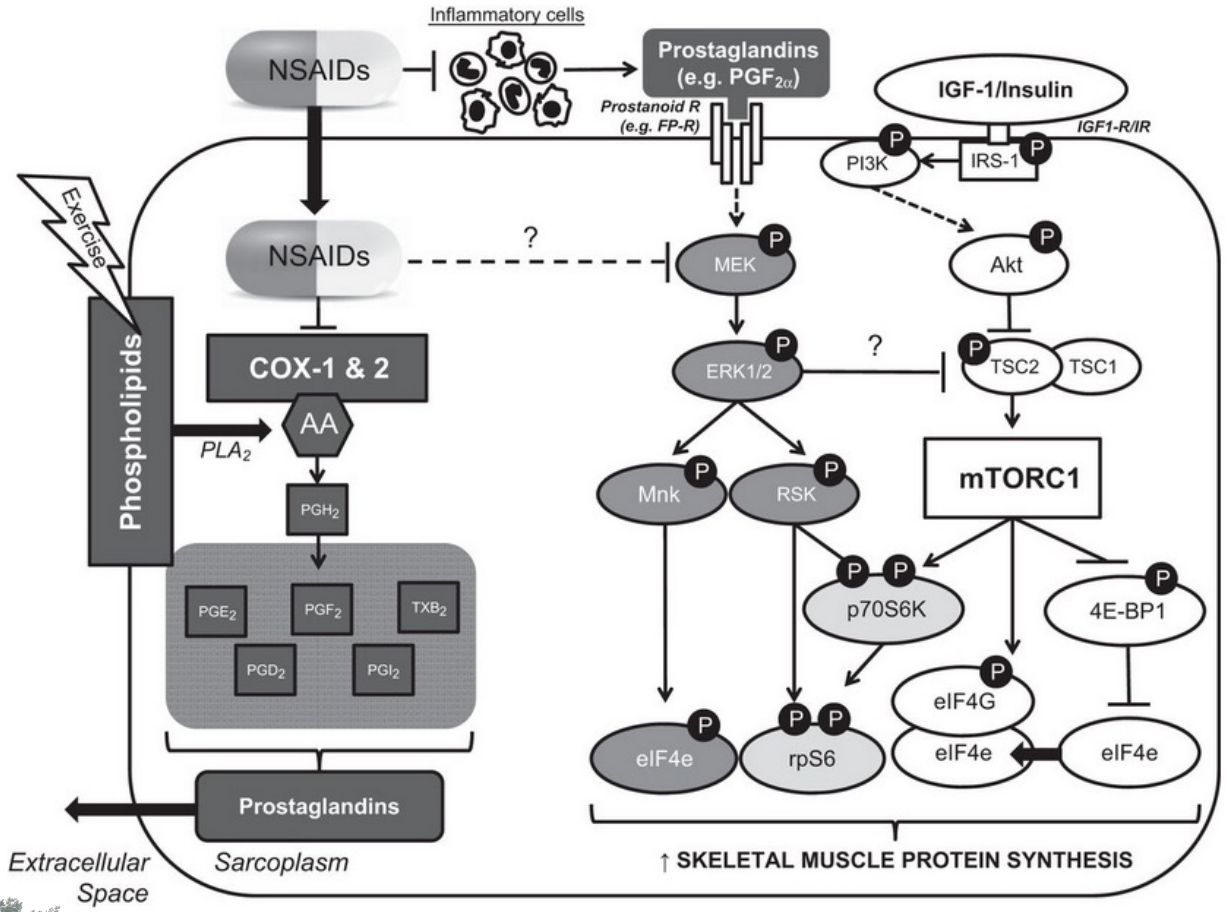
Circulation
Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

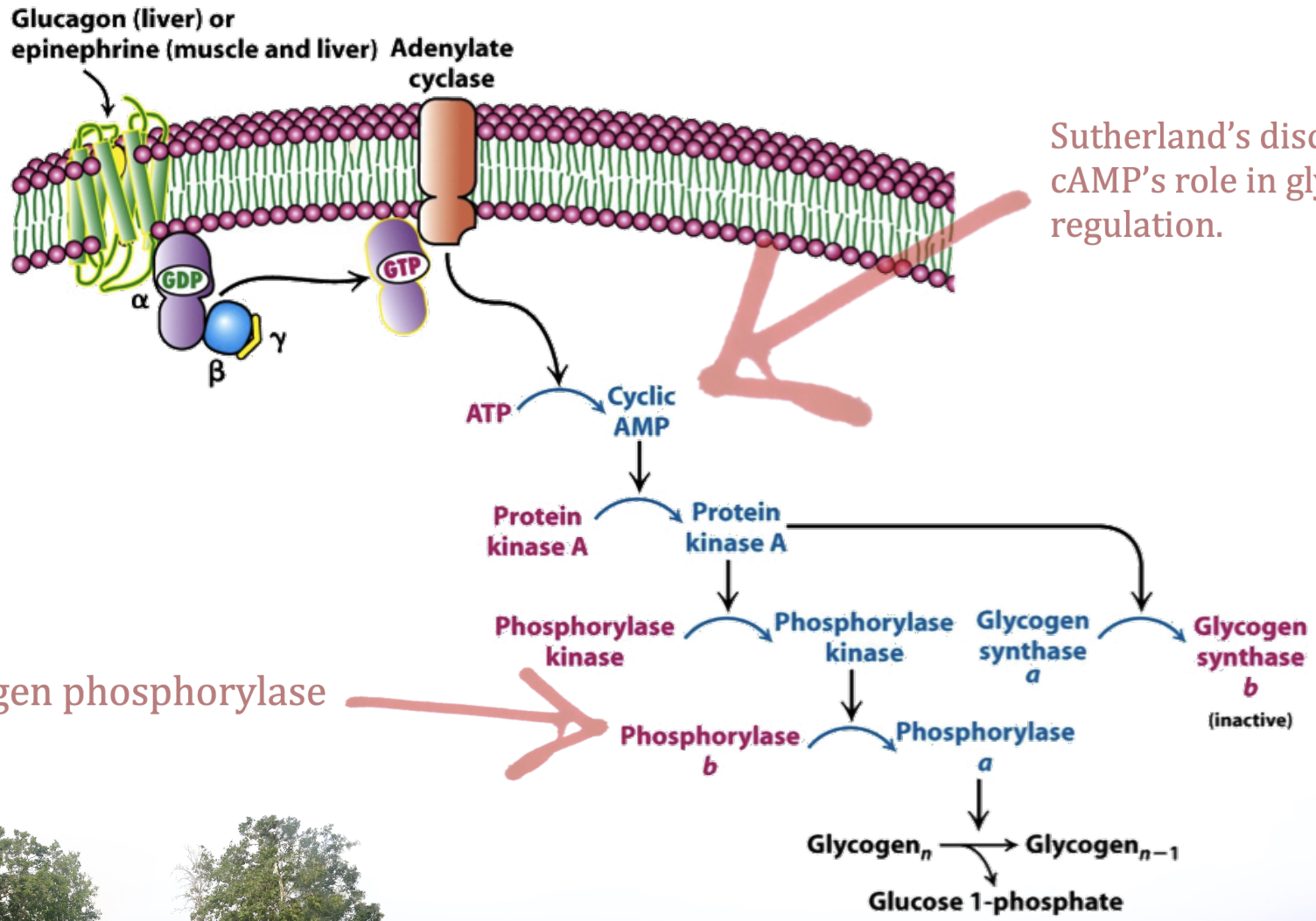
**Anabolic-Androgenic Steroids : Worse for the Heart Than We Knew?**
Matthew W. Parker and Paul D. Thompson
*Circ Heart Fail* 2010;3;470-471;
DOI: 10.1161/CIRCHEARTFAILURE.110.957720
Circulation: Heart Failure is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1941-3289. Online ISSN: 1941-3297

After ~9 consistent years of monstrous doses, your heart might not "squeeze" quite as well. Regarding the subjects: *"The AAS users were remarkable for both their steroid dose and duration of use."*

# Signaling cascades you should know by now:



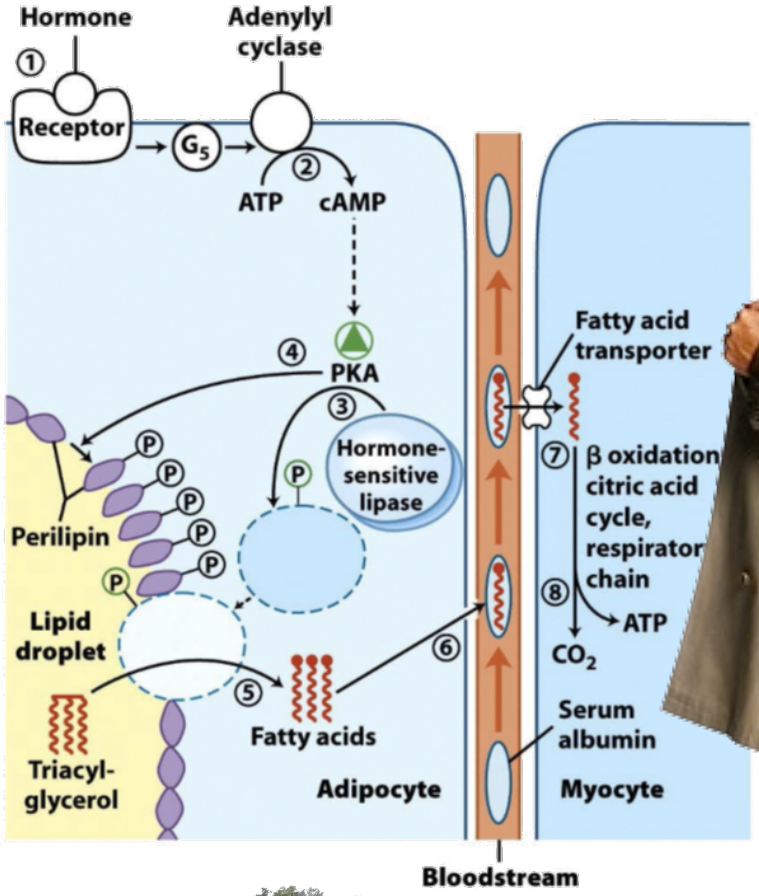

# Signaling cascades you should know by now:

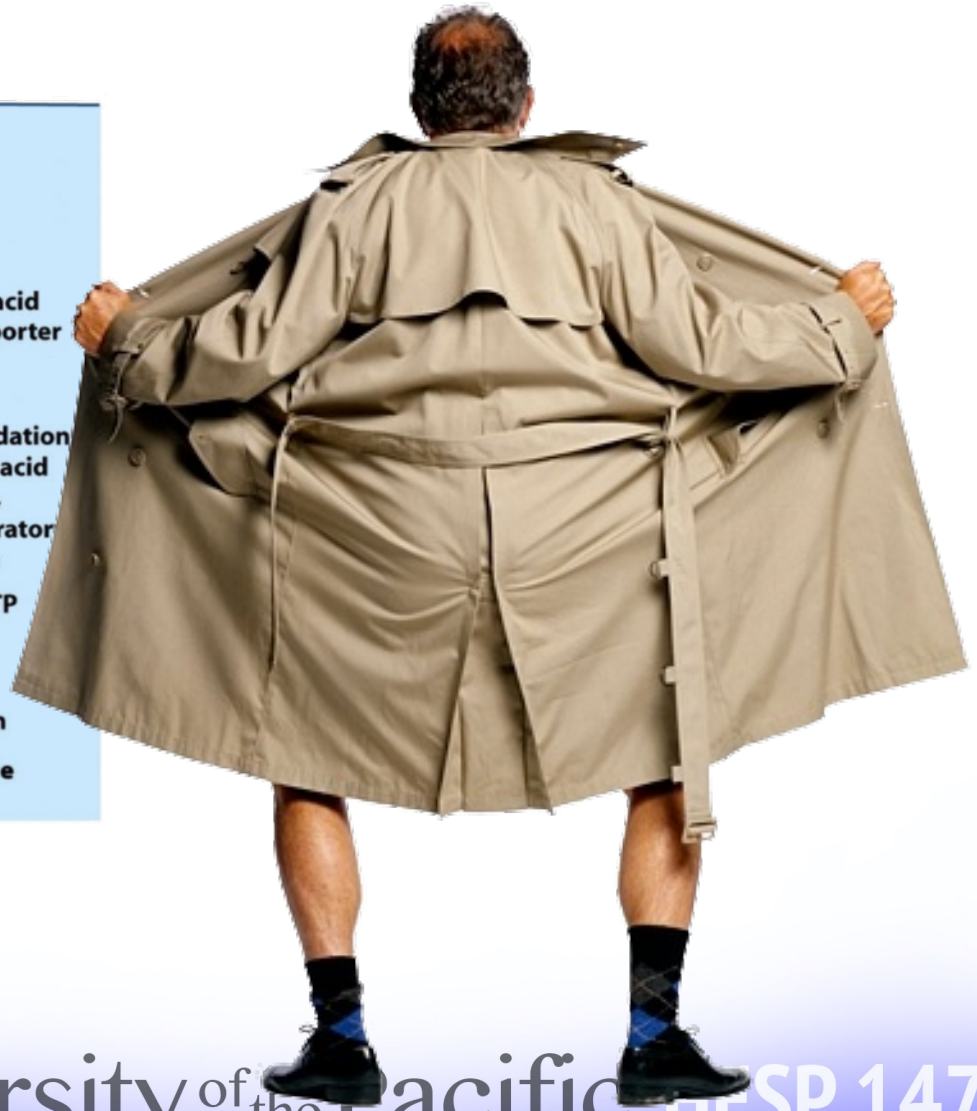



Sutherland's discovery: cAMP's role in glycogen regulation.

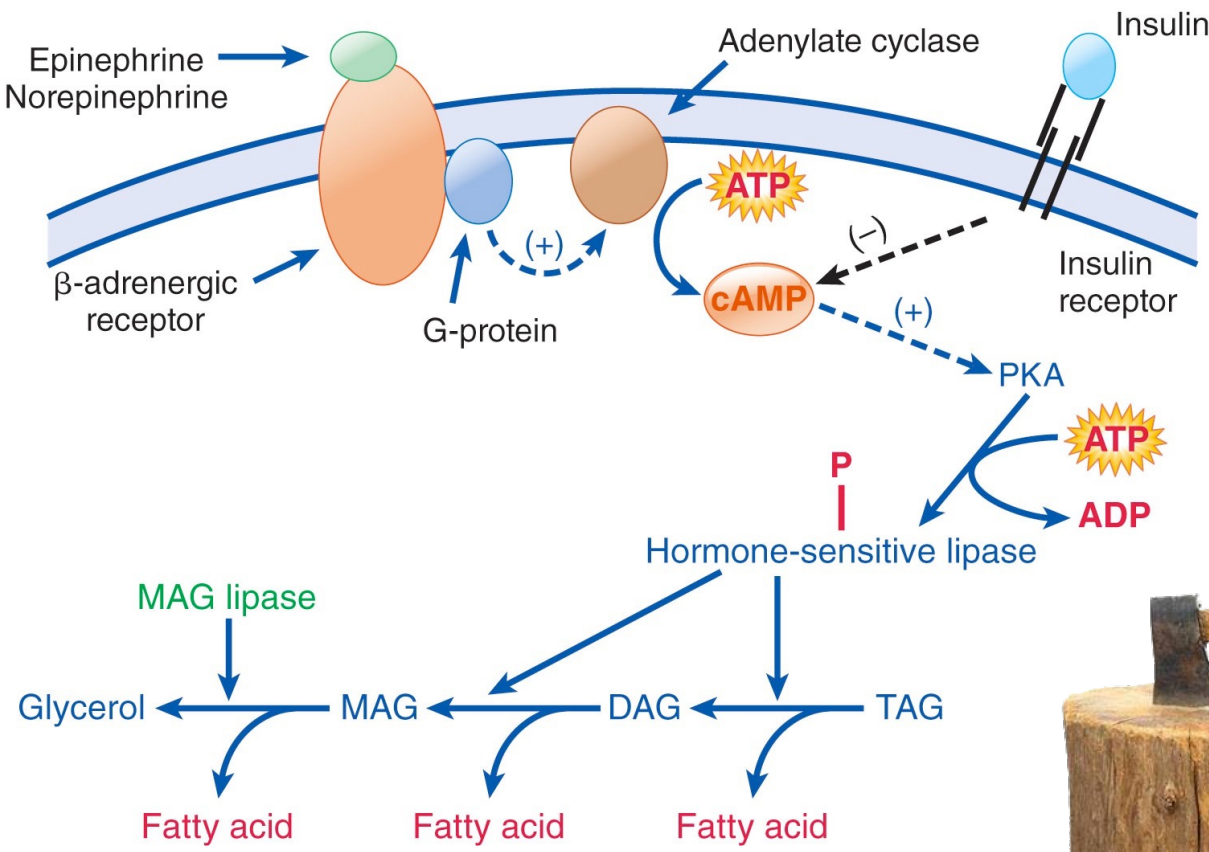
Glycogen phosphorylase

# Signaling cascades you should know by now:



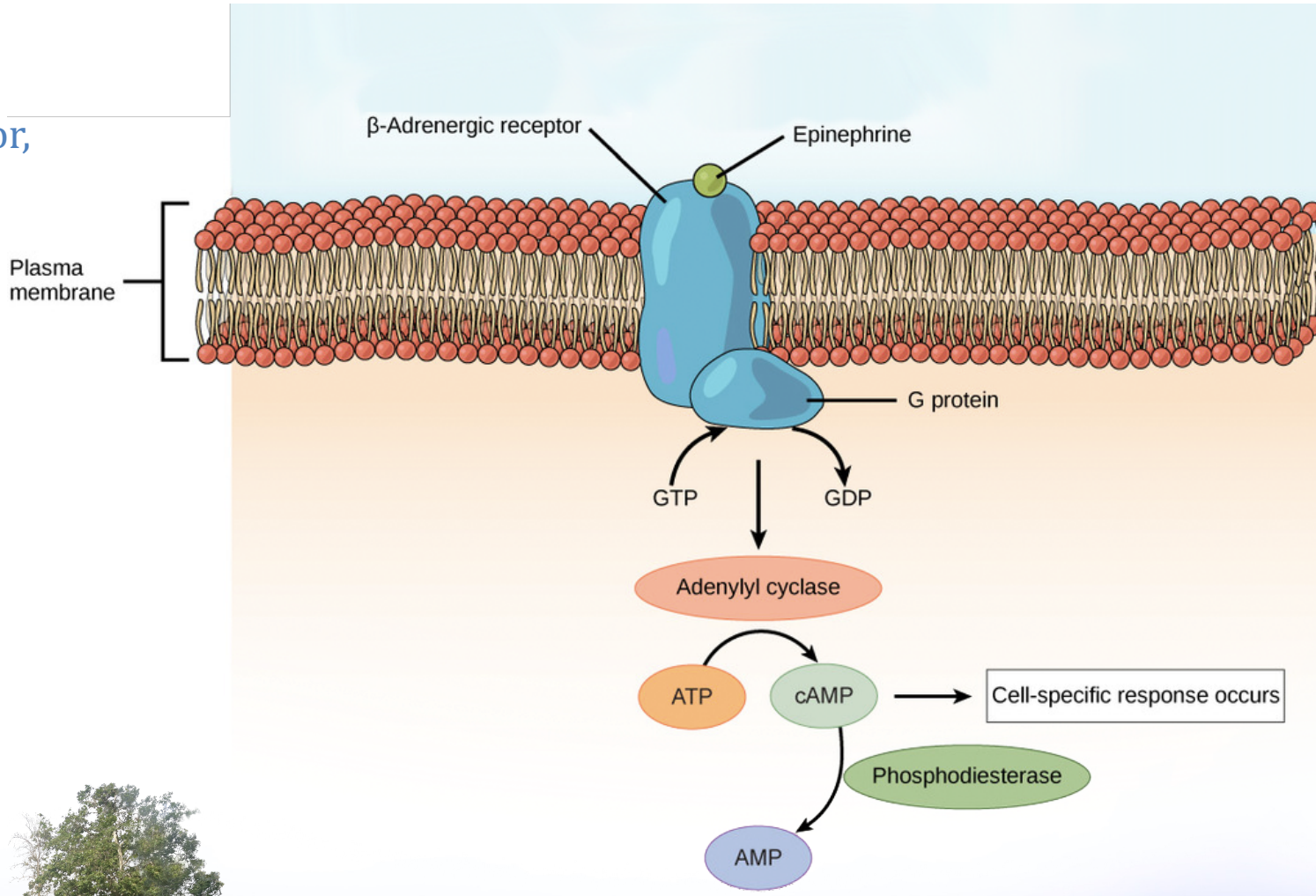



# Signaling cascades you should know by now:

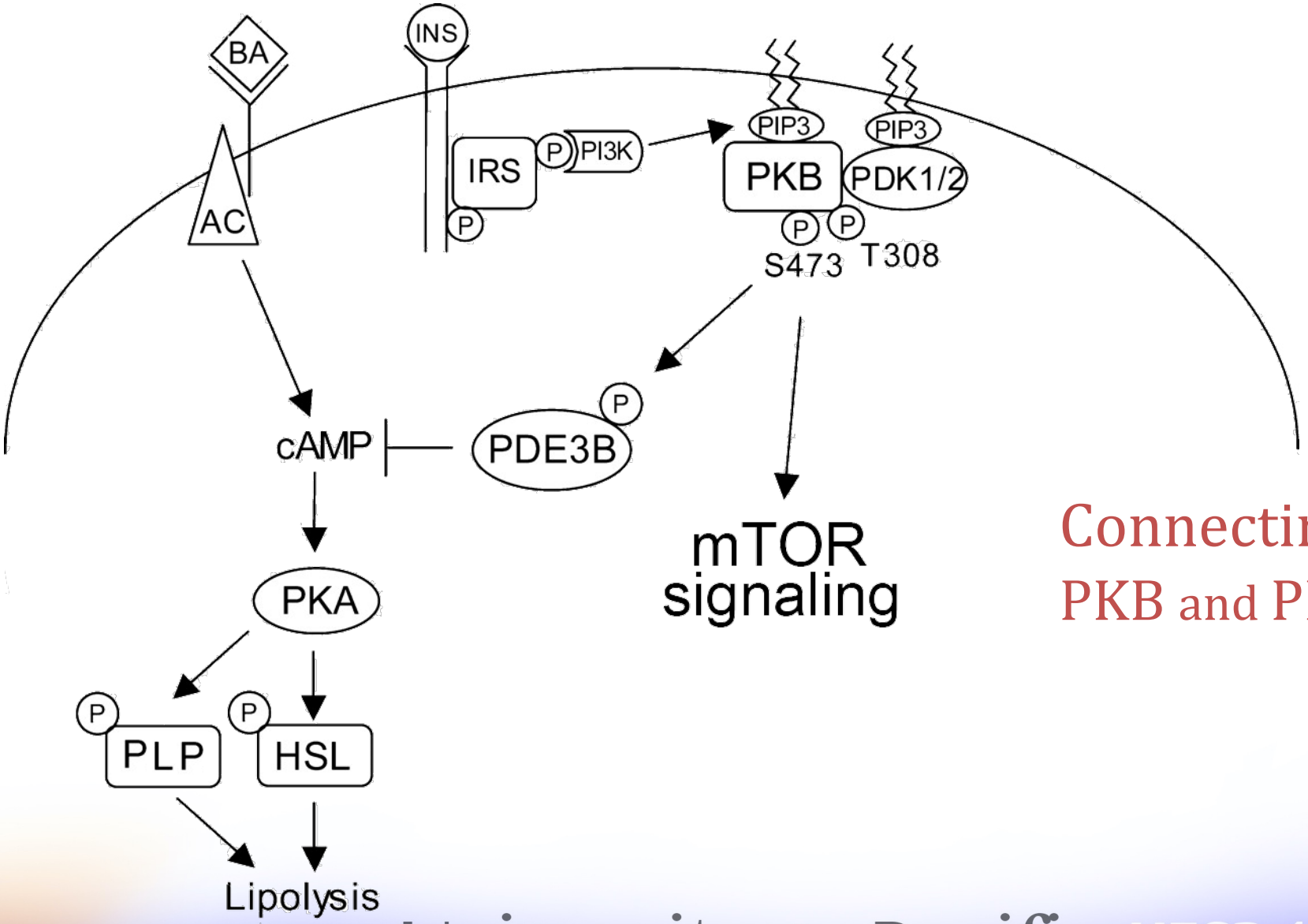



# Signaling cascades you should know by now:

Downstream from the insulin receptor, PI3K or PKB will phosphorylate (activate) PDE.

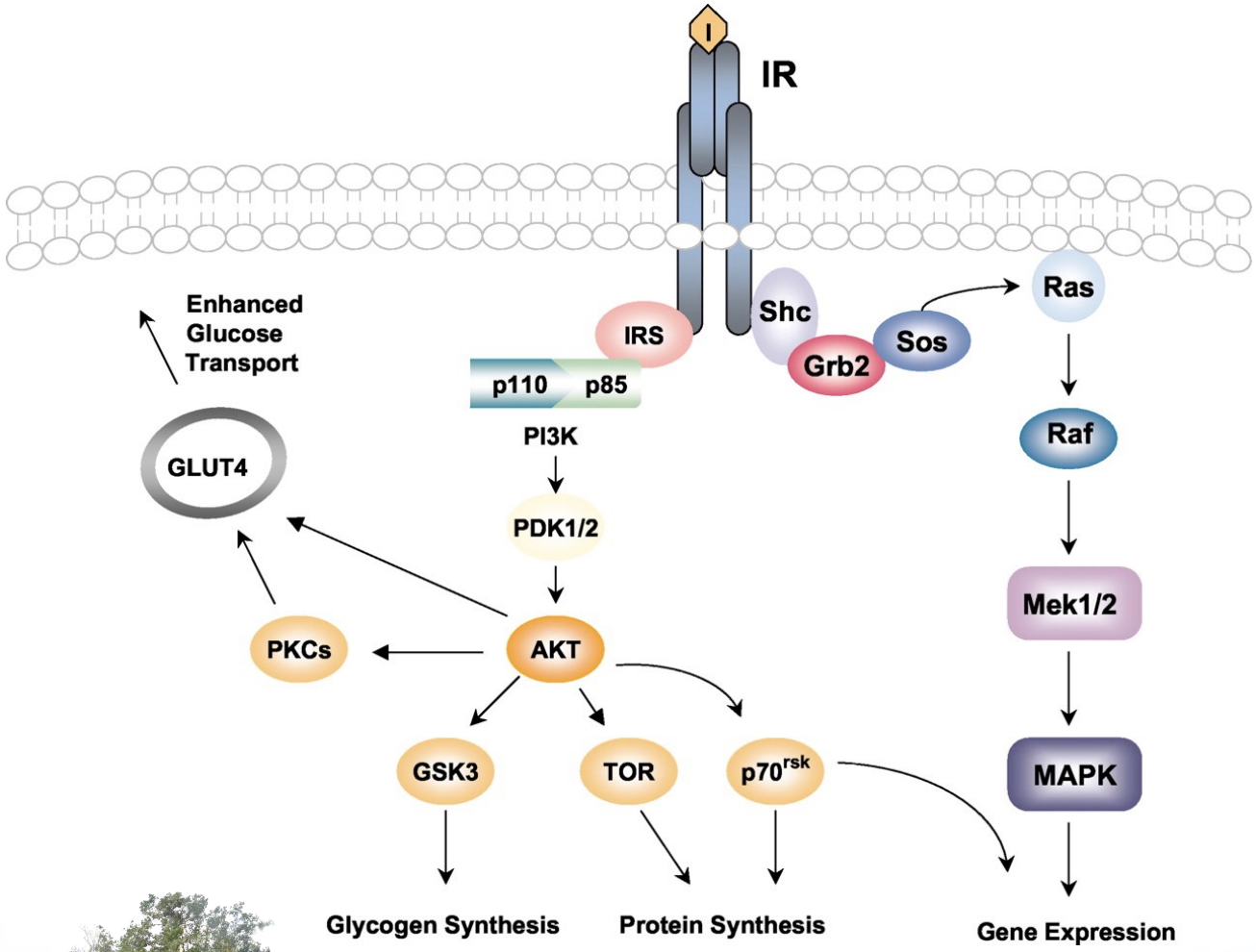



# Signaling cascades you should know by now:



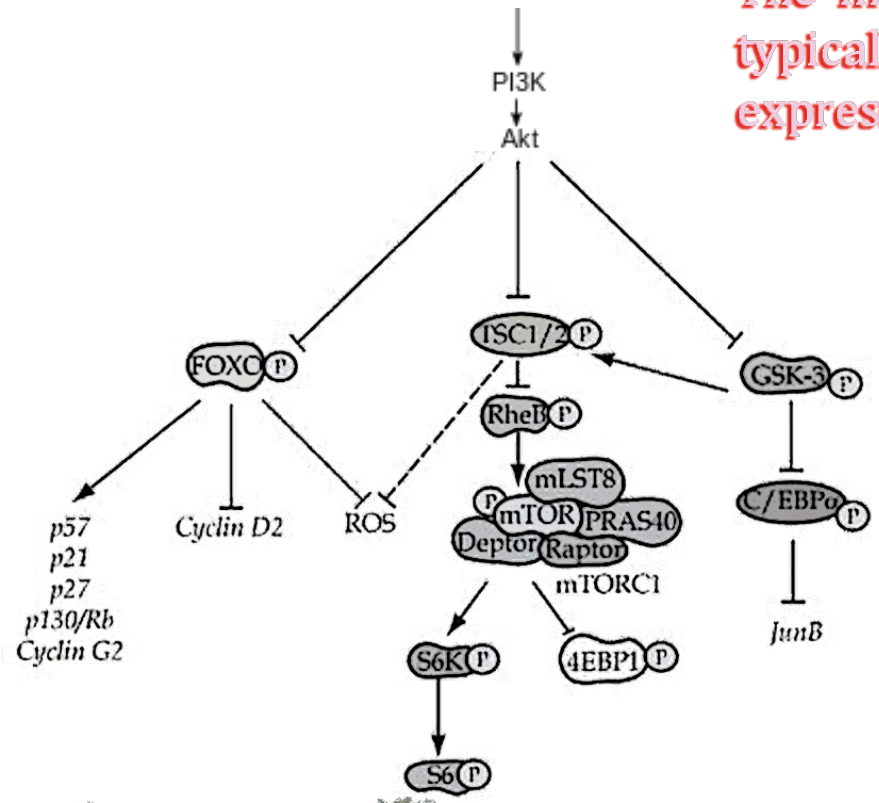

Connecting
PKB and PKA

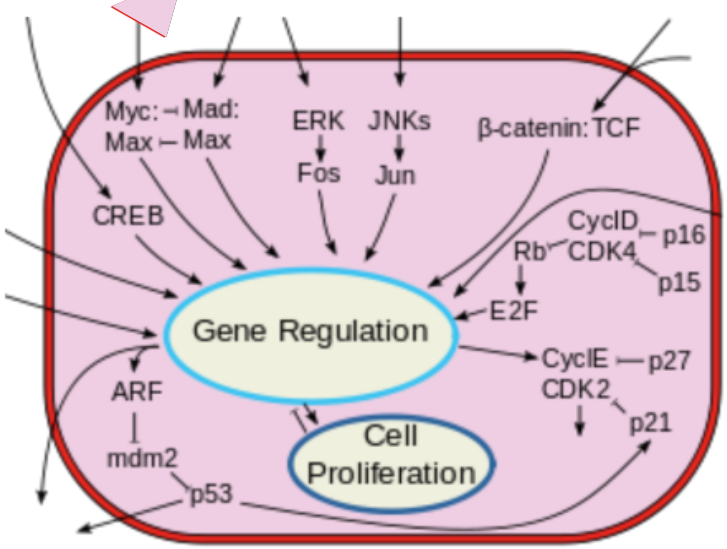
# Signaling cascades you should know by now:




# Signaling cascades you should know by now:

The finish line of a signaling cascade is typically in the nucleus, regulating genetic expression.




# Differences between Complex 1 and Complex 2

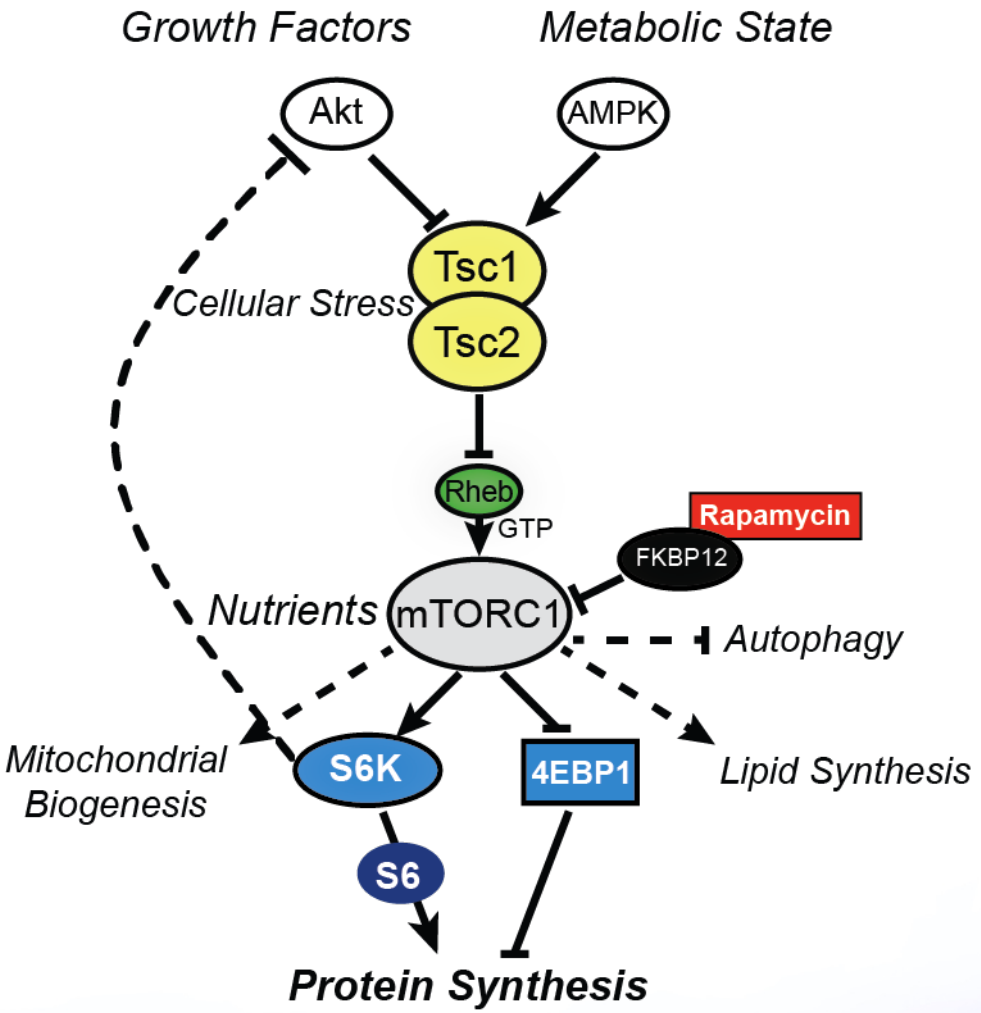
**COMPLEX ONE**
mTOR enzyme
Raptor (regulatory associated protein of target of rapamycin)
MLST8 (mammalian lethal with SEC13 protein 8)

**COMPLEX TWO**
mTOR enzyme
Rictor (rapamycin-insensitive companion of target of rapamycin)
MLST8 (mammalian lethal with SEC13 protein 8)
MSIN1 (mammalian stress-activated protein kinase interacting protein 1)

**COMPLEX ONE**
mTOR enzyme
Raptor
MLST8

TSC1/2
Rheb
4EBP1
P70S6K
rpS6

DEPTOR
PRAS40




# REVIEW: mTOR Complex 2

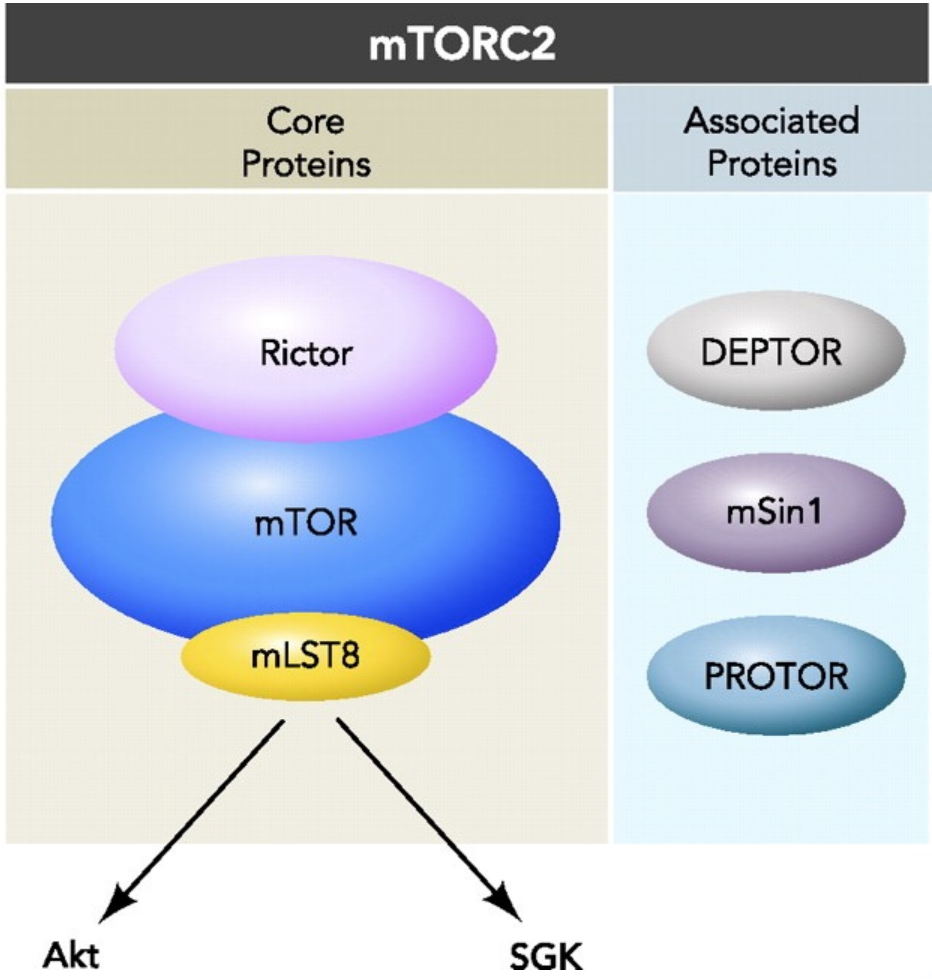
mTORC2 regulates: protein translation, organization of actin cytoskeletons, ion transport, and metabolism.

mTORC2 phosphorylates: PKB, SGK, and PKCα.

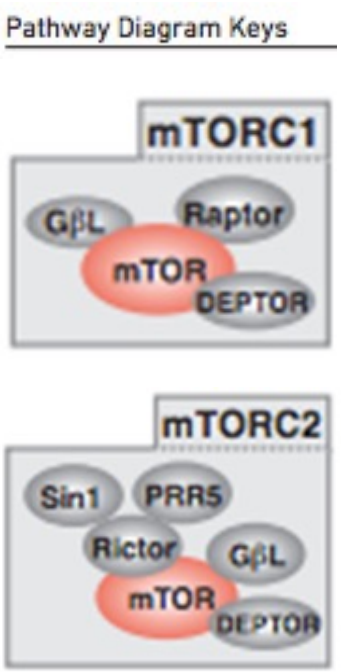
SGK1 (serum-and-glucocorticoid-induced protein kinase 1) regulates ion and solute transport in epithelia (e.g., inhibits inhibitors of epithelial sodium channel).

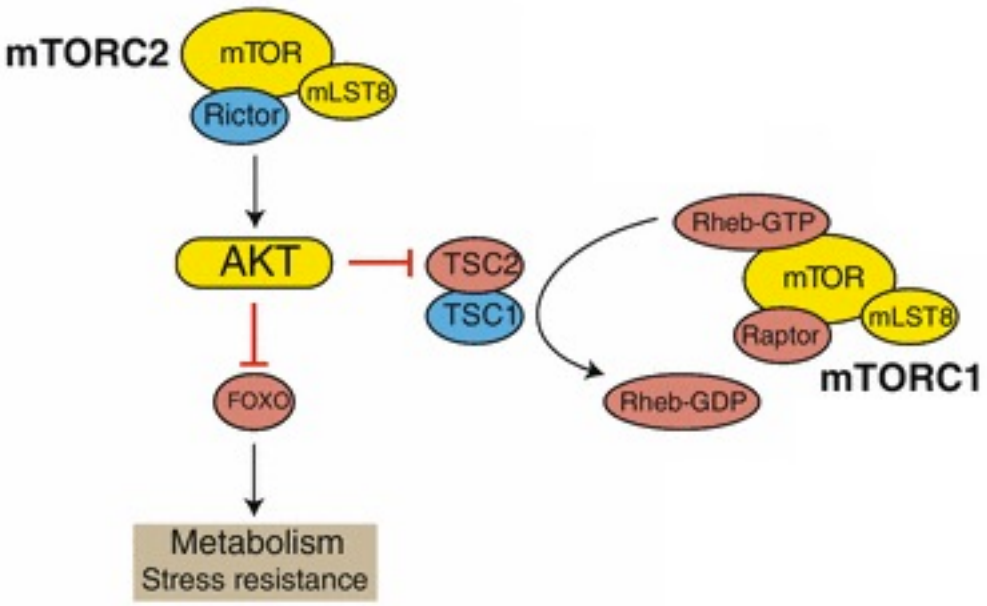
mSin1 recruits SGK1 (but not PKB) to the mTOR complex to be phosphorylated. mSin1 is required for mTORC2 formation.

Protor-1 also seems necessary for SGK1 to be phosphorylated (doesn't seem to do anything else).




# Linking complex 1 to complex 2:



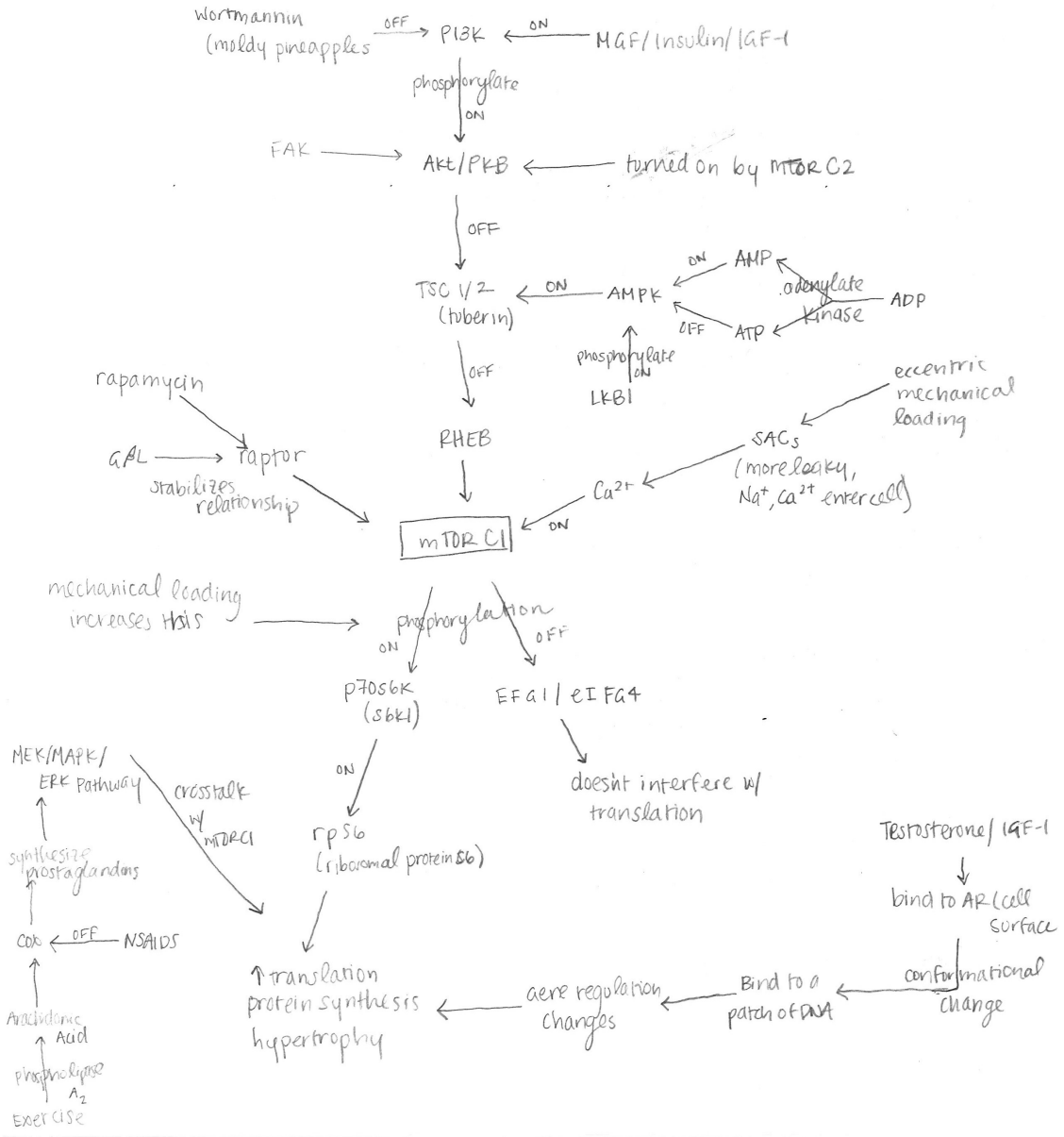




**REVIEW: mTOR**

HESP 147 | **EXAM 3 of 4** | November, 2015

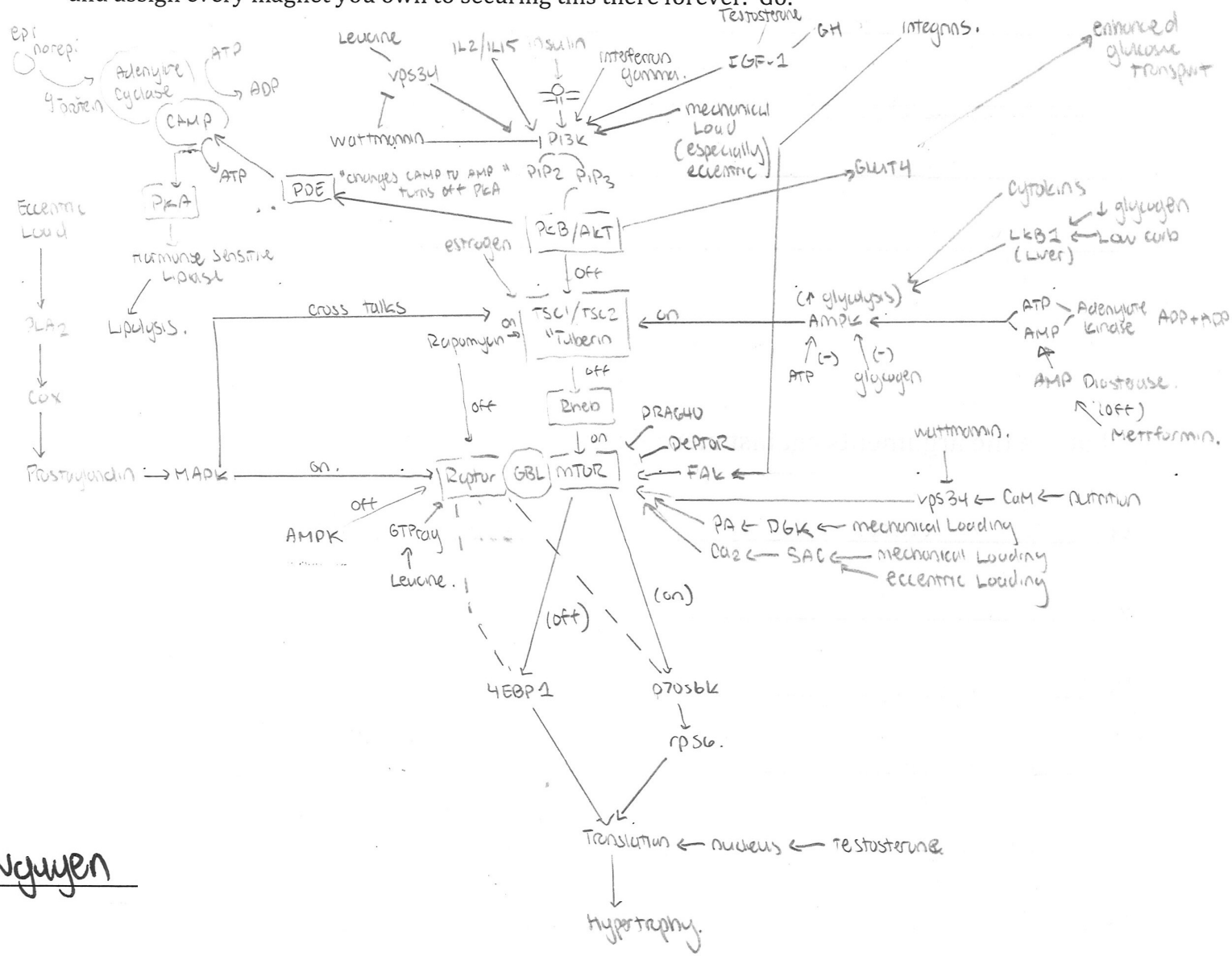
NAME Sara Mackey

**25.** Draw mTOR complex 1. Not just three core proteins; be very thorough on this one. Upstream/downstream, etc. Show me what you know for lots of points.



**REVIEW: mTOR**

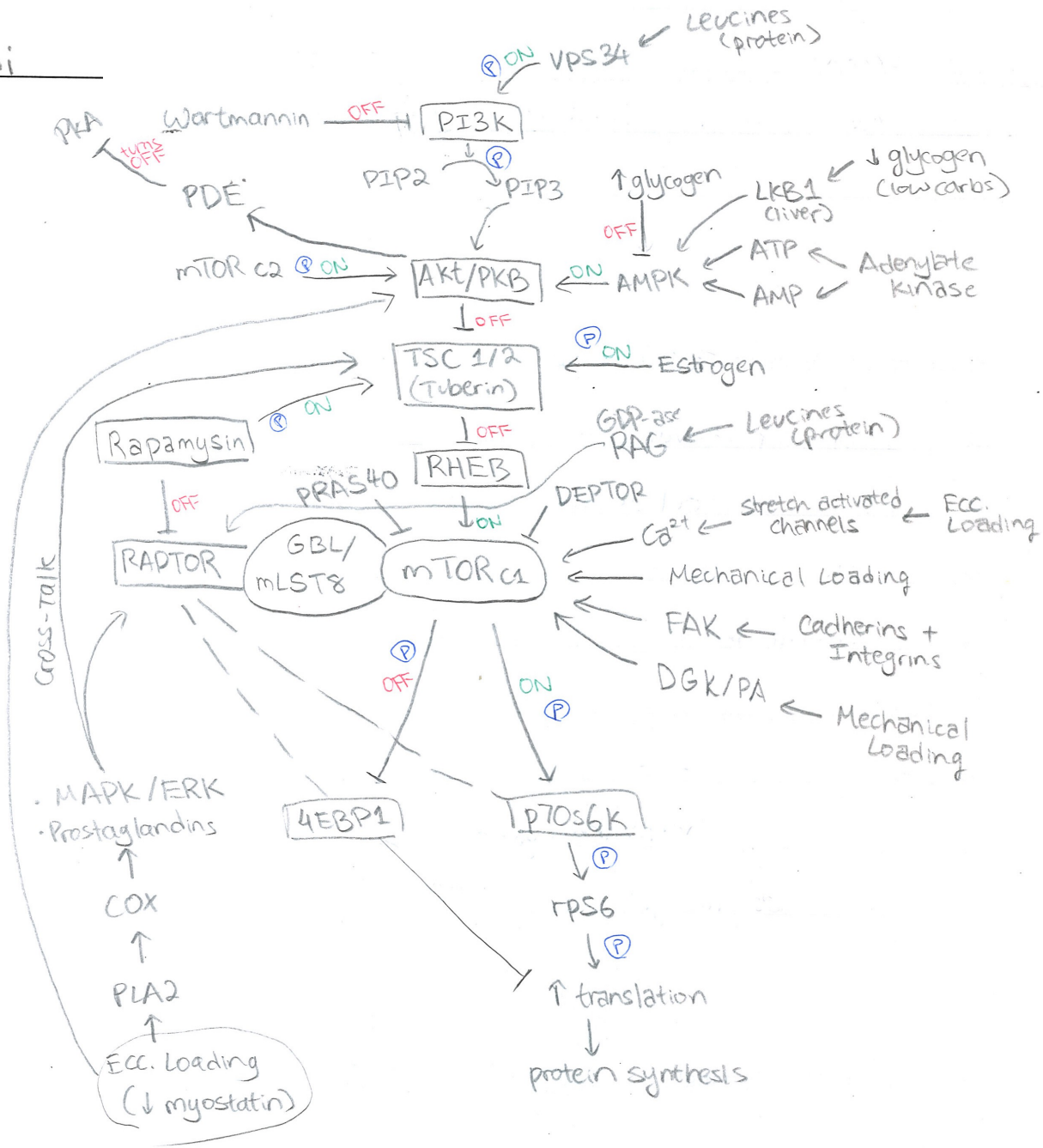
**For 16 points, draw mTOR Complex 1.** Be ridiculously detailed in your illustration. You have a whole page to fill. Write small (like this big) and fill it up. When I pass back the exams, you can keep this page. Your answer should be so thorough that you purge everything else on your fridge and assign every magnet you own to securing this there forever. Go:



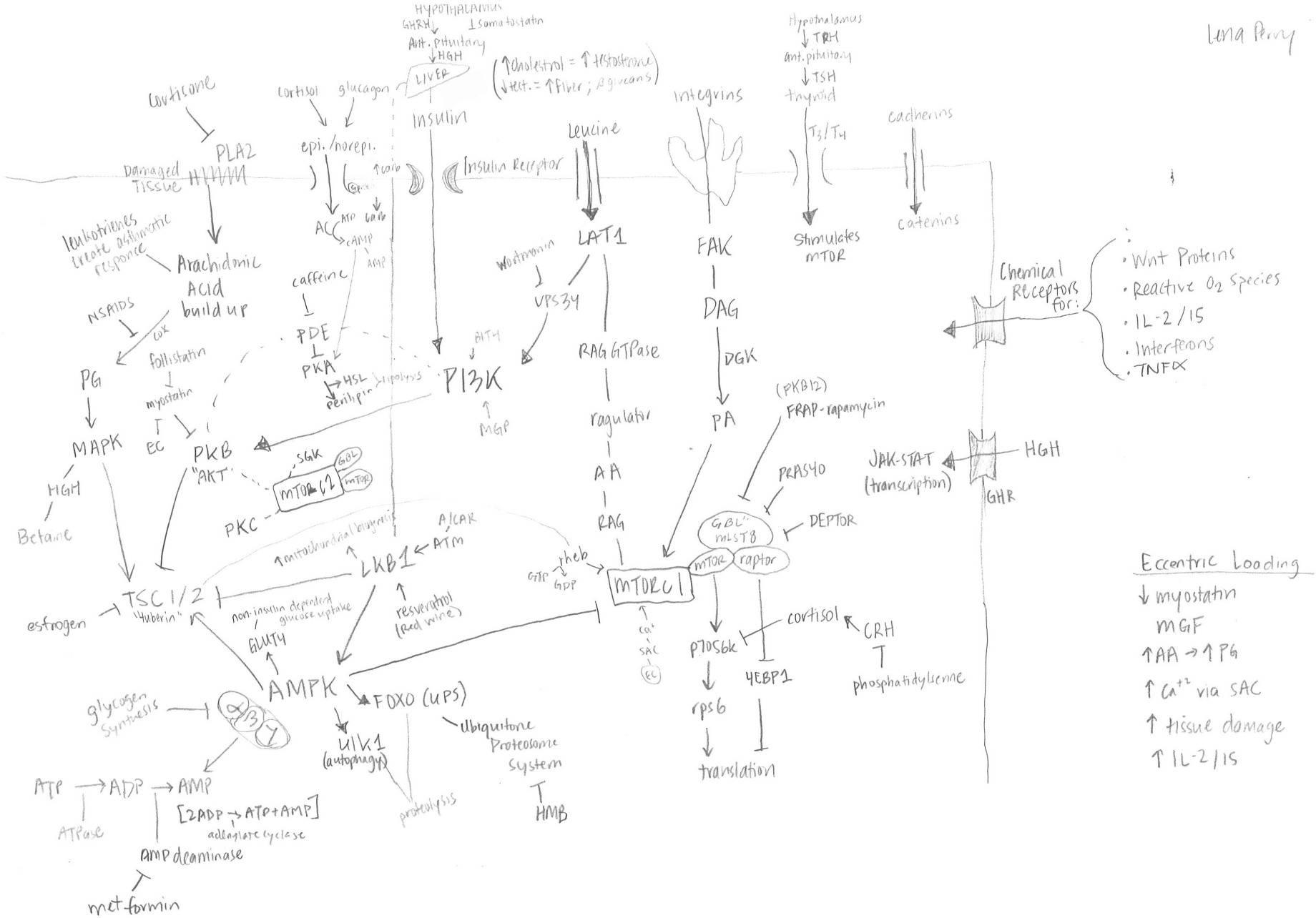

NAME Peter Nguyen

**REVIEW: mTOR**

NAME Yuki Asami

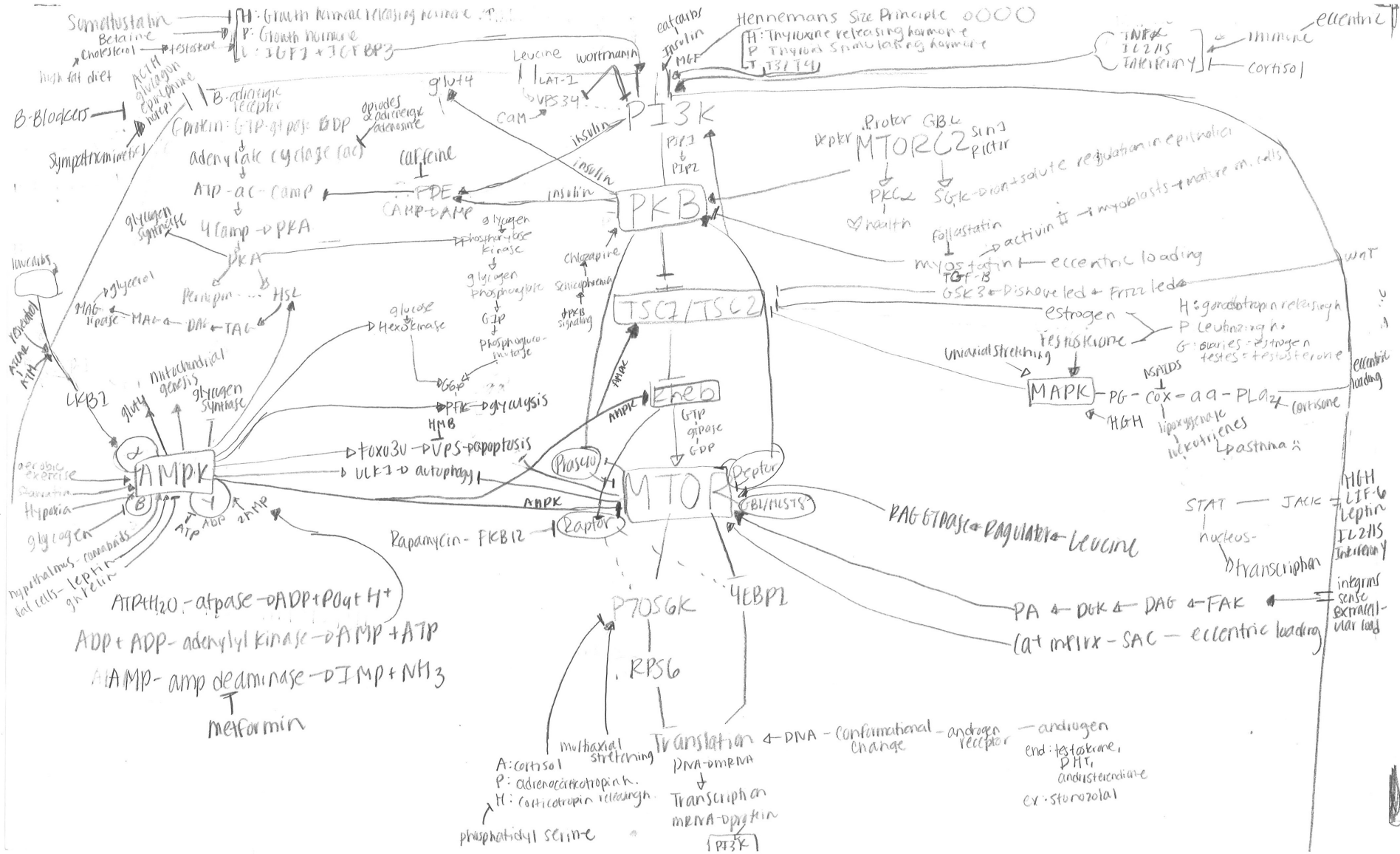


# REVIEW: mTOR


Luna Perry
HYPOTHALAMUS
GHRH
⊥ somatostatin
Ant. Pituitary
↓HGH
LIVER
(↑Cholesterol = ↑testosterone
↓test. = ↑Fiber ; β glucans)
Hypothalamus
↓TRH
ant. pituitary
↓TSH
thyroid
T3/T4
Cortisone
Cortisol
glucagon
Insulin
Leucine
Integrins
cadherins
Damaged Tissue
PLA2
epi. /norepi.
Insulin Receptor
LAT1
FAK
Stimulates mTOR
Catenins
Leukotrienes create asthmatic response
Arachidonic Acid build up
AC
ATP
cAMP
AMP
caffeine
Wortmannin
VPS34
DAG
Chemical Receptors for:
• Wnt Proteins
• Reactive O2 species
• IL-2/15
• Interferons
• TNFα
NSAIDS
cox
PG
follistatin
myostatin
EC
PDE
PKA
HSL
perilipin
lipolysis
PI3K
MGP
RAG GTPase
ragulator
AA
RAG
DGK
PA
(PKB12)
FRAP-rapamycin
PRAS40
JAK-STAT (transcription)
HGH
GHR
MAPK
HGH
Betaine
PKB "AKT"
SGK
GβL
mTOR
mTORC2
PKC
↑mitochondrial biogenesis
AICAR
ATM
LKB1
TSC1/2 "tuberin"
estrogen
non-insulin dependent glucose uptake
GLUT4
resveratrol (red wine)
GTP
rheb
GDP
mTORC1
GβL
mLST8
mTOR
raptor
DEPTOR
Ca+
SAC
EC
p70S6k
4EBP1
cortisol
CRH
phosphatidylserine
rps6
translation
AMPK
FOXO (UPS)
glycogen Synthesis
α β γ
Ulk1 (autophagy)
proteolysis
Ubiquitone Proteosome System
HMB
ATP → ADP → AMP
ATPase
[2ADP → ATP+AMP]
adenylate cyclase
AMP deaminase
met-formin
Eccentric Loading
↓ myostatin
MGF
↑AA → ↑PG
↑ Ca+2 via SAC
↑ tissue damage
↑ IL-2/15

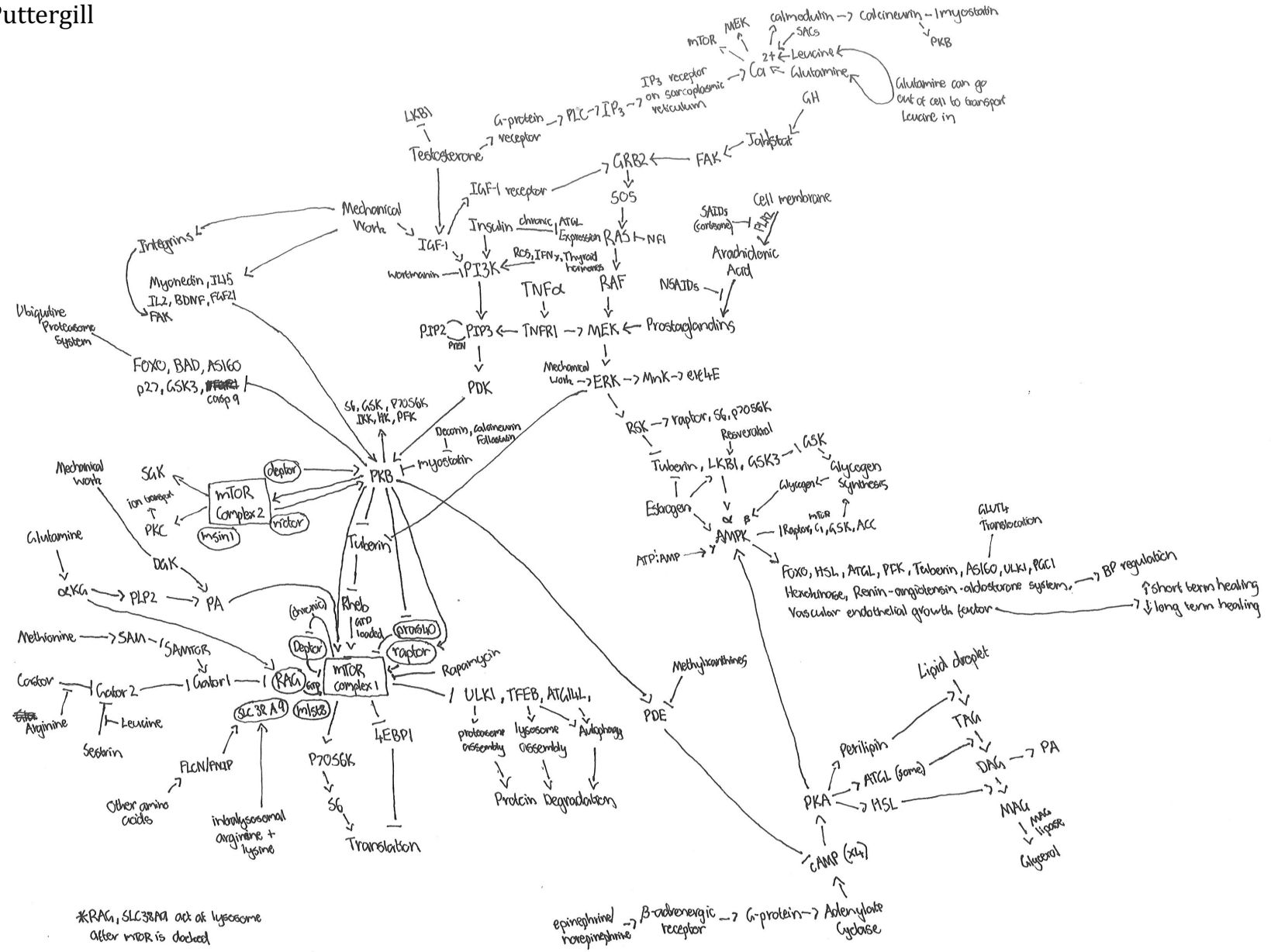
# REVIEW: mTOR

Cynthia Villalobos



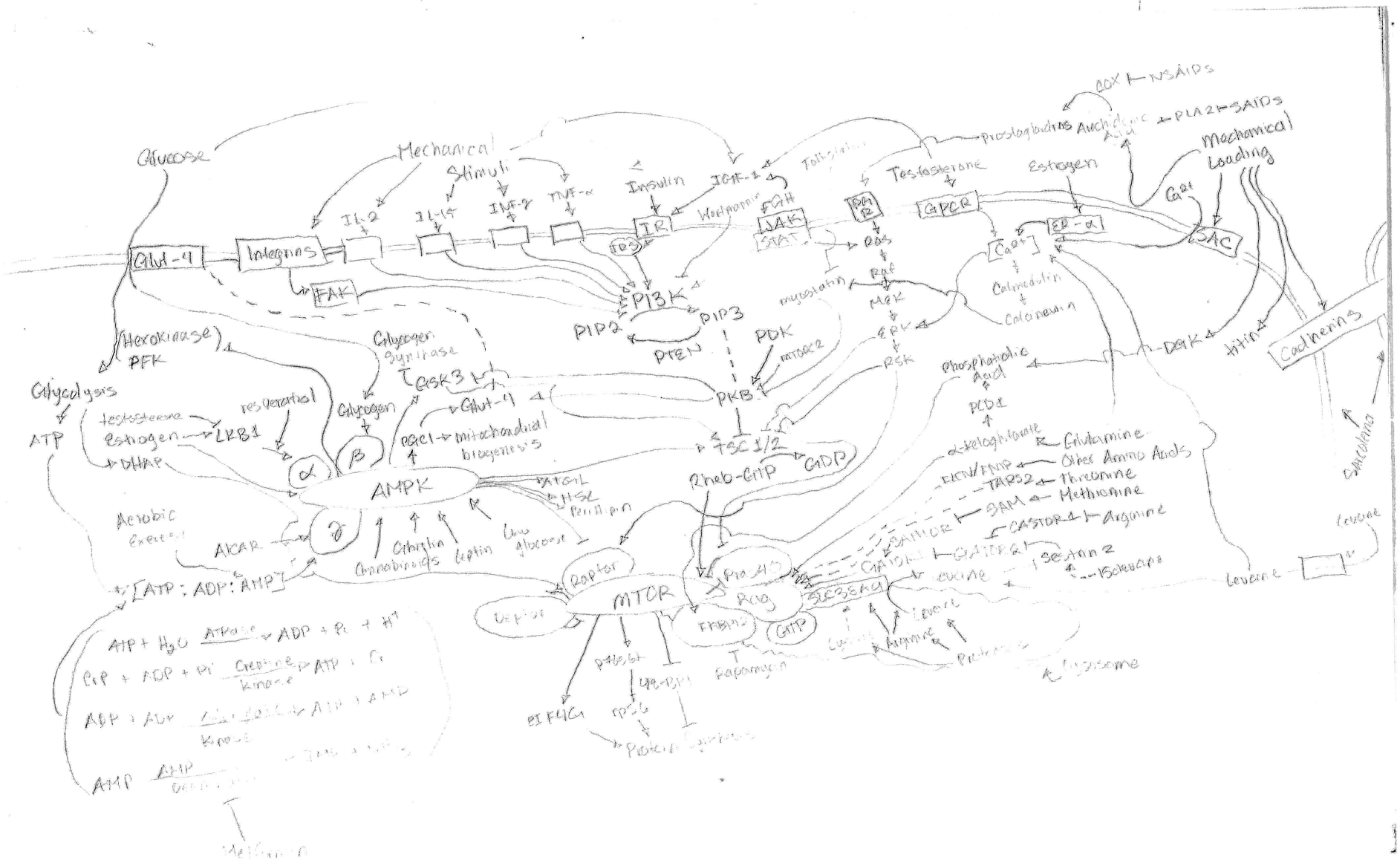
# REVIEW: mTOR

Liam Puttergill



# REVIEW: mTOR

Alex Roque



# The mTORC1 Relay Race

PI3K (phosphatidylinositol 3 kinase) gets activated by something.

This phosphorylates PIP2 (to PIP3).

PIP3 docks PKB where it is phosphorylated (activated) by PDK. PKB does a lot. One thing: inhibit the Tsc complex.

Tsc1/2 (2 is tuberin) normally turns off Rheb by hydrolyzing its GTP. Rheb-GTP binds to mTOR, turning it on.

mTORC1 phosphorylates p70s6k (or S6K1; ribosomal protein S6 kinase, 70 kDa, polypeptide 1) and 4E-BP1 (eukaryotic translation initiation factor 4E-binding protein 1) and, downstream from that, eIF4G (eukaryotic initiation factor 4G) binding.

p70s6k phosphorylation positively regulates rpS6 (ribosomal protein S6). That leads to translation of mRNAs, increasing translation capacity.

When 4E-BP1 is phosphorylated, it is deactivated, which leads to increased *rates* of translation initiation, increasing translational efficiency.

Translation: ribosomes synthesize protein using mRNA transcript.

**Result:** hypertrophy (as a result of translational capacity *and* efficiency).

# Big Picture

## What are the things that turn on mTOR (and induce hypertrophy)?

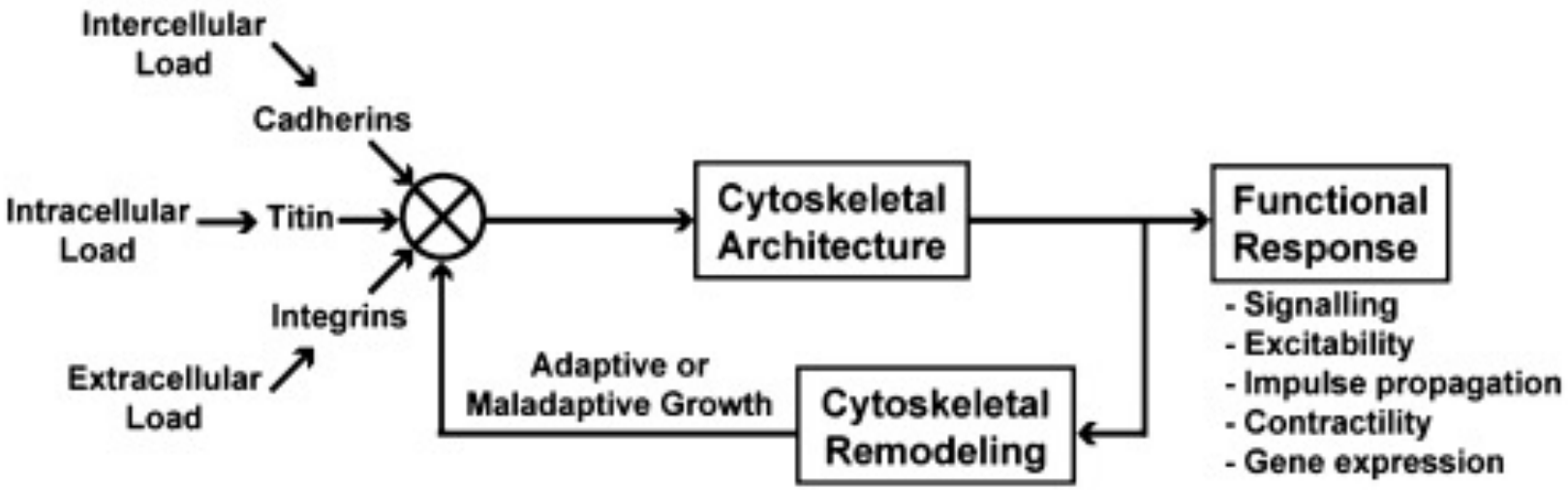
**1. Chemicals.** Explain… What are five examples? How do those things signal mTOR?

**2. Mechanical tension.** What are three examples? What's mechanotransduction?

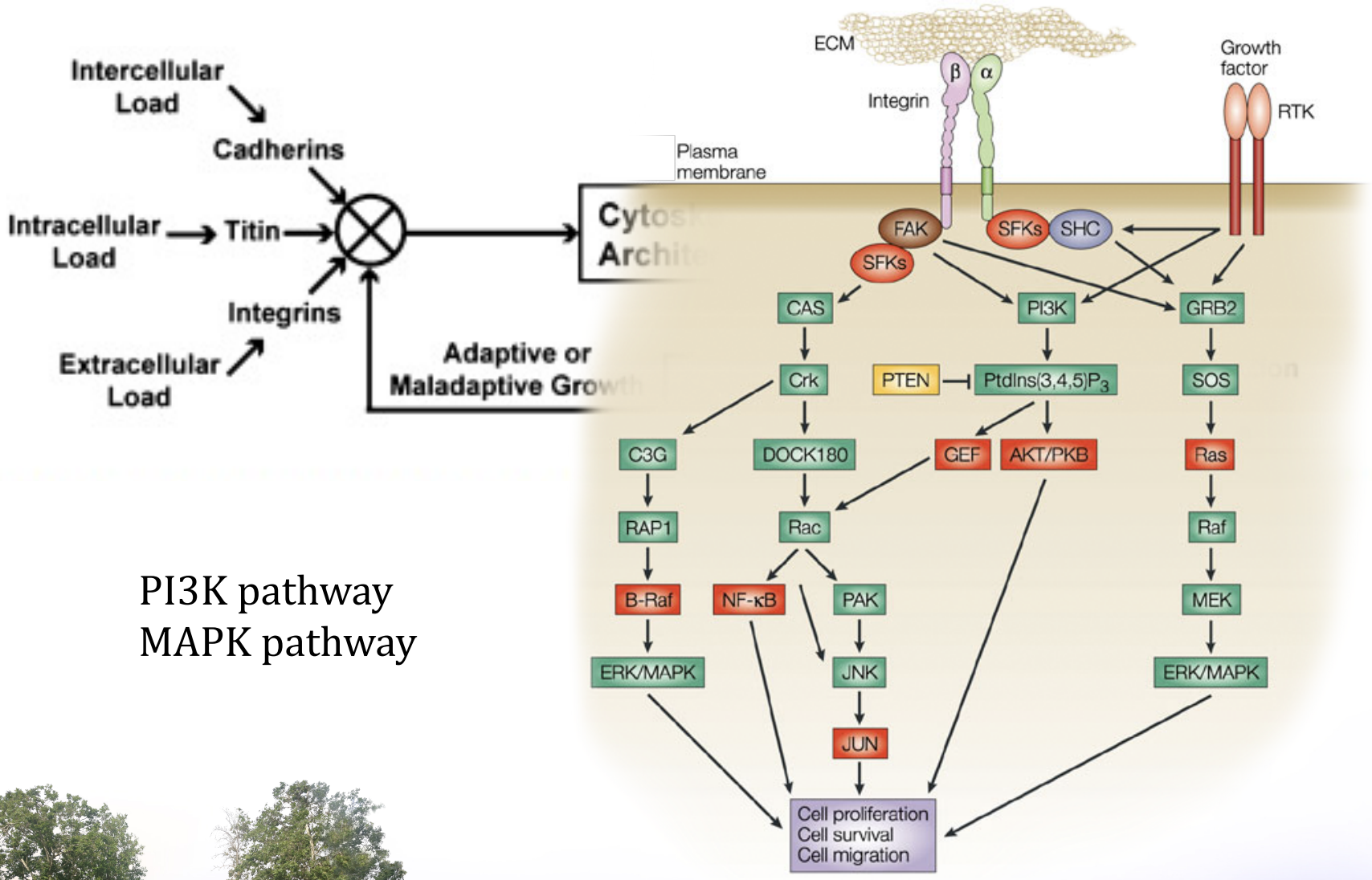
**3. Endocrine system.** What are five examples?

1. Prostaglandins
2. Specific interleukins (IL-2, IL-15)
3. Interferon γ
4. TNF-α
5. Wnt proteins
6. Myostatin (negative)
7. Reactive oxygen species (depending on dose)

 Mechanical Signaling of Complex I

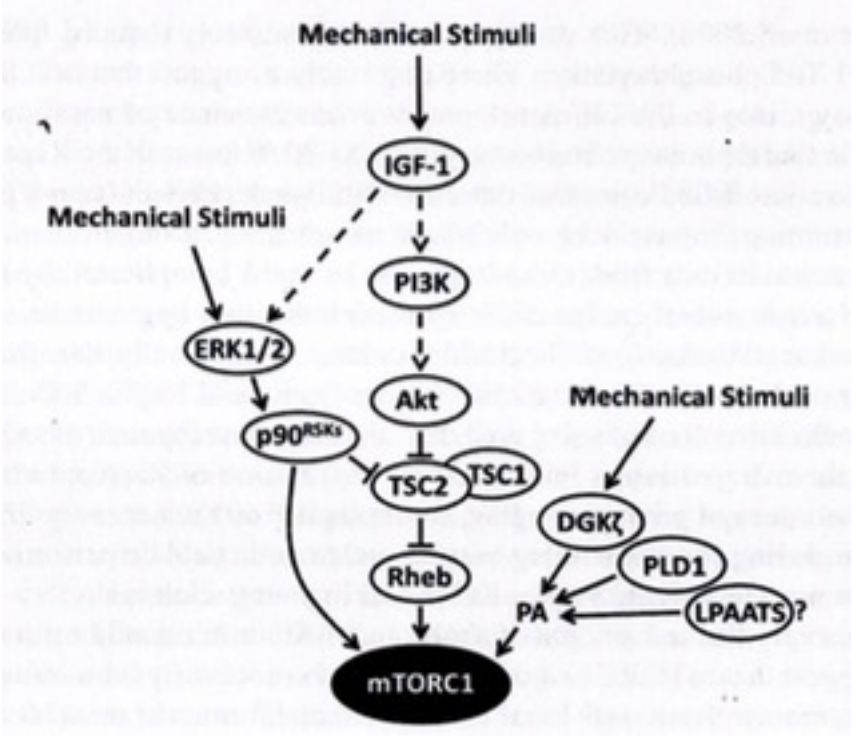



# Mechanical Signaling of Complex 1




PI3K pathway
MAPK pathway

# Mechanical Signaling of Complex 1




PI3K pathway
MAPK pathway
DGK pathway

1. Insulin
2. IGF/MGF (i.e., mechano growth factor)
3. Thyroid hormones (T3/T4)
4. Growth Hormone (largely through IGF)
5. Testosterone
6. Estrogen

# Big Picture

## What are the things that turn on mTOR (and induce hypertrophy)?

# Chemicals

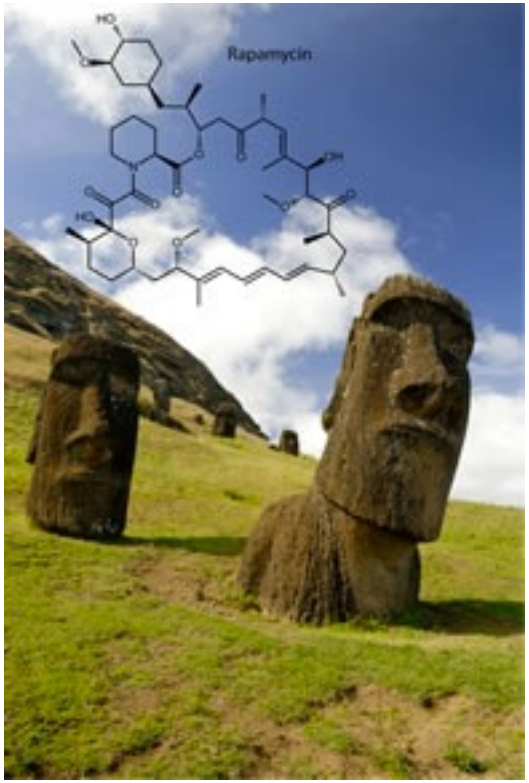
Prostaglandins, IL-2, IL-15, interferon γ, reactive oxygen species, Wnt, TNFα, myostatin (negative). Works through MAPK and PI3K pathways.

# Mechanical tension

Mostly integrins, titin, cadherens.
Works through lots of pathways (PI3K, MAPK, DGK-PA, SAC, probably more).

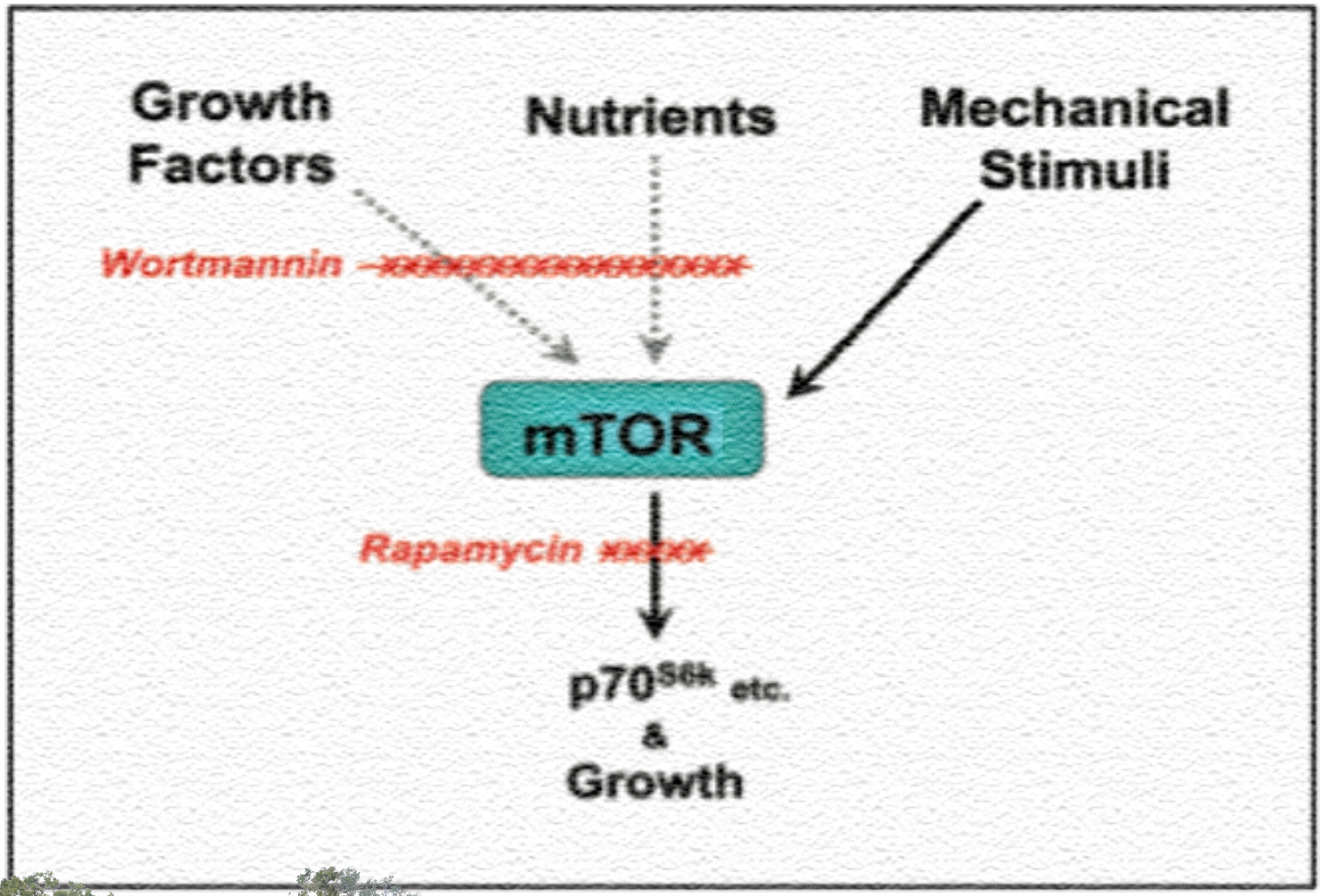
# Endocrine system

Insulin, IGF/MGF, thyroid hormones (T3, T4), hGH, testosterone, estrogen.
Aside from steroid hormone effects, works through PI3K pathway.




*Vs.*

 Exogenous mTOR Inhibitors




Eur J Appl Physiol (2008) 102:253–263
DOI 10.1007/s00421-007-0588-3

INVITED REVIEW

## Mechanical stimuli of skeletal muscle: implications on mTOR/p70s6k and protein synthesis

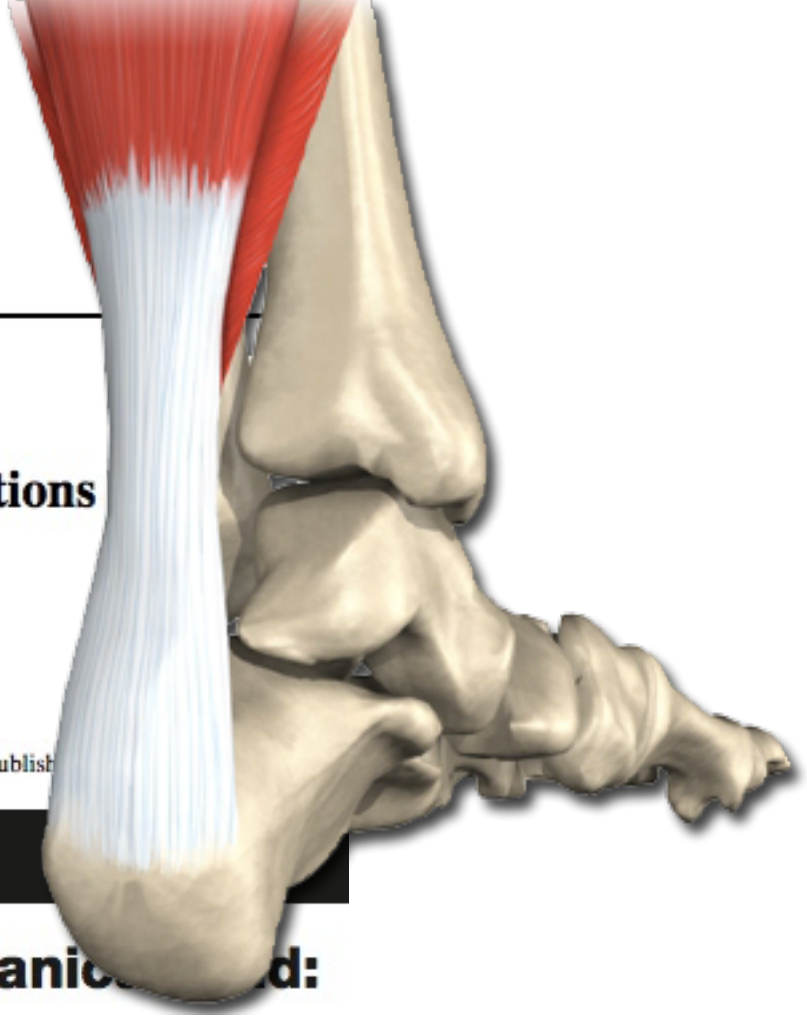
Nelo Eidy Zanchi · Antonio Herbert Lancha Jr

Appl. Physiol. Nutr. Metab. 34: 328–335 (2009) doi:10.1139/H09-010 Publish

REVIEW / SYNTHÈSE

## Changes in muscle mass with mechanic d: possible cellular mechanisms[1]

Espen E. Spangenburg



Tendons don't have inflammation.
So how does a tendon heal?

American Journal of Physiology - Endocrinology and Metabolism Published 1 July 1999 **Vol.** 277 **no.** 1, E1-E10

invited review

# AMP-activated protein kinase, a metabolic master switch: possible roles in Type 2 diabetes

W. W. WINDER[1] AND D. G. HARDIE[2]
[1]*Department of Zoology, Brigham Young University, Provo, Utah 84602;*
*and* [2]*Department of Biochemistry, The University, Dundee DD1 5EH, Scotland, United Kingdom*

*Am J Physiol Cell Physiol* 303: C475–C485, 2012.
First published June 13, 2012; doi:10.1152/ajpcell.00125.2012.

# The role of AMP-activated protein kinase in the coordination of skeletal muscle turnover and energy homeostasis

**Anthony M. J. Sanchez,[1,2] Robin B. Candau,[1,2] Alfredo Csibi,[3] Allan F. Pagano,[1,2] Audrey Raibon,[1] and Henri Bernardi[1]**

*"AMPK is considered as a key enzyme in conditions of cellular energy deficit and is able to inhibit metabolic pathways that consume energy and reciprocally to increase mechanisms that produce energy."*

AMP-***activated*** protein kinase.

Under normal conditions, you don't have a bunch of AMP, so AMPK is inactive.

ATP Hydrolysis:

$$ATP^{4-} + H_2O \leftarrow ATPase \rightarrow ADP^{3-} + HPO_4^{2-} + H^+$$

**Enzyme:** *Adenylate Kinase*

$$2\ ADP \rightleftharpoons ATP + AMP$$

| | | | |
|---|---|---|---|
| At Rest | 1.0 mM | 5mM | 0.2mM |
| At Work | 1.5 mM | 4mM | 0.8Mm |

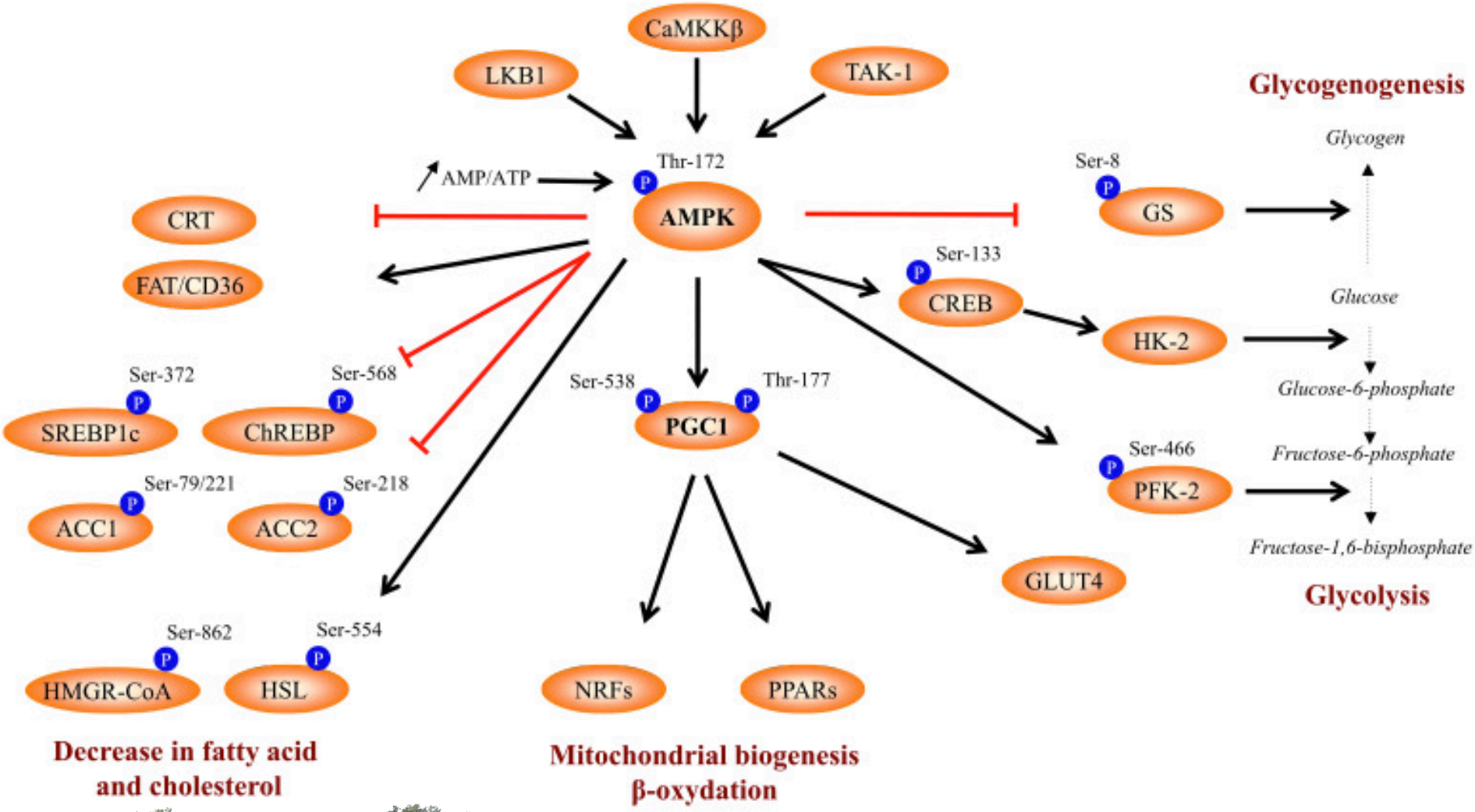
Now you have lots of AMP.

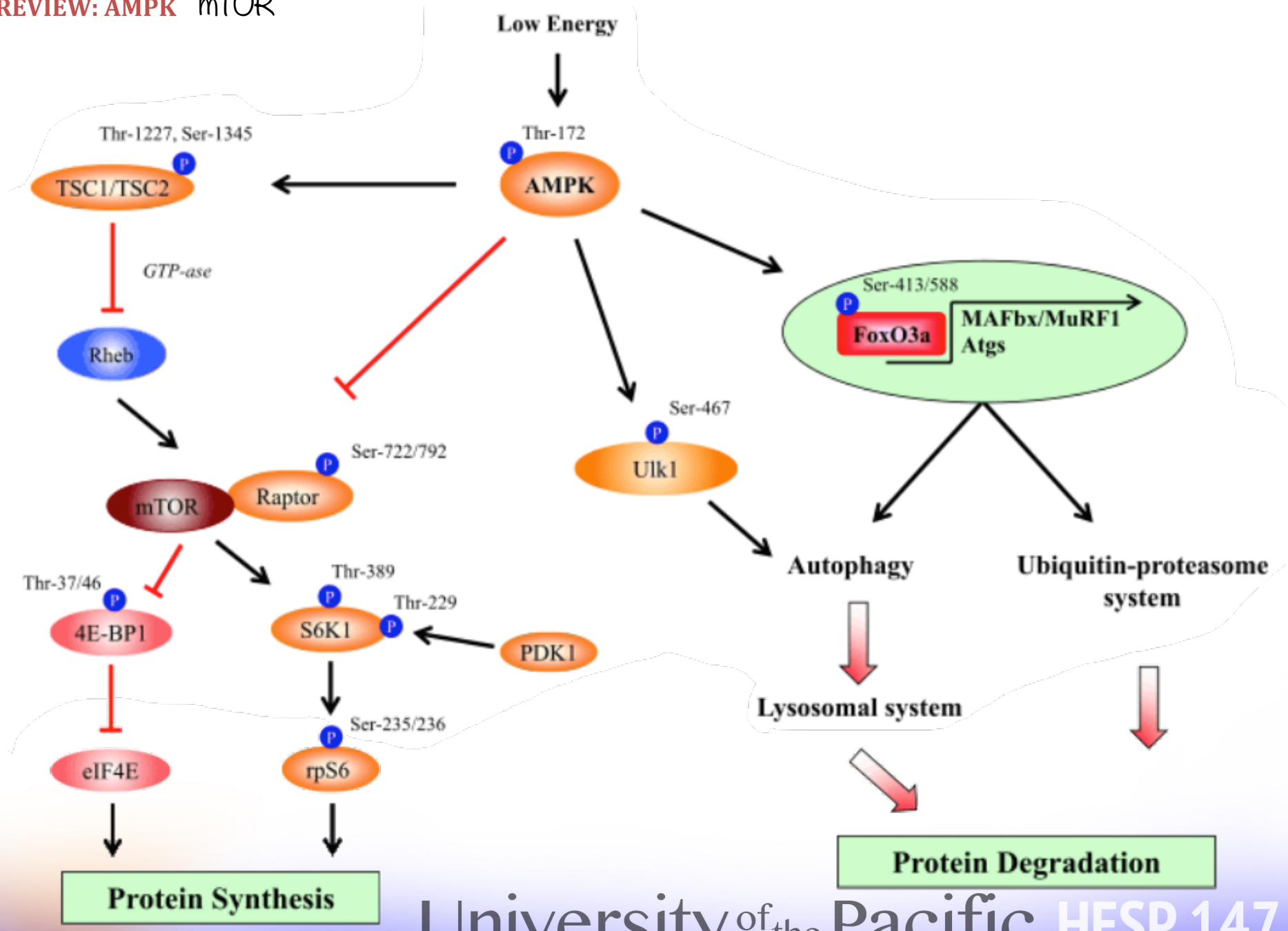
AMP binds to AMPK; that activates it.

When *ATP* binds to AMPK, that inhibits it.

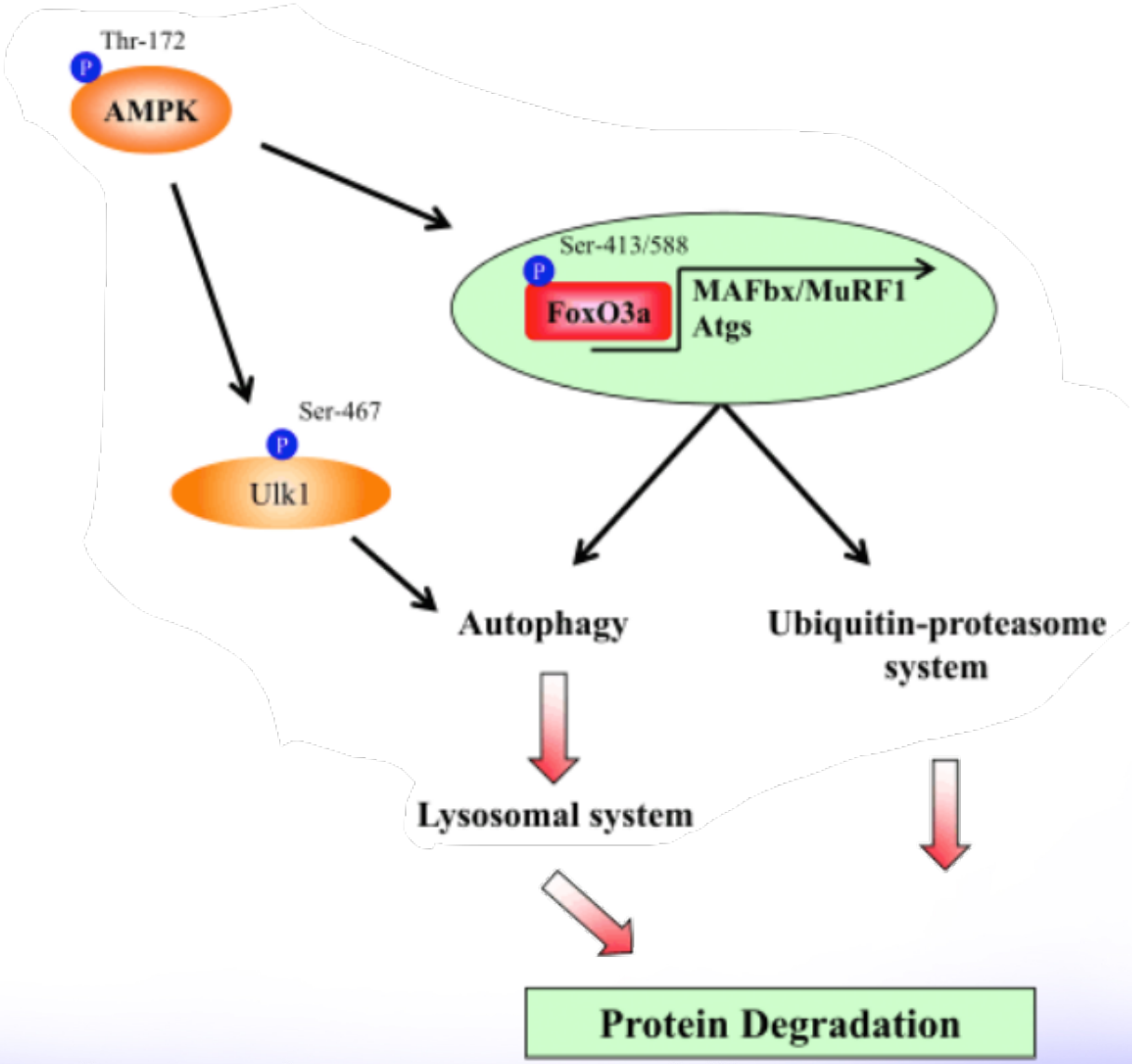
ATP and AMP compete for AMPK γ subunits.

*AMPK has α, β, and γ subunits; α is catalytic; β and γ are regulatory.*
*The interacting domains for ATP, ADP, and AMP are on the γ units.*

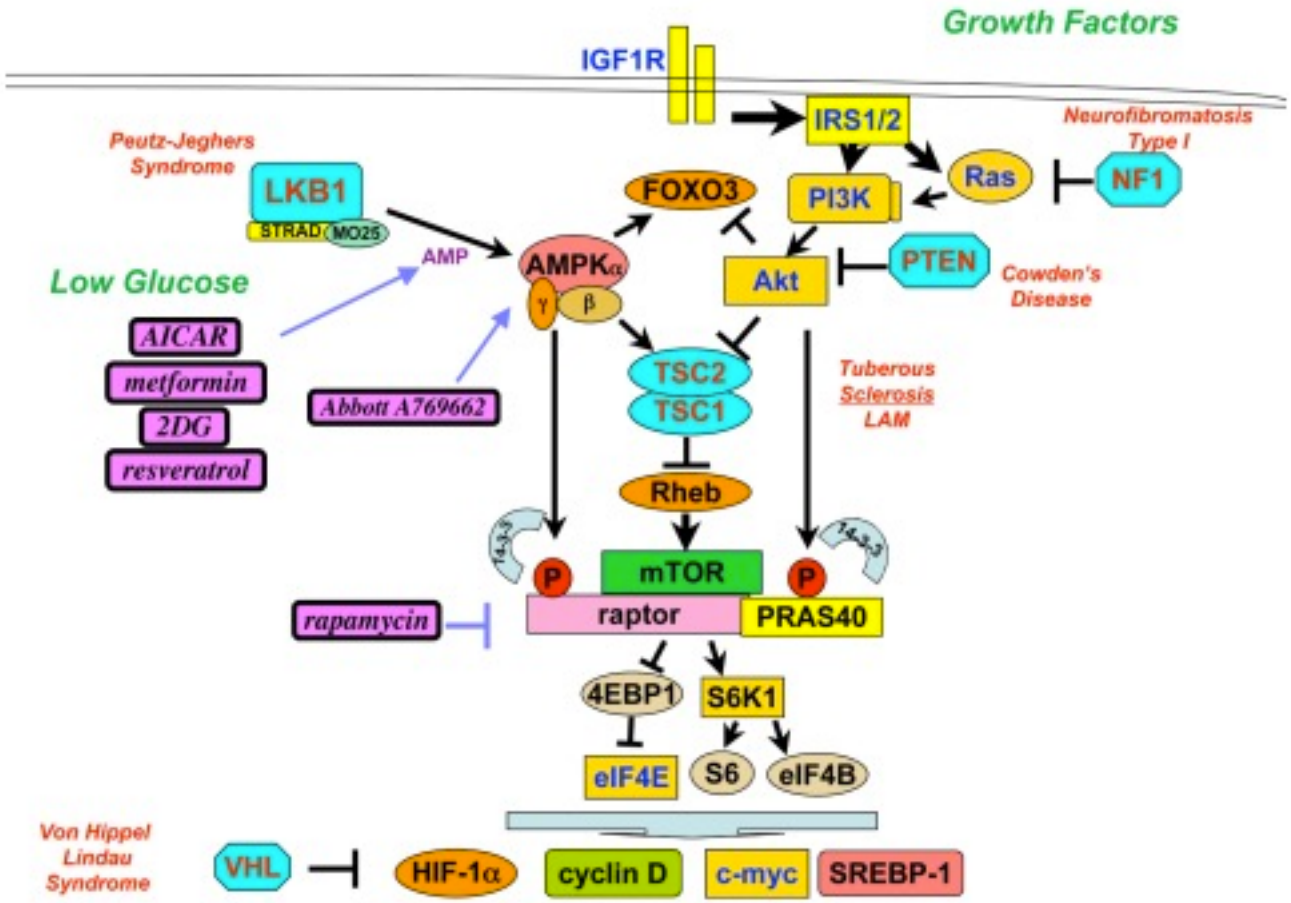

CaMKKβ
LKB1
TAK-1
AMP/ATP
Thr-172
AMPK
CRT
FAT/CD36
Ser-372
SREBP1c
Ser-568
ChREBP
Ser-79/221
ACC1
Ser-218
ACC2
Ser-862
HMGR-CoA
Ser-554
HSL
Ser-538
Thr-177
PGC1
NRFs
PPARs
Ser-8
GS
Glycogenogenesis
Glycogen
Ser-133
CREB
HK-2
Glucose
Glucose-6-phosphate
Ser-466
PFK-2
Fructose-6-phosphate
Fructose-1,6-bisphosphate
GLUT4
Glycolysis
Decrease in fatty acid and cholesterol
Mitochondrial biogenesis β-oxydation


Low Energy
Thr-1227, Ser-1345
TSC1/TSC2
Thr-172
AMPK
GTP-ase
Rheb
Ser-413/588
FoxO3a
MAFbx/MuRF1
Atgs
Ser-467
Ulk1
Ser-722/792
mTOR
Raptor
Thr-37/46
4E-BP1
Thr-389
Thr-229
S6K1
PDK1
Autophagy
Ubiquitin-proteasome system
Lysosomal system
Ser-235/236
eIF4E
rpS6
Protein Synthesis
Protein Degradation

# Protein Degradation




# Activation of AMPK




Cytokines and drugs can also activate AMPK.


Metformin inhibits AMP deaminase.
What would that cause?

AMPK is trying to turn off ATP consumption and turn on ATP synthesis.

If something is costing the body ATP (e.g., protein synthesis) it gets turned off.

At the same time, if something helps ATP production/generation (e.g., glycolysis and mitochondrial biogenesis), it gets turned on.

"For muscle growth to occur, the rate of protein synthesis must exceed that of protein breakdown. Since protein synthesis can account for up to 30–50% of the cellular energy expenditure, a reduction in protein synthesis seems an efficient mechanism to save energy. One critical signaling pathway controlling protein synthesis during skeletal muscle growth involves the mammalian target of rapamycin (mTOR) kinase."

Front Biosci (Landmark Ed). 2009; 14: 19–44.

**AMPK: Lessons from transgenic and knockout animals**

Benoit Viollet[1*], Yoni Athea[2], Remi Mounier[1], Bruno Guigas[34], Elham Zarrinpashneh[5], Sandrine Horman[4], Louise Lantier[1], Sophie Hebrard[1], Jocelyne Devin-Leclerc[1], Christophe Beauloye[5], Marc Foretz[1], Fabrizio Andreelli[16], Renee Ventura-Clapier[2], Luc Bertrand[5]

Mice who are deficient in AMPK get huge (in a relative sense).

Developing musculature is about 1.5 times larger:

**Lantier L, Mounier R, Leclerc J, Pende M, Foretz M, Viollet B.** Coordinated maintenance of muscle cell size control by AMP-activated protein kinase. *FASEB J* 24: 3555–3561, 2010.

They're more responsive (hypertrophically) to mechanical loading:

**Mounier R, Lantier L, Leclerc J, Sotiropoulos A, Pende M, Daegelen D, Sakamoto K, Foretz M, Viollet B.** Important role for AMPKalpha1 in limiting skeletal muscle cell hypertrophy. *FASEB J* 23: 2264–2273, 2009

## *Increasing* AMPK activity facilitates muscle atrophy:

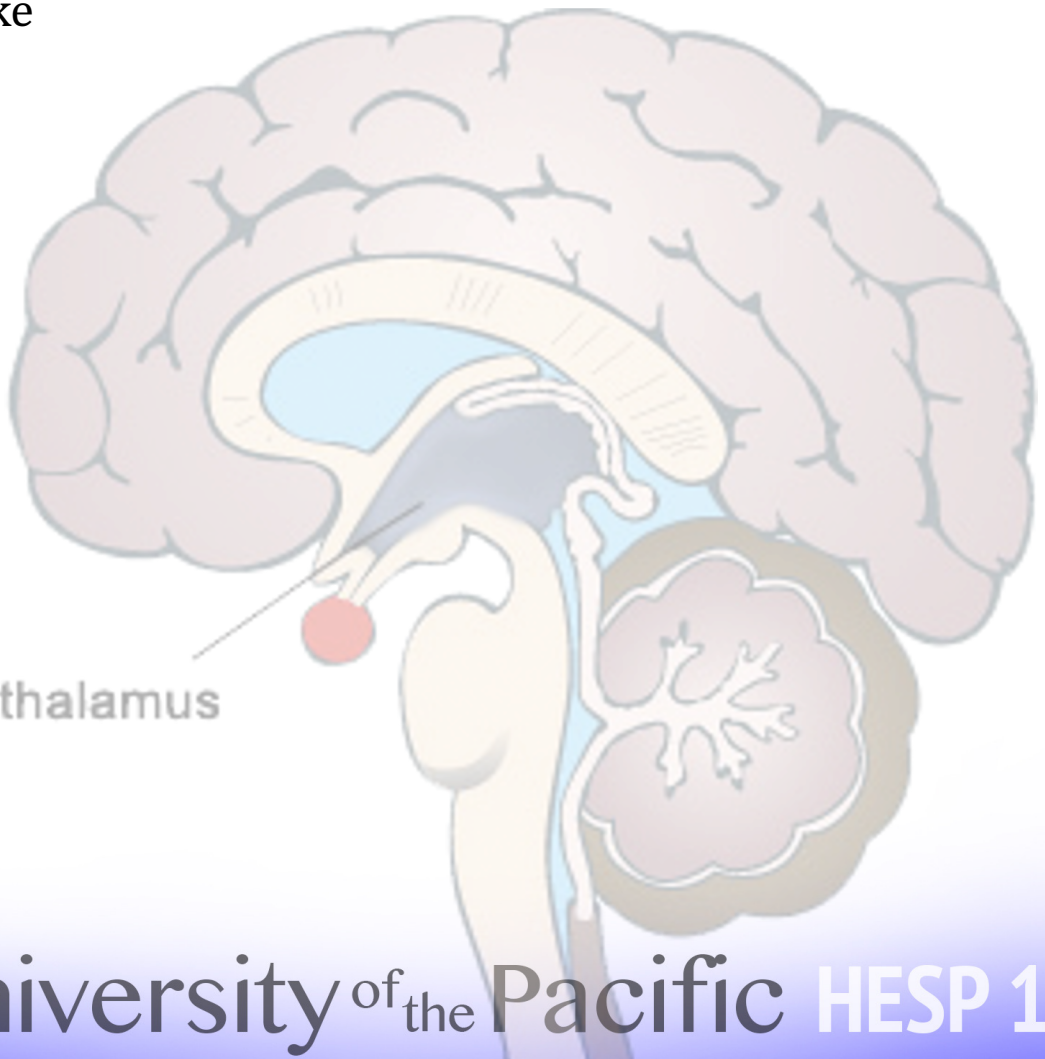
**Nakashima K, Yakabe Y.** AMPK activation stimulates myofibrillar protein degradation and expression of atrophy-related ubiquitin ligases by increasing FOXO transcription factors in C2C12 myotubes. *Biosci Biotechnol Biochem* 71: 1650–1656, 2007.

**Nystrom GJ, Lang CH.** Sepsis and AMPK activation by AICAR differentially regulate FoxO-1, -3 and -4 mRNA in striated muscle. *Int J Clin Exp Med* 1: 50–63, 2008.

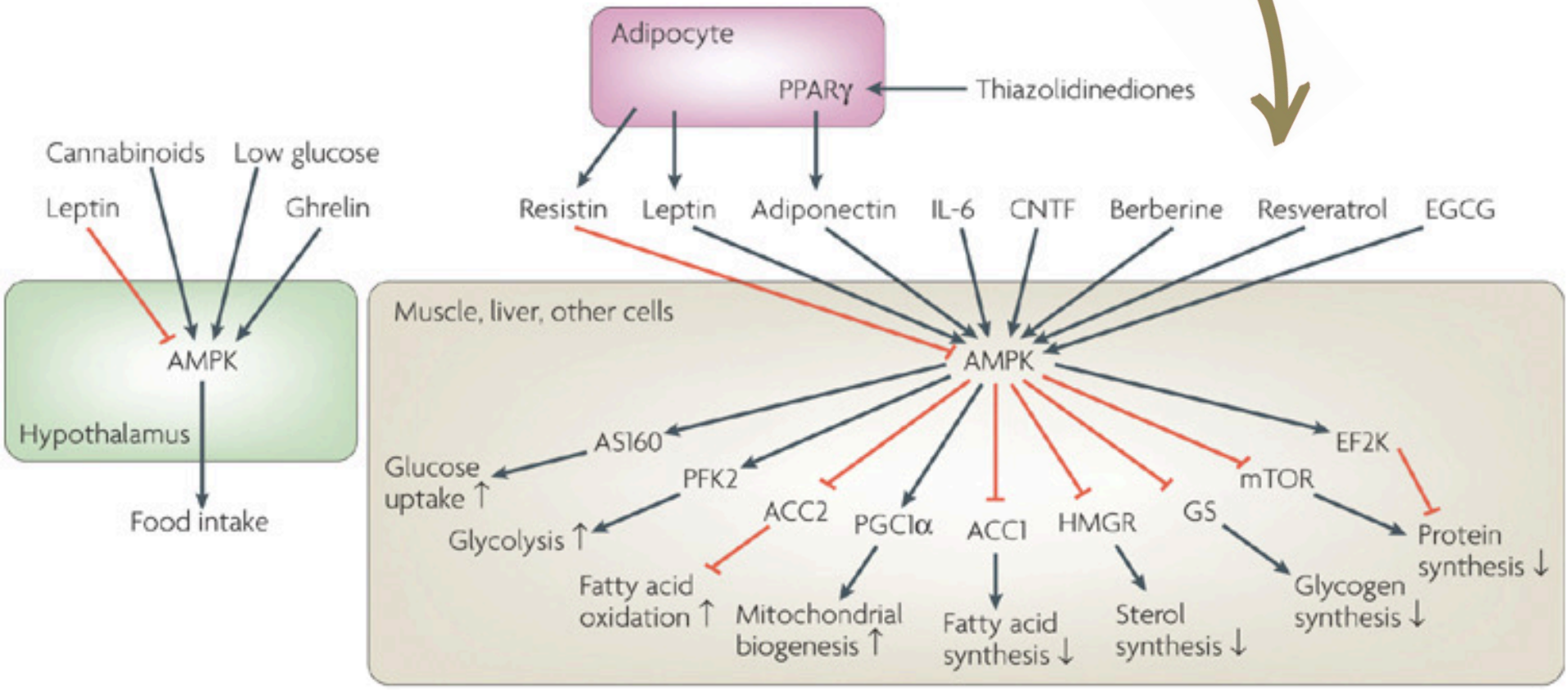
**AMPK in the hypothalamus:**

If something is *inhibiting* food intake (e.g., leptin), it's inhibiting AMPK.

If something is *stimulating* intake (e.g., cannabinoids), that thing is stimulating AMPK.



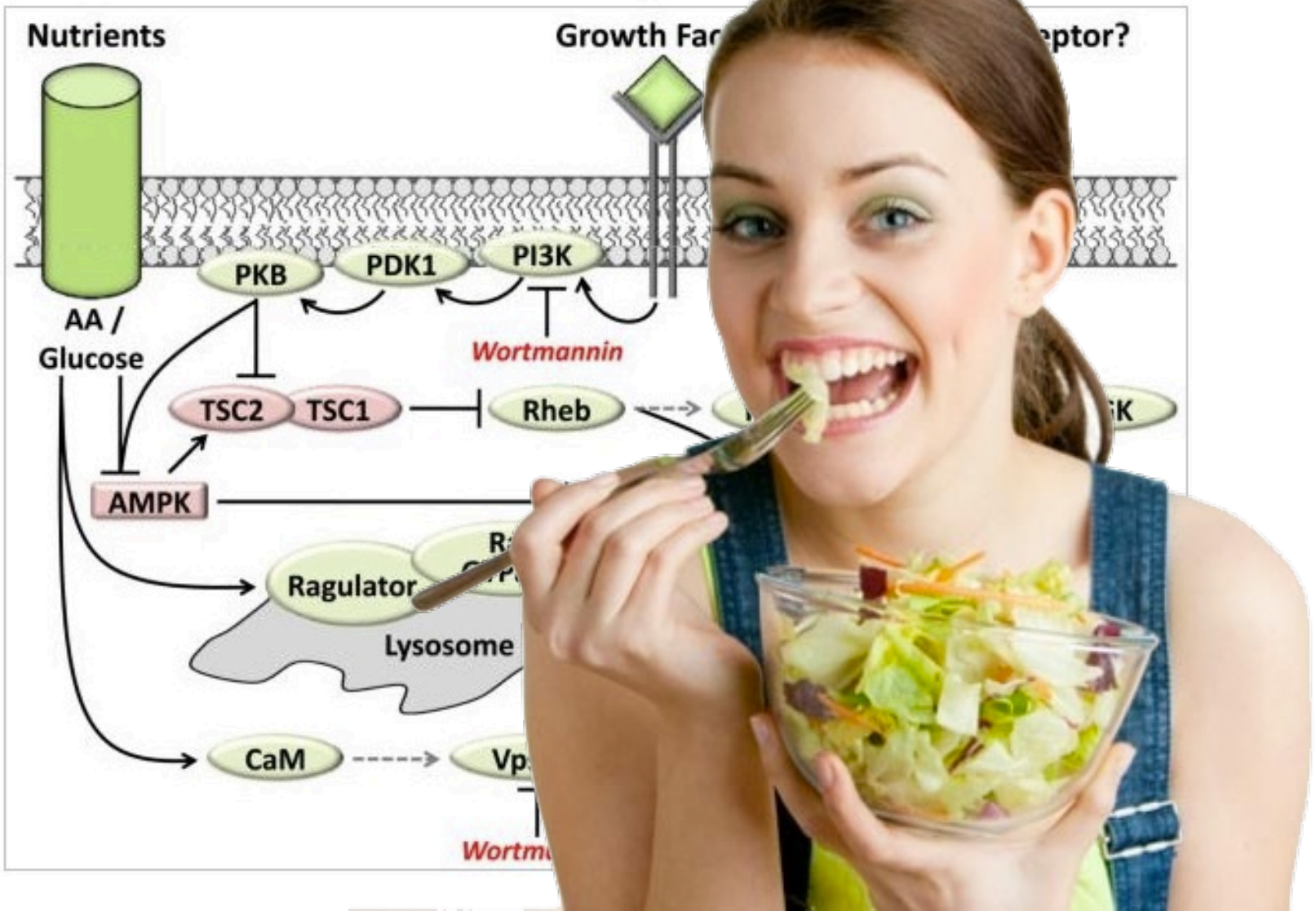

# *Lots of stuff in the hypothalamus*
# *...and in other cells (e.g., muscle)*

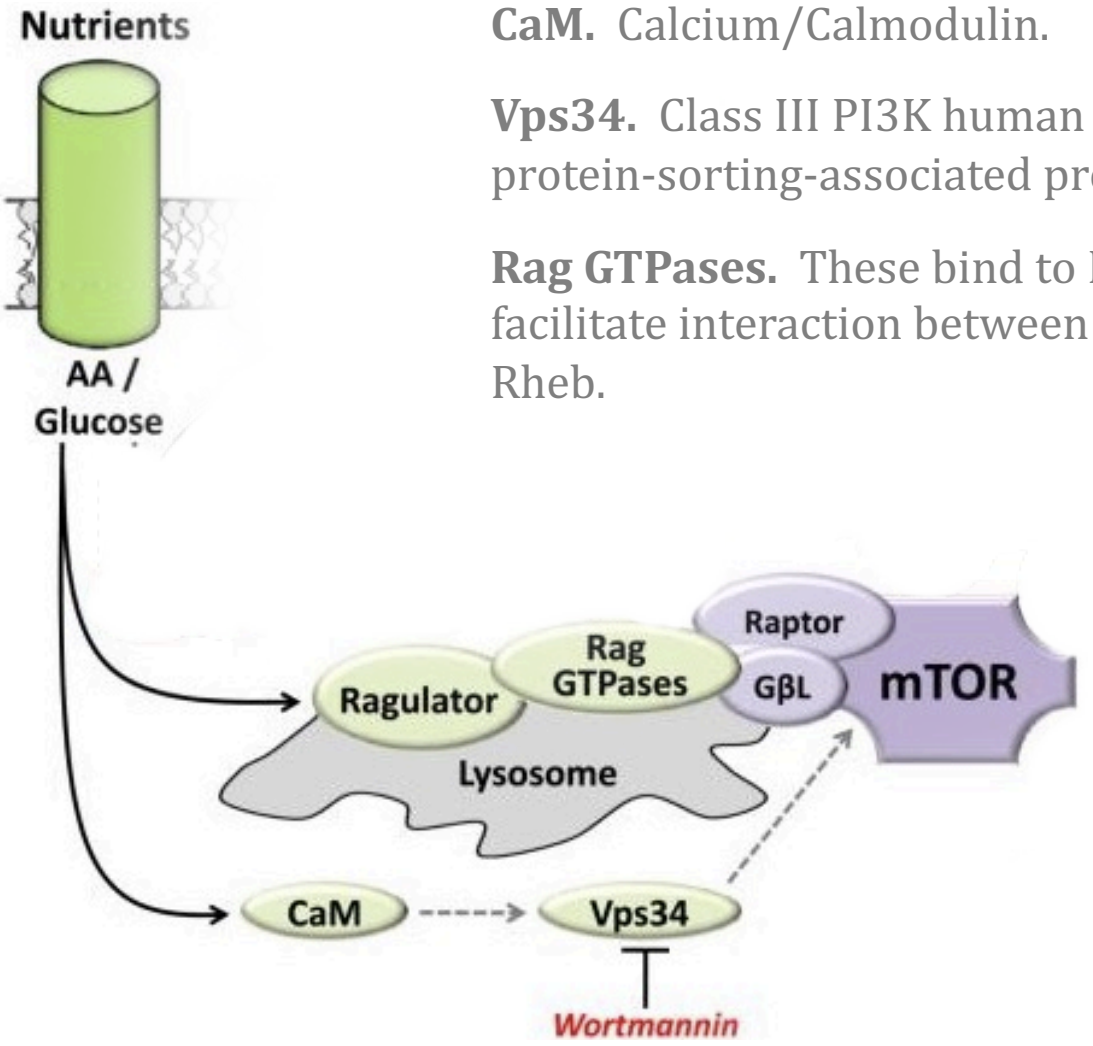



# mTOR. Activation. Inhibition.

*Int J Biochem Cell Biol.* 2011 September ; 43(9): 1267–1276. doi:10.1016/j.biocel.2011.05.007.

**Mechanotransduction and the Regulation of mTORC1 Signaling in Skeletal Muscle** Troy A. Hornber

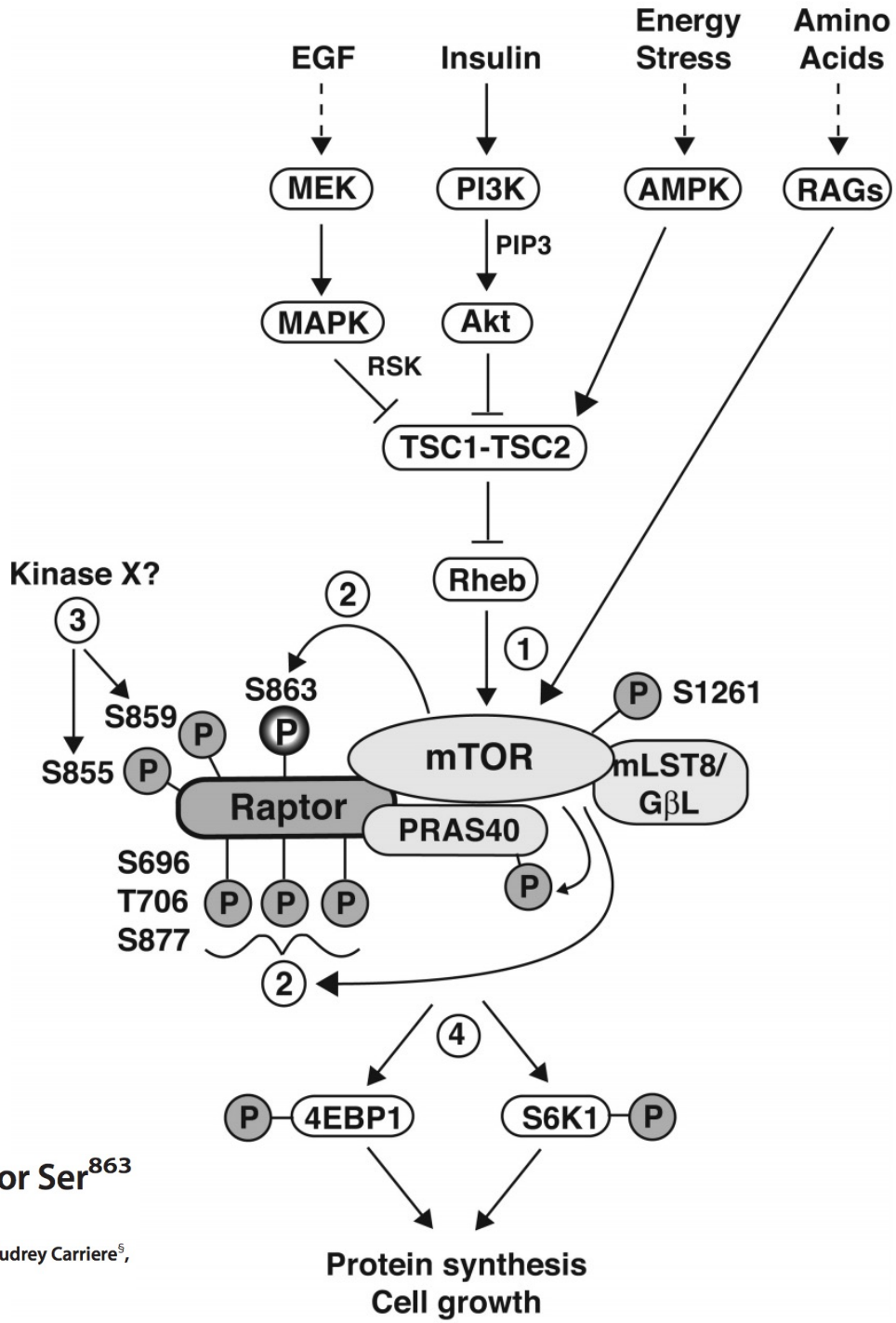





**CaM.** Calcium/Calmodulin.

**Vps34.** Class III PI3K human vacuolar protein-sorting-associated protein 34

**Rag GTPases.** These bind to Raptor and facilitate interaction between mTOR and Rheb.

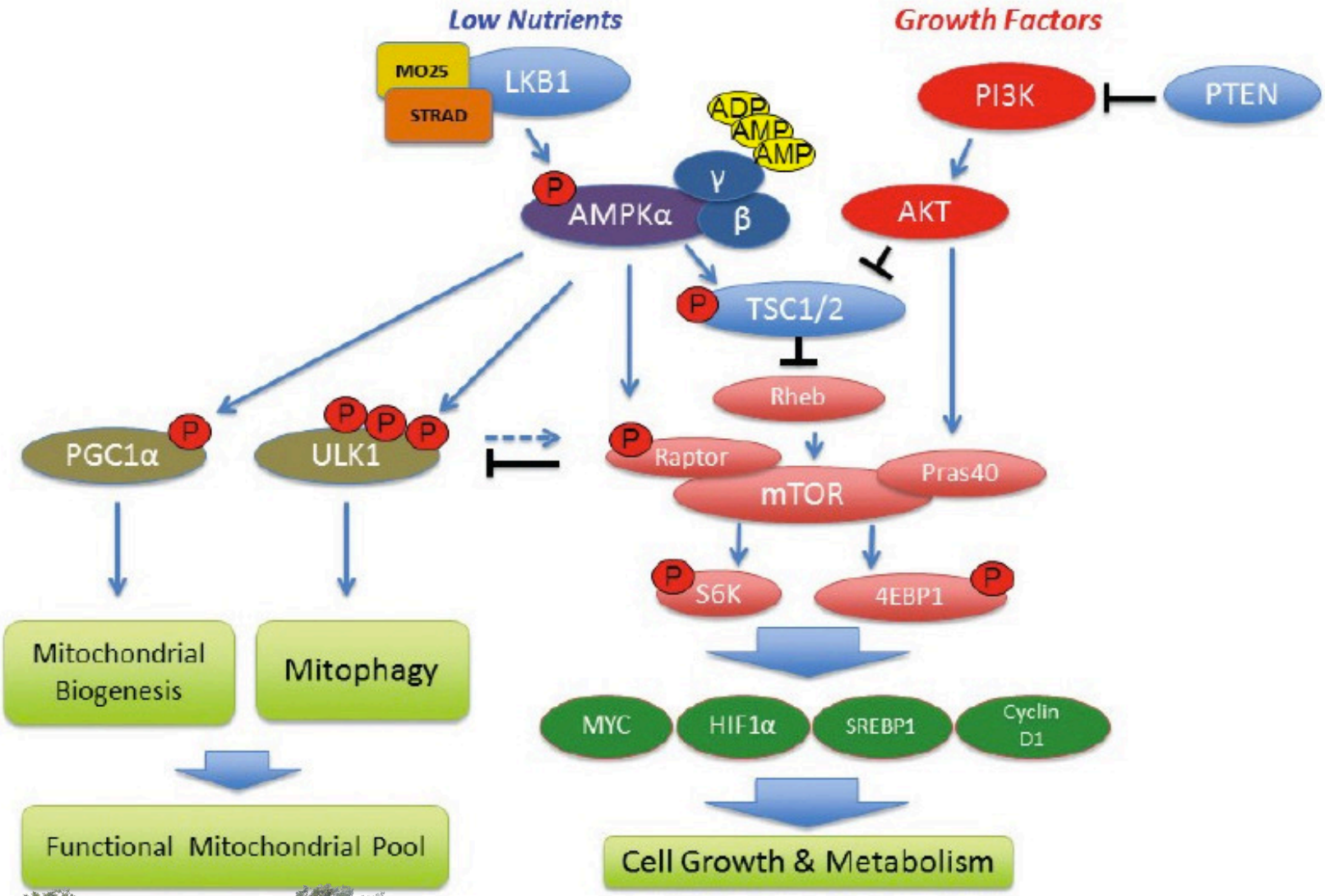



THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 285, NO. 1, pp. 80–94, January 1, 2010

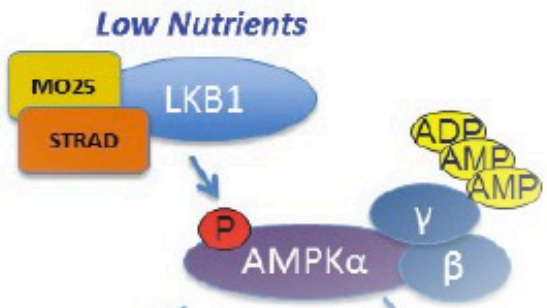
## Regulation of mTOR Complex 1 (mTORC1) by Raptor Ser[863] and Multisite Phosphorylation*[S]

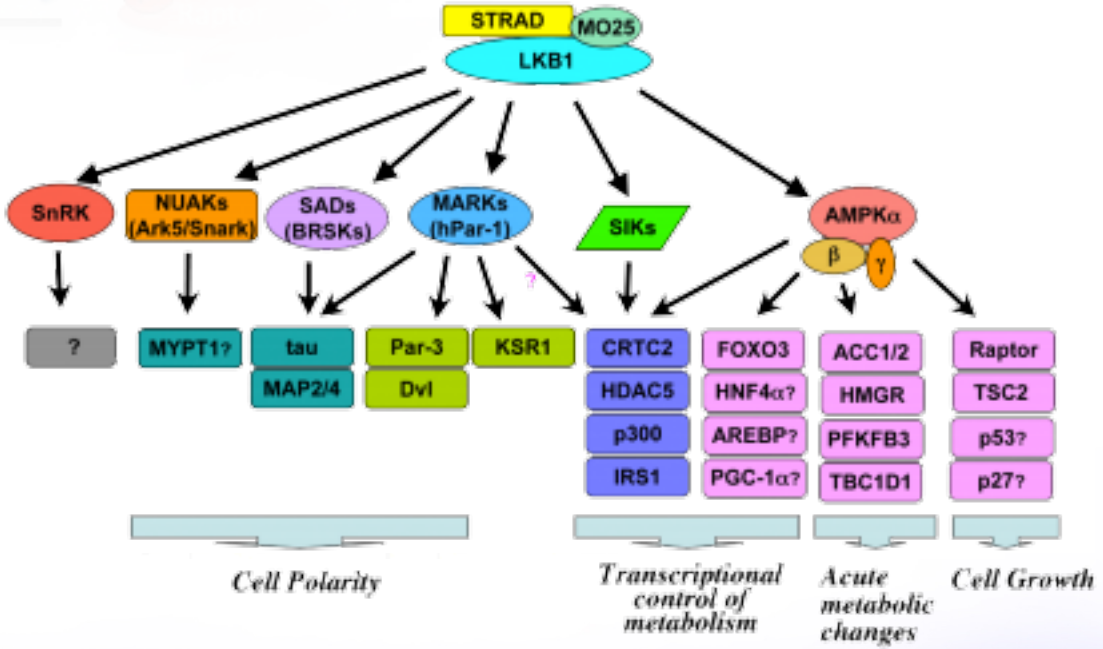
Kathryn G. Foster[‡1], Hugo A. Acosta-Jaquez[‡1], Yves Romeo[§], Bilgen Ekim[‡], Ghada A. Soliman[‡¶], Audrey Carriere[§], Philippe P. Roux[§], Bryan A. Ballif[‖], and Diane C. Fingar[‡¶2]

# REVIEW: Nutrition and mTOR




# Nutrition:




LKB1 = Liver Kinase B1

LKB1 activates AMPK (among other things)

# Applications / Considerations

SCIENCE VOL 310 18 NOVEMBER 2005

## Regulation of Yeast Replicative Life Span by TOR and Sch9 in Response to Nutrients

Matt Kaeberlein,[1]* R. Wilson Powers III,[1] Kristan K. Steffen,[2] Eric A. Westman,[2] Di Hu,[2] Nick Dang,[2] Emily O. Kerr,[2] Kathryn T. Kirkland,[2] Stanley Fields,[1,3] Brian K. Kennedy[2]*

GENES & DEVELOPMENT 20:174–184 © 2006

## Extension of chronological life span in yeast by decreased TOR pathway signaling

R. Wilson Powers III,[1,2] Matt Kaeberlein,[1] Seth D. Caldwell,[1] Brian K. Kennedy,[3] and Stanley Fields[1,4,5]

Development 2004 131: 3897-3906; doi: 10.1242/dev.01255

## The TOR pathway interacts with the insulin signaling pathway to regulate *C. elegans* larval development, metabolism and life span

Kailiang Jia, Di Chen and Donald L. Riddle*

*Curr Biol*. 2004 May 25; 14(10): 885–890. doi:10.1016/j.cub.2004.03.059.

## Regulation of Lifespan in *Drosophila* by Modulation of Genes in the TOR Signaling Pathway

Pankaj Kapahi, Brian M. Zid, Tony Harper, Daniel Koslover, Viveca Sapin, and Seymour Benzer*
Division of Biology 156-29 California Institute of Technology Pasadena, California 91125

*Nature*. 2009 July 16; 460(7253): 392–395. doi:10.1038/nature08221.

## Rapamycin fed late in life extends lifespan in genetically heterogeneous mice

David E. Harrison*,1, Randy Strong*,2, Zelton Dave Sharp[3], James F. Nelson[4], Clinton M. Astle[1], Kevin Flurkey[1], Nancy L. Nadon[5], J. Erby Wilkinson[6], Krystyna Frenkel[7], Christy S. Carter[8], Marco Pahor[8,†], Martin A. Javors[9], Elizabeth Fernandez[2], and Richard A. Miller*,10
[1]The Jackson Laboratory, Bar Harbor, ME 04609 USA

*Lifespan . . .*

# mTOR–Muscle Adaptation Relationship

What causes hypertrophy?

*Vs.*

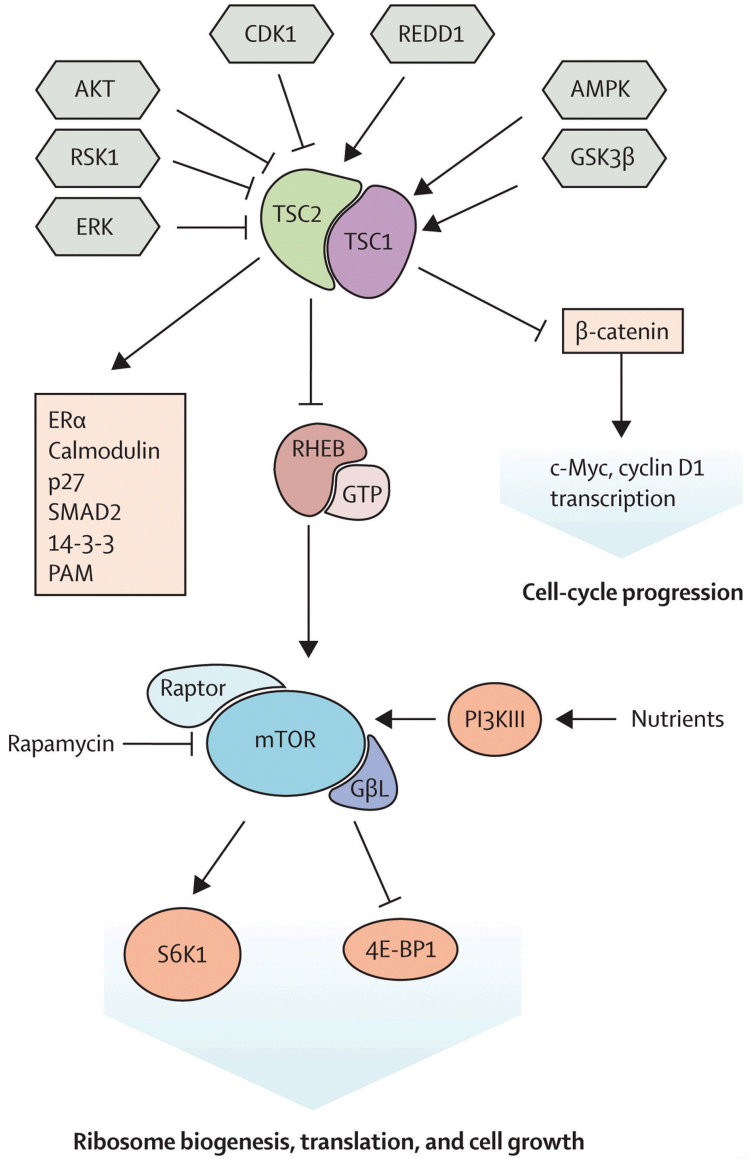
# Maximizing Activation:

## What causes hypertrophy?

**What conditions maximize the chemical, mechanical, and endocrine responses in the body?**

Heavy lifting, using multiple (or at least large) muscle groups.

**Why?**



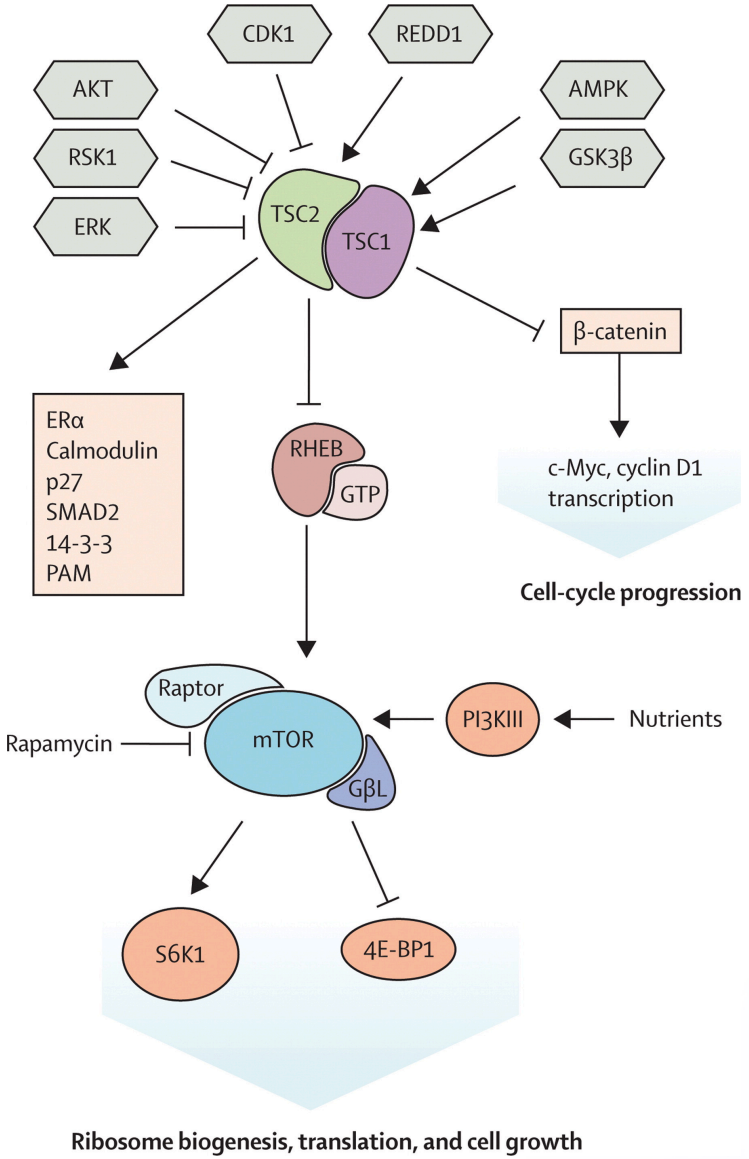

# Maximizing Activation:

## What causes hypertrophy?

**What conditions maximize the chemical, mechanical, and endocrine responses in the body?**

**Chemical.** The presence (and action) of the inflammatory response is proportionate to the amount of damage sustained.

vs.

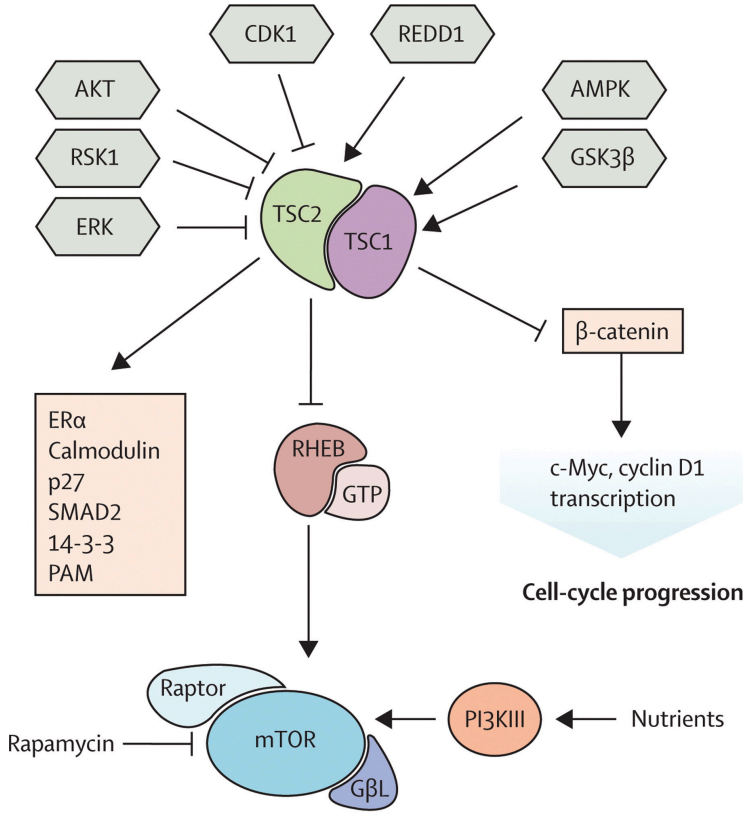



# Maximizing Activation:

## What causes hypertrophy?

**What conditions maximize the chemical, mechanical, and endocrine responses in the body?**

**Mechanical.** When load is the stimulus for signal transduction, the only fibers that benefit from those signals are those that produce them. *(Size principle!)*




# Maximizing Activation:

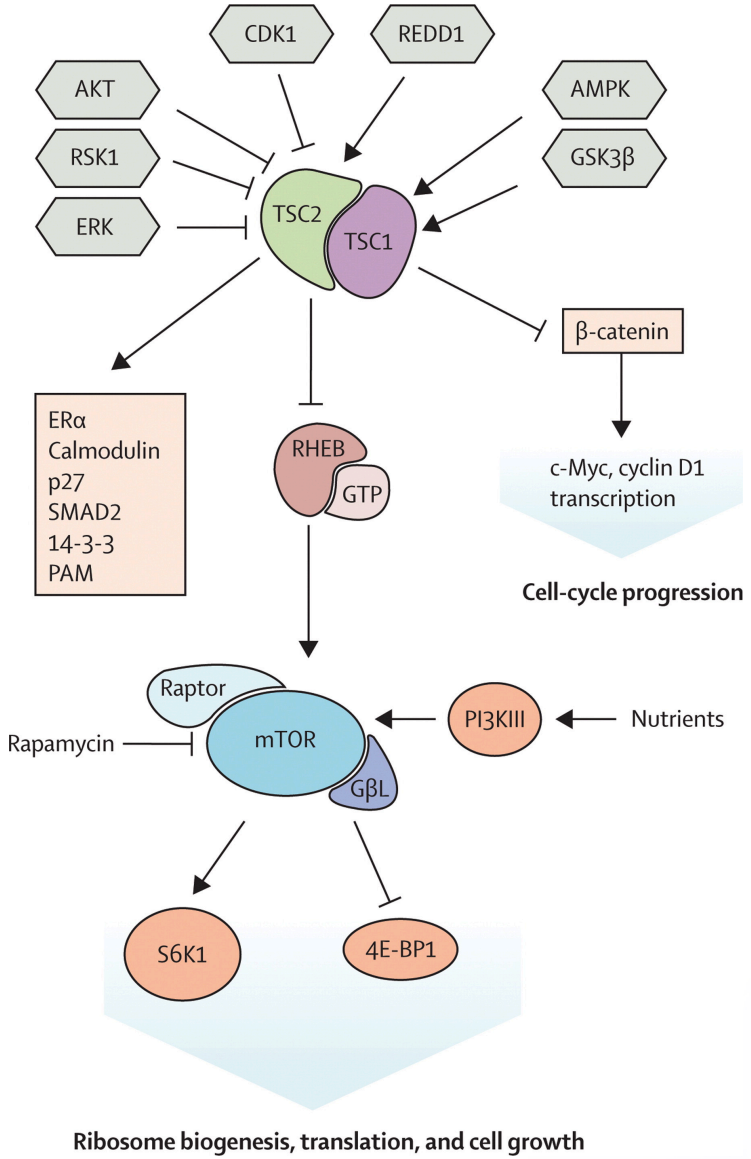
## What causes hypertrophy?

**What conditions maximize the chemical, mechanical, and endocrine responses in the body?**

**Hormonal.** Using more tissue affects androgen production *and* binding.

Muscle mass involved, intensity, duration affect the amount of T and IGF in circulation.

Recruitment of type II fibers appears to upregulate ARs more than type I fibers and the activation of muscle cells appears to enhance AR binding. *(Size principle!)*



# Maximizing Activation:

## What causes hypertrophy?

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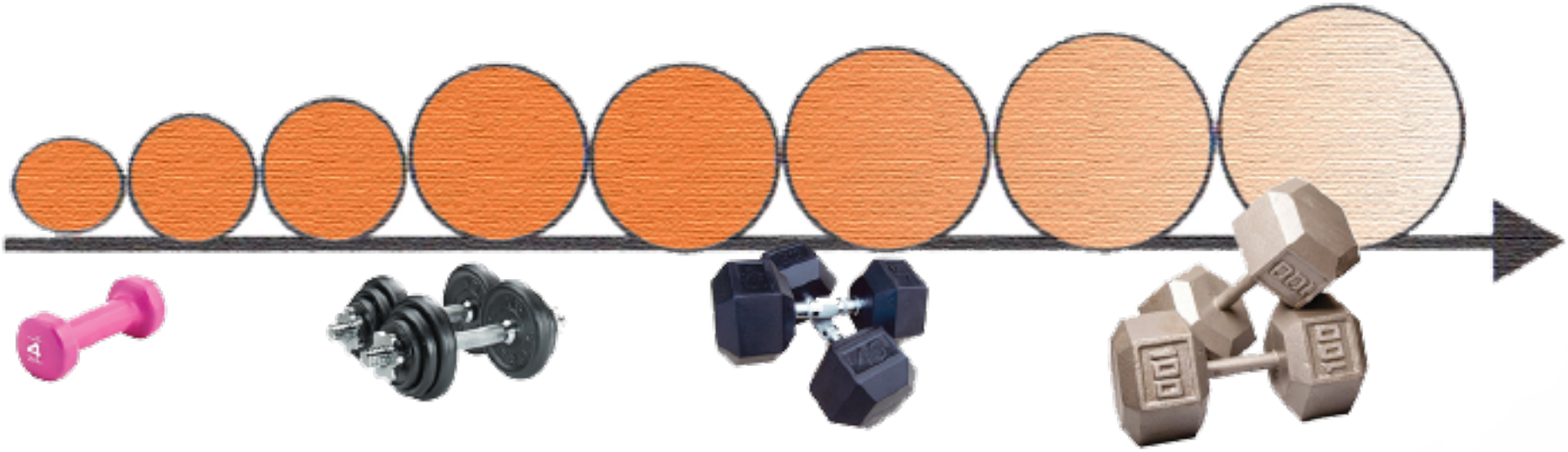
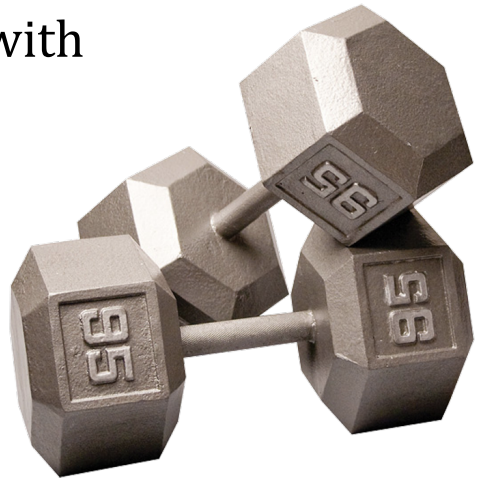


# Maximizing Activation:

## Applications for the weight room

Discrepant interpretations and applications of size principle and its relationship with mTOR signaling and hypertrophy.




The mere *activation* of motor units is not the whole story.

# Maximizing Activation:

## Concentric *vs.* Eccentric Forces

**Which is better for mTOR activation?**

# Maximizing Activation:

## Concentric *vs.* Eccentric Forces

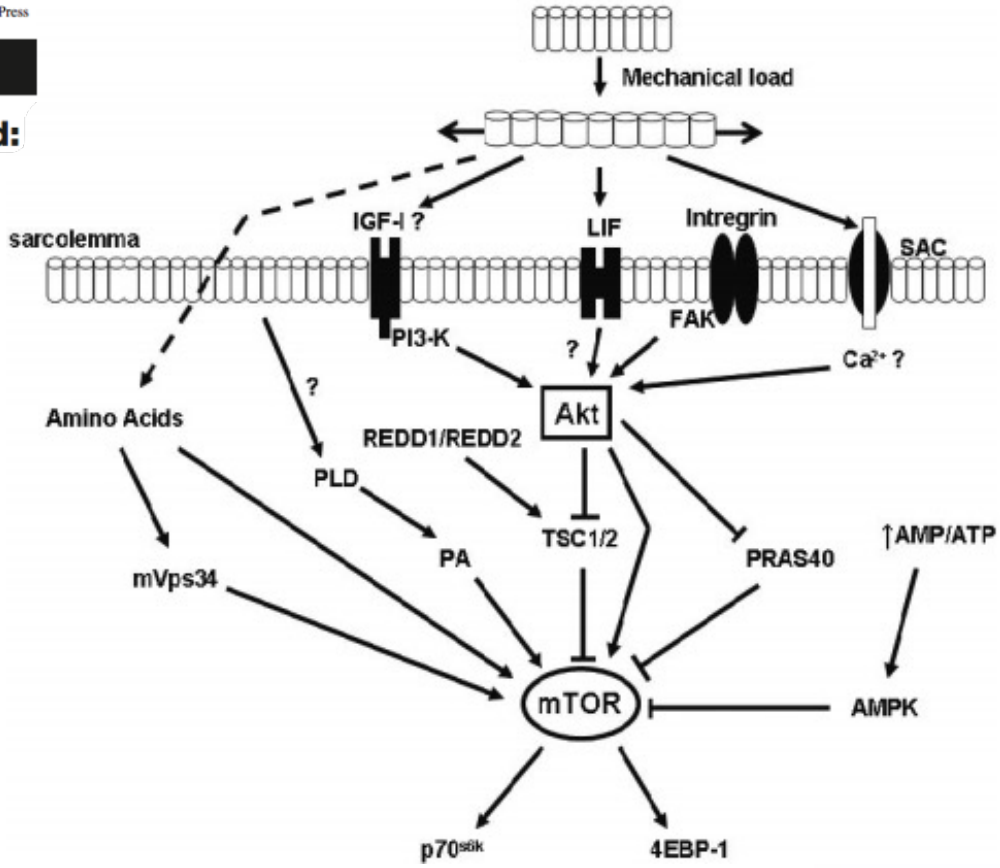
Stretch-activated channels (SACs).

Appl. Physiol. Nutr. Metab. 34: 328–335 (2009) doi:10.1139/H09-010 Published by NRC Research Press

REVIEW / SYNTHÈSE

**Changes in muscle mass with mechanical load: possible cellular mechanisms[1]**

Espen E. Spangenburg




mTOR seems to be sensitive to levels of intracellular calcium.

Introducing SAC inhibitors while loading the muscle = attenuation of PKB activation.

*One* explanation for increased mTOR signaling in eccentric muscle actions.

* Eliasson et al. (2006) in humans.
* Nader and Esser (2001) in rodents.

# Maximizing Activation:

## Concentric *vs.* Eccentric Forces

*J Appl Physiol*
91: 693–702, 2001.

Insight into skeletal muscle mechanotransduction: MAPK activation is quantitatively related to tension

LOUIS C. MARTINEAU AND PHILLIP F. GARDINER

With the use of a rat plantaris in situ preparation, a wide range of peak tensions was generated through passive stretch and concentric, isometric, and eccentric contractile protocols, and the resulting phosphorylation of c-Jun $NH_2$-terminal kinase (JNK), extracellular regulated kinase (ERK), and p38 MAPKs was assessed. Isoforms of JNK and ERK MAPKs were found to be phosphorylated in a tension-dependent manner, such that eccentric > isometric > concentric > passive stretch. Peak tension was found to be a better predictor of MAPK phosphorylation than time-tension integral or rate of tension development.

# Maximizing Activation:

## Concentric *vs.* Eccentric Forces

*J Appl Physiol*
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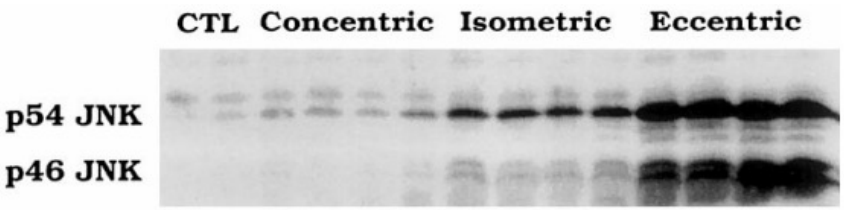
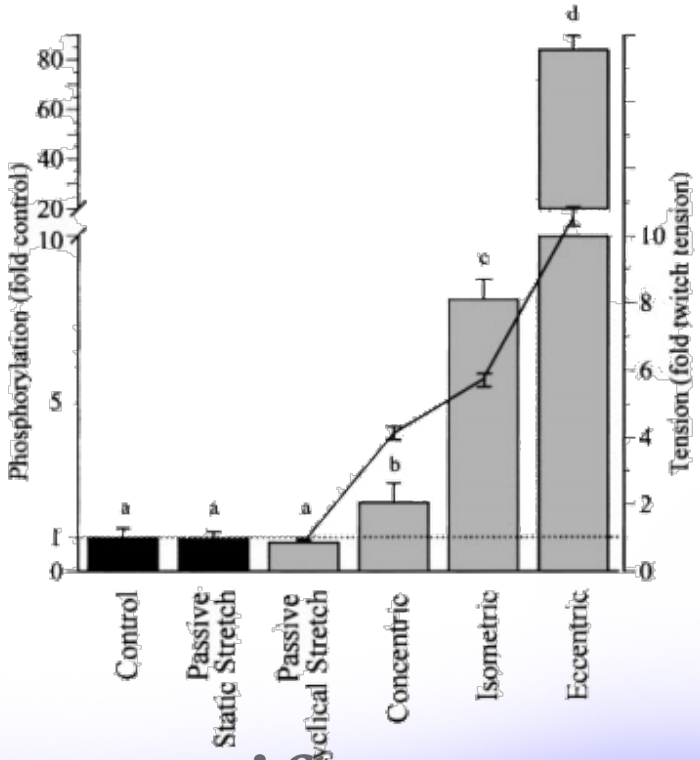



MAPK activation based on different types of muscle activity.




# Maximizing Activation:

## Concentric *vs.* Eccentric Forces

Eccentric muscle activation also seems to activate IGFs and especially MGF (mechano-growth factor) more.

Exercise-induced muscle damage seems to be a major trigger for the increase in MGF levels and eccentric stress is what causes the damage.

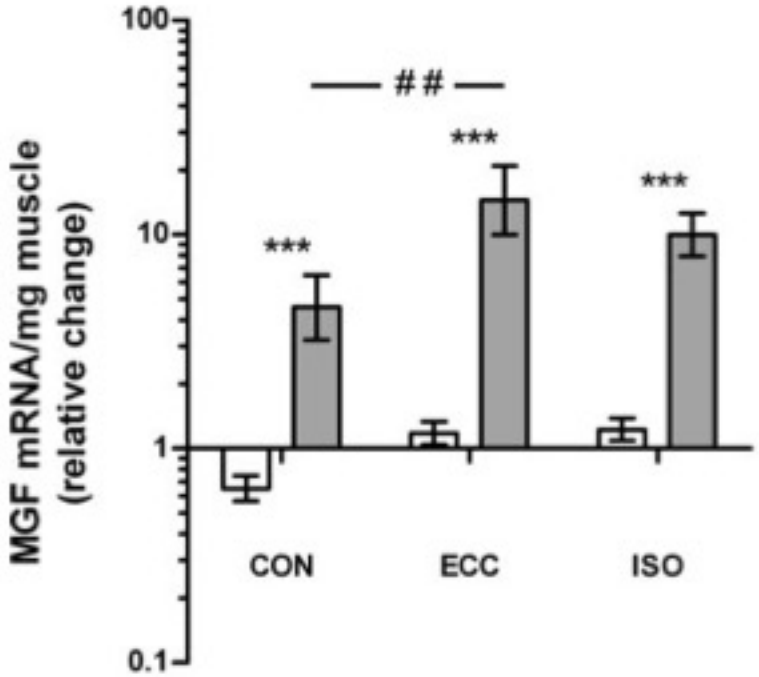
*J Appl Physiol* 102: 573–581, 2007.

Short-term strength training and the expression of myostatin and IGF-I isoforms in rat muscle and tendon: differential effects of specific contraction types

K. M. Heinemeier,[1]* J. L. Olesen,[1]* P. Schjerling,[3,4] F. Haddad,[2]
H. Langberg,[1] K. M. Baldwin,[2] and M. Kjaer[1]

# Maximizing Activation:

## Concentric *vs.* Eccentric Forces

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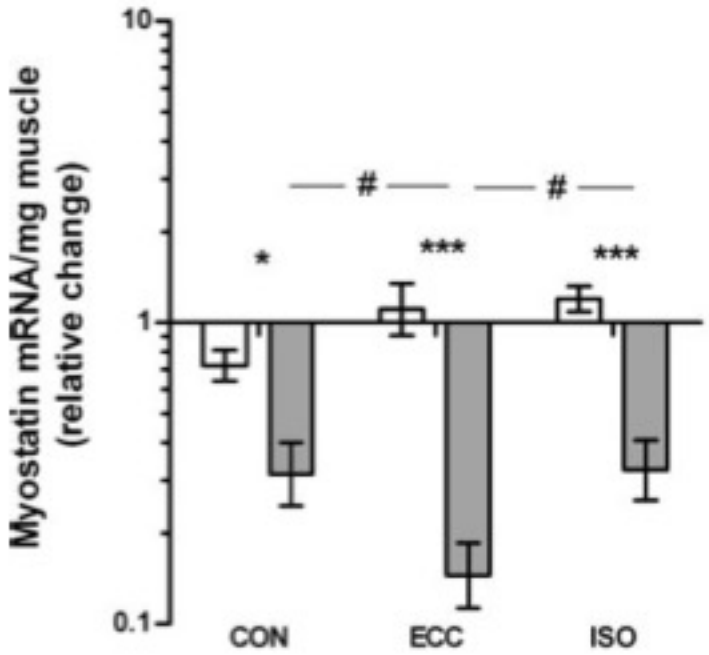
H. Langberg,[1] K. M. Baldwin,[2] and M. Kjaer[1]

# Maximizing Activation:

## Concentric *vs.* Eccentric Forces

Eccentric muscle activation also seems to ***decrease*** myostatin.

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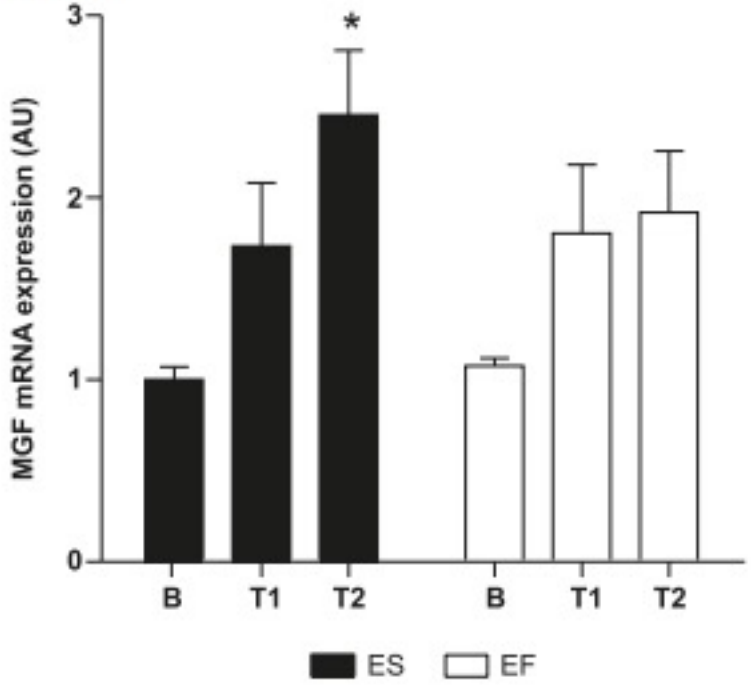
H. Langberg,[1] K. M. Baldwin,[2] and M. Kjaer[1]

# Maximizing Activation:

## Concentric *vs.* Eccentric Forces

Slow eccentric stress may generate more MGF than fast eccentric stress (30° per second vs. 210° per second).

**Fig. 2.** Mechano growth factor (MGF) mRNA expression in ES and EF. EE, eccentric exercise; ES, slow EE; EF, fast EE; B, baseline; T1, immediately after EE; and T2, 2 h after EE. *, $p < 0.05$ compared with B.




Appl. Physiol. Nutr. Metab. **36**: 283–290 (2011)

**Effect of eccentric exercise velocity on akt/mtor/p70$^{s6k}$ signaling in human skeletal muscle**

**Hamilton Roschel, Carlos Ugrinowistch, Renato Barroso, Mauro A.B. Batista, Eduardo O. Souza, Marcelo S. Aoki, Mario A. Siqueira-Filho, Ricardo Zanuto, Carla R.O. Carvalho, Manoel Neves Jr., Marco T. Mello, and Valmor Tricoli**

# Maximizing Activation:

## Concentric *vs.* Eccentric Forces

*Am J Physiol Cell Physiol* 301: C938–C946, 2011.

The $\alpha_7\beta_1$-integrin accelerates fiber hypertrophy and myogenesis following a single bout of eccentric exercise

**Tara N. Lueders,[1,2] Kai Zou,[1,2] Heather D. Huntsman,[1,2] Benjamin Meador,[1] Ziad Mahmassani,[1,2] Megan Abel,[1,2] M. Carmen Valero,[1,2] Kimberly A. Huey,[3] and Marni D. Boppart[1,2]**

Some of the mechanical pathways are still pretty hazy.

# Maximizing Activation:

## Type I *vs.* Type II Muscle Fibers

**Which is better for mTOR activation?**

# Maximizing Activation:

## Type I *vs.* Type II Muscle Fibers

**Which is better for mTOR activation?**

Some mechanical stimuli activate PKB-mTOR-S6K1; others don't.

Workloads that involve **a low load and high duration don't**.
Workloads that involve **a high load and short duration do**.

Greater mechanical intensity (larger stimulus) seems necessary:


**1.** Atherton et al. (2005). Selective activation of AMPK- PGC-1alpha or PKB-TSC2-mTOR signaling can explain specific adaptive responses to endurance or resistance training-like electrical muscle stimulation. FASEB J., 19: 786–788.

**2.** Dreyer et al. (2006). Resistance exercise increases AMPK activity and reduces 4E-BP1 phosphorylation and protein synthesis in human skeletal muscle. J Physiol., 576: 613–624.

**3.** Sakamoto et al. (2002). Contraction regulation of Akt in rat skeletal muscle. J Biol Chem, 277: 11910–11917.

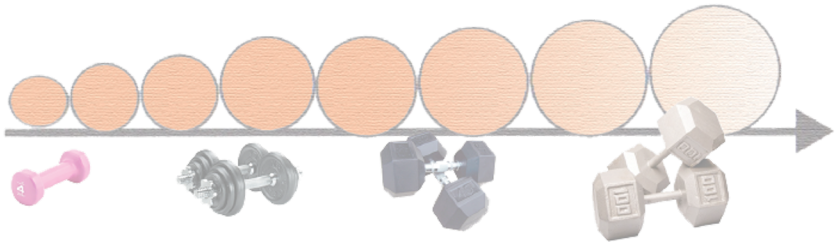

# Maximizing Activation:

## Type I *vs.* Type II Muscle Fibers

**Which is better for mTOR activation?**

Type II fibers are more susceptible to mTOR-signaled hypertrophy than type I fibers.

Phosphorylation of p70s6k is less dramatic in a muscle group that contains a higher concentration of type I fibers.



If you want more signaling, recruit higher threshold motor units.

* Baar and Esser (1999).

Henneman!

# Maximizing Activation:

## Type I *vs.* Type II Muscle Fibers

If lower intensity resistance training is combined with reductions of blood flow to the working tissue (via vascular occlusion), p70s6K was activated and protein synthesis increased.

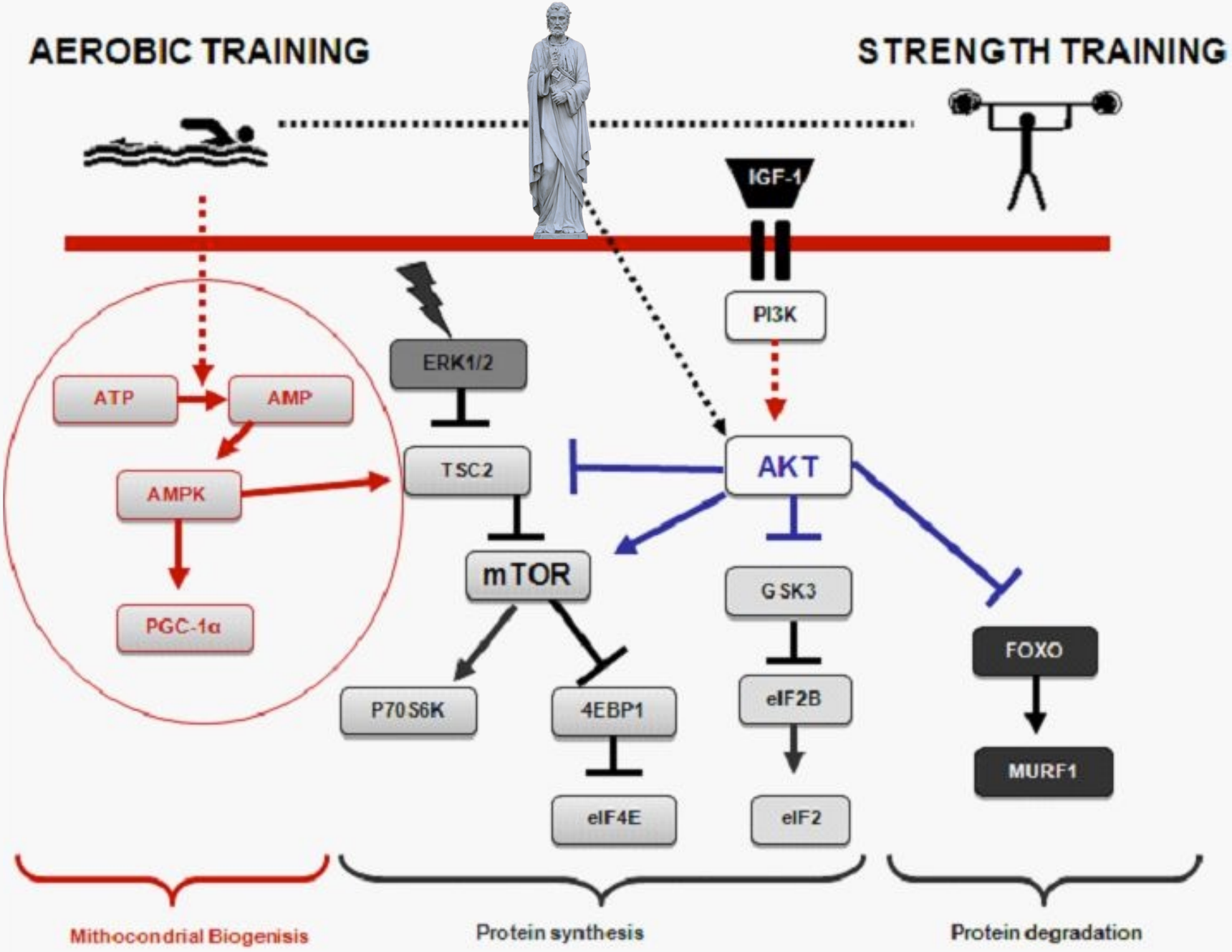
Fujita S, Abe T, Drummond MJ, Cadenas JG, Dreyer HC, Sato Y, Volpi E, Rasmussen BB. (2007). Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *Journal of Applied Physiology*, 103: 903–910.

# Maximizing Activation:

## Combining Aerobic-Anaerobic?

**Yes or no?**

And why?


AEROBIC TRAINING
STRENGTH TRAINING
IGF-1
PI3K
ERK1/2
ATP
AMP
AMPK
PGC-1α
TSC2
AKT
mTOR
GSK3
FOXO
P70S6K
4EBP1
eIF2B
MURF1
eIF4E
eIF2
Mithocondrial Biogenisis
Protein synthesis
Protein degradation

# Maximizing Activation:

## Specificity of adaptation

*Proceedings of the Nutrition Society* (2004), **63**, 331–335 DOI:10.1079/PNS2004357


*The 12th Conference of the International Research Group on the Biochemistry of Exercise was held at Maastricht University, Maastricht, The Netherlands on 13–16 July 2003*

## Symposium 5: Muscle hypertrophy: the signals of insulin, amino acids and exercise

# Mechanotransduction and the regulation of protein synthesis in skeletal muscle

T. A. Hornberger and K. A. Esser*
*Muscle Biology Laboratory, School of Kinesiology (m/c 194), University of Illinois, Chicago, 901 W Roosevelt Road, Chicago, IL 60608, USA*

### Specificity in mechanotransduction

In addition to being able to sense mechanical stimuli, it also appears that muscle cells can differentiate between different types of mechanical forces. For example, in skeletal muscle chronic longitudinal stretch produces growth in length but not cross-section (sarcomere deposition in series to the long axes), while chronic functional overload produces cross-sectional growth with no changes in length (sarcomere deposition is parallel to the long axes).

# Specificity of Adaptation

## Alfredson protocol

If all you do is stretch, this signal probably gets filtered out.

If there's an increase in *tension* (i.e., load) at the same time, the signal seems to be amplified.

Thus remodeling and repair and regeneration and restructuring of the tissue that produced the signal.

# Specificity of Adaptation

Other components of the FITT principle (in addition to type) matter too: Frequency, intensity, and duration affect signaling responses.

**Resistance training stimuli** (especially eccentric and high force stresses) causes mTOR/p70s6k to be activated.

**Aerobic/oxidative stimuli** promote mitochondrial biogenesis; they do not activate mTOR and p70s6k.

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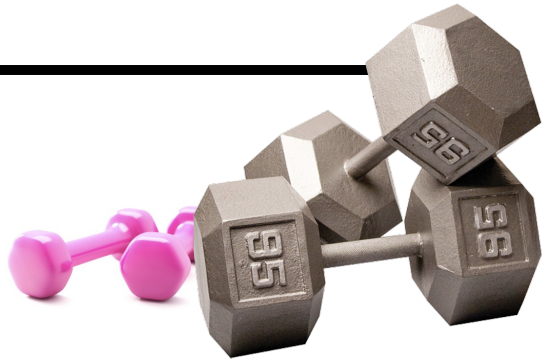
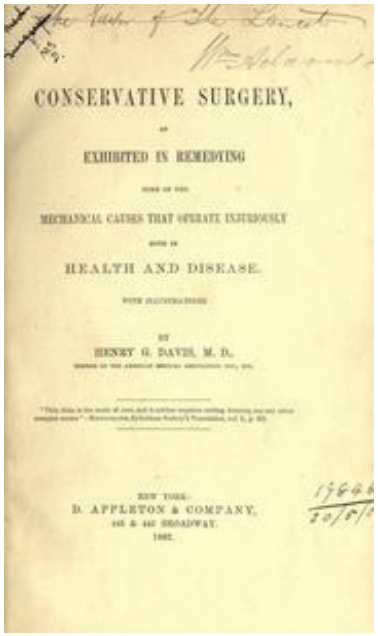
Discrepant interpretations and applications of size principle and its relationship with mTOR signaling and hypertrophy.



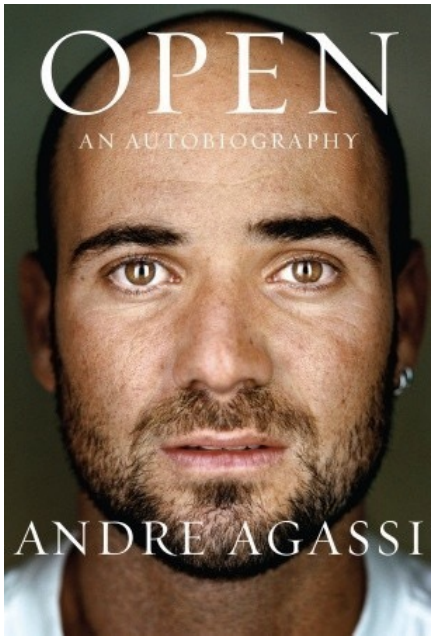
The mere *activation* of motor units is not the whole story.

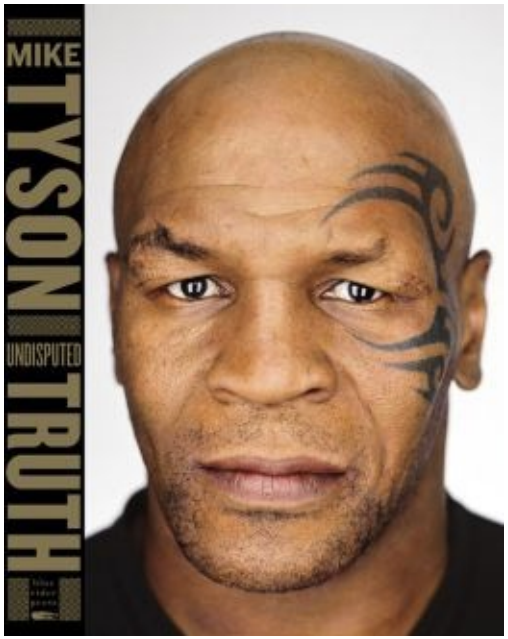
# Specificity of Adaptation

Mechanotransduction:

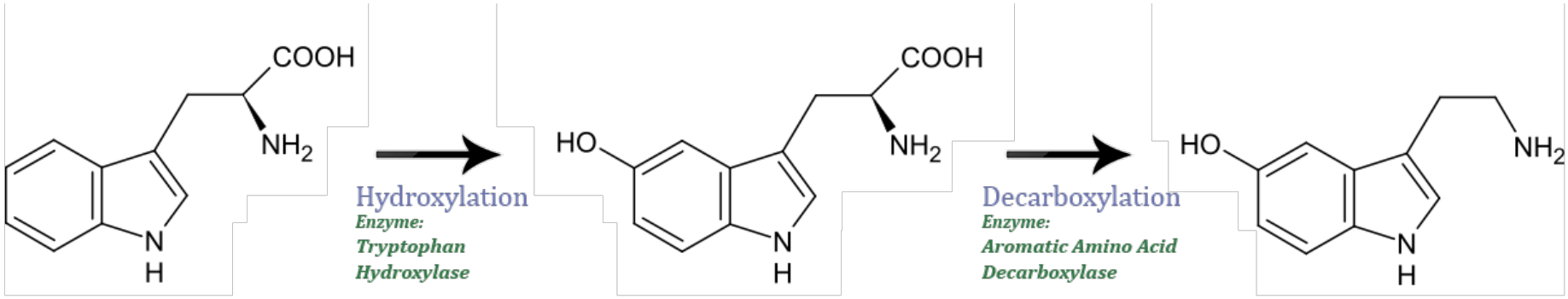






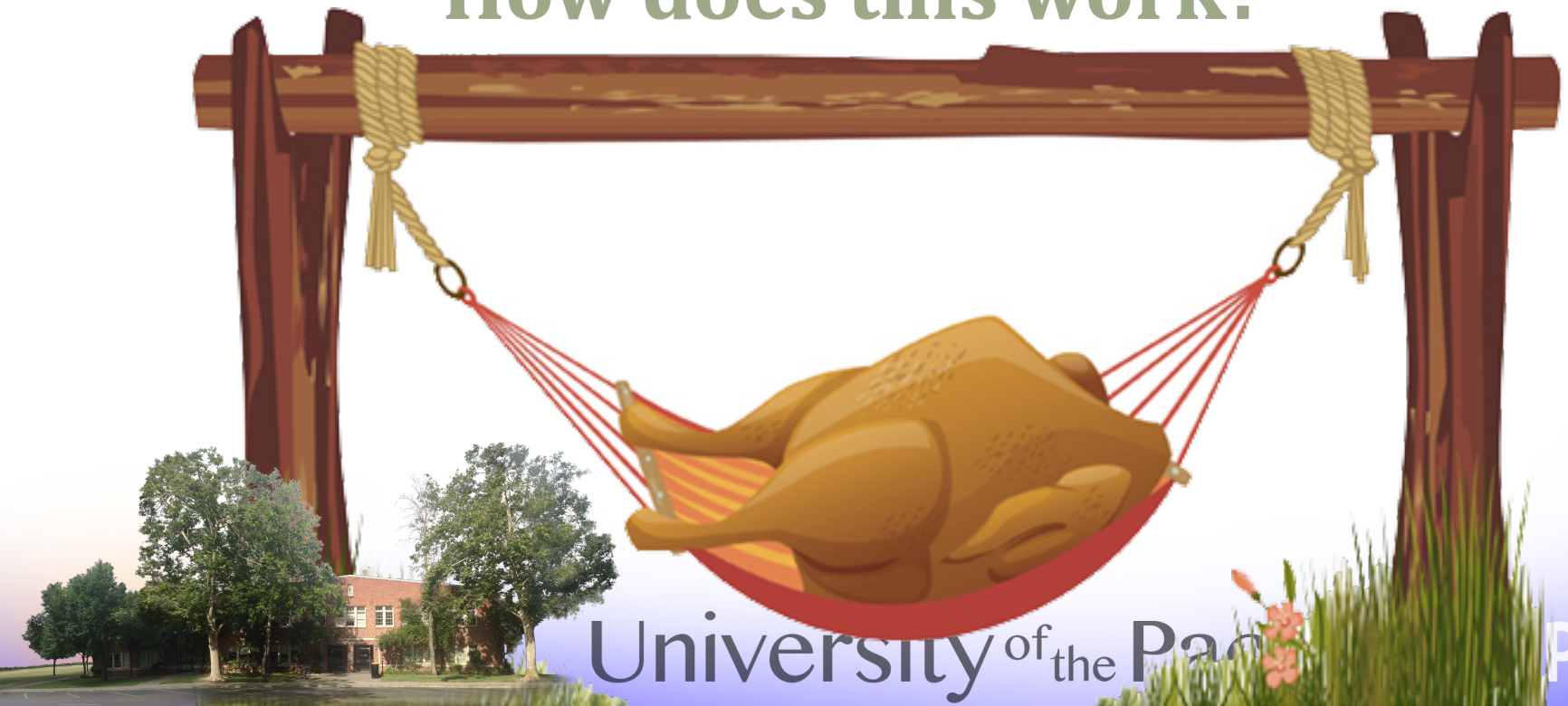




Specificity of Adaptation



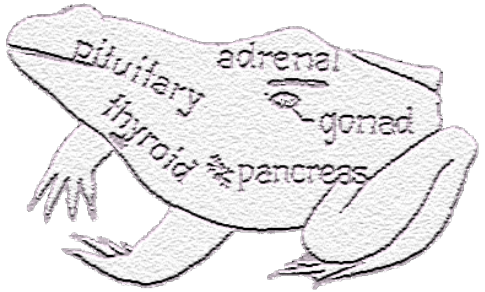

Tryptophan 5-hydroxy-L-tryptophan Serotonin

# How does this work?



# SOME REVIEW QUESTIONS

# Questions you should be able to answer

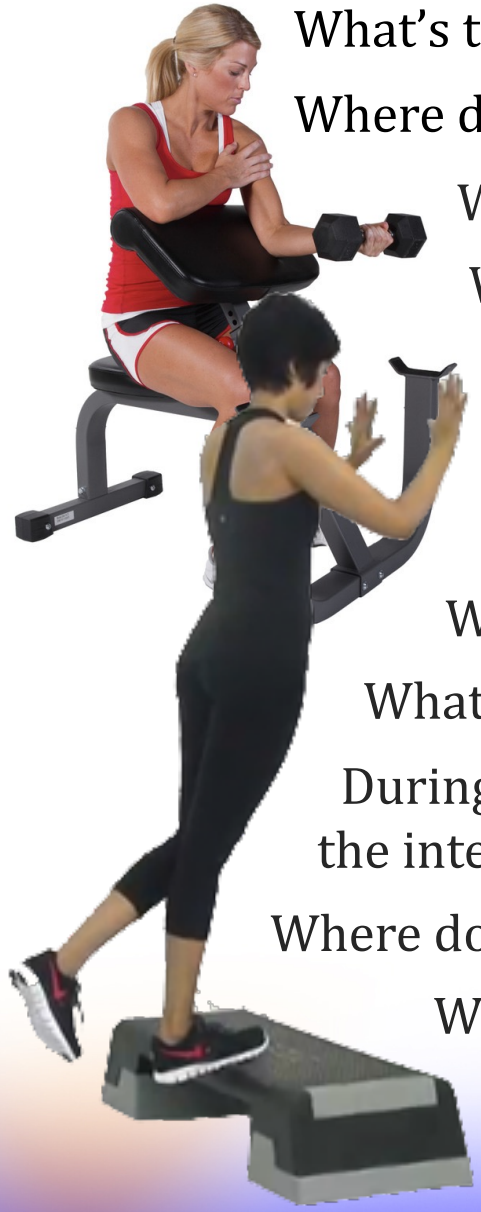



When and how did the study of endocrinology get started?
*Neuro*endocrine: what does that mean?
Chemical messengers: short range vs. long range?
What are the different classifications of hormones?
What are the differences between them (synthesis, function, etc.)?
Anabolic vs. catabolic hormones?
Hormone receptors: how do those work?
Autocrine, paracrine, and endocrine: what are those and what's an example of each?
Binding proteins: what do they do and what are two examples?
Earl Wilbur Sutherland, Jr. discovered something in Carl Cori's lab. What was it?
What does adenylate cyclase do? What gets created and, downstream from that, what gets activated? And what does that thing do? Phosphorylase kinase? Perilipin? Hormone-sensitive lipase? Know those signaling cascades.
What is GLUT4 translocation? It's downstream from…?
How does insulin affect lipolysis? What's PDE?
How does insulin activate it? What's adipose triglyceride lipase? What is insulin's effect on it?

# Questions you should be able to answer

What cell types are multinucleated? Why is that important? What's a nuclear domain?
What's myostatin? What's follistatin?
What's IGF? It has its own receptors, but what else can it bind to?
Where and how is most of it produced?
What is the primary androgen interacting with skeletal muscle?
How is that produced (what "axis")?
On the subject of "axis", what regulates x? (What is the starting line of just about every axis? And what are some other axes?)
What is a "diurnal rhythm"? What does it apply to (example)?
GHRH vs. somatostatin? Where are those released and what's the difference?
What is the main way hGH exerts its metabolic effects on muscle tissue?
What general actions does (and doesn't) growth hormone do?
What is "protein turnover"?

# Questions you should be able to answer



What's the difference between PKA and PKB?

Where do PKA and PKB interact?

What is hypertrophy?

What changes in the muscle?

Why does hypertrophy happen?

How does hypertrophy happen?

What's a cell signaling cascade?

Why are they important (what's the point of having them)?

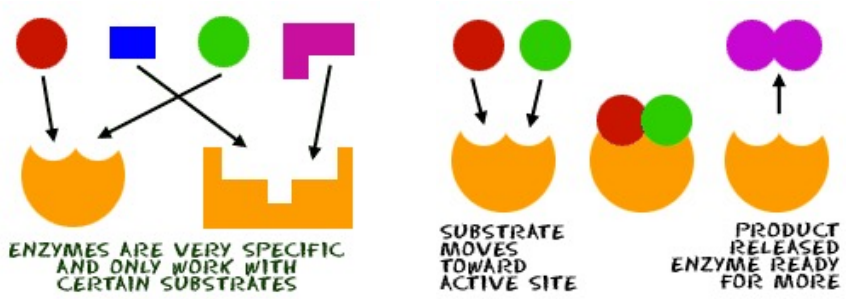
What types of things get these cascades started?

During transduction, what generally activates or deactivates the intermediates?

Where do these cascades generally end?

What's an upstream variable? Downstream?

# Questions you should be able to answer




What is metabolism?

What are enzymes?

How do enzymes work?

How do enzymes affect your metabolism?

What happens when an enzyme is activated / positively modulated?

What happens when an enzyme is deactivated / negatively modulated?

What is allosteric control?

What is competitive inhibition?

What is noncompetitive inhibition?

What is uncompetitive inhibition?

~~What is mixed inhibition?~~

What is suicide inhibition?

What is enzyme inhibition via accumulation of product?

What is enzyme activation/deactivation by phosphorylation?

What is the pathway regulating glycogen synthase / phosphorylase activity?

# Questions you should be able to answer

What is an androgen?

What do exogenous and endogenous mean?

Name an endogenous steroid. Name an exogenous one.

What is the problem with "natural" as a description of an athlete?

Anabolic steroids and the heart? What do we know about that?

Anabolic steroids and the liver? What are two problems? Can they be avoided?

What's the leading cause of liver toxicity?

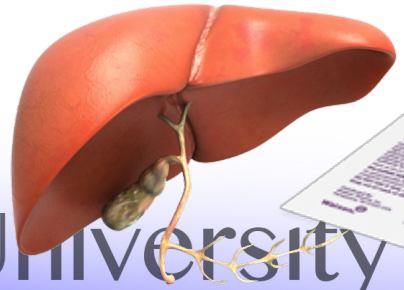
How is does? Ha ha ha! Pork hank burrow!

Steroids in sport: yes or no (I leave this up to you)?

We talked about nine arguments against anabolic steroids. What are they?

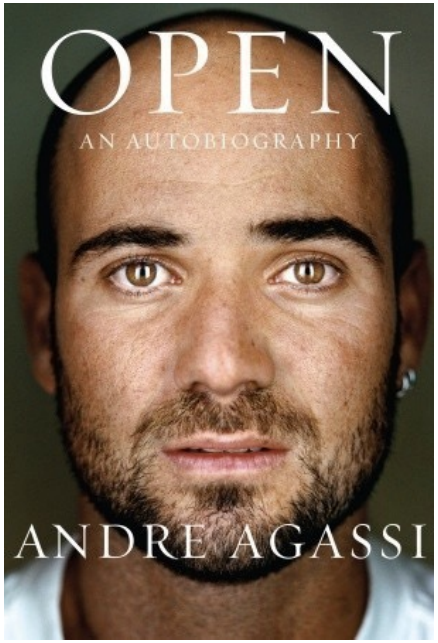
What is "first pass hepatic metabolism"?

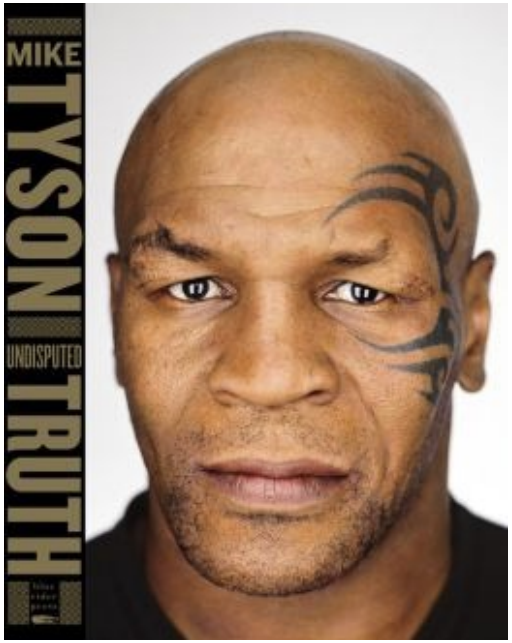
Androgens and myonuclei?

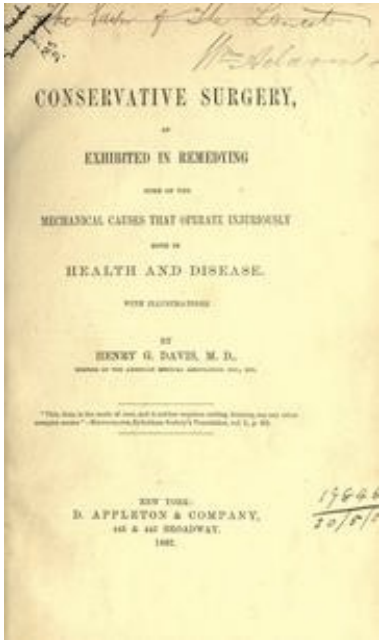



# Questions you should be able to answer

Be able to talk about cell signaling responses from the perspective of specificity of adaptation.





CONSERVATIVE SURGERY,

EXHIBITED IN REMEDYING

MECHANICAL CAUSES THAT OPERATE INJURIOUSLY

HEALTH AND DISEASE.

HENRY G. DAVIS, M. D.

D. APPLETON & COMPANY,


Das Gesetz

Transformation der Knochen

# Questions you should be able to answer

Be able to talk about cell signaling responses from the perspective of fitness.

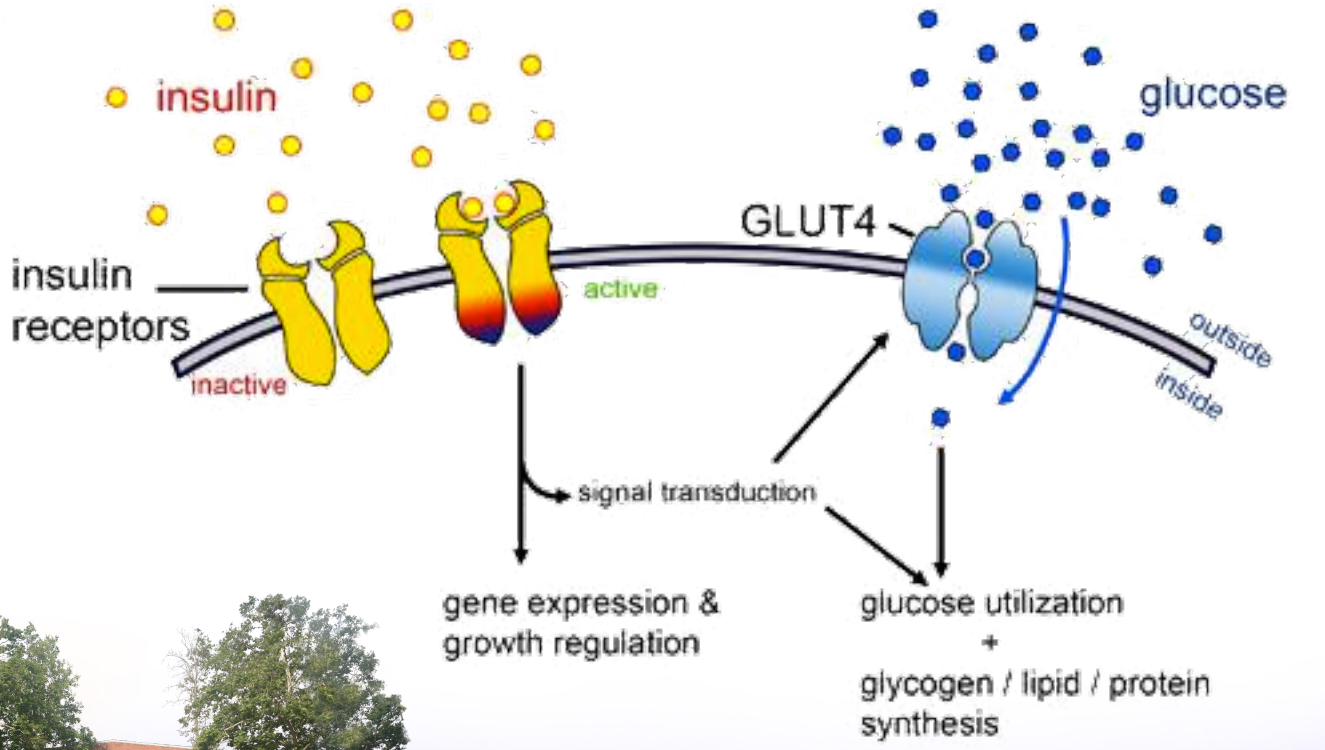

# Questions you should be able to answer

What's the difference between insulin and steroid hormones?

What about thyroid hormones; what's weird about those?

What is insulin's main function? How does it accomplish that function?

What do I draw in insulin signaling?




# Questions you should be able to answer

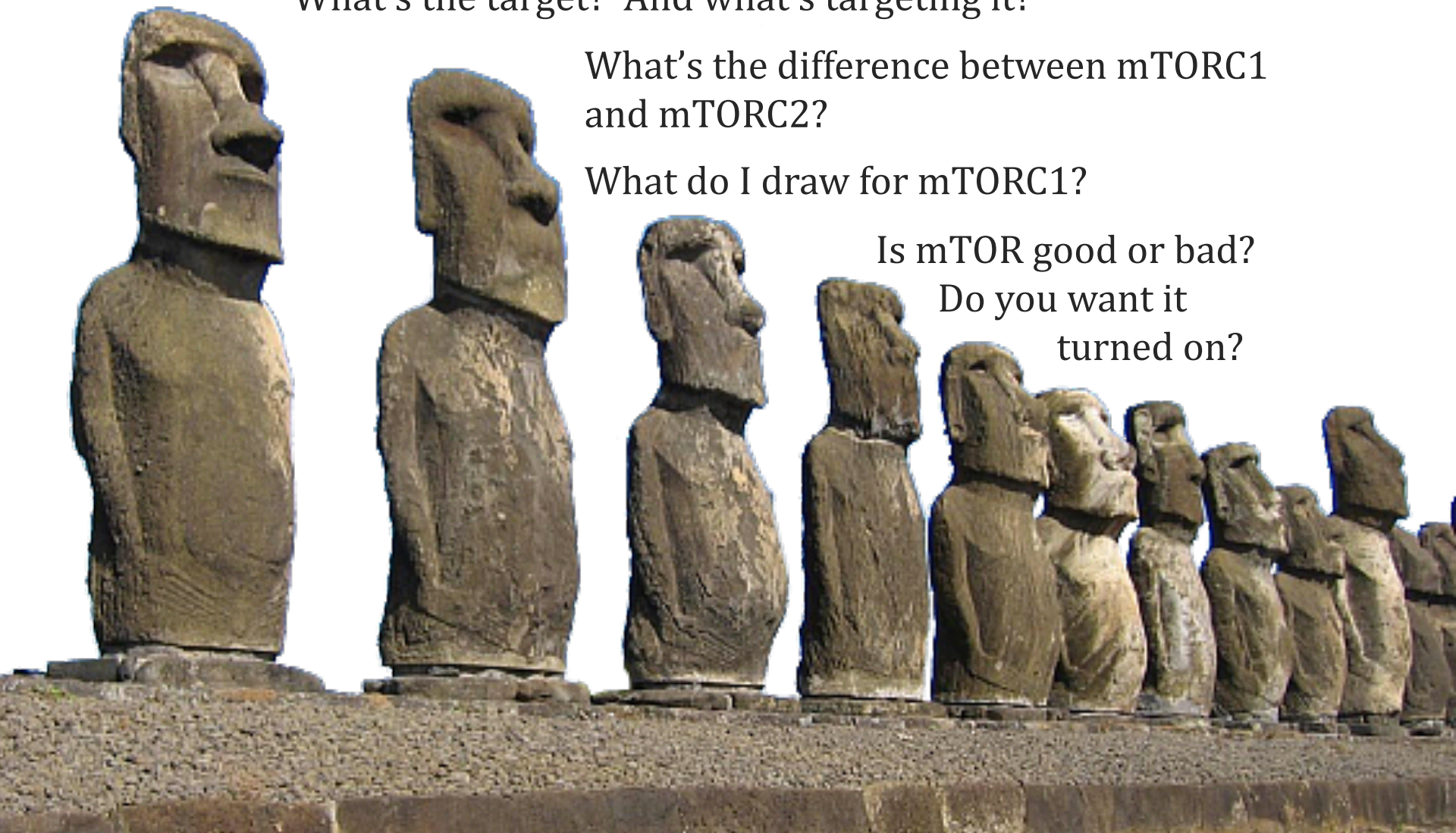
What is mTOR? What does the m stand for? What about the TOR?

What's the target? And what's targeting it?

What's the difference between mTORC1 and mTORC2?

What do I draw for mTORC1?

Is mTOR good or bad? Do you want it turned on?



# Questions you should be able to answer

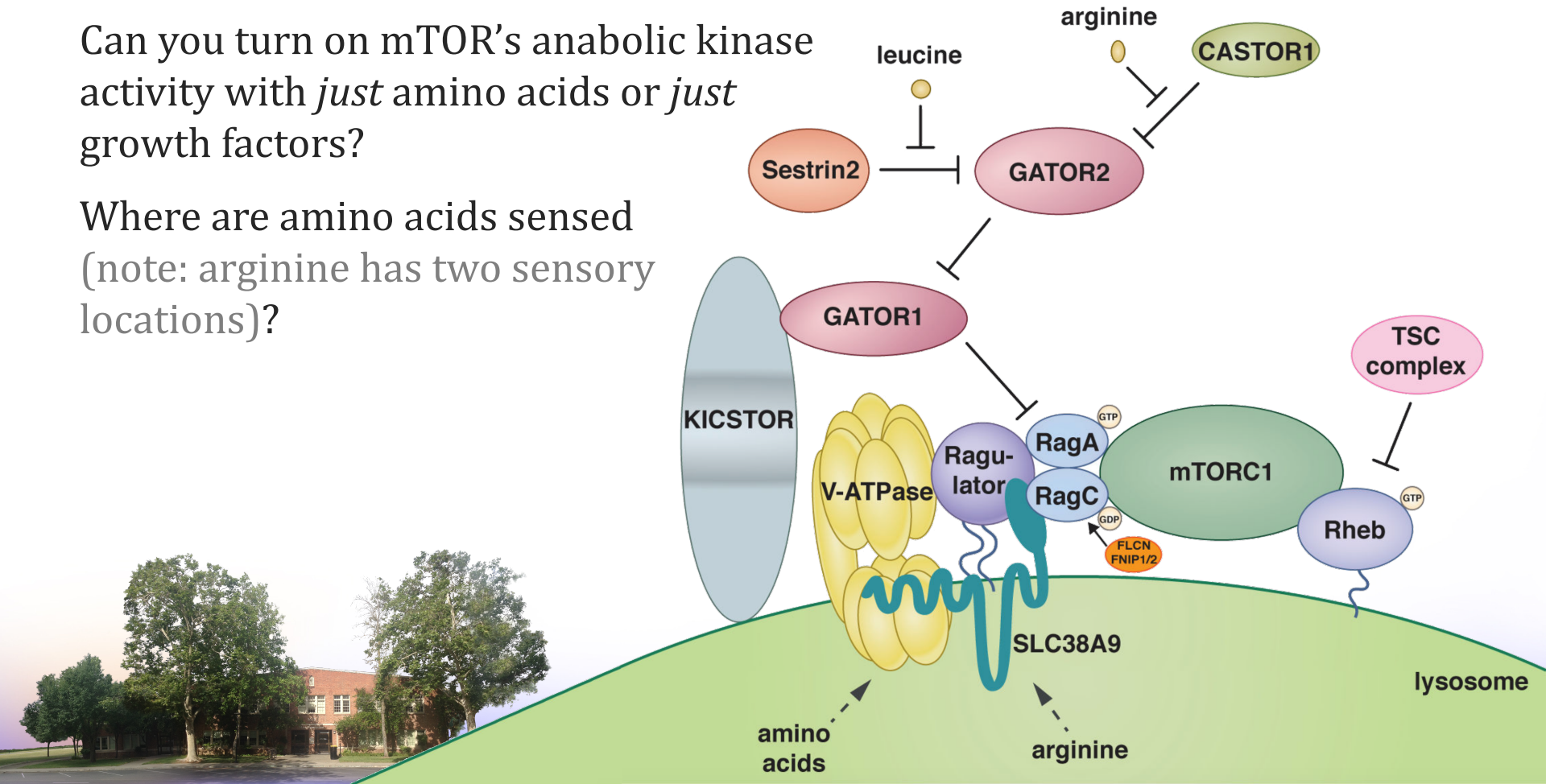
How do proteins signal mTOR different from carbohydrates?

What amino acids do the bulk of the signaling?

Why does a lysosome appear in these pictures?

Can you turn on mTOR's anabolic kinase activity with *just* amino acids or *just* growth factors?

Where are amino acids sensed (note: arginine has two sensory locations)?



# Questions you should be able to answer

What's AMPK?  How is it activated?

What is adenylate *kinase* (as opposed to cyclase)?

What is the relationship between glycogen and AMPK?

What is AMPK's role in mTOR signaling?

What is AMPK's role in the hypothalamus?

What does AMPK do to lipolysis and glycolysis?

What's the relationship between AMPK and mitochondria?

How does Metformin interact with mTOR?

What muscle fiber type signals mTOR more?  Why?

mTOR activation: Concentric, isometric, or eccentric?

# Questions you should be able to answer

What are transcription and translation?

Mechanotransduction, FAK, PI3K, and non-PI3K mTOR signaling…?

Upstream, downstream, and "midstream": phosphorylation cascades?
Where does a signaling cascade usually begin and end?

Men vs. women. Know the hypertrophic hormonal differences.

What is the liver's role in hypertrophic signaling?

What is the role of prostaglandins in hypertrophic signaling?

What's upstream and downstream from PKA? From PKB?

Primary endogenous and exogenous inhibitors of mTOR?

Activating muscle fibers: effect on sensitivity of androgen receptors to circulating androgens?

# What enzyme stiffarms mTOR?


**Why** does AMPK do that?
**How** does AMPK do that?
**How** does AMPK get activated?

# AMPK has *α, β, and γ subunits.*

*α is catalytic; β and γ are regulatory.*

*What binds to the β subunits?*
*What effect does that have?*

*What binds to the γ subunits?*
*What effect does that have?*

How do you eliminate AMP? What's a medication that inhibits AMP deaminase?

# The End.  Be ready…