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Regulation of mTOR by Growth Factors, Nutrition and Exercise Impact on Muscle Protein Synthesis

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Regulation of mTOR by Growth Factors, Nutrition and Exercise

Impact on Muscle Protein Synthesis

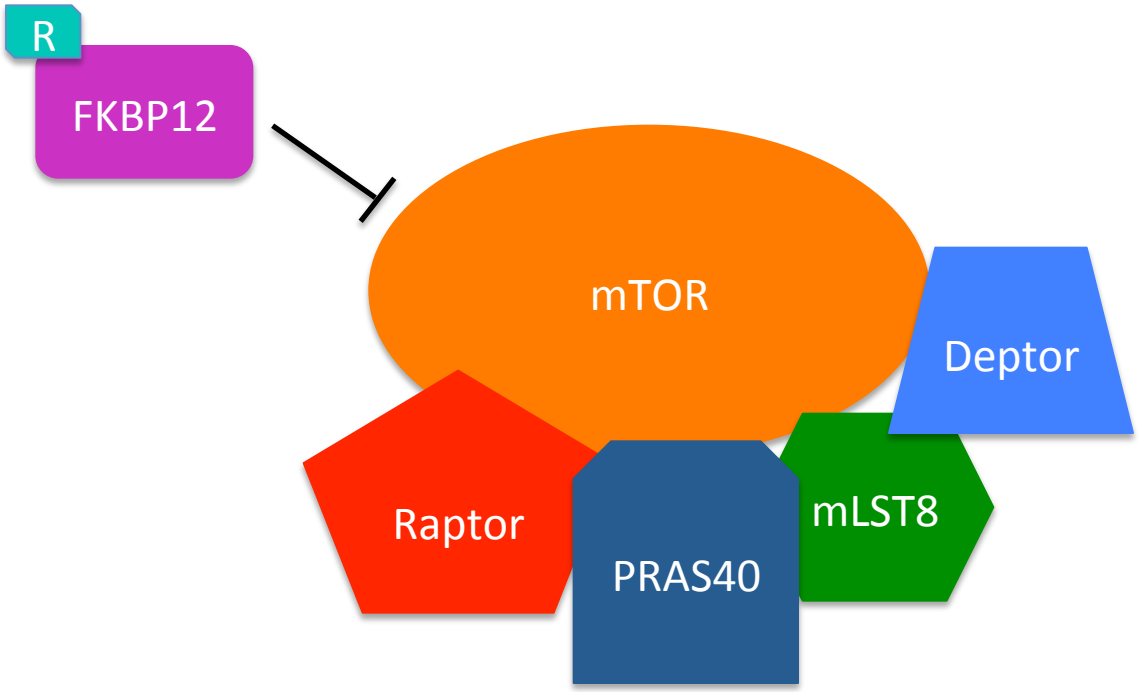
John L. Ivy, PhD

University of Texas at Austin

mTOR

- mTOR: Mammalian Target of Rapamycin
- mTOR protein is a serine-threonine kinase that belongs to the phosphoinositide 3-kinase family of proteins
- mTOR is found in two distinct protein complexes
    - mTOC1 (rapamycin sensitive) – cell growth
    - mTOC2 (rapamycin insensitive) – cytoskeletal organization

mTOC1 Protein Complex



- mTOR: mammalian target of rapamycin
- Raptor: regulatory-associated protein of mTOR
- mLST8: mammalian lethal with Sec 13 protein
- PRAS40: proline-rich Akt substrate 40 kD
- Deptor: DEP domain-containing mTOR-interacting protein
- FKBP12: FK506 binding protein of 12 kD (R: rapamycin)

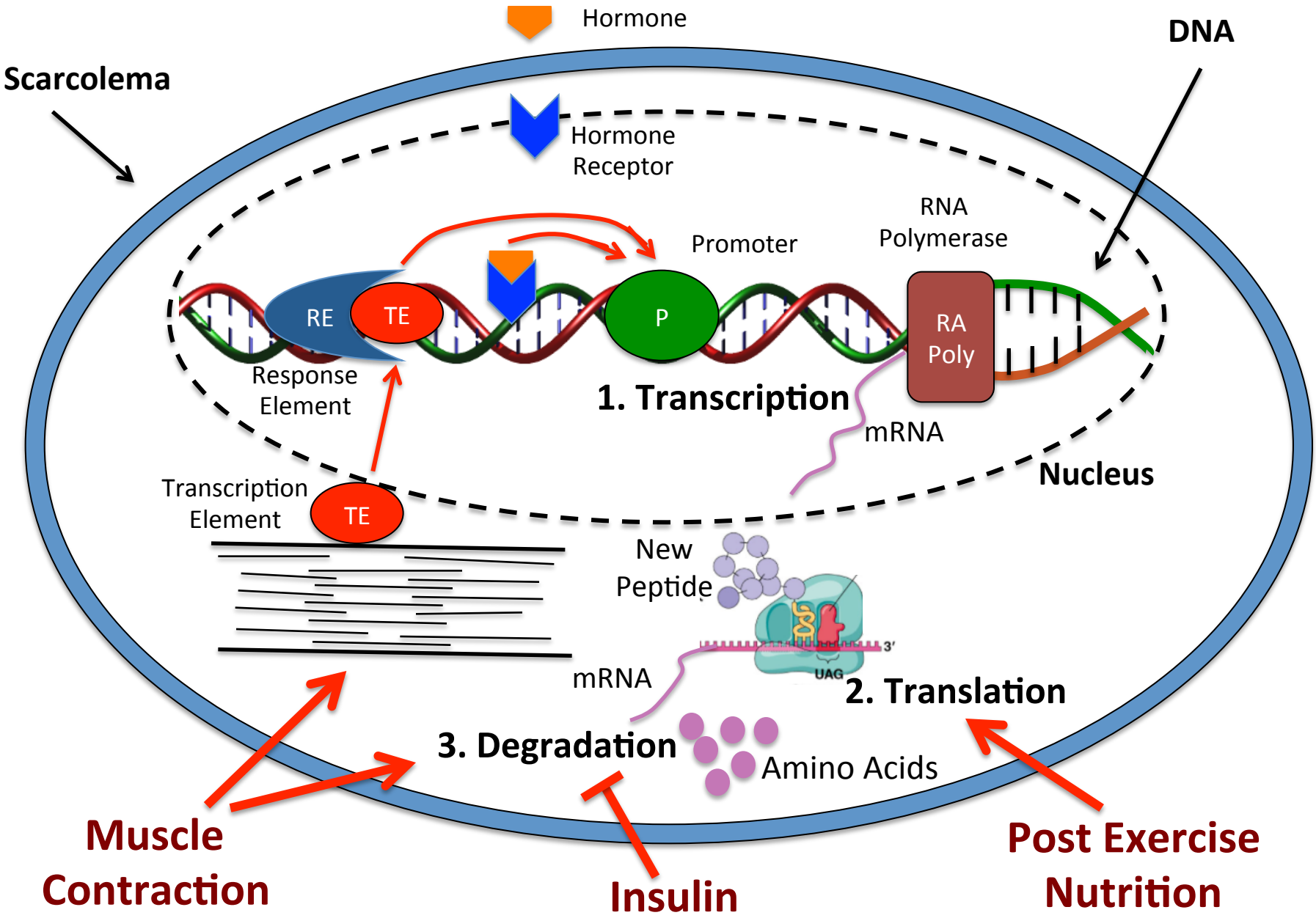
Protein Synthesis

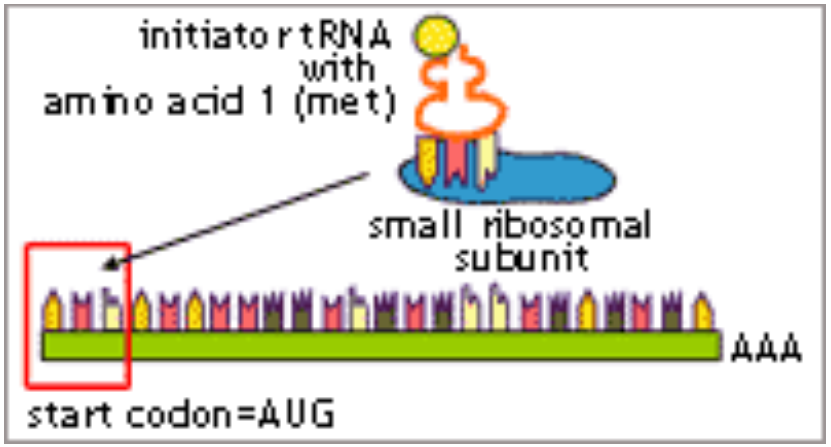
- The process by which individual amino acids are connected by peptide bonds in a specific order dictated by the nucleotide sequence in DNA, which involves the processes of transcription and translation

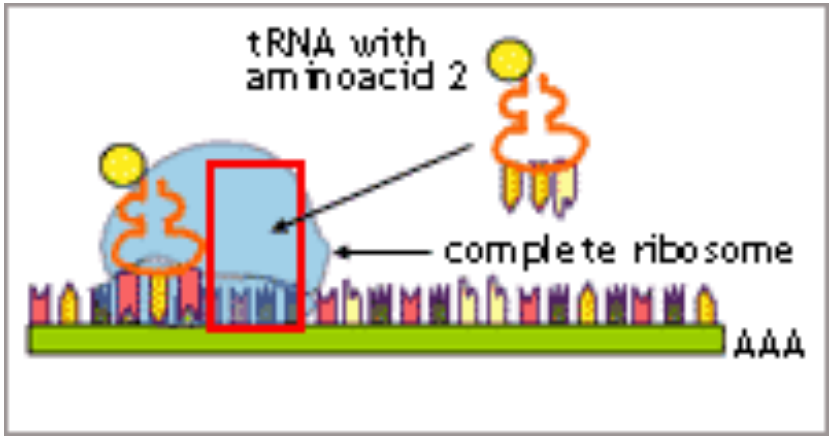
  Transcription - is the first step of gene expression, in which a particular segment of DNA is copied into RNA by the enzyme RNA polymerase

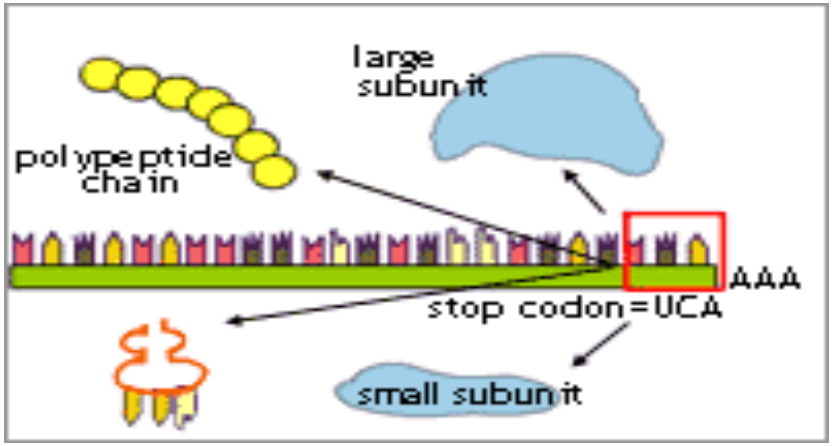
  Translation - mRNA is decoded by a ribosome to produce a specific amino acid chain or polypeptide

Protein Synthesis and Degradation









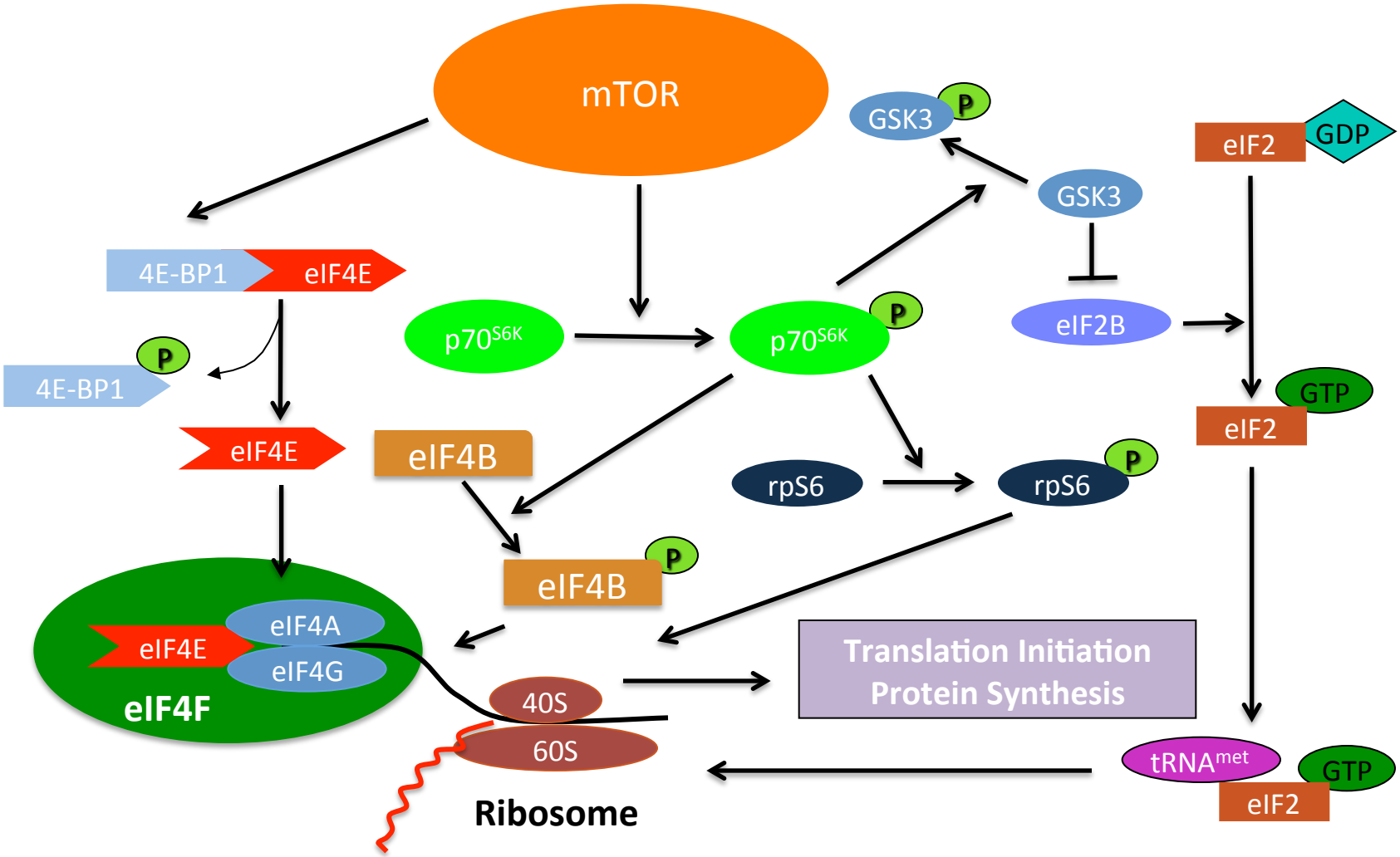
Steps in Translation

1. Initiation: The ribosome *assembles* around the target mRNA. The first tRNA is attached at the start codon. (*initiation thought to be rate-limiting step for protein synthesis*)

2. **Elongation**: The tRNA transfers an amino acid to the tRNA corresponding to the next codon. The ribosome then moves to the next mRNA codon to continue the process, creating an amino acid chain.

3. Termination: When a stop codon is reached, the ribosome releases the polypeptide.

mTOR Pathway

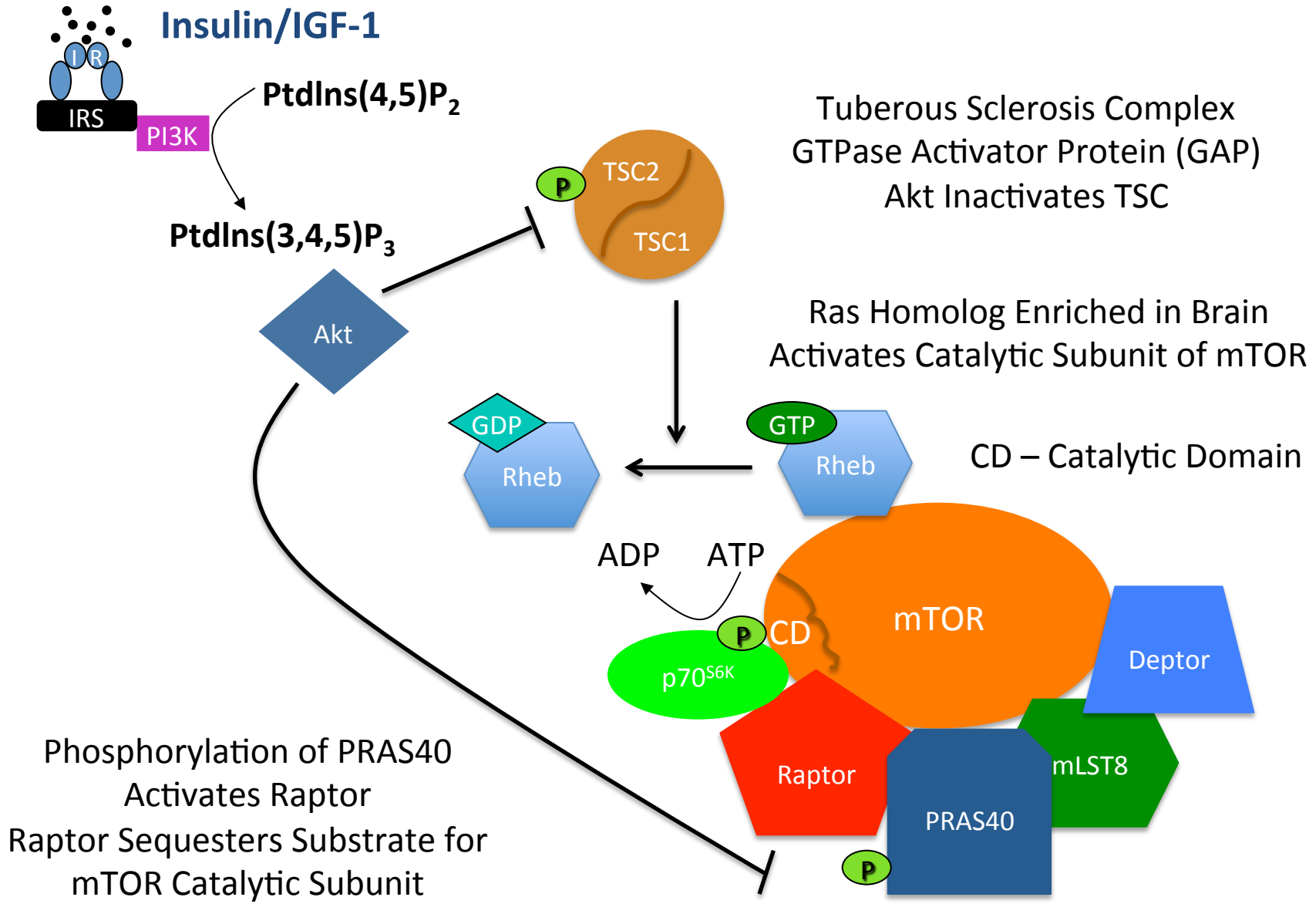


Elongation: Peptide Chain

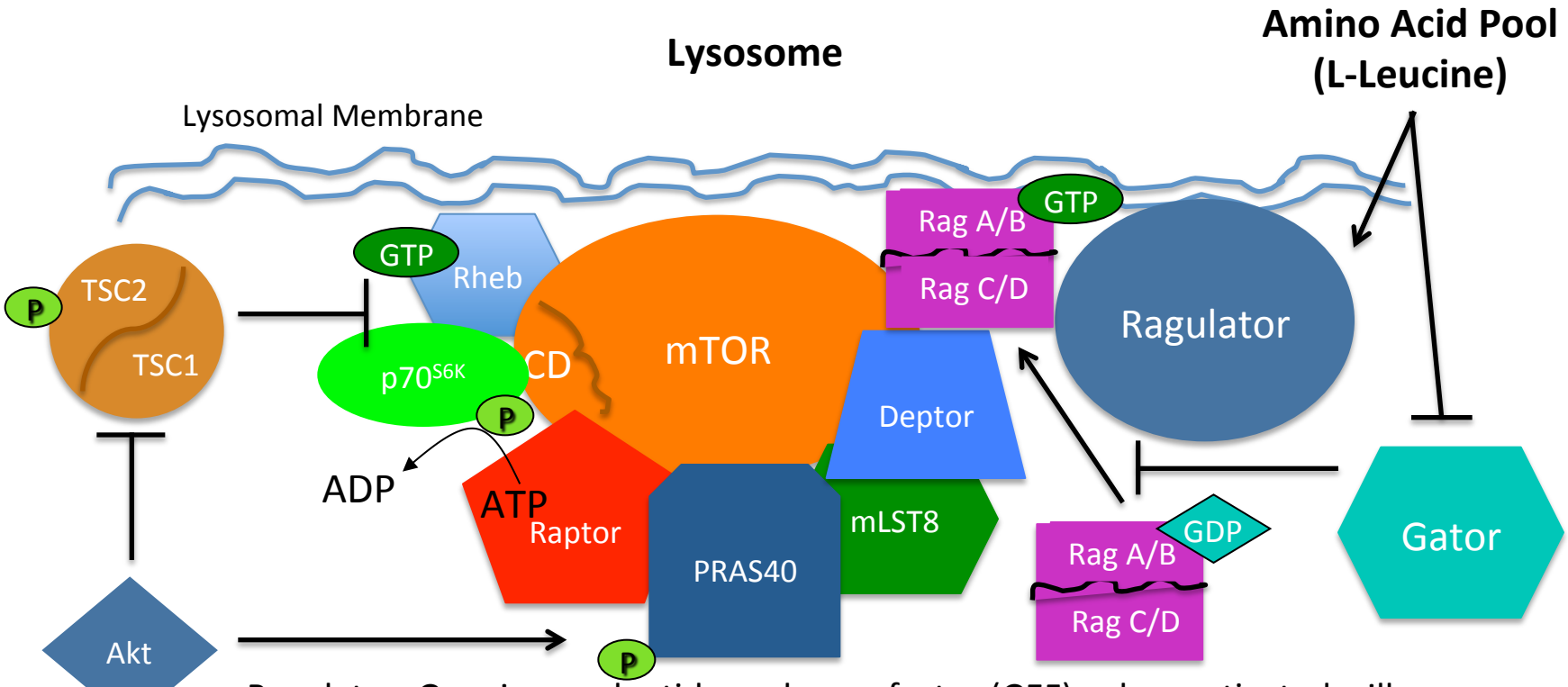
mTOR Activity Required for Increase in Muscle Mass

- mTOR activity is increased following resistance exercise
- Rapamycin inhibits mTOR activty
- Rapamycin administration during a resistance training program blocks protein synthesis and muscle hypertrophy
- Rapamycin also blocks protein/amino acid activated protein synthesis
- Rapamycin does not affect basal protein synthesis

mTOR Activation by Growth Factors



Activation of mTOR by Amino Acids



Ragulator: Guanine nucleotide exchange factor (GEF), when activated will convert GDP to GTP

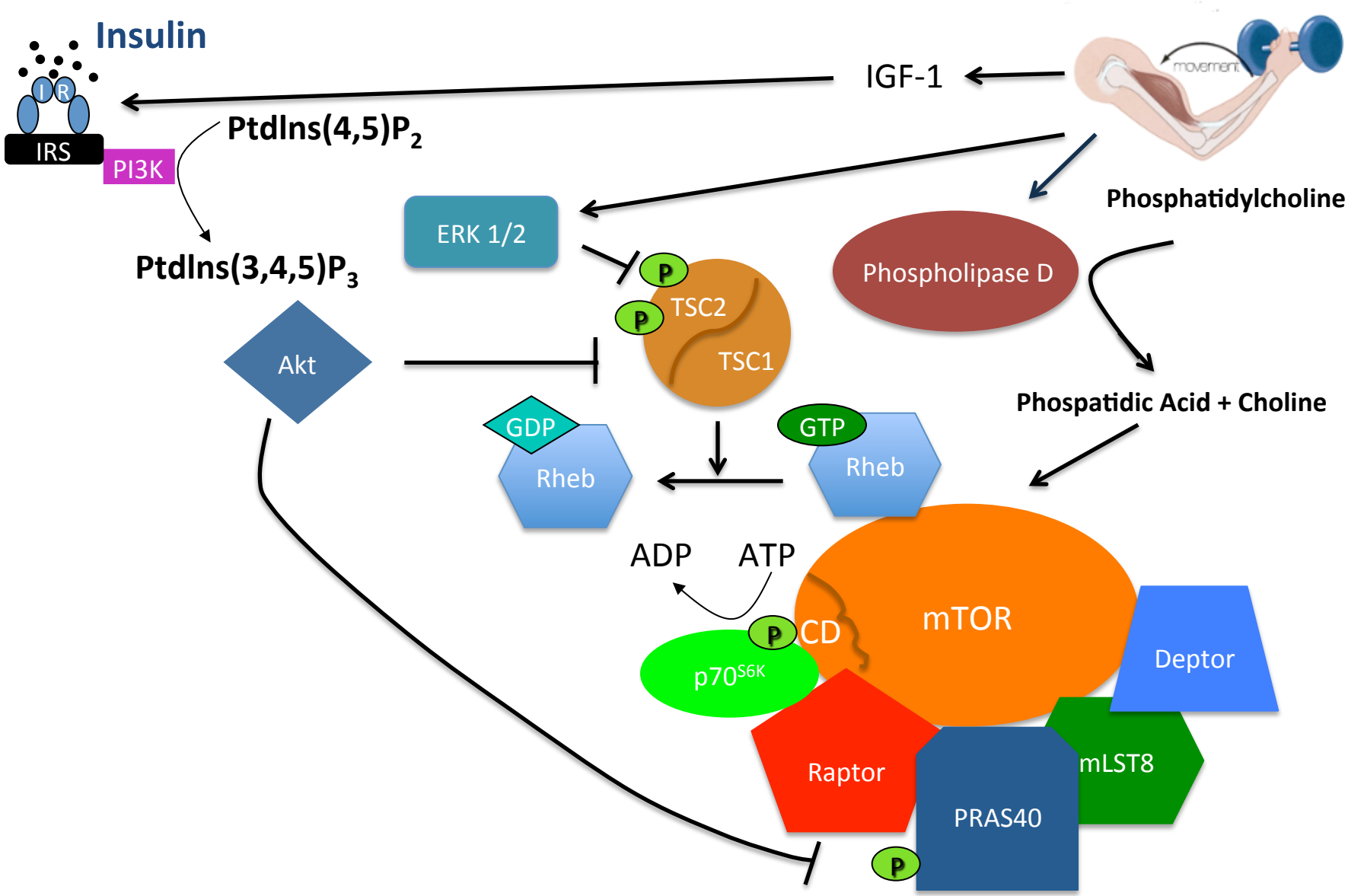
Gator: GAP activity towards Rags, will activate GTPase and convert GTP to GDP

Rag: Ras related GTP binding , when GTP-bound it will recruit mTOR to lysomomal membrane where it will bind and be activated by Rheb

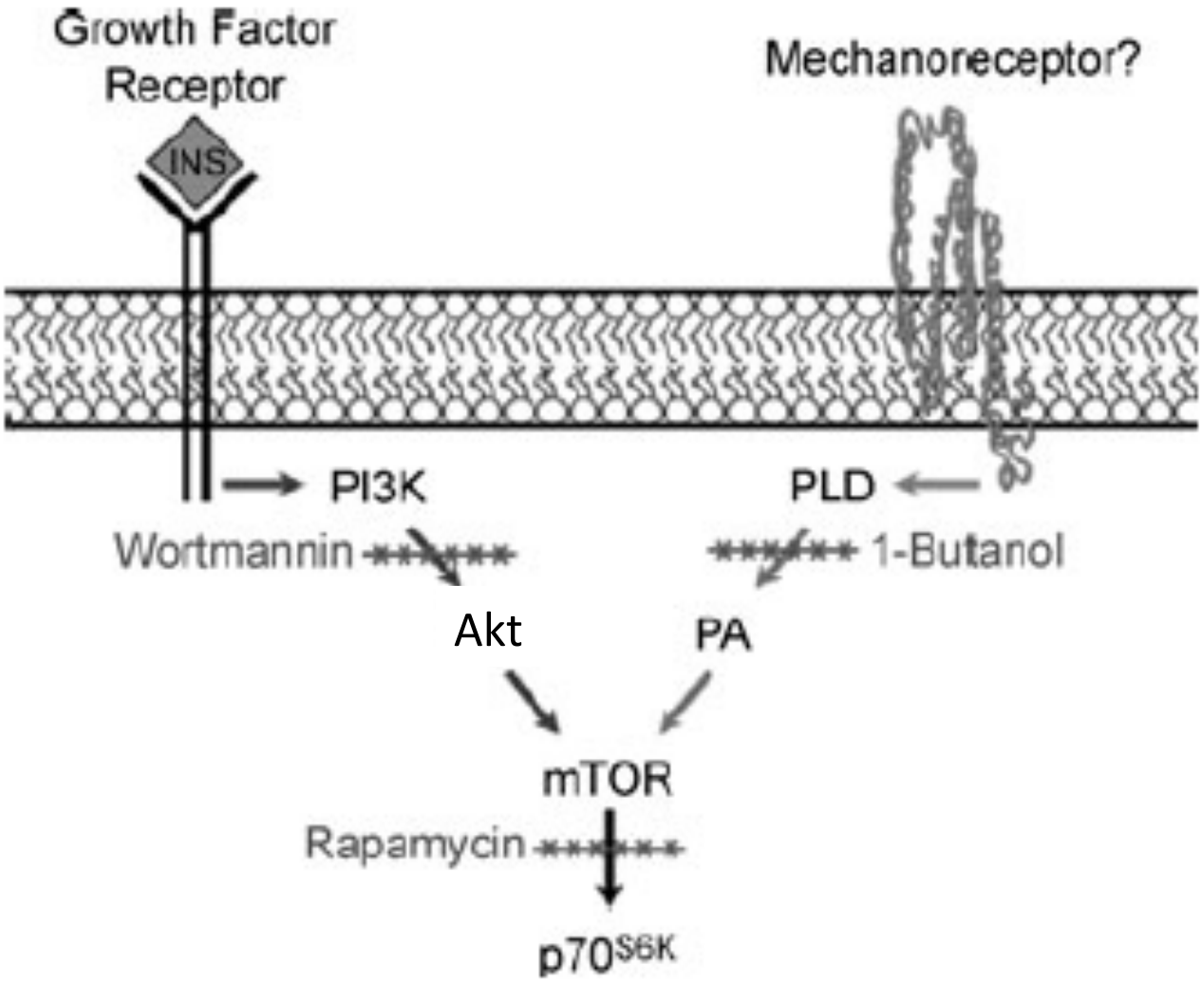
*Insulin activates mTOR by a separate mechanism than AA and therefore their effects on mTOR and protein synthesis are additive

*Remove L-Leucine from lysosome stops activation of mTOR

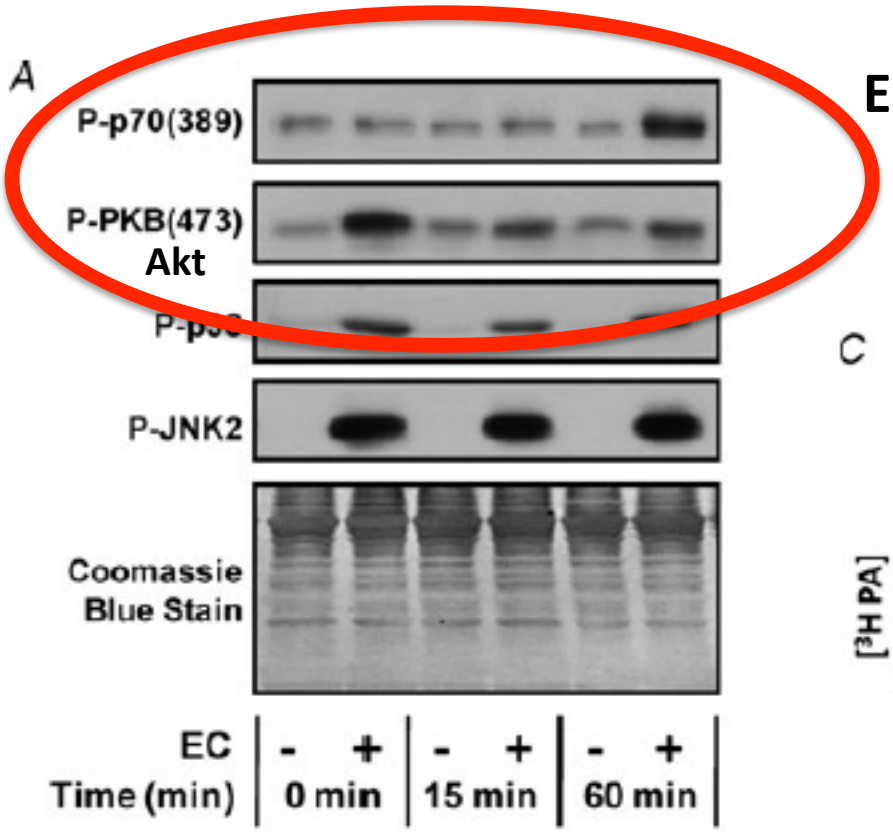
mTOR Activation by Muscle Contraction

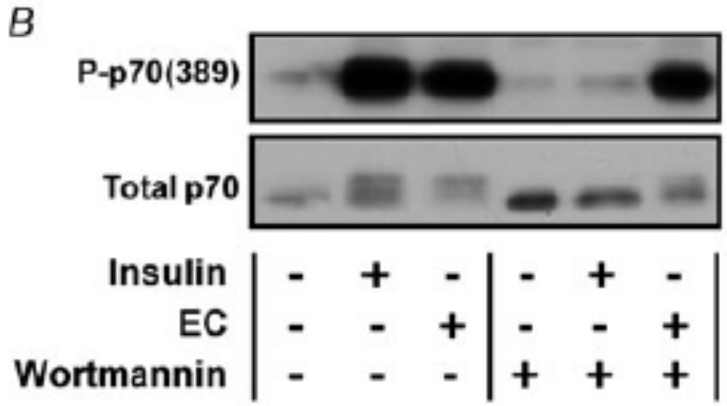


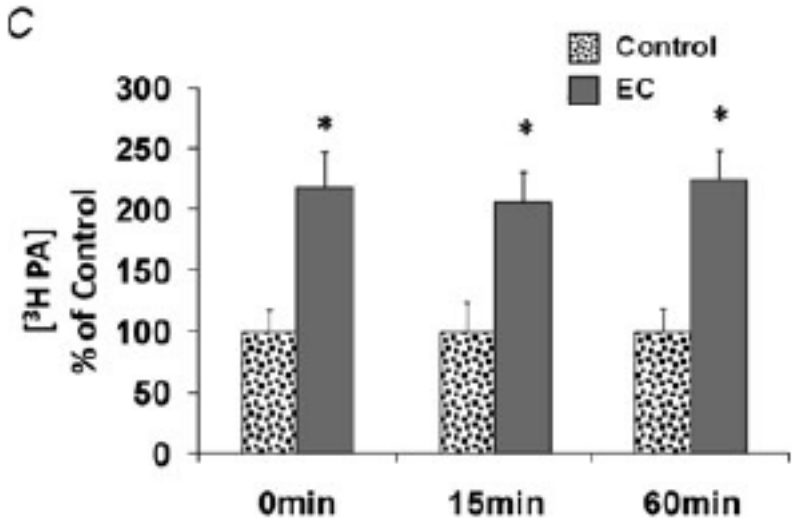
Specific Inhibitors of mTOR Activation

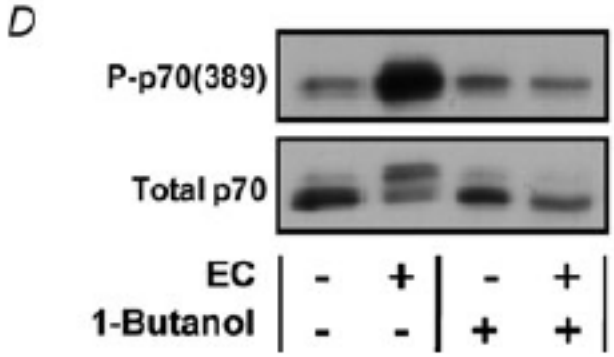


EDL Muscle Undergoing Eccentric Contractions *In Vitro*







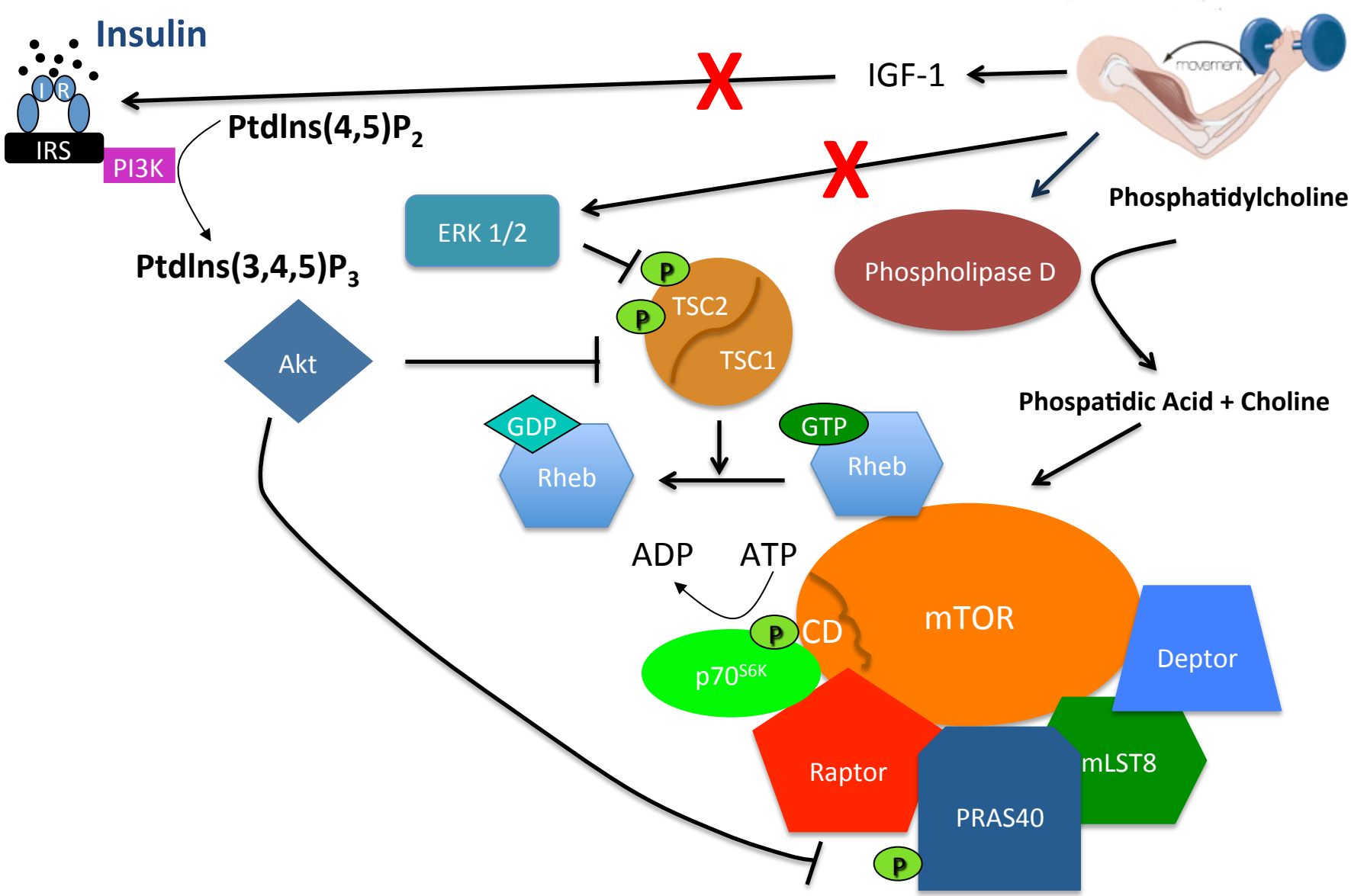


O'Neil et al. J Physiol 587: 3691-3701, 2009

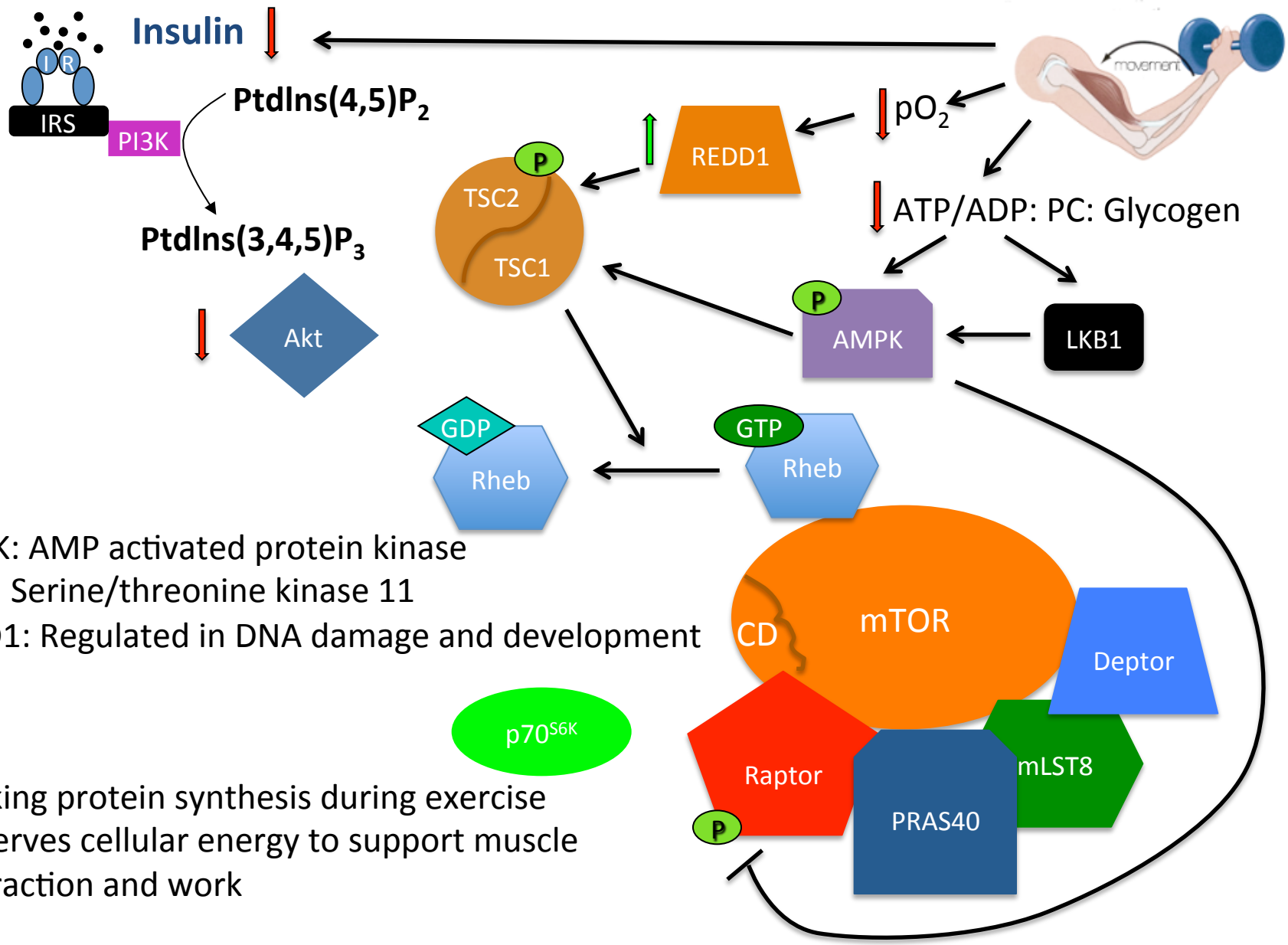
mTOR Activation by Muscle Contraction

- Blocking mTOR activity with rapamycin blocks contraction-induced muscle protein synthesis (mTOR activation required)
- Blocking activation of PI-3 kinase/Akt with wortmannin does not prevent activation of mTOR with muscle contraction (IGF-1 activation not necessary)
- Inhibition of TSC is not required for contraction induced muscle protein synthesis (ERK 1/2 activation is not necessary)
- Blocking phospholipase D activity does inhibit contraction-induced activation of protein synthesis (activation of phospholipase D necessary)

mTOR Activation by Muscle Contraction



mTOR Activation During Exercise

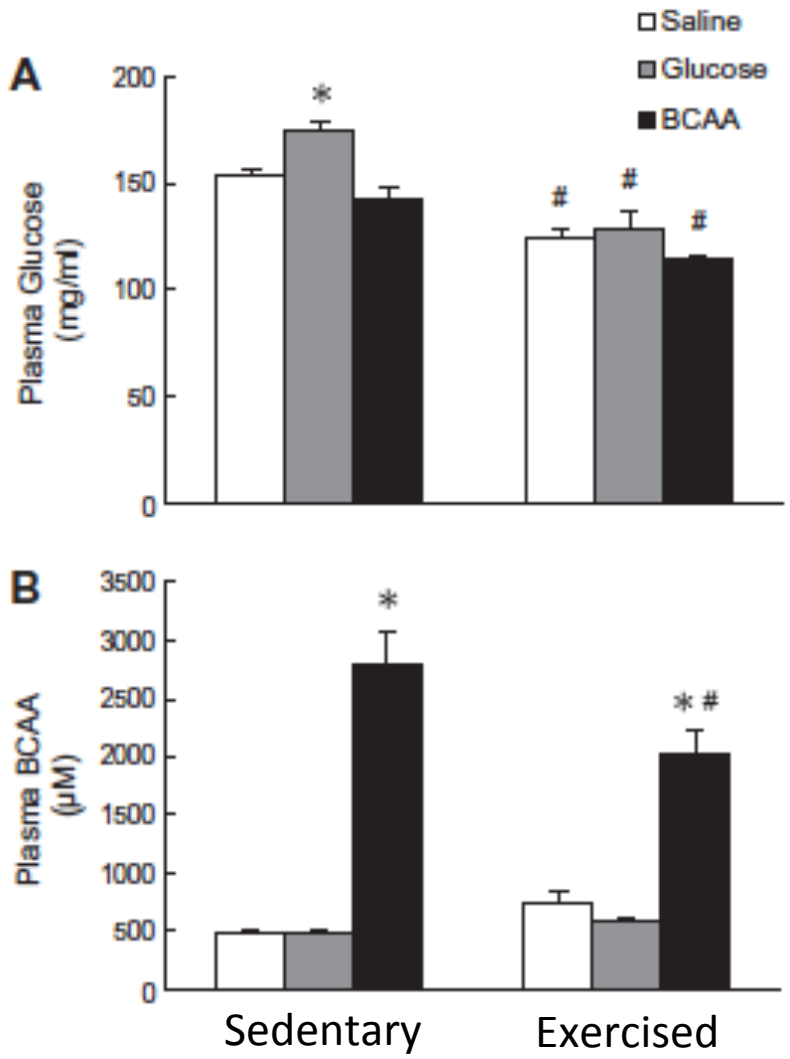


AMPK: AMP activated protein kinase
LKB1: Serine/threonine kinase 11
REDD1: Regulated in DNA damage and development

Blocking protein synthesis during exercise conserves cellular energy to support muscle contraction and work

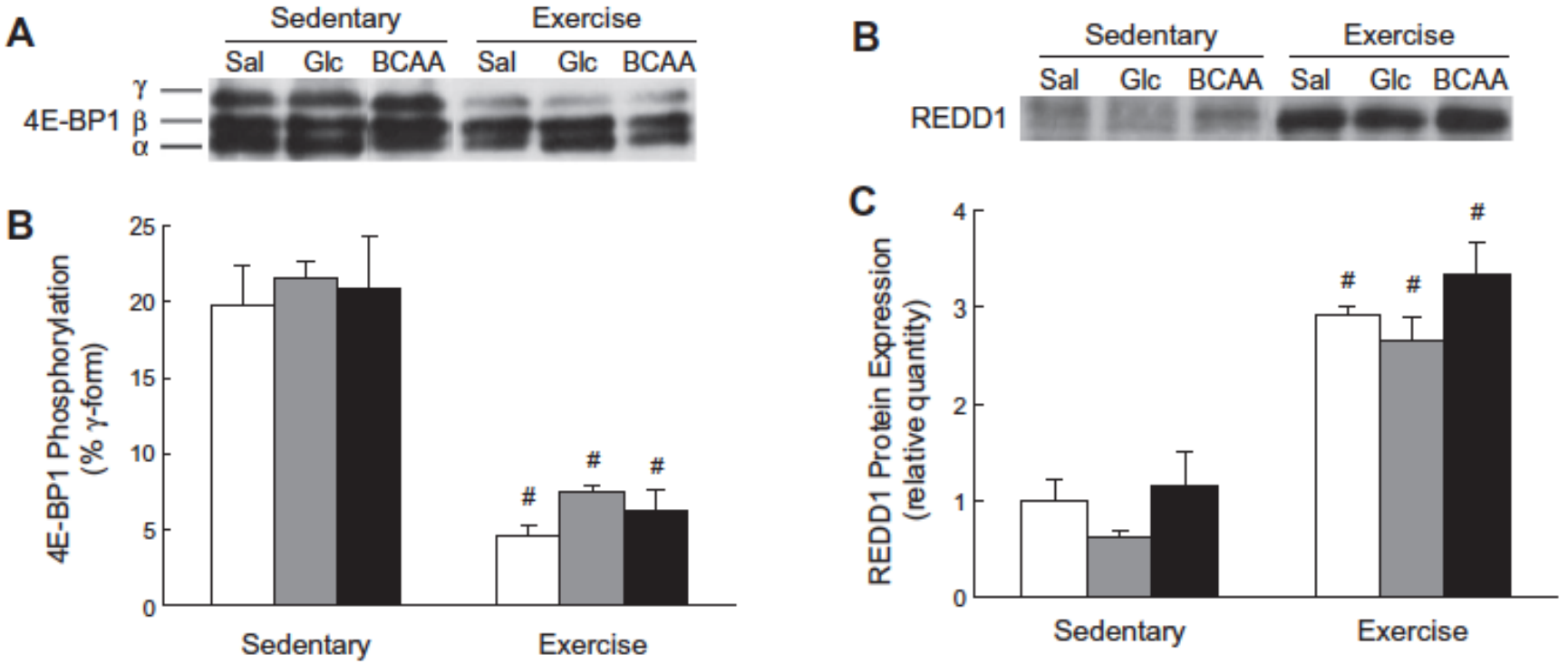
Does Feeding During Exercise Prevent Suppression of mTOR Activity?

Rats were administered saline, glucose (135 mg/100g BW), or BCAA (135 mg/100g BW) by oral gavage 30 min before exercise.



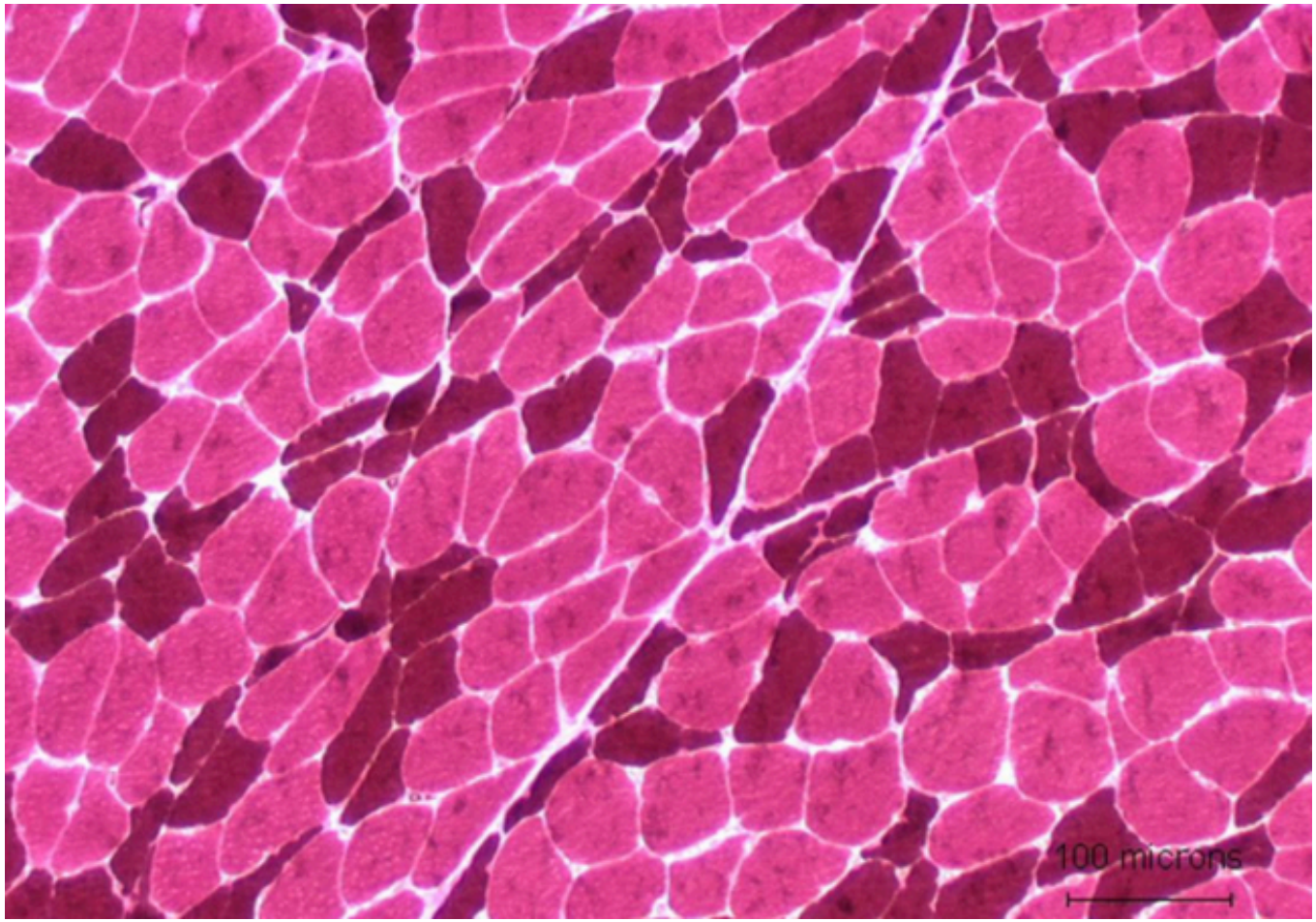
Murakami T et al. BBRC 405: 615-619, 2011

Phosphorylation of 4E-BP1 and Expression of REDD1

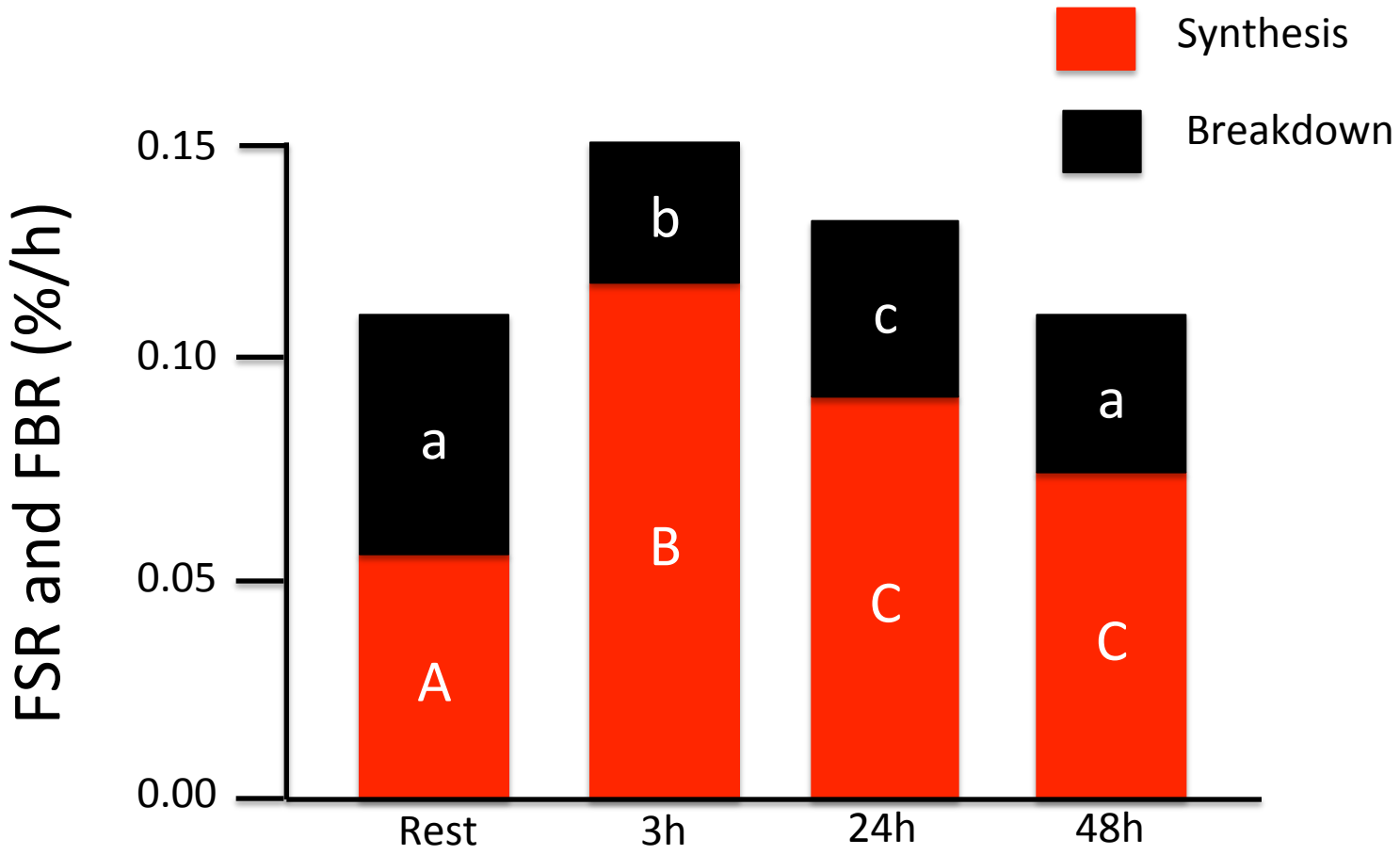


Murakami T et al. BBRC 405: 615-619, 2011

Effect of Exercise on Muscle Protein Synthesis



Muscle Protein Synthesis and Breakdown Before and After Resistance Exercise

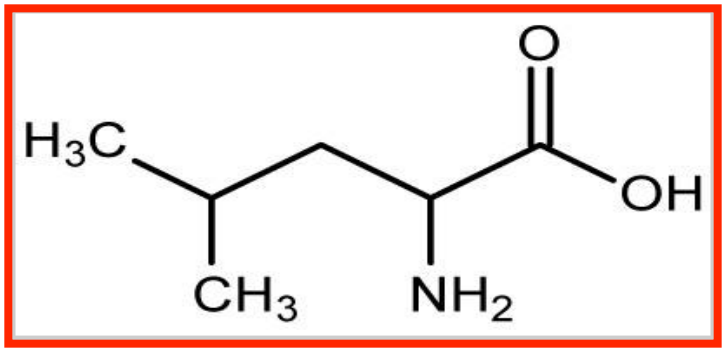


Means with different letters are significantly different ($p \leq 0.05$)

Differences between protein synthesis and breakdown equals net protein balance

Phillips SM et al. Am J Physiol Endrino Metab 273:E99-E107, 1997

Protein or Amino Acid Supplementation Following Resistance Exercise

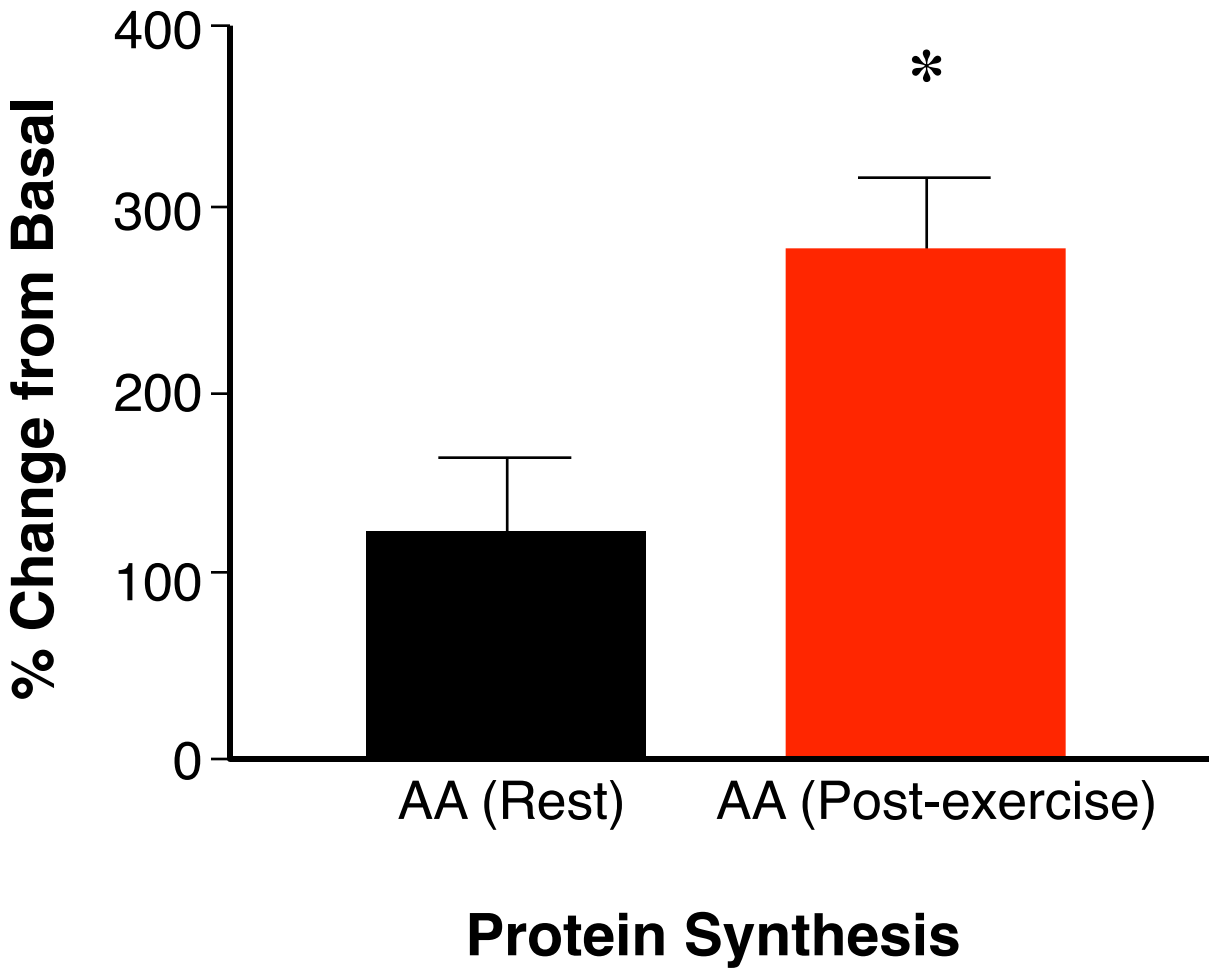


L-Leucine

Experimental Design

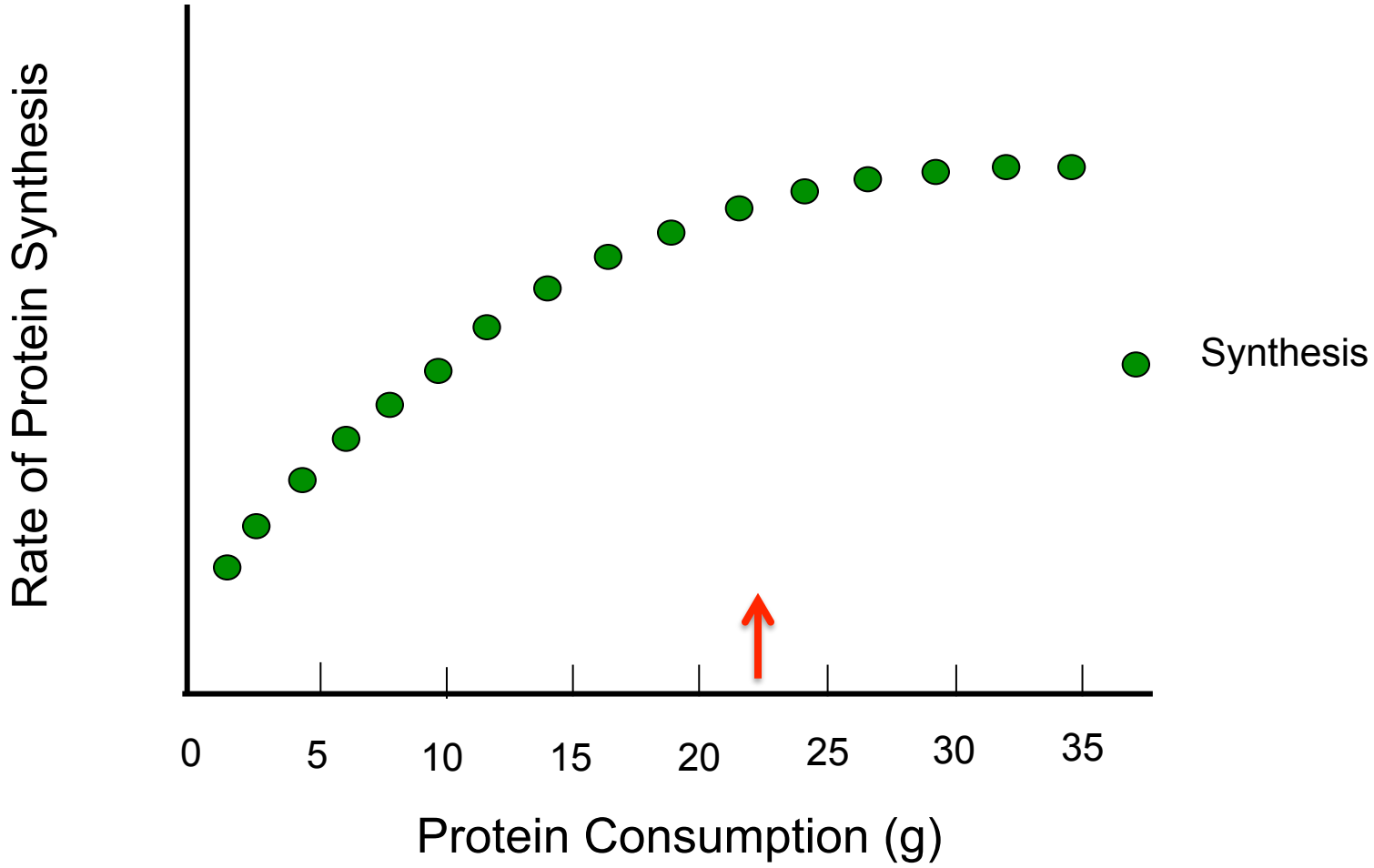
- Intravenous infusion of a balanced amino acid mixture at rest and after a leg resistance exercise protocol
- Exercise was knee extensions
- Infusion started

Biolo et al. Am. J. Physiol. 1997

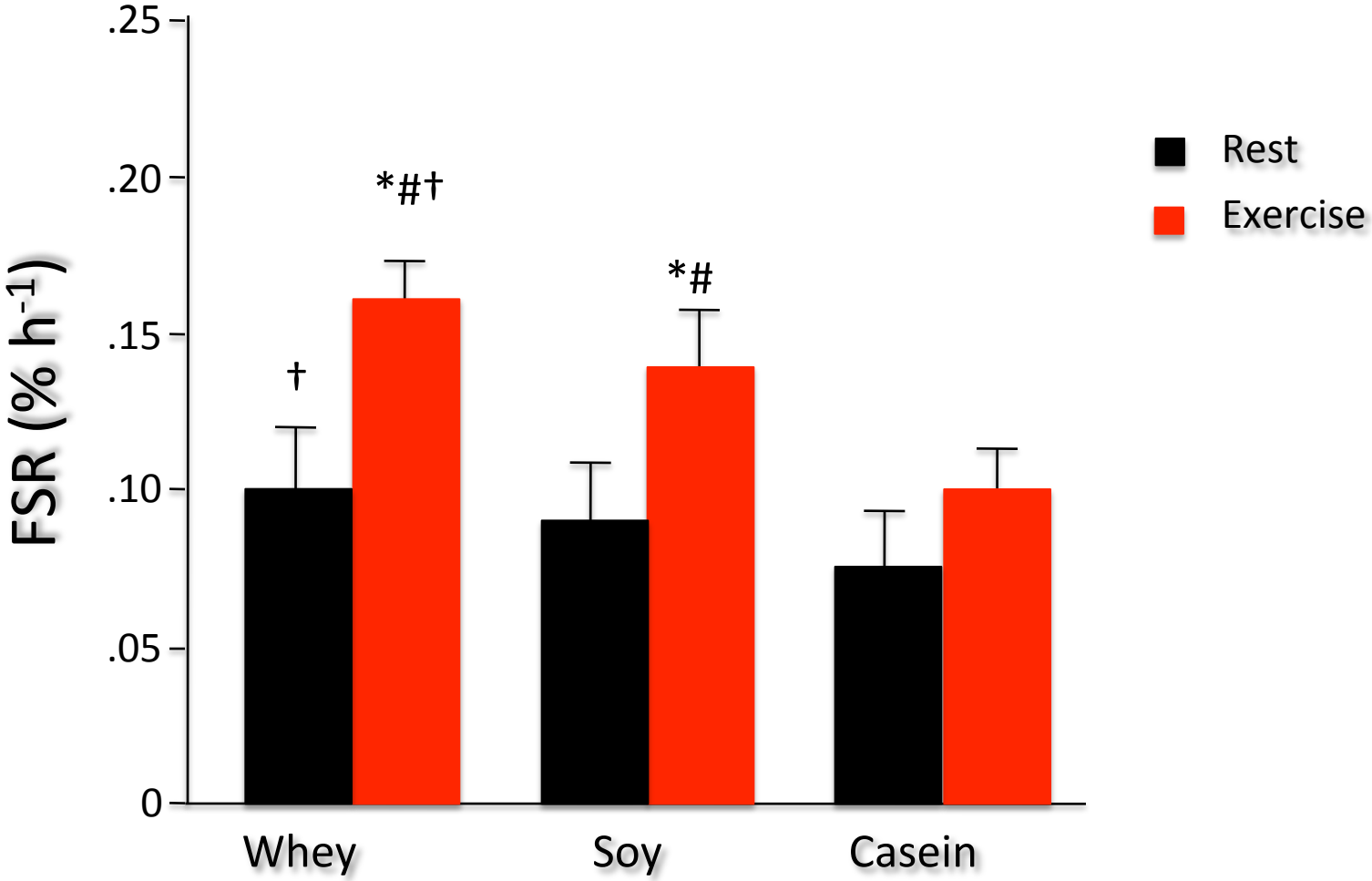


Biolo et al. Am. J. Physiol. 1997

Protein Synthesis and Degradation with Increasing Protein with Meal

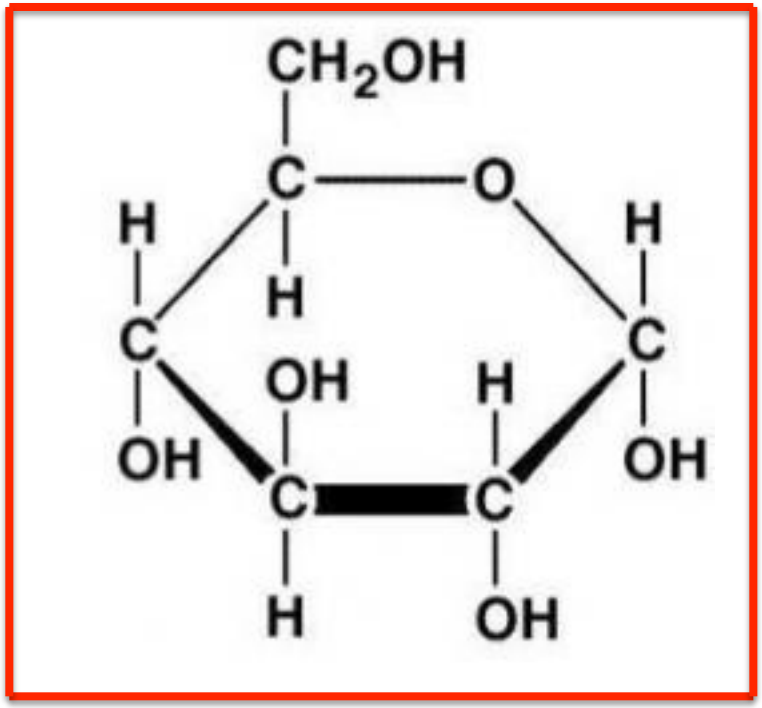


Type of Protein for Post Exercise Supplement is Important



Tang et al. J Appl Physiol 107:987-992,2009

Effect of Exercise plus CHO on Muscle Protein Synthesis

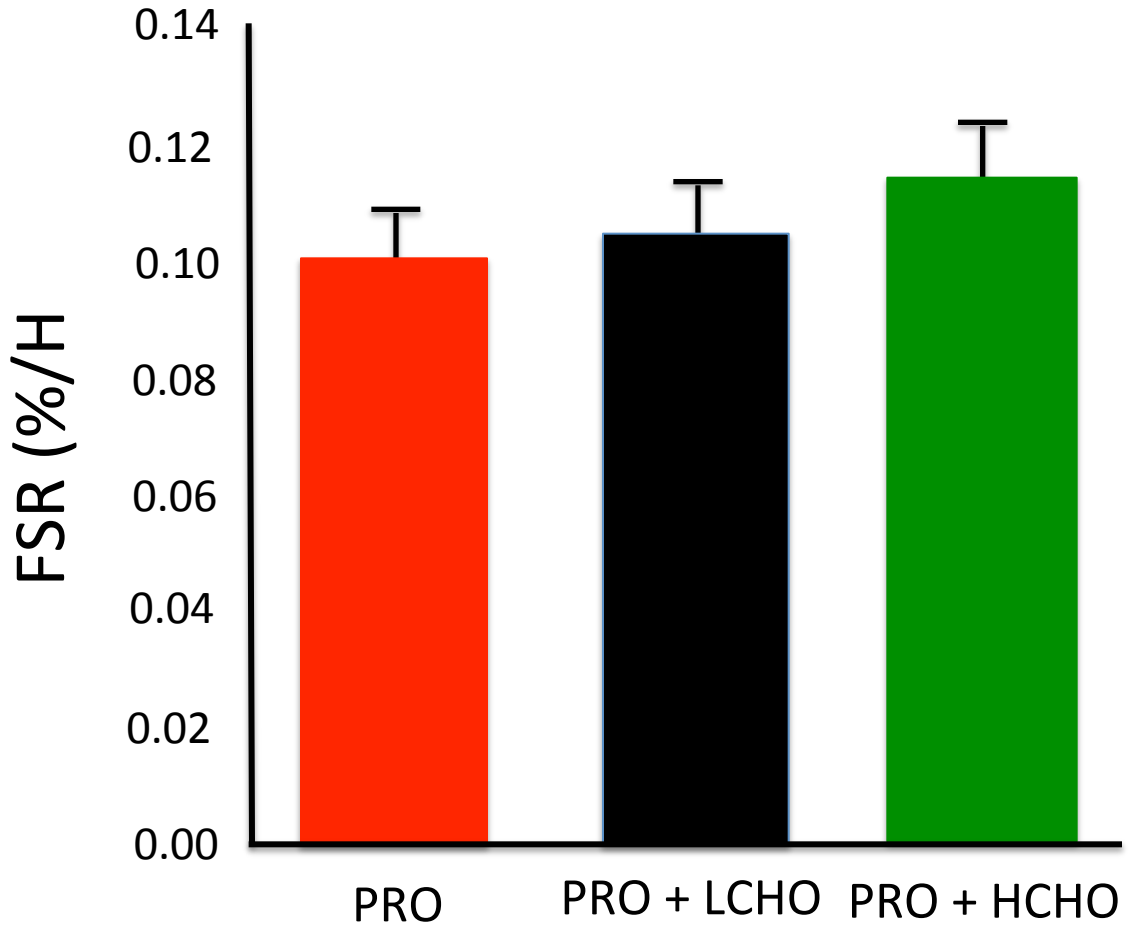


D-glucose

Muscle Protein Synthesis Following Exercise and Protein/CHO

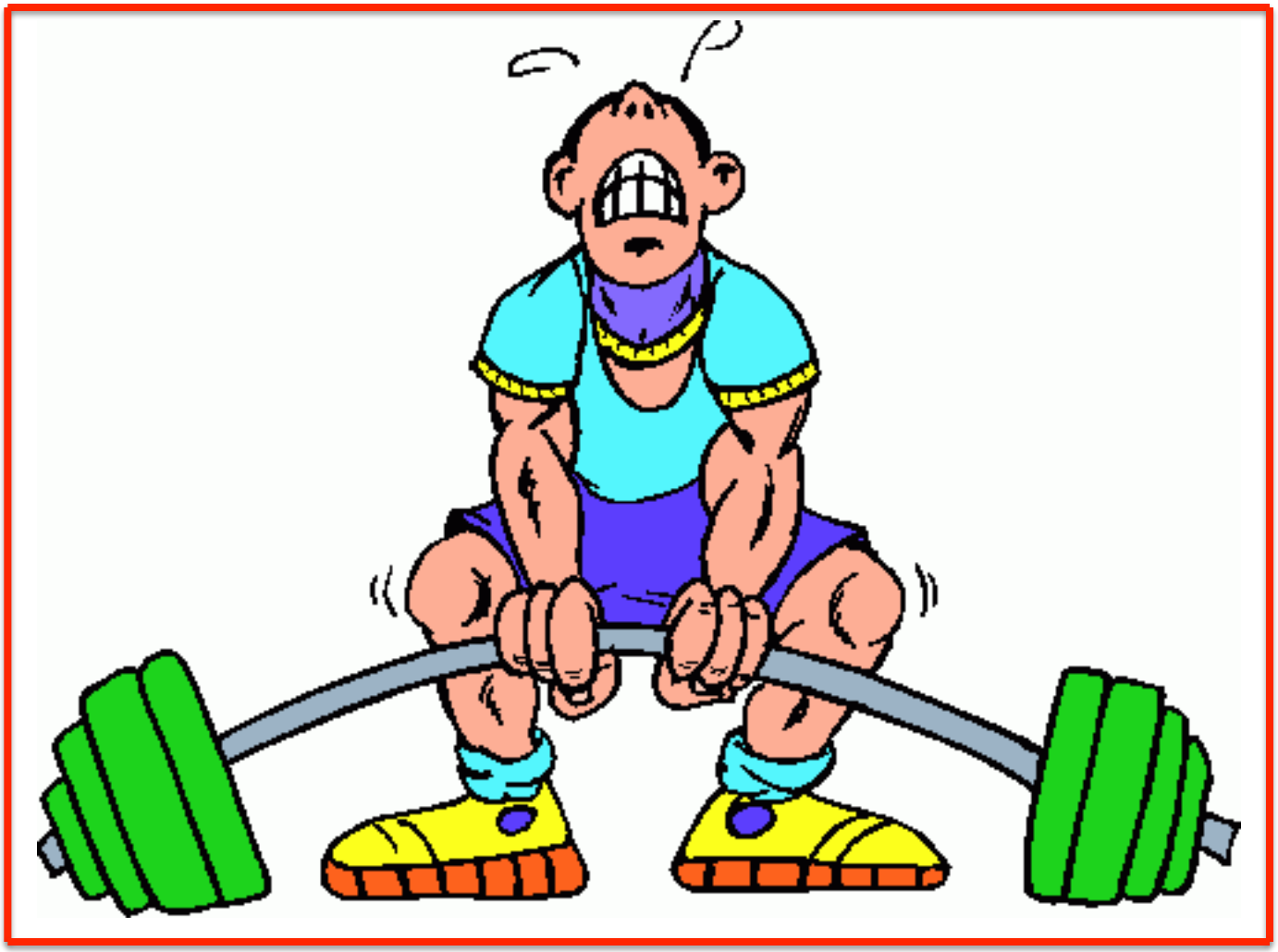
- 10 subjects performed both upper and lower body resistance exercise lasting ~ 1 hour
- Subjects received a beverage volume of 2.5 ml/kg every 30 min to ensure a given dose of 0.3 g/kg of a casein protein hydrolysate per hour combined with either:
- 0 g/kg•h^{-1} carbohydrate (PRO treatment),
- 0.15 g/kg•h^{-1} carbohydrate (PRO LCHO treatment),
- or 0.6 g/kg•h^{-1} carbohydrate (PRO HCHO treatment).

Koopman R et al. Am J Physiol 293:E496-E504, 2007



Koopman R et al. Am J Physiol 293:E496-E504, 2007

Studies Support the Use of CHO in a PRO Supplement Post Exercise

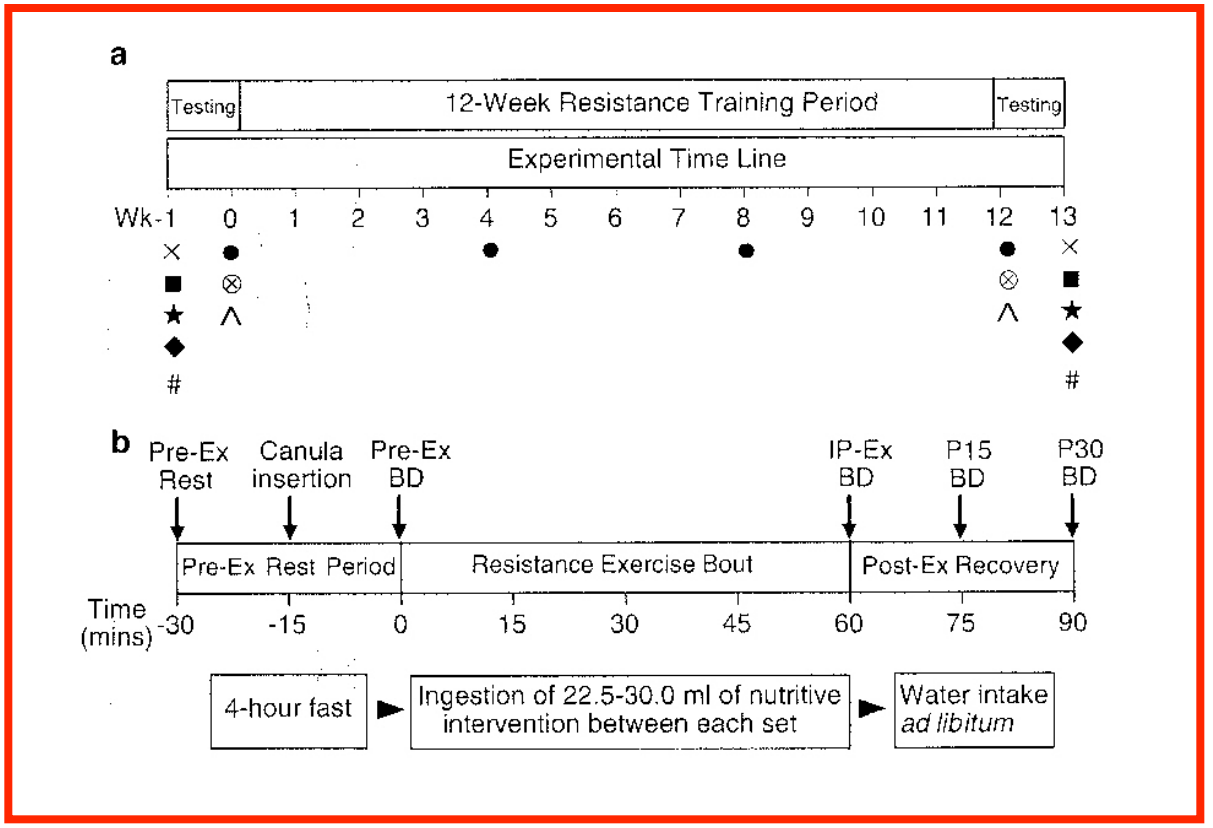


Carbohydrate and Amino Acid Supplementation

Bird et al. EJAP, 97:225-238, 2006.

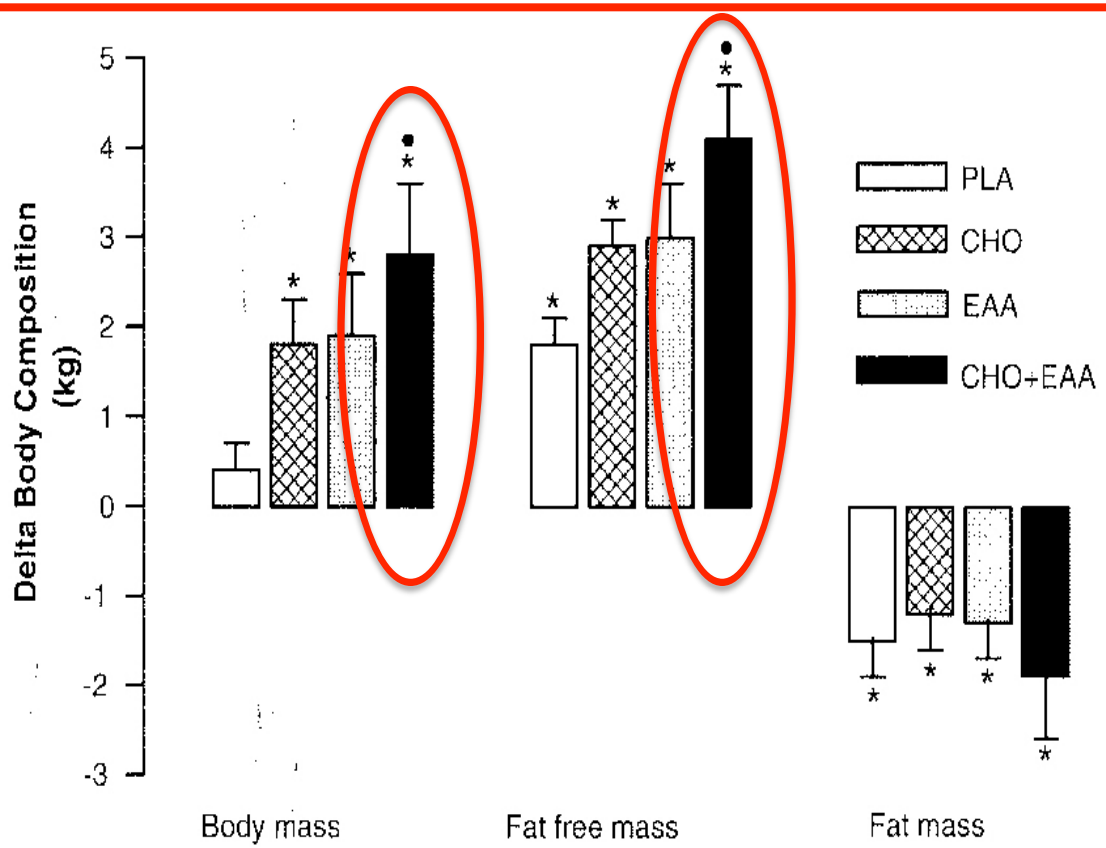
- 32 subjects trained for 12 weeks while consuming several different nutritional interventions

- Supplements consumed during exercise and post exercise:
  - Placebo
  - 6% CHO solution
  - 6 g EAA
  - CHO + EAA



Carbohydrate and Amino Acid Supplementation

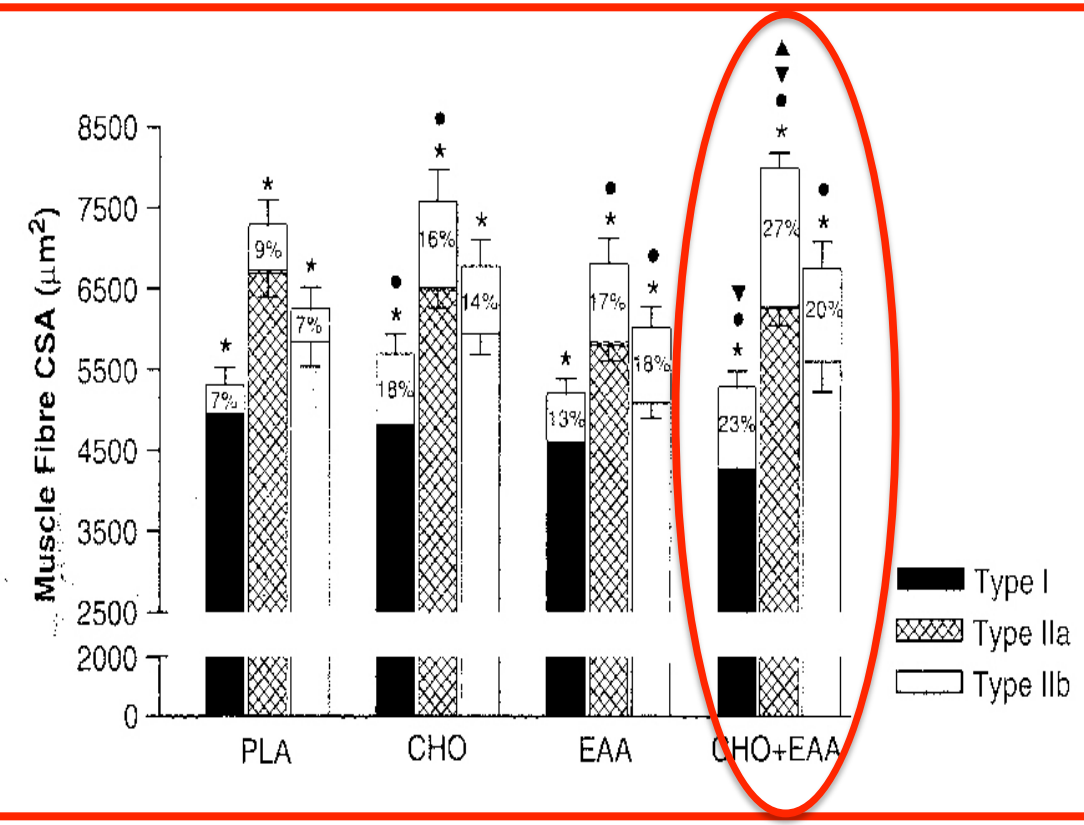
Fig. 2 Body composition changes following 12 weeks of resistance training. Significant difference ($P < 0.05$) from baseline value, *. Treatment group pre- to post-training change is significantly different ($P < 0.05$) from PLA (*filled circle*)



Bird et al. EJAP, 97:225-238, 2006.

Carbohydrate and Amino Acid Supplementation

Fig. 3 Muscle fibre CSA of type I, IIa, and IIb before (*solid bars*) and after (*open bars*) 12 weeks of resistance training. *Post-training muscle fibre CSA is significantly different ($P < 0.05$) from pre-training. Treatment group change in muscle fibre CSA is significantly different ($P < 0.05$) from PLA (*filled circle*), CHO (*up filled triangle*), and EAA (*down filled triangle*)



Bird et al. EJAP, 97:225-238, 2006.

Effects of exercise and insulin infusion on protein synthesis and degradation

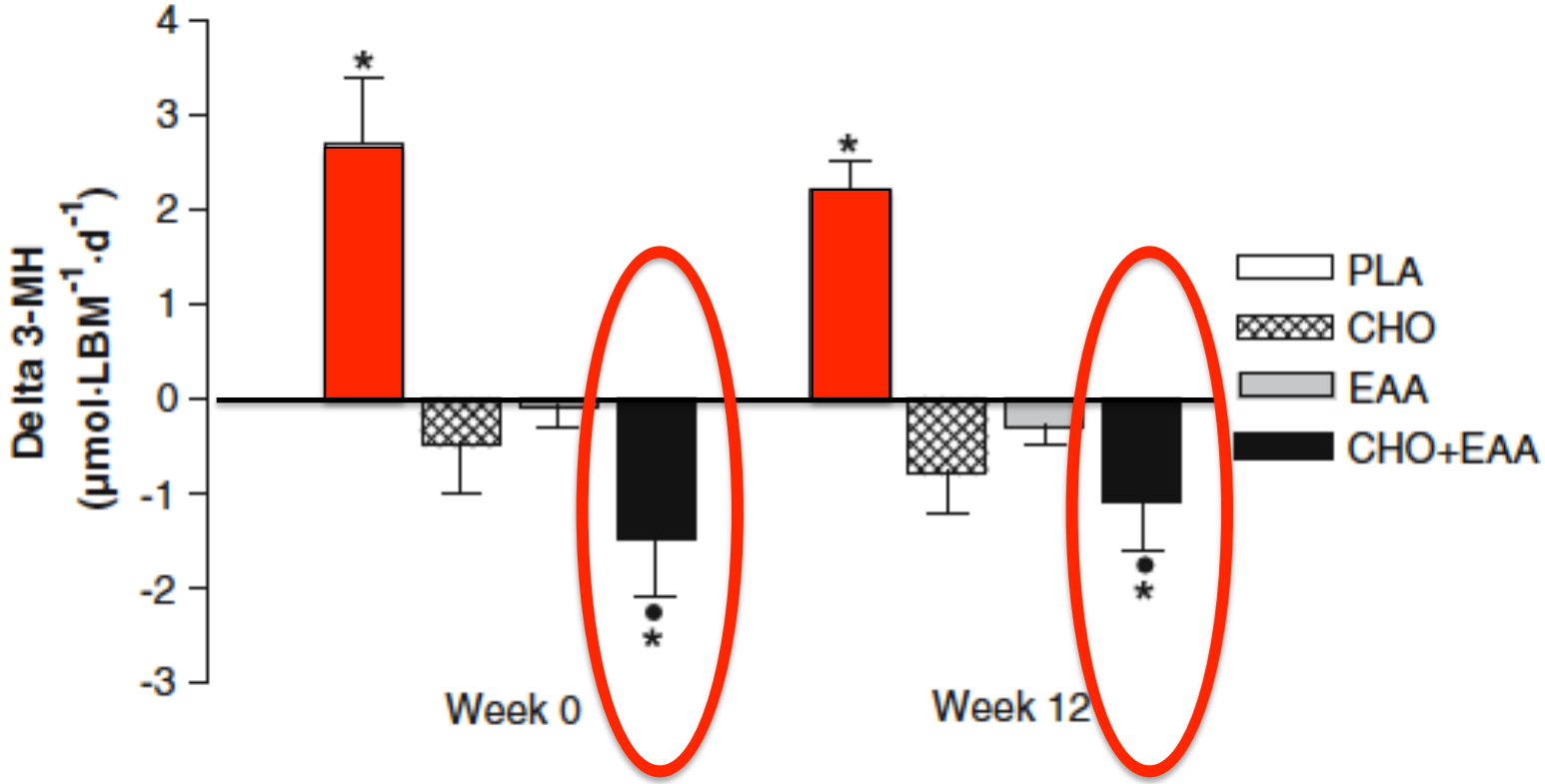
	Protein Synthesis	Protein Degradation	Net
Without Insulin			
Rest	30±7	46±8	-16
Post Exercise	65±10	74±10	-9
With Insulin			
Rest	51±4	48±3	3
Post Exercise	64±9	52±9	12

Units are nmol•min^{-1}•100 ml leg volume.

Biolo et al. Diabetes (1999).

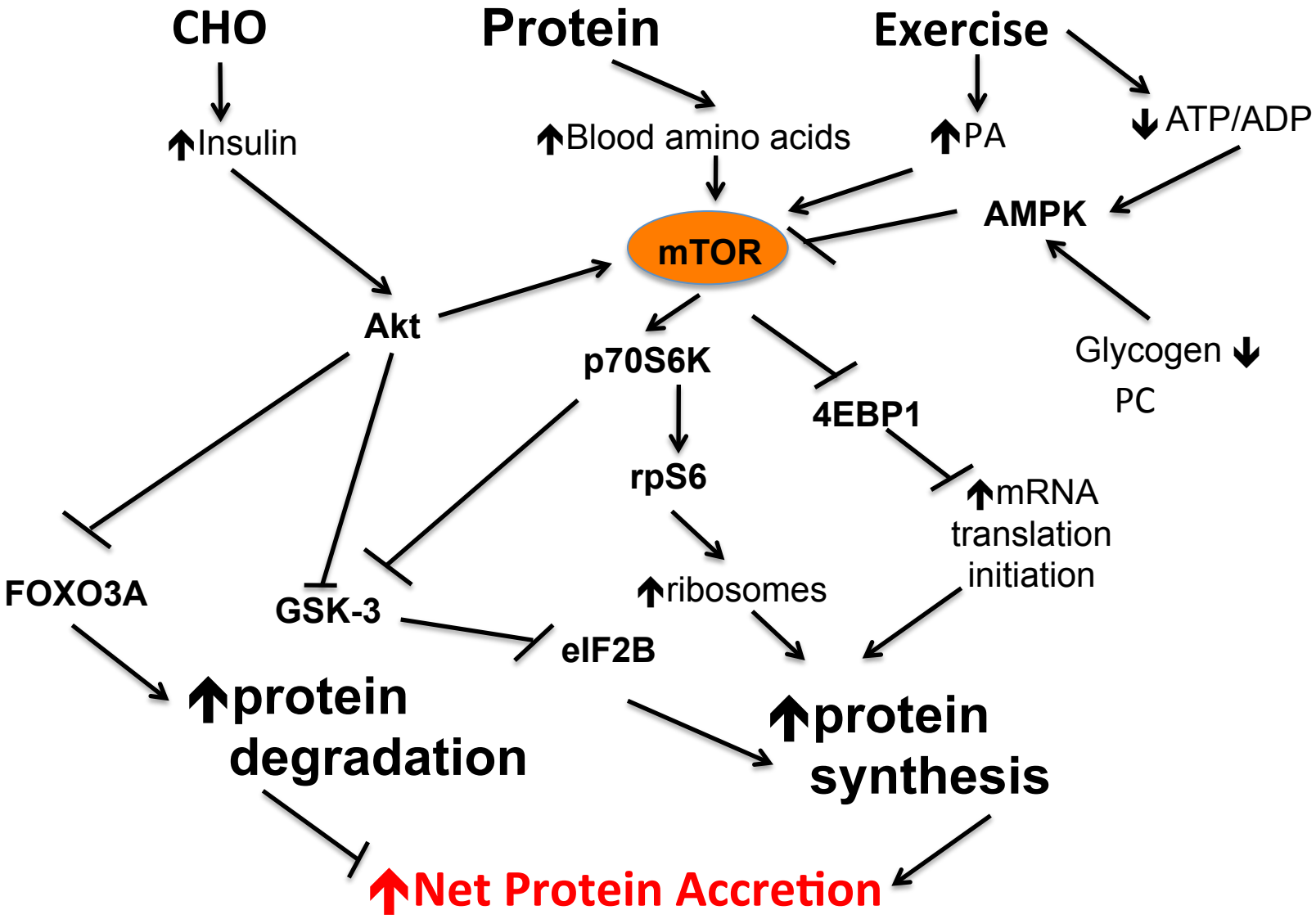
Carbohydrate and Amino Acid Supplementation

3-methyl-histine release

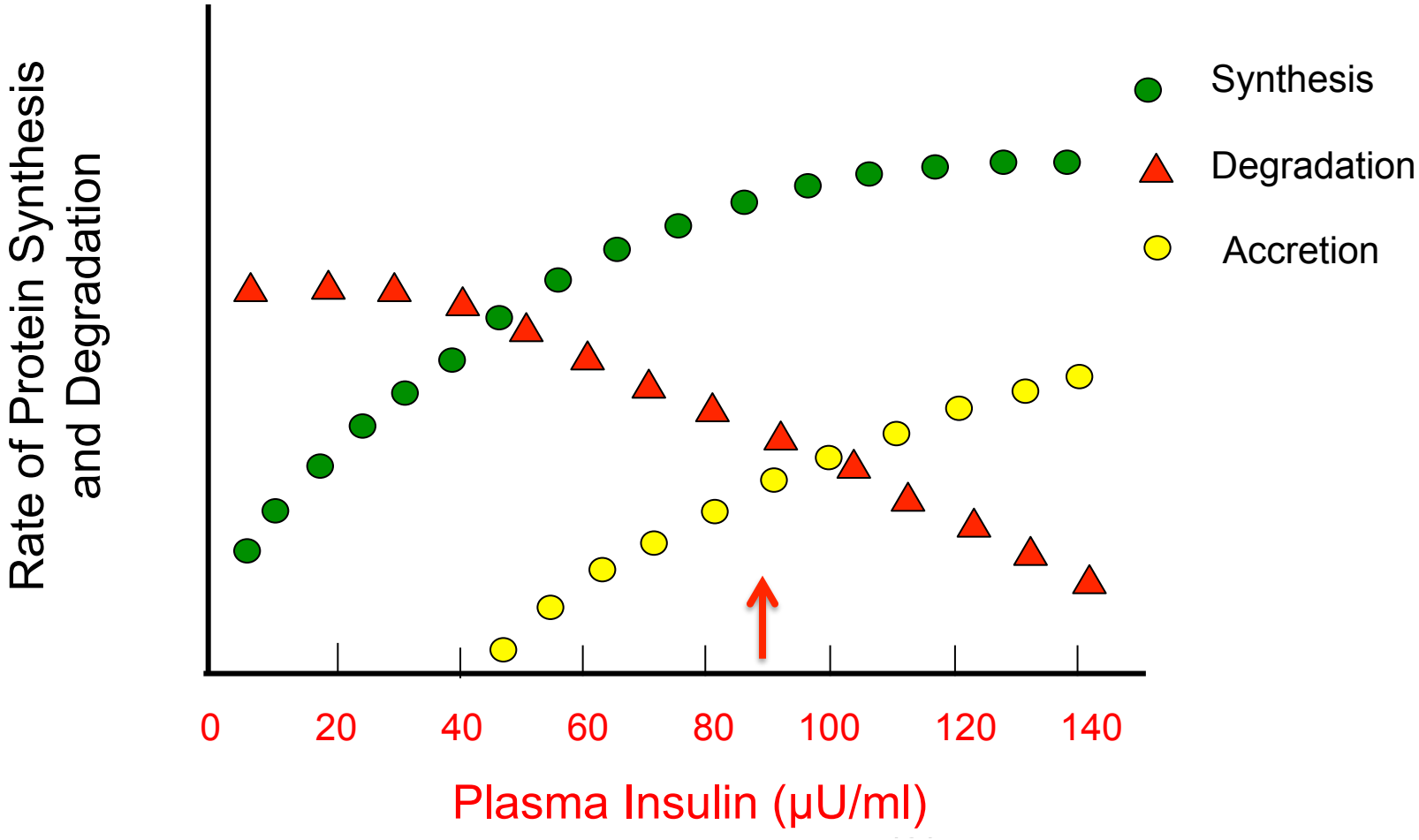


Bird et al. EJAP, 97:225-238, 2006.

mTOR Signaling Pathway



Protein Synthesis and Degradation with Increasing Protein with Meal



Effect of Phospatidic Acid Supplementation on Resistance Exercise Training Adaptations

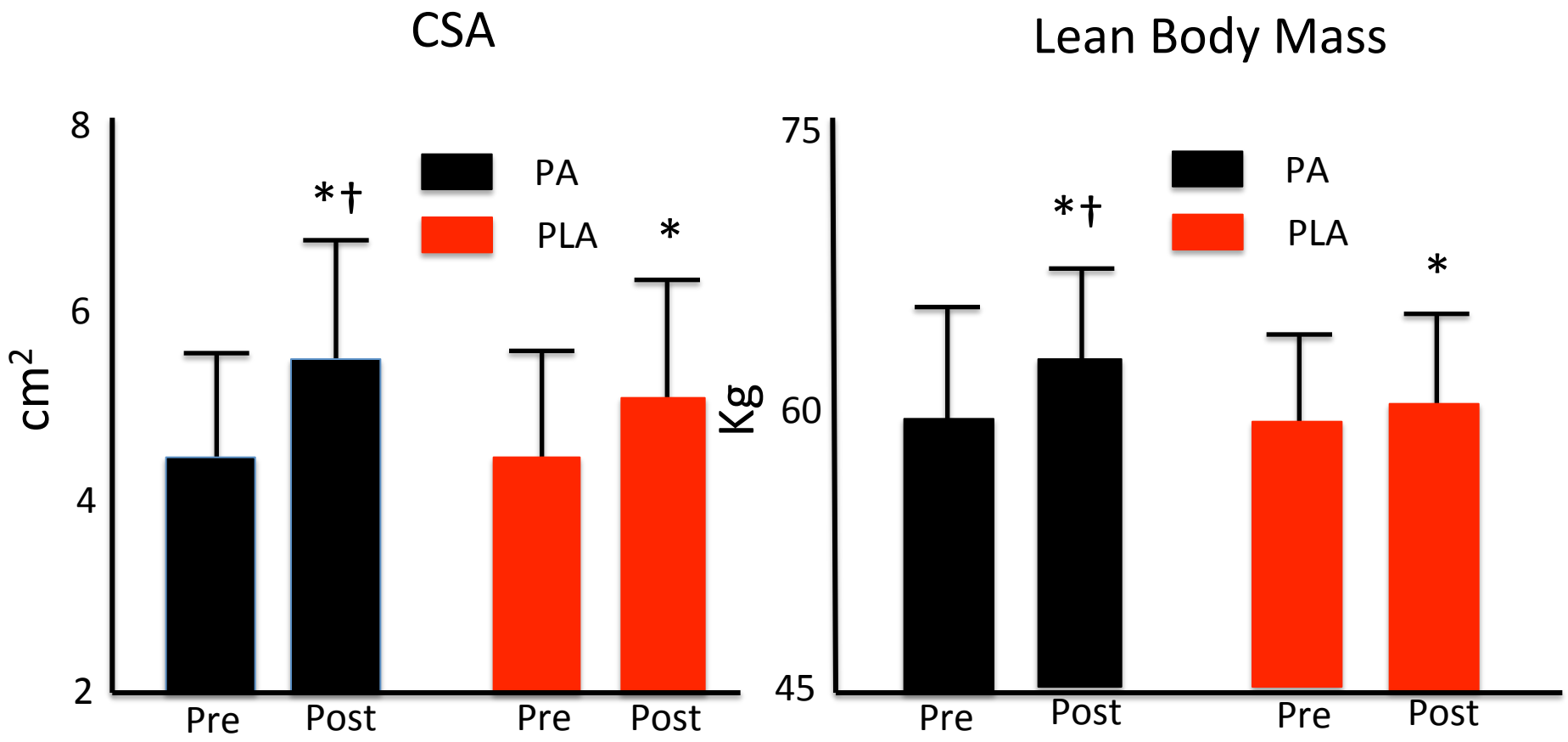
- 28 subjects were randomly assigned to one of two treatment groups (14 subjects per group):

  Placebo

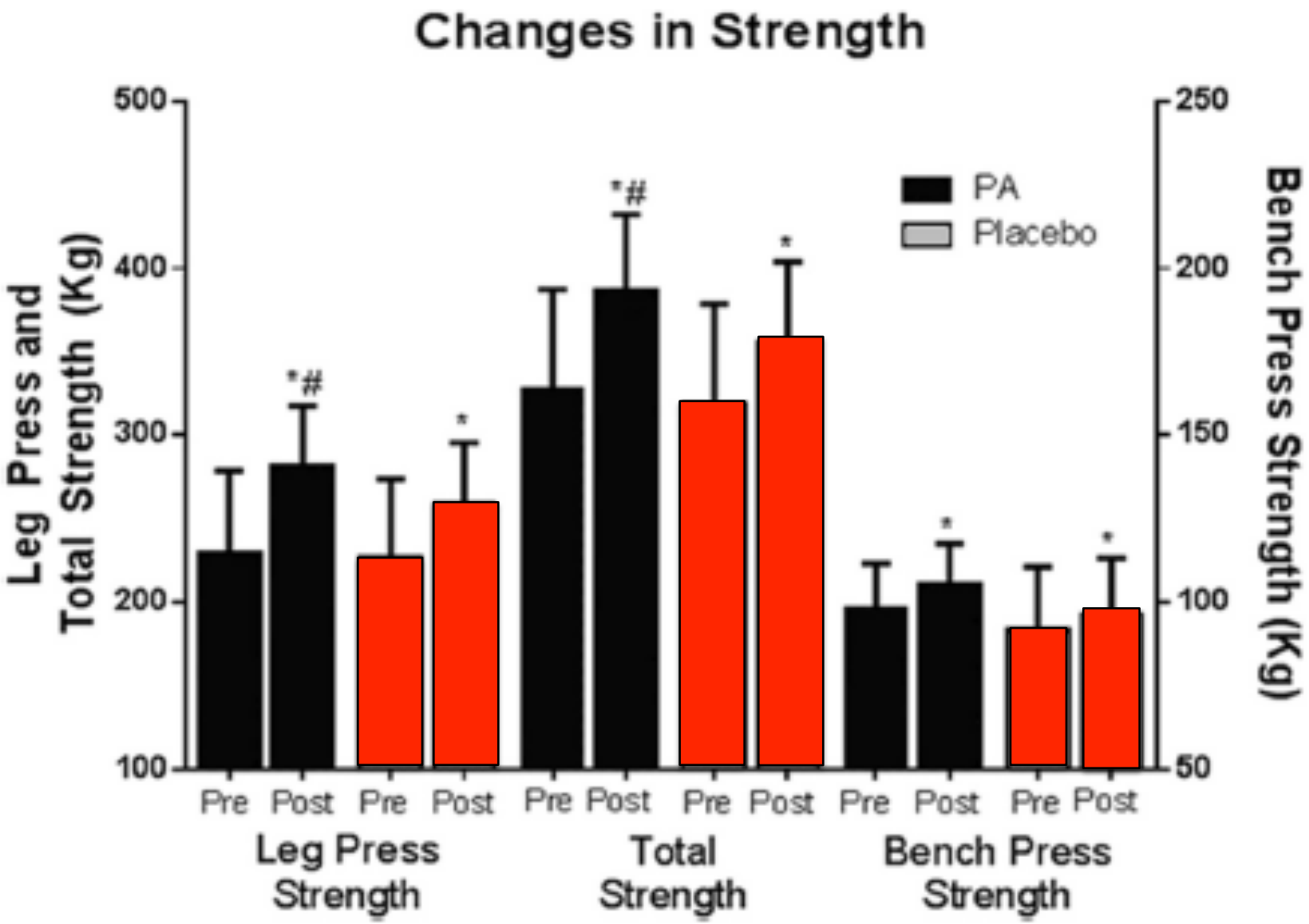
  Phosphatidic Acid (750 mg/d) from soy
- Subjects completed an 8 week periodized whole-body resistance training program
- Tested for changes in body composition by DEXA, muscle hypertrophy (CSA of the rectus femoris) and muscle strength (1 RM for bench press and leg press)

Joy JM et al. Nutr Metab 11:29-39, 2014

Changes in CSA Rectus Femoris and Lean Body Mass



Joy JM et al. Nutr Metab 11:29-39, 2014



Joy JM et al. Nutr Metab 11:29-39, 2014

Summary

- mTOR is a serine-threonine kinase with two configurations (mTOC1 and mTOC2). mTOC1 is sensitive to rapamycin and responsible for cell growth and training adaptation
- mTOR is responsible for activation of translation initiation and therefore control of protein synthesis
- Growth factors, nutrition and muscle contraction can regulate mTOR activity
- Growth factors activate mTOR via the IRS-1/PI-3 kinase/Akt pathway
- Nutrition (primarily L-leucine) activates mTOR by activating Rag A/B, which recruits the mTOC1 complex to a lysosomal membrane where it can interact with Rheb
- Muscle contraction activates mTOR by generating phosphatidic acid, which binds to the mTOR protein

Summary completed

- During exercise, mTOR is inactivated by activation of AMP Kinase and increased expression of REDD1
- Post exercise net protein balance is remains negative until nutrient intervention
- Providing protein and/or L-leucine will act additively with muscle contraction to increase muscle protein synthesis and produce a positive net protein balance
- The addition of CHO to a post workout protein supplement does not enhance muscle protein synthesis. However, it will reduce the rate of protein breakdown and increase net protein accretion
- Taking a phosphatidic acid supplement (750 mg) daily may increase the rate of muscle and strength development during a resistance exercise training program

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