UNDERSTANDING PROTEIN, AMINO ACIDS, AND BRANCHED-CHAIN AMINO ACIDS

Hosted by Dr Anne Holdoway

with expert guest speaker Professor Philip Atherton

Supported by an educational grant from Nutrinovo

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PROFESSOR PHILIP J ATHERTON

Chair of Clinical, Metabolic & Molecular Physiology

School of Medicine, Medical School, Royal Derby Hospital, UK

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

MRC Medical Research Council

NIHR | Nottingham Biomedical Research Centre

Centre Of Metabolism, Ageing & Physiology
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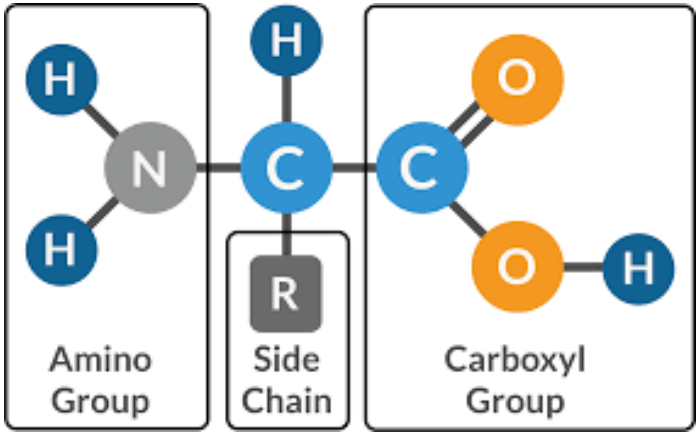
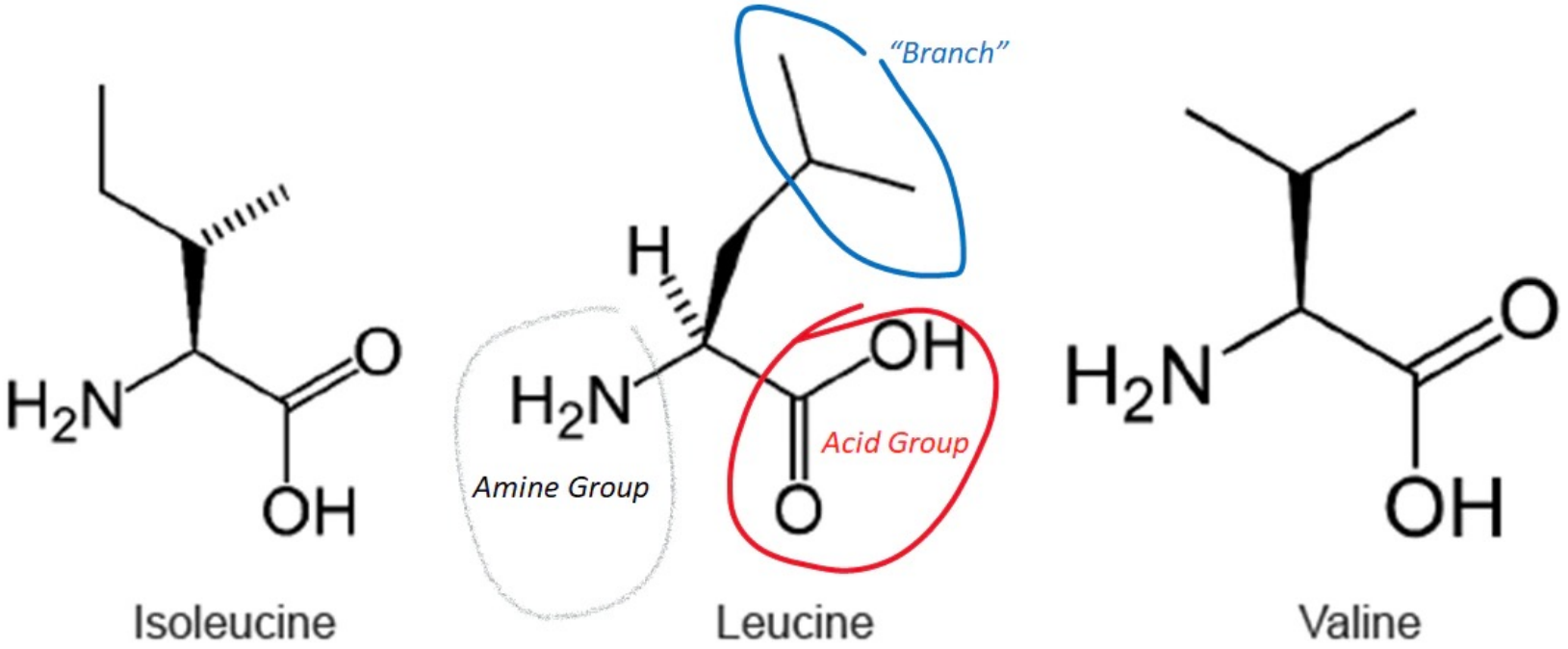
LEARNING OUTCOMES

By the end of this webinar, you should be able to:

- Describe the classification of amino acids and branched chain amino acids
- Explain what is meant by the “leucine argument”
- Describe how the body uses protein and how this differs depending on factors such as age
- Define protein quality and discuss the considerations of protein quality with regards to medical nutrition products
- Define protein digestibility and describe some ways to measure protein digestibility

WHAT IS AN AMINO ACID?





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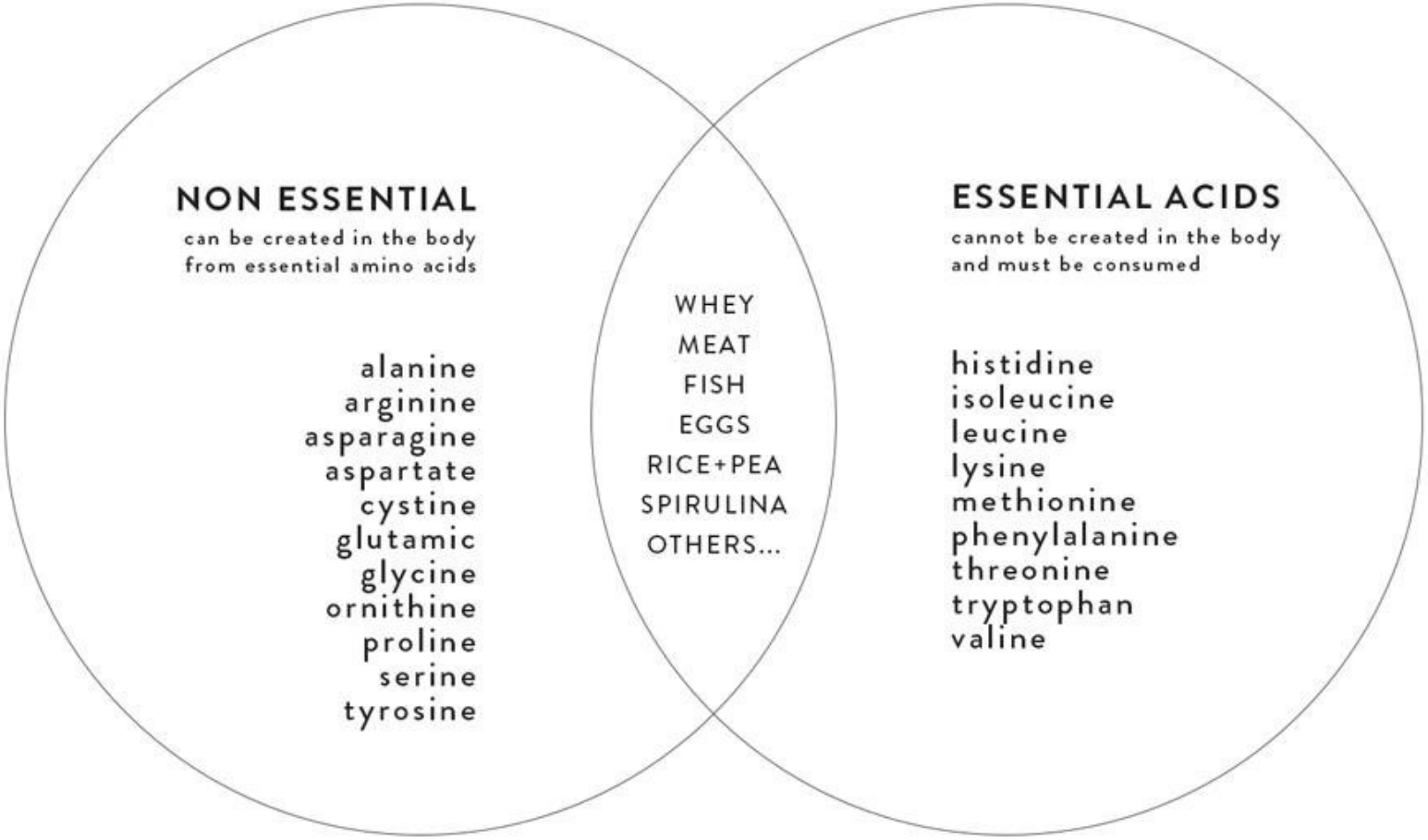
AMINO ACID CLASSIFICATION…

- Dietary proteins contain diverse mixtures of both essential amino acids (EAA) and non-essential amino acids (NEAA)



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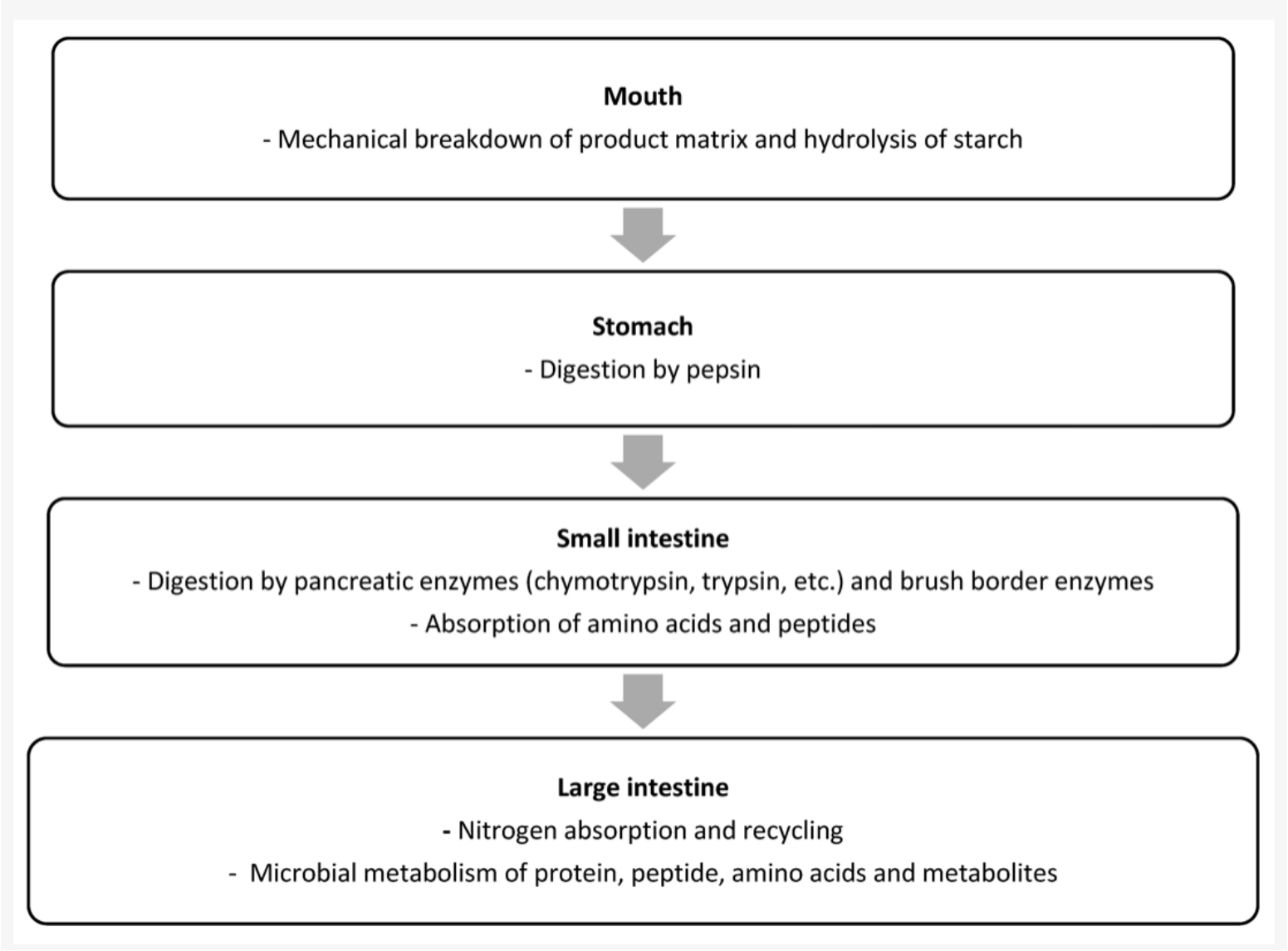
PROTEIN'S ROUTE TO ALL TISSUES



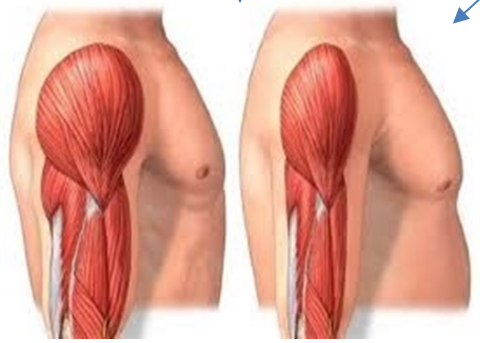
- Adhikari S, Schop M, de Boer IJM, Huppertz T. Protein Quality in Perspective: A Review of Protein Quality Metrics and Their Applications. *Nutrients.* 2022 Feb 23;14(5):947.

BODY PROTEIN IS CONCENTRATED IN MUSCLE!

Cancers

Diabetes

Critical Care/Intensive Care Unit (ICU)



Rheumatoid Arthritis

Chronic Organ Failures

~50% of total body protein!

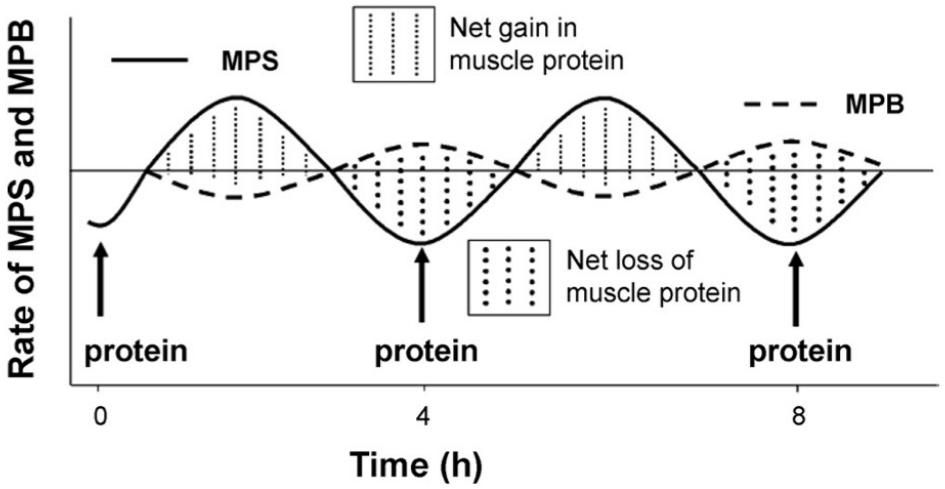
Obesity

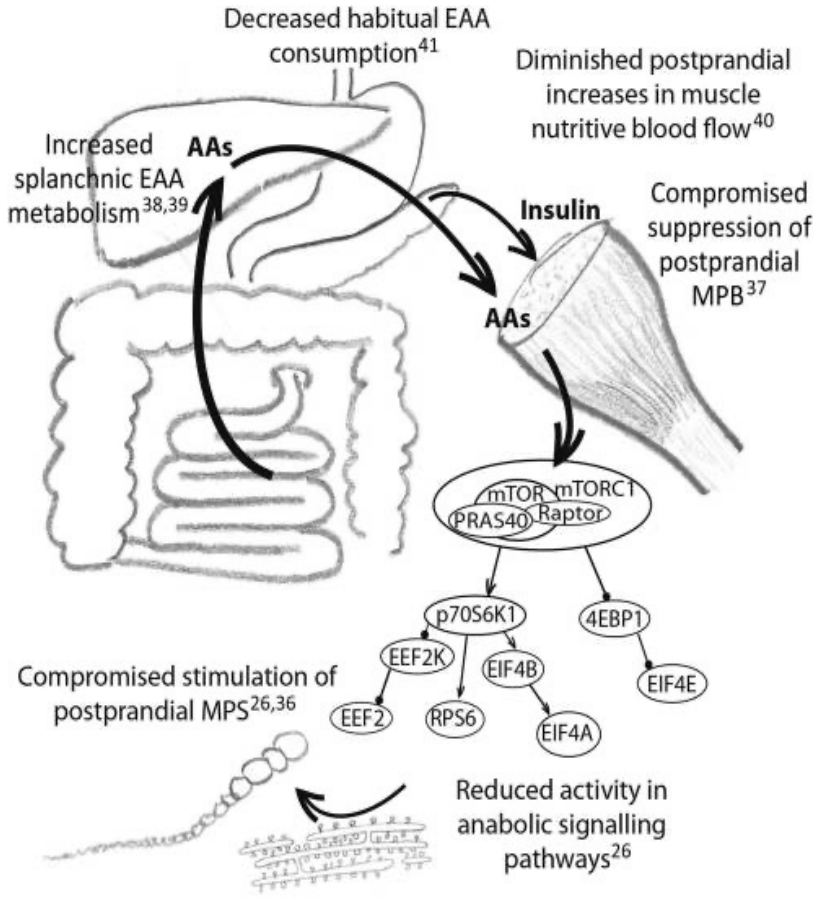
Chronic Obstructive Pulmonary Disease

Ageing

Underlies muscle research in nutrition

MISHANDLING OF DIETARY PROTEIN…?



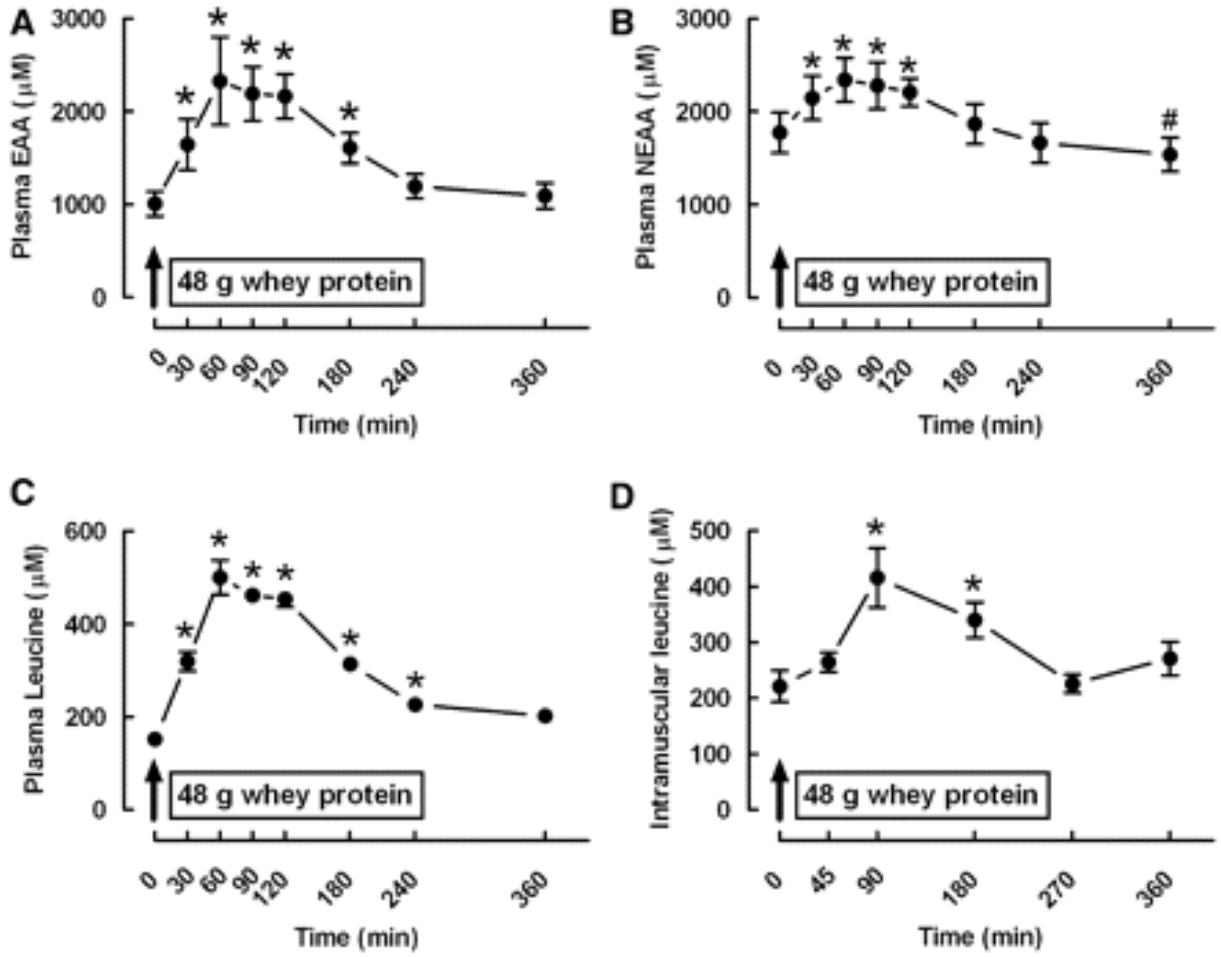


↑ Muscle protein breakdown ↓ Muscle protein synthesis **= Muscle atrophy**

AA=Amino Acid; EAA=Essential Amino Acid; EEF2=Eukaryotic Elongation Factor 2; EEF2K=Eukaryotic Elongation Factor 2 Kinase; EIF= Eukaryotic Initiation Factor; MPB=Muscle Protein Breakdown; MPS=Muscle Protein Synthesis; mTOR=Mechanistic Target of Rapamycin; mTORC1= Mechanistic Target of Rapamycin Complex 1; p70S6K1=Ribosomal Protein S6 Kinase; PRAS40= Proline-Rich Akt Substrate of 40 kDa; RPS6= Ribosomal Protein S6; 4EBP1= 4E-Binding Protein

- Phillips SM, Glover EI, Rennie MJ. Alterations of protein turnover underlying disuse atrophy in human skeletal muscle. *J Appl Physiol (1985)*. 2009 Sep;107(3):645-54.
- Mitchell WK, Wilkinson DJ, Phillips BE, Lund JN, Smith K, Atherton PJ. Human Skeletal Muscle Protein Metabolism Responses to Amino Acid Nutrition. *Adv Nutr*. 2016 Jul 15;7(4):828S-38S.

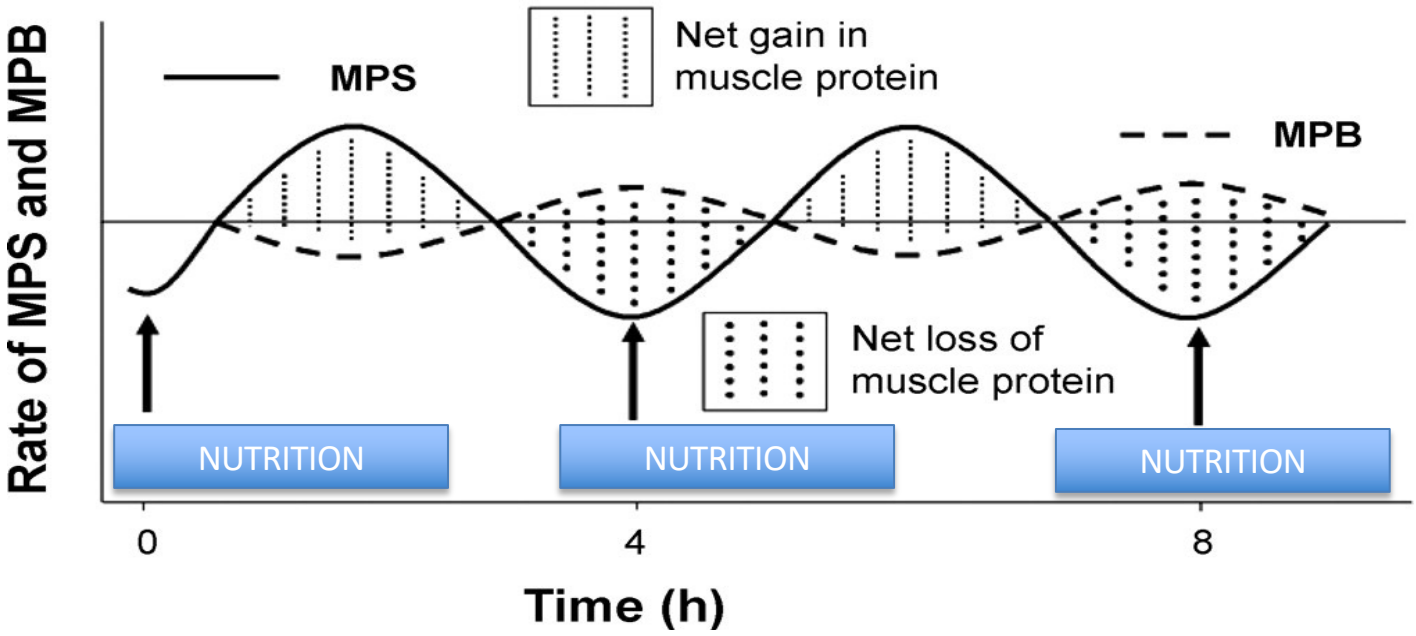
DIETARY PROTEIN AND SYSTEMIC APPEARANCE OF AMINO ACIDS



EAA: Essential amino acid; NEAA: Non-essential amino acid

- Atherton PJ, Etheridge T, Watt PW, Wilkinson D, Selby A, Rankin D, et al. Muscle full effect after oral protein: time-dependent concordance and discordance between human muscle protein synthesis and mTORC1 signaling. *Am J Clin Nutr*. 2010 Sep 15;92(5):1080-88.

NUTRITIONAL REGULATION OF MUSCLE PROTEIN TURNOVER



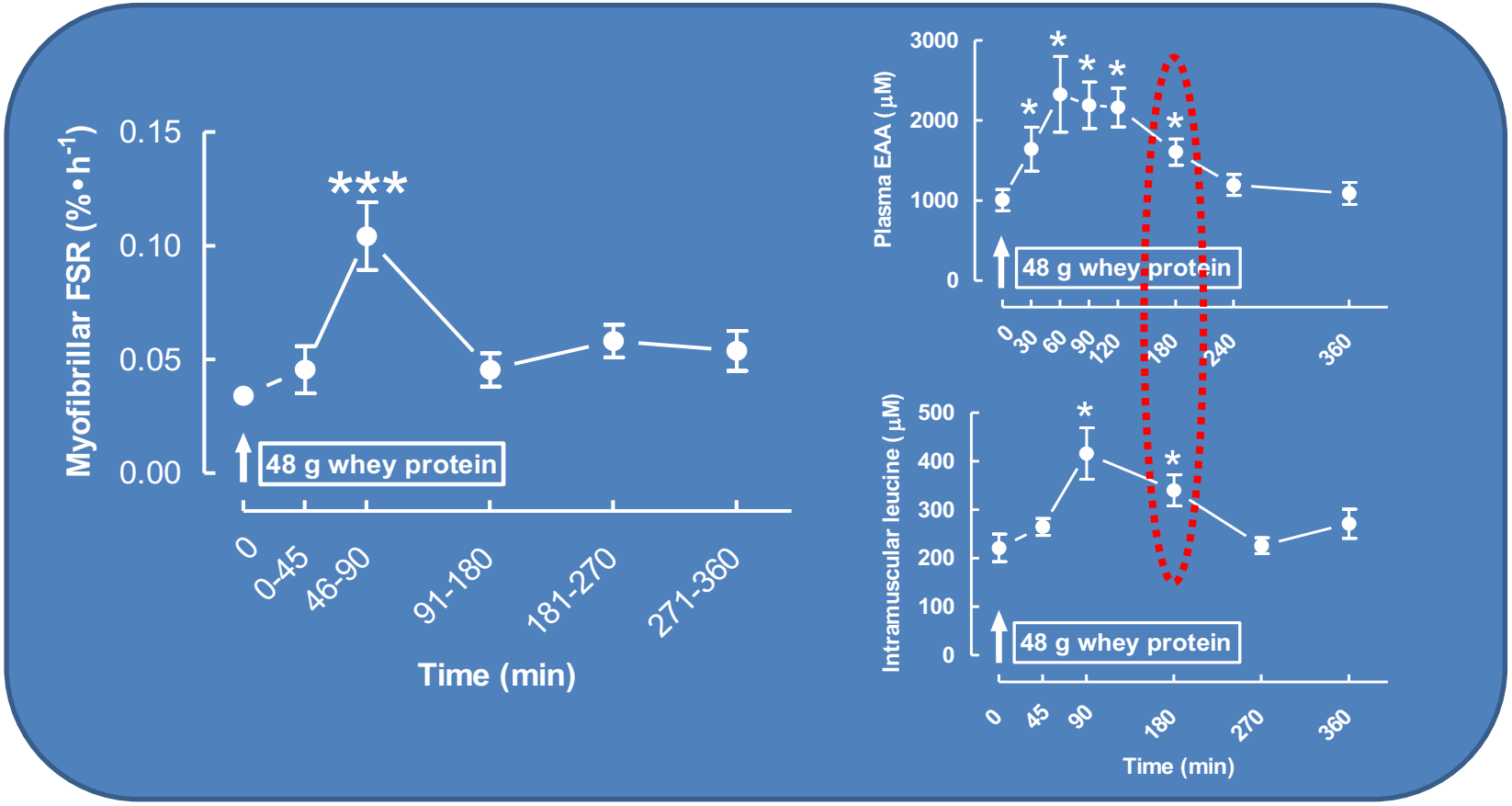
The progression in terms of nutritional regulation of muscle protein synthesis (MPS):

Mixed meal ➡ AA ➡ EAA ➡ BCAA ➡ Leucine

AA: Amino acid; BCAA: Branched chain amino acid; EAA: Essential amino acid; MPS: Muscle protein synthesis; MPB: Muscle protein breakdown

- Burd NA, Tang JE, Moore DR, Phillips SM. Exercise training and protein metabolism: influences of contraction, protein intake, and sex-based differences. *J Appl Physiol (1985)*. 2009 May;106(5):1692-701.

MUSCLE PROTEIN SYNTHESIS (MPS) RESPONSE TO PROTEIN INTAKE

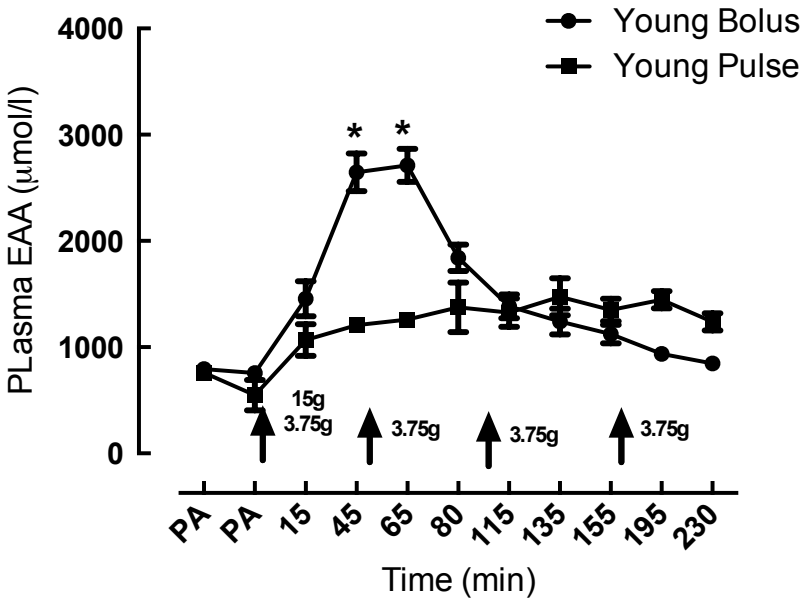


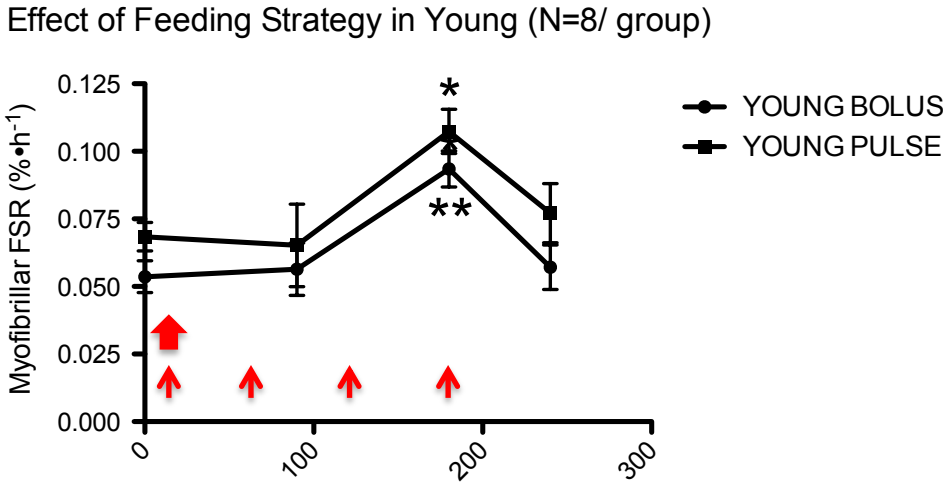
This we termed “muscle full”

EAA: Essential amino acid; FSR: Fractional synthetic rate

- Atherton PJ, Etheridge T, Watt PW, Wilkinson D, Selby A, Rankin D, et al. Muscle full effect after oral protein: time-dependent concordance and discordance between human muscle protein synthesis and mTORC1 signaling. *Am J Clin Nutr*. 2010 Sep 15;92(5):1080-88.

PLASMA AMINOACIDEMIA AND MUSCLE PROTEIN SYNTHESIS (MPS)





Smaller doses may need to be within a window of time…

BOLUS: 1×15 g; PULSE: 4×3.75 g EAA

EAA: Essential amino acid; FSR: Fractional synthetic rate

- Mitchell WK, Phillips BE, Williams JP, Rankin D, Lund JN, Smith K, et al. A Dose- rather than Delivery Profile–Dependent Mechanism Regulates the "Muscle-Full" Effect in Response to Oral Essential Amino Acid Intake in Young Men. J Nut. 2015 Feb; 145(2):207-14.
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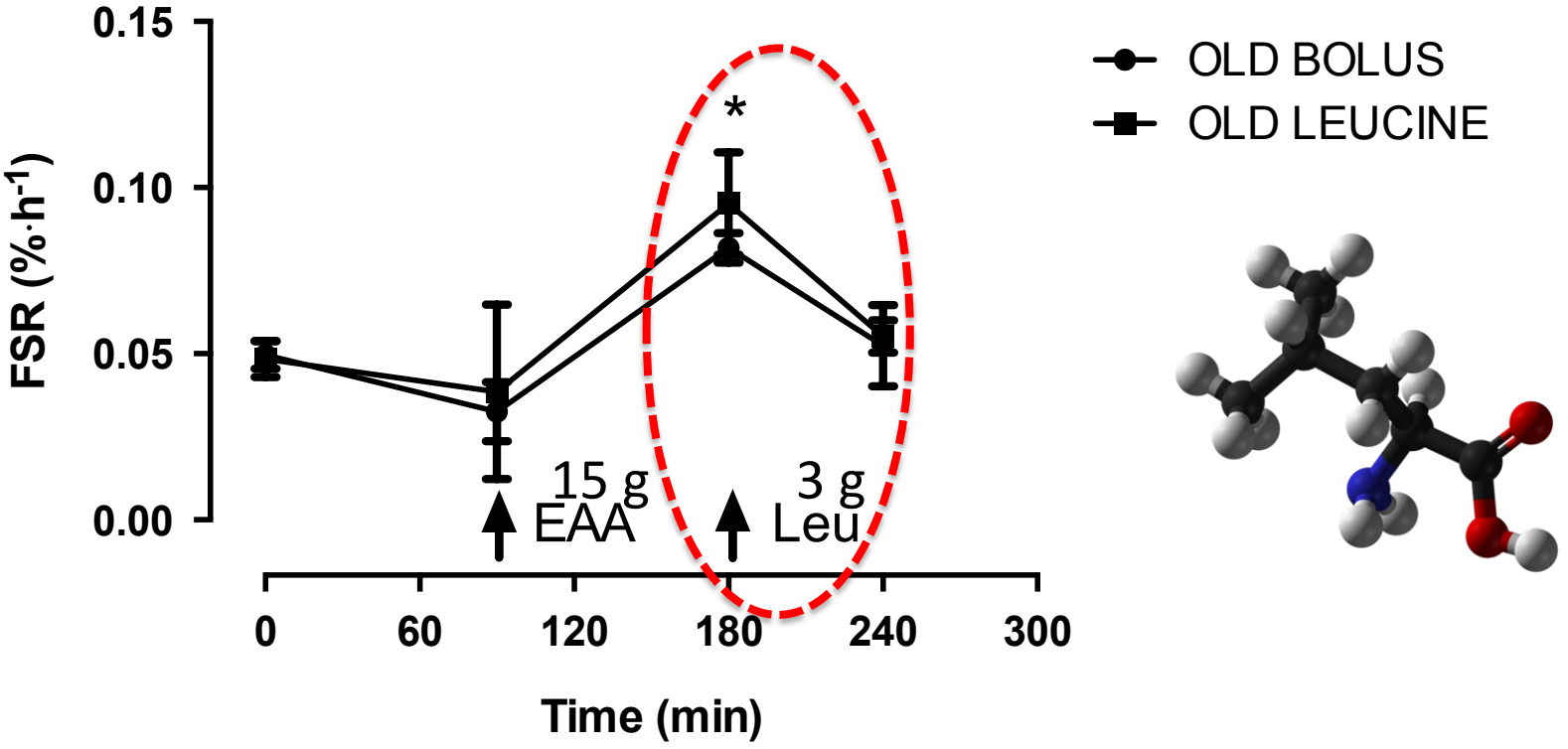
"TACHYPHYLAXIS" OF MUSCLE PROTEIN SYNTHESIS (MPS)

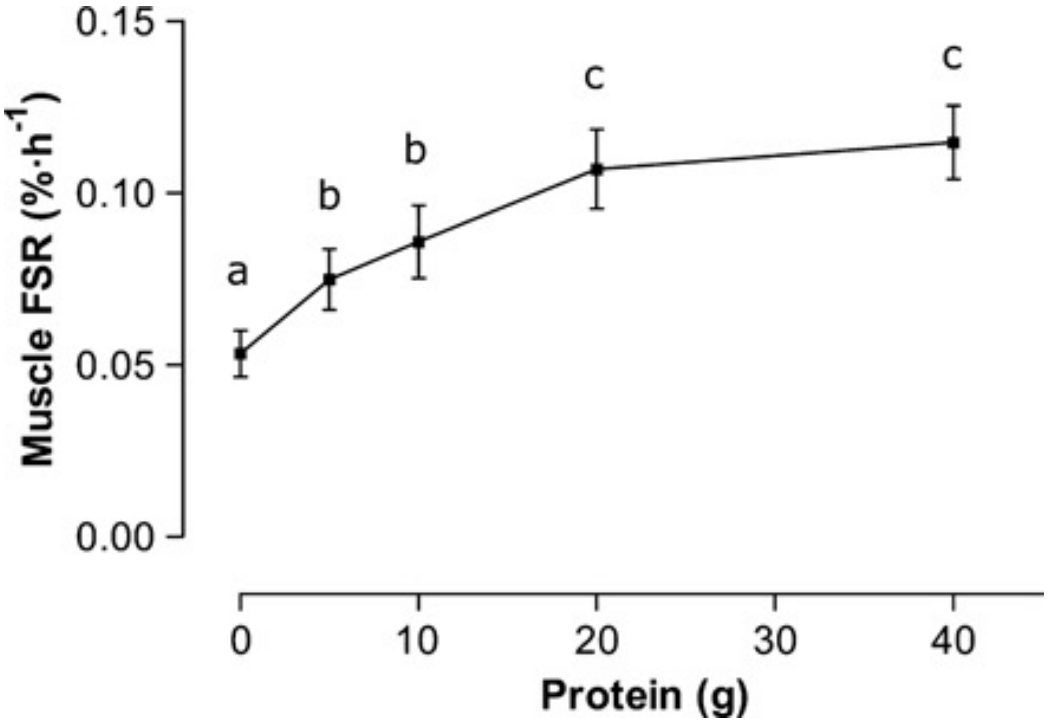


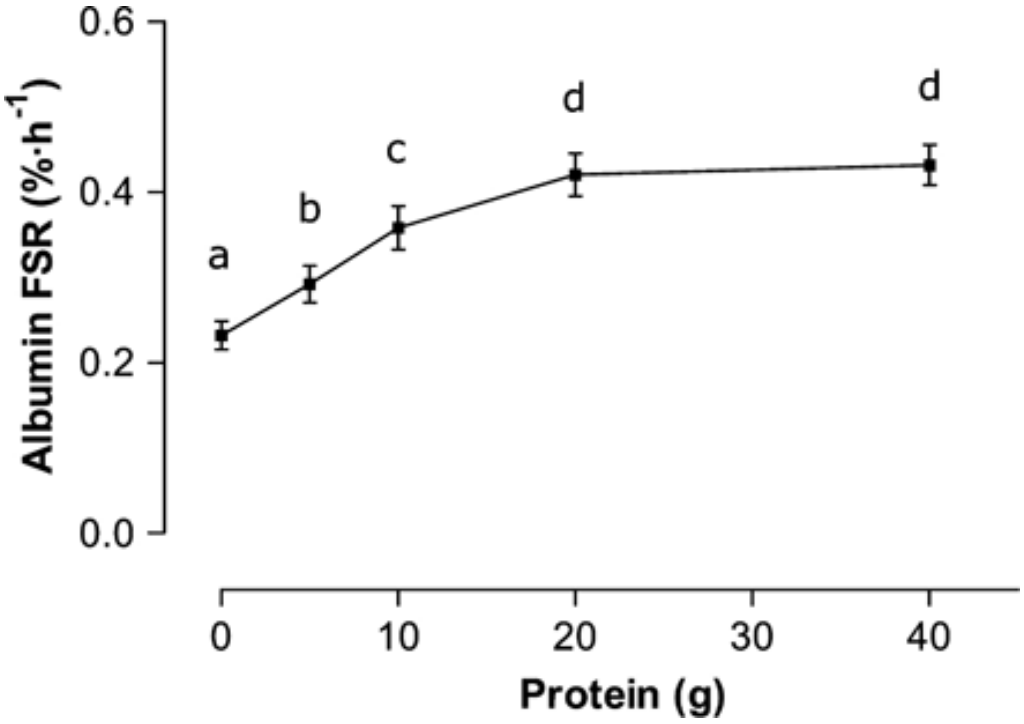
Muscles remain refractory to the anabolic effects of additional substrate (i.e., 3 g leucine) --- cannot overcome muscle full!

EAA: Essential amino acid; FSR: Fractional synthetic rate

- Mitchell WK, Phillips BE, Hill I, Greenhaff P, Lund JN, Williams JP, et al. Human skeletal muscle is refractory to the anabolic effects of leucine during the postprandial muscle-full period in older men. *Clin Sci (Lond)*. 2017 Nov;131(21):2643-53.

PROTEIN DOSE RESPONSE

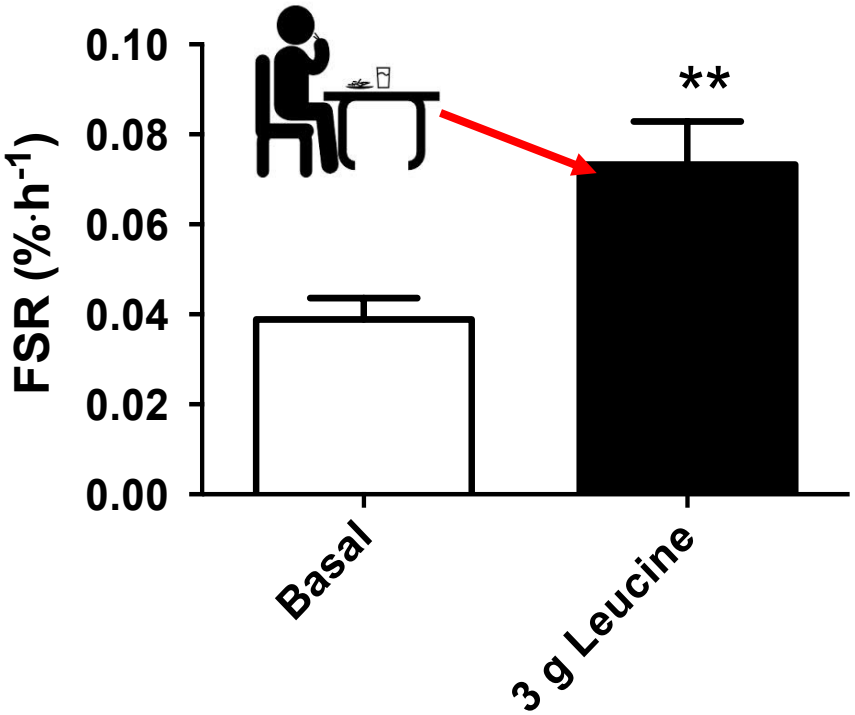


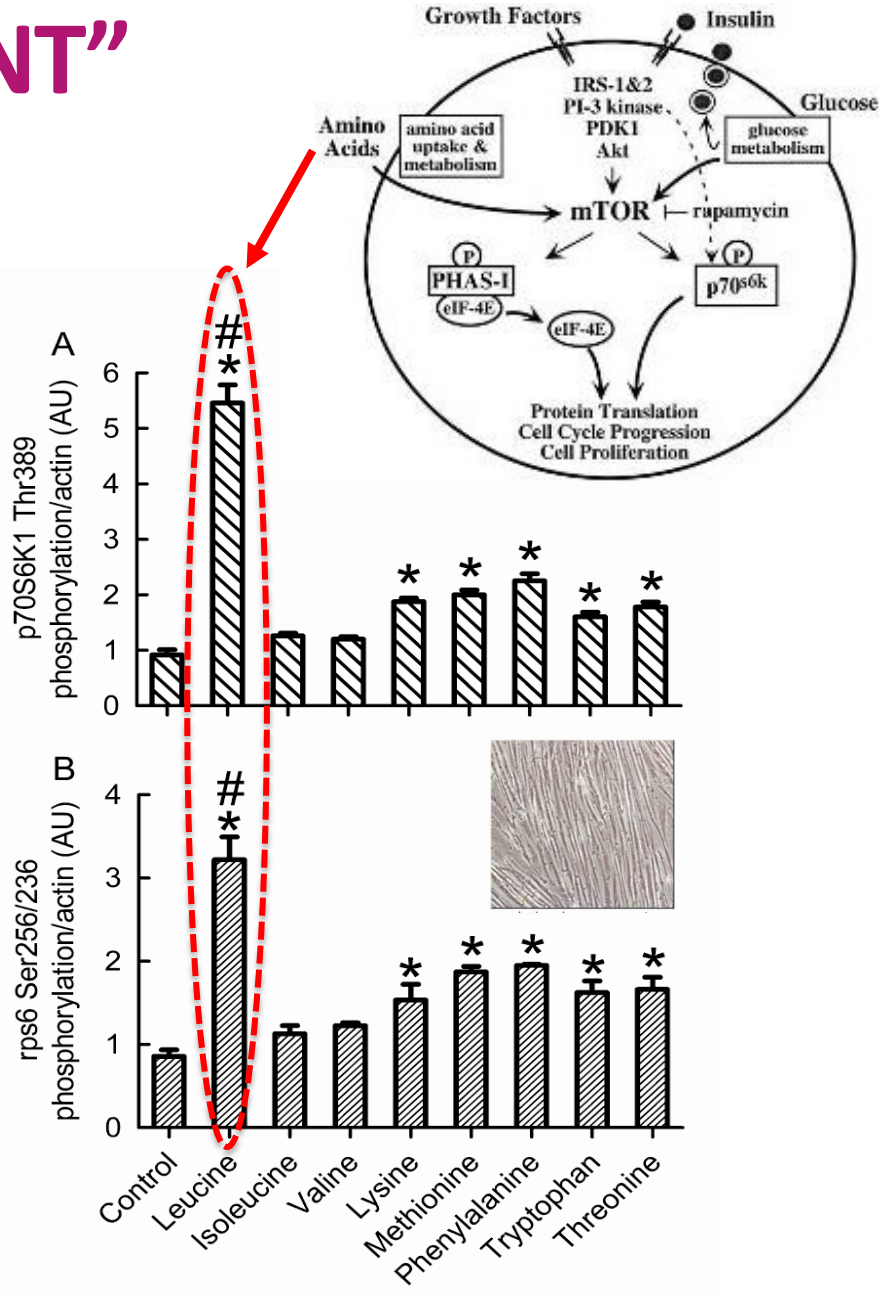


FSR: Fractional synthetic rate

- Moore DR, Robinson MJ, Fry JL, Tang JE, Glover EI, Wilkinson SB, et al. Ingested protein dose response of muscle and albumin protein synthesis after resistance exercise in young men. *Am J Clin Nutr.* 2009 Jan;89(1):161-168.

THE "LEUCINE ARGUMENT"





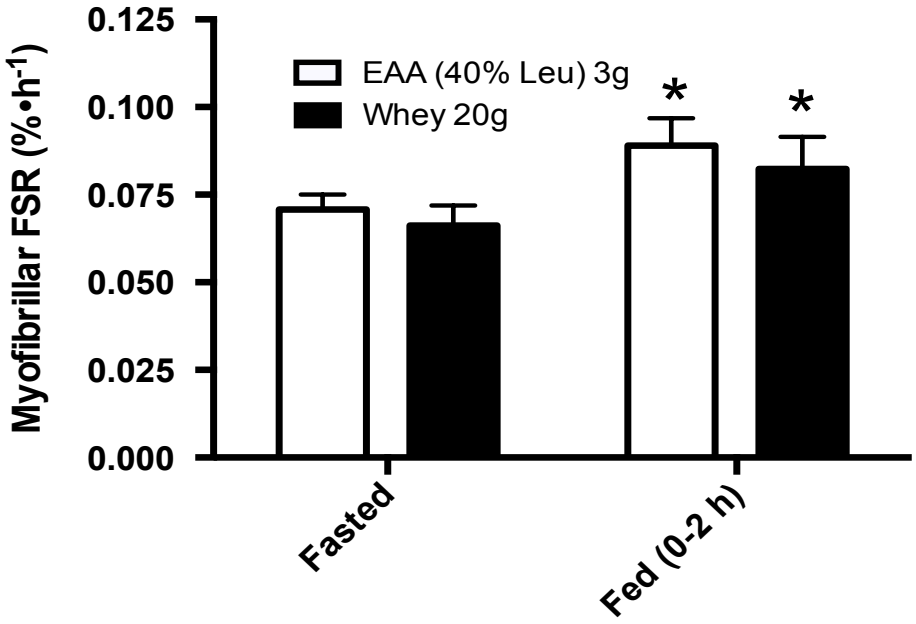
NB. All other AA are ultimately needed…

FSR: Fractional synthetic rate

- Wilkinson DJ, Hossain T, Hill DS, Phillips BE, Crossland H, Williams J, et al. Effects of leucine and its metabolite β-hydroxy-β-methylbutyrate on human skeletal muscle protein metabolism. *J Physiol*. 2013 Jun 1;591(11):2911-23.
- Atherton PJ, Smith K, Etheridge T, Rankin D, Rennie MJ. Distinct anabolic signalling responses to amino acids in C2C12 skeletal muscle cells. *Amino Acids*. 2010 May;38(5):1533-9.

PROTEIN *QUANTITY* OR LEUCINE *CONTENT*?

	LEAA (3 g), g	WP (20 g), g
L-Leucine	1.2	2
L-Isoleucine	0.32	1.4
L-Valine	0.33	1.2
L-Threonine	0.28	1.4
L-Lysine	0.5	1.8
L-Methionin	0.1	0.4
L-Histidine	0.05	0.4
L-Phenylalar	0.2	0.6
L-Tryptopha	0.02	0.4

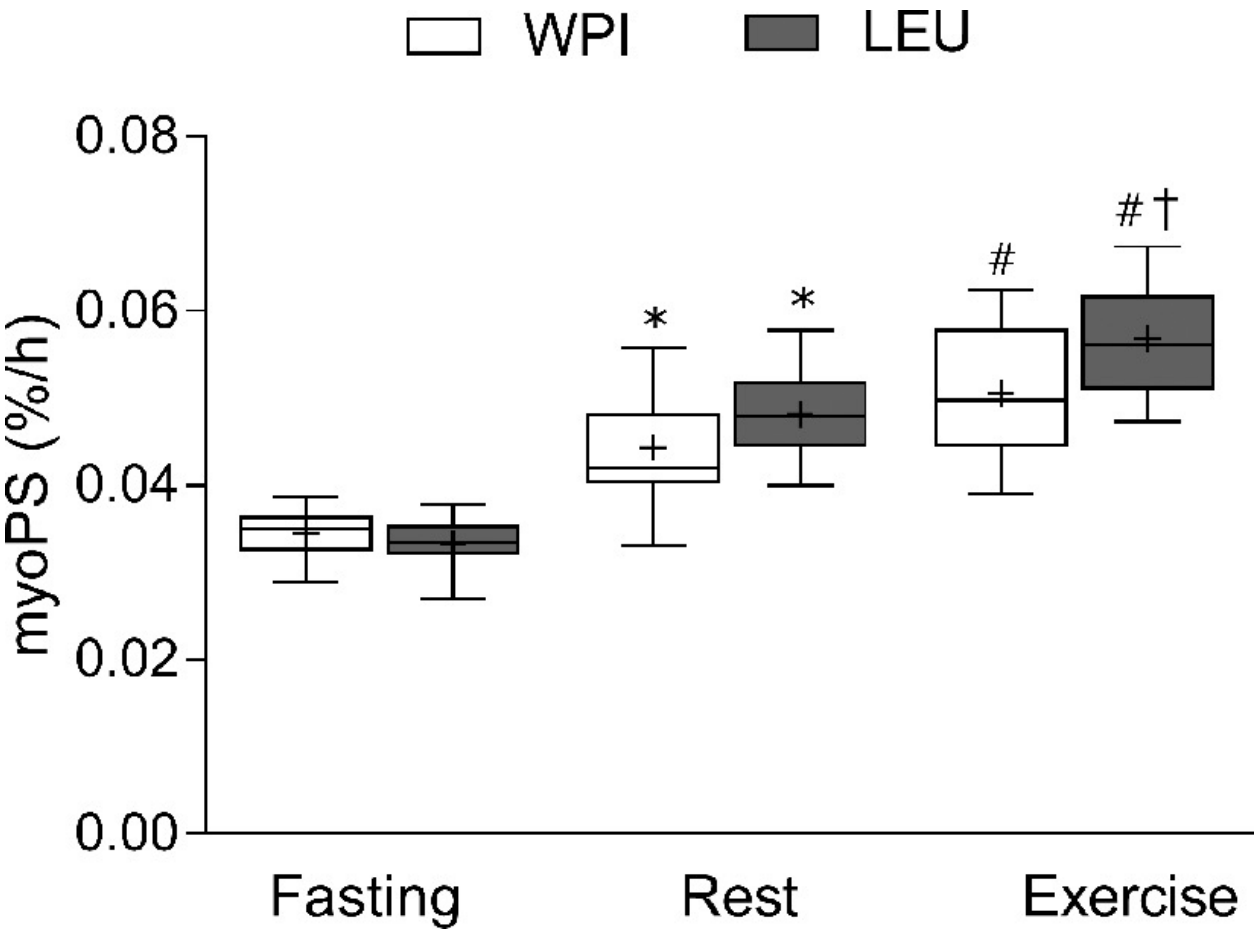


*Whey protein is exchangeable...

EAA: Essential amino acid; FSR: Fractional synthesis rate; LEAA: leucine-enriched essential amino acids; WP: Whey protein

- Bukhari SSI, Phillips BE, Wilkinson DJ, Limb MC, Rankin D, Mitchell WK, et al. Intake of low-dose leucine-rich essential amino acids stimulates muscle anabolism equivalently to bolus whey protein in older women at rest and after exercise. *Am J Physiol Endocrinol Metab*. 2015 Jun 15;308(12):E1056-65.
- Wilkinson DJ, Hossain T, Hill DS, Phillips BE, Crossland H, Williams J, et al. Effects of leucine and its metabolite β-hydroxy-β-methylbutyrate on human skeletal muscle protein metabolism. *J Physiol*. 2013 Jun 1;591(11):2911-23.

PROTEIN QUANTITY OR LEUCINE CONTENT?



WPI = Whey protein isolate

LEU = Milk Protein + 3 g L-Leu

=

2 X PROTEIN

myoPS: myofibrillar protein synthesis

- Dervies MC, McGlory C, Bolster DR, Kamil A, Rahn M, Harkness L, et al. Leucine, Not Total Protein, Content of a Supplement Is the Primary Determinant of Muscle Protein Anabolic Responses in Healthy Older Women. J Nutr. 2018 Jul;148(7):1088-95.

“Digestibility of protein is typically defined as the proportion of ingested protein that is hydrolysed into amino acids, di- and tripeptides, which are available for absorption”

“The most common methods calculate a value for protein quality based on the first limiting amino acid in relation to a reference pattern”

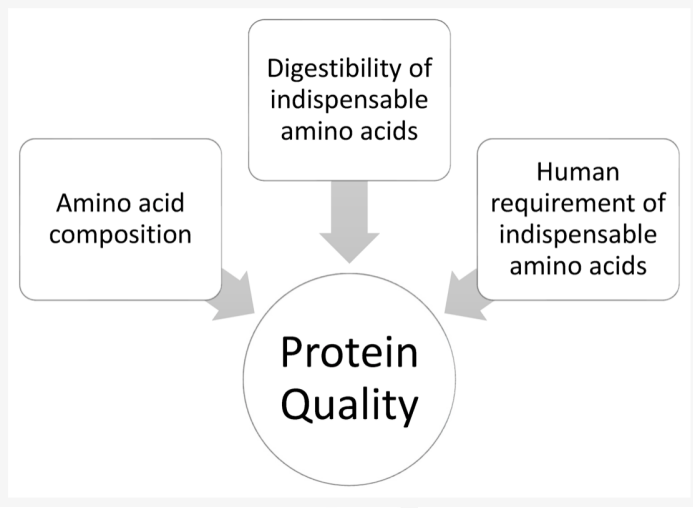
RECOMMENDED REFERENCE PATTERN FOR INDISPENSABLE AMINO ACIDS (IN MG/G PROTEIN) FOR HUMANS IN DIFFERENT AGE GROUPS

Age (Years)	His	Ile	Leu	Lys	SAA *	AAA **	Thr	Trp	Val
0–0.5	21	55	96	69	33	94	44	17	55
0.5–3	20	32	66	57	27	52	31	8.5	43
>3	16	30	61	48	23	41	25	6.6	40

* SAA = Sulphur-containing amino acids (Cys + Met); ** AAA = Aromatic amino acids (Phe + Tyr).

- FAO Dietary Protein Quality Evaluation in Human Nutrition: Report of an FAO Expert Consultation; FAO: Auckland, New Zealand, 2013.
- Joint WHO/FAO/UNU Expert Consultation Protein and Amino Acid Requirements in Human Nutrition; WHO: Geneva, Switzerland, 2007; ISBN 9241209356.

HOW IS PROTEIN QUALITY DEFINED - *OFFICIALLY*?



Digestion

Ileal Digesta
- Digestible Indispensable Amino Acid Score (DIAAS)

Faeces
- Protein Digestibility Corrected Amino Acid Score (PDCAAS)
- Net Protein Utilization (NPU) ✧
- Biological Value (BV) ✧

Metabolism

Blood
- Dual Isotope Tracer Method

Urine
- Net Protein Utilization (NPU) ✧
- Biological Value (BV) ✧

Body Weight
- Protein Efficiency Ratio (PER)
- Net Protein Retention (NPR)

✧ Combination of Faeces & Urine

- Adhikari S, Schop M, de Boer IJM, Huppertz T. Protein Quality in Perspective: A Review of Protein Quality Metrics and Their Applications. *Nutrients.* 2022 Feb 23;14(5):947.

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DIGESTIBILITY VALUES OF A) FOOD ITEMS AND, B) FOOD GROUPS

Table 4. Overview of digestible indispensable amino acid score (DIAAS) values, including the first limiting indispensable amino acid (IAA_{lim}) and its standardized ileal digestibility (SID) as well as the species in which testing was performed and the protein reference pattern against which DIAAS was calculated for different food items. Items are ranked from highest to lowest DIAAS value [1].

Food Item	Food Group	DIAAS Value (%)	IAA_{lim}	SID of IAA_{lim} (%)	Test Species	Protein Reference Pattern	References
Dry milk	Dairy	144	SAA	94	Pig	>3-year-old	[77]
Bacon (smoked-cooked)	Pork	142	Valine	95	Pig	>3-year-old	[79]
Milk protein concentrate	Dairy	141	SAA	101	Pig	>3-year-old	[57]
Pork loin (medium)	Pork	139	Valine	95	Pig	>3-year-old	[79]
Whey protein concentrate	Dairy	133	Histidine	97	Pig	>3-year-old	[57]

Table 5. Overviewed of the range for digestible indispensable amino acid score (DIAAS) values, the first limiting indispensable amino acid (IAA_{lim}) and its standardized ileal digestibility (SID) for different food groups. For IAA_{lim}, data in brackets indicate total amount of times the IAA was IAA_{lim} in the food group, followed by the number of occurrences for which this was for a product with DIAAS < 100 and the number of occurrences for which this was for a product with DIAAS > 100. Data from Table 4.

Food Group	Number of Food items	DIAAS Value (Range)	SID IAA_{lim} (Range)	IAA_{lim}
Beef	11	80–130	95–99	Valine (n = 8/5/3), Leucine (n = 2/1/1), SAA * (n = 1/0/1)
Cereals	25	1–77	13–96	Lysine (n = 23/23/0), SAA * (n = 2/2/0)
Dairy	8	97–144	94–101	SAA (n = 4/0/4), Histidine (n = 4/1/4)

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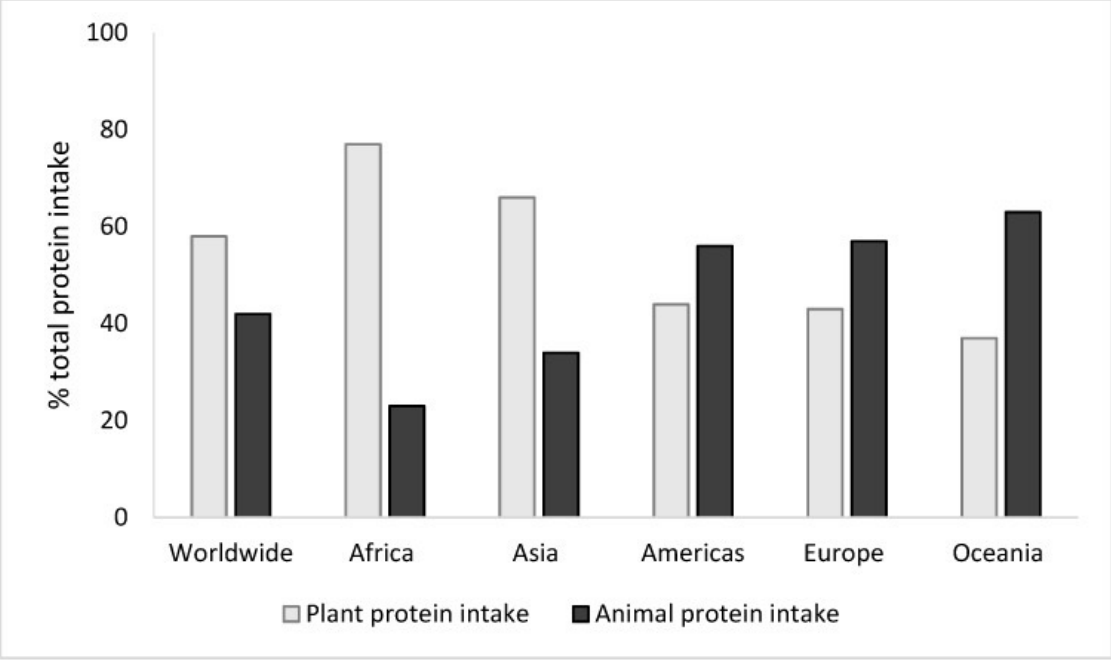
A MAJOR CURRENT FOCUS IS ON PLANT VS. ANIMAL PROTEIN SOURCES

- Is dietary protein quality at odds with sustainable foods aims?



Pre-digestion / hydrolysis

Protein source / blends

Adjuvant exercise?

- Berrazaga I, Micard V, Gueugneau M, Walrand S. The Role of the Anabolic Properties of Plant- versus Animal-Based Protein Sources in Supporting Muscle Mass Maintenance: A Critical Review. *Nutrients*. 2019 Aug;11(8):1825.

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PROTEIN QUALITY IN MEDICAL NUTRITION: CONSIDERATIONS

- ✓ Sufficiency
- ✓ Digestibility
- ✓ Avoidance of rate-limiting AA (in relation to each feed)
- ✓ Palatability
- ✓ Volume and texture (e.g., in relation to dysphagia/satiation)
- ✓ Use of protein matrices
- ✓ Sustainability

AA: Amino acid

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- Prof Beth Phillips
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- Prof Paul Greenhaff
- Dr Matt Brook

The University of Nottingham
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Centre Of Metabolism, Ageing & physiology
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MRC Medical Research Council

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Technical Support: Mrs Amanda Gates, Ms Paula Scaife

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Q&A

THANK YOU!