Exercise Metabonomics

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Terms

- Metabonomics: the study of the metabolic responses of living systems to pathophysiological stimuli or genetic modification.
- Exercise metabonomics: the study of the metabolic responses to physical exercise.

Terms

- Exercise: planned and structured bodily movement aiming at learning and improving one or more skills or improving and maintaining one or more capacities.
- Physical activity: any bodily movement produced by muscle activation and leading to energy expenditure.

Exercise

- The most potent healthy modulator of metabolism.
- Numerous effects depending on exercise parameters and exerciser characteristics.

Exercise Parameters

- Type (endurance, resistance, etc.)
- Intensity
- Duration
- Program (in intermittent exercise)
- Ambient temperature
- Altitude
- Partial pressure of oxygen
- Regularity

Exerciser Characteristics

- Sex
- Age
- Dietary status (incl. supplementation)
- Training status
- Health status
- Medication
- Genetics

Utility of Exercise Metabonomics

- Deepen understanding of animal metabolism.
- Discover biomarkers of exercise depending on exercise parameters and exerciser characteristics.
- Apply findings to improve sport performance.
- Apply findings to improve health and wellbeing.

Designing an Exercise Metabonomics Study

Observation

- The participants perform exercise on their own.
- The researchers compare different levels of physical activity.

Intervention

- The researchers dictate the exercise to the participants.
- The researchers compare pre- to post-intervention.

Observation Studies

Cross-sectional

Participants are examined at a single point in time.

Longitudinal

Participants are examined at least twice over a long period.

Intervention Studies

Acute

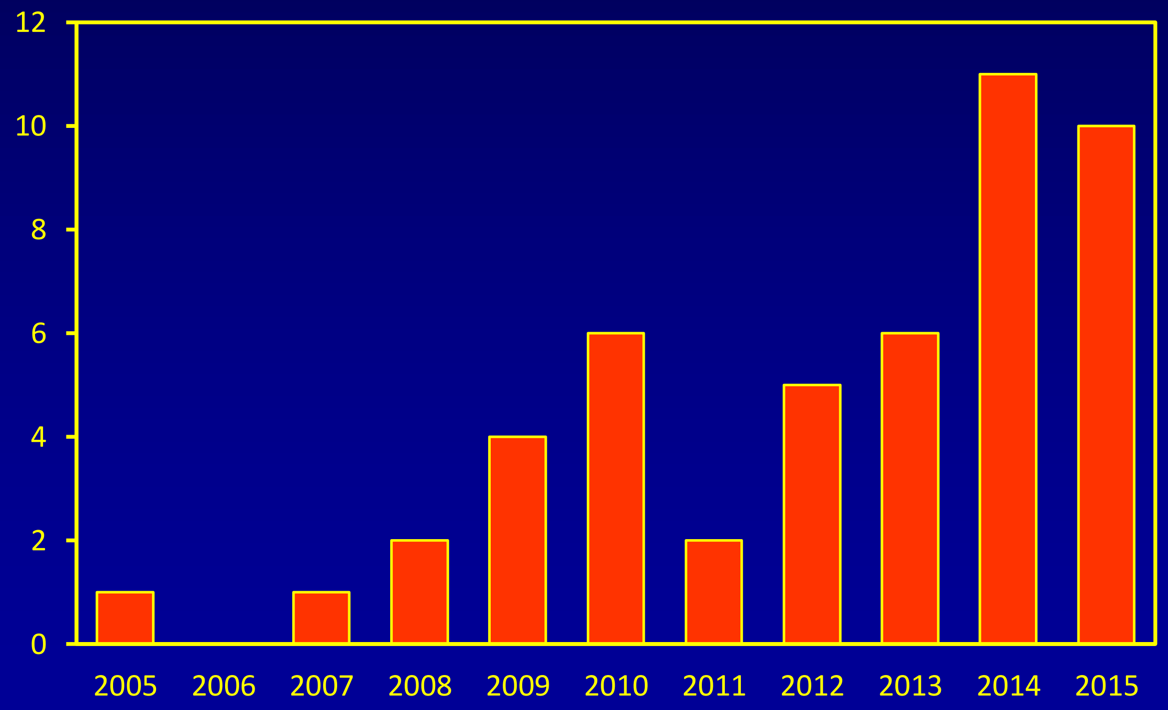
Participants perform one exercise session.

Long-term or chronic

Participants perform many exercise sessions over a prolonged time period.

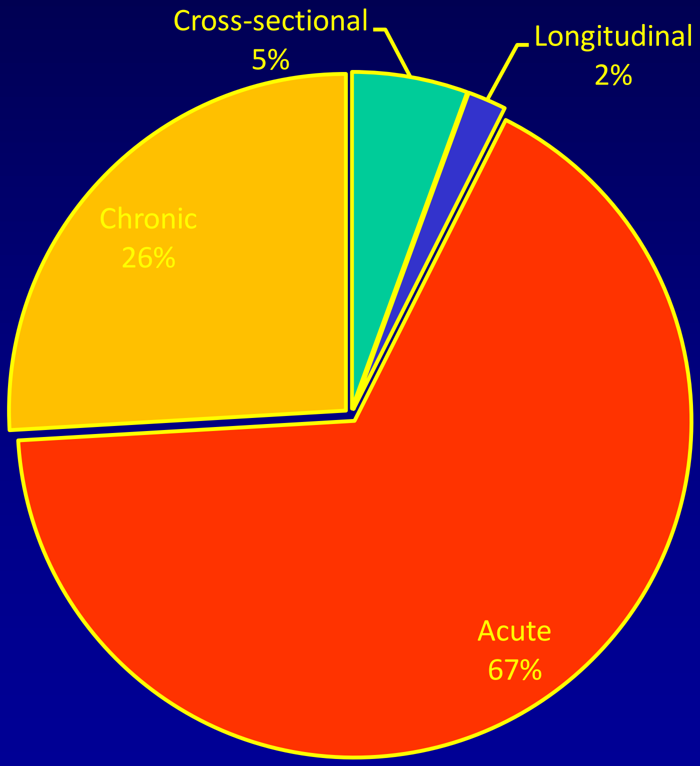
Exercise Metabonomics Studies

- 50 original studies since 2005



Geographical Distribution

Study Design



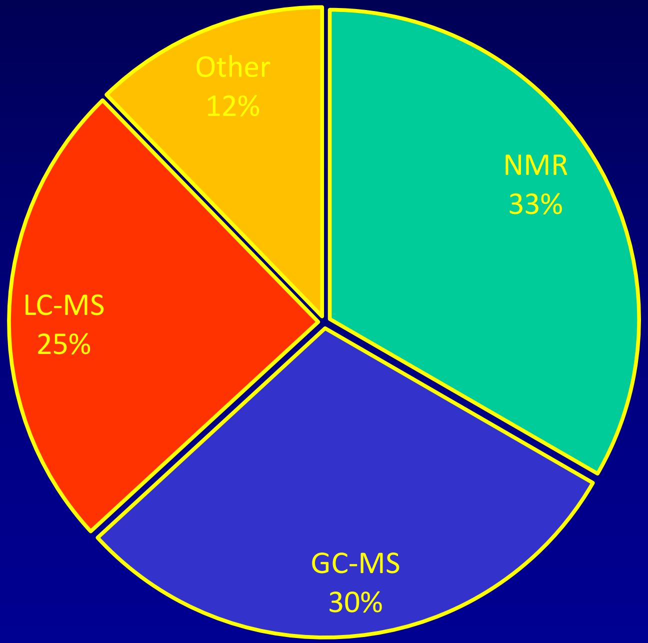
Species

- Human, 45
- Mouse, 2
- Rat, 2
- Horse, 1

Biological Matrix

- Blood, 37
- Urine, 14
- Muscle, 2
- Liver, 1
- Saliva, 1
- Exhaled air, 1

Analytical Techniques Used



Exercise Parameters

- Type (endurance, resistance, etc.)
- Intensity
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- Program (in intermittent exercise)
- Ambient temperature
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- Partial pressure of oxygen
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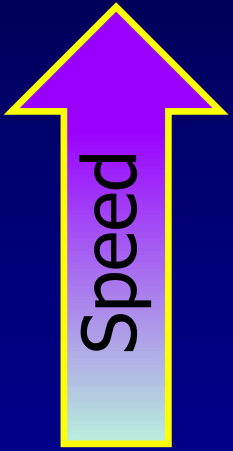
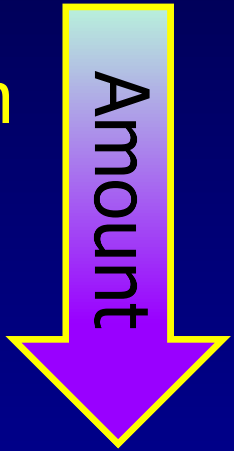
Energy Systems in Exercise

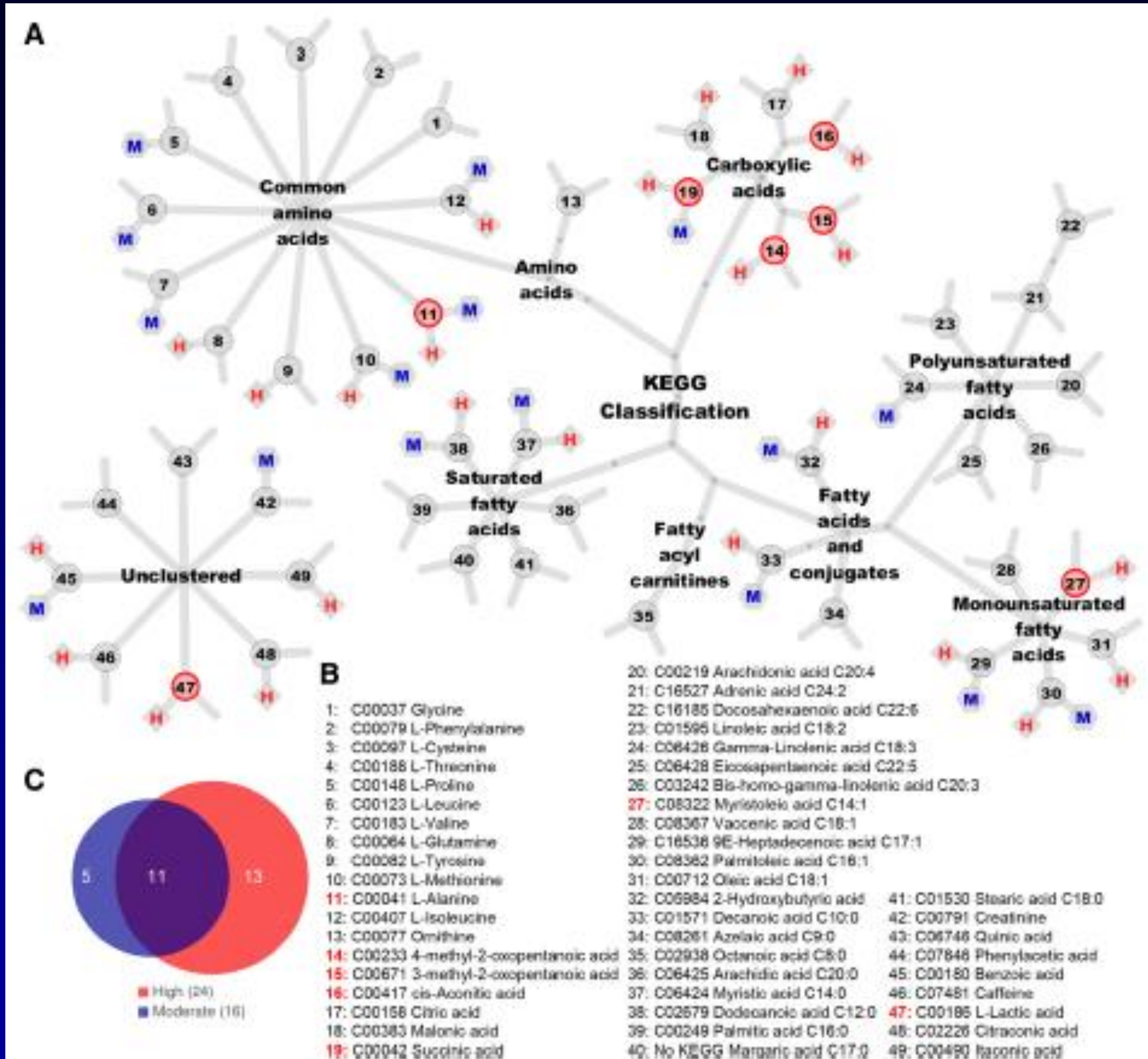


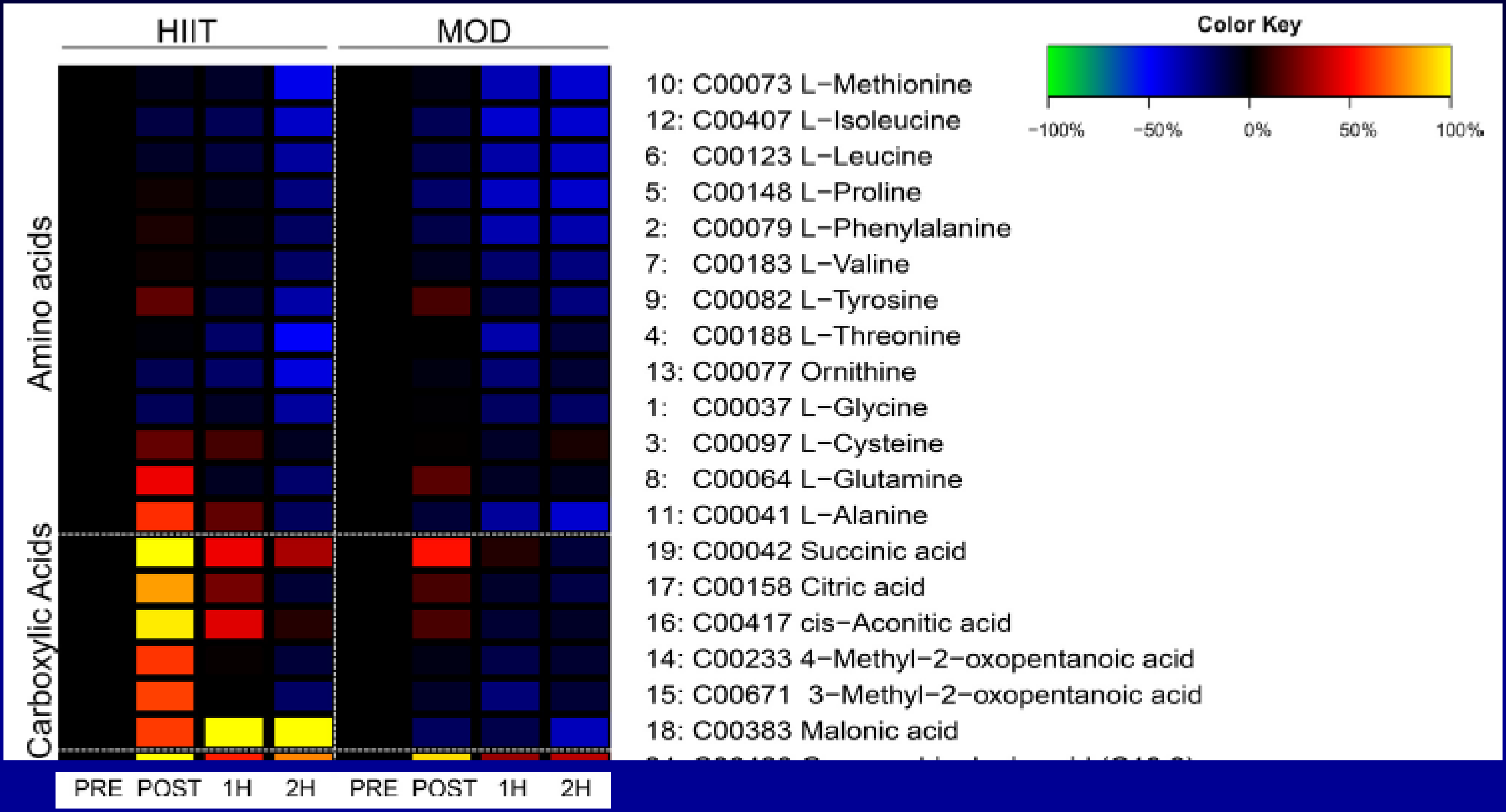
- The phosphocreatine system
- The lactate system
- The oxygen system



Peake et al., *Am J Physiol Endocrinol Metab* 307: E539, 2014

- Male athletes performed high-intensity interval exercise (HIIT) and continuous moderate-intensity exercise (MOD) of the same energy expenditure.
- Metabolites were measured in plasma, pre- and post-exercise, by GC-MS-based metabolomics.
- HIIT causes a greater metabolic perturbation.


A
Common amino acids
Amino acids
Carboxylic acids
KEGG Classification
Polyunsaturated fatty acids
Saturated fatty acids
Unclustered
Fatty acyl carnitines
Fatty acids and conjugates
Monounsaturated fatty acids
B
1: C00037 Glycine
2: C00079 L-Phenylalanine
3: C00097 L-Cysteine
4: C00188 L-Threonine
5: C00148 L-Proline
6: C00123 L-Leucine
7: C00183 L-Valine
8: C00064 L-Glutamine
9: C00082 L-Tyrosine
10: C00073 L-Methionine
11: C00041 L-Alanine
12: C00407 L-Isoleucine
13: C00077 Ornithine
14: C00233 4-methyl-2-oxopentanoic acid
15: C00671 3-methyl-2-oxopentanoic acid
16: C00417 cis-Aconitic acid
17: C00158 Citric acid
18: C00383 Malonic acid
19: C00042 Succinic acid
20: C00219 Arachidonic acid C20:4
21: C16527 Adrenic acid C24:2
22: C16185 Docosahexaenoic acid C22:6
23: C01595 Linoleic acid C18:2
24: C06426 Gamma-Linolenic acid C18:3
25: C06428 Eicosapentaenoic acid C22:5
26: C03242 Bis-homo-gamma-linolenic acid C20:3
27: C08322 Myristoleic acid C14:1
28: C08367 Vaccenic acid C18:1
29: C16536 9E-Heptadecenoic acid C17:1
30: C08362 Palmitoleic acid C16:1
31: C00712 Oleic acid C18:1
32: C05984 2-Hydroxybutyric acid
33: C01571 Decanoic acid C10:0
34: C08261 Azelaic acid C9:0
35: C02938 Octanoic acid C8:0
36: C06425 Arachidic acid C20:0
37: C06424 Myristic acid C14:0
38: C02679 Dodecanoic acid C12:0
39: C00249 Palmitic acid C16:0
40: No KEGG Margaric acid C17:0
41: C01530 Stearic acid C18:0
42: C00791 Creatinine
43: C06746 Quinic acid
44: C07846 Phenylacetic acid
45: C00180 Benzoic acid
46: C07481 Caffeine
47: C00186 L-Lactic acid
48: C02226 Citraconic acid
49: C00490 Itaconic acid
C
5
11
13
High (24)
Moderate (16)


HIIT
MOD
Color Key
-100%
-50%
0%
50%
100%
Amino acids
Carboxylic Acids
10: C00073 L−Methionine
12: C00407 L−Isoleucine
6: C00123 L−Leucine
5: C00148 L−Proline
2: C00079 L−Phenylalanine
7: C00183 L−Valine
9: C00082 L−Tyrosine
4: C00188 L−Threonine
13: C00077 Ornithine
1: C00037 L−Glycine
3: C00097 L−Cysteine
8: C00064 L−Glutamine
11: C00041 L−Alanine
19: C00042 Succinic acid
17: C00158 Citric acid
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14: C00233 4−Methyl−2−oxopentanoic acid
15: C00671 3−Methyl−2−oxopentanoic acid
18: C00383 Malonic acid
PRE POST 1H 2H PRE POST 1H 2H

Effect of Exercise Program on the Selection of Energy Sources

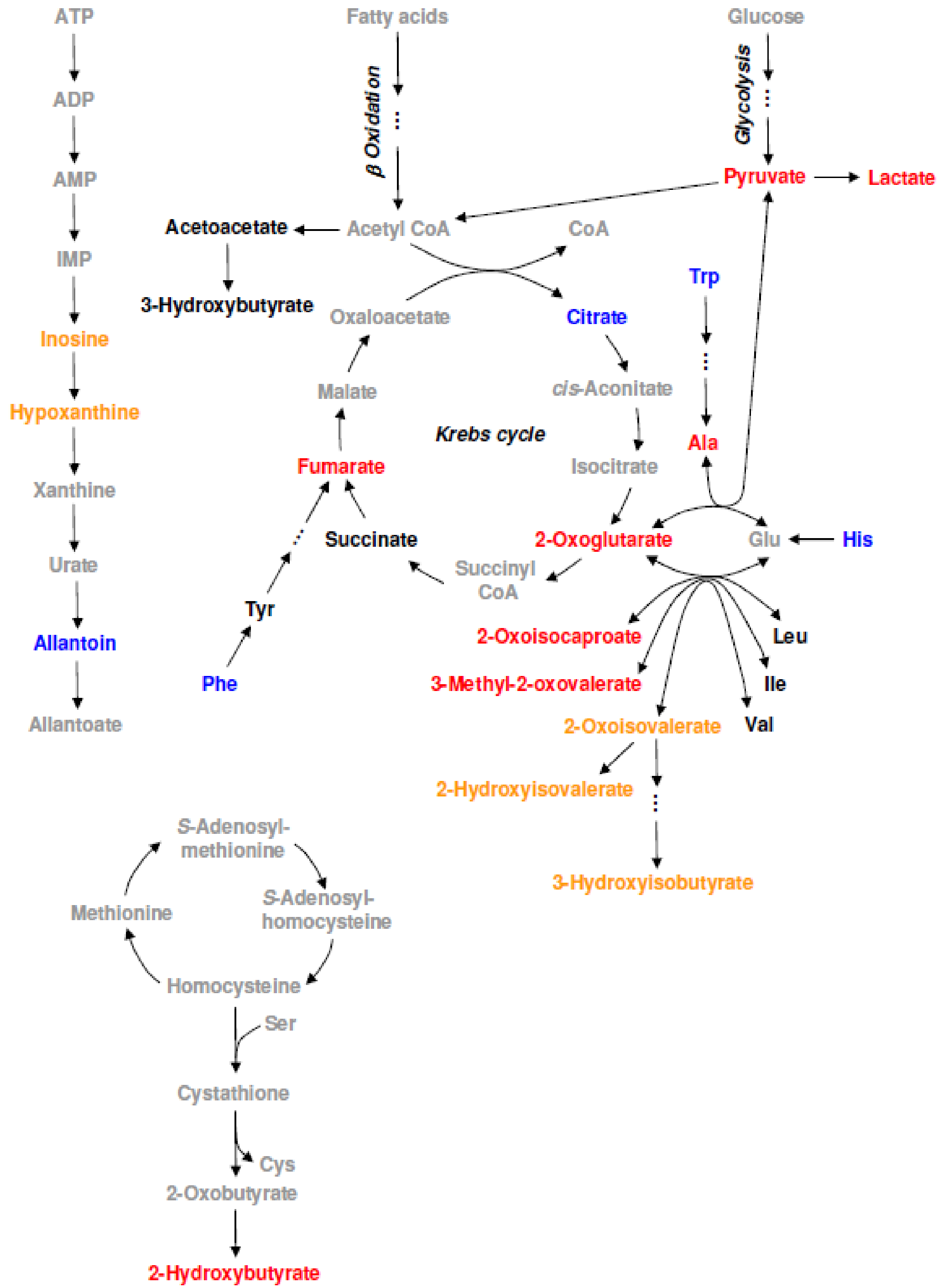
- When exercise is not performed at a steady pace, the duration and intensity of its different parts affect the selection of energy sources.
- In general, low-intensity or rest periods are used to replenish energy sources used during high-intensity periods.
- Duration of the former may affect the selection of energy sources in the latter.

Pechlivanis et al., *J Proteome Res* 9: 6405, 2010

- Young men performed three sets of two 80-m sprint runs separated by 20 min.
- The two runs in each set were separated by either 10 s (“short interval”) or 1 min (“long interval”).
- Metabolites were measured in urine pre- and post-exercise by ^{1}NMR-based metabolomics.

Findings

- The levels of 22 metabolites changed with exercise.
- The short interval resulted in higher levels of lactate, pyruvate, alanine, compounds of the Krebs cycle, and 2-oxoacids of branched-chain amino acids compared to the long interval.



ATP
ADP
AMP
IMP
Inosine
Hypoxanthine
Xanthine
Urate
Allantoin
Allantoate
Fatty acids
β Oxidation
Glucose
Glycolysis
Pyruvate
Lactate
Acetoacetate
Acetyl CoA
CoA
3-Hydroxybutyrate
Oxaloacetate
Citrate
Trp
Malate
cis-Aconitate
Krebs cycle
Ala
Fumarate
Isocitrate
Succinate
2-Oxoglutarate
Glu
His
Succinyl CoA
Tyr
2-Oxoisocaproate
Leu
3-Methyl-2-oxovalerate
Ile
Phe
2-Oxoisovalerate
Val
2-Hydroxyisovalerate
3-Hydroxyisobutyrate
S-Adenosyl-methionine
Methionine
S-Adenosyl-homocysteine
Homocysteine
Ser
Cystathione
Cys
2-Oxobutyrate
2-Hydroxybutyrate

Findings

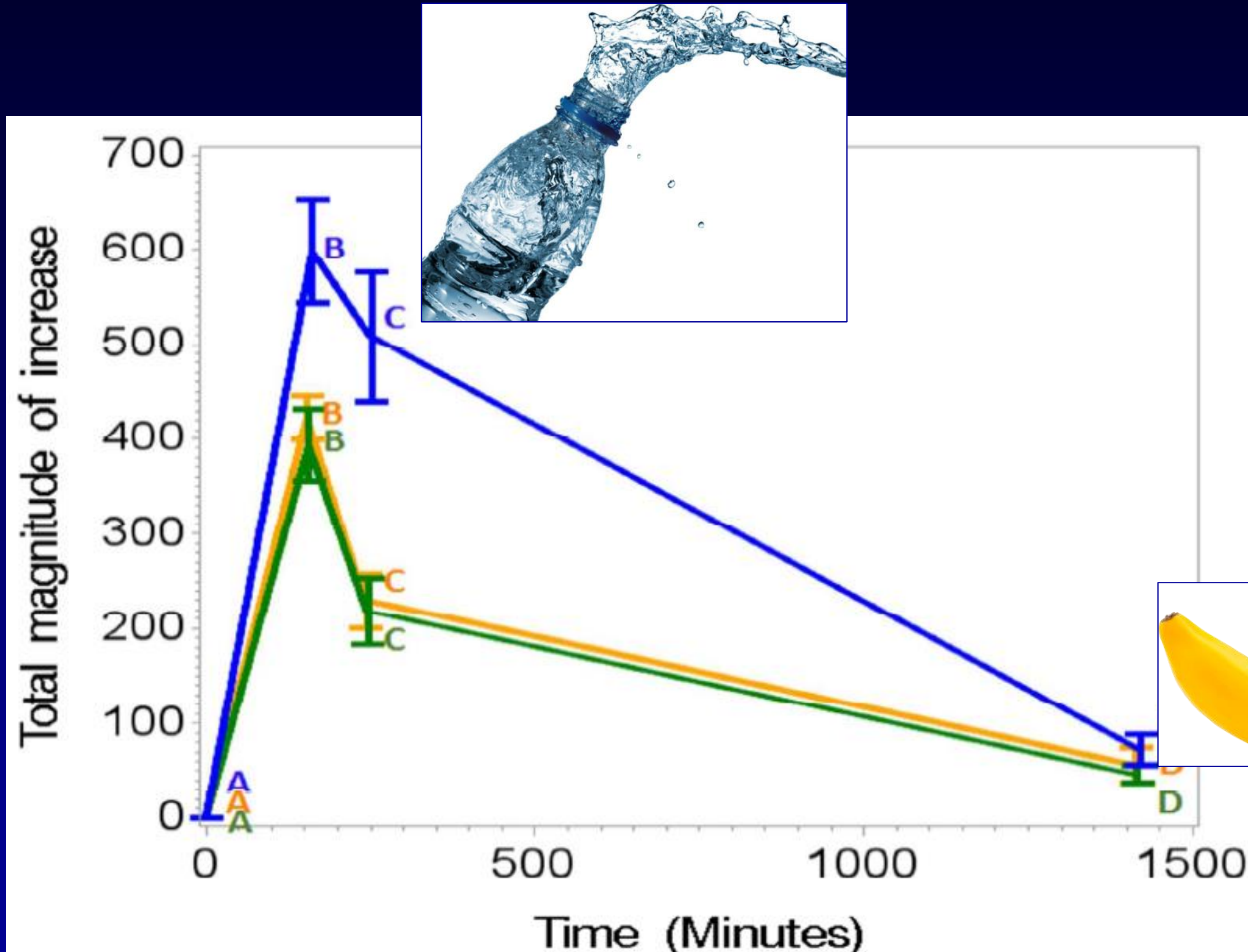
- Greater activation of glycolysis after the short *vs* long interval due to limited resynthesis of phosphocreatine.
- Greater metabolic perturbation with the short interval.
- Differentiation of the urinary metabolome not only by exercise but by the duration of the interval between repeated bouts.

Exerciser Characteristics

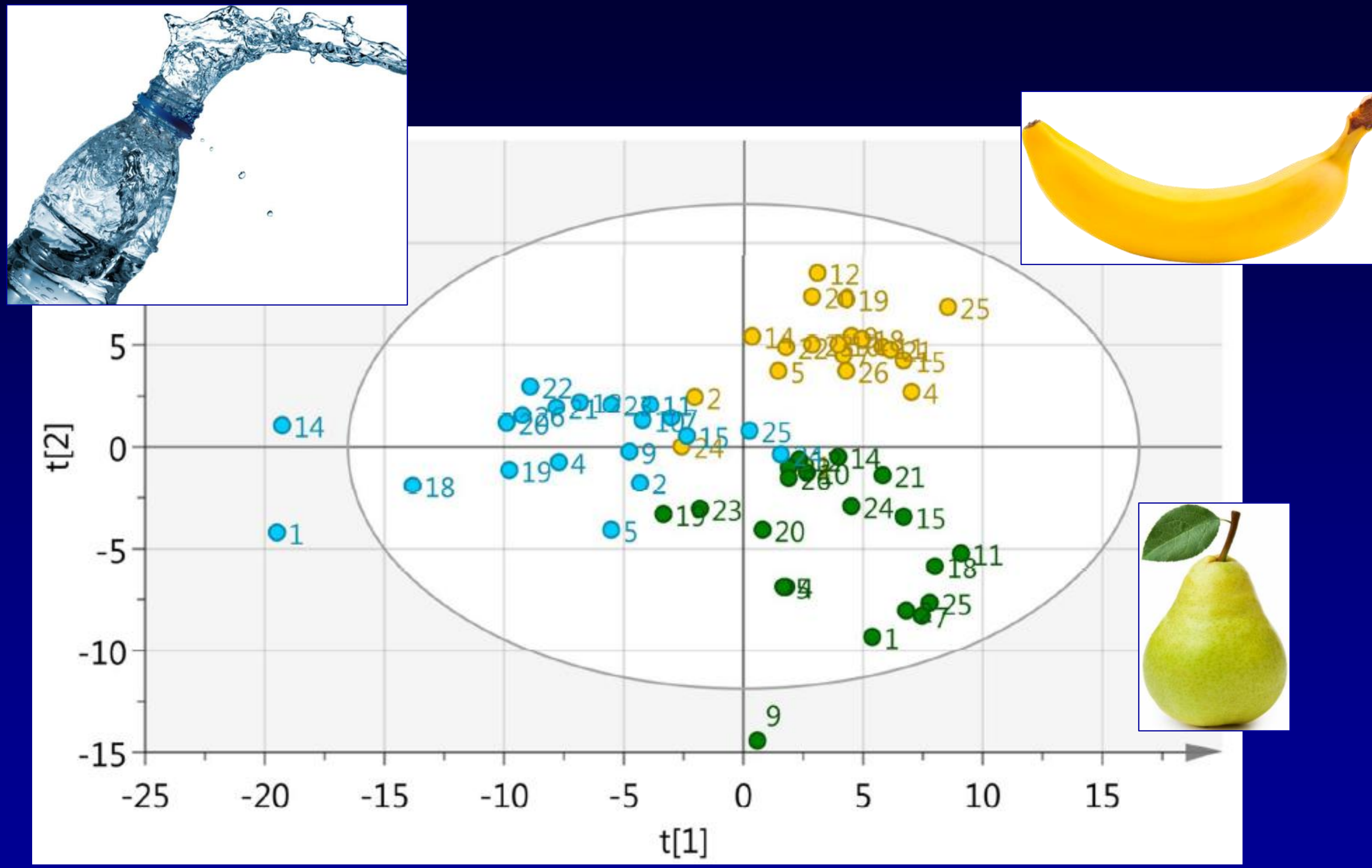
- Sex
- Age
- Dietary status (incl. supplementation)
- Training status
- Health status
- Medication
- Genetics

Nieman et al., *J Proteome Res* 14: 5367, 2015

- Male athletes cycled for 75 km while consuming water, bananas, or pears.
- Metabolites were measured in plasma pre-, immediately post-, 1.5 h post-, and 21 h post-exercise by UPLC-MS/MS-based metabolomics.
- 107 metabolites (primarily lipid-related) increased more than 2-fold during water consumption, with a $\simeq$ 50% reduction in magnitude during banana and pear recovery.



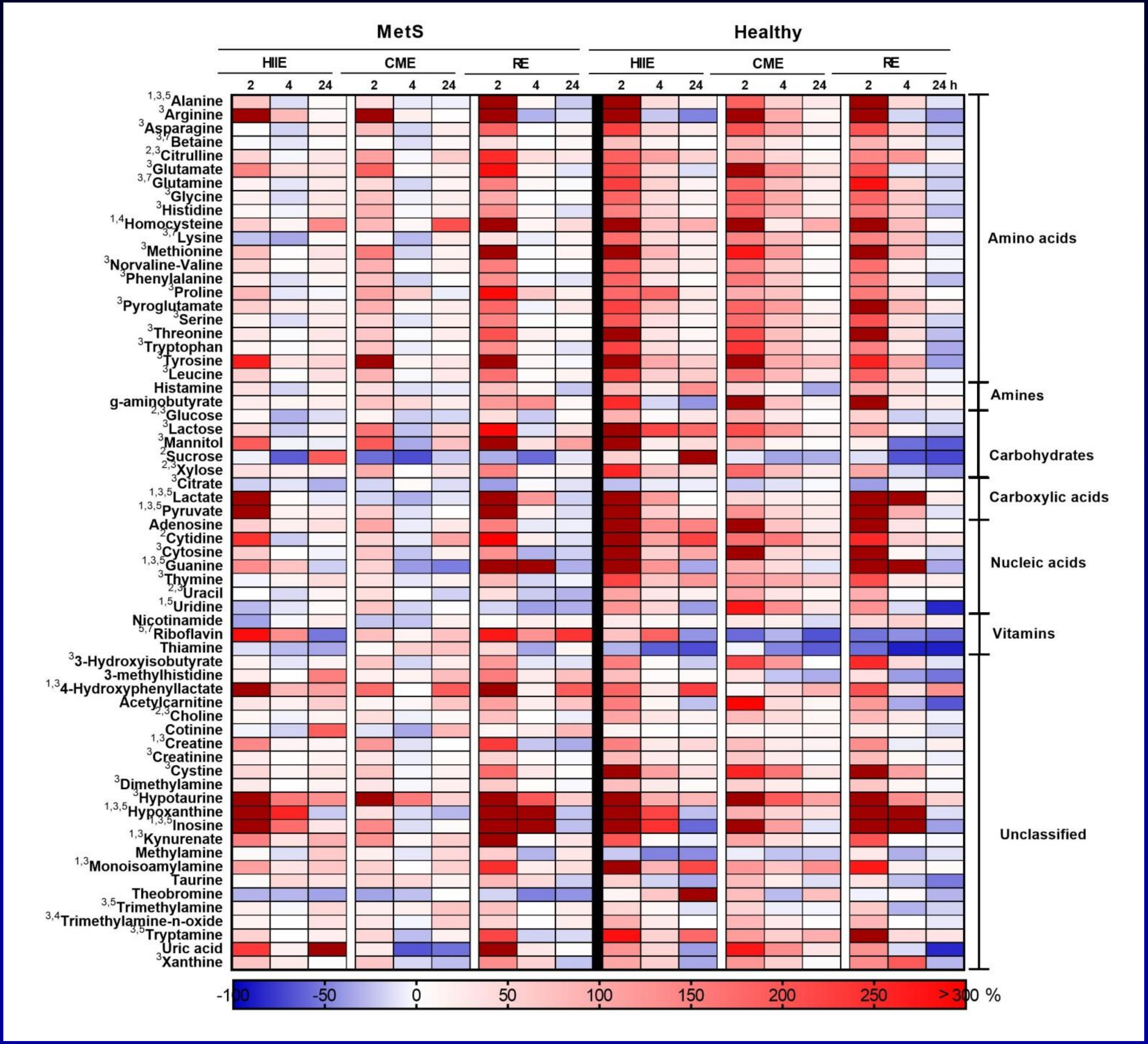
Sum of fold increase of metabolites that increased more than 2-fold post-exercise



PLS-DA score plots

Siopi et al., unpublished

- Middle-aged sedentary men with and without signs of the metabolic syndrome (MetS) performed resistance exercise (RE), high-intensity interval exercise (HIIE), and continuous moderate-intensity exercise (CME) in addition to a rest condition.
- Metabolites were measured in urine pre-exercise (0 h) and at 2, 4 and 24 h by UPLC-MS/MS-based metabolomics.


MetS
Healthy
HIIE
CME
RE
2
4
24
24 h
[1,3,5]Alanine
[3]Arginine
[3]Asparagine
[3,7]Betaine
[2,3]Citrulline
[3]Glutamate
[3,7]Glutamine
[3]Glycine
[3]Histidine
[1,4]Homocysteine
[3,7]Lysine
[3]Methionine
[3]Norvaline-Valine
[3]Phenylalanine
[3]Proline
[3]Pyroglutamate
[3]Serine
[3]Threonine
[3]Tryptophan
[3]Tyrosine
[3]Leucine
Histamine
g-aminobutyrate
[2,3]Glucose
[3]Lactose
[3]Mannitol
[2]Sucrose
[2,3]Xylose
[3]Citrate
[1,3,5]Lactate
[1,3,5]Pyruvate
Adenosine
[2]Cytidine
[3]Cytosine
[1,3,5]Guanine
[3]Thymine
[2,3]Uracil
[1,5]Uridine
Nicotinamide
[5,7]Riboflavin
Thiamine
[3]3-Hydroxyisobutyrate
3-methylhistidine
[1,3]4-Hydroxyphenyllactate
Acetylcarnitine
[2,3]Choline
Cotinine
[1,3]Creatine
[3]Creatinine
[3]Cystine
[3]Dimethylamine
[3]Hypotaurine
[1,3,5]Hypoxanthine
[1,3,5]Inosine
[1,3]Kynurenate
Methylamine
[1,3]Monoisoamylamine
Taurine
Theobromine
[3,5]Trimethylamine
[3,4]Trimethylamine-n-oxide
[3,5]Tryptamine
Uric acid
[3]Xanthine
Amino acids
Amines
Carbohydrates
Carboxylic acids
Nucleic acids
Vitamins
Unclassified
-100
-50
0
50
100
150
200
250
>300 %

Conclusions

- Exercise metabonomics affords a holistic view of the effect of exercise on animal (including human) metabolism.
- Small differences in exercise parameters or exerciser characteristics can cause measurable differences in the metabolic fingerprint.
- Unexpected effects and candidate biomarkers are discovered, calling for further investigation.

Conclusions (cont'd)

- Exercise metabonomics can be used to locate metabolic disorders of clinical interest.
- Exercise metabonomics may be added to the diagnostic arsenal and identify new targets for therapeutic intervention.