

1 **“Nutraceuticals” in relation to human skeletal muscle and exercise**

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11 Running Title: Nutrients, muscle and exercise

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23 **Abstract**

24 Skeletal muscles have a fundamental role in locomotion and whole body metabolism,
25 with muscle mass and quality being linked to improved health and even lifespan.
26 Optimising nutrition in combination with exercise is considered an established,
27 effective ergogenic practice for athletic performance. Importantly, exercise and
28 nutritional approaches also remain arguably the most effective countermeasure for
29 muscle dysfunction associated with ageing and numerous clinical conditions e.g.
30 cancer cachexia, COPD and organ failure, via engendering favourable adaptations
31 such as increased muscle mass and oxidative capacity. Therefore, it is important to
32 consider the effects of established and novel effectors of muscle mass, function and
33 metabolism in relation to nutrition and exercise. To address this gap, in this review we
34 detail existing evidence surrounding the efficacy of a non-exhaustive list of
35 macronutrient, micronutrient and “nutraceutical” compounds alone and in
36 combination with exercise in relation to skeletal muscle mass, (protein and fuel)
37 metabolism and exercise performance (i.e. strength and endurance capacity). It is long
38 established that macronutrients have specific roles and impacts upon protein
39 metabolism and exercise performance i.e. protein positively influences muscle muscle
40 mass and protein metabolism, whilst carbohydrate and fat intakes can influence fuel
41 metabolism and exercise performance. Regarding novel nutraceuticals, we show the
42 following ones in particular may have effects in relation to: 1) muscle mass/protein
43 metabolism: leucine, hydroxyl β -methylbutyrate, creatine, vitamin-D, ursolic acid and
44 phosphatidic acid, and 2) exercise performance: (i.e. strength or endurance capacity);
45 hydroxyl β -methylbutyrate, carnitine, creatine, nitrates and β -alanine.

46 **Key words: nutrients, metabolism, exercise, skeletal muscle, nutraceuticals**

47

48 **Introduction**

49 Skeletal muscle represents the largest organ in the body, comprising ~40% of whole
50 body mass (123). The functions of skeletal muscle extend beyond the widely
51 recognized role of locomotion, serving as the bodies' largest tissue for glucose storage
52 and utilization (101, 121) and a primary site of lipid metabolism (104). Muscle also
53 stores ~40% of total body amino acids (AA), that can act as a source of fuel and an
54 AA substrate for other tissues in times of illness or fasting via release of glucogenic,
55 ketogenic AA (264). Changes in muscle mass are regulated by dynamic turnover of
56 the muscle protein pool (~1-1.5 %/day) with skeletal muscle mass remaining constant
57 when muscle protein synthesis (MPS) and muscle protein breakdown (MPB) are in
58 balance (8). During situations of muscle growth, (e.g. resistance exercise training
59 (RET) combined with AA substrate), net MPS exceeds MPB (8). Conversely, net
60 MPB is greater than MPS in conditions of muscle loss (e.g. bed rest, cachexia and
61 sarcopenia (75)); in humans such wasting conditions are typically predominantly due
62 to reduced MPS under fasted and/or fed conditions (191)). In addition to the
63 regulation of muscle and function being clinically relevant, optimal strategies to
64 promote growth, maintenance of muscle mass and exercise performance (i.e. strength
65 and endurance capacity) are of great interest to performance scientists. Therefore, a
66 major area of interest surrounds the role of macronutrients, micronutrients and
67 nutraceuticals that influence muscle metabolism and function.

68

69 The consumption of nutritional supplements with “ergogenic” claims occurs in many
70 populations including athletes (186), the elderly (24), chronic disease sufferers (78)
71 and sedentary (201) adults, often without sound empirical evidence. As such there is a
72 need to review the continually growing area of nutrients/ nutraceuticals and associated

73 mechanisms on aspects of skeletal muscle health, in order to formulate evidenced-
74 based recommendations. Indeed, previous reviews have summarized the effects of
75 multiple nutrient/nutraceutical compounds on aspects of skeletal muscle metabolism
76 and exercise performance (53, 171). Often such reviews target a specific population
77 (e.g. athletes), endpoint (i.e. aerobic performance), or dosing regime (e.g. timing and
78 amount). As such, the present review adopts a more wide-ranging scope, including
79 data irrespective of age, training status, or other independent variables, in order to
80 highlight universal skeletal muscle effects of each nutritional compound.

81

82 Herein, we detail existing evidence for a non-exhaustive list of established and
83 emerging nutrients in relation to some or all of the following endpoints: 1) muscle
84 mass; 2) metabolism (protein and fuel) and, 3) exercise performance (i.e. strength and
85 endurance capacity). Since nutrition and exercise are the two key modifiable lifestyle
86 factors for maintaining muscle health, this review will critique available literature
87 examining the muscular responses to nutrient supplementation alone, nutrient
88 supplementation plus acute exercise and chronic nutrient supplementation combined
89 with chronic exercise training (i.e. more than one bout of exercise). We shall include
90 responses to both resistance exercise (RE)/RET and endurance exercise/endurance
91 exercise training (EE/EET) since exercise mode may differentially influence muscular
92 responses to nutrition. Lastly, due to the emerging nature of some nutrients, where
93 mechanisms have not been well defined in humans, data from other models (e.g.
94 cell/rodents) have been drawn upon where necessary. Therefore, this review should be
95 of interest to scientists, clinicians, and athletes aiming to optimize muscle mass and
96 function in clinical and athletic populations. Out of the scope of this review are a
97 selection of established nutrients with purported effects on muscle (e.g. caffeine and

98 green tea) due to the large volume of existing review literature available.
99 Furthermore, some emerging nutrients (e.g. tomatidine and minerals) have been
100 omitted from this review due to the paucity of existing literature. We therefore direct
101 readers to the following publications for further reading regarding nutrients not
102 discussed herein (53), in particular; caffeine (96), green tea (114), tomatidine (69) and
103 minerals (209). Since we have not performed a systematic analysis, we apologize to
104 those whose work we have not alluded to.

105

106 **Definitions of macro/micronutrients and “nutraceuticals”**

107 From the outset it is important that we define what is meant when we refer to
108 macronutrients, micronutrients and nutraceuticals, since the classification can be
109 misinterpreted due to obscure classification boundaries. Proteins, fats and
110 carbohydrate (CHO) are required by the body in large amounts (i.e. g/kg/day), and are
111 therefore termed macronutrients (139). Micronutrients are defined as vitamins and
112 trace elements (minerals) (212, 213) essential to our diet, albeit in small amounts (i.e.
113 mg/kg/day), to maintain normal physiological and metabolic function. Nutraceuticals
114 is an emerging term within the scientific literature, which has not been well defined.
115 A recent review defined a nutraceutical as a nutrient compound “with added extra
116 health benefits” (i.e. in addition to the basic nutritional value contained in foods)
117 (210). For the purpose of this review we define a nutraceutical as: “a compound that
118 alone or in tandem with exercise, impacts major physiological end-point(s)” e.g.
119 effectors of whole body metabolism, skeletal muscle mass and/or whole body/muscle
120 function.

121

122 **Established macronutrients and exercise**

123 Providing a mixed macronutrient feed containing protein, CHO and fat stimulates
124 MPS (200). The absolute stimulation of MPS is highly dependent on the AA content,
125 with the provision of AA alone being sufficient to maximally stimulate MPS (15); this
126 effect is entirely attributable to the essential AA (EAA) (218). Of the EAA, the
127 branched chain AA (BCAA) provide the most potent anabolic stimulation (9),
128 particularly leucine (9, 256). This stimulation of MPS by AA is highly dose
129 dependent and saturable, with maximal stimulation provided by between 20-40g of
130 high quality protein (166, 167, 230, 263)) or 10-20g of EAA (58). Furthermore, this
131 MPS stimulation is finite, where following an initial lag-period of ~30 minutes during
132 I.V infusion (or ~45-60 minutes following oral ingestion – to allow for the digestion,
133 absorption and transport of AA into the systemic circulation), the rate of MPS is
134 increased ~2-3-fold reaching a maximum by 1.5-3h. Subsequently rates of MPS
135 return to baseline (~2-3h post ingestion) despite continued plasma and muscle AA
136 availability and elevated anabolic signaling (7). Thereafter, muscle remains refractory
137 to further stimulation for an as yet undefined period; a phenomenon coined “muscle
138 full” (7). This ~2-3h period of MPS stimulation can be extended depending on the
139 type and dose of AA and macronutrient co-ingestion in combination with RE (51).
140 The timing of protein ingestion in close proximity to the performance of acute RE,
141 which when performed alone stimulates MPS for ~48h (190), is thought to be
142 important. This is because there is an enhanced sensitivity of the muscle to the
143 anabolic properties of AA for at least 24h post-exercise (36), synergistically
144 impacting MPS. However, protein ingestion before (236), during (14), 1h or 3h (199)
145 after RE have all elicited similar post-exercise increases in MPS.
146

147 The mechanisms underlying the anabolic effects to nutrition involve both the
148 stimulation of MPS (200) and suppression of MPB (255); however, it is generally
149 accepted that increases in MPS is the primary driver (8). Following transportation into
150 the muscle cell, leucine in particular stimulates mammalian target of rapamycin
151 complex-1 (mTORC1) (9), which is considered a key regulator of cell growth.
152 mTORC1 activation leads to the phosphorylation of the downstream translation
153 initiation factors 4E-binding protein (4EBP1) and 70-kDa ribosomal protein S6 kinase
154 1 (p70S6K1) (see Figure 1), stimulating the binding of eukaryotic initiation factor 4A
155 (eIF4A) and 4E (eIF4E) to 4G (eIF4G) to form the 4F (eIF4F) complex (135). The
156 eIF4F complex promotes the assembly of the 48S preinitiation complex, via
157 mediating the binding of mRNA to the 43S preinitiation complex, thereby promoting
158 MPS (135). Currently the AA sensor coupling intracellular AA signaling to mTORC1
159 remains to be fully defined, although Rag GTPases (207), leucyl-tRNA synthetase
160 (105) and sestrin2 (265) are all proposed candidates. This has led to intense interest
161 into the development of novel leucine enriched supplementation regimes to aid
162 maintenance of muscle mass (44, 249). Unlike dietary protein, neither fats nor CHO
163 lead to a direct stimulation of MPS (91, 95, 138); nonetheless, they can influence the
164 bioavailability of AA when provided as part of a mixed meal - slowing plasma AA
165 appearance and increasing AA retention (84) without blunting muscle anabolism (95).
166 Finally, CHO (as well as AA (172, 173)) are insulin secretagogues, positively
167 impacting net muscle anabolism via inhibition of MPB (255) (rather than stimulation
168 of MPS (102, 255)).
169
170 Exercise combined with feeding extends the stimulation of MPS (59) thereby
171 delaying the “muscle full” set-point (8). It is the cumulative stimulation of muscle

172 protein turnover with repeated bouts of exercise and feeding that drives exercise-
173 induced skeletal muscle remodeling and hypertrophy (29). The impact of
174 macronutrient supplements on exercise adaptation is multifarious. It is established that
175 CHO intake helps to spare muscle and liver glycogen stores, whilst also leading to a
176 more rapid recovery of these stores post exercise (47, 162). The benefits of chronic
177 protein supplementation alongside exercise are more inconsistent, with a number of
178 studies showing positive (120, 134, 259) or negligible findings (149, 198, 242).
179 However, a recent meta-analysis suggested that overall, protein supplementation does
180 lead to an augmentation of muscle mass and strength gains during chronic RET (49).
181 To conclude, it is now well established that macronutrients play key roles in
182 promoting muscle mass maintenance/ growth and functional adaptations. Future work
183 should focus on identifying the underlying cellular mechanisms and associated
184 refractory period of “muscle-full”.

185

186 **Emerging nutraceuticals and exercise**

187

188 *Leucine metabolites*

189 Leucine, as a BCAA can be metabolized within muscle, engendering the possibility
190 that its metabolites harbor anabolic effects. For instance, the keto-acid derivative of
191 leucine metabolism, alpha-ketoisocaproate (KIC), was shown to stimulate MPS when
192 provided by infusion; however this effect could simply be due to KIC being reversibly
193 transaminated to leucine (74). There is however, good evidence of anabolic activities
194 of the more distal leucine metabolite, β -hydroxy- β -methylbutyrate (HMB) produced
195 via cytosolic KIC dioxygenase (174). Ingestion of ~3g HMB in humans elicited
196 comparable increases in MPS to 3g of leucine, whilst also suppressing MPB

197 independently of insulin (256). Similarly to leucine, the stimulation of MPS by HMB
198 is attributable to enhanced mTORC1 signaling (256). In order to understand the
199 insulin-independent suppression of MPB associated with HMB, numerous molecular
200 targets associated with different proteolytic pathways (beclin 1, calpain 1, MuRF1,
201 Mafbx and cathepsin L) have been investigated, although no detectable changes in the
202 protein abundance or post-translational modifications were observed (256). Although
203 it has been previously shown that there is a disparity between protein breakdown and
204 the abundance in proteolytic proteins (102). It should be noted that only small
205 amounts of HMB (~5%) are generated from normal leucine metabolism (137)
206 meaning that in order to obtain 3g of HMB (a commonly supplemented amount) one
207 would have to consume 60g leucine (260). Thus, when supplementing with
208 physiological doses of leucine it is unlikely that HMB is the main anabolic
209 constituent, hence the practical use of HMB as a stand alone nutritional supplement.

210

211 Indeed, longer term studies have found that HMB preserved muscle mass during
212 periods of disuse (65), while year long supplementation of HMB (plus arginine and
213 lysine) in the elderly led to improved preservation of lean body mass, possibly due to
214 an augmentation in muscle protein turnover (10). Although, since HMB was
215 administered as part of a nutritional cocktail it is impossible to delineate whether
216 HMB was solely responsible for the effects on lean body mass. However, recent
217 meta-analysis of 287 elderly participants (147 HMB-supplemented and 140 controls)
218 found HMB supplementation led to greater gains in muscle mass compared to
219 controls, indicating HMB is an effective ergogenic aid, at least in the elderly
220 population, for preventing the loss of lean body mass (268). These anabolic properties
221 of HMB have also been suggested to facilitate favorable RET adaptations. For

222 example, supplementation of HMB (3g/day) with RET for between 4 and 7 weeks led
223 to heightened increases in muscle strength (181), lean body mass (261) and fat free
224 mass (174) compared with RET alone. However, not all studies have reported positive
225 effects; for instance RET for 1 month combined with between 3 to 6g/day of HMB
226 did not change parameters of body composition in RE trained males (140). In this
227 latter case, HMB was provided in its calcium form (CaHMB) (140), which compared
228 to the free acid form (FA-HMB), may have lower bioavailability and therefore might
229 not enhance anabolism to the same extent (82) (though this premise remains to be
230 tested).

231

232 Another ergogenic effect of HMB is the purported ability to attenuate exercise-
233 induced muscle damage (EIMD). For example, oral HMB supplementation (3g/day
234 for 6 weeks) in EE athletes attenuated the increase in creatine phosphokinase and
235 lactate dehydrogenase (plasma markers of EIMD) after a 20 km time trial run
236 compared to placebo (136). This protective effect of HMB may be due to HMB being
237 a precursor of *de novo* cholesterol synthesis (175), which is critical for cell membrane
238 (sarcolemmal) maintenance. Thus, HMB may maintain muscle membrane integrity
239 during bouts of damaging exercise.

240

241 Furthermore, HMB has been shown to be efficacious for improving EE performance.
242 For example, Vukovich et al. (2001) reported that HMB in combination with EE
243 prolonged the time to reach the onset of blood lactate accumulation and VO_{2PEAK} ,
244 although via an unknown mechanism (246). Others have investigated markers of
245 endurance performance following high intensity interval training (HIIT) with or
246 without HMB supplementation. To exemplify, following 5 weeks of HIIT-based

247 running in combination with 3g/d ca-HMB, VO_{2MAX} improved more compared to
248 placebo (144). The authors speculated that the performance benefits were attributable
249 to the preservation of the cell-membrane, however membrane stability was not
250 measured in the study and thus no mechanistic conclusions can be drawn.
251 Furthermore, HMB in untrained participants potentiated the effects of HIIT on
252 physical working capacity at the onset of neuromuscular fatigue, compared to HIIT
253 training alone (163).

254

255 In summary, the literature supports a role for HMB supplementation in promoting: 1)
256 muscle mass, demonstrated by the preservation or increase in muscle mass when
257 combined with RET, 2) muscle metabolism, since HMB stimulates MPS and inhibits
258 MPB, and 3) aerobic and strength performance. However, data reporting negligible
259 effects of HMB does exist (140, 214); prior exercise training history and/or being
260 accustomed to an exercise stimulus may determine the effectiveness of the
261 intervention. This is supported by evidence that HMB supplementation combined
262 with RET in trained individuals had no effect on muscle strength or lean body mass
263 versus placebo (214). Further research is warranted which rigorously investigates: 1)
264 the mechanisms regulating the insulin-independent suppression of MPB associated
265 with HMB supplementation, 2) the effects of novel and accustomed exercise in
266 combination with HMB on endurance performance, and 3) the effects of EET and
267 HMB on muscle mass.

268

269 *Creatine*

270 Creatine (Cr) is an endogenously formed metabolite synthesised from arginine,
271 glycine and methionine (20). Found almost exclusively in skeletal muscle, Cr levels

272 can be increased via endogenous synthesis in the liver and pancreas or exogenously
273 from foodstuff, particularly meat and fish (43, 99). Following oral consumption of Cr,
274 Cr is absorbed into the systemic circulation and is taken up by skeletal muscle via the
275 sarcolemal Na^+/Cl^- -dependent transporter, soluble carrier family 6 member 8
276 (SLC6A8) (126). Intramuscular Cr can then be phosphorylated to phosphocreatine in
277 a reversible reaction facilitated by the enzyme, creatine kinase. During high energy
278 demands, the phosphate of phosphocreatine plus free ADP is used for ATP synthesis
279 (126). Another fate of intramuscular Cr is the conversion to the end-product
280 creatinine, which due to its muscle exclusivity correlates with muscle mass (110).
281 Creatinine diffuses out of the muscle cell and is removed from the body via urine
282 (126). Oral Cr administration (20-30g/day for 2 or more days) increases total muscle
283 Cr stores by >20%, of which 20-30% is stored in the form of phosphocreatine (PCr)
284 (107). The greatest Cr loading effects are seen in those with the lowest basal Cr pool
285 levels i.e. vegetarians (99), thus basal muscle Cr levels are an important determinant
286 of Cr uptake (43, 107). The ergogenic effects of Cr are facilitated by elevated resting
287 PCr, which sustains PCr-mediated ATP resynthesis during intense anaerobic exercise
288 (42) primarily in fatigue susceptible type II fibers (43), thus improving acute high
289 intensity performance. Increased basal muscle PCr levels also expedite the
290 replenishment of PCr stores during recovery from intense exercise, leading to
291 improved performance over repeated bouts of sprint exercise (43, 99). For example,
292 20g/day of Cr for 5 days led to sustained isokinetic torque compared to placebo
293 during repeated bouts of maximal voluntary contractions (100). Similar results have
294 been obtained when employing different exercise modes such as cycling (18, 70). In
295 contrast, some studies have shown no effect of Cr supplementation on exercise
296 performance (55, 170, 219, 234). For example, despite increased total muscle Cr

297 following 5 days 30g Cr (and 30g dextrose) supplementation, there were no
298 improvements in sprint exercise performance (219). A lack of ergogenic effect may
299 be attributable to the small total muscle Cr levels of ~12mmol/kg/dry weight (219),
300 where previous reports show total Cr of >20 mmol/kg dry mass results in ergogenic
301 benefit (42). Factors affecting the extent to which muscle Cr stores increase are not
302 well known, although pre-existing muscle Cr, exercise (107) and CHO ingestion (98)
303 may be potential factors. Also in regards to performance, Cr supplementation
304 improves the rate of functional recovery following exercise (54), which might be
305 mediated by Cr promoting gene expression thereby aiding MPS during the recovery
306 periods (54, 258), ultimately increasing the deposition of newer functional proteins
307 for improved functional recovery. Indeed, Cr supplementation will also increase
308 muscle PCr, which might increase local rephosphorylation from ADP to ATP (54),
309 thus providing more energy for contraction. As such, performance during successive
310 bouts is maximized (i.e. can work at higher training loads) which, in-turn, may
311 contribute to the gains in strength observed when combined with RET (31, 63, 66).

312

313 In addition to energetic impacts, evidence supports a role for chronic Cr
314 supplementation, typically provided as a loading dose (i.e. ~5 days of 20/30g)
315 followed by maintenance doses (~ 5g) (32), for increasing muscle mass (25, 31, 245).
316 For example 12 weeks RET plus Cr (25g/day for the first week, followed by a
317 maintenance dose of 5g/day for the rest of the training duration) resulted in
318 significantly greater fat free mass, strength and fibre cross sectional area gains
319 compared to placebo (245). Similarly, 14 weeks of whole body RET (3 x/week)
320 combined with Cr (5g/day plus 2g dextrose) led to significantly greater gains in fat
321 free mass (31). Furthermore, a recent meta-analysis concluded that Cr

322 supplementation combined with RET elicited further increases in fat free mass
323 compared to RET alone (albeit in older adults) (66). This meta-analysis reported a
324 weighted mean difference (WMD) of 1.33kg for RET combined with Cr (66),
325 compared to 0.69kg for RET with protein (49) demonstrating the potent ergogenic
326 effect of Cr on fat free mass. The mechanisms regulating the effects of Cr on muscle
327 mass remain to be fully elucidated; although it is known that acute provision of Cr
328 does not directly stimulate MPS either with (152) or without RE (153). However, Cr
329 did augment the satellite cell (SC) response following RE (178), which may
330 contribute to hypertrophic gains since increased SC content is observed following
331 chronic RET (241). Although the contribution of SC to hypertrophy is still debated
332 (158), theoretically the nucleus content in hypertrophying muscle fibres becomes
333 diluted such that additional nuclei are required for continued growth. As such, SC
334 fuse and donate nuclei to the pre-existing muscle fibres, thereby increasing the
335 transcriptional capacity of the muscle cell and thus the potential for growth (30).
336 Additionally, augmented PCr availability and ATP resynthesis during intense exercise
337 likely permits greater work output. Greater work may be a factor which stimulates
338 greater muscle gene expression thereby promoting muscle mass accretion observed
339 with Cr supplementation (32, 204, 257). It is possible that changes in fat free mass
340 may be in part attributable to the osmotic potential of elevated intracellular Cr leading
341 to myocellular water retention (204, 273). This potential increase in cell volume from
342 Cr-induced fluid retention may then act as an anabolic signal, activating intracellular
343 signalling cascades that maintain cellular function (204). For example, the attachment
344 complex protein focal adhesion kinase (FAK), which is critical for osmosensing and
345 hypertrophic signalling (56), is up-regulated following Cr supplementation (204).

346

347 To summarize, Cr supplementation is capable of increasing total muscle Cr stores
348 which improves performance via maintaining PCr mediated ATP re-synthesis,
349 although not all studies have shown improved exercise performance. Beyond
350 performance, chronic Cr supplementation combined with RET is capable of
351 stimulating muscle mass accretion. Although, acute affects of Cr supplementation on
352 MPS are not shown, potentiating RET capacity and enhanced recovery likely mediate
353 increased muscle mass. Further studies are needed to firmly establish factors which
354 determine the variability of Cr storage in muscle, since this could have implications
355 for optimizing the dosing regime of Cr.

356

357 *Carnitine*

358 Carnitine is synthesized endogenously from AA precursors and can also be obtained
359 exogenously from the diet, particularly red meat, with the majority of whole body
360 carnitine (95%) being stored in skeletal muscles (26). Carnitine has well documented
361 roles in regulating the translocation of long-chain fatty acids into the mitochondrial
362 matrix for subsequent β -oxidation (223). This process is regulated via the
363 mitochondrial enzyme carnitine palmitoyltransferase 1 (CPT1) catalysing the
364 esterification of carnitine with long-chain acyl-coA (223). The long chain
365 acylcarnitine is transported across the mitochondrial membrane into the mitochondrial
366 matrix, concurrently with the exchange of free carnitine from the mitochondrial
367 matrix (94). Inside the mitochondrial matrix, acylcarnitine is transesterified to long
368 chain acyl-CoA and free carnitine via carnitine palmitoyltransferase 2 (CPT2) (223).
369 Subsequently, the long chain acyl-CoA is able to undergo β -oxidation. Readers are
370 directed towards the review by Stephens et al., (223) for a more comprehensive
371 overview regarding the role of carnitine in fatty acid translocation.

372

373 Therefore, increasing muscle carnitine content could hypothetically enhance fat
374 oxidation whilst sparing glycogen, therein posing an attractive ergogenic strategy for
375 delaying fatigue during prolonged aerobic exercise and aiding body weight control by
376 promoting fat oxidation. However, a number of studies have failed to increase muscle
377 carnitine via intravenous infusion despite increasing plasma carnitine availability
378 (225). Similarly, oral consumption of carnitine acutely (220) and chronically (247)
379 failed to increase muscle carnitine levels. It is likely the poor bioavailability of oral
380 carnitine and rapid urinary clearance (106) explain, at least partly, why carnitine
381 supplementation alone does not increase muscle carnitine stores (225). Consequently,
382 several strategies have been tested to stimulate muscle carnitine accretion; concurrent
383 hyperinsulinaemia and hypercarnitinaemia increased human muscle carnitine content
384 by ~15% (225) and carnitine plus CHO supplementation promoted muscle carnitine
385 accretion (211). Mechanisms by which insulin can facilitate increased muscle
386 carnitine are purported to be due to insulin increasing Na⁺-dependent active transport
387 of carnitine into the muscle via organic cation transporter (OCTN2) (225). Similarly,
388 Na⁺-dependent uptake of AA (274) and Cr (97) by skeletal muscle is increased by
389 insulin, thereby supporting the proposed mechanisms of carnitine uptake (225).
390 However, CHO in addition to protein blunts the stimulation of muscle carnitine
391 uptake (211). This was previously suggested to be related to AA inhibiting carnitine
392 intestinal absorption (233), however, since the combination of CHO and protein led to
393 greater plasma and urinary carnitine versus CHO alone, this suggests otherwise (211).
394 The precise mechanisms underlying the blunting effect of protein on carnitine uptake
395 into skeletal muscle remain to be fully identified.

396

397 By increasing muscle carnitine content, human fuel metabolism can be manipulated.
398 For example, acute increases in resting skeletal muscle carnitine content led to an
399 inhibited glycolytic flux (denoted by reduced lactate) and CHO oxidation
400 (demonstrated via reduced pyruvate dehydrogenase complex activity) concurrent with
401 increased muscle glycogen and long-chain acyl-CoA accumulation (224). These
402 studies therefore support the notion that carnitine can enhance fat oxidation whilst
403 sparing glycogen. A subsequent study by the same group found a 30% increase in
404 muscle carnitine content following dietary carnitine (1.36g) and CHO (80g) twice a
405 day for 6 months and a ~55% reduction in glycogen use during low intensity exercise
406 (30 minutes cycling at 50% VO_{2max}) compared to controls (250). Additionally,
407 following 3 months supplementation, carnitine and CHO feeding prevented the 2kg
408 increase in body mass, which was seen in the control group (250). The authors
409 speculate that the lack of increase in body mass in the carnitine group may be due to
410 carnitine-induced increases in long-chain fatty acid oxidation (250).

411

412 Subsequent studies have supported the role of carnitine combined with CHO for the
413 prevention of fat gain, which was associated with increased fat oxidation during low
414 intensity exercise (227). Conversely, increased CHO but not fat oxidation during
415 steady-state exercise has been reported following 2 weeks of carnitine
416 supplementation (3g/day carnitine and tartrate combined with CHO meals) (1), and 1
417 month of carnitine intake (3g/day carnitine and tartrate) had no effect on substrate
418 oxidation during steady-state exercise (27). These findings conflict with those
419 reported at rest and differ from hypotheses which suggest limited carnitine availability
420 may limit fat oxidation during exercise (224). Interestingly, in the study by Broad and
421 colleagues (27) there was no mention of daily carnitine supplementation being co-

422 ingested with supplemental CHO, which is critical for increasing muscle carnitine
423 stores (226). Therefore the protocol might have been suboptimal for increasing
424 muscle carnitine stores, which was not measured within the study, and thus may
425 explain the negligible effect of carnitine on substrate utilisation.

426

427 Thus, insulin-stimulated carnitine uptake is capable of increasing muscle carnitine
428 stores (when combined with CHO), which promotes fat oxidation, spares muscle
429 glycogen and thereby improves endurance performance. Further work is required to
430 fully elucidate the mechanisms regulating the blunting of carnitine uptake when
431 combined with CHO and protein.

432

433 n-3 polyunsaturated fatty acids

434 n-3 polyunsaturated fatty acids (n-3 PUFA), contain a double bond at the third
435 carbon atom from the end of the carbon chain. Abundantly found in walnuts and oily
436 fish, there are 3-types of n-3 PUFA: 1) alpha-linoleic acid (ALA), 2)
437 eicosapentaenoic acid (EPA), and 3) docosahexaenoic acid (DHA). n-3 PUFA serve
438 well established roles as critical components of cell membranes and as substrates for
439 lipid signaling (37). Early evidence demonstrated a role for n-3 PUFA in muscle
440 anabolism when n-3 PUFA-enriched feed provided to growing steers increased the
441 phosphorylation of anabolic signaling and the non-oxidative whole-body disposal of
442 AA, representative of increased whole-body protein synthesis (85). Additionally,
443 fish oil containing 18% EPA attenuated the loss of skeletal muscle following 30%
444 burn in guinea pigs, which may be mediated by EPA reducing inflammatory related
445 prostanoids (4). Hence there is interest for the application of n-3 PUFA as a
446 nutritional supplement in humans. It has been suggested that fish oil

447 supplementation in humans may increase muscle n-3 PUFA content (160), have
448 anti-inflammatory properties (128) via reduced leukotriene B4 formation (an inducer
449 of inflammation) (79) and attenuate the loss of muscle mass in disease states,
450 possibly via reductions in pro-inflammatory cytokines (203). Furthermore, n-3
451 PUFA might potentiate anabolic responses to nutrition in skeletal muscle. In support
452 of this, 8 weeks n-3 PUFA supplementation (1.86g EPA plus 1.5g DHA/day) was
453 shown to augment hyperaminoacidaemia-hyperinsulinemia induced increases in
454 mixed MPS compared to corn oil controls in young, middle aged and older adults
455 (215, 216). Indeed, enhanced phosphorylation of mTORC1 and the downstream
456 target p70S6K1 were observed in young, middle aged and older adults (215, 216).
457 However, MPS increases were observed in the context of hyperaminoacidaemia and
458 hyperinsulinemia, which may not be physiologically obtainable. Moreover,
459 supplementation of n-3 PUFA for 3 (151) and 6 months (217) led to increases in
460 muscle mass and function in older adults. A recent study in C₂C₁₂ skeletal muscle
461 cells found a 25% increase in MPS following EPA that was not observed following
462 DHA (131), suggesting that EPA may be the more anabolic constituent of n-3
463 PUFAs. Interestingly, both EPA and DHA stimulated p70S6K1, thus EPA might
464 stimulate MPS via a p70S6K1 independent mechanism (131).

465

466 Despite being less well defined, these positive effects of n-3 PUFA on muscle
467 appear to be recapitulated when combined with exercise (202). Supplementation
468 during 3 months RET promoted increases in muscle strength in older women (202),
469 suggesting that n-3 PUFA could have a positive role on muscle protein metabolism
470 by enhancing the anabolic response to RE (90). Despite recent contrasting findings
471 that chronic fish oil supplementation failed to increase muscle anabolism in younger

472 people under rested and exercise trained conditions (161), the lack of pre- and post-
473 intervention measurements confound interpretation of these results. Additionally,
474 positive findings regarding the efficacy of n-3 PUFA supplementation have been
475 largely observed in older adults. Because ageing associates with blunted anabolic
476 responses to AA and exercise, the muscular benefits of n-3 PUFA may be more
477 pronounced in those in which anabolic responses are already sub-optimal.

478

479 Whilst the combination of EE and n-3 PUFA have not been investigated in the
480 context of muscle mass and protein metabolism, there is sound evidence to suggest
481 that n-3 PUFA supplementation may alter fuel metabolism by improving metabolic
482 flexibility, i.e. the ability to switch between using fat or CHO as a fuel source. For
483 example, 6g/day of fish oil for 3 weeks led to a 35% increase in fat oxidation
484 following a glucose or fructose bolus (61). In the context of exercise, 3 weeks fish
485 oil supplementation (6g/day) led to a non-significant trend for greater fat oxidation
486 during an acute bout of cycling (90 minutes at 60% O_2 output), a possible
487 compensatory response for the lower CHO oxidation (62). Further studies have
488 found significantly greater fat oxidation during EE in humans following 3 weeks
489 fish oil supplementation (119). Although, each of these studies lacked
490 comprehensive investigation into the mechanisms regulating changes in metabolic
491 flexibility, n-3 PUFA have been shown to mediate the up-regulation of genes
492 regulating mitochondrial biogenesis, such as peroxisome proliferator-activated
493 receptor-alpha ($PPAR\alpha$) and -gamma ($PPAR\gamma$) and the transcription factor nuclear
494 respiratory factor 1 (NRF1) in mice (146), offering a potential explanation for these
495 findings. Additionally, rats fed a low fat diet supplemented with DHA had higher
496 oxygen consumption and apparent K_m for ADP in permeabilised muscle fibres

497 compared to placebo, indicative of improved mitochondrial function (103). Thus,
498 effects on mitochondrial biogenesis and function may underpin the synergistic
499 effects of n-3 PUFA and EE-associated metabolic adaptation.

500

501 Collectively, n-3 PUFA supplementation beneficially effects muscle protein
502 metabolism, which may contribute to chronic gains in muscle mass, and also shows
503 promise for impacting metabolic flexibility. Further human research is warranted
504 which investigates the effects of EPA and DHA individually on aspects of skeletal
505 muscle health to establish which is the main anabolic constituent.

506

507 *Nitrates*

508 Nutrients that contain dietary inorganic nitrates (e.g. beetroot and lettuce) or related
509 precursors (e.g. arginine) can increase nitric oxide (NO) availability, which is
510 capable of modulating muscle-related processes including contraction, glucose
511 homeostasis, blood flow (127) and satellite cell activation (5, 35). Following oral
512 ingestion of dietary nitrate-rich foods, nitrate (NO_3^-) is reduced to nitrite (NO_2^-) via
513 nitrate reductases within the mouth (68). Subsequently, NO_2^- is converted into NO
514 and additional reactive nitrogen species in the acidic environment of the stomach
515 (2). Oral NO_3^- increases plasma NO_3^- and NO_2^- levels, indicating nitrates are
516 bioavailable. With regards to muscle protein turnover, these compounds are thought
517 to promote anabolism via improving blood flow (through increased NO production),
518 thus enhancing nutrient delivery to the muscle, providing more substrates for MPS.
519 However, it has been shown on several occasions that enhanced muscle blood flow
520 does not augment anabolic responses in young or older males (164, 187–189).
521 Nonetheless, dietary arginine (the principle substrate for endothelial nitric oxide

522 synthase (eNOS) for endogenous production of NO) supplementation did increase
523 the weight of the soleus and EDL muscle in obese rats (125). However, in humans
524 Tang and colleagues found oral arginine (10g), of which approximately 70% is
525 bioavailable following ingestion (154), had no effect on muscle blood flow or MPS
526 when provided alone or in combination with AA or acute RE (232). In contrast,
527 vasodilatory effects of arginine have been shown when administered by IV infusion
528 at higher doses (30g) (23). By comparison, the peak in plasma arginine was
529 considerably lower following 10 g of oral arginine ($\sim 225 \mu\text{mol}\cdot\text{L}^{-1}$) (232) versus 30g
530 IV infused arginine ($\sim 6223 \mu\text{mol}\cdot\text{L}^{-1}$) (23), thus the dose of arginine used by Tang
531 and colleagues may not have been sufficient to increase plasma arginine to an
532 amount which elicits effects on vasodilation. In fact the authors project that on the
533 premise of 70% bioavailability, a total of ~ 43 g of oral arginine would have been
534 required to reach similar plasma levels reported following IV infusion (232). An
535 alternative may be to utilize the arginine precursor citrulline (156), which bypasses
536 splanchnic extraction (267). Supplementation of citrulline in rodents was shown to
537 stimulate MPS (179) via the mTORC1 pathway (193). However, similar effects
538 have not been observed in humans, since there was no additional impact of citrulline
539 (10g), when co-ingested with whey, on MPS or blood flow with or without acute RE
540 versus whey combined with non-essential AA (NEAA) (52). Lastly, flavanols such
541 as in cocoa (39, 109) also promote vasodilation via NO pathways (80, 132). It was
542 recently reported that despite an acute dose of cocoa flavanols (350mg) increasing
543 macro- and microvascular blood flow, this was not associated with enhanced muscle
544 anabolic responses to nutrition (188), suggesting in healthy individuals nutrient
545 delivery is not rate-limiting for muscle anabolism (189).

546

547 In contrast to muscle mass and strength related studies, a plethora of research has
548 investigated the effects of nitrates and EE on whole body metabolism and endurance
549 performance. An early study by Larsen et al. (2007) reported that sodium nitrate
550 supplementation reduced the O₂ cost of submaximal cycling exercise (148), whilst
551 similar results have reported following nitrate-rich beetroot juice supplementation
552 (11), indicative of improved aerobic metabolism or mechanical efficiency (147). In
553 addition to metabolic improvements, nitrate supplementation provided in the form of
554 500ml beetroot juice improved 4 and 16.1km cycling time trial performance in
555 trained cyclists (145). These improvements are likely attributable to an enhanced
556 rate of PCr recovery (239) increasing the rate of ATP synthesis, although this
557 mechanism remains speculative at present. Emerging evidence from cell culture
558 studies suggests nitrate supplementation enhances mitochondrial biogenesis and
559 oxidative metabolism via increased 5'adenosine monophosphate-activated protein
560 kinase (AMPK) and peroxisome proliferator-activated receptor γ co-activator 1 α
561 (PCC-1 α) gene expression (240), though *in vivo* data is lacking. Although others
562 have also reported nitrate-mediated improvements in EE performance have been
563 shown (169, 269), several authors have shown no improvements (6, 48, 254). For
564 example, consuming 140ml of beetroot juice 2.5h prior to a 1h cycling time trial did
565 not improve time trial performance in trained cyclists compared to placebo (48).
566 These discrepant findings may be explained by methodological differences such as
567 the dose of nitrates (since the increase in plasma NO₃⁻ and NO₂⁻ is somewhat dose
568 dependent (270)), control of nitrate intake, the source of nitrates provided and the
569 training status of the participants. For example, since numerous studies demonstrate
570 nitrate supplementation to have no beneficial effect on performance in well trained
571 participants (6, 48, 254), it is likely that fitness status influences the ergogenic

572 potential of nitrate supplementation (127). Indeed, higher plasma levels of NO_2^-
573 were present in trained versus untrained participants pre and post acute exercise
574 (195). This may be explained by higher nitric oxide synthase (NOS) activity (159)
575 and/ or higher plasma nitrate values (195) in trained participants.

576

577 Thus, it is established that nitrates reduce the O_2 cost of aerobic exercise. Further *in*
578 *vivo* work is required to understand whether larger oral doses, than those already
579 tested, of arginine can enhance vasodilation and effects protein metabolism, across
580 different ages. Furthermore, precise mechanisms regulating the nitrate-induced
581 beneficial effect on O_2 cost remain to be delineated *in vivo*.

582

583 *β -alanine and carnosine*

584 β -alanine (BA) is a beta AA produced endogenously in the liver found primarily in
585 meat (238). BA is the rate-limiting precursor for the synthesis of carnosine, which is
586 a dipeptide of BA and histidine that improves the muscle buffering capacity (222).
587 BA supplementation has generated interest as an ergogenic aid since early studies
588 found BA supplementation capable of increasing muscle carnosine stores by ~40-
589 65% demonstrating good bioavailability; a consistent and reproducible finding (16,
590 108, 222). Although the extent to which carnosine content increases may be
591 dependent on the dosing protocol (108). Other factors have been shown to cause
592 muscle carnosine variability, including gender, age, dietary BA intake,
593 vegetarianism (76) and fibre type distribution, since carnosine content is double in
594 type II compared to type I fibres (38). The regulation of muscle carnosine stores
595 from dietary/ supplemental sources is still under investigation (222). Oral BA may
596 be transported across the gut via the H^+ -coupled PAT1 AA transporter (235), which

597 increases plasma availability of BA for muscle carnosine synthesis. Transport of BA
598 into skeletal muscle has been shown to be regulated via both peptide transporter 2
599 (PEPT2) (67) and the taurine transporter (TauT) (237), although this remains to be
600 confirmed in humans. Once within the muscle cell, BA and sarcoplasmic histidine
601 synthesize carnosine via carnosine synthase (222).

602

603 Increased muscle carnosine stores may increase RE work capacity via regulation of
604 the muscle buffering capacity during RE, and therefore has gained interest into the
605 potential of BA supplementation for promoting RE/T adaptations (133). However,
606 10 weeks RET combined with 6.4g/day BA did not enhance body mass or strength
607 changes in twenty-six males, despite increased muscle carnosine (133).

608

609 During high intensity exercise, the build up of H⁺ ions reduces the intramuscular pH
610 leading to fatigue likely due to acidosis-induced reductions in ATP generation (205).
611 Increased muscle carnosine, via BA supplementation, is capable of reducing
612 intramuscular acidity during high intensity exercise therefore enhancing exercise
613 performance (57, 112, 229). For example, 4 and 10 weeks of BA supplementation
614 increased cycling capacity (total work done) in untrained males when cycling at
615 110% of maximum power (112), hypothesized to be due to improved intracellular
616 buffering. In sprint-trained athletes, 4-5 weeks BA supplementation (4.8 g/day) led
617 to increased knee torque but did not enhance sprint performance (64). Importantly,
618 this study found increased muscle carnosine stores (+47%), demonstrating that it is
619 possible to increase muscle carnosine even in trained athletes (64). Women
620 supplemented with BA for 28 days delayed the onset of neuromuscular fatigue

621 (denoted by improved ventilatory threshold, physical working capacity and time to
622 exhaustion), likely the result of improved intracellular buffering capacity (228).

623

624 BA supplementation is associated with paresthesia (i.e. flushing) following acute
625 doses of ≥ 800 mg (60, 108). This side effect is deemed dose-dependent and likely
626 relating to BA plasma kinetics (108). Compared to pure BA, slow releasing BA
627 capsules eliminated all paresthesia side effects, most likely explained by the
628 attenuated BA plasma concentration and delayed time to peak (60), and thus offer a
629 suitable alternative supplement option.

630

631 BA supplementation may therefore be implemented to increase muscle carnosine
632 stores which, in turn enhances acute EE performance, likely mediated via an
633 enhanced intracellular buffering capacity. However, the effects of BA combined with
634 RET needs to be studied further *in vivo*.

635

636 **Micronutrients: vitamins and exercise**

637 Vitamins are essential for many metabolic processes, however consuming vastly more
638 or less than recommended can likely result in toxicity or deficiency, respectively
639 (212), which can be detrimental for muscle health. For example, vitamin D (VitD)
640 deficiency has been linked to muscle wasting (86) and as such, vitamins have been
641 implicated in regulating muscle mass, metabolism and performance as discussed
642 below.

643

644 *Vitamin D*

645

646 VitD is a steroid hormone, the deficiency of which in humans throughout the world is
647 reaching epidemic levels mostly due to reduced sun exposure (116). VitD deficiency
648 is prevalent in many debilitating conditions including osteoporosis and rickets (116,
649 117) and is associated with reduced muscle mass and strength (244). For example,
650 rodent models have demonstrated VitD deficiency induced muscle loss, a
651 consequence of increased MPB and reduced MPS compared to controls (17). The
652 VitD receptor (VDR) is present in many tissues including muscle (89) which has led
653 to increasing interest in the effects of VitD on muscle metabolism. Although
654 conflicting reports exist regarding the presence of the VDR (192, 251), these
655 discrepancies are most likely due to the use of non-validated antibodies, lack of
656 controls or differences in antibody specificity (89).

657

658 Following sun exposure or consumption of VitD-rich dietary sources/ supplements,
659 circulating VitD bound to VitD binding protein (DBP) increases, and transports to the
660 liver where hydroxylation (via 25-hydroxylase) generates 25-hydroxyvitamin D
661 (25D). A second hydroxylation in the kidney (via 1α -hydroxylase) produces the
662 biologically active form of VitD ($1,25(\text{OH})_2\text{D}$) (87). Mechanisms underpinning the
663 effects of VitD on muscle metabolism are not fully understood but are believed to be
664 in part related to the regulation of gene expression via the VDR or secondary
665 messenger protein signaling (194). The binding of $1,25(\text{OH})_2\text{D}$ to the VDR causes
666 conformational changes, allowing VDR to heterodimerize with the retinoid X receptor
667 (RXR). This complex then binds to VitD response elements (VDREs) on the DNA,
668 promoting gene transcription (45, 87). $1,25(\text{OH})_2\text{D}$ may also have non-genomic
669 effects on intramuscular signaling by binding to a cell surface receptor (40), which, in
670 turn, this activates intracellular signaling pathways such as the Akt and mitogen-

671 activated protein kinases (MAPK) pathway (33). For example, VitD treatment
672 increased myotube size, down-regulated myostatin (88), up-regulated Akt (33) and
673 sensitized the Akt/ mTORC1 pathway and MPS responses to leucine and insulin
674 (206) in muscle cell cultures. Thus, there is growing *in vitro* evidence for an anabolic
675 role of VitD in skeletal muscle. In humans, supplementation of VitD has been
676 proposed to increase muscle strength (13), function (83, 252), fibre area (46, 208,
677 221), lean body mass (72) and reduce falls (83, 130), although a recent meta-analysis
678 found no overall effects of VitD supplementation on muscle mass (13). Of
679 importance, benefits of VitD supplements are observed particularly in the elderly or in
680 those who are VitD deficient (13), which may be a potential explanation for some of
681 the discrepant findings within the literature.

682

683 Since VitD supplementation has been suggested to promote muscle mass and
684 function, concurrent VitD supplementation with RET may be expected to potentiate
685 exercise-induced adaptations. Indeed, 4 months VitD₃ supplementation (1920IU/day
686 plus 800mg/day calcium) in combination with lower-body RET for 3 months led to a
687 greater reduction in myostatin mRNA expression, a negative regulator of muscle
688 mass, and a greater change in the percentage of type IIa muscle fibres in young males
689 (3). However, these changes did not translate into greater muscle strength or
690 hypertrophy above RET alone (3). Elderly adults undertaking RET combined with
691 VitD improved muscle quality (strength/ cross sectional area) more so than young
692 males, thus demonstrating that elderly individuals may benefit more from VitD
693 supplementation (3). VitD insufficient (according to VitD ranges by (118))
694 overweight and obese adults did not augment gains in lean body mass compared to
695 placebo following 3 months RET and 4000IU/day VitD₃ (41). This may be due to the

696 fact that VitD is deposited in body fat, reducing bioavailability (266) and requiring
697 greater levels of VitD supplementation to promote muscle anabolism in this
698 population. Similarly, others reported no change in body composition after 9 months
699 supplementation of 400IU/day and RET 2x/week in overweight males and females
700 (34). Since no change in body composition was seen in the training only group either,
701 these findings may resulted from low training adherence (~53%) (34).

702

703 Therefore, while there is some evidence to suggest an emerging role for the
704 supplementation of VitD for the promotion of muscle mass and protein metabolism,
705 more high-quality *in vivo* work is required. For example, investigations into the direct
706 effect of VitD on MPS in humans are needed, as are more acute and chronic EE
707 studies in order to understand the potential synergistic effects of VitD
708 supplementation and exercise on muscle health. These studies need to be well
709 controlled, accounting for basal VitD status and should determine true VitD
710 bioavailability.

711

712 *Vitamins C and E (i.e. “antioxidants”)*

713 High levels of free radicals (an atom with a single unpaired electron) and reactive
714 oxygen species (ROS) can disrupt protein homeostasis (196). This is likely due to
715 ROS promoting catabolism via increases in the ubiquitin-conjugating activity (150)
716 and diminishing anabolism via attenuation of MPS and signaling proteins (182), with
717 evidence for these mechanisms arising from cell culture studies. It is therefore thought
718 that consuming dietary antioxidants (i.e. vitamin C (VitC) and E (VitE)) capable of
719 donating an electron to neutralize free radicals (168), may reduce ROS thus
720 minimizing disruption of protein homeostasis. For instance, a positive relationship

721 was observed between VitC intake and appendicular lean body mass (209), which
722 may be related to the fact that muscle is a major storage site for VitC (253).
723
724 However, physiological levels of ROS such as that produced during exercise (248)
725 promote gene expression (e.g. manganese superoxide dismutase (MnSOD)) (185) and
726 cell signaling (e.g. c-Jun N-terminal kinases and MAPK's) (92, 185) in healthy
727 skeletal muscle. Thus, it may be hypothesized that provision of antioxidants combined
728 with RET could hamper exercise-induced adaptations. Human studies assessing the
729 interactions of RET and antioxidant supplementation have produced varied results
730 with support for positive (22, 143), negative (19, 184) and negligible (21, 184) effects
731 of antioxidants. For example, greater gains in fat free mass were observed following 6
732 months RET combined with VitC (1000mg/day) and VitE (600mg/day) compared to
733 RET alone, postulated to be a result of antioxidants increasing protein synthesis,
734 although this was not measured (22, 143). However, 3 months supplementation of
735 daily VitC (1000mg) and VitE (235mg) alongside whole body RET led to blunted
736 gains in total lean body mass and muscle thickness (19). Ten weeks whole body RET
737 combined with 1000mg VitC and 235mg VitE daily found negligible effects on acute
738 MPS and muscle mass, however, the phosphorylation of anabolic signaling proteins
739 was blunted compared to placebo (184). Supporting the lack of ability to potentiate
740 exercise-induced adaptations, RET and antioxidants increased fat free mass but no
741 more than RET alone (21). This may be a result of the low participant numbers or due
742 to the fact that the participants were not vitamin deficient, therefore it may be that
743 additional vitamin intake provides little or no added benefits. The absorption of
744 antioxidants, particularly VitC, may also be limited, (21) further reducing the
745 antioxidant-induced anabolic potential. Another factor which may explain the efficacy

746 of antioxidant supplements is the age of participants since the elderly have an altered
747 redox status (184), which could impact the efficacy of the antioxidants.

748

749 Detrimental and negligible interactions have also been reported following EE and
750 antioxidant supplementation (183, 272). For example, daily VitC (1000mg) and VitE
751 (235mg) during an 11 week EE training program consisting of steady-state and HIIT
752 in humans led to blunted increases in mitochondrial protein content, indicative of
753 blunted mitochondrial biogenesis, although no differences were observed in VO_{2Max}
754 compared to placebo (183). Similarly, VitC hampered running time to exhaustion in
755 rats, perhaps a result of impaired mitochondrial biogenesis (93). Others have reported
756 no alterations in EE-induced adaptations (measured as maximal O_2 consumption,
757 power output and workload at lactate threshold) following antioxidant
758 supplementation (272). Differences in the antioxidant dosing regimes might explain
759 some divergent findings between studies (183). Thus, whilst VitC and VitE are vital
760 for maintaining health, the benefits of supplementation are debatable and are likely to
761 depend on the age group deficiency status. The poor bioavailability described in
762 several studies may further impact any benefits of supplementation (21).

763

764 Currently, it is difficult to conclude whether antioxidant supplementation is beneficial
765 or detrimental for muscle mass, protein metabolism and performance/adaptation.
766 Close and colleagues highlighted that confusion and misguided conclusions are often
767 drawn due to inappropriate methodological techniques (53). As an example, the lipid
768 peroxidation marker, thiobarbituric acid reactive substances (TBARS), can be the
769 result of non-redox related sources and is thus no longer recommended for use as an
770 oxidative stress marker (81), yet is often published in the context of antioxidant

771 supplementation (111, 155, 157). It is believed that diets rich in fruits and vegetables
772 as opposed to large supplemental doses of antioxidants are preferable since no
773 investigations to date support attenuations in adaptations to training in response to
774 fruits and vegetables, which have naturally occurring antioxidants (53).

775

776 **Emerging Nutraceuticals**

777 *Ursolic acid*

778 Despite the paucity of research at present, other novel nutraceuticals have gained
779 recent attention for their potential to promote muscle mass, protein metabolism and/or
780 exercise adaptations. For example, the naturally occurring phytochemical ursolic acid
781 (UA) found in apple peel has drawn attention since UA supplemented mice gained
782 7% muscle weight (142), suggesting UA may be capable of promoting muscle
783 hypertrophy (71, 124, 141, 142). UA-induced hypertrophic effects are proposed to be
784 due to the attenuation of atrophy-related genes MuRF1 and atrogin-1, and the up-
785 regulation in IGF gene expression (142). Contrary to this, UA incubations in cell
786 cultures was reported to inhibit leucine-stimulated mTORC1 signaling by inhibiting
787 mTORC1 localization to the lysosome (180), a key step in AA-induced anabolic
788 signaling (207). Research is warranted to detail the effects of UA on muscle
789 metabolism in humans.

790

791 With regards to exercise interactions, UA injection following RE in rats stimulated
792 p70S6K1 at 1h and was maintained 6h later, which began the descent to baseline in
793 the exercise only group, reflecting prolonged mTORC1 activity and thus anabolic
794 potential when RE is combined with UA (177). Despite an unclear mechanism, the
795 authors speculated that IGF-I may contribute to the UA-induced p70S6K1 activation,

796 and previous work supports this hypothesis (142). Contrary, data in humans (not in
797 the context of UA) shows no change in IGF-I but increased anabolic signaling after
798 acute RE (28). In RE trained males, RET 6 x/week (at 60-80% of 1-RM) for 2 months
799 combined with 450mg/day UA improved leg strength but had no effect on lean body
800 mass, although RET alone also had no effects on lean body mass (12). This may be
801 due the fact that the participants had >3 years RET experience, and hypertrophic
802 responses predominate in the early stages of RET (29). To the author's knowledge, no
803 evidence exists regarding UA supplementation combined with EE. An important issue
804 to consider is the low and variable bioavailability of UA following oral ingestion,
805 likely due to its lack of solubility in aqueous solutions (113). This could markedly
806 impact its potential as a nutraceutical. However, recent efforts have been made to
807 improve the bioavailability of UA and other triterpenoids by, for instance, using nano-
808 liposomes to aid solubility (271). The varied and low bioavailability of UA in humans
809 is demonstrated by the lack of UA content in some participants following a 1g oral
810 dose, and in those that did display UA content, it was only observed up to 12h post
811 consumption (113). Additional findings show oral UA ingestion (3g) lead to increased
812 plasma UA 2 and 6h post-exercise (50). As such, the true bioavailability of UA in
813 response to time and dose should be investigated further.

814

815 *Phosphatidic acid*

816 Phosphatidic acid (PA) is a diacyl-glycerophospholipid found endogenously in
817 mammalian cell membranes that can be obtained exogenously from raw cabbage
818 (231). Both endogenous and exogenous PA are believed to positively influence
819 muscle protein metabolism, whereby endogenous PA can be increased by RE and
820 directly binds to mTORC1 influencing MPS. Exogenous PA indirectly stimulates

821 mTORC1 activation (77, 165) via extracellular-signal regulated protein kinase
822 (ERK) dependent (262), and phosphatidylinositol-3-kinase (PI3K) independent
823 (176) mechanisms, and may also attenuate MPB via attenuation of atrophy-related
824 genes (210). Exogenous PA in cultured muscle cells also prevented atrophy in the
825 presence of the atrophy-inducing substances tumor necrosis factor alpha (TNF- α)
826 and dexamethasone (122). Recently, acute PA supplementation in rodents tended to
827 increase MPS in the fasted state, however, PA blunted the whey protein induced rise
828 in MPS (165). Possibly the addition of PA to whey alters the pathways of mTORC1
829 activation thus shifting peak MPS (165); research is needed to understand the
830 signaling responses of PA alone versus PA plus whey. In a human case study, orally
831 ingested PA metabolized into lysophosphatidic acid (LPA) and glycerophosphate,
832 increased plasma PA and LPA 30 minutes post-ingestion (of 1.5g PA), which
833 plateaued at 1-3h and remained elevated above baseline at 7h (197). Thus, it seems
834 PA is bioavailable in humans, although beyond 7h post-ingestion the bioavailability
835 is unknown and further studies with a larger cohort are needed to determine the true
836 bioavailability of PA. PA supplementation (750mg daily) combined with 2 months
837 supervised whole body RET in RE trained males found increased lean body mass
838 and cross sectional area compared to the placebo group (129). Conversely, others
839 have shown non-significant increases (+2.6%) in lean body mass, despite utilizing a
840 similar RET and supplementation programme (115). The differential findings
841 between these studies may be due to the fact that training was unsupervised in the
842 later study. To our knowledge no data currently exists assessing the interactions of
843 PA plus EE.

844

845 **Combined nutraceuticals**

846 Although not the focus of this review, it is worth speculating that combining
847 nutraceuticals may provide multiple benefits to skeletal muscle health or potentiate
848 skeletal muscle health benefits in response to exercise. Consequently, some studies
849 have investigated the potential of combined nutritional ‘cocktails’. For example, a
850 supplement containing PA, HMB and VitD in combination with 2 months RET led
851 to greater gains in lean body mass and strength compared to the placebo group,
852 providing support that the combined supplement possessed anabolic properties (73).
853 The combination of VitD, leucine and whey twice daily in tandem with RET 3
854 x/week for 13 weeks prevented the loss of appendicular muscle mass during
855 intentional weight loss in obese males and females (243). The caveat with
856 implementing combined nutritional supplementation is that it is difficult to attribute
857 changes in the endpoint to the responsible individual/ or combination of nutrients,
858 unless rigorous study designs are implement with adequate control groups.

859

860 **Conclusion and Future Directions**

861 While it is extremely unlikely that a single nutraceutical will prove to be a ‘magic
862 bullet’, it is clear that certain nutraceuticals, under certain conditions, do indeed
863 possess ergogenic potential. Of the nutrients discussed herein, strong evidence exists
864 for leucine, HMB and Cr for muscle mass; leucine and HMB for protein metabolism;
865 carnitine for fuel metabolism and leucine, HMB, carnitine, Cr, nitrates and β -alanine
866 for athletic (strength or endurance) performance. Further empirical *in vivo* evidence is
867 required to firmly establish the currently emerging roles of VitD, UA and PA for
868 promoting muscle mass and n-3 PUFA, UA and PA for muscle protein metabolism.
869 This review highlights: 1) the need for better controlled longer duration human
870 studies which investigate the role of individual nutrients on muscle mass, protein/ fuel

871 metabolism and indices of exercise performance/ adaptation, 2) the lack of *in vivo*
872 “mechanistic” studies, and 3) the need to determine the bioavailability of emerging
873 nutrients.

874

875 **Acknowledgments**

876 CS Deane PhD student funded by Bournemouth University. DJ Wilkinson is a post-
877 doctoral research fellow funded through the MRC-ARUK Centre for Musculoskeletal
878 Ageing Research. The MRC-ARUK Centre for Musculoskeletal Ageing Research
879 was funded by grants from the Medical Research Council [grant number
880 MR/K00414X/1] and Arthritis Research UK [grant number 19891] awarded to the
881 Universities of Nottingham and Birmingham. The authors declare no conflicts of
882 interest.

883

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1813

1814 **(INSERT FIGURE HERE)**

1815

1816 **Figure 1. Proposed metabolism and mechanisms of action for nutrients/ nutraceuticals.**

1817 → represents activation; → represents purported activation; --| represents purported suppression; ? unknown; 4EBP1 4E binding protein-1; AA

1818 amino acids; AMPK 5' AMP-activated protein kinase; AO antioxidants; ATP adenosine triphosphate; CARNS carnosine synthase; CHO

1819 carbohydrate; CK creatine kinase; EDG-2 endothelial differentiation gene; eEF2 eukaryotic elongation factor 2; eIF4E eukaryotic initiation

1820 factor 4E; HMB β-hydroxy-β-methylbutyrate; MPS muscle protein synthesis; mTORC1 mammalian target of rapamycin complex 1; NO₃⁻;

1821 nitrate; NO₂⁻ nitrite; NO nitric oxide; OCTN2 organic cation transporter 2; PA phosphatidic acid; PAT1 proton-coupled amino acid transporter 1;

1822 PEPT2 peptide transporter 2; PGC-1α peroxisome proliferator-activated receptor-γ coactivator-1α; RPS6 ribosomal protein S6; SLC6AS Solute

1823 Carrier Family 6 Member 8; TauT taurine transporter; UA ursolic acid; VDR vitamin D receptor; VDRE vitamin D response elements; VitD;

1824 vitamin D; VitD₃; active vitamin D.

1825

1826

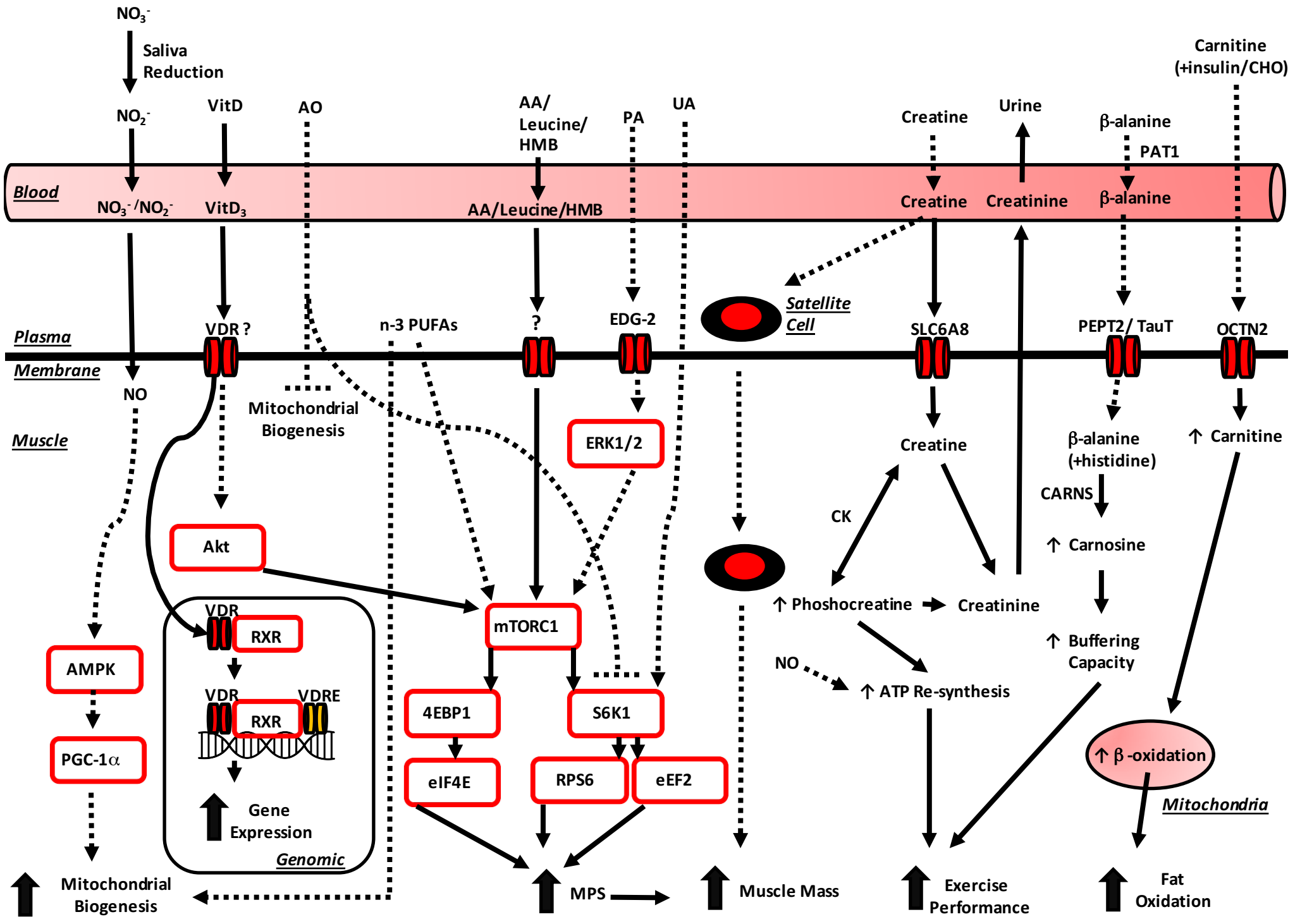
1827

1828 **Table 1.** Summary of studies in humans demonstrating positive, negative or negligible effects of established and emerging macronutrients,
1829 micronutrients and nutraceuticals on skeletal muscle mass, metabolism and performance with or without exercise

1830 **(INSERT TABLE HERE)**

1831

1832 ↓ decrease, ↑ increase, > larger, ↔ no change, 1-RM: one repetition maximum; AA: amino acids; Arg: arginine; AS: antioxidant supplement;
1833 β-ala: beta-alanine; BRJ: beetroot juice; BW: body weight; CAR: carnitine; CHO: carbohydrate; CON: control; CONC: concentric; CPK:
1834 creatine phosphokinase; CR: creatine; CSA: cross-sectional area; d: day/s; EAA: essential amino acids; ECC: eccentric; EE: energy expenditure;
1835 EET: endurance exercise training; F: females; FFM: fat free mass; FO: fat oxidation; FSR: fractional synthesis rate; g: grams; h: hours; HIIT:
1836 high intensity interval training; HMB: β-hydroxy-β-methylbutyrate; kg: kilograms; km: kilometer; LBF: leg blood flow; LBM: lean body mass;
1837 LCA-CoA: long-chain acyl-CoA; LDH: lactate dehydrogenase; LEU: leucine; n-3 PUFAs: n-3 polyunsaturated fatty acids; NEAA: non-essential
1838 amino acids; M: males; Max: maximal; MBV: microvascular blood volume; Mg: milligrams; Min: minute; ml: milliliter; mmol: millimolar;
1839 MPO: mean power output; MPB: muscle protein breakdown; MPS: muscle protein synthesis ; mRNA: messenger ribonucleic acid; mTOR:
1840 mammalian target of rapamycin; NaNO₃: sodium nitrate; NS.: non-significant; O: old; O₂: oxygen; OBLA: onset of blood lactate accumulation;
1841 p70S6K1: ribosomal s6 kinase 1; PDH: pyruvate dehydrogenase; PLA: placebo; P_{max}: maximal power output; PPO: peak power output; PRO:
1842 protein; PWC_{FT}: Physical working capacity at the onset of neuromuscular fatigue threshold; Reps: repetitions ; RE: resistance exercise ; RET:
1843 resistance exercise training; TART: tartrates; TC: total carnitine; TT: time trial; TTE: time to exaution; TUG: timed up and go; TWD: total work
1844 done; VitD: vitamin D; VT: ventilatory threeshold; Wk/s: week/s; Y: young; yr: year; Yo-Yo IR1: Yo-Yo intermittent recovery level 1



Author	Classification	Subjects	Nutrient	Exercise/Condition	Results	Comment	Endpoint
Macronutrients							
Bennet 1989	Macronutrient	7 M	Mixed AA	–	↑ MPS	AA alone maximally stimulate MPS	Metabolism
Smith 1998	Macronutrient	23 M	EAA NEAA	–	↑ MPS ↔	EAA driver of increased MPS	Metabolism
Casperson 2012	Macronutrient	8 M	12g/d LEU 13d	–	↑ MPS ↑ mTOR signalling	LEU increases MPS	Metabolism
Wall 2013	Macronutrient	24 M	n=12: 20g PRO n=12: 20g PRO + 2.5g LEU	–	> ↑ MPS following PRO+LEU vs. PRO	LEU co-ingestion with PRO potentiates MPS	Metabolism
Leucine Metabolites							
Nissen 1996	Nutraceutical	28 M	n=15: 3g/d HMB n=13: PLA 7wks	RET 6*wk 7wks	HMB ↑ LBM > placebo HMB ↑ strength	HMB plus RET potentiates gains in LBM	Mass Performance

Wilkinson 2013	Nutraceutical	15 M	n=8: 3.42g HMB (2.42g pure HMB) n=7: 3.42 g LEU	-	HMB & LEU ↑ MPS, HMB ↑ mTOR signalling > LEU, HMB ↓ MPB	HMB promotes ↑ MPS and ↓ MPB	Metabolism
Deutz 2013	Nutraceutical	4 M 15 F	n=11: 3g/d HMB n=8: PLA	10d bed rest	HMB ↔ LBM PLA ↓ LBM	HMB preserves muscle mass during disuse	Mass
Baier 2009	Nutraceutical	38 M 39 F	n=40: 2 or 3g HMB, 1.5 or 2.25g lysine, 5 or 7.5 g arginine & 0.1g ascorbic acid n=37: PLA 1yr	-	↑ FFM	AA cocktail enhanced muscle mass	Mass
Panton 2000	Nutraceutical	39 M 36 F	n=36: HMB (3g/d) n=39: PLA	RET 3*wk 4 wks	↑ strength > PLA	HMB improved muscle function	Performance
Wilson 2014	Nutraceutical	20 M	n=11: HMB (3g/d) n=9: PLA	Periodised RET 12 wks	↑ strength, power and LBM vs. PLA	HMB enhances muscle function & hypertrophy	Mass Performance

Vukovich 2001	Nutraceutical	8 M	n=8: 3g/d HMB n=8: 3g/d LEU n=8: 3g/d PLA 2wks	-	HMB ↑ time to reach VO _{2peak} HMB & LEU ↑ OBLA	HMB improves aerobic performance	Performance
Miramonti 2016	Nutraceutical	22 M 15 F	n=14: 3g/d HMB n=14: 3g/d PLA n=9: CON 4 wks	HIIT 3*wk 4 wks	↑ PWC _{FT} following HMB > PLA & CON	HMB & HIIT improves aerobic performance	Performance
Knitter 2000	Nutraceutical	5 M 8 F	n=8: 3g/d HMB n=5: PLA 6 wks	Running >30 km/wk	Attenuated ↑ in CPK & LDH post 20 km run following HMB	HMB ameliorates aspects of muscle damage	Performance

Creatine

Greenhaff 1993	Nutraceutical	9 M 3 F	n=6: 20g/d CR + 1g/d glucose/ n=6: 24g/d glucose 5d	5 x 30 max voluntary contractions, before and after supplementation	CR ↓ peak torque decline	CR sustains performance	Performance
Birch 1994	Nutraceutical	14 M	n=7: CR 20g/d n=7: PLA 5d	3 x 30 sec max cycling sprints	CR ↑ PPO, MPO and total work output during 1 st sprint	CR increases aspects of power output	Performance

Earnest 1995	Nutraceutical	8 M	n=4: 5g/d CR n=4: PLA 2-4 wks	3 x 30 sec max cycling 1-RM test 70% of 1-RM until fatigue	CR ↑ total anaerobic work during cycling sprints, ↑ BW, ↑ total lifting volume	CR enhances muscle function	Mass & Performance
Cooke 1995	Nutraceutical	12 M	n=6: 5g CR + 1g glucose n=6: PLA 5d	Max cycling sprint	↔ in power indices	CR does not affect power output	Performance
Mujika 1996	Nutraceutical	11 M 9 F	n=10: 20g/d CR n=10: PLA 1 wk	20, 50 & 100 m max swim	No difference in race time between groups	CR has no ergogenic benefits on sprint performance	Performance
Snow 1998	Nutraceutical	8 M	n=4: 30g/d CR + 30g/d dextrose n=4: PLA 5d	20 sec max cycling	CR did not affect power indices	CR has no ergogenic benefits on sprint performance	Performance
Thompson 1996	Nutraceutical	10 F	n=5: 2g/d CR n=5: PLA 6 wks	6 wks swimming (part of a swim team)	↔ in lean mass, resynthesis of PCr or performance time	CR has no effect on body composition, anaerobic or aerobic performance	Mass & Performance
Cooke 2009	Nutraceutical	14 M	n=7: 0.1-0.3g/kg/d CR + CHO n=7: CHO 19d	4 sets, 10 ECC reps @ 120% of CONC 1-RM for 3 leg exercises	CR+CHO ↑ isokinetic & isometric strength during recovery vs. CHO	CR improves functional recovery	Performance

Volek 1999	Nutraceutical	19 M	n=10: 25 g/d 1 wk, 5 g/d 11 wks CR n=9: PLA	RET 12 wks	> ↑ in strength, CSA, following CR vs. PLA	CR potentiates RET-induced muscle adaptations	Mass & Performance
Brose 2003	Nutraceutical	15 M 13 F	n=14: 5g/d CR + 2g dextrose n=14: pla	RET 3*wk, 14 wks	> ↑ in FFM and strength following CR vs. PLA	CR potentiates RET-induced mass and functional adaptations	Mass & Performance
Carnitine							
Stephens 2006	Nutraceutical	7 M	n=7: 5h CAR infusion (15 mg/kg prime, 10 mg/kg h constant) n=7: PLA	-	CAR ↑ muscle glycogen, LCA-CoA & ↓ PDH complex activity, lactate vs. PLA	CAR can inhibit CHO oxidation	Fuel Metabolism
Wall 2011	Nutraceutical	14 M	n=7: 2 g CAR + 80 g CHO n=7: 80 g CHO 2*d, 24 wks	30 mins cycling @ 50% VO _{2max} , 30 mins at 80% VO _{2max} , 30 min all- out	@ 50% VO _{2max} carnitine ↓ glycogen use	CAR spares muscle glycogen	Metabolism & Performance
Stephens 2013	Nutraceutical	12 M	n=6: 1.36 CAR + 80g CHO n=6: 80g CHO 2*d, 12 wks	30 min cycling @ 50% VO _{2max}	CAR ↑ LCA-CoA ↑ fat mass in CHO	CAR prevented fat mass gain	Metabolism

Abramowicz 2005	Nutraceutical	6 M 6 F	n=12: 1*3g CAR + TART n=12: 3g/d CAR + TART, 14d n=12: PLA, 14d	60 min cycling @ 60% VO _{2max}	CAR + TART for 14d ↑ CHO oxidation in M vs. PLA No effect on FO	CAR & TART promote CHO oxidation during exercise	Metabolism
Broad 2005	Nutraceutical	15 M	n=15: 3g/d CAR + TART n=15: PLA 4 wks	90 min cycling @ 65% VO _{2max} , 20 km TT	FO and CHO similar between CAR & TART vs. PLA during exercise TT duration ↓ in PLA only	CAR & TART enhance energy metabolism or endurance performance	Energy Metabolism & Performance
n-3 PUFAs							
Smith 2011	Nutraceutical	5 M 4 F	4g/d n-3 PUFAs 8 wks	–	↑ MPS & ↑ mTOR signalling during hyperinsulinaemia- hyperaminoacidaemia	n-3 PUFAs augments acute anabolic responses	Metabolism
Smith 2011	Nutraceutical	15 M 29 F	n=29: 4 g/d n- 3 PUFAs n=15: corn oil 6 months	–	n-3 PUFAs ↑ mass & ↑ strength vs. corn oil	n-3 PUFAs promotes muscle growth	Mass
Huffman 2004	Nutraceutical	7 M	n-3 PUFAs 4 g/d 3 wks	60 mins running @ 60% VO _{2max}	↑ fat EE	Chronic n-3 PUFAs promote fat oxidation during exercise	Metabolism

Logan 2015	Nutraceutical	24 F	n=12: 2g/d EPA + 1g/d DHA n=12: PLA 12 wks	Pre & post exercise testing	n-3 PUFAs ↑ LBM, ↑ rate of FO & ↓ TUG	n-3 PUFAs promotes fat metabolism, muscle mass and function	Mass, Fat Metabolism and Performance
Smith 2015	Nutraceutical	10 M 29 F	N=29: 1.86g/d EPA + 1.5 g/d DHA N=25: PLA 24 wks	-	n-3 PUFAs ↑ muscle volume & strength vs. PLA	n-3 PUFAs preserve muscle mass and function	Mass & Performance
Rodacki 2012	Nutraceutical	45 F	n=15: 400 g/d EPA + 300g/d DHA 90d + RET n=15: 400 g/d EPA + 300g/d DHA 150d + RET N=15: RET	RET 3*wk, 12 wks	> ↑ in peak torque following n3-PUFAs vs. RET	n3-PUFAs potentiate strength adaptations to RET	Strength Performance
McGlory 2016	Nutraceutical	19 M	n=10: 5g/d n3-PUFAs n=9: PLA 8 wks	Acute RE 3 sets, 10 reps @ 70% 1-RM	Rest and exercise MPS similar following n3-PUFAs vs. PLA ↑ p70S6K1 after RE in PLA only	n3-PUFAs does not potentiate RE-induced metabolic responses	Metabolism
Delarue 1996	Nutraceutical	4 M 1 F	n=5: 6g/d n-3 PUFAs n=5: PLA 3 wks	-	n-3 PUFAs ↑ FO & ↓ CHO oxidation	n-3 PUFAs manipulates energy metabolism	Energy Metabolism

Delarue 2003	Nutraceutical	6 M	n=6: 6g/d n-3 PUFAs n=6: PLA 20d	Acute 90 min cycling @ 60% max O ₂ output	n-3 PUFAs tended to ↑ FO and ↓ CHO oxidation > PLA	n-3 PUFAs might manipulate energy metabolism during exercise	Energy metabolism
Nitrates/Blood flow							
Tang 2011	Nutraceutical	8 M	n=8: 10g EAA + 10g Arg n=8: PLA	Unilateral acute RE, 5 sets 8-10 reps	↑ in blood flow and MPS following RE similar in Arg vs. PLA	Arg has no additive effects on muscle blood flow or MPS	Protein Metabolism
Churchward-Venne 2014	Nutraceutical	21 M	n=7: 45g Whey n=7: 10g citrulline + 15g whey n=7: 10g NEAA + 15g whey	Acute RE: 6x8-10 reps @ 80% 10-RM knee extension	No ↑ in MPS, blood flow or perfusion following citrulline+whey vs. NEAA+whey	No additive effect of citrulline on metabolism	Protein Metabolism
Phillips 2016	Nutraceutical	20 M	n=10: 350 mg cocoa flavanol n=10: CON	-	↑ LBF and MBV following cocoa flavanol ↔ MPS following cocoa flavanol vs. CON	Cocoa flavanols improve vascular but not MPS responses to nutrition	Protein Metabolism
Lansley 2011	Nutraceutical	9 M	n=9: 500 ml BRJ n=9: 500 ml PLA	4 & 16.1 km cycling TT	↑ TT performance	Nitrates improve TT performance	Performance
Larsen 2007	Nutraceutical	9 M	n=9: 0.1mmol kg/d NaNO ₃ n=9: PLA 3d	Sub-max and max cycling	NaNO ₃ ↓ V _{O2} at sub-max vs. PLA	NaNO ₃ reduced O ₂ cost during sub-max exercise	Performance

Bailey 2009	Nutraceutical	8 M	n=8: 500ml/d BRJ n=8: PLA 6d	Moderate & intense exercise	BRJ ↓V _{O2} during moderate exercise vs. PLA BRJ ↑ TTE during intense exercise	BRJ can reduce O ₂ cost & improve exercise tolerance	Performance
Muggeridge 2014	Nutraceutical	9 M	n=9: 1*70ml BRJ n=9: PLA	15 min steady state, 5 min rest, 16.1 km TT	BRJ ↓V _{O2} during moderate exercise vs. PLA TT performance was faster following BRJ	BRJ enhances endurance performance	Performance
Wylie 2013	Nutraceutical	14 M	n=14: 490ml BRJ over 30h n=14: PLA	Yo-Yo IR1	BRJ ↑ Yo-Yo IR1 performance vs. PLA	BRJ improved high intensity running performance	Performance
Arnold 2015	Nutraceutical	10 M	n=10: 70 ml BRJ n=10: PLA	Incremental treadmill running + 10km TT	BRJ did not change TTE during incremental exercise or time to completion in the TT vs. PLA	BRJ does not enhance endurance running	Performance
Cermak 2012	Nutraceutical	20 M	n= 20: 1*140 ml BRJ n=20: PLA	1h cycling TT	TT performance & power output similar between BRJ vs. PLA	BRJ does not improve endurance performance	Performance
Wilkerson 2012	Nutraceutical	8 M	n=8: 1*500ml BRJ n=8: PLA	50 mile cycling TT	No difference between BRJ vs. PLA for completion time & power output Trend for BRJ ↓V _{O2}	BRJ did not improve TT performance	Performance
β-alanine and Carnosine							
Kendrick 2008	Nutraceutical	26 M	n=13: 6.4g/d β-ala n=13: PLA 4 wks	RET 4*wk, 10 wks	Similar ↑ in strength & body mass	No additive effect of β-ala on strength, mass	Mass & Performance

Hill 2007	Nutraceutical	25 M	n=13: 4-6.4g/d β -ala n=12: PLA	-	4 & 10 wks of β -ala \uparrow TWD during cycling	β -ala improves exercise capacity	Performance
Derave 2007	Nutraceutical	15 M	n=8: 4.8g/d β -ala n=7: PLA 4-5wks	Track & field ~5*wk	β -ala \uparrow knee torque during repetitive exercise bouts	β -ala attenuates fatigue	Performance
Stout 2007	Nutraceutical	22 F	n=11: 3.2-6.4g/d β -ala n=11: PLA 4 wks	-	β -ala \uparrow PWC _{FT} , VT & TTE	β -ala delays the onset of neuromuscular fatigue	Performance

VitD

Agergaard 2015	Micronutrient	17 M, Y 17 M, O	n=7 Y, 7 O: 1920 IU/d VitD + 800 mg/d calcium n=10 Y, 10 O: 800 mg/d calcium 16 wks	RET 3*wk @ 65-85% 1-RM, 12 wks	Fibre type IIa %age $> \uparrow$ & myostatin mRNA $> \downarrow$ in Y VitD vs. Y pla No difference in the \uparrow of CSA and strength in VitD vs. calcium	But no additive effect on mass or strength	Mass and Performance
Carrilo 2013	Micronutrient	11 M 12 F	n=10: 4000 IU/d VitD n=13: PLA	RET 3*wk @ 70-80% 1-RM, 3 months	\leftrightarrow LBM following VitD or PLA \uparrow peak power following VitD	VitD has no impact on mass but can improve muscle power	Mass & Performance
Bunout 2006	Micronutrient	10 M 86 F	n=24: 800 mg/d calcium + 400 IU/d VitD n=24: 800 mg/d calcium n=24: 800 mg/d calcium	RET 2*wk, 9 months	$>$ improvement in TUG in VitD + RET vs. RET	VitD enhances muscle function	Performance

			+ 400 IU/d VitD + RET n=24: 800 mg/d calcium & RET				
Ceglia 2013	Micronutrient	21 F	4000 IU/d VitD 4 months	–	↑ type I/II CSA	VitD increases muscle fibre size	Mass
VitC and VitE							
Bobef 2010	Micronutrient	23 M, 25 F	n=11: AS (1000 mg/d VitC & 600 mg/d VitE) n=12: PLA n=13: RET n=12: AS+RET	RET 3*wk @ 80% 1-RM, 6 months	> ↑ FFM in AS+RET vs. PLA, RET or AS.	AS potentiates RET-induced gains in FFM	Mass
Bjørnsen 2015	Micronutrient	34 M	n=17: AS (1000 mg/d VitC + VitE 235 mg/d) n=17: PLA	RET 3*wk, 3 months	> ↑ in total LBM and muscle thickness in PLA vs. AS	AS blunt ↑ in total LBM	Mass
Paulsen 2014	Micronutrient	21 M 11 F	n=17: AS (1000 mg/d VitC + 235 mg/d VitE) n=15: PLA	RET 4*wk, 10 wks	> ↑ p38 MAPK, p70S6K, ↑ ERK1/2 in PLA vs. AS Similar changes in FSR, CSA & total LM	AS altered protein signalling but not muscle hypertrophy	Mass & Metabolism
Labontè 2008	Micronutrient	27 M 34 F	600 mg VitE + 1000 mg VitC 6 months	RET 3*wk, 6 months	> ↑ FFM compared to RET alone	AS potentiate FFM gains	Mass

Bobef 2011	Micronutrient	27 M 30 F	n=11: AS (1000 mg/d VitC + 600 mg/d VitE) n=12: PLA n=13: RET n=12: AS+RET	RET 3*wk @ 80% 1-RM, 6 months	Similar ↑ in FFM and strength in AS+RET vs. RET	AS do not maximize strength or mass gains	Mass & Performance
Paulsen 2014	Micronutrient	26 M 28 F	n=27: AS (1000 mg/d VitC + 600 mg/d VitE) n=27: PLA	EET 3-4*wk, 11 wks	Similar ↑ in VO _{2max} ↔ COX4 and PGC-1α	AS hampered mitochondrial cellular adaptations	Performance
Yfanti 2010	Micronutrient	21 M	n=11: AS (500 mg/d VitC + VitE 400 IU/d) n=10: PLA 16 wks	EET 5*wk, 12 wks	Similar ↑ in VO _{2max} , P _{max} , workload at LT, muscle glycogen, muscle enzyme activity	AS have no effect on adaptation to EET	Performance
Gomez-Cabrera 2008	Micronutrient	14 M	n=5: VitC 1g/d + EET n=9: EET	EET 3*wk 65-80% of VO _{2max} , 8 wks	Similar ↑ in VO _{2max}	VitC has no effect on adaptation to EET	Performance
Ursolic Acid							
Bang 2014	Nutraceutical	16 M	n=9: 450 mg/d UA n=7: PLA	RET 6*wk @60- 80% 1-RM, 8 weeks	> ↑ strength vs. PLA ↔ LBM in UA or PLA	UA promotes gains in strength but not LBM	Performance
Phosphatidic Acid							
Joy 2014	Nutraceutical	28 M	n=14: 750 mg/d PA n=14: PLA	RET 3*wk, 8 wks	> ↑ LBM, CSA & strength vs. PLA	PA potentiates RET-induced mass and strength gains	Mass & Performance

Hoffman 2012	Nutraceutical	16 M	n=7: 750 mg PA n=9: PLA	RET 4*wk @ 70% 1-RM, 8 wks	NS. ↑ LBM & strength	PA did not potentiate RET-induced gains in mass or strength	Mass & Performance
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