"Nutraceuticals" in relation to human skeletal muscle and exercise

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Abstract

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

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

Introduction

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

The consumption of nutritional supplements with "ergogenic" claims occurs in many populations including athletes (186), the elderly (24), chronic disease sufferers (78) and sedentary (201) adults, often without sound empirical evidence. As such there is a need to review the continually growing area of nutrients/ nutraceuticals and associated mechanisms on aspects of skeletal muscle health, in order to formulate evidenced-based recommendations. Indeed, previous reviews have summarized the effects of multiple nutrient/nutraceutical compounds on aspects of skeletal muscle metabolism and exercise performance (53, 171). Often such reviews target a specific population (e.g. athletes), endpoint (i.e. aerobic performance), or dosing regime (e.g. timing and amount). As such, the present review adopts a more wide-ranging scope, including data irrespective of age, training status, or other independent variables, in order to highlight universal skeletal muscle effects of each nutritional compound.

Herein, we detail existing evidence for a non-exhaustive list of established and emerging nutrients in relation to some or all of the following endpoints: 1) muscle mass; 2) metabolism (protein and fuel) and, 3) exercise performance (i.e. strength and endurance capacity). Since nutrition and exercise are the two key modifiable lifestyle factors for maintaining muscle health, this review will critique available literature examining the muscular responses to nutrient supplementation alone, nutrient supplementation plus acute exercise and chronic nutrient supplementation combined with chronic exercise training (i.e. more than one bout of exercise). We shall include responses to both resistance exercise (RE)/RET and endurance exercise/endurance exercise training (EE/EET) since exercise mode may differentially influence muscular responses to nutrition. Lastly, due to the emerging nature of some nutrients, where mechanisms have not been well defined in humans, data from other models (e.g. cell/rodents) have been drawn upon where necessary. Therefore, this review should be of interest to scientists, clinicians, and athletes aiming to optimize muscle mass and function in clinical and athletic populations. Out of the scope of this review are a selection of established nutrients with purported effects on muscle (e.g. caffeine and green tea) due to the large volume of existing review literature available. Furthermore, some emerging nutrients (e.g. tomatidine and minerals) have been omitted from this review due to the paucity of existing literature. We therefore direct readers to the following publications for further reading regarding nutrients not discussed herein (53), in particular; caffeine (96), green tea (114), tomatidine (69) and minerals (209). Since we have not performed a systematic analysis, we apologize to those whose work we have not alluded to.

Definitions of macro/micronutrients and "nutraceuticals"

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

Established macronutrients and exercise

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

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

Exercise combined with feeding extends the stimulation of MPS (59) thereby delaying the “muscle full” set-point (8). It is the cumulative stimulation of muscle protein turnover with repeated bouts of exercise and feeding that drives exercise-induced skeletal muscle remodeling and hypertrophy (29). The impact of macronutrient supplements on exercise adaptation is multifarious. It is established that CHO intake helps to spare muscle and liver glycogen stores, whilst also leading to a more rapid recovery of these stores post exercise (47, 162). The benefits of chronic protein supplementation alongside exercise are more inconsistent, with a number of studies showing positive (120, 134, 259) or negligible findings (149, 198, 242). However, a recent meta-analysis suggested that overall, protein supplementation does lead to an augmentation of muscle mass and strength gains during chronic RET (49). To conclude, it is now well established that macronutrients play key roles in promoting muscle mass maintenance/ growth and functional adaptations. Future work should focus on identifying the underlying cellular mechanisms and associated refractory period of "muscle-full".

Emerging nutraceuticals and exercise

Leucine metabolites

Leucine, as a BCAA can be metabolized within muscle, engendering the possibility that its metabolites harbor anabolic effects. For instance, the keto-acid derivative of leucine metabolism, alpha-ketoisocaproate (KIC), was shown to stimulate MPS when provided by infusion; however this effect could simply be due to KIC being reversibly transaminated to leucine (74). There is however, good evidence of anabolic activities of the more distal leucine metabolite, β-hydroxy-β-methylbutyrate (HMB) produced via cytosolic KIC dioxygenase (174). Ingestion of ~3g HMB in humans elicited comparable increases in MPS to 3g of leucine, whilst also suppressing MPB independently of insulin (256). Similarly to leucine, the stimulation of MPS by HMB is attributable to enhanced mTORC1 signaling (256). In order to understand the insulin-independent suppression of MPB associated with HMB, numerous molecular targets associated with different proteolytic pathways (beclin 1, calpain 1, MuRF1, Mafbx and cathepsin L) have been investigated, although no detectable changes in the protein abundance or post-translational modifications were observed (256). Although it has been previously shown that there is a disparity between protein breakdown and the abundance in proteolytic proteins (102). It should be noted that only small amounts of HMB (~5%) are generated from normal leucine metabolism (137) meaning that in order to obtain 3g of HMB (a commonly supplemented amount) one would have to consume 60g leucine (260). Thus, when supplementing with physiological doses of leucine it is unlikely that HMB is the main anabolic constituent, hence the practical use of HMB as a stand alone nutritional supplement.

Indeed, longer term studies have found that HMB preserved muscle mass during periods of disuse (65), while year long supplementation of HMB (plus arginine and lysine) in the elderly led to improved preservation of lean body mass, possibly due to an augmentation in muscle protein turnover (10). Although, since HMB was administered as part of a nutritional cocktail it is impossible to delineate whether HMB was solely responsible for the effects on lean body mass. However, recent meta-analysis of 287 elderly participants (147 HMB-supplemented and 140 controls) found HMB supplementation led to greater gains in muscle mass compared to controls, indicating HMB is an effective ergogenic aid, at least in the elderly population, for preventing the loss of lean body mass (268). These anabolic properties of HMB have also been suggested to facilitate favorable RET adaptations. For example, supplementation of HMB (3g/day) with RET for between 4 and 7 weeks led to heightened increases in muscle strength (181), lean body mass (261) and fat free mass (174) compared with RET alone. However, not all studies have reported positive effects; for instance RET for 1 month combined with between 3 to 6g/day of HMB did not change parameters of body composition in RE trained males (140). In this latter case, HMB was provided in its calcium form (CaHMB) (140), which compared to the free acid form (FA-HMB), may have lower bioavailability and therefore might not enhance anabolism to the same extent (82) (though this premise remains to be tested).

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

Furthermore, HMB has been shown to be efficacious for improving EE performance. For example, Vukovich et al. (2001) reported that HMB in combination with EE prolonged the time to reach the onset of blood lactate accumulation and VO_{2PEAK}, although via an unknown mechanism (246). Others have investigated markers of endurance performance following high intensity interval training (HIIT) with or without HMB supplementation. To exemplify, following 5 weeks of HIIT-based running in combination with 3g/d ca-HMB, VO_{2MAX} improved more compared to placebo (144). The authors speculated that the performance benefits were attributable to the preservation of the cell-membrane, however was membrane stability was not measured in the study and thus no mechanistic conclusions can be drawn. Furthermore, HMB in untrained participants potentiated the effects of HIIT on physical working capacity at the onset of neuromuscular fatigue, compared to HIIT training alone (163).

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

Creatine

Creatine (Cr) is an endogenously formed metabolite synthesised from arginine, glycine and methionine (20). Found almost exclusively in skeletal muscle, Cr levels can be increased via endogenous synthesis in the liver and pancreas or exogenously from foodstuff, particularly meat and fish (43, 99). Following oral consumption of Cr, Cr is absorbed into the systemic circulation and is taken up by skeletal muscle via the sarcolemal Na^+/Cl^--dependent transporter, soluble carrier family 6 member 8 (SLC6A8) (126). Intramuscular Cr can then be phosphorylated to phosphocreatine in a reversible reaction facilitated by the enzyme, creatine kinase. During high energy demands, the phosphate of phosphocreatine plus free ADP is used for ATP synthesis (126). Another fate of intramuscular Cr is the conversion to the end-product creatinine, which due to its muscle exclusivity correlates with muscle mass (110). Creatinine diffuses out of the muscle cell and is removed from the body via urine (126). Oral Cr administration (20-30g/day for 2 or more days) increases total muscle Cr stores by >20%, of which 20-30% is stored in the form of phosphocreatine (PCr) (107). The greatest Cr loading effects are seen in those with the lowest basal Cr pool levels i.e. vegetarians (99), thus basal muscle Cr levels are an important determinant of Cr uptake (43, 107). The ergogenic effects of Cr are facilitated by elevated resting PCr, which sustains PCr-mediated ATP resynthesis during intense anaerobic exercise (42) primarily in fatigue susceptible type II fibers (43), thus improving acute high intensity performance. Increased basal muscle PCr levels also expedite the replenishment of PCr stores during recovery from intense exercise, leading to improved performance over repeated bouts of sprint exercise (43, 99). For example, 20g/day of Cr for 5 days led to sustained isokinetic torque compared to placebo during repeated bouts of maximal voluntary contractions (100). Similar results have been obtained when employing different exercise modes such as cycling (18, 70). In contrast, some studies have shown no effect of Cr supplementation on exercise performance (55, 170, 219, 234). For example, despite increased total muscle Cr following 5 days 30g Cr (and 30g dextrose) supplementation, there were no improvements in sprint exercise performance (219). A lack of ergogenic effect may be attributable to the small total muscle Cr levels of ~12mmol/kg/dry weight (219), where previous reports show total Cr of >20 mmol/kg dry mass results in ergogenic benefit (42). Factors affecting the extent to which muscle Cr stores increase are not well known, although pre-existing muscle Cr, exercise (107) and CHO ingestion (98) may be potential factors. Also in regards to performance, Cr supplementation improves the rate of functional recovery following exercise (54), which might be mediated by Cr promoting gene expression thereby aiding MPS during the recovery periods (54, 258), ultimately increasing the deposition of newer functional proteins for improved functional recovery. Indeed, Cr supplementation will also increase muscle PCr, which might increase local rephosphorylation from ADP to ATP (54), thus providing more energy for contraction. As such, performance during successive bouts is maximized (i.e. can work at higher training loads) which, in-turn, may contribute to the gains in strength observed when combined with RET (31, 63, 66).

In addition to energetic impacts, evidence supports a role for chronic Cr supplementation, typically provided as a loading dose (i.e. ~5 days of 20/30g) followed by maintenance doses (~ 5g) (32), for increasing muscle mass (25, 31, 245). For example 12 weeks RET plus Cr (25g/day for the first week, followed by a maintenance dose of 5g/day for the rest of the training duration) resulted in significantly greater fat free mass, strength and fibre cross sectional area gains compared to placebo (245). Similarly, 14 weeks of whole body RET (3 x/week) combined with Cr (5g/day plus 2g dextrose) led to significantly greater gains in fat free mass (31). Furthermore, a recent meta-analysis concluded that Cr supplementation combined with RET elicited further increases in fat free mass compared to RET alone (albeit in older adults) (66). This meta-analysis reported a weighted mean difference (WMD) of 1.33kg for RET combined with Cr (66), compared to 0.69kg for RET with protein (49) demonstrating the potent ergogenic effect of Cr on fat free mass. The mechanisms regulating the effects of Cr on muscle mass remain to be fully elucidated; although it is known that acute provision of Cr does not directly stimulate MPS either with (152) or without RE (153). However, Cr did augment the satellite cell (SC) response following RE (178), which may contribute to hypertrophic gains since increased SC content is observed following chronic RET (241). Although the contribution of SC to hypertrophy is still debated (158), theoretically the nucleus content in hypertrophying muscle fibres becomes diluted such that additional nuclei are required for continued growth. As such, SC fuse and donate nuclei to the pre-existing muscle fibres, thereby increasing the transcriptional capacity of the muscle cell and thus the potential for growth (30). Additionally, augmented PCr availability and ATP resynthesis during intense exercise likely permits greater work output. Greater work may be a factor which stimulates greater muscle gene expression thereby promoting muscle mass accretion observed with Cr supplementation (32, 204, 257). It is possible that changes in fat free mass may be in part attributable to the osmotic potential of elevated intracellular Cr leading to myocellular water retention (204, 273). This potential increase in cell volume from Cr-induced fluid retention may then act as an anabolic signal, activating intracellular signalling cascades that maintain cellular function (204). For example, the attachment complex protein focal adhesion kinase (FAK), which is critical for osmosensing and hypertrophic signalling (56), is up-regulated following Cr supplementation (204).

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

Carnitine

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

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

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

Subsequent studies have supported the role of carnitine combined with CHO for the prevention of fat gain, which was associated with increased fat oxidation during low intensity exercise (227). Conversely, increased CHO but not fat oxidation during steady-state exercise has been reported following 2 weeks of carnitine supplementation (3g/day carnitine and tartrate combined with CHO meals) (1), and 1 month of carnitine intake (3g/day carnitine and tartrate) had no effect on substrate oxidation during steady-state exercise (27). These findings conflict with those reported at rest and differ from hypotheses which suggest limited carnitine availability may limit fat oxidation during exercise (224). Interestingly, in the study by Broad and colleagues (27) there was no mention of daily carnitine supplementation being co-ingested with supplemental CHO, which is critical for increasing muscle carnitine stores (226). Therefore the protocol might have been suboptimal for increasing muscle carnitine stores, which was not measured within the study, and thus may explain the negligible effect of carnitine on substrate utilisation.

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

n-3 polyunsaturated fatty acids

n-3 polyunsaturated fatty acids (n-3 PUFA), contain a double bond at the third carbon atom from the end of the carbon chain. Abundantly found in walnuts and oily fish, there are 3-types of n-3 PUFA: 1) alpha-linoleic acid (ALA), 2) eicosapentaenoic acid (EPA), and 3) docosahexaenoic acid (DHA). n-3 PUFA serve well established roles as critical components of cell membranes and as substrates for lipid signaling (37). Early evidence demonstrated a role for n-3 PUFA in muscle anabolism when n-3 PUFA-enriched feed provided to growing steers increased the phosphorylation of anabolic signaling and the non-oxidative whole-body disposal of AA, representative of increased whole-body protein synthesis (85). Additionally, fish oil containing 18% EPA attenuated the loss of skeletal muscle following 30% burn in guinea pigs, which may be mediated by EPA reducing inflammatory related prostanoids (4). Hence there is interest for the application of n-3 PUFA as a nutritional supplement in humans. It has been suggested that fish oil supplementation in humans may increase muscle n-3 PUFA content (160), have anti-inflammatory properties (128) via reduced leukotriene B4 formation (an inducer of inflammation) (79) and attenuate the loss of muscle mass in disease states, possibly via reductions in pro-inflammatory cytokines (203). Furthermore, n-3 PUFA might potentiate anabolic responses to nutrition in skeletal muscle. In support of this, 8 weeks n-3 PUFA supplementation (1.86g EPA plus 1.5g DHA/day) was shown to augment hyperaminoacidaemia-hyperinsulinemia induced increases in mixed MPS compared to corn oil controls in young, middle aged and older adults (215, 216). Indeed, enhanced phosphorylation of mTORC1 and the downstream target p70S6K1 were observed in young, middle aged and older adults (215, 216). However, MPS increases were observed in the context of hyperaminoacidaemia and hyperinsulinemia, which may not be physiologically obtainable. Moreover, supplementation of n-3 PUFA for 3 (151) and 6 months (217) led to increases in muscle mass and function in older adults. A recent study in C_2C_{12} skeletal muscle cells found a 25% increase in MPS following EPA that was not observed following DHA (131), suggesting that EPA may be the more anabolic constituent of n-3 PUFAs. Interestingly, both EPA and DHA stimulated p70S6K1, thus EPA might stimulate MPS via a p70S6K1 independent mechanism (131).

Despite being less well defined, these positive effects of n-3 PUFA on muscle appear to be recapitulated when combined with exercise (202). Supplementation during 3 months RET promoted increases in muscle strength in older women (202), suggesting that n-3 PUFA could have a positive role on muscle protein metabolism by enhancing the anabolic response to RE (90). Despite recent contrasting findings that chronic fish oil supplementation failed to increase muscle anabolism in younger people under rested and exercise trained conditions (161), the lack of pre- and post-intervention measurements confound interpretation of these results. Additionally, positive findings regarding the efficacy of n-3 PUFA supplementation have been largely observed in older adults. Because ageing associates with blunted anabolic responses to AA and exercise, the muscular benefits of n-3 PUFA may be more pronounced in those in which anabolic responses are already sub-optimal.

Whilst the combination of EE and n-3 PUFA have not been investigated in the context of muscle mass and protein metabolism, there is sound evidence to suggest that n-3 PUFA supplementation may alter fuel metabolism by improving metabolic flexibility, i.e. the ability to switch between using fat or CHO as a fuel source. For example, 6g/day of fish oil for 3 weeks led to a 35% increase in fat oxidation following a glucose or fructose bolus (61). In the context of exercise, 3 weeks fish oil supplementation (6g/day) led to a non-significant trend for greater fat oxidation during an acute bout of cycling (90 minutes at 60% O_2 output), a possible compensatory response for the lower CHO oxidation (62). Further studies have found significantly greater fat oxidation during EE in humans following 3 weeks fish oil supplementation (119). Although, each of these studies lacked comprehensive investigation into the mechanisms regulating changes in metabolic flexibility, n-3 PUFA have been shown to mediate the up-regulation of genes regulating mitochondrial biogenesis, such as peroxisome proliferator-activated receptor-alpha (PPARα) and -gamma (PPARγ) and the transcription factor nuclear respiratory factor 1 (NRF1) in mice (146), offering a potential explanation for these findings. Additionally, rats fed a low fat diet supplemented with DHA had higher oxygen consumption and apparent *K*m for ADP in permeabilised muscle fibres compared to placebo, indicative of improved mitochondrial function (103). Thus, effects on mitochondrial biogenesis and function may underpin the synergistic effects of n-3 PUFA and EE-associated metabolic adaptation.

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

Nitrates

Nutrients that contain dietary inorganic nitrates (e.g. beetroot and lettuce) or related precursors (e.g. arginine) can increase nitric oxide (NO) availability, which is capable of modulating muscle-related processes including contraction, glucose homeostasis, blood flow (127) and satellite cell activation (5, 35). Following oral ingestion of dietary nitrate-rich foods, nitrate (NO_3^-) is reduced to nitrite (NO_2^-) via nitrate reductases within the mouth (68). Subsequently, NO_2^- is converted into NO and additional reactive nitrogen species in the acidic environment of the stomach (2). Oral NO_3^- increases plasma NO_3^- and NO_2^- levels, indicating nitrates are bioavailable. With regards to muscle protein turnover, these compounds are thought to promote anabolism via improving blood flow (through increased NO production), thus enhancing nutrient delivery to the muscle, providing more substrates for MPS. However, it has been shown on several occasions that enhanced muscle blood flow does not augment anabolic responses in young or older males (164, 187–189). Nonetheless, dietary arginine (the principle substrate for endothelial nitric oxide synthase (eNOS) for endogenous production of NO) supplementation did increase the weight of the soleus and EDL muscle in obese rats (125). However, in humans Tang and colleagues found oral arginine (10g), of which approximately 70% is bioavailable following ingestion (154), had no effect on muscle blood flow or MPS when provided alone or in combination with AA or acute RE (232). In contrast, vasodilatory effects of arginine have been shown when administered by IV infusion at higher doses (30g) (23). By comparison, the peak in plasma arginine was considerably lower following 10 g of oral arginine (~225 $\mu mol \cdot L^{-1}$) (232) versus 30g IV infused arginine (~6223 $\mu mol \cdot L^{-1}$) (23), thus the dose of arginine used by Tang and colleagues may not have been sufficient to increase plasma arginine to an amount which elicits effects on vasodilation. In fact the authors project that on the premise of 70% bioavailability, a total of ~43 g of oral arginine would have been required to reach similar plasma levels reported following IV infusion (232). An alternative may be to utilize the arginine precursor citrulline (156), which bypasses splanchnic extraction (267). Supplementation of citrulline in rodents was shown to stimulate MPS (179) via the mTORC1 pathway (193). However, similar effects have not been observed in humans, since there was no additional impact of citrulline (10g), when co-ingested with whey, on MPS or blood flow with or without acute RE versus whey combined with non-essential AA (NEAA) (52). Lastly, flavanols such as in cocoa (39, 109) also promote vasodilation via NO pathways (80, 132). It was recently reported that despite an acute dose of cocoa flavanols (350mg) increasing macro- and microvascular blood flow, this was not associated with enhanced muscle anabolic responses to nutrition (188), suggesting in healthy individuals nutrient delivery is not rate-limiting for muscle anabolism (189).

In contrast to muscle mass and strength related studies, a plethora of research has investigated the effects of nitrates and EE on whole body metabolism and endurance performance. An early study by Larsen et al. (2007) reported that sodium nitrate supplementation reduced the O_2 cost of submaximal cycling exercise (148), whilst similar results have reported following nitrate-rich beetroot juice supplementation (11), indicative of improved aerobic metabolism or mechanical efficiency (147). In addition to metabolic improvements, nitrate supplementation provided in the form of 500ml beetroot juice improved 4 and 16.1km cycling time trial performance in trained cyclists (145). These improvements are likely attributable to an enhanced rate of PCr recovery (239) increasing the rate of ATP synthesis, although this mechanism remains speculative at present. Emerging evidence from cell culture studies suggests nitrate supplementation enhances mitochondrial biogenesis and oxidative metabolism via increased 5'adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor γ co-activator 1α (PCC-1α) gene expression (240), though *in vivo* data is lacking. Although others have also reported nitrate-mediated improvements in EE performance have been shown (169, 269), several authors have shown no improvements (6, 48, 254). For example, consuming 140ml of beetroot juice 2.5h prior to a 1h cycling time trial did not improve time trial performance in trained cyclists compared to placebo (48). These discrepant findings may be explained by methodological differences such as the dose of nitrates (since the increase in plasma NO_3^- and NO_2^- is somewhat dose dependent (270)), control of nitrate intake, the source of nitrates provided and the training status of the participants. For example, since numerous studies demonstrate nitrate supplementation to have no beneficial effect on performance in well trained participants (6, 48, 254), it is likely that fitness status influences the ergogenic potential of nitrate supplementation (127). Indeed, higher plasma levels of NO_2^- were present in trained versus untrained participants pre and post acute exercise (195). This may be explained by higher nitric oxide synthase (NOS) activity (159) and/ or higher plasma nitrate values (195) in trained participants.

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

β-*alanine and carnosine*

β-alanine (BA) is a beta AA produced endogenously in the liver found primarily in meat (238). BA is the rate-limiting precursor for the synthesis of carnosine, which is a dipeptide of BA and histidine that improves the muscle buffering capacity (222). BA supplementation has generated interest as an ergogenic aid since early studies found BA supplementation capable of increasing muscle carnosine stores by ~40-65% demonstrating good bioavailability; a consistent and reproducible finding (16, 108, 222). Although the extent to which carnosine content increases may be dependent on the dosing protocol (108). Other factors have been shown to cause muscle carnosine variability, including gender, age, dietary BA intake, vegetarianism (76) and fibre type distribution, since carnosine content is double in type II compared to type I fibres (38). The regulation of muscle carnosine stores from dietary/ supplemental sources is still under investigation (222). Oral BA may be transported across the gut via the H^+-coupled PAT1 AA transporter (235), which increases plasma availability of BA for muscle carnosine synthesis. Transport of BA into skeletal muscle has been shown to be regulated via both peptide transporter 2 (PEPT2) (67) and the taurine transporter (TauT) (237), although this remains to be confirmed in humans. Once within the muscle cell, BA and sarcoplasmic histidine synthesize carnosine via carnosine synthase (222).

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

During high intensity exercise, the build up of H^+ ions reduces the intramuscular pH leading to fatigue likely due to acidosis-induced reductions in ATP generation (205). Increased muscle carnosine, via BA supplementation, is capable of reducing intramuscular acidity during high intensity exercise therefore enhancing exercise performance (57, 112, 229). For example, 4 and 10 weeks of BA supplementation increased cycling capacity (total work done) in untrained males when cycling at 110% of maximum power (112), hypothesized to be due to improved intracellular buffering. In sprint-trained athletes, 4-5 weeks BA supplementation (4.8 g/day) led to increased knee torque but did not enhance sprint performance (64). Importantly, this study found increased muscle carnosine stores (+47%), demonstrating that it is possible to increase muscle carnosine even in trained athletes (64). Women supplemented with BA for 28 days delayed the onset of neuromuscular fatigue (denoted by improved ventilatory threshold, physical working capacity and time to exhaustion), likely the result of improved intracellular buffering capacity (228).

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

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

Micronutrients: vitamins and exercise

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

Vitamin D

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

Following sun exposure or consumption of VitD-rich dietary sources/ supplements, circulating VitD bound to VitD binding protein (DBP) increases, and transports to the liver where hydroxylation (via 25-hydroxylase) generates 25-hydroxyvitamin D (25D). A second hydroxylation in the kidney (via 1α-hydroxylase) produces the biologically active form of VitD ($1,25(OH)_2D$) (87). Mechanisms underpinning the effects of VitD on muscle metabolism are not fully understood but are believed to be in part related to the regulation of gene expression via the VDR or secondary messenger protein signaling (194). The binding of $1,25(OH)_2D$ to the VDR causes conformational changes, allowing VDR to heterodimerize with the retinoid X receptor (RXR). This complex then binds to VitD response elements (VDREs) on the DNA, promoting gene transcription (45, 87). $1,25(OH)_2D$ may also have non-genomic effects on intramuscular signaling by binding to a cell surface receptor (40), which, in turn, this activates intracellular signaling pathways such as the Akt and mitogenactivated protein kinases (MAPK) pathway (33). For example, VitD treatment increased myotube size, down-regulated myostatin (88), up-regulated Akt (33) and sensitized the Akt/ mTORC1 pathway and MPS responses to leucine and insulin (206) in muscle cell cultures. Thus, there is growing *in vitro* evidence for an anabolic role of VitD in skeletal muscle. In humans, supplementation of VitD has been proposed to increase muscle strength (13), function (83, 252), fibre area (46, 208, 221), lean body mass (72) and reduce falls (83, 130), although a recent meta-analysis found no overall effects of VitD supplementation on muscle mass (13). Of importance, benefits of VitD supplements are observed particularly in the elderly or in those who are VitD deficient (13), which may be a potential explanation for some of the discrepant findings within the literature.

Since VitD supplementation has been suggested to promote muscle mass and function, concurrent VitD supplementation with RET may be expected to potentiate exercise-induced adaptations. Indeed, 4 months $VitD_3$ supplementation (1920IU/day plus 800mg/day calcium) in combination with lower-body RET for 3 months led to a greater reduction in myostatin mRNA expression, a negative regulator of muscle mass, and a greater change in the percentage of type IIa muscle fibres in young males (3). However, these changes did not translate into greater muscle strength or hypertrophy above RET alone (3). Elderly adults undertaking RET combined with VitD improved muscle quality (strength/ cross sectional area) more so than young males, thus demonstrating that elderly individuals may benefit more from VitD supplementation (3). VitD insufficient (according to VitD ranges by (118)) overweight and obese adults did not augment gains in lean body mass compared to placebo following 3 months RET and 4000IU/day $VitD_3$ (41). This may be due to the fact that VitD is deposited in body fat, reducing bioavailability (266) and requiring greater levels of VitD supplementation to promote muscle anabolism in this population. Similarly, others reported no change in body composition after 9 months supplementation of 400IU/day and RET 2x/week in overweight males and females (34). Since no change in body composition was seen in the training only group either, these findings may resulted from low training adherence (~53%) (34).

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

Vitamins C and E (i.e. "antioxidants")

High levels of free radicals (an atom with a single unpaired electron) and reactive oxygen species (ROS) can disrupt protein homeostasis (196). This is likely due to ROS promoting catabolism via increases in the ubiquitin-conjugating activity (150) and diminishing anabolism via attenuation of MPS and signaling proteins (182), with evidence for these mechanisms arising from cell culture studies. It is therefore thought that consuming dietary antioxidants (i.e. vitamin C (VitC) and E (VitE)) capable of donating an electron to neutralize free radicals (168), may reduce ROS thus minimizing disruption of protein homeostasis. For instance, a positive relationship was observed between VitC intake and appendicular lean body mass (209), which may be related to the fact that muscle is a major storage site for VitC (253).

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

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

Currently, it is difficult to conclude whether antioxidant supplementation is beneficial or detrimental for muscle mass, protein metabolism and performance/adaptation. Close and colleagues highlighted that confusion and misguided conclusions are often drawn due to inappropriate methodological techniques (53). As an example, the lipid peroxidation marker, thiobarbituric acid reactive substances (TBARS), can be the result of non-redox related sources and is thus no longer recommended for use as an oxidative stress marker (81), yet is often published in the context of antioxidant supplementation (111, 155, 157). It is believed that diets rich in fruits and vegetables as opposed to large supplemental doses of antioxidants are preferable since no investigations to date support attenuations in adaptations to training in response to fruits and vegetables, which have naturally occurring antioxidants (53).

Emerging Nutraceuticals

Ursolic acid

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

With regards to exercise interactions, UA injection following RE in rats stimulated p70S6K1 at 1h and was maintained 6h later, which began the descent to baseline in the exercise only group, reflecting prolonged mTORC1 activity and thus anabolic potential when RE is combined with UA (177). Despite an unclear mechanism, the authors speculated that IGF-I may contribute to the UA-induced p70S6K1 activation, and previous work supports this hypothesis (142). Contrary, data in humans (not in the context of UA) shows no change in IGF-I but increased anabolic signaling after acute RE (28). In RE trained males, RET 6 x/week (at 60-80% of 1-RM) for 2 months combined with 450mg/day UA improved leg strength but had no effect on lean body mass, although RET alone also had no effects on lean body mass (12). This may be due the fact that the participants had >3 years RET experience, and hypertrophic responses predominate in the early stages of RET (29). To the author's knowledge, no evidence exists regarding UA supplementation combined with EE. An important issue to consider is the low and variable bioavailability of UA following oral ingestion, likely due to its lack of solubility in aqueous solutions (113). This could markedly impact its potential as a nutraceutical. However, recent efforts have been made to improve the bioavailability of UA and other triterpenoids by, for instance, using nano-liposomes to aid solubility (271). The varied and low bioavailability of UA in humans is demonstrated by the lack of UA content in some participants following a 1g oral dose, and in those that did display UA content, it was only observed up to 12h post consumption (113). Additional findings show oral UA ingestion (3g) lead to increased plasma UA 2 and 6h post-exercise (50). As such, the true bioavailability of UA in response to time and dose should be investigated further.

Phosphatidic acid

Phosphatidic acid (PA) is a diacyl-glycerophospholipid found endogenously in mammalian cell membranes that can be obtained exogenously from raw cabbage (231). Both endogenous and exogenous PA are believed to positively influence muscle protein metabolism, whereby endogenous PA can be increased by RE and directly binds to mTORC1 influencing MPS. Exogenous PA indirectly stimulates mTORC1 activation (77, 165) via extracellular-signal regulated protein kinase (ERK) dependent (262), and phosphatidylinositol-3-kinase (PI3K) independent (176) mechanisms, and may also attenuate MPB via attenuation of atrophy-related genes (210). Exogenous PA in cultured muscle cells also prevented atrophy in the presence of the atrophy-inducing substances tumor necrosis factor alpha (TNF-α) and dexamethasone (122). Recently, acute PA supplementation in rodents tended to increase MPS in the fasted state, however, PA blunted the whey protein induced rise in MPS (165). Possibly the addition of PA to whey alters the pathways of mTORC1 activation thus shifting peak MPS (165); research is needed to understand the signaling responses of PA alone versus PA plus whey. In a human case study, orally ingested PA metabolized into lysophosphatidic acid (LPA) and glycerophosphate, increased plasma PA and LPA 30 minutes post-ingestion (of 1.5g PA), which plateaued at 1-3h and remained elevated above baseline at 7h (197). Thus, it seems PA is bioavailable in humans, although beyond 7h post-ingestion the bioavailability is unknown and further studies with a larger cohort are needed to determine the true bioavailability of PA. PA supplementation (750mg daily) combined with 2 months supervised whole body RET in RE trained males found increased lean body mass and cross sectional area compared to the placebo group (129). Conversely, others have shown non-significant increases (+2.6%) in lean body mass, despite utilizing a similar RET and supplementation programme (115). The differential findings between these studies may be due to the fact that training was unsupervised in the later study. To our knowledge no data currently exists assessing the interactions of PA plus EE.

Combined nutraceuticals

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

Conclusion and Future Directions

While it is extremely unlikely that a single nutraceutical will prove to be a ‘magic bullet’, it is clear that certain nutraceuticals, under certain conditions, do indeed possess ergogenic potential. Of the nutrients discussed herein, strong evidence exists for leucine, HMB and Cr for muscle mass; leucine and HMB for protein metabolism; carnitine for fuel metabolism and leucine, HMB, carnitine, Cr, nitrates and β-alanine for athletic (strength or endurance) performance. Further empirical *in vivo* evidence is required to firmly establish the currently emerging roles of VitD, UA and PA for promoting muscle mass and n-3 PUFA, UA and PA for muscle protein metabolism. This review highlights: 1) the need for better controlled longer duration human studies which investigate the role of individual nutrients on muscle mass, protein/ fuel metabolism and indices of exercise performance/ adaptation, 2) the lack of *in vivo* "mechanistic" studies, and 3) the need to determine the bioavailability of emerging nutrients.

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(INSERT FIGURE HERE)

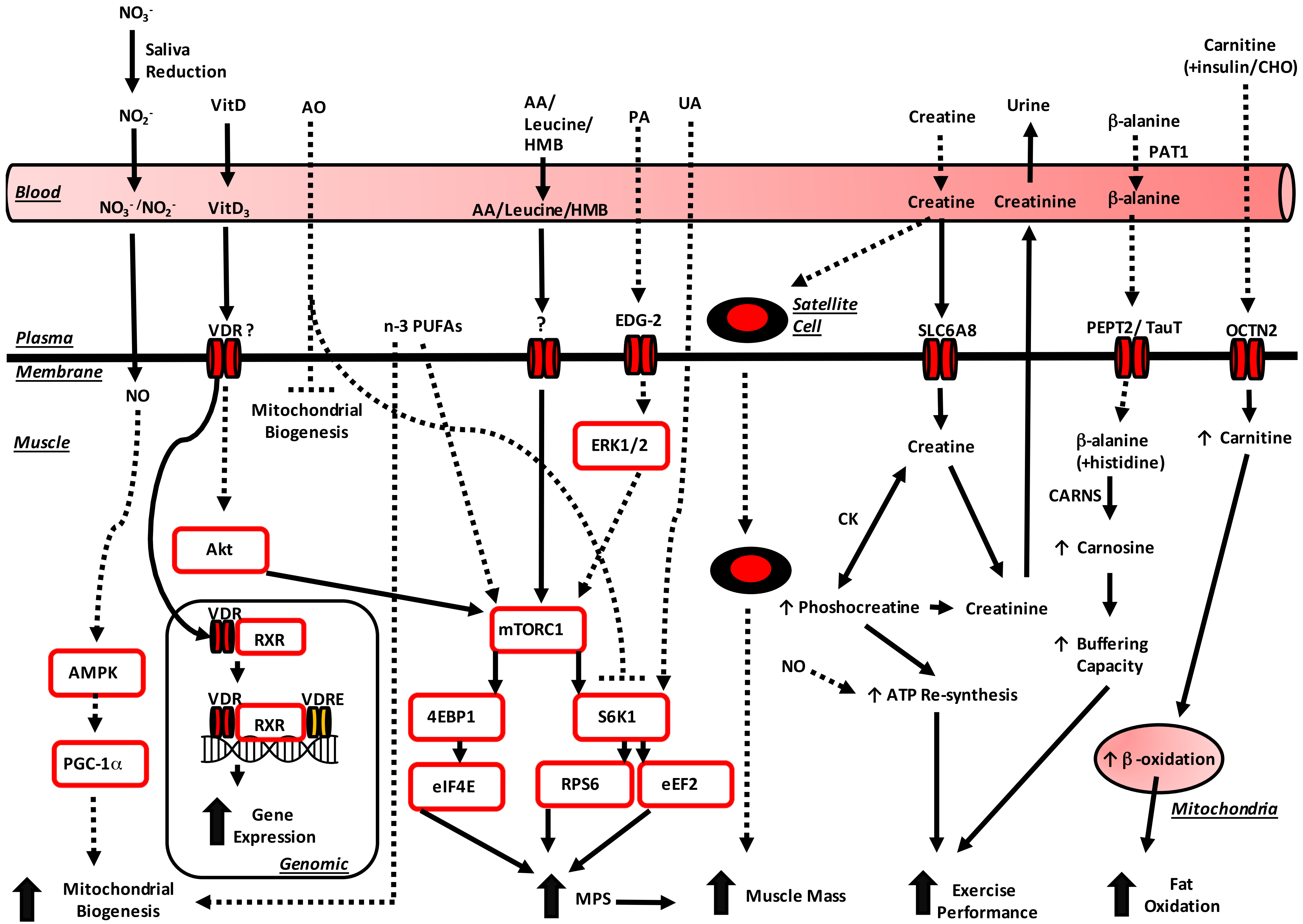
Figure 1. Proposed metabolism and mechanisms of action for nutrients/ nutraceuticals.

→ represents activation; ⇢ represents purported activation; --| represents purported suppression; ? unknown; 4EBP1 4E binding protein-1; AA amino acids; AMPK 5' AMP-activated protein kinase; AO antioxidants; ATP adenosine triphosphate; CARNS carnosine synthase; CHO carbohydrate; CK creatine kinase; EDG-2 endothelial differentiation gene; eEF2 eukaryotic elongation factor 2; eIF4E eukaryotic initiation factor 4E; HMB β-hydroxy-β-methylbutyrate; MPS muscle protein synthesis; mTORC1 mammalian target of rapamycin complex 1; NO_3^-; nitrate; NO_2^- nitrite; NO nitric oxide; OCTN2 organic cation transporter 2; PA phosphatidic acid; PAT1 proton-coupled amino acid transporter 1; PEPT2 peptide transporter 2; PGC-1α peroxisome proliferator-activated receptor-γ coactivator-1α; RPS6 ribosomal protein S6; SLC6AS Solute Carrier Family 6 Member 8; TauT taurine transporter; UA ursolic acid; VDR vitamin D receptor; VDRE vitamin D response elements; VitD; vitamin D; $VitD_3$; active vitamin D.

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

(INSERT TABLE HERE)

↓ decrease, ↑ increase, > larger, ←→ no change, 1-RM: one repetition maximum; AA: amino acids; Arg: arginine; AS: antioxidant supplement; β-ala: beta-alanaine; BRJ: beetroot juice; BW: body weight; CAR: carnitine; CHO: carbohydrate; CON: control; CONC: concentric; CPK: creatine phosphokinase; CR: creatine; CSA: cross-sectional area; d: day/s; EAA: essential amino acids; ECC: eccentric; EE: energy expenditure; EET: endurance exercise training; F: females; FFM: fat free mass; FO: fat oxidation; FSR: fractional synthesis rate; g: grams; h: hours; HIIT: high intensity interval training; HMB: β-hydroxy-β-methylbutyrate; kg: kilograms; km: kilometer; LBF: leg blood flow; LBM: lean body mass; LCA-CoA: long-chain acyl-CoA; LDH: lactate dehydrogenase; LEU: leucine; n-3 PUFAs: n-3 polyunsaturated fatty acids; NEAA: non-essential amino acids; M: males; Max: maximal; MBV: microvascular blood volume; Mg: milligrams; Min: minute; ml: milliliter; mmol: milimolar; MPO: mean power output; MPB: muscle protein breakdown; MPS: muscle protein synthesis ; mRNA: messenger ribonucleic acid; mTOR: mammalian target of rapamycin; $NaNO_3$: sodium nitrate; NS.: non-significant; O: old; O_2: oxygen; OBLA: onset of blood lactate accumulation; p70S6K1: ribosomal s6 kinase 1; PDH: pyruvate dehydrogenase; PLA: placebo; P_{max}: maximal power output; PPO: peak power output; PRO: protein; PWC_{FT}: Physical working capacity at the onset of neuromuscular fatigue threshold; Reps: repititions ; RE: resistance exercise ; RET: resistance exercise training; TART: tartrates; TC: total carnitine; TT: time trial; TTE: time to exaution; TUG: timed up and go; TWD: total work done; VitD: vitamin D; VT: ventilatory thresehold; Wk/s: week/s; Y: young; yr: year; Yo-Yo IR1: Yo-Yo intermittent recovery level 1



NO_3^-
Saliva Reduction
NO_2^-
VitD
AO
AA/ Leucine/ HMB
PA
UA
Creatine
Urine
β-alanine
PAT1
Carnitine (+insulin/CHO)
Blood
NO_3^-/NO_2^-
$VitD_3$
AA/Leucine/HMB
Creatine
Creatinine
β-alanine
Satellite Cell
Plasma
Membrane
VDR ?
n-3 PUFAs
?
EDG-2
SLC6A8
PEPT2/ TauT
OCTN2
NO
Mitochondrial Biogenesis
ERK1/2
Creatine
β-alanine (+histidine)
↑ Carnitine
Muscle
CARNS
CK
↑ Carnosine
Akt
mTORC1
↑ Phoshocreatine
Creatinine
AMPK
VDR
RXR
↑ Buffering Capacity
NO
↑ ATP Re-synthesis
VDR
VDRE
RXR
4EBP1
S6K1
eIF4E
RPS6
eEF2
↑ β -oxidation
PGC-1α
Gene Expression
Genomic
Mitochondria
Mitochondrial Biogenesis
MPS
Muscle Mass
Exercise Performance
Fat Oxidation

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 ↑ 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 ↑ 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 ↑ 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 > ↑ & myostatin mRNA > ↓ in Y VitD vs. Y pla No difference in the ↑ 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	←→ LBM following VitD or PLA ↑ 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				
Bobeuf 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

Bobeuf 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