RESEARCH ARTICLE

The Ability of Carnitine to Act as a Type 1 Histone Deacetylase Inhibitor May Explain the Favorable Impact of Carnitine Supplementation on Mitochondrial Biogenesis in the Elderly

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Abstract

A number of studies have shown that carnitine supplementation – alone or in conjunction with supplemental lipoic acid - promotes mitochondrial biogenesis (MB) in skeletal, muscle, and brain of aging rodents; no such effect is seen in younger animals. These findings parallel clinical studies in which supplemental carnitine improves physical and mental energy in elderly humans, while decreasing body fat and increasing lean mass – effects that have not been achieved with carnitine in younger people. The age dependence of these phenomena appears to reflect the fact that tissue carnitine levels, especially those in muscle, decline during aging; carnitine supplementation restores higher, more youthful tissues carnitine levels in aging animals, but has relatively little impact in this regard on younger ones. The effect of supplemental carnitine on MB in aging animals appears to be mediated, in whole or in part, by increased expression of PPARγ-coactivator-1α (PGC-1α), a key driver of MB. There is recent evidence that, in low millimolar intracellular concentrations such as those seen in skeletal muscle, carnitine functions as an inhibitor of type 1 histone deacetylases (HDACs). Moreover, it has been reported that drug inhibitors of these deacetylases boost mRNA and protein expression of PGC-1α, presumably by promoting transcription of the *PGC-1a* gene; these drugs also amplify MB. It is therefore proposed that intracellular carnitine provides a moderate tonic inhibition of type 1 HDACs that supports *PGC1α* transcription and that diminishes with age as tissue carnitine levels decline; hence, carnitine supplementation in the elderly restores youthful expression of PGC-1α and promotes MB. The complementary impact of lipoic acid on MB may reflect the fact that the promoter of the gene coding for nuclear respiratory factor-1 (NRF-1) contains antioxidant response elements; hence, NRF-1 transcription is promoted by phase 2 inducers such as lipoic acid. PGC-1α and NRF-1 collaborate in driving the expression of mitochondrial proteins. Additional nutraceutical measures which may likewise support MB – citrulline, taurine, N-acetylcysteine, high-dose biotin, and astaxanthin – are discussed. The adverse impact of metabolic syndrome on MB in skeletal muscle may be mediated by toll-like receptor 4 (TLR4) signaling stimulated by saturated fatty acids; antagonists of TLR4 signaling, possibly including ferulic acid and phycocyanobilin, may therefore promote MB in the context of metabolic syndrome. Restoration of youthful MB in the elderly may have favorable impacts on physical capacity and cognitive function, body composition, insulin sensitivity, and oxidative stress.

Key Words – mitochondrial biogenesis, carnitine, elderly, PGC-1a, NRF-1, histone deacetylase, phase 2

Restoring Youthful Tissue Carnitine Levels Promotes Mitochondrial Biogenesis

Studies show that levels of total and free carnitine decline in the skeletal muscle and certain other tissues of rodents as they age, likely owing to decreased expression of the membrane carnitine transporter, OCTN2.[1-3] This is a sodium symporter; thus, active transport of carnitine is driven by the transmembrane sodium gradient.[4] Supplementation with L-carnitine or acetyl-L-carnitine has been shown to restore intracellular membrane stores to more youthful levels in the heart, skeletal muscle, and cerebral cortex of aged rodents – whereas such supplementation has a more modest and less significant impact on intracellular carnitine levels in the tissues of younger rodents.[2, 5] Skeletal muscle levels of total and free carnitine have also been reported to be lower in elderly than in younger humans. The content of free + acetyl-L-carnitine in vastus lateralis muscle of healthy young males has been determined to be about 20 mmol/kg dry mass; assuming that muscle is 75% water, this corresponds to a concentration of about 5 mM.[6]

Several studies have shown that supplementation with carnitine or acetylcarnitine can boost mitochondrial biogenesis (MB) in various tissues of aged rodents; no such effect is seen in younger rodents, likely reflecting the fact that such supplementation impacts tissue carnitine levels more notably in elderly animals.[7-11] This effect of carnitine is paralleled – and likely mediated – by increased mRNA and protein expression of PPARgamma-coactivator-1alpha (PGC-1α) in the supplemented rodents. PGC-1α, by serving as a crucial coactivator for various transcription factors required for MB – such as nuclear respiratory factors-1 and -2, PPARα, and estrogen-related receptor-α – plays an essential role in driving mitochondrial biogenesis.[12]

Carnitine-Mediated Inhibition of Histone Deacetylase 3 May Boost *PGC-1α* Transcription

To date, the mechanism whereby restoration of youthful tissue carnitine levels boosts MB has remained unclear. However, free carnitine, in low millimolar concentrations such as those seen in healthy skeletal muscle, can function as a direct, concentration-dependent inhibitor of type 1 histone deacetylases (HDACs); acetyl-L-carnitine shares this property.[13, 14] Moreover, drug inhibitors of these deacetylases have been shown to boost mRNA and protein expression of PGC-1α, while also enhancing mitochondrial biogenesis; this likely reflects increased transcription of the *PGC-1α* gene.[15] The down-regulatory impact of HDAC activity on *PGC-1α* expression appears to be mediated by HDAC3.[15] We propose that free carnitine in skeletal muscle and other tissues functions to provide a mild tonic inhibition of HDAC3, and that this inhibition declines as cellular levels of carnitine decline with age. Hence, by restoring youthful intracellular carnitine levels, carnitine supplementation of elderly rodents – and likely humans – can decrease HDAC3 activity, boost PGC-1α expression and activity, and thereby enhance MB.

Whereas pharmaceutical inhibitors of HDAC3 could presumably be employed to boost MB, the advantage of using carnitine for this purpose is that it clearly is safe and well tolerated – as it would only be expected to restore the physiological degree of HDAC inhibition present in young people.

Functional Consequences of Up-Regulated Mitochondrial Biogenesis

Supplementation of elderly humans with carnitine or acetylcarnitine has been found to enhance perceived mental and physical energy levels while also decreasing fat mass and enhancing lean mass.[16-19] Increased MB in skeletal muscle and likely also the brain may play a role in this phenomenon. Intriguingly, a mis-sense mutation (Gly482Ser) of PGC-1α has been linked to increased risk for obesity and diabetes in humans; this likely reflects an important role for efficient MB in maintenance of metabolic health.[20] Indeed, decreased mitochondrial DNA (relative to nuclear DNA) in peripheral blood is associated with insulin resistance and increased diabetes risk, as well as a decreased rate of lipid oxidation during a euglycemic clamp.[21-23] It stands to reason that a deficit of mitochondrial mass will compromise the efficiency with which free fatty acids can be oxidized, leading to greater triglyceride storage in adipocytes and other tissues, and promoting increased synthesis of lipid mediators such as diacyglycerol and ceramide that can induce insulin resistance. Moreover, it is reasonable to expect that restoration of a more normal mitochondrial mass will have favorable consequences for physical and cognitive capacities in the elderly by improving the efficiency of ATP generation.

Even though carnitine has no radical scavenging activity, it has shown antioxidant activity in various contexts. Supporting MB and other effects of PGC-1α may help to explain this effect, as newly synthesized mitochondria, protected by mitochondrial antioxidant proteins whose synthesis is promoted by PGC-1α, could be expected to generate fewer oxidants than aging mitochondria whose respiratory chains have accumulated damage from oxidant exposure. Theoretically, higher intracellular free carnitine levels might also oppose NADPH oxidase activation in certain contexts (such as excessive fatty acid exposure associated with metabolic syndrome or fatty diet) by buffering acyl-coA levels and thereby impeding de novo synthesis of diacylglycerols.

Complementarity of Carnitine With Phase 2 Inducers in Promotion of Mitochondrial Biogenesis

Curiously, a number of studies have reported that supplementation with acetyl-L-carnitine and lipoic acid has a complementary impact on MB in aging rodents.[24-28] Some of these studies have focused on the utility of this strategy for boosting mitochondria levels in the brains of aging rodents, an effect associated with improved memory performance. Moreover, a cell culture study supports the possibility that this strategy could help prevent or control Parkinson's disease by improving the quality of mitochondria in the substantia nigra.[28] The basis of the complementarity between acetyl-L-carnitine and lipoic acid in these regards has not yet been explained. However, it should be noted that the gene coding for nuclear respiratory factor-1 (NRF-1), a transcription factor whose interaction with PGC-1a promotes transcription of a number of genes required for MB, including Tfam and complementary factors that enable transcription and replication of mitochondrial DNA, contains several functional antioxidant response elements in its promoter; hence, activation of the Nrf2 transcription factor by phase 2 inducer nutraceuticals – such as lipoic acid[29-31] - can be expected to boost NRF-1 expression.[32, 33] Hence, a simple model for the complementarity of carnitine and lipoic acid in the promotion of MB emerges – lipoic acid boosts expression of NRF-1, and (acetyl)carnitine, by restoring more youthful

tissue carnitine levels in the aged, enhances the level of its coactivator, PGC-1α. Consistent with this model, other phase 2 inducers, such as ferulic acid and sulforaphane, have been shown to stimulate MB – and likewise might be expected to complement carnitine's activity in this regard.[34-36] Moreover, nrf2 activity helps to keep new mitochondria functionally youthful by promoting expression of antioxidant enzymes that protect mitochondrial DNA and the respiratory chain from oxidative damage.[35]

Nutraceuticals May Also Aid Post-Translational Activation of PGC-1α

The chief stimulant to increased PGC-1α expression in skeletal muscle is exercise (naturally!), which boosts transcription of the *PGC-1α* gene via episodic surges in cytosolic calcium, oxidant production, and AMP+ADP level. Calcium, by activating calmodulin-activated kinase 4 and the phosphatase calcineurin, boosts the activity of the CREB and MEF2 transcription factors (respectively), which bind to the *PGC-1α* promoter.[37] AMP-activated kinase (AMPK), which is activated by an exercise-induced reduction in ATP, also boosts *PGC-1α* transcription, likely owing to increased binding of upstream stimulatory factor-1 and transcription factor EB to the *PGC1-α* promoter.[37-41] p38 MAP kinase, activated by an acute surge in oxidant production during exercise, stimulates *PGC-1α* transcription by activating MEF2 as well as ATF2.[42-44] Catecholamine- or glucagon-mediating activation of adenylate cyclase likewise boosts PGC-1α expression, via CREB.[37]

However, PGC-1*a* activity is also regulated post-translationally. (Curiously, measures which boost this activity also enhance PGC-1α expression, as PGC-1α functions as a coactivator for MEF2 in transcription of the *PCG1α* gene.[45]) The ability of PGC-1α to promote transcription of its target genes is boosted by phosphorylations conferred directly by AMPK and p38 MAP kinase; additionally, Sirt1 activity boosts PGC-1α's coactivational potential by removing inhibitory acetyl groups.[37] This latter effect appears to be contingent on a prior phosphorylation mediated by AMPK; hence, AMPK and Sirt1 appear to act as a "tag team" in supporting PGC-1α's bioactivity. Curiously, these enzymatic activities interact in a supportive manner. AMPK enhances Sirt1 activity by somehow boosting the NAD+/NADH ratio.[46, 47] Sirt1 in turn promotes AMPK activity by increasing the cytoplasmic localization and activation of LKB1, one of the upstream kinases which confers an activating phosphorylation on AMPK.[48, 49] Moreover, LKB1 acts as an upstream activator of p38 MAP kinase.[50] Hence, these enzymes work cooperatively in supporting PGC-1α activity. It is notable that both AMPK and Sirt1 are activated by signals reflecting cellular energy starvation (elevated AMP+ADP/ATP ratio; increased NAD+NADH ratio); the consequent activation of PGC-1a and MB boosts the cell's ability to oxidize substrate, and hence boosts the cell's bioenergy status.

The drug metformin and nutraceutical berberine are believed to aid glycemic control in diabetics via activation of AMPK; hence, they have potential for promoting MB.[51-53] However, these agents are thought to work via partial inhibition of complex 1 of the mitochondrial respiratory chain; this diminishes the efficiency of oxidative phosphorylation, inducing a rise in AMP and ADP that promotes AMPK activation; increased superoxide production by complex I is another likely consequence.[54-56] Hence, while these agents may promote mitochondrial biogenesis, their impact on the quality of mitochondrial bioactivity is more equivocal.

Multiple rodent studies demonstrate that nitric oxide (NO) generated within skeletal muscle supports MB by boosting PGC-1α activity; this effect is abolished when AMPK is inhibited.[57-61] NO's impact in this regard appears to be mediated by cGMP and protein kinase G (PKG). Up-regulation of Sirt1 expression has been observed when NO bioactivity is boosted, and this arguably could explain NO's ability to promote PGC-1α activity, as well as the dependency of this effect on AMPK.[62, 63] Of the several transcription factors that have been shown to bind the Sirt1 promoter and promote Sirt1 transcription, Sp1 is notable in that previous studies have shown that PKG can confer an activating phosphorylation on it.[64-66] Hence, it is proposed that NO bioactivity supports PGC-1α bioactivity by activating transcription of Sirt1 via Sp1. To the extent that aging, exercise, or pathologies promote uncoupling of NO synthase in skeletal muscle or other tissues, restoration of effective NO synthase function with citrulline or high-dose folate might thus have potential for supporting PGC-1α function and mitochondrial biogenesis.[67-70] The impact of elevations of asymmetric dimethylarginine (ADMA), a physiological uncoupler of NO synthase, on mitochondrial biogenesis, has received little study to date; one report concludes that increased ADMA in diabetic rats impairs hepatic mitochondrial biogenesis.[71] Nonetheless, supplementation with citrulline or arginine – which antagonizes the uncoupling activity of ADMA – has been shown to boost expression of PGC-1α and PGC-1α-regulated genes in the skeletal muscle of rodents.[72, 73] Whether peroxynitrite-mediated uncoupling of NO synthase can play a significant physiological role in muscle function does not appear to be known; high-dose folate reverses this effect in the vascular system.[69, 70] Measures which support endothelial NO synthase activity might be expected to aid exercise performance indirectly, by aiding adaptive endothelium-dependent vasodilation of the muscle vasculature during exercise.[74]

Since the impact of NO on MB is mediated by cGMP, agents which directly interact with soluble guanylate cyclase to promote cGMP generation may also have potential for activating MB. Drugs known as guanylate cyclase stimulator and activators have this property, and are being developed as cardiovascular drugs.[75] However, the vitamin biotin, in concentrations roughly 2 orders of magnitude higher than its physiological level, likewise activates soluble guanylate cyclase; since it boost this activity by no more than 2-3 fold, it is well tolerated even in very high doses.[76-79] The possibility of employing high-dose biotin to stimulate PGC-1alpha activity and MB has previously been suggested, but no studies have yet addressed this approach.[80] High-dose biotin supplementation has however been reported to activate AMPK in hepatocytes and adipose tissue.[81, 82]

Endogenously-generated hydrogen sulfide (H_2S) has also been found to have a supportive role in mitochondrial biogenesis.[83, 84] This effect has been traced, at least in part, to the ability of H_2S to reversibly inhibit protein phosphatase 2-A (PP2A) via sulfhydration of its cysteine groups.[83] Since PP2A functions to inhibit AMPK activity by reversing the activating phosphorylation of Thr-172 , this predicts that H_2S can support PGC-1α activity and MB by up-regulating AMPK activity.[85] The possibility that H_2S might act in additional ways to promote MB – as by supporting NO bioactivity – merits further attention.[86, 87] Endogenous H_2S synthesis can be stimulated by boosting the availability of its precursor cysteine – as can be achieved with N-acetylcysteine supplementation.[88] Recent studies demonstrate that supplemental

taurine can increase the expression of enzymes that generate H_2S – cystathionine beta-synthase and cystathionine gamma-lyase – in the vasculature and brain of rodents.[89, 90] Whether this phenomenon likewise obtains in skeletal muscle is currently unknown. Intriguingly, however, taurine administration has been reported to boost AMPK activation in rat skeletal muscle and myotubes.[91, 92]

Mitochondrial Capacity for Fatty Acid Oxidation is Boosted By Astaxanthin, a PPARα Agonist

Much of the benefit of increased MB is mediated by increased capacity for free fatty acid (FFA) oxidation. The transcription factor PPARα, after forming a heterodimer with the retinoid X receptor and binding to its coactivator PGC-1α, stimulates the transcription of genes which promote mitochondrial oxidation of fatty acids and ketogenesis, including carnitine palmitoyl transferases (CPT) 1a and 2, acyl-CoA oxidase, acetyl-CoA acetyl transferase, and uncoupling protein 2 (UCP2).[93, 94] Pharmaceutical agonists for PPARα, such as fenofibrate, tend to ameliorate the dyslipidemia associated with metabolic syndrome, in large part owing to an up-regulation of mitochondrial FFA oxidation in the liver; they have also been shown to decrease risk for cardiovascular events in those with metabolic syndrome.[94, 95] There is recent evidence that astaxanthin, a natural carotenoid that is an exceptionally effective scavenging antioxidant for biological membranes, can also serve as a potent PPARα agonist; in daily intakes as low as 8 mg, it has been shown to improve serum lipid profile in metabolic syndrome.[96-102] PPARα agonists may also act indirectly to increase expression of PGC-1α. Such agonists increase hepatic synthesis and release of fibroblast growth factor 21 (FGF21), which in turn acts on adipocytes to boost their production of the adipokine adiponectin.[103-107] In many tissues expressing adiponectin receptors, this hormone stimulates activation of AMPK[108-110] – which, as we have seen, increases PGC-1α activity both at the transcriptional and post-translational level. This may explain a recent report that dietary astaxanthin increases PGC-1α expression in the skeletal muscle of mice; adiponectin is known to activate AMPK and drive MB in skeletal muscle.[108, 109, 111-113]

Astaxanthin also supports efficient mitochondrial function by providing antioxidant protection to mitochondrial membranes, including the oxidant-vulnerable respiratory chain; this can be of particular merit in the context of ischemia-reperfusion.[114] When reperfusion induces a burst of mitochondrial superoxide generation, oxidant damage to this chain can up-regulate mitochondrial superoxide production; by minimizing this oxidant damage, astaxanthin tends to blunt this feed-forward mechanism.[115, 116] And astaxanthin has also shown phase 2 inductive activity in rodents and in cell cultures; whether this is a significant effect in the modest doses currently used for human supplementation remains to be seen.[117-121]

Krill oil may be employed as a source of supplemental astaxanthin, as it is rich in high-bioavailability esters of astaxanthin as well as long-chain omega-3 fatty acids, oxidized metabolites of which can also act as PPARα agonists.[122-125]

Additional nutraceuticals which may merit further research consideration in regard to their impact on MB include nitrate salts – which, after bacterial reduction to nitrite, can be further reduced to NO in muscle and other tissues; nicotinamide riboside, which potentially can boost Sirt1 activity by increasing its substrate NAD+; and

pyrrolquinolone quinone (PQQ), a vitamin-like compound which for obscure reasons has been found to promote MB in rodents and cell cultures.[126-133]

Systemic Inflammation Suppresses PGC-1α Expression via Classical NF-kappaB Activation

Disorders associated with systemic inflammation, such as chronic obstructive pulmonary disease, heart failure, diabetes, and metabolic syndrome are characterized by decreased mitochondrial content in skeletal muscle and other tissues, likely owing to the impact of pro-inflammatory cytokines and/or excessive exposure to saturated fatty acids.[134-137] Several studies demonstrate that activation of the classical NF-kappaB pathway is a key mediator of this phenomenon, and that such activation provokes decreased expression of PGC-1α mRNA.[134, 136, 138, 139] Since preliminary protein synthesis is needed for NF-kappaB to trigger this effect, it seems likely that NF-kappaB induces a protein or proteins which either inhibit PGC1α transcription, or which decrease the half-life of PGC-1α mRNA.[134] Additionally, nuclear p65 has been shown to inhibit PGC-1α's coactivational activity by binding to it directly.[140] Hence, measures which decrease classical NF-kappaB activation may support PGC-1α activity in the context of systemic inflammation.

Excessive exposure to saturated fatty acids likely plays a role in the down-regulation of PGC-1α expression associated with metabolic syndrome and diabetes. Markers of mitochondrial biogenesis including PGC-1α expression correlate inversely with plasma free fatty acid level, and a lipid infusion suppresses the expression of PGC-1α in human skeletal muscle.[137, 141] *In vitro*, exposure to palmitate – but not oleate - likewise down-regulates PGC-1α expression in a skeletal muscle cell line, and this effect is contingent on activation of NF-kappaB.[136] This effect of palmitate does not appear to be mediated by *de novo* synthesis of diacylglycerol or ceramide.[136] Rather, other research indicates that palmitate activates NF-kappaB in skeletal muscle via toll-like receptor-4 (TLR4), the expression of which is elevated in individuals who are obese or diabetic; monoclonal antibodies targeting TLR4 prevent palmitate from activating NF-kappaB in primary myotubes.[142] A complex formed between fetuin A and palmitate or other saturated fatty acids – but not unsaturates – can act as an agonist for TLR4.[143] This model therefore suggests that the adverse impact of metabolic syndrome on MB in skeletal muscle might be offset by measures targeting TLR4 signaling.

Although ferulic acid acts as a phase 2 inducer and can be expected to promote MB via NRF-1 induction, it exerts an additional anti-inflammatory effect and, in particular, opposes TLR4 signaling.[144] Limited evidence suggests that this effect reflects an inhibitory interaction with the MyD88 adaptor protein, a key mediator of TLR4 signaling.[144, 145] Although the impact of ferulic acid on MB in skeletal muscle has not yet been assessed, ferulic acid administration (500 mg daily) has been found to up-regulate PGC-1α mRNA expression in human monocytes.[34] Hence, it would be of interest to determine whether ferulic acid supplementation could partially reverse the down-regulation of PGC-1α expression and MB associated with metabolic syndrome. Ferulic acid might also act to oppose TLR4 signaling by decreasing hepatic production of fetuin A, an effect demonstrated in high-fat-fed diabetic rats; the up-regulatory effect of high fat exposure on hepatic expression of fetuin A is mediated by NF-kappaB.[146, 147]

NADPH oxidase plays a mediating role in the TLR4 signaling that activates NF-

kappaB.[148-150] Moreover, there is recent evidence that skeletal muscle NOX2 is required for induction of insulin resistance in the skeletal muscle of rats fed a high-fat diet.[151] Phycocyanobilin (PhyCB), a biliverdin metabolite that acts as a light-harvesting chromophore in cyanobacteria (such as spirulina) and certain blue-green algae, shares the ability of biliverdin/bilirubin to inhibit NADPH oxidase complexes, an effect which likely largely accounts for spirulina's potent antioxidant/anti-inflammatory activities in rodent studies.[152-154] Intriguingly, a recent clinical study found that spirulina supplementation boosts VO_2max and exercise endurance in human subjects – most notably in those who are obese.[155] Hence, it is conceivable that PhyCB has a favorable impact on PGC-1α expression and MB in the context of metabolic syndrome. On the other hand, activation of NOX2 during exercise is responsible for a stimulation of p38 MAP kinase activity that boosts PCG-1α activity.[44] Hence, the impact of PhyCB on MB of skeletal muscle may be context dependent.

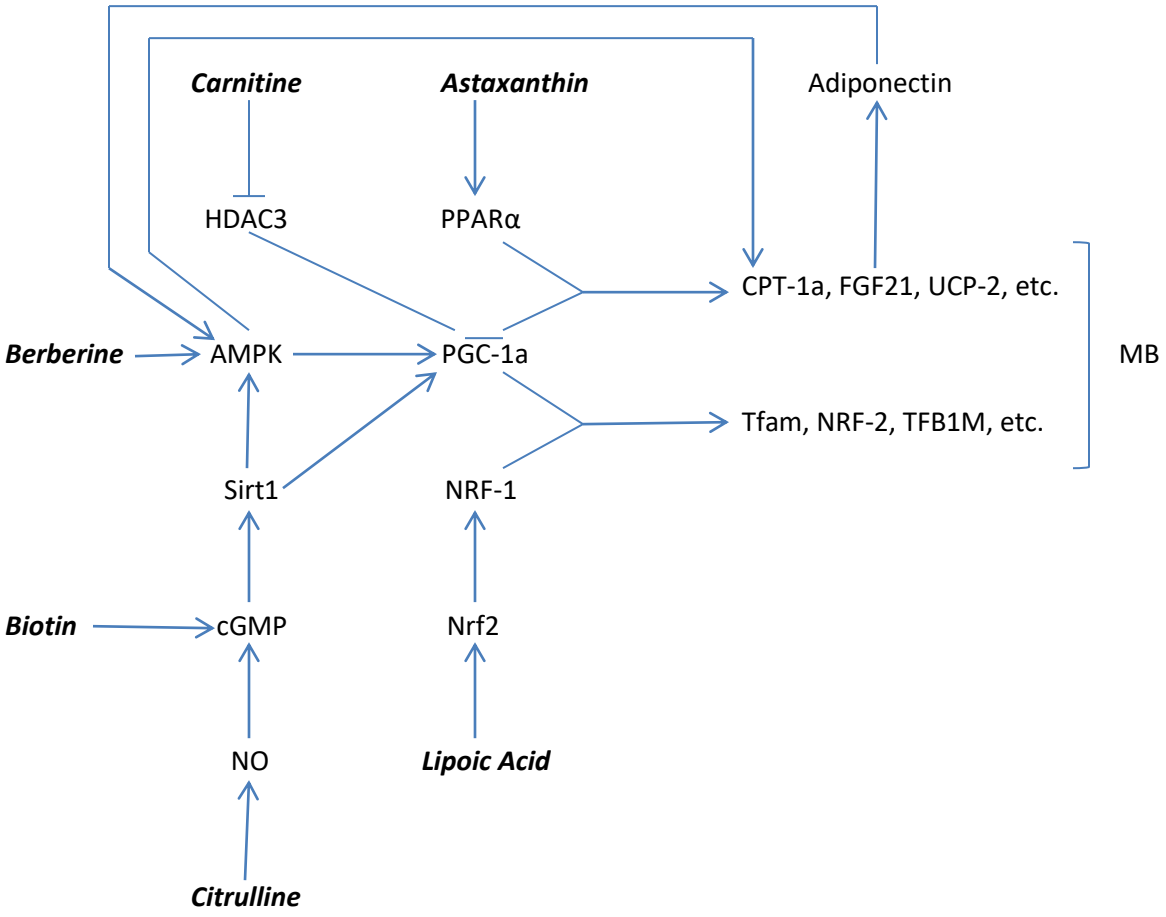

Figure: Nutraceutical strategies for supporting mitochondrial biogenesis (MB) and efficient fatty acid oxidation. The effect of supplemental carnitine will be of most significance in the elderly. Astaxanthin and lipoic acid with also boost antioxidant protection for mitochondria. In skeletal muscle, exercise training will also boost PGC-1α expression and activity by multiple mechanisms.

Summing Up

Restoration of youthful tissue levels of carnitine in aging rodents has been found to up-regulate PGC-1α expression and MB. A likely reason is that carnitine acts as an inhibitor of type I histone deacetylases – more specifically, HDAC3 – which oppose the transcription of the *PGC-1α* gene. If this hypothesis is correct, pre-treatment with potent inhibitors of type 1 HDACs should blunt or eliminate the impact of carnitine status on PGC-1α expression. Co-administration of phase 2 inducers such as lipoic acid complements the impact of carnitine on MB, and this is attributable, at least in part, to the fact that NRF-1 expression is phase 2-inducible via antioxidant response elements in its promoter; concurrent induction of both PGC-1α and NRF-1 should have a very potent impact on MB, as they collaborate in promoting expression of proteins required for the replication of mitochondrial DNA and the formation of functional mitochondria. Phase 2 inducers will also help to insure that newly-formed mitochondria have effective antioxidant defenses.

Ancillary strategies, entailing the activation of AMPK, Sirt1, and p38 MAP kinase, could be employed to boost PGC-1α activity via post-translational modifications. Agents which support NO bioactivity, mimic it via activation of guanylate cyclase, which enhance H_2S production, or which directly activate Sirt1 may be useful in this regard: these may include citrulline, high-dose biotin, N-acetylcysteine, and taurine. Metformin and berberine, clinically effective activators of AMPK, may be useful in this regard as well, although their inhibitory effects on complex I of the mitochondrial respiratory chain may undercut their ability to optimize mitochondrial function.

The PPARα transcription factor, co-activated by PGC-1α, boosts expression of mitochondrial enzymes which catalyze FFA oxidation and ketogenesis; acting in the liver, it also promotes PGC-1α expression systemically by inducing FGF21-adiponectin signaling. PPARα agonists, such as the natural carotenoid astaxanthin, hence promote the biogenesis of mitochondria with high capacity for FFA oxidation. Moreover, astaxanthin can provide potent antioxidant protection for mitochondrial membranes and the respiratory chain.

PGC-1α expression and MB in skeletal muscle are decreased in chronic inflammatory states and metabolic syndrome, an effect which appears to be mediated by activation of classical NF-kappaB signaling. The impact of metabolic syndrome in this regard may be mediated largely by activation of TLR4. By opposing TLR4 signaling, ferulic acid and PhyCB may have potential for boosting MB in the context of metabolic syndrome.

Hence, it may be feasible to devise complex nutraceutical strategies for enhancing MB; such strategies may be of particular benefit in the elderly or those with metabolic syndrome. Moreover, exercise training can be expected to boost MB in the exercised muscles. Maintaining optimal tissue levels of efficiently functioning mitochondria may be expected to favorably impact physical and possibly cognitive performance, diminish cellular oxidative stress, and help to prevent or reverse insulin resistance and inappropriate weight gain.

Conflicts of Interest – Mark McCarty consults for a nutraceutical company which sells several of the nutraceuticals mentioned in this essay. He is also co-inventor and co-owner of a US patent covering nutraceutical uses of phycocyanobilin oligopeptides.

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