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# Behaviorally-Mediated Entrainment of Whole-Body Metabolic Processes: Conservation and Evolutionary Development of Mitochondrial Respiratory Complexes

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

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The relaxation response derives its health benefits by reestablishing “normal” equilibria between the sympathetic and parasympathetic branches of the autonomic nervous system. Recent work suggests that this behavioral training provides positive effects on mitochondrial bioenergetics, insulin secretion, and reductions in pro-inflammatory and stress-related pathways. We have previously contended, however, that correlative associations of relaxation training with positive changes in gene expression in selected biological systems are strongly suggestive of adaptive physiological changes, but do not elucidate an underlying, clinically compelling, unified mechanism of action consistent with its purported positive health effects. We surmise that any plausible model of behaviorally-mediated regulatory effects on whole-body metabolic processes must be intrinsically broad-based and multifaceted via integration of differential contributions of functionally interactive peripheral and CNS organ systems. Accordingly, the initiation of multiple cellular protective/anti-bio-senescence processes may have emerged during evolutionary development to ensure the survival of hybrid prokaryotic/eukaryotic progenitor cells, given the evolution of oxidative metabolism and its associated negative byproducts. As an essential corollary, preservation and adaptation of multifaceted regulatory molecules, notably nitric oxide, paralleled the development of eukaryotic cell types via multifaceted stereo-selective recognition and conformational matching by complex biochemical and molecular enzyme systems. Hence, the relaxation response may be a manifestation of a metabolic corrective process/response, that may now include cognition (“awareness”).

**MeSH Keywords:** **Adenosine Triphosphate • Mitochondria • Nervous System • Nitric Oxide • Oxygen Consumption • Relaxation**

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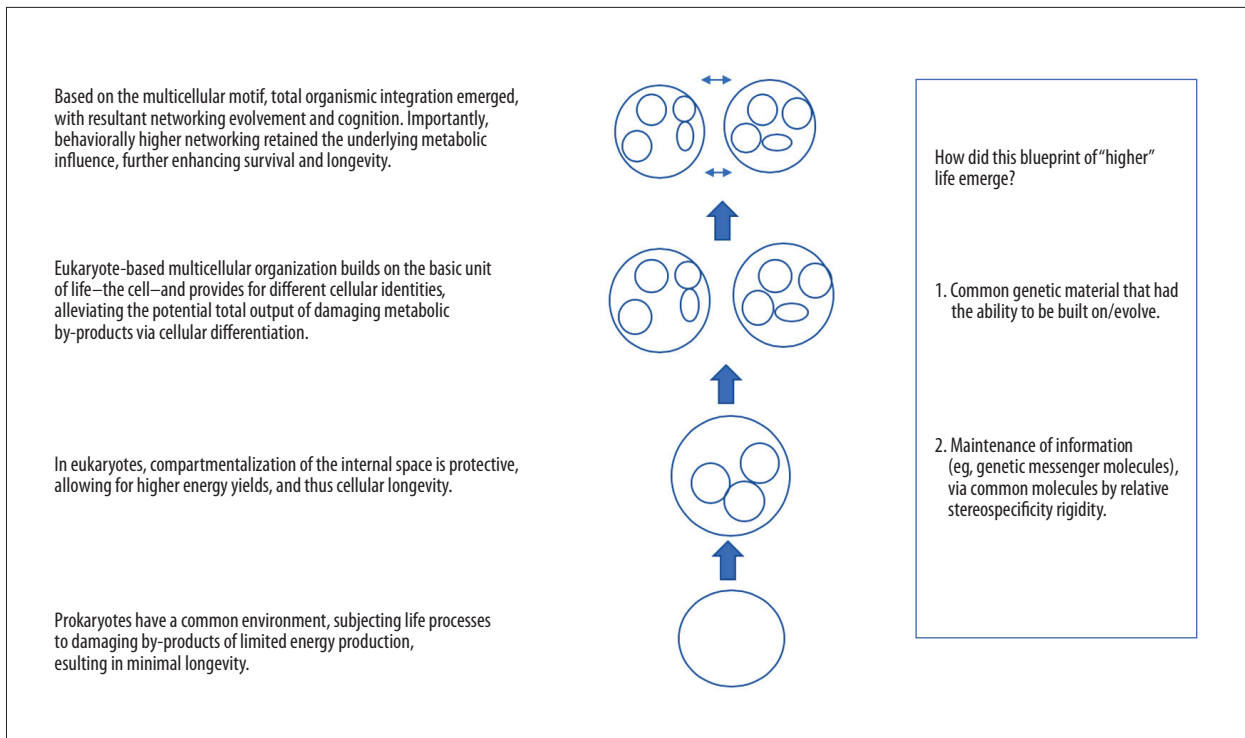
Previously it has been surmised that the health benefits of behaviorally-mediated relaxation response (RR) training exercises are functionally dependent on reestablishing “normal” equilibria between the sympathetic and parasympathetic branches of the autonomic nervous system [1,2]. Recently, RR practitioners’ blood gene expression data have suggested that behavioral training provides positive effects on mitochondrial bioenergetics, insulin secretion, and reductions in pro-inflammatory and stress-related pathways in circulating leukocytes [3]. We have previously contended, however, that correlative associations of RR training with positive changes in gene expression in selected biological systems are strongly suggestive of adaptive physiological changes, but do not elucidate an underlying, clinically compelling, unified mechanism of action consistent with its purported positive health effects [4]. In this regard, a recent publication highlighted the practical and theoretical advances in understanding the health-generating aspects of brain-mind-body practices, including Tai Chi Chuan, Qigong, and cognitive training exercises from psychological, physiological, neurobiological, and immunological perspectives [5]. It follows that any plausible model of behaviorally-mediated regulatory effects on whole-body metabolic processes must be intrinsically broad-based and multifaceted via integration of differential contributions of functionally interactive peripheral and central nervous system (CNS) organ systems.

In light of the above, we propose that the self-sustaining/reinforcing properties of mind-body exercise practices with associated feelings of wellness and relaxation are functionally associated with widespread coordinated enhancement of local circuit physiological events leading to a summated whole-body metabolic advantage (Figure 1) [4]. A significant body of empirical research has functionally linked enhanced bioenergetics and whole-body metabolic advantage to “synchronous entrainment of temporally-ordered mitochondrial electron transport activities and optimized ATP production within complex organ systems” [4]. Mechanistically, homeostatic preservation of cellular metabolic processes is especially dependent on the level of tissue oxygenation and regulated mitochondrial respiration and O<sub>2</sub> utilization. From a perspective of pathophysiological/pro-inflammatory disorders, alterations in homeostatic regulation of cellular bioenergetics in metabolically compromised peripheral and CNS tissues are functionally associated with aberrant oxygen free radical production due to dysregulation of mitochondrial O<sub>2</sub> utilization [4]. It follows that a likely first approximation of a putative unified mechanism of action by which mind-body practices promote positive health effects should focus on key physiological sequelae of controlled breathing exercises that can positively affect cortical-limbic integration of CNS respiratory rhythms, fine-tuned integration of brain stem respiratory centers, and facilitation of pulmonary gas exchange [4].

Within our proposed working model, behaviorally-mediated enhancements of whole-body cellular bioenergetics indicate a convergence of biochemical and biophysical processes within the mitochondrial matrix, resulting in optimized synthesis of ATP from ADP and inorganic phosphate via recognized chemiosmotic-driven events. Furthermore, positive evolutionary pressure has segregated these physiochemical processes to the organelle’s inner membrane via coordinated expression of complexes I, III, and IV of the respiratory chain [6,7]. A large body of clinical and pre-clinical literature has established a key regulatory role for the free radical gas nitric oxide (NO) in maintaining normative rates of mitochondrial respiration and O<sub>2</sub> utilization [4]. Furthermore, dynamic recycling of NO and inorganic nitrite by intra-mitochondrial nitrite reductases has been empirically demonstrated to represent a biochemical switching mechanism intimately linked to minute variations in O<sub>2</sub> tension according to normoxic/hypoxic environmental conditions [4,7–10]. These homeostatic physiological effects are translated into temporal changes in tonic and phasic intra-mitochondrial NO production that are designed to exert profound inhibitory effects on the rate of electron transport, H<sup>+</sup> pumping, and O<sub>2</sub> consumption [6,11,12].

A significant body of research has linked the dynamics of intra-mitochondrial NO expression to the production of reversible post-translational modifications of discrete subunits of complexes I, III, and IV (also designated cytochrome c oxidase, COX) of the respiratory chain [13–15]. For example, COX-mediated NO oxidation represents a key biochemical mechanism for retention/recycling of physiologically important NO equivalents within a dynamic intra-mitochondrial nitrite pool that is critically important for maintaining cellular bioenergetics parameters during periods of physiological stress [7,16–19]. Conversely, enzymatic reduction of nitrite to NO within the reduced COX heme a<sub>3</sub>/CuB active site provides physiologically significant O<sub>2</sub>-sparing effects under hypoxic/anoxic environmental conditions [20].

We have provided a brief critical review that supports the pivotal role of dynamically synchronized mitochondria expressed by diverse cell types distributed throughout human body tissues and organ systems to effectively transduce the effects of coordinated mind-body training in producing positive health effects [4]. Operationally, we contend that behaviorally-mediated entrainment of whole-body metabolic processes involves widespread targeting and integration of local circuit mitochondrial function to achieve summated enhancement of cellular bioenergetics. The existential and life-sustaining potential of cognitively driven regulation and reinforcement of metabolic processes of diverse cell types almost certainly reflects evolutionary development of biochemical and molecular correction/protection mechanisms designed to ensure single-cell integrity within discrete micro-domains.



**Figure 1.** Cognitive processes evolved from higher nervous system networking, while maintaining the neural modulatory control of energy processes at the cellular level.

In conclusion, ongoing empirical research and considerable debate have supported endosymbiotic theories of mitochondrial origin from free-living prokaryotic progenitors. Accordingly, we surmise that the initiation of multiple cellular protective/antibio-senescence processes may have emerged at early stages of evolutionary development to ensure the survival of hybrid prokaryotic/eukaryotic progenitor cells (Figure 1). As an essential corollary, preservation and adaptation of multifaceted regulatory molecules, notably NO, paralleled the development of eukaryotic cell types via multifaceted stereo-selective recognition and conformational matching by complex biochemical and molecular enzyme systems [21]. Consistent with continued evolution of complex peripheral and CNS cellular signaling/communication pathways, the primacy of high-efficiency mitochondrial bioenergetics is of existential importance. As a consequence, complex behavioral entrainment of cognitive and motor activities can

now be functionally linked to fine-tuned regulation of summated cellular metabolic processes. In effect, “mood” and “thinking” modalities may be incorporated into coordinated mind-body training exercises designed to positively modulate whole-body energy demand. Finally, the integrity of functionally integrated whole-body bioenergetics now appears to be reciprocally and synergistically dependent on the metabolic and genomic health of collective populations of human microbiota [4,22,23]. In similar fashion, the essential character of the human microbiome may be entrained or filtered to contain metabolically favorable strains of microbiota in response to higher-order behavioral and/or dietary regimens.

**Conflict of interest**

None.

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