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Augmentation of Whole-Body Metabolic Status by Mind-Body Training: Synchronous Integration of Tissue- and Organ-Specific Mitochondrial Function

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The objective of our concise review is to elaborate an evidence-based integrative medicine model that incorporates functional linkages of key aspects of cortically-driven mind-body training procedures to biochemical and molecular processes driving enhanced cellular bioenergetics and whole-body metabolic advantage. This entails the adoption of a unified biological systems approach to selectively elucidate basic biochemical and molecular events responsible for achieving physiological relaxation of complex cellular structures. We provide accumulated evidence in support of the potential synergy of voluntary breathing exercises in combination with meditation and/or complementary cognitive tasks to promote medically beneficial enhancements in whole-body relaxation, anti-stress mechanisms, and restorative sleep. Accordingly, we propose that the widespread metabolic and physiological advantages emanating from a sustained series of complementary mind-body exercises will ultimately engender enhanced functional integration of cortical and limbic areas controlling voluntary respiratory processes with autonomic brainstem neural pattern generators. Finally, a unified mechanism is proposed that links behaviorally-mediated enhancements of whole-body metabolic advantage to optimization of synchronous regulation of mitochondrial oxygen utilization via recycling of nitrite and nitric oxide by iron-sulfur centers of coupled respiratory complexes and nitrite reductases.


MeSH Keywords: **Mind-Body Therapies • Relaxation Therapy • Respiration • Breathing Exercises • Cognition • Mitochondria • Metabolism • Nitric Oxide • Nitrites • Nitrite Reductases**

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Background

A recent editorial has highlighted practical and theoretical advances in understanding the health-promoting aspects of brain-mind-body practices including Tai Chi Chuan, Qigong, and cognitive training exercises from psychological, physiological, neurobiological, and immunological perspectives [1]. Previously, it has been hypothesized that the efficacy of the relaxation response (RR) as an alternative anti-stress medical vehicle is heavily dependent on its ability to reset homeostatic equilibria between the sympathetic and parasympathetic branches of the autonomic nervous system [2,3]. More recently, gene expression data obtained from blood samples of RR practitioners reflect positive effects on mitochondrial bioenergetics, insulin secretion, and reductions in pro-inflammatory and stress-related pathways in circulating leukocytes [4]. Despite the restrictive nature of the data sets, complementary series of bioinformatics analyses suggested that RR training procedures may engender medically beneficial changes in molecular and biochemical events at the cellular and organ level as a consequence of integrated cortically- and peripherally-driven neural processes. We contend, however, that correlative associations of RR training with positive gene expression changes in selected biological systems do not provide a basic unified mechanism of action that incorporates key behavioral, biochemical, and cellular components within a plausible working model. As an overall construct, we propose that the ability of empirically determined sets of mind-body exercises to achieve feelings of wellness and relaxation is mechanistically dependent on the self-sustaining/reinforcing properties of whole-body metabolic advantage realized as widespread coordinate enhancement of local circuit physiological events.

From this stated mechanistic perspective, whole-body metabolic advantage can only be achieved by synchronous entrainment of temporally-ordered mitochondrial electron transport activities and optimized adenosine triphosphate (ATP) production within complex organ systems. Because homeostatic maintenance of cellular metabolic processes is critically dependent on the degree of tissue oxygenation and regulated mitochondrial respiration, it appears that behaviorally-mediated enhancements of coordinated respiratory rhythms and pulmonary gas exchange are required to achieve medically beneficial endpoints. As a clinical corollary, restoration of normative homeostatic regulation of cellular bioenergetics in peripheral and central nervous system (CNS) tissues has been demonstrated to alleviate deleterious pro-inflammatory conditions associated with enhanced oxygen free radical production due to dysregulation of mitochondrial respiration.

Functional Sequelae of Voluntary Breathing Exercises: Coordinate Enhancement of Coupled Respiratory Rhythms and Physiological Processes

In light of the aforementioned, we provide accumulated evidence in support of the potential synergy of voluntary breathing exercises in combination with meditation and/or complementary cognitive tasks to promote medically beneficial enhancements in whole-body relaxation, anti-stress mechanisms, and restorative sleep. Accordingly, we propose that the widespread metabolic and physiological advantages emanating from sustained series of complementary mind-body exercises will ultimately engender enhanced functional integration of cortical and limbic areas controlling voluntary respiratory processes [5] with medullary and pontine regulatory neuronal groups mediating involuntary inspiratory and expiratory respiratory rhythms [6–8]. An additional layer of regulatory complexity may be contributed by differential effects of controlled nasal breathing to selectively activate olfactory-associated limbic structures involved in reinforcement of diverse behavioral processes [9–13].

A potential focal point for elucidation of medically beneficial effects of controlled breathing is provided by collected pre-clinical electrophysiological studies demonstrating distinct regional patterns of respiration-linked low-frequency (5–10 Hz) oscillations with superimposed 40–100 Hz gamma power modulations in several regions of rodent brain that include olfactory bulb, hippocampus, prelimbic and parietal cortices [9–11,14–16]. Accordingly, respiratory entrainment and region-specific coupling between slow rhythms and superimposed fast gamma oscillations may represent a major mechanism underlying temporal organization of both sensory and cortical activities by complex voluntary and involuntary breathing rhythms [11,14–16]. Recently, respiration-coupled oscillations were detected in prefrontal cortical and visual regions as well as subcortical thalamic, amygdala and ventral hippocampal structures in freely moving mice and during rapid eye movement (REM) sleep [16]. Notably, these results support an integrative role of synchronized, phase-locked, inspiratory and expiratory respiratory rhythms across sensory, cortical, and limbic CNS areas underlying sensory, motor, cognitive, and affective processes [11,16]. In sum, Heck et al. provided an expanded empirical/theoretical framework linking the translational relevance and potential importance of these recent findings to mind-body medical practices, i.e., mental training [11]. The authors contend that volitional modifications of respiratory behavior, commonly experienced in yogic breathing and stress reducing respiratory exercises, may help to synchronize large portions of the cortical network and mediate positive changes in cognitive, meditative, and emotional states. Furthermore, these processes may underlie normative mechanisms mediating the normal relaxation and restorative sleep (Figure 1).

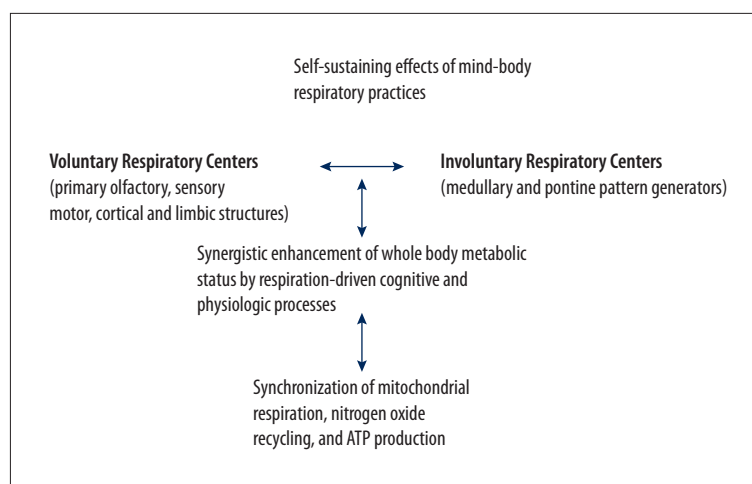


Figure 1. A proposed model linking respiration-driven mind-body training procedures to enhanced cellular bioenergetics and whole-body metabolic advantage via synchronized mitochondrial activities. This includes the following: A) Self-sustained series of complementary mind-body breathing exercises are proposed to engender enhanced functional integration of cortical and limbic areas controlling voluntary respiratory processes with autonomic brainstem neural pattern generators; B) Self-sustaining or behaviorally-reinforcing properties of mind-body practices are proposed to be functionally linked to optimal enhancement of the metabolic status of reciprocally interactive neuronal and non-neuronal regulatory centers located within CNS and peripheral domains; and C) Unified mechanism of action, suggesting that widespread metabolic and physiological advantages engendered by extended series of mind-body practices are mediated by optimized synchronous regulation of mitochondrial O_2 utilization via recycling of nitrite and nitric oxide by iron-sulfur centers of coupled respiratory complexes and nitrite reductases.

Complementary preclinical studies have selectively focused on the putative functional role of respiration-linked, non-odorant, sensory airflow through the nasal cavity on olfactory, cortical, and limbic CNS structures [12,17]. Functional magnetic resonance imaging (fMRI) activity patterns in the olfactory bulb of male rats elicited by mechanical airflow through the nasal cavity were more broadly distributed as compared to those evoked by odorant stimulation and were associated with significant reductions in heart rate, spontaneous respiratory rate, and EEG β -band oscillations [12]. The authors hypothesized that airflow rhythms encoded by primary olfactory mechanoreceptors in the nasal cavity are associated with regulation of physiological processes mediated by CNS areas receiving projections from olfactory structures and provide a partial explanation for the positive effects of controlled breathing exercises in mind-body medical practices [12]. Furthermore, in a rodent model of conditioned, fear-induced, freezing behavior, disruption of primary olfactory input significantly reduced respiration-locked 4-Hz oscillatory rhythms in the prelimbic prefrontal cortex (pLPFC) with resultant prolongation of freezing periods [17]. These results indicate that primary olfactory inputs may provide significant regulatory modulation of rhythmic activity in the pLPFC, a CNS structure critical for expression of conditioned fear behaviors. Accordingly, the potential translational value of both studies [12,17] relates to the selective association of nasal breathing and primary olfactory mechanoreceptor sensory coding with higher order integration of cortical and limbic areas controlling both motor and emotional aspects of voluntary respiratory processes [5].

A clinical pilot study was designed to test the hypothesis elaborated here; i.e., odorless mechanoreceptor sensory stimulation of the olfactory epithelium is coupled to the modulation of cognitive and affective processes within deeper CNS areas [13]. Following odorless stimulation of the olfactory epithelium in test subjects, enhanced delta-theta EEG activity over cortical and limbic areas were observed and correlated to altered psychometric tests and/or experienced states of consciousness. The authors concluded that putative functional linkages between nasal breathing, CNS electrical activity, and subjective/affective experience provide plausible neurophysiological bases for evaluating medically beneficial effects of respiration-based meditative practices [13]. A complementary neurophysiological clinical study monitored the breathing cycle throughout widespread cortical/limbic sites and inferred a fundamental role of breathing-related oscillations in driving CNS neuronal activity [18]. These collected data were consistent with an earlier study utilizing intracranial EEG data from a cohort of patients with refractory epilepsy demonstrated respiration-linked oscillatory activity in piriform cortex with functional linkages limbic/cortical areas including amygdala and hippocampus [19]. Interestingly, oscillatory power was observed to peak during inspiration and dissipated when breathing was diverted from nose to mouth, thereby providing additional support for the pivotal role of nasal breathing in coordinating higher order cortical and limbic oscillations and associated behavioral endpoints. Consistent with these observed effects, parallel behavioral experiments

showed that the breathing cycle enhanced fear discrimination and memory retrieval in epileptic patients.

Functional Sequelae of Voluntary Breathing Exercises: Coordinate Enhancement of Autonomic Physiological Processes and Brainstem Neural Circuits

As discussed, respiratory entrainment of CNS region-specific coupling between slow rhythms and superimposed fast gamma oscillations appears to mediate regulatory synchronicity between interactive cortical and limbic networks. Accordingly, behavioral modifications of voluntary respiratory activities, commonly experienced in yogic breathing and stress reducing respiratory exercises, are predicted to engender positive changes in cognitive, meditative, and emotional states [11], as stated earlier. In contrast, regulation of involuntary respiratory processes involves complex integration of rhythmic motor activities driven by functionally organized brainstem neural circuits comprising the respiratory central pattern generator (CPG) [6]. A wealth of recent studies has focused on the functional organization of discrete cellular groupings within the CPG, notably the medullary pre-Bötzinger and Bötzinger complexes [7,8] and pontine Kölliker-Fuse nuclei [20] that regulate adaptive modulation of rhythmic breathing patterns in response to temporal fluctuations of circulating CO₂ and O₂ concentrations. Genetic or pathophysiological disruptions of brainstem respiratory pattern generators have been associated with severe physiological disorders including chronic dyspnea [21,22], obstructive sleep apnea [23,24], and related breathing syndromes such as dyspnea [22,25]. Interestingly, a recent preclinical study demonstrated that metabolically compromised astrocytes within the pre-Bötzinger complex decreased rhythmic breathing patterns and exercise capacity in conscious rats [26]. The authors observed that metabolic impairment of astrocyte function resulted in significantly reduced respiratory responses to hypoxia and hypercapnia, presumably due to inhibition of ATP production and release as a purinergic signaling molecule.

In light of the aforementioned, prior neuroanatomical studies have demonstrated caudal projections of cortical and limbic structures associated with cognitive and affective processes [5] to brainstem neuronal groups mediating involuntary inspiratory and expiratory respiratory rhythms [6–8]. Functional linkages of cortical and brainstem respiratory centers is suggested by a clinical pilot study where volitional slow/deep breathing exercises were observed to mediate positive therapeutic effects on autonomic tone via sympathetic coupling of cardiovascular and respiratory processes [27]. In a subsequent human study, simulated slow yogic breathing exercises at a rate of 6 breathes per minute were demonstrated to mediate beneficial CNS effects on cardiovascular function and cardiorespiratory control

in response to hypoxic challenge [28]. Following hypoxic exposure, complementary fMRI analyses monitored activated *loci* within mid pons, bilateral amygdalae, anterior insular and occipitotemporal cortices. The authors concluded that controlled slow breathing positively modulates autonomic responses to hypoxia via coordinate activation of cardiorespiratory brainstem structures and forebrain/limbic regions involved in volitional breathing and affective and visceral responses to psychological and physiological threats.

A Proposed Mechanism of Action Linking Mind-Body Training to Activation of Mitochondrial Processes

Convergent lines of evidence presented here strongly suggest that the self-sustaining properties of mind-body training appear to be highly dependent on the degree of metabolic integrity of reciprocally interactive neuronal and non-neuronal regulatory centers located within CNS and peripheral domains. As a key biochemical corollary, potential health benefits of behaviorally-mediated enhancements of coordinated respiratory rhythms and pulmonary gas exchange are critically linked to homeostatic maintenance of state-dependent changes in tissue oxygenation and regulated mitochondrial respiration. Accordingly, we have elaborated and extend a proposed mechanism of action linking mind-body training exercises to enhanced metabolic advantage and cellular ATP production that is critically linked to synchronized mitochondrial function involving physiological activation of O₂-dependent recycling of nitric oxide (NO) and inorganic nitrite by intra-mitochondrial nitrite reductases [29–32] (Figure 2). Interestingly, a prior clinical study has drawn a potentially important association of RR training with a reduction in volumetric O₂ consumption linked to enhanced concentrations of exhaled NO [4,33]. Production and release of constitutive NO or exogenous administration of NO donors have been empirically demonstrated to engender synergistic enhancement of airway smooth muscle relaxation and promote enhanced alveolar/pulmonary gas exchange [34] (Figure 2).

Requisite enhancement of eukaryotic cellular bioenergetics indicates a convergence of metabolic processes within the mitochondrial matrix for optimal synthesis of ATP from adenosine diphosphate (ADP) and inorganic phosphate via chemiosmotic H⁺ gradient formation and utilization. Positive evolutionary pressure has segregated this physiochemical process to the organelle's inner membrane via coordinate expression of complexes I, III, and IV of the respiratory chain [31,35]. Importantly, it appears that the chemical reactivity of NO within narrow spatial and temporal domains supports its biological role as a pluripotent chemical effector/regulator of flavonoid-, quinone-, and cytochrome-catalyzed electron transport within eukaryotic mitochondria [36]. Within this functional context,

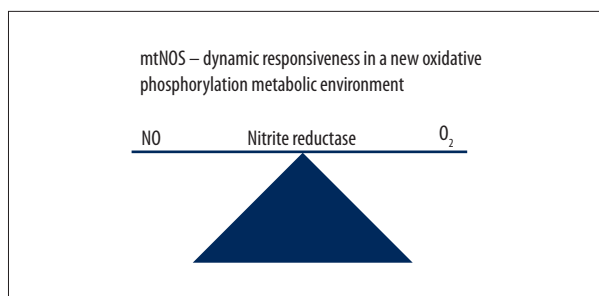


Figure 2 Nitrite Reductase and its numerous forms have been associated with modulating nitric oxide (NO) levels in both prokaryotes and eukaryotes. This ability was challenged with the emergence of oxygen (O₂) as a major player in metabolic processes. To meet this new oxygen presence, constitutive nitric oxide synthase evolved with the capability of dynamic responsiveness supplying the right amount of NO in particular situations, e.g., relaxation and restorative sleep, while being balanced with nitrite levels.

empirical studies have demonstrated that tonic and phasic intra-mitochondrial NO production exerts profound inhibitory effects on the rate of electron transport, H⁺ pumping, and O₂ consumption [35–37] by engendering reversible post-translational modification of discrete subunits of complexes I, III, and IV (also designated cytochrome c oxidase, COX) of the respiratory chain [38–40] (Figure 3). COX-mediated NO oxidation provides a 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 [31,41–44]. Conversely, enzymatic reduction of nitrite to NO within the reduced COX heme a₃/CuB active site provides a significant physiological advantage during hypoxic/anoxic environmental conditions due to its O₂-sparing effects [45].

In addition to COX, the critical role of molybdenum-dependent nitrite reductases in maintaining intra-mitochondrial NO/nitrite

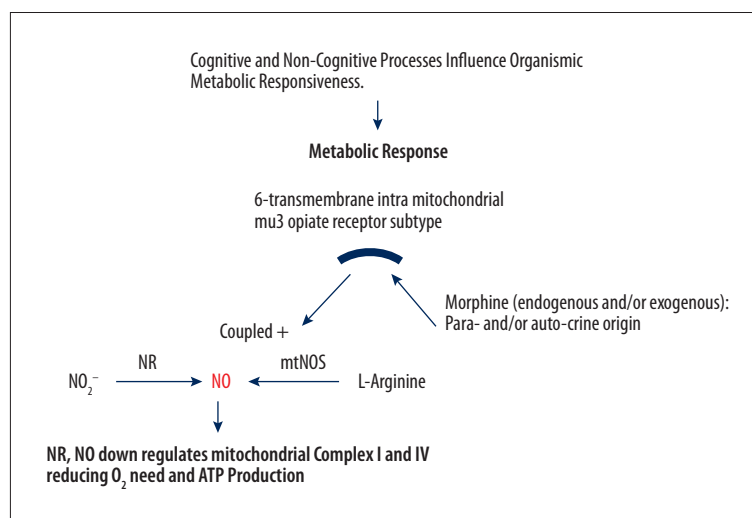


Figure 3. Cognition provides us with the potential to modulate many physiological functions, e.g., respiration. Hence, we can induce a state of calm besides sleep itself. In this regard, we may set the “degree” of our alert state by associating this ability with reward and analgesic (short-term) actions when safety in our environment exists. Cognition, thus, can induce synchronous calming actions (e.g., meditation, breathing, etc.), which occurs via “trickle down” cellular and molecular levels of regulation to initiate metabolic coordination and “cleansing”. This process was favored during evolution because it provides for longevity (DNA integrity), needed for the genetic material to be maintained in an intelligent organism that required a long learning period. Furthermore, the overall organismic processes needed to create a calm metabolic appropriate response were not only used in the brain reward system and elsewhere but in modulating the mitochondrial energy output so that, it as well, was appropriate, e.g., endogenous morphine as noted in the figure and the potential for cannabinoid and estrogen signaling as well may be involved via NO coupling in mitochondria [50–53]. For example, endogenous morphine liberates NO in mitochondria slowing down oxygen utilization, e.g., ATP production. This is mediated by the opiate alkaloid selective mu3 opiate receptor subtype coupling to constitutive nitric oxide synthase. This momentary and normally occurring rhythmic pulsatile action can be prolonged or increased along with its levels, allowing for greater free radical scavenging [54]. Additionally, we have shown morphine and 17-β-estradiol to be stronger than cannabinoids in stimulating NO release constitutively, suggesting this may represent degrees of modulatory control on vascular and immune tissues [52,53]. The “extra influence of estrogen in females may also represent a cyclic higher level of modulation due to cyclic tissue growth and may be involved with various protective process in women [53]. We now surmise that this convergent cNOS coupling occurs in mitochondria as well with cannabinoid and estrogen as just noted. NO₂⁻ – nitrite; NR – nitrite reductase; NO – nitric oxide; mtNOS – mitochondrial nitric oxide synthase.

cycling has been established, as previously reviewed [29]. It has also been established that inorganic nitrate which is converted to inorganic nitrite via the action of nitrate reductases will provide additional synergistic production of physiologically desirable intra-mitochondrial NO [46,47]. In sum, inorganic nitrite, previously thought to represent an inert metabolite of cellular nitrogen metabolism, appears to represent an essential precursor to dynamic production of NO in response to physiological demands [29,30,48,49] (Figure 3). Given the pluripotent role of NO as a selective, temporally-defined chemical regulator of mitochondrial respiration and cellular bioenergetics, the expansion of prokaryotic denitrification systems into mitochondrial NO/nitrite cycling complexes represents a series of evolutionary modifications of existential proportions.

Conclusions

In conclusion, we provide a proposed, biological systems-based, mechanism of action linking mind-body training exercises to

enhanced metabolic advantage and cellular ATP production, which is critically linked to synchronized mitochondrial function, involving physiological activation of O₂-dependent recycling of NO and inorganic nitrite. This broad-based biochemical/molecular mechanism is consistent with a model that economically projects state-dependent optimization of cellular and complex tissue energy metabolism in functionally interactive CNS and peripheral regulatory centers as its unifying principle. The primordial nature of O₂-dependent recycling of NO and inorganic nitrite as an existential regulatory mechanism underlying relaxation phenomena is reflected by its widespread expression in prokaryotic phyla and subsequent evolution in eukaryotic mitochondrial respiratory complexes [49]. Finally, potential points of intervention for optimization of medically beneficial effects of mind-body practices may reside in the monitored coupling of controlled nasal breathing exercises with nutraceutical agents capable of enhancing mitochondrial function via synchronized NO/nitrite recycling (Figure 3).

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