



Regulation of gene expression by yoga, meditation and related practices: A review of recent studies

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ABSTRACT

Integrative medicine (IM) approaches have gained significant interest in recent years to provide a solution for the health care challenges we face today. Yogic cognitive-behavioral practices are among the most widely used IM approaches and include diverse practices such as yoga asanas, meditation, breathing exercises, Qi Gong, Tai Chi Chih, and various others. Studies to date suggest that these yogic/meditative practices have significant positive effects on the mind–body system and thereby can increase wellness and support the healing process from disease. Previous work has provided evidence for both psychological and physiological effects of these practices; however, the mechanisms of these effects, especially at the molecular level, have largely been missing. Three recent studies started to provide some of this information through gene expression profiling in circulating immune cells, which support the hypothesis that yogic/meditative practices have a measurable effect at the molecular level. These studies are reviewed herein and some future perspectives are considered.

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1. Introduction

The current health care delivery systems in the Western world have significant challenges, not only in terms of the dramatically escalating costs, but also in terms of the quality of health care provided (Committee on Quality of Health Care in America, Institute of Medicine, 2001; Blendon et al., 2001; Taylor, 2001; Snyderman and Weil, 2002). This is, at least in part, the reason for the increasing interest in integrative medicine (IM) approaches to health and wellness (Snyderman and Weil, 2002; Barnes et al., 2008; Nahin et al., 2009). In addition to providing the best possible conventional care, IM focuses on preventive maintenance of health with emphasis on diet, lifestyle, stress management, and emotional well-being (Snyderman and Weil, 2002). IM encourages patients to be active participants in their health care, as well as asking physicians to view patients with all aspects of their being, and not only physical bodies (Snyderman and Weil, 2002). To achieve these goals, in addition to depending on the latest in scientific findings and evidence based approaches, IM taps on time-tested traditional modalities to increase health and wellness, as well as helping treat disease states, at least as adjunct regimens.

One of the most widely used IM approaches is yogic cognitive-behavioral practices, including yoga asanas, meditation, breath-

ing exercises, Qi Gong, Tai Chi Chih, etc. (referred to as yogic/meditative practices from now on). In general, these practices stem from Asia, although similar practices may be found in many traditions in other parts of the world. The increasingly wide use of these practices triggered numerous research studies, especially in recent decades, which suggest that yogic/meditative practices have significant positive effects on the mind–body system and thereby can increase wellness and support the healing process from disease (for reviews, see Astin et al., 2003; Arias et al., 2006; Bushell et al., 2009; Kuntsevich et al., 2010). For example, studies on meditative therapies suggested that they can effectively reduce psychological distress which in turn can have important clinical implications in nonpsychotic mood and anxiety disorders (for reviews, see da Silva et al., 2009; Gangadhar and Varambally, 2011; Chen et al., 2012). The general understanding is that psychosocial distress is linked to various disease states, such as depression, cardiovascular disease, and cancer, as well as its more well-appreciated role in psychiatric disorders (Cohen et al., 2007); yogic/meditative practices effectively counter psychological distress and thereby support healing and wellness (Arias et al., 2006; Chen et al., 2012; da Silva et al., 2009; Gangadhar and Varambally, 2011).

The effects of yogic/meditative practices extend to physiological parameters such as humoral factors, the nervous system and the immune system (for reviews, see Arias et al., 2006; Ospina et al., 2007; Kuntsevich et al., 2010). For example, these practices were shown to have positive effects on the heart rate,

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blood pressure, and low density lipoprotein (LDL) cholesterol, and decrease the levels of salivary cortisol, the 'stress hormone'. These findings are consistent with a downregulation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS) both of which are known to be over activated by our western lifestyle. In addition, yogic/meditative practices increase vagal activity (Bernardi et al., 2001); together with the effects on the HPA axis and SNS, they could thus have favorable immune and endocrine outcomes. For example, a two-month hatha yoga intervention resulted in a 22% and 20% reduction, respectively, in the proinflammatory cytokine interleukin-6 (IL-6) and C-reactive protein (CRP), compared to minimal changes in chronic heart failure patients receiving standard medical care (Pullen et al., 2008). Furthermore, a yoga breathing based program resulted in increased antioxidant enzyme production (Sharma et al., 2003).

Despite these and numerous other studies, the exact physiological mechanisms that may give rise to the psychological and physiological effects of yogic/meditative practices are currently unknown. In particular, the molecular and cellular mechanisms of these wide-ranging effects, from psychological states to brain activity to immune function, are not known and a systems biology approach is required to precisely map the exact pathways involved. Recent studies started to provide some of this information through pathway specific or global gene expression profiling in polymorphonuclear cells (PBMCs) or neutrophils from the blood, the tissue which is most easily available for this type of investigation in humans. Below is a brief overview of this approach and a description of the three published studies to date on yogic/meditative practices using gene expression profiling, their comparative analysis, and some future perspectives.

2. Genetics of yogic practices

2.1. Short review of the tools

One of the central questions in molecular biology is how the identical genetic material in the cells of an organism can give rise to numerous cell types of different morphology and function. This diversity has been linked to differential expression of gene sets in different cell types that then determine cell function and fate. Differential gene expression is also at the basis of a cell's ability to respond to cues from the environment and activate gene programs only when needed. In addition to these roles in normal physiology, perturbations occur in gene expression in pathological conditions that are currently being explored to identify possible diagnostic or prognostic markers, as well as therapeutic targets. Thus, there has been a keen interest in understanding regulation of gene expression in different settings for decades.

The advent of microarray technology overcame the shortcomings of earlier techniques, such as Northern analysis, by allowing simultaneous assessment of changes in expression levels of thousands of RNA species (Schena et al., 1995) thus making it possible to study alterations in the full transcriptomes of different cell types under various physiological conditions as well as disease states. Currently, next-generation sequencing technologies are increasingly being used for multidimensional examination of the transcriptome (Morozova et al., 2009).

Two previous studies have used the microarray technology and another one used pathway specific reverse transcription-polymerase chain reaction (RT-PCR) to assess possible changes in basal gene expression in PBMCs in circulation upon regular practice of yogic/meditative techniques (Li et al., 2005; Dusek et al., 2008; Sharma et al., 2008). These are summarized below.

2.2. Studies to date

In the first and most in-depth study, despite small number of subjects, gene expression differences were investigated in neutrophils of 6 Asian Qigong practitioners compared with 6 healthy Asian controls (Li et al., 2005). The Qigong group had practiced the program for at least 1 year that consisted of a cognitive component in addition to practice that lasted 1–2 h daily. Neutrophils were isolated from fresh blood and gene expression profiling was performed using microarrays that could interrogate approximately 12,000 genes. Among these, 250 genes were consistently different in expression between the Qigong and the control groups, with 132 down regulated and 118 up regulated genes. Among the differentially expressed genes, there was down regulation of genes related to the ubiquitin degradation pathway, as well as genes that encode ribosomal proteins. Cellular stress response genes were generally down regulated in Qigong practitioners compared to controls, but the expression of two of the heat shock proteins were increased. Expression of some genes that are related to immunity were also increased in the Qigong group, such as interferon gamma (IFN- γ) and IFN-related and IFN-regulated genes. Possible functional implication of this observation was indicated by increased neutrophil bactericidal activity in an *in vitro* assay in cells isolated from Qigong practitioners compared with controls. Furthermore, the lifespan of normal neutrophils was increased while those of inflammatory neutrophils was decreased through apoptosis, or programmed cell death. The authors interpreted these results as beneficial since delayed neutrophil apoptosis has been linked to a number of chronic inflammatory injuries resulting from enhanced immunity (Summers et al., 2010). Despite questions of generalizability and underlying mechanisms, and the small number of subjects, these data suggested that Qigong practice may exert beneficial effects on immunity, metabolic rate, and apoptosis through modulating gene expression.

The second study (Dusek et al., 2008) evaluated possible gene expression changes triggered by the 'relaxation response' (RR), a bodily state characterized by decreased oxygen consumption, increased exhaled nitric oxide, and reduced psychological distress (Wallace et al., 1971; Benson et al., 1974). An interesting aspect of the study was that the 'mind/body' practices employed by the test subjects to elicit RR were quite diverse, ranging from vipassana or insight meditation, mantra meditation, and transcendental meditation, to breath focus, Kripalu or Kundalini Yoga, and repetitive prayer. The study included 19 long-term (average 9.4 years of practice) RR practitioners (Group M) along with 20 healthy controls who were tested at baseline (Group N1) and who underwent eight weeks of training in guided relaxation techniques and were tested again (Group N2). Blood was drawn, PBMCs were isolated, and global transcriptome profiles were determined using microarrays that could interrogate approximately 47,000 genes and gene variants. Pairwise comparisons of the transcriptomes between the three groups were then performed. 2209 genes (1275 up- and 934 down-regulated) were found to be differentially expressed between Groups M and N1, 1504 genes (774 up- and 730 down-regulated) between Groups M and N2, and 1561 genes (874 up- and 687 down-regulated) between Groups N1 and N2. Interestingly, 595 genes were differentially expressed specifically in Group M suggesting that the expression profile is different in long-term practitioners of the RR compared with the other two groups. Similarly, 428 genes were shared between the short and long-term RR groups (Groups M and N2), but not with the control group, suggesting that these may represent changes characteristic of the RR. Gene ontology and gene set enrichment analyses indicated that differential gene expression impacted a variety of cellular pathways, such as oxidative phosphorylation, ubiquitin-dependent protein catabolism, nuclear mRNA splicing, ribosome,

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