Review Article

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The potential positive epigenetic effects of various mind-body therapies (MBTs): a narrative review

https://doi.org/10.1515/jcim-2021-0039
Received February 16, 2021; accepted June 7, 2021;
published online June 22, 2021

Abstract: Mind-body therapies (MBTs), such as mindfulness, meditation, yoga, and tai-chi, are said to improve quality of life by contributing to positive thinking and reducing overall distress. MBTs not only play a role in reducing stress and anxiety, but they are also found to epigenetically affect genes and other areas in our genomes that are implicated in inflammation, stress, and distress. This review analyzes the role of MBTs in reducing the epigenetic changes as reported in five previously conducted controlled studies found in the NCBI PubMed database. The methylation of the tumor necrosis factor gene, implicated in psychological distress, was shown to significantly decrease for the women who performed yoga. For people who took part in mindfulness meditation, there was a significant alteration in a variety of modifications of histone deacetylase enzymes as well as their expression patterns when compared to the control group. Other studies found that long-term meditators had slower biomarkers of aging, known as epigenetic clocks, and methylation in genes associated with immune cell metabolism and inflammation. Different genomic regions known as CpG dinucleotide sites ("CpG islands") were also found to be epigenetically altered in participants of tai-chi. These controlled studies were promising evidence on the potential of MBTs to affect the epigenetics of an individual. This information will be useful in diagnostic, therapeutic, and preventative measures, and can be an addition to western medicine, in a way that is more holistic and beneficial to the individual.

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Keywords: epigenetics; mind-body therapy; mindfulness meditation; tai-chi; yoga.

Introduction

Mind-body therapies (MBT), also known as integrated therapies, are a group of healing techniques that focus on the interaction of cognition, emotions, and behaviors to enhance physical health and function. Goals of these therapies include the promote of relaxation via present-centered focus, to enhance the mind's positive impact over physical well-being, and to improve overall health and wellness. These therapies are utilized throughout the world to enhance disease prevention, health promotion, and as an adjunct to traditional medical treatments [1]. Examples of MBT techniques include meditation, hypnosis, biofeedback, prayer, yoga, and mindfulness and have benefits that expand across ages and conditions. According to the National Health Interview Survey and American Academy of Pediatrics, MBTs are ranked among the top 10 integrative medicine practices that have been shown to be effective and safe in decreasing pain and discomfort, ease anxiety, and improve symptoms of various disorders such as post-traumatic stress disorder and fibromyalgia [2–4]. They can also be used to empower individuals with mental and physical illnesses that could, otherwise, have detrimental effects on the mind and body. Research on MBTs have not only shown considerable evidence of correlation with alleviating stress and anxiety, but they also have shown a large effect on human physiology at a genetic and epigenetic level [5, 6]

Epigenetics is the study of gene expression rather than that of the genetic code itself. Epigenetic changes are heritable changes in response to variations in behavior and environment. These consist of specific covalent modifications of materials outside the genetic code itself, such as DNA methylation, phosphorylation of the cytosine-guanosine dinucleotile units ('CpG islands') and histone modifications [7]. The CpG islands are the major sites of these epigenetic changes. These epigenetic changes may serve as markers of various biological processes in health and illnesses because

they are correlated with aging, activities such as exercise, certain environmental stimuli including sunlight exposure, as well as human diseases such as cancer and alcohol use disorders [8]. Similarly, epigenetic effects have been found in various MBTs, showing that these therapies can directly affect the structure of DNA and chromosomes. These changes have positive effects that lead to lower stress, lower anxiety, and a healthier lifestyle. This paper will be exploring research on the epigenetic effects of various MBTs to demonstrate how important MBTs are in addition to conventional medical treatments.

Methodology

Studies on the epigenetic role of MBTs were obtained from NCBI PubMed between 2010 and 2019. Various MBTs taken into consideration were yoga, mindfulness meditation, and tai-chi due to their significant role in classical Eastern traditions and their recent prevalence in the West. The search builder utilized "((yoga OR "mind-body therapies" OR "tai chi" OR meditat*)) AND epigenet*." Studies selected included the effect of MBIs on epigenetics and were controlled trials and/or were papers detailing the relationship between epigenetics and mind-body therapy in relation to yoga, meditation, or tai-chi. Five publications met this criteria and were reviewed for this current paper [8–12]. A section on stress was included in this paper in order to have a basic understanding of the epigenetic changes that can occur due to stress, and how anti-stress MBTs can aid in potentially reversing stress induced epigenetic effects.

Results

Each subsection discusses a specific MBT and focuses on the studies, discussing and analyzing their design, conclusions, and implications (Table 1).

Epigenetics and yoga

A paper published in the International Journal of Yoga stressed the importance of epigenetics in the health of the mind and body, specifically articulating that the negative impacts of a lifestyle devoid of proper diet and exercise can be reversed both physically and epigenetically in order to reduce medical issues caused by such a lifestyle [13].

To support this, researchers examined the effects of yoga on markers of inflammation and DNA methylation in chronically stressed women by conducting a pilot study that examined epigenetic DNA methylation patterns by comparing participants of a yoga intervention with a control group [9]. The study used a randomized subsample of 28 out of 116 women who reported psychological distress. Those identified as chronically stressed had a score of 16+ on Kessler Psychological Distress Scale. The study enrolled this group of women in an eight week yoga intervention program where sessions were 1 h long and occurred biweekly. The women who were eligible were required to be free from acute infection for at least two weeks prior to the biochemical assessment, and had to refrain from ingesting alcohol for at least 48 h prior to the assessment. If there were serious physiological conditions that could interfere with the interpretation of biochemical data, such as blood cancers, autoimmune diseases, and inflammatory bowel diseases, women were excluded from the study [9].

Specific candidate proteins were measured and were identified by researchers as those that were historically found to play a role in psychological distress and modified by yoga practice. These proteins included IL-6, TNF, and C-reactive protein (CRP). Serum samples were collected at the beginning of the study for both the yoga and control group. Eight weeks later, post-treatment with the yoga intervention, serum and whole blood samples were collected. In a follow-up one month after this collection, DNA methylation patterns were explored longitudinally in a non-controlled trial and were compared to the control group with an identical timeline of collection and analysis for standardization purposes.

Results of the study suggested that there were no differences between the control and sample group in mean methylation across CRP or IL6 regions. However, the women in the yoga group had 4.5% lower mean methylation levels of TNF when compared to the control group. This finding supports that yoga may introduce epigenetic changes on immunomodulators. When the age and waist-to-height ratio was adjusted and included in the analysis, the TNF finding still remained. When examining individual CpG units, the decreased methylation for the post-yoga sample showed a decrease for the TNF site at CpG site 1 (Cohen's *d* as 1.11) and at sites 4, 5, and 6 (Cohen's d as 1.00). Statistical analysis also showed a moderate elevation of IL-6 in the yoga group(9). Therefore, results showed a strong association between the eight-week yoga intervention group and decreased methylation of TNF and a moderate effect showing higher IL-6 levels in the yoga group. Though IL-6 is classically known to be pro-inflammatory, it is also implicated in the neuroprotective effect of exercise on mood and regenerative effects based on its signalling mechanism [9]. While results were found in a relatively small sample population, epigenetics is a growing field, and the

Table 1: Studies discussed in narrative review.

Author and year	MBT	Sample characteristics	Key findings
Ren et al. 2012 [8]	Tai-chi	– 500 females – 45–88 years old – 237 tai-chi practitioners of at least three years who did tai-chi at least 1 h per week and a control group of 263 females who never participated in tai-chi	– Analysis of methylation profiles revealed: six CpG marks from three different chromosomes showed a significant difference between tai-chi practitioners and the control group – A slower decline in age-related DNA methylation of all six CpG sites in the tai-chi sample was observed in comparison to control group
Harkess et al. 2016 [9]	Yoga	– 28 females – "Middle-aged" from 35 to 50 years old – 11 participated in an eight-week yoga intervention program where sessions were 1 h long and occurred biweekly and 15 were in the control group	– No differences between control and yoga group in mean methylation across *CRP* or *IL6* regions – Women in the yoga group had a 4.5% lower mean methylation levels of *TNF* compared to control group – Strong association between eight-week yoga intervention group and moderate effect of higher IL-6 levels in the yoga group
Kaliman et al. 2014 [10]	Mindfulness meditation	– 40 participants – Age (controls: 50.38 ± 8.96; meditators: 49.89 ± 11.18)[a] – 19 subjects who practiced mindfulness meditation (daily for at least three years as well as at least three intensive retreats) and 21 subjects with no meditation experience	– Meditators had reduced expression of genes that code for histone deacetylase enzymes (*HDAC2, 3* and *9*) – Meditators had increased global histone modifications (*H4ac*) and lower expression of pro-inflammatory genes such as *RIPK2* – Lower levels of *RIPK2* and *HDAC2* genes were associated with a faster cortisol recovery
Chaix et al. 2019 [11]	Mindfulness meditation	– 40 participants (34 analyzed)[a] – Age (controls: 50.38 ± 8.96; meditators: 49.89 ± 11.18) – 19 experienced meditators (daily for at least three years as well as at least three intensive retreats) and 21 controls	– All chromosomes, except five, had 61 meditation-sensitive DNA methylation sites distributed across genes associated with immune response and aging in peripheral blood mononuclear cells
Chaix et al. 2017 [12]	Mindfulness meditation	– 38 participants (34 were analyzed)[a] – Age (controls: 50 ± 9.55; meditators: 49 ± 10.20) – 18 subjects who practiced mindfulness meditation (daily for at least three years as well as at least three intensive retreats) and 20 subjects with no meditation experience	– Meditation group data showed a negative correlation between intrinsic epigenetic age acceleration and years of regular meditation practice

[a]Participants in Mindfulness Meditation studies [10–12] were from a similar cohort of individuals, though each study analyzed different epigenetic markers.

study was one of the first to explore the relationship between yoga and epigenetics.

Epigenetics and mindfulness meditation

Mindfulness meditation is an MBT that cultivates attention intentionally on internal and external stimuli, such as our breath or the sounds we hear around us. Mindfulness meditation has become widely used across the United States and among many cultures, and is found to have positive effects on psychological, neurological, endocrine, and immunologic systems [10]. In an experiment, researchers studied 19 subjects who practiced mindfulness meditation and 21 subjects with no meditation experience in order to determine whether there were any differences in gene expression before and after a mindfulness meditation-based intervention. Those who were selected to be participants in the mindfulness meditation group had to practice meditation daily for at least three years, with 30 min of meditation in a sitting position daily. It was also required for these people to have attended and participated in three intensive retreats for a duration of five or more days. In contrast, those in the control group participated in leisure activities in the same environment [10, 14].

Researchers analyzed gene expression through quantitative-real time polymerase chain reaction assays. The analysis was done on genes from peripheral blood mononuclear cells (PBMCs) that are implicated in circadian activity, chromatin modulation, and inflammation.

Groups also engaged in the Trier Social Stress Test (TSST) in which participants were put in conditions where stress is induced. Researchers found that meditators had reduced expression of genes that code for the histone deacetylase enzymes (*HDAC2, 3* and 9). Additionally, the meditators had increased global histone modifications (*H4ac*) and also had lower expression of pro-inflammatory genes such as *RIPK2* (Receptor Interacting Pro-Kinase2) and *COX2*. After both groups were exposed to the TSST, lower levels of *RIPK2* and *HDAC2* genes were associated with a faster cortisol recovery. This is significant, as cortisol is a stress hormone and *RIPK2* and *HDAC2* genes are decreased in meditators, showing that meditation has an association with faster recuperation from stress [10]. This study supports that mindfulness meditation not only downregulates the expression of the *HDAC*s genes involved in the epigenetic mechanisms, but also reduces the pro-inflammatory mediators; thus, suggesting preventive and therapeutic potentials.

The relationship between aging and epigenetic changes is a promising direction for further exploration. Aging has strong effects on epigenetic mechanisms such as DNA-methylation: this relationship can be quantitatively measured which provides the basis of the "epigenetic clock" – the biological marker for aging, stress, and age-related chronic diseases [12]. The epigenetic clock is essentially a biochemical test to measure the level of DNA methylations in an individual from which the extent of aging can be determined. One study examined how meditation practice influenced one's epigenetic clocks [11, 12]. Scientists calculated the Intrinsic Epigenetic Age Acceleration (IEAA) in long-term meditators (n=18) and meditation-naïve controls (n=20). Long-term meditators were defined as individuals who had at least three years of practice with daily sitting meditation for at least 30 min a day, as well as attendance to at least three intensive retreats in mindfulness and compassion-related meditations. The control group had no prior experience with meditation. Results showed that, though the IEAA was similar in both groups, the older controls had higher IEAAs than younger controls (demarcated at age 52). This is expected, as older controls are likely to have higher biomarkers associated with aging. In comparison, the meditation group had a negative correlation when comparing the relationship between IEAA and years of regular meditation practice. These results were calculated by measuring the DNA methylation age in meditators and controls ($p<0.001$ in all cases). This relationship points towards the idea that regular meditation practice can help slow down the epigenetic clock and help as a prevention strategy for age acceleration [12]. Interestingly, in ancient India and China, yoga was prescribed to prevent aging for centuries [15].

Another study by the same group of researchers analyzed DNA methylation sites (DMS) in peripheral blood mononuclear cells of long-term meditators (n=19) and meditation-naïve controls (n=21), though only 17 of each group could be analyzed [11]. It is worthwhile to note that the three studies mentioned in this section utilized a similar cohort of people, but used different analyses in each. The PBMCs of both groups were obtained at 8:00 am (Time 1) and at 4:00 pm (Time 2) on the same day. In between the two time points, the meditation group had an intensive day of mindfulness, whereas the controls stayed in the same environment and conducted leisurely activities. The baseline methylation profiles for the two groups received at Time 1 had no significant baseline differences. To determine the DMS between the groups, the researchers used stringent criteria for differential methylation detection: a false discovery rate adjusted p-value below 0.05 and a difference in methylation level of at least 3%. This led to 61 sites that were differentially methylated after the meditation intervention. Scientists found that all chromosomes, except 9,15, 18, 20, and 21, had these 61 meditation-sensitive DMS distributed across them. Meditation-sensitive DMS were also more significantly found in proximal promoters and first exons of genes ($p<0.05$) as well as in CpG Islands ($p<10^{-4}$). DMS were enriched in genes mostly associated with immune cell metabolism and aging. In addition, these genes were also related to binding sites for several transcription factors involved in immune response and inflammation, such as *COX2* expression, and other functions such as DNA repair, the Fanconi anemia pathway, and modulation of telomerase activity. These results suggest that even a short meditation intervention in those who have made mindfulness meditation a part of their daily life may rapidly influence the epigenome at sites involved in immunity and DNA stability.

Epigenetics and tai-chi

Tai-chi is a widely practiced MBT that has its roots in traditional Chinese practice. It is believed to improve physiological and psychological quality of life and general well-being through strengthening the body's energy force, the qi (chi). Ren et al. [8] conducted a study to determine if tai-chi practice results in epigenetic changes. The study analyzed the DNA methylation profiles of 60 different CpG-dinucleotide marks from a sample of 237 female tai-chi practitioners between 45 and 88 years old. Enrolled participants were tai-chi practitioners for over three years who have had engaged in yang-style tai-chi for at least an hour per week. Researchers then compared the marks to a control group of 263 females who

matched the experimental group participants' age range, but never participated in tai-chi.

DNA from buccal samples were taken from participants and were used for methylation analysis of specific genetic loci by mass spectrometry. The loci selected were implicated with age-related DNA methylation change. In these loci, 60 CpG islands were investigated out of which six CpG marks (17p_7, Xp13_1, Rad50_2, Rad50_10, G6PD_6, and G6PD_7) from three different chromosomes showed a significant difference between the tai-chi practitioners and the control group ($p<0.05$)[8]. Four of the six CpGs were shown to have losses in DNA methylation, while two of them had gains in DNA methylation when they were compared to the controls. Specifically, the age/timing patterns between some loci were also seen in the tai-chi sample. For the Rad50_2 and Xp13_1 loci, the effects of tai-chi were observable from age 45 onwards. For the other four marks, the methylation differences were not significant until after 50–55 years of age. The researchers predicted that this could be due to tai-chi not having any effect on methylation profiles of the four CpGs until this specific age range. Overall, a slower decline in DNA methylation of all six CpG sites in the tai-chi sample was observed when compared to the control sample. This supports the idea that tai-chi reduces the aging induced epigenetic changes that come with an increase of age. It further suggests that DNA methylation can be used as a potential epigenetic biomarker to assess the therapeutic efficacy of of tai-chi in health and illnesses.

Conclusions

Although limited in number, these five studies have demonstrated that MBTs such as meditation, yoga, and tai-chi affect epigenetic changes. More studies need to be conducted on each MBT, with larger sample sizes and fewer confounding variables, to determine with greater certainty the extent and magnitude of these epigenetic changes.

Preliminary research has shown that individuals who practiced yoga and mindfulness meditation have reduced methylation levels of various enzymes involved in epigenetic mechanisms, as well as reduced pro-inflammatory markers. Research on participants who practice tai-chi have shown slower decline in DNA methylation in loci implicated in aging. As a result and upon review of the literature, MBTs are shown to be integral in positively affecting health, not only through changes in our mental and physical health, but also by influencing the expression of our genetic code. These findings, although preliminary, have promising potential implications in preventive, diagnostic and therapeutic medicine.

Acknowledgments: Dr. Angela DiBenedetto, PhD, Professor of Biology, Villanova University, for instilling passion in me and for participating in meaningful conversation that led to the conception of this paper.
Research funding: There was no funding for this review.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Authors state no conflict of interest.
Informed consent: Not applicable.
Ethical approval: Not applicable.

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