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Mindfulness Based Stress Reduction: An Integrated View of Physiological and Molecular Aspects of Mindfulness Intervention on Stress Management

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ABSTRACT:- Stress is a protective response generated inside the body towards external and internal factors. Though the initial stress helps the individual stay more focused, energetic and alert, overwhelming long term stress results in an array of negative health consequences leading to morbidity and mortality. Stress can cause fluctuations in inflammatory markers, neurobiological circuits, immunological responses and stress hormones, and the underpinning intrinsic genetic mechanisms have been disentangled over the last few years. Mindfulness, being the practice of paying attention to the thoughts of the present moment and accepting them without judgment has known to improve the functions of the brain regions such as prefrontal cortex and hippocampus while diminishing the activity of amygdale. The impact of mindfulness based stress reduction (MBSR) on autonomic, inflammatory and immune markers and the associated positive physiological consequences have been unraveled. Pro-inflammatory gene expression regulation primarily through NF-κB signaling pathway, differential CpG methylation in confined genomic locations along with the improved telomere length and the telomerase activity are considered as the crucial factors underlining the physiological, psychological, behavioral and cellular responses in the MBSR practitioners. Clinical and non-clinical communities who followed MBSR have shown greater improvements in the body functioning and their overall performances.

Keywords: Inflammatory and immune markers, Mindfulness, NF-κB signaling pathway, Pro-inflammatory gene expression, Stress responses

I. INTRODUCTION

Stress is a very common scenario which is experienced by most of the people in day today lives. Various demands coming from the working environment, relationships, families and other various sources can cause stress on people. The brain as the center of the stress modulation, implements various behavioral and physiological responses as adaptive strategies to stress (allostasis), while it might lead to pathologies (allostatic overload) if the responses are used excessively [1]. Stress could be acted as a motivator towards one's behavior where it is an essential component of the survival. Though it is required in certain levels for survival, if it is not managed properly it may even lead to excessive and chronic stress [2]. The chronic stress can exacerbate psychological disorders such as anxiety, mood disorders, depression [3, 4] and physical disorders including cardiovascular disorders, respiratory disorders, autoimmune diseases, gastrointestinal problems, sleep disorders, cirrhosis etc. [3, 5, 6].

To date, a plethora of studies have received a great deal of attention on various strategies to manage and alleviate the stresses. Certain religion coping methods and spirituality [7- 9], physical exercises [10, 11], altruism [12, 13] social connection and support [14, 15], meditation [16, 17], relaxation techniques, psycoeducation, coping skills training and cognitive reconstituting [18, 19] music therapy [20, 21], yoga [22], complex decongestive therapy which is a type of massage therapy [23] are known to be effective in adjustment to different types of psychological distresses over the past decades. The effects of mindfulness which is a type of meditation on stress mitigation and the associated improved cognitive function, physiological and psychological well-being of the stressed people also have long been discussed in the previous literature [24, 25]. In light of this, this review summarizes the burgeoning body of research regarding the effectiveness of mindfulness based stress reduction strategies to cope up the stress conditions in both clinical and non-clinical communities in terms of physiological and molecular aspects.

II. STRESS ASSOCIATED PHYSIOLOGICAL CHANGES

In the acute and chronic stress conditions, alterations can be occurred in neurochemistry and the molecular aspects of the brain. Unlike the healthy brains, unhealthy brains are very poor in adopting with neural circuitries in response to stressful conditions [26]. Adaptive changes are observed in specific regions of the brain including hippocampus, amygdale and pre frontal cortex. Changes in the density and morphology of the dendritic spines including dendritic shrinkage and loss of spines in the hippocampus have been observed with exposure to stress [27]. Acute stress was found to be causing increased spine density of basolateral amygdale neurons while chronic stress was causing expansion of the basolateral amygdale dendrites [28]. Moreover, chronic stress has caused shrinkage of dendrites [29] and loss of spines [30] in the medial amygdale. Additionally, debranching and shrinkage of dendrites was shown in medial prefrontal cortex neurons while expansion of dendrites was found in orbitofrontal cortical neurons [31, 32].

Studies have demonstrated the impact of acute stress on the immunologic functions of individuals with regard to circulating and stimulated markers of inflammation [33, 34]. However, the degree of immunological responses were varying among the individuals with large, little or no response [33, 35]. Prolong stress was found to be associated with release of abnormal levels of stress hormones, inflammatory markers and the activation of neurobiological circuits [26, 36, 37].

III. STRESS ASSOCIATED MOLECULAR CHANGES

Upon the activation of sympathatic nervous system by psychosocial stresses, extracellular biochemical signals such as neurotransmitters, hormones or growth factors induce the intracellular molecules such as transcription factors through signal transduction which culminates in the alteration of gene expression [38-40]. The opposite actions of two transcription factors (TFs); glucocorticoid receptor (GR) in endocrine system and nuclear factor kappa light-chain enhancer of activated B cells (NF-κB) in immune system mediate the ultimate harmful stress response towards a particular stress, by which defective action of GR leads to increased NF-κB mediated inflammatory effects [41]. Antineurogenic and behavioral responses of chronic stress are suggested to be mediated by downstream signaling of NF-κB [42], where the higher activity of NF-κB TF in stressed patients up-regulates pro-inflammatory genes while the lower activity of NF-κB represses the expression of pro-inflammatory genes resulting an impaired inflammation [43]. NF-κB mediated gene expression produces pro-inflammatory cytokines including IL-Iβ, IL-6 and TNF-α [44-46]. An in depth analysis of NF-κB mediated signal transduction is elaborated in the Fig. 1.

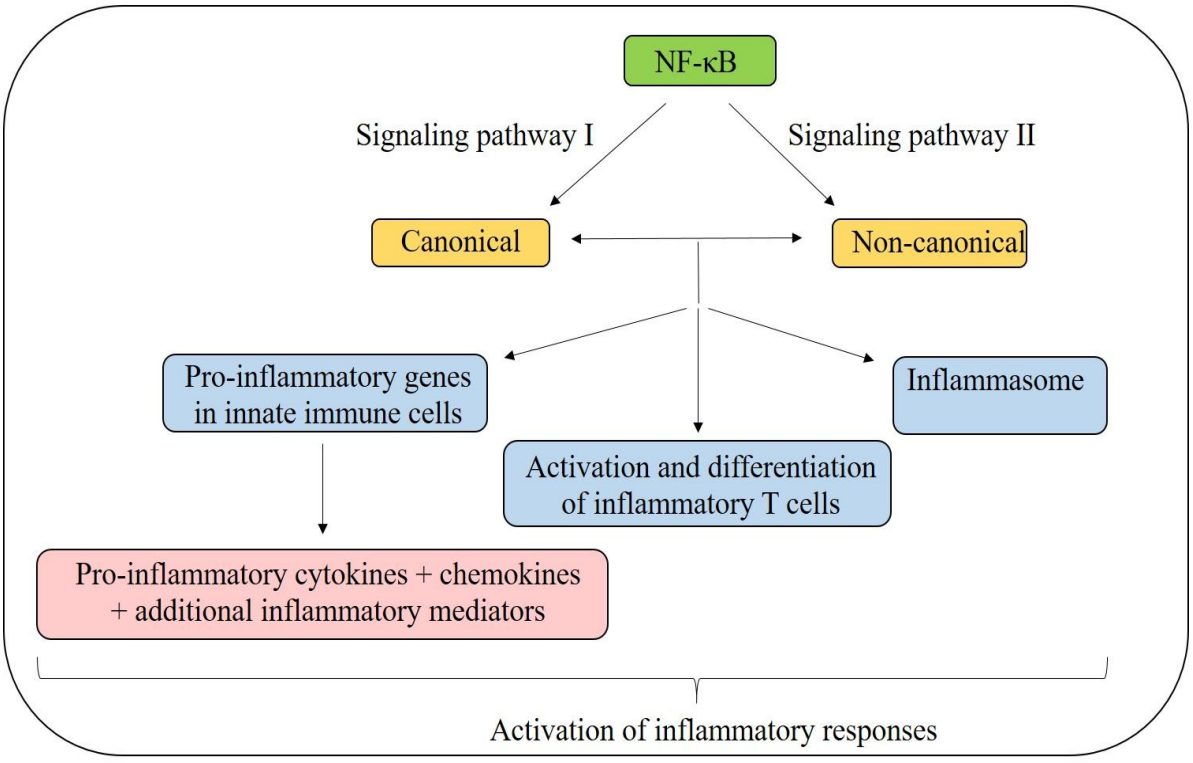

Figure 1 NF-κB mediated signal transduction

NF-κB mediated immune, inflammatory and inflammasome related responses are primarily regulated by canonical and non-canonical signaling mechanisms [47, 48]. The activation of NF-κB induces the expression of pro-inflammatory genes in innate immune cells which encode cytokines, chemokines and additional inflammatory mediators [49-51]. Triggering, differentiation and the effector function of inflammatory T cells and the regulation of inflammasome are also modulated by NF-κB [52, 53]. Together, upon the activation of NF-κB downstream signaling, the components of the innate and adaptive immune systems stimulate the inflammatory responses ultimately leading to the inflammatory diseases [54].

Cumulative lifelong stress can modulate epigenetics, wherein it accelerates the epigenetic clock and the associated age related chronic diseases thereby, increases the mortality and morbidity of the individual [55-58]. This modulation is mediated by altering the gene expression through DNA methylation, histone modifications and repressing the activity of miRNAs [59] in the absence of a change in the DNA sequence [60, 61]. Differential methylation of inflammatory and innate immunity mediated genes are known to induce downstream intracellular cascades thereby, modulate physiological and behavioral responses towards stress [62]. Psychological stress activates the miR-124 mediated down regulation of glucocorticoid receptor (GR) mRNA expression specifically in dentate gyrus which is a part of the hippocampus. Moreover, prolonged stress accounts for a substantial DNA methylation of discrete CpG sites within *Nr3c1 gene* (GR gene) [63]. Differential DNA methylation in oxytocin (OXTR) receptor is known to have impaired interactions with hypothalamic-pituitary-adrenal axis [64] and cardiovascular stress reactivity [65, 66], and alterations in blood cell compositions [67]. In addition, growing body of evidence propose correlations between epigenetic changes and telomere lengths in regulation of multiple stress associated cell responses. Accordingly, increased DNA methylation levels of GPR31 receptor, which functions in metastasis and extravasation are found to be associated with increased telomere lengths (TL)s [68] whereas, that of *SERPIN3G* gene which mediates immune cell maintenance [69], intracellular cytotoxicity [70] and autoimmune diseases [71] negatively correlates with TLs [68].

Stress also regulates the TL and telomerase activity (TA) within the cell. The stress induced responses are resulted by shorten telomeres and lower levels of telomerase. Telomeres being the end DNA protective caps, thus securing the genome integrity [72] and telomerase being the mediator which maintains the telomere length by adding nucleotide residues to the telomere DNA [73] are known to be coupled with the changes in an array of physiological functions including stress associated inflammation, oxidative stress [74] and T cell function [75]. Together, all these facts elucidates that long time perceived stress can result in multiple negative effects in physiological and behavioral responses through transcription factor modulated altered gene expression, epigenetic modification mediated gene expression changes and telomere degradation.

IV. MINDFULNESS BASED STRESS REDUCTION (MBSR)

Mindfulness is a type of awareness achieved by focusing on the present moment in a non-judgmental manner [76]. Mindfulness interventions have become very popular for last two decades [77], and it is being extensively practiced through courses, workshops, internet programmes and apps around the world [78]. Mindfulness interventions are widely used in the college students in order to remove pessimistic attitudes and thereby, to enhance the academic carriers [79, 80]. However, variety of mindfulness based therapies is available and are supported by several studies including mindfulness based stress reduction (MBSR) [81], mindfulness-based cognitive therapy (MBCT) [82], acceptance and commitment therapy [83], and dialectical behavioral therapy [84]. Out of these, MBSR and MBCT are the techniques which have been meticulously evaluated [85]. Mindfulness can be integrated into day-today activities so called “informal practice” and also in a distinct time period where the focus is only towards the mindfulness development which is called as “formal practice” [78]. Both of these practices are incorporated in mindfulness based stress reduction technique [86]. Mindfulness based stress reduction was introduced by Jon Kabat-Zinn to change the negative impression towards chronic pain [87]. This involves two hour session of meditation, yoga and body scanning per week for eight week sessions. It’s practiced daily at home with subsequent retreat. The responses generated in the body upon the exposure to a particular stress and the MBSR mediated stress management are depicted in the Fig. 2.

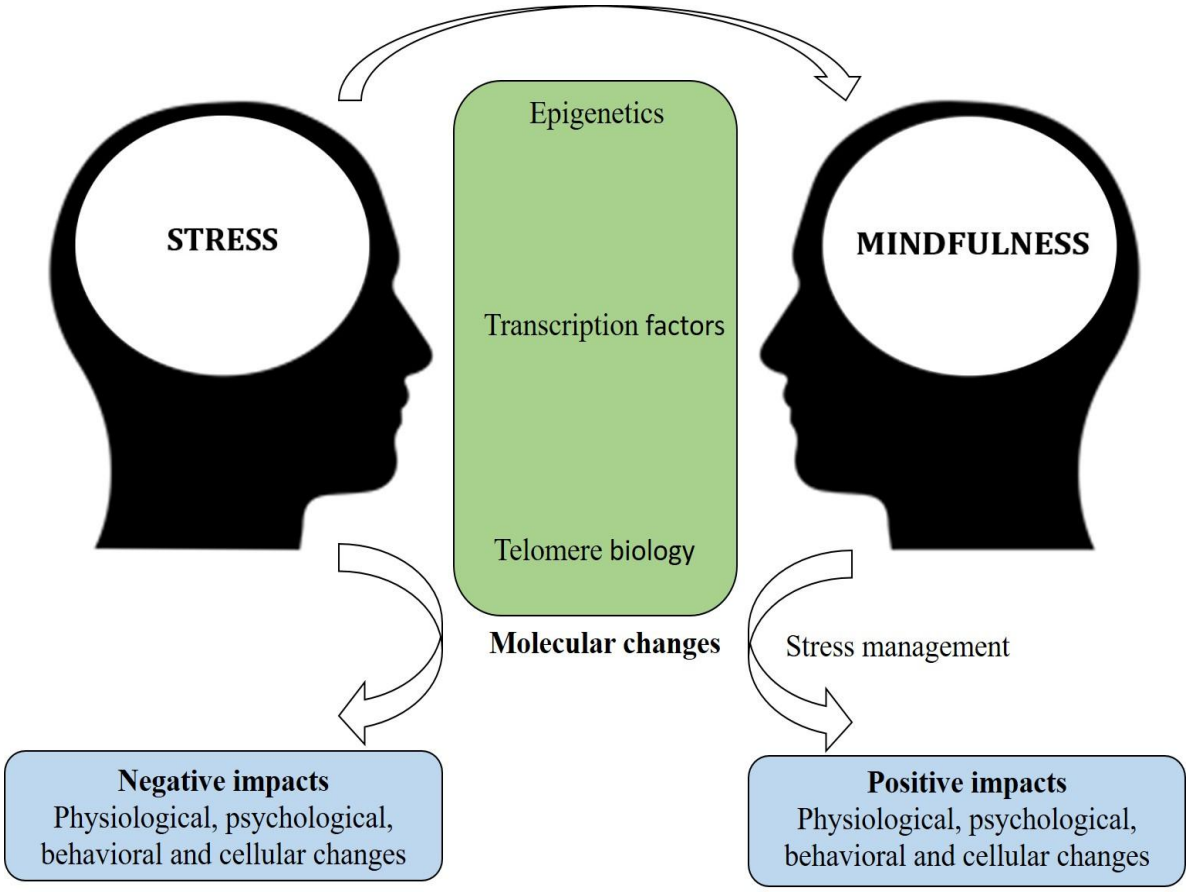

Figure 2 Mindfulness based stress reduction

Stress induce various genetic alterations in the body such as epigenetics and transcription factor modulated gene expression changes and telomere degradation which lead to an array of negative physiological, psychological, behavioral and cellular changes. Mindfulness based stress reduction strategies could reverse the molecular changes regulating multiple effects which benefits in alleviating the stress related negative consequences.

V. PHYSIOLOGICAL BASIS OF MBSR

Physiological aspect of the MBSR has been assessed extensively in literature in patients with vascular diseases, cancers, immune suppressed patients, inflammatory diseases including arthritis, obese individuals and as well as in healthy people. Biological markers that were evaluated in these studies include; neurological, autonomic, immune, inflammatory and endocrine markers. Neurological effects of the MBSR have widely been evaluated in the clinical as well as in the non-clinical populations in the literature. Activity of the amygdale, the area of the brain which is responsible for fight or flight responses is found to be decreased [88]. In addition, improved activity and the functional connectivity of the prefrontal cortex region with salience network [89], superior temporal gyrus, visual cortex, hippocampus and posterior cingulated cortex [90, 91] have been revealed. In contrast, the prefrontal cortex is shown to have a negative connectivity with the amygdale [92]. Furthermore, hippocampus, a region of the brain which is mainly responsible for learning, memory and emotional behavior was found to be increased in volume in the individuals who practiced MBSR [93]. Moreover, the impact of MBSR on the autonomic markers is evidenced by reasonable effects on systolic and diastolic blood pressure [94]. With regard to immune markers, the patients whose immune functions were diminished had been demonstrated with increased natural killer cell activity (NKCA) [95], CD4 + T-cells and Telomere lengthening after practicing MBSR [96]. The effects of MBSR on inflammatory markers include decreased levels of salivary and plasma cortisol [95, 97], C-Reactive protein (CRP), Nuclear Factor Kappa B (NF-κB), which is a precursor of pro-inflammatory cytokines [96] and increased levels of Th-1 pro-inflammatory cytokines and Th-2 anti-inflammatory cytokines [95, 96]. The influence of MBSR on endocrine markers includes decreased fasting blood glucose levels which could be due to an improved adherence to the diet and exercises [98].

VI. MOLECULAR BASIS OF MBSR

Mindfulness practices which involve a high consciousness of the present situation have proven effects on reversing pro-inflammatory genes through a set of transcription and regulatory factors, thus, ensure the well-being of the individual with a better ability to manage the stress conditions. Mindfulness based programs can induce a set of favorable cellular genomic responses in cancer patients [99], irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) [100], community adults [101, 102] and long-term experienced meditators [103]. NF-κB, being the key signaling pathway responsible for the downstream signal transduction induces the proinflommatory gene expression, mostly in monocytes and dendrocytes. The practitioners who followed a particular mindfulness program have known to down-regulate NF-κB along with tumor necrosis factor, which is a potent stimulator of NF-κB pathway. Conversely, the anti-inflammatory glucocorticoid receptor (GR) and interferon regulating factors (IRF) are known to be up-regulated majorly in B lymphocytes [99]. The activation of downstream signaling can repress the expression of pro-inflammatory genes such as *RIPK2* (receptor-interacting serine-threonine kinase 2) and *COX2* (cyclooxygenase) thereby, reducing the inflammation related cellular responses followed by a more rapid cortisol recovery. Moreover, considerable changes in global modification of histones (H4ac and H3K4me3) and histone deacetylase gene (HDAC 2, 3, and 9) silencing have been noted in 8-h mindfulness practitioners and their influence on the expression of the other genes have also been uncovered [104].

Certain physiological processes such as inflammation and immunity which are severely being affected under stress conditions are highly regulated by some TFs and the motifs for these TFs such as KLF15, EGR1, EGR2, SP3, SP4 are enriched with differentially methylated sites [105-111]. Among these TFs, EGR1 and SP3 are known to regulate the stress response to DNA damage [112]. Not only the DNA motifs for TFs, but also certain genes such as *TNFSF13B* and *PRF1* responsible for immunity and inflammation are known to be differentially methylated [113, 114]. Studies show that reduced methylation levels in *SLC6A4* gene encoding a depression associated serotonin transporter, the gene *FKBP5* encoding the HPA related FK506 binding protein 5 [115] and other fatty acid metabolism genes are coupled with favorable stress responses in those who followed MBSR programs [116]. However, as previously shown by Garcia-Campayo et al., (2018), in *NR4A2* and *KBTBDH* genes, the methylation is not confined to the individual CpG islands sites, rather they also could be found in several CpG islands in specific genomic locations, and many of the differentially methylated regions are placed nearby the telomere regions [103]. It is also suggested that the TL has an association with methylation levels in subtelomeric DNA, in those who practiced mindfulness based programs with compared to non-meditators [68].

Telomere length and telomerase activity which are highly influenced by the long-term stress in psychological and physiological disorders are known to be improved by the high awareness of the current moment. Genes encoding for human telomerase constituents such as telomerase RNA (hTR) and telomerase reverse transcriptase protein (hTERT) have known to increase their expression under reduced stress levels and thus, known to function in restoration the telomere synthesis [117] in patients who were under hypertension. The restoration of telomere activity resulted in retarding the cellular senescence and associated cell death [118]. Also, the mindfulness related programs are known to have improvements related to telomere activity for other negative psychological conditions such as dementia [119], anxiety [120], and physiological effects such as cancer [68], metabolic health [120], cellular alterations in peripheral blood mononuclear cells [121], and behavioral aspects including eating behavior [120]. Together these facts suggest that the MBSR could protect the immune system by preventing it from aging via epigenetic modulation, telomere biology and chromatin remodeling [112].

VII. THE APPLICATIONS OF MBSR

The efficacy of MBSR is evaluated in various physical disorders including cancer, cardiovascular diseases, chronic headache, and metabolic diseases including diabetes mellitus, HIV, multiple sclerosis, chronic pain, rheumatoid arthritis, fibromyalgia syndrome and psychological disorders including anxiety disorder, depression and stress (Table 1). In all these studies, the efficacy of MBSR is evaluated mainly with regard to physiological, psychological and behavioral aspects. In addition to these clinical populations, the effects of MBSR are further assessed with nonclinical populations. A meta-analysis done by Khoury et al., (2015) have demonstrated larger effects of MBSR on stress, moderate effects on anxiety, depression, distress and quality of life and also a small effect on burnout in 2668 healthy individuals utilizing 29 studies [122]. Moreover, a systematic review with a meta-analysis has shown clinically significant outcomes in older adults immediately after MBSR interventions [123]. With respect to health care system, high demand of stress placed on health care professionals and the associated physiological and psychological disorders [124, 125] have effectively been managed with MBSR [126].

Table 1 Applications of MBSR in physiological, psychological and behavioral responses

Type of the Effect	Measures	Disease	References
Physiological	Immune	Cancer, HIV/AIDS, fibromyalgia syndrome	[127-129]
	Inflammatory	Cancer, cardiovascular diseases, rheumatoid arthritis, fibromyalgia syndrome	[129-132]
	Endocrine	Diabetes mellitus	[133]
	Neurological	Chronic headache, HIV/AIDS, chronic pain	[134-136]
	Autonomic	Cardiovascular diseases, diabetes mellitus	[137, 138]
Psychological	Depression	Cancer, cardiovascular diseases, HIV/AIDS, multiple sclerosis, diabetes mellitus, rheumatoid arthritis	[139-144]
	Anxiety	Cancer, cardiovascular diseases, multiple sclerosis, diabetes mellitus, anxiety disorder	[142, 145-148]
	Stress	Cancer, cardiovascular diseases, chronic headache, HIV/AIDS, multiple sclerosis, diabetes mellitus	[147, 149-153]
	Fear	Cancer	[154]
Behavioral	Sleep	Cancer, insomnia	[155, 156]
	Mood	Cancer	[157]
	Fatigue	Cancer, multiple sclerosis	[158, 159]
	Personality traits	Cancer	[160]

VIII. CONCLUSIONS

Due to the complex, more competitive and busy life styles with more targets and goals to be accomplished in day today lives, stress has become often inevitable and thus, leading to many negative health effects in terms of physiological, mental and behavioral aspects. Stress in both diseased persons and healthy individuals could be effectively managed by MBSR programs by letting them to get avoid from the habitual thinking patterns. The molecular basis of beneficial physiological, psychological and behavioral changes of MBSR interventions have long been unraveled however, the genes, transcription factors, epigenetic modulation and telomere maintenance are yet to be fully discerned in detail. In this context, the MBSR has been recognized as an effective complementary therapy alongside conventional medicines or treatments to ameliorate the stress-affected life styles. However, certain limitations in most of the studies that have been carried out so far can be compensated by randomized control trials with high methodological qualities and large sample sizes which improve the validity of the results. Furthermore, long time follow ups are often recommended to assure the prolong effects of MBSR therapies.

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