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Effect of meditation on neurophysiological changes in stress mediated depression

Eshvendar Reddy Kasala [a,*], Lakshmi Narendra Bodduluru [a], Yogeshwar Maneti [a], Rajesh Thipparaboina [b]

[a] Department of Pharmacology & Toxicology, National Institute of Pharmaceutical Education and Research, Bhangagarh, Guwahati 781032, Assam, India
[b] Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Balanagar, Hyderabad 500037, Andhra Pradesh, India

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A B S T R A C T

Meditation is a complex mental practice involving changes in sensory perception, cognition, hormonal and autonomic activity. It is widely used in psychological and medical practices for stress management as well as stress mediated mental disorders like depression. A growing body of literature has shown that meditation has profound effects on numerous physiological systems that are involved in the pathophysiology of major depressive disorder (MDD). Although meditation-based interventions have been associated with improvement in depressive symptoms and prevention of relapse, the physiological mechanisms underlying the therapeutic effects of meditation are not clearly defined and even paradoxical. This paper reviews many of the physiological abnormalities found in cytokine & stress mediated depression and the reversal of these anomalies by different meditation techniques.

1. Introduction

Major depression is the most common disabling psychiatric disorder that has been estimated to affect 21% of the world's population [1]. According to reports published by World Health Organization (WHO), it is estimated that by 2030 depression will be the leading cause for disability worldwide. [2] MDD is defined in DSM-IV (Diagnostic and statistical manual of mental disorders-IV), as a condition characterized by loss of interest in usual activities and/or diminished ability to experience pleasurable activities (anhedonia), together with a range of other features including anergia, changes in sleep and appetite, sadness, and suicidal tendency [3]. Although meta-analyses from epidemiological studies indicate that depression is largely heritable [4], intense stress for long period has been attributed as one of the crucial components in the emergence of major depression [5]. Chronic stress activates peripheral and central immune systems accompanied with the release of inflammatory mediators. Activated immune system mediates the process of depression by means of its interaction with the nervous and neuroendocrine systems through regulating the synthesis, metabolism and reuptake of monoamines, over activation of hypothalamus-pituitary-adrenal (HPA) axis and by reducing neurogenesis [5,6].

At present, there are several types of classical antidepressants in clinical practice, including tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI), noradrenergic reuptake inhibitors (NARI) and serotonin and noradrenaline reuptake inhibitors (SNRI) [7,8]. But, there is no long-term cure for depression. Conventional behavioral and pharmacological treatments, though not a cure, have shown effectiveness in the alleviation of symptoms. However, dissatisfaction has arisen with psychopharmacological interventions due to their profound side effects, escalating prescription rates, and recent uncertainties on the effectiveness and long-term benefits [9,10]. This shifted the trend towards the use of innovative conceptual and therapeutic models of care such as complementary and alternative medicine for management of various psychological disorders, one of these is Meditation [11]. Meditation is essentially a physiological state of reduced metabolic activity different from sleep – that elicits physical and mental relaxation and is reported to enhance psychological balance and emotional stability [12,13]. At the therapeutic level, there has been a greater degree of interest and enthusiasm to explore the potential of meditation as antidepressant tool or as an adjuvant to the established modalities of psychiatric treatment like psychotherapy as it is cost-effective and presumably free of side effects and this has been observed in many studies [14–16]. There are many possible neurophysiological

* Corresponding author. Department of Pharmacology & Toxicology, NIPER, Guwahati, Assam, India. Tel.: +91 9700820750.
E-mail address: ishreddy4@gmail.com (E.R. Kasala).

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changes that occur during meditation, even though they may not occur in every type of practice. To date there has been no overall review of such research findings in this field. This present paper reviews briefly about meditation its effects on stress mediated depression and the mechanisms underlying depression physiology.

2. Meditation

Meditation is a term covering a large variety of mental practices that involve voluntary changes in states and contents of consciousness. It is constituent of major religions such as Hinduism and Buddhism and variants are encountered in other religions as well, found in all cultures and regions, both West and East [16]. Meditation continues to be used as a self-help and self-mastery technique, and as an adjunct to psychotherapy [14,15]. Meditation is one of the well-known mind–body training methods which help in the management of stress, enhancing mental and physical development. Well-known meditation techniques include Raj Yoga, Mantra, Mindfulness Meditation (MM), Vipassana, Transcendental Meditation (TM), Kundalini, Sudershan Kriya (SK), Kirtan Kriya, Sahaj Samadhi, Osho's Meditations, Silence, integrative body–mind training (IBMT) and Pranayama (P). Increasing evidence suggests that meditation practices may impact different physiological pathways such as neurotransmission, immune and neuroendocrine systems, which are affected by stress and are relevant to disease development and progression [17–19].

2.1. Stress mediated depression: role of HPA axis and sympathetic nervous system (SNS)

Psychological stress is a common risk factor involved in the development of major depression in every culture examined, and most initial episodes of major depression are preceded by an identifiable stressor [20]. The association between stress and depression has already been established by many observations: a) Individuals who are depression-prone have a higher than expected incidence of early noxious stress. b) Depressive events are frequently coupled with major life changes. c) Acute stress-induced hormonal and behavioral changes are very much similar to the symptom complex of depression; and d) Hypercortisolism is a consistent characteristic of the classic form of major depression as seen in persistent stress [21].

Psychological stress leads to the activation of the HPA axis and the SNS [22]. Following activation of HPA axis in response to an acute stressor, hypersecretion of the neuropeptide hormone corticotrophin-releasing hormone (CRH) from the hypothalamus takes place [23]. CRH travels to the anterior pituitary gland and stimulates the secretion of adrenocorticotrophic hormone (ACTH), which in turn, is released into the bloodstream and eventually reaches the adrenal cortex where it stimulates the release of cortisol. This release of cortisol in response to an acute stressor is believed to be involved in promoting survival functions, such as increasing blood pressure and blood sugar levels, while concurrently conserving energy from non-vital functions by suppressing reproductive, immune and digestive functions [24,25]. The levels of cortisol are regulated by means of negative feedback mechanism. Dysregulated HPA axis functionality is one of the characteristic features of MDD, and is demonstrated by altered feedback inhibition, as seen by increased circulatory cortisol and non-suppression of cortisol following administration of dexamethasone [26,27]. This is in part attributed by GC (Glucocorticoid) resistance/impairment of the GC-mediated negative feedback of the HPA axis which results from alterations in the GC receptor function, sensitivity and number, ultimately results in the production of various proinflammatory cytokines by increasing the expression of NF-κB (nuclear factor kappa B) [22].

Sympathetic nervous system activated by stressors, result in release of epinephrine (E) and norepinephrine (NE) into the general circulation by activating adrenal medulla. So released NE and E acting through alpha and beta adrenergic receptors, can increase NF-κB DNA binding in relevant immune cell types, including macrophages, resulting in the release of proinflammatory cytokines [28,29]. In contrast parasympathetic nervous system (PNS) pathways serve to inhibit NF-κB activation and decrease the inflammatory response. These effects are mediated by the release of acetylcholine (Ach), which by binding to the nicotinic Ach receptor is able to inhibit activation of NF-κB [30].

Peripherally released inflammatory cytokines by activation of NF-κB, can access the brain and influence all of the relevant pathophysiological domains. Cytokines access the brain by (i) entry through leaky regions such as circumventricular organs, (ii) binding to cytokine specific transport molecules expressed on brain endothelium and (iii) activation of vagal afferent fibers which transmit cytokine signals to specific brain nuclei such as the nucleus of the solitary tract. Once cytokine signals reach the brain, there is a cytokine network within the brain that amplifies and transpose relevant signals into those that interact with pathophysiologic pathways that are known to be involved in the development of depression, leading to: (i) alteration in metabolism of relevant neurotransmitters such as 5HT and DA; (ii) activation of CRH in the paraventricular nucleus (PVN) and the subsequent production and/or release of ACTH and cortisol (iii) disruption of synaptic plasticity through alterations in relevant growth factors such as brain-derived neurotrophic factor (BDNF) and (iv) Generation of oxidative stress via glutamatergic hyperactivity, increased cellular calcium concentrations, mitochondrial damage, free radical generation [22,31,32] (Fig. 1).

2.2. Brain abnormalities in depression

Neuroimaging studies have shown that MDD is accompanied by structural and functional abnormalities in several brain areas, many of which are parallel to those found in chronic stress. These areas include; prefrontal cortex (PFC), anterior cingulate cortex (ACC), hippocampus, basal ganglia and amygdala [33,34].

Amygdala: The amygdala is a part of the limbic system. The previous studies reported a reduction in glial cell density in the amygdala when a person is sad or clinically depressed. Numerous neuroimaging studies (fMRI; functional magnetic resonance imaging, PET; positron emission tomography, SPECT; single positron emission computer tomography) on amygdala have found that blood flow and metabolism is abnormally higher in depressed patients compared to healthy controls [35–37].

PFC: PFC exerts an inhibitory influence on the amygdala and therefore disruption of the PFC disinhibits the amygdala, which is generally observed in depression [38]. Several subregions of the frontal lobe have been shown to be functioning abnormally during depression, including dorsolateral prefrontal cortex (DLPFC), and ventromedial prefrontal cortex (VMPFC) and orbitofrontal cortex (OFC). Neuroimaging studies revealed that reduction in gray matter volume, blood flow and metabolism, whereas increase in white matter lesions in PFC of depressed patients [36,37,39].

Hippocampus: Hippocampus found to be hypoactive during depression. Neuroimaging studies have consistently shown that depression is associated with reduction in gray matter volume, neuronal cells, serotonergic binding, blood flow and metabolism of hippocampus [37,40,41].

ACC: The ACC is another prefrontal area in which blood flow and metabolism are decreased in unipolar and bipolar depressives.

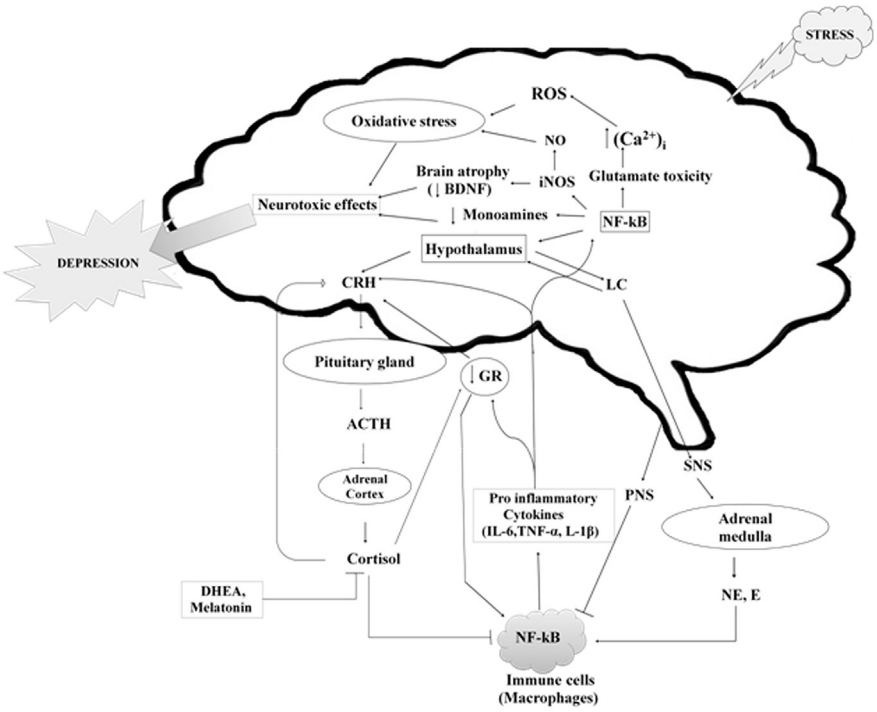

Fig. 1. Schematic diagram illustrating the pathways involved in the pathophysiology of depression. Physiological and physical stressors trigger two main stress effector pathways namely HPA and SNS pathway. Activation of HPA axis finally leads to release of cortisol, and the levels of cortisol is regulated by means of feedback loop mechanism. Dysregulated HPA axis in conjunction with downregulation of GC receptors, activation of NA pathway, leads to release of proinflammatory cytokines. The peripheral cytokines in association with the central cytokine network contributes to pathophysiology of depression by reducing monoamine levels, loss of synaptic plasticity by lowering neurotrophins (BDNF), generation of oxidative stress through glutamate excitotoxicity and elevation in intracellular calcium. This increased destructive process with diminished protective mechanisms (DHEA, antioxidants, and anti-inflammatory) may culminate in cellular damage, apoptosis and physical disease.

Volumetric reduction and reduced serotonergic binding in the ACC has been found in depressed compared with controls. Hypoactivation of the dorsal region of the ACC is associated with depression, and increased activity in this area has been found to coincide with successful antidepressant treatment [37,42,43].

Basal ganglia: In addition to the prefrontal and limbic circuitry, there is considerable data supporting the involvement of the basal ganglia and specifically, the striatum, which is found to be hypoactive in the MDD. Available literature supports the reduction in volume, neuronal density, blood flow and metabolism of basal ganglia in persons with depression [37].

2.3. Reversal of depression physiology by meditation

The physiological changes associated with meditation are reviewed in following headings (Table 1)

1. Neurochemical correlates
2. Neuroendocrinal correlates
3. Neurobiological correlates
4. Immune and inflammatory correlates

2.4. Neurochemical correlates

Several neurotransmitter systems implicated in HPA axis regulation have been hypothesized to be dysfunctional in major depression [43].

2.4.1. Serotonin (5-HT)

5-HT has been described as the major neurochemical system in the brain found to be dysregulated in patients with major depression [44]. These findings include, reduced CSF and urinary

Table 1
Neurophysiological changes associated with meditation.

S. no	Neurophysiological changes	Parameter	Observed change
1	Neurochemical	5-HT	Increased
		NE	Decreased
		GABA	Increased
		β-END	Increased
		Glutamate	Decreased
		DA	Increased
		Melatonin	Increased
2	Neuroendocrinal	Cortisol	Decreased
		CRH and ACTH	Decreased
		DHEA	Increased
3	Neurobiological	Parasympathetic activity	Increased
		Sympathetic activity	Decreased
		PFC activity	Increased
		Amygdala activity	Decreased
		Hippocampal volume and activity	Increased
		ACC activity	Increased
		BDNF levels	Increased
4	Immune and inflammatory	Proinflammatory cytokines (IL-1,IL-6,*__IL-10__, L-1b, TNF-α, IFN-γ)	Decreased
		Oxidative stress markers	Decreased
		Anti inflammatory cytokines (IL-4)	Increased
		NK cell cytotoxicity	Increased
		Telomerase activity	Increased
		NF-κB	Decreased
		C-reactive protein	Decreased
		Immunoglobulin A	Increased
		T-lymphocytes	Increased

Though IL-10, an anti-inflammatory cytokine, it is associated with cancer induced depression.

concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT in drug-free depressed patients; reduced concentrations of 5-HT and its metabolites in postmortem brain tissue of depressed and (or) suicidal patients [45]. Meditation's effects on 5-HT have mixed results. It has been observed in several studies that there is an increase in urinary excretion of 5-HT metabolites after meditation; this is thought to be mediated by stimulation of lateral hypothalamus and PFC during meditation [46]. In contrary to the above finding, in some studies it was found that, in experienced mediators initial baseline levels of 5-HT were higher but decreased following meditation practice [47].

2.4.2. Norepinephrine

NE is the other monoamine which is believed to be dysfunctional in depression [44]. NE is located mainly in the sympathetic postganglionic neurons and its concentration increases when the sympathetic tone is increased due to psychological stress [48]. Many studies have revealed that depressed patients have elevated levels of urinary and CSF concentrations of the NE metabolites such as 3- methoxy, 4-hydroxyphenylethylene glycol (MHPG) and its sulphated derivative [49]. The finding of lower concentrations of this hormone in meditation practitioners could reflect a lower sympathetic tone. Studies have also demonstrated low urinary and plasma levels of catecholamine metabolites after regular practice of TM in subjects with abnormally high levels [48]. Decrease in NE release from the locus ceruleus during meditation may decrease the production of CRH, which would ultimately decrease cortisol levels. However these findings do not coincide with those found by Lang et al. [50], who found higher levels of urinary catecholamines and plasma NE in advanced meditators in comparison with beginners in the technique, though the same authors described a lack of increased NE after physical exercise in these practitioners.

2.4.3. Gamma amino butyric acid (GABA)

GABA is the primary inhibitory neurotransmitter in the brain. There is a body of evidence which, although less voluminous than that for the monoamine hypothesis, strongly supports a GABAergic dysfunction in depression [44]. GABA synthesis, cortical GABA-A receptors and cortical GABA neurons were reported to be low in frontal cortex and striatum of depressed patients. Deficit in CSF and plasma GABA levels seen in depressed patients is reversed by chronic SSRI [51]. It has been found that GABA levels in the brain increase significantly after a yoga and TM. This potential increase in GABA has been proposed as a possible mechanism explaining the benefit that TM and yoga on depressive disorders associated with low GABA [52].

2.4.4. Dopamine (DA)

Evidence from clinical investigations support the finding that depressed patients have reduced cerebrospinal levels of homovanillic acid (HVA), the major metabolite of DA in the central nervous system. Neuroimaging studies of depressed patients have found decreased ligand binding to the DA transporter and increased DA binding potential in the caudate and putamen, a finding consistent with the interpretation that depressed subjects have a functional deficiency of synaptic DA [53]. A PET study using ^{11}C-Raclopride to measure the dopaminergic tone during Yoga nidra meditation demonstrated a significant increase in DA levels during the meditation practice. [54] In another study significant elevation of plasma DA levels through mind–body training was established [55].

2.4.5. Glutamate

Interest in studying the role of glutamate in depression has increased significantly, following the clinical findings of the antidepressant potential of N-methyl D-aspartate (NMDA) receptor antagonists. Increased activity of the glutamatergic system and NMDA receptor agonism is associated with depressed mood, and a reduction of the glutamatergic activity i.e NMDA receptor antagonism mediated increase of 5-HT levels in the brain exerts antidepressant effect [44]. Proton magnetic resonance spectroscopy (PMRS) study in long-term Zen meditators was shown to decrease glutamate levels significantly in the left thalamus of brain [56]. In contrast to the above finding increased glutamate was observed in another such study, where they proposed that excess glutamate mediated excitotoxicity was kept in control by limiting the production of enzyme N-acetylated-α-linked-acidic dipeptidase that converts the endogenous NMDAr antagonist N-acetylaspartylglutamate (NAAG) to glutamate [57].

2.4.6. β-endorphin (β-END)

β-END is an endogenous opioid neurotransmitter found in the neurons of both central and peripheral nervous system. Clinical study reports reveal that deficient levels of β-END is observed in MDD, and upon treatment with antidepressants there is an increase in β-END level in blood plasma indicating a positive response to therapy [58]. Yogic meditation practice shown to increase the levels of β-END by glutamate mediated stimulation of arcuate nucleus of the hypothalamus, thereby exert antidepressant effect. This may be responsible for effects such as decreased pain, blissful and euphoric sensations during meditation [57].

2.4.7. Melatonin

Melatonin is an important neurotransmitter derived from 5-HT that influences mood and behavior. Comprehensive literature available supports melatonin as an anti-stress hormone as it activates the immune system and counteracts the immunosuppressive effects of stress [59]. Low melatonin levels have been described as a 'trait marker' for depression and tend to rise with the remission. Although one study failed to find an effect of meditation on melatonin levels in cancer patients who have undergone mindfulness [60], various other studies have shown that meditation is coupled with a sharp increase of plasma melatonin [47,61]. Stimulation of the pineal gland by the lateral hypothalamus is considered to be responsible for this hike in melatonin. The increased melatonin level results in calmness and decreased awareness of pain, usually seen during meditation.

2.5. Neuroendocrinal correlates

2.5.1. HPA axis

As mentioned earlier HPA axis has been found abnormal in psychiatric disorders, and in particular major depression. Accumulating evidence suggests that significant percentage of depressed patients have increased levels of cortisol in the saliva, plasma and urine, increased levels of CRH, ACTH and increased size and activity of the pituitary and adrenal glands [26,27]. Meditation techniques like TM, BM, yoga, tai chi, cognitive-behavior therapy, and qi-training have been associated with reduction in HPA over activation by decreasing elevated levels of CRH, ACTH and cortisol [57,60,62].

2.5.2. Dehydroepiandrosterone (DHEA)

DHEA and its sulfate ester (DHEAS) are major secretary products of the human adrenal. DHEAS is the measurable form of DHEA in the bloodstream which acts as a buffer against stress-related hormones (anticortisol effect). Stress lowered DHEA levels are correlated with depressive mood, whereas higher levels of DHEA have been coupled with enhanced immune function and mood in

humans [63]. Meditative practices appear to improve the endocrine balance toward positive mood (high DHEA, lower cortisol) [46,60].

2.6. Neurobiological correlates

2.6.1. Autonomic nervous system

Depression is associated with a hyperactivation of the sympathetic stress response system, as manifested by enhanced HPA axis and increased levels of acute phase proinflammatory cytokines. At the same time, parasympathetic influences are reduced in depression, as evidenced by lower vagal tone [26,27]. Several studies have examined the physiological state accompanying active meditation (TM, BM, IBMT and MM) and have characterized it as a wakeful hypometabolic state of parasympathetic dominance and sympathetic attenuation, as evidenced by reductions in respiratory rate, decreases in tidal volume, serologic drop in lactate levels, and increases in basal skin resistance [12,64].

2.6.2. Structural and functional changes of brain in depression

Brain imaging (such as fMRI, PET, SPECT) and electroencephalographic technologies have revealed that meditation can change brain structure and functions. The amygdala, the main seat of emotion shows decreased activity during meditation [65]. PFC is the prominent site of alteration, and it downregulates neural activity in the amygdala and these two areas share reciprocal connections [38]. Increased thickness of central PFC is detected in long termed meditators. The left PFC and ACC are remarkably active during meditation, associated with reduction of activity of the limbic system, thus decreased negative emotion [57,66]. Meditation, specifically SK yoga has been shown to promote neurogenesis in the hippocampus, and reverse depression-related atrophy and neuroplasticity by increasing BDNF, a strong antidepressant [67,68]. fMRI data showed increase in activation of brain areas (DLPFC, hippocampus/parahippocampus, temporal lobe and ACC) during the Relaxation Response that are dysfunctional or hypoactive in depression [67]. Buddhist meditation shown to increase blood flow and metabolism in the PFC and ACC during meditation [57]. In one cross-sectional study, meditation practitioners were found to have improved thickness of specific cortical regions [69]. Meditation is also associated with increase in gray matter density of brain regions which are involved in emotion regulation and self-referential processing [70]. Using DTI (diffusion tensor imaging) technique, IBMT demonstrated the time-course of improved efficiency of white matter (white matter neuroplasticity) in ACC as measured by fractional anisotropy (FA) [71]. Depressed individuals often have greater right than left frontal brain EEG activity (frontal brain asymmetry) compared to non-depressed individuals, whereas MM showed to increase the relative left central activity after practice (Decreased frontal brain asymmetry) [19]. Yoga Nidra meditation by using 11C-raclopride PET technique established that increase of endogenous DA release in the ventral striatum and suggested meditation may suppress cortico-striatal glutamatergic transmission [54].

2.7. Immune and inflammatory correlates

Immune changes are a common physiological concomitant of stress and depression. HPA axis hyperactivity is a marker of GC resistance, i.e ineffective action of GC hormones on target tissues could lead to immune activation and equally, inflammation could stimulate HPA axis activity via both a direct action of cytokines on the brain and indirectly by inducing GC resistance [26,27]. As described earlier, many depressed individuals show suppression of specific immunity (natural killer cell activity, antibodies) and increased inflammatory cytokines (Interleukin (IL)-4, IL-6, IL-10 and TNF-α) compared to non-depressed individuals [72]. Meditation has been found to decrease markers of inflammation such as high sensitivity C-reactive protein, IFN-γ, TNF-α, IL-6, IL-10 (associated with cancer associated depression) and lymphocyte-1b (L-1b), whereas it increases the levels of anti-inflammatory cytokines like IL-4 [73]. It also lowers oxidative stress by increasing the transcriptional expression of anti-oxidative enzymes like glutathione S-transferase, Cu–Zn–SOD (Cu–Zn- superoxide dismutase), Mn- SOD, glutathione peroxidase (GPX), and catalase (CAT) [74]. MBSR and Yogic practices downregulate the stress mediated upregulation of pro-inflammatory NF-κB-related gene expression in circulating leukocyte [75]. Other Studies suggest that meditation reverses the negative impact of stress on the immune system by increasing cell-mediated immune response (e.g., varicella-zoster virus (VZV) specific cell-mediated immunity) [76,77], greater rise in antibody titers in response to influenza vaccine. [19] Meditation practices have shown to improve telomerase activity thereby preventing telomere shortening associated with chronic psychological stress mediated MDD [78]. After stressful events, reduced lymphocyte proliferative responses and altered absolute and relative numbers of lymphocyte subsets have been reported. Meditation practices have found to increase the number of lymphocytes (both CD4 T cells and CD4/CD8 cell ratio) and their activity [53,79]. In a study of cancer patients, SK and Pranayam mediation practices were shown to reduce stress and improve immune functions by increasing the natural killer (NK) cells and their activity significantly [53,80].

3. Conclusion

Major depression is a mood disorder that is often accompanied by the impairment of cognitive function. Although many classical antidepressants were found useful in the treatment of this mental illness, the decreased remission rate is the major problem associated with them and an alternate therapeutic modality is needed. As discussed earlier dysregulated HPA axis, increased sympathetic tone and raise in proinflammatory cytokines were the major causes of stress induced depressive disorder. Meditation, the mind-body training is increasingly being used as adjuvant therapy because of its positive effects. Increasing literature states that meditation raise the levels of monoamines, increase parasympathetic activity, reduce oxidative stress, enhance levels of endogenous antioxidants (glutathione) and activity of antioxidant enzymes (CAT, SOD, GPX, Glutathione reductase). However, these studies are often limited by their small sample size, and additional research on large samples of demographically diverse population are needed to determine the efficacy and effectiveness of meditation as independent therapeutic approach and to translate this empirical findings into more effective clinical practice in the treatment of depression.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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