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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.