Review Article

Hypothalamo-Pituitary-Adrenal axis and Brain during Stress, Yoga and Meditation: A Review

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Abstract

Daily challenges of life produce stress. Adaptation to stressful challenges requires maintenance of homeostasis by activation of neural, neuroendocrine and neuroendocrine-immune mechanisms. This has been called "allostasis" or "stability through change". Allostatic responses alter Hypothalamo-Pituitary-Adrenocortical axis function this causes altered levels of cortisol in the form of continuous high level of cortisol. Cortisol crosses blood brain barrier and change the architecture of brain by action on glucocorticoid and mineralocorticoid receptors present mainly on hippocampus, amygdala, prefrontal cortex, hypothalamus and thus alter the learning, thinking of stressed person. But recent researches showed that yoga and meditation reverse the effect of stress by decreasing the cortisol levels, increasing the blood flow with in brain near ventricles and other places, stimulating the brain and induce neurogenesis and synaptogenesis i.e. increases neural plasticity. Present review discusses Hypothalamo-Pituitary-Adrenal axis (HPA) axis working during stress exposure, brain changes by raised cortisol due to HPA axis activation and also discuss the effect of yoga and meditation on HPA axis and brain to reverse the deleterious effects of stress.

Keywords: Amygdala, Cortisol, Glutamate, Hypothalamo-pituitary-adrenocortical (HPA) axis, Hippocampus, Prefrontal cortex (PFC), Yoga, Meditation.

Introduction

The word "stress" refers to facing "daily challenges in life". According to Elliot and Eisdorfer's taxonomy five categories of stressors - acute time-limited stressors, brief naturalistic stressors, stressful event sequences, chronic stressors and distant stressors [1]. Stress can be "positive stress", "good stress" or "eustress" when person doing challenging work, assignment, studying hard during preparation for competitive examination or training. Stress can be "distress" or "toxic stress" when person face illness, hospitalization or death of loved ones, being abused or neglected, separation/death of spouce, legal stress, family stress, unemployment and hazardous work environment [2]. Brain is the central organ of stress.

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The developing brain as well as adult brain changes its architecture after stress exposure by neuronal replacement, synapse turnover, dendritic remodelling. Eustress build brain circuitary stronger and produce resilient brain. A Young person if exposed to chronic stress during early days of life such as abuse and neglect have been prone to develop mental problems in the form of anxiety, depression, substance abuse and less able to cope with daily life stress [3, 4].Most healthy individuals have the ability to control unwanted negative thoughts, worries and off task thinking easily but individuals with stress loss this ability and their mind wander from thought to thought. Stress significantly influences learning and memory [5]. Maintenance of body homeostasis by activation of neural, neuroendocrine and neuroendocrine-immune mechanisms is needed to adapt for stress. This is called "allostasis" or "stability through change". Allostatic responses alter the functions of Hypothalamo-Pituitary-Adrenocortical **(**HPA) axis = stress axis, nervous system, cardiovascular system, gastrointestinal system and immune system. Altered level of stress hormone –

glucocorticoid (cortisol in human) and suppressed neural plasticity also found in stressed patients [3]. Clinical Studies on patients suffered from chronic stress and Major depressive disorders (MDD) showed changes in the brain regions – hypothalamus, hippocampus, prefrontal cortex (PFC), and amygdala. Stress activates release of neurotransmitters serotonin, norepinephrine and dopamine [6].Researchers found that Stress shorten the telomere length which causes premature aging at cellular level, causing premature death of cells of body and brain cells [7]. Researchers showed that living in enriched environment – learning new skills, listening good music; adapting relaxation techniques – meditation & yoga in day to day life; doing stretching exercises, help to keep the brain healthy, mind sharp, prevent age related decline in memory, concentration, information processing and improve the ability to regulate thoughts. Studies showed that brain aging is reversible and stimulation of brain by learning new things activate neurogenesis and repeated practice make synaptogenesis strong, powerful and efficient [8, 9].

Yoga and meditation can reduce the effect of stress on brain by decreasing cortisol levels and thus also affect neural plasticity. Studies on long term meditators showed increase in the thickness of their cerebral cortex. Studies showed that structural changes in the brain can occur in as little as 8 weeks duration by a mindfulness-based stress reduction (MBSR) program. Studies performed on undergraduate students undergone meditation training demonstrated increased ability to control stress and lower anxiety, depression, anger and fatigue [10, 11].This review paper discusses effect of stress on HPA axis functioning and changes in brain architecture by raised cortisol due to activation of HPA axis and the effect of yoga and meditation on HPA axis and brain architecture to reverse the deleterious effects of stress.

Working of HPA axis during stress exposure

When someone exposed to stress, the centromedian, basal and lateral amygdaloid (fear center) nuclei sends distress signal to the HPA axis, cerebral cortex, midbrain and other regions of brainstem which regulate adaptive responses to stress. Hypothalamus communicates directly to adrenal medulla through the autonomic nervous system (ANS) to release adrenaline (epinephrine). Adrenaline triggers the "fight–or-flight response". Adrenaline work as alarm hormone and disappears immediately after completion of the stress situation. "Adrenalin surge" remain the "first response to stress exposure" [12-14]. After completion of initial adrenalin surge, the hypothalamus activates the "second component" of the stress response system – "the hormonal system". The Hypophysio-trophic neurosecretory neurons present in the medial parvocellular division of the paraventricular nucleus (PVN) of hypothalamus synthesize and release neuropeptide hormones-Corticotropin releasing factor/ hormone (CRF/CRH); and Arginin vasopressin (AVP). CRH plays a key role in regulating the basal and stress activated HPA axis. CRH/CRF reaches to the anterior pituitary via portal vessels; binds to CRF receptors; stimulates Adrenocorticotropic hormone (ACTH) synthesis and release into the systemic circulation to reach adrenal cortex. ACTH binds to adrenal cortex receptors and induces zona fasciculata for cortisol (Glucocorticoid) synthesis and release. ACTH release is facilitated by the plasma level of cortisol. Cortisol is also known as body's "stress hormone". Cortisol is a steroid hormone so easily cross blood brain barrier and produce its effect on brain through glucocorticoid receptor (GR) and mineralocorticoid receptors (MR) [15]. In normal conditions, cortisol regulates its own secretion via a negative feedback mechanism by activation of GR and MR in the anterior pituitary, PVN of hypothalamus and hippocampus i.e. sufficient amount of cortisol inhibits release of both CRH and ACTH and terminates the HPA axis response. This negative feedback response is responsible for optimal secretion of cortisol in normal conditions. In brain MR is mainly present in limbic areas (more in the hippocampus, moderate in the amygdala and few in PFC). MR occupied first even in very low cortisol level. After stress exposure ACTH secretion is detectable within 5 minutes and cortisol secretion is detectable within less than 15 minutes [16-18].In normal conditions, Cortisol released rhythemically with both a circadian and an ultradian (pulsatile) pattern. At midnight (around 4 am or 3-5 hours after onset of sleep) very low or undetectable cortisol levels present in the blood. Cortisol level builds up overnight and reaching to peak in the early morning (around 8 am). Cortisol levels then decline slowly throughout the day. Ideally, once the stressor has been removed, a feedback loop within the hormonal system will restore normal levels of cortisol, and bring the body back into balance. However, chronic stress conditions prevent this rebalancing and cortisol levels remain elevated persistently due to continuous activation of HPA axis i.e. chronic stress can produce continuous high cortisol levels. This glucocorticoid circadian rhythm disruption leads to disease [19-21].This circadian rhythm is regulated by the main circadian oscillator (pacemaker)

lie in the suprachiasmatic nucleus (SCN), located in hypothalamus. Continuous elevated cortisol circulates in the body and put effect on whole body because GR are present in every cell of body including neurons of the brain. In brain GR are located predominantly in the hippocampus, PFC, amygdala, and PVN of hypothalamus. High elevated cortisol downregulate hippocampal GR. In normal conditions these hippocampal GR send negative feedback to the HPA axis. Thus during stressed condition due to downregulation of hippocampal GR due to raised cortisol level in brain the HPA axis continuously remain activated and raised brain cortisol change the brain architecture [22].

After 30 minutes of stress exposure glutaminergic system activates. Glutamate is an excitatory amino acid (EAA) and predominant excitatory neurotransmitter in the human body especially in human brain. Glutamate is also a potent neurotoxin responsible for toxic neuronal death of post synaptic neurons by creating free radicals. This is called 'glutamate neurotoxicity' (GNT). Cells in PVN of hypothalamus, hippocampus, PFC and the anterior pituitary gland express glutamate receptors. Glutamate also plays a major regulatory role in activation of HPA axis to stress. Glutamate is precursor for brain's main inhibitory neurotransmitter GABA. Glutamate play role in the physiologic process of learning and memory [23-25].

The role of bed nucleus of Stria Terminalis (BNST/BST) in Regulation of HPA axis

BNST/BST acts as key relay center for HPA axis and regulate the HPA axis activity in response to stress. The BNST is sexually dimorphic gray matter structure (cluster of about 12 and 18 subnuclei), located in the basal forebrain surrounding the caudal part of anterior commissure, stria terminalis and expanded at its caudal and rostral end. Caudal end form part of amygdala because bundle of axons connects BNST with the amygdaloid nuclei. This connnection is known as "extended amygdala". Rostral end lying ventral to the lateral septal area and dorsal to the hypothalamic preoptic area is referred to as the BNST. In BNST descending cortical informations meets with ascending informations (interoceptive, exteroceptive and systemic stressors such as haemorrhage, hypertension) regarding potential homeostatic changes during acute stress. BNST connect limbic forebrain structures such as the ventral subiculum, centromedian amygdala, hypothalamic and brainstem region–locus coeruleus of dorsal pons contain noradrenergic cell bodies. BNST has reciprocal connections with the centromedial amygdala, receives projections from the hippocampus and medial prefrontal cortex (mPFC) [26].

Anterolateral and posteromedial subdivisions of BNST send direct projections to CRH containing parvocellular regions of the PVN (providing direct actions on HPA axis output). Anatomical studies indicate that the vast majority of BNST input to the parvocellular PVN is GABAergic that is largely inhibitory input to HPA axis output neurons. Lesion of Posteromedial BSNT regions potentiates stress responses, results in elevated corticosterone release [27].

Brain architecture change due to raised cortisol level and its effect

MRI studies showed that raised serum cortisol lowers total cerebral brain volume (shrinks the brain), low occipital and frontal lobe gray matter volumes (the ratio of the brain's white matter to gray matter is higher) especially hippocampus, PFC, amygdala. Hippocampus, amygdala and PFC play critical role in complex behaviour, cognition and also regulate autonomic and HPA axis stress response [28, 29].

In hippocampal dentate gyrus raised cortisol level causes disruption of synaptic plasticity by loss of dendritic spines, dendritic shrinkage, neuronal shrinkage, neuronal death and suppression of neurogenesis. These changes in hippocampus are associated with memory deficits. Hippocampus is responsible for learning, memory of daily events, spatial memory, mood regulation and helps shut off stress response. Normally, in healthy brain, in hippocampal dentate gyrus neurogenesis occur throughout life. In the hippocampus glucocorticoid and mineralocorticoid both receptors are present and GABA is the key neurotransmitter. GABA is important for the control of thoughts [28, 29]. GABA is primary inhibitory neurotransmitter in the brain. Research studies showed negative correlation between GABA activity and anxiety i.e. lower GABA levels and GABA receptors are associated with higher levels of anxiety [30]. In panic disorders decreased GABA activity was found in hippocampus, lingual gyrus, middle temporal gyrus, visual cortex, orbital cortex and insula [31].Raised cortisol causes dendritic debranching and dendritic shrinkage in mPFC. Dendritic shrinkage is associated with cognitive rigidity. mPFC is most sensitive area of brain even to mild stressors. Dopaminergic system lies in mPFC. PFC is responsible for executive functions such as decision making, problem solving ability, working memory, self regulatory behaviour such as mood, impulses and helps shut off the stress response. These changes in PFC may be responsible for age

related loss of resilience, impaired memory, circadian disruption and extinction of fear memory. Orbitofrontal cortical neurons expand dendrites which denote increased vigilance during stress [28, 29].Efferents from Hippocampal CA1 and subiculum go to the PFC. For better learning and memory good connection of hippocampus to the PFC is required. The PFC disrupt hippocampal retrieval processes or thought relay [28, 29].Raised level of cortisol builds up (increases the size, activity level, and number of neural connections) fear center of brain k/as Amygdala (Greek word means almond). Acute traumatic stressors increased spine density on basolateral amygdala (BLA) neurons. Chronic stress produces expansion of BLA dendrites, while loss of spine in medial amygdala. Amygdala influences our likes and dislikes, thinking, memories and social interactions with others. Our amygdala reads other person emotions within milliseconds and activates, prepare us for flight and fight behaviour. The amygdala facilitates emotional responses such as pleasure, fear, anxiety and aggression and turns on stress hormones. An enlarged and hyperactive amygdala, along with abnormal activity in other parts of the brain, leads to disturbances in sleep and activity patterns [28, 29].

Effects of Yoga and Meditation in brain architecture

Research studies showed that yoga and meditation techniques alleviate stress and anxiety by producing varying neurophysiological effects.

Yi-Yuan Tang et al did their study to see the effect of 4-weeks integrative body-mind training (IBMT)-a form of mindfulness meditation on white matter of brain by the help of non-invasive magnetic resonance imaging (MRI)-based technique known as diffuse tensor imaging (DTI) to delineate white matter fibers in vivo. They found improved fractional anisotropy (FA) in areas surrounding the anterior cingulate cortex, reduction in radial diffusivity (RD) and axial diffusivity (AD). Reduction in RD and AD interprets improved myelin and axonal density respectively. Their study results demonstrate improved white matter neuroplasticity in the form of increase myelin as well as axonal density [32].Gotink RA and Vernooij MW did a cross sectional MRI study on 3742 participants to determine the effect of yoga, meditation practices on amygdala and hippocampal volume. They found that regular meditation and yoga practices lower right amygdala volume and lower left hippocampus volume [33]. Reduction in volume of amygdala associated with stress reduction [34].Sara Lazar et al found cortical thickness of brain regions associated with attention, interoception and sensory processing in 20 participants on extensive insight meditation technique than matched controls. In older participants PFC and right anterior insula thickness was most pronounced. This study suggests that regular meditation hold age-related cortical thinning [35].Yoga and meditation increases GABAergic tone by increasing and activating PFC region. PFC activates the reticular nucleus of the thalamus (RE), which in turn produces GABA. Due to this reason meditators have a higher threshold of cognition, concentration and alertness - functions controlled by the PFC [36, 37].

Discussion

The nervous system is made up of neurons and non-neuronal cells termed neuroglia (glial cells) [38]. Functional neurons generated by neural stem cells (NSC's) actively during embryonic period, reduced in the early postnatal period, and at low rate in the adult [39]. During the embryonic period neurons arise from the ependymal/neuroepithelial cells (NEP's) of ventricular zone and migrate to the entire brain. Ependymal/NEP's cells divide to form neuroblasts (primitive nerve cells) and gliablasts (primitive supporting cells). Gliablast formation started after neuroblasts. Neuroblasts differentiate into neurons and gliablasts differentiate into glial cells – oligodendrocytes and astrocytes. The third glial cell– **Microglia, an** endogenous immune cell of the brain, originates from an embryonic monocyte cell lineage of yolk sac and invades the brain during early development [38]. Neuroglial cells do not generate action potential, but convey information by transient changes in intracellular calcium concentration – "Calcium Signalling". For normal brain activity glia-neuron communication is essential. In the CNS particularly in thalamus, the glia: neuron ratio has been as high as 17:1[40].Microglia has ameboid morphology with high ramifications. Microglia fending off infections and maintain neural plasticity by building and remodelling of neural circuits. All pathological changes in brain result from activation of microglial cells. Oligodendrocytes wrap myelin sheaths around axons in the white matter of central nervous system (CNS). Astrocytes are Star shaped, bushy cells with dozen of fine radiating process ensheathe the synapse. Astrocytes can multiply any time during healing process following CNS injury. Abundant cytoplasmic intermediate filaments make them rigid to support brain. Glycogen granules within astrocytes act as immediate source of glucose for neurons invested by its process. Maintenance of the glutamate and GABA

neurotransmitter pools is dependent on the synthesis of glutamine in astrocytes because astrocytic processes contain mitochondria and specific cytosolic enzymes.

Overproduction of astrocytes lay down scaffolding and abnormal neural connections [39]. In the adult, NSC's found in specific neurogenic "niches," in the subventricular zone (SVZ) of the lateral ventricles, the subgranular zone (SGZ), between the granule cell layer and the hilus of the hippocampal dentate gyrus (DG) and other brain regions such as substantia nigra, striatum, amygdala and neocortex [40-44]. These NSC's mature into neurons. Adult neurogenesis is sensitive to several external stimuli and sensory stimuli. Enriched environment such as physical activity, exercise, expanded learning opportunities, increased social interaction increases neurogenesis in the dentate gyrus of hippocampus [45]. While aging, stress and drugs (nicotine, opiates, amphetamines, cocain etc.) decrease hippocampal neurogenesis [46]. Study showed that running doubled the number of surviving newborn cells [47].

Normally, during adulthood NSC's mature predominantly into neurons, astrocytes and very few oligodendrocytes are formed. According to Daniela Kaufer, neuroscientist at UC Berkeley lab elevated cortisol during chronic stress flips the maturation of NSC's in such a way that they mature predominantly into oligodendrocytes and only few neurons and astrocytes are formed. Oligodendrocytes go on to produce more myelin sheath. Myelin formation can be good or bad, depending on time or place. This change leads to disproportion of gray matter versus white matter [48-50]. Normal proportion of gray matter (densely packed nerve cell bodies and glia cells) to white matter (myelinated axons = tracts) is 1:1. Gray matter is necessary for thinking, computing and decision making [40]. White matter affects brain functions such as learning, modulating the distribution of action potentials, acting as a relay and coordinating communication between different brain regions. People with high cortisol levels had lower memory, thinking skills and slightly lower total brain volume than those with normal levels. Stressful life events in previously normal subject are associated with decrease gray matter volume in the anterior cingulated cortex, the hippocampus and the parahippocampal gyrus within a 3 month period [51].

It is currently estimated that approximately 10% of the brain's cells (around one in 10 brain cells) are microglia. Microglia help in healthy brain development by monitoring synaptic function, maintaining synaptic integrity, rearrange synapses by pruning synapses and constantly trimming the excess fat of myelin sheath. Thus microglia builds strong neural circuits and resilient brain structure. When microglia contacts a synapse; the synapse head sends out thin projections called filopodia to them. Around 15 synapse heads extended filopodia toward a single microglia. [52]. Stress promotes significant structural remodelling of microglia, enhances the release of pro-inflammatory cytokines from microglia. Cytokine produce inflammation; inflammation abnormally activate microglia and increase their numbers. In chronic stress, neurons in the PFC produce signals that trigger microglia to prune the portion of PFC neurons near synaptic connections. PFC neurons loose a portion of their synaptic connections and maladaptive neural circuit formed [53].

Studies showed that architecture of brain can be changed by neurogenesis and synaptogenesis. The neural pathways and circuits can be change by optimising cortisol levels by optimisation of HPA axis by exercise. Researchers showed that exercise increases endothelial cell proliferation, level of vascular growth factor and angiogenesis throughout the brain especially in the dentate gyrus in young adult animals. In dentate gyrus, new cells are clustered close to blood vessels and proliferate in response to vascular growth factors. Thus angiogenesis and increased cerebral blood flow may contribute to neurogenesis [54, 55].

Regular practice of yoga and meditation unites/connect the mind with body through a series of postures, breathing exercises. By lengthening the exhalation in comparision to the inhalation the tone of sympathetic nervous system increase which can reduce stress instantly. The benefits of yoga include reduction of stress, tension, increased strength, balance and flexibility of muscles, blood pressure reduction and reduction in noradrenalin and cortisol levels. Regular yoga practice improves depression by significant increase in serotonin [5-hydroxytryptamine (5-HT)] levels at nerve synapses, which in turn helps in lifting the mood of the individual. Yoga also decreases the levels of monoamine oxidase (MAO), en enzyme that breaks down neurotransmitters and cortisol. Yoga and meditation function as a preventive medicine. Therefore, yoga and meditation are highly recommended to everyone and not limited to patients suffering from disease [56-58].

Kislay kumar et al studied effect of yoga and meditation on serum cortisol level in first-year medical students and found 4.8% decrease in morning serum cortisol

level (572.18±168.03 to 544.98±139.89) in yoga group and 3.4% increase in morning serum cortisol level (558.89±162.69 to 577.26±254.5) in control group. Serum cortisol level is considered as the marker of stress and inflammation. High cortisol level indicates high stress level [59].

Hennekens MR assessed effect of yoga on the level of salivary cortisol in nursing students. He found significant decrease in post asana salivary cortisol level in comparision to pre asana (PREA) salivary cortisol level [60].

A short term (30-minutes per day for 5-days) integrative body-mind training (IBMT) – a form of meditation, significantly enhance cerebral blood flow (CBF) in left subgenual/adjacent ventral anterior cingulate cortex (ACC), mPFC and insula and thus improve positive mood and neuroplasticity in the form of improve attention and self regulation. Left ACC and insula are critical brain areas in self-regulation. Yoga and meditation provide extra energy to neurons and glial cells by enhance capillary vasculation. The neuropil (neurons, glial cells, capillaries, combined together) expands, thickening the cortex [61,62].

To improve and create brain health feed your brain well by taking a diet rich in protein, fiber, antioxidants, beta carotene, omega-3 fatty acids, fruits, vegetables, vitamin C and E. Give your brain a workout or stimulation by brain teasing puzzles, learning new language. Add regular mild to moderate physical exercise, walking, swimming in your day to day life. Spending time in nature may synchronize the mind with nature. Relaxation techniques such as deep, relaxed breathing, stretching help in relieving stress by getting plenty of oxygen. By changing our lifestyle and food habits, give ample time to sleep, rest we can decrease cortisol levels. A well rested brain reinvents itself than exhausted and stressed brain [1].

Conclusion

Stress is unavoidable in present scenario of our modern world. Daily life stress makes chronic negative physical, mental and emotional impact. It is well known that "Prevention is better than cure" so we should try to prevent emergence of stress. If due to any reason we cannot able to prevent stress then try to stop progression of acute stress into chronic stress. Because yoga and meditation work at multiple levels (decrease cortisol level, stimulate brain and increase cerebral blood flow which help in neurogenesis and synaptogenesis, maintain brain architecture, affect the mood elevating neurotransmitter) we must include yoga and meditation in our routine. Due to the observed direct and indirect benefits of various yoga practices on physiological and neuropsychological aspect, in India, schools offer courses in yoga and "Yoga day" is celebrated on 21st June.

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