Review article

Potential biomarkers of emotional stress induced neurodegeneration

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ABSTRACT

Mental health is a matter of great significance and interest both socially and scientifically. The present review aims to provide an informative platform about the classical biomarkers available to identify and diagnose the neurodegeneration induced by emotional stress and depression. Present article provides an expert comprehensive overview of the universally accepted markers and their mechanism of action involved in emotional stress assessment and its management. This envisioned piece of work emphasize on the incorporation of clinical markers in classical psychiatry experiments will make the information more significant, reliable and universally accepted. The information summaries in the article will facilitates the researchers of clinical psychiatry, neuropharmacology and neuropsychiatry in management of depressive disorders along with the identification of possible neurodegenerative association.

1. Introduction

The human brain is the most interesting and complex organ composed of 100 billion neurons and more than ten thousand times glial cells and neurons of similar genetic origin. The brain is the prime organ that performs a vital role to sense, perceive, process, memorize and deliver information to perform various functions along with the management of various emotions [1].

Emotions are the set of mental statuses those are controlled by the plethora of chemical and neurological events within the central nervous system and results in various feelings including contentment, happiness, sadness, love, etc. However, happiness, sadness, fear, anger, disgust, surprise are some basic emotions present in every human being, which works as building blocks to express various cognitive appraisals and they give rise to various other emotions such as Amusement, Contentment, Excitement, Contempt, Embarrassment, Relief, Pride, achievement, Guilt, Satisfaction, Shame, liking, disliking, hate, etc. The brain is the sole authority organ that is responsible for physiological emotional health [2]. Emotions can be combined to form different feelings and could be temporary or long-lasting. Shifting moods tumultuous emotion, impulsive or erratic behaviors are some of the signs of emotional dysregulation [3]. Emotional stress may actually mediate, promote or even cause mental disorder like depression including major depressive disorders [4].

In combination with the classical neurogenesis various complementary process including neuronal migration, axodendritic projection, myelinization, synaptogenesis, and neurochemical differentiation takes place in the brain, which coordinates the balance between emotions, cognition, and behavior. Neuroinflammation is the brains response against any injury, insult or disease or infection. Similar to any physical trauma brain does response to emotional trauma and results in activation of neurodegenerative pathways. Emotional stress and depression are fairly considered symptom of many neurodegenerative disorders including dementia, mild cognitive impairment (MCI), dementia and Alzheimer's disease (AD), Parkinson's disease (PD) etc. but the coin has another side that could be a possible hope to prevent the progression of neurodegeneration at an early state with proper diagnosis and management of emotional stress exposure. Microglia, the primary modulator of inflammation in central nervous system gets activate in response to local or systemic insult. Glial activation results in a prompt activation of pro inflammatory and anti-inflammatory cytokines leading the immune activation which further results in "sickness behavior" [5].

A biomarker is a pathological, clinical, physiological and anatomical measurement of biological processes within the body in respect to any specific condition for therapeutic intervention [6].

A stressor in the context of this review will refer to any environmental demand that exceeds the physiological regulation capacity of an organism, in particular during the situations of unpredictability and uncontrollability [7]. A little stress is not so bad for the evaluation, growth, and adaptation but when the limits of stress exceed it could result in depression. Stress could be divided into three distinct types including "good stress", "tolerable stress" and "toxic stress" [8]. But

when a mood swing, mania, depression or mood inconsistency starts interfering with the person's ability to function and behavior, it termed as a mood disorder. It could be hyperactive like mania or it could be hypoactive like depression. Not only this but also many times some intermediate conditions also diagnosed in patients such as bipolar disease [7].

According to the Diagnostic and Statistical Manual of Mental Health, fifth edition (DSM-5) an appropriate diagnosis of major depressive disorders, at least five of the 9 DSM-V symptoms must be present continuously for a minimum 2-week period. Thesis symptoms include depressed mood; markedly diminished interest or pleasure in - almost - all activities; significant weight loss when not dieting or weight gain; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate, or indecisiveness; recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide [9].

Not only short-term stress leads to various disorders but many past influences also affect the individual's response to stress due to the biological imprinting of early life neglect or abuse. Various mediators affect the active alteration of the brain during stress and depressive disorders [10,11]. Any external or internal insult to the physical and emotional framework of an individual affects the neuroinflammation, neuro-degeneration feedback loop with a simultaneous alteration or lingering of neurotransmitter pool and biochemical regulators (Hurley and Tizabi, 2013). These mediators and biological markers affect the formation and completion of distinct biochemical and electrochemical processes including the neuronal connections, synaptic plasticity, retraction or expansion of dendritic pathways, increment or decrement of synapse density and loss of resilience, activation of different brain regions [12–14]. Excitatory amino acids and glucocorticoids play a key role, along with a growing list of extra and intracellular mediators, including endocannabinoids and brain, derived neurotrophic factor (BDNF). The long-term exposure of such stress results in a continuous changing pattern of gene expression via epigenetic mechanisms involving histone modifications and cytosine gG Guanine rich residue methylation/hydroxy-methylation as well as the activity of retrotransposons that may alter genomic stability. Elucidation of the underlying mechanisms of plasticity and vulnerability of the brain, which provides a basis for understanding the efficacy of interventions for anxiety and depressive disorders [15].

Hippocampus, amygdala, prefrontal cortex, structural remodeling, neurogenesis, epigenetics, retrotransposons, cytoskeleton, nuclear pore complex proteins, cell adhesion, resilience, glucocorticoids, excitatory amino acids, BDNF, corticotrophin releasing factor (CRF), endocannabinoids, circadian rhythms are some ultimate factors that drive and manage the surge of emotional stress and depression [16,17].

2. Inflammatory biomarkers

Symptoms of depression activate the inflammatory immune system, especially that of pro-inflammatory cytokines that are signaling molecules those normally released by immune cells. Hence higher levels of cytokines in circulation and in brain regions work as a biomarker for determination of depression [18].

2.1. Interleukine-1 (IL-1β)

IL-1β is a key mediator in a variety of behavioral actions of stress and depression [19]. This cytokine usually expressed in hypothalamus, hippocampus, cerebral cortex and thalamus [20]. IL-1 β is a key pro-inflammatory cytokine that involved in depression. It is regulated by a purinergic, ATP-gated cation channel of the P2X family P2X7 receptor [21]. The IL-1β and IL-6 were positively associated with the anger and the anxiety state. The plasmatic and salivary levels of IL-1β and IL-6 are

associated with an emotional difference during stress. During the depression, cytokine variations promote the enzyme indoleamine 2,3-dioxygenase (IDO) and stimulate the release of neurotoxic metabolites in vivo (kynurenic acid, quinolinic acid, or 3-hydroxykynurenine) and establish oxidative stress [22].

2.2. Interleukin 6 (IL-6)

IL-6 is pro-inflammatory cytokine and an anti-inflammatory myokine, which is encoded by the IL-6 gene. Overexpression of IL-6 is associated with a wide range of depressive symptomatology [23,24]. During depression the overexpression of IL-6 may directly affect the brain functioning and production of neurotransmitter's production.

Functions of IL-6 during the depression and mood disorders is mediated through the expression of brain-derived neurotrophic factor (BDNF) in the brain. The epigenetic effects of IL-6 work with hypermethylation of the BDNF promoter, which results in the decrease of neural network in the hippocampus and associated brain parts during the depression [25,26]. IL-6 has pro-inflammatory and immunoresponsive. Numerous studies identify IL-6 as a key proinflammatory factor in the pathogenesis of depression [27–29]. Elevated serum levels are under consideration as a future diagnostic marker and a predictive parameter of response to treatment during the systemic consequences of psychological stress mediating with stress through the hypothalamic-pituitary-adrenal (HPA) axis [30,31].

Elevated circulating levels of IL-6, mediates the activation of the HPA axis and its metabolic consequences like catecholamines release leading to insulin resistance, coagulation abnormalities and endothelial dysfunction [32].

2.3. Tumor necrotic factor (TNF-α)

Tumor necrosis factor alpha (TNFα) is also known as cachexin or cachectin belongs to TNF superfamily. However, CD4+ lymphocytes, Natural killer cells, neutrophils, mast cells, eosinophils, and neurons also produce it but still macrophages are considered as a chief producer of TNFα [33]. TNF is initially formed as a type II transmembrane protein. This integrated form of 233-amino acid, which by proteolytic cleavage converts into soluble homotrimeric cytokine (sTNF). metalloprotease TNF alpha converting enzyme (TACE) mediates the formation of final biologically active forms of it, which is triangular pyramid shape and weighs around 17-kDa in humans [34]. This cytokine is a cell signaling protein that could works as endogenous pyrogen and mediates acute phase reactions during systemic inflammations. TNF-α. is a pleiotropic cytokine that stimulates in physiological and pathological conditions. An elevated concentration of TNF-α is an active indicator of neuro-psychic manifestations in patients with mood disorders and depression [35]. Higher concentrations of TNF-α is considered as a clinical marker for the patients of Bipolar disorder [36].

3. Neuroendocrine biomarkers

There are many neurotransmitters and neuropeptides that show alterations in mood disorders. The monoamine-deficiency theory states that depletion of the neurotransmitters serotonin, norepinephrine or dopamine in the central nervous system is the underlying pathophysiological basis of depression [37].

3.1. Serotonin

Serotonin is a multifaceted monoamine neurotransmitter, which is extensively studied neurotransmitter in depression. It is responsible for the expression of various feelings and emotions. The indoleamine serotonin is synthesized from tryptophan and modulates the cognition, reward, learning, memory and emotional stability [38]. Low serotonin levels have a possible link with the emotional stress and depression. The

most direct evidence for an abnormally reduced function of the central serotonergic system comes from studies using tryptophan depletion, which reduces central serotonin synthesis [39]. Selective serotonin re-uptake inhibitors are widely popular antidepressants. They enhance the monoamine concentration in the brain and thus contribute in the management of wellbeing [40,41].

3.2. Dopamine

Dopamine is a neurotransmitter that is chemically 3,4-dihydroxy-phenylethyl amine. Dopamine as an intermittent product formed during the biosynthesis of noradrenaline. When tyrosine hydroxylated to DOPA (3,4-dihydroxyphenylalanine), then decarboxylation takes place to produce to dopamine. Balance in dopamine concentration is very important for the performance of various vital functions including emotion, mood, sleep, memory, learning, concentration, and motor control [42]. A drop in the synthesis of this neurotransmitter or the disturbance in the dopamine receptors present in the brain can lead a person towards emotional instability or depression. Anhedonia, which is a core symptom of Major depressive disorder, involves downregulation of dopamine activity [37].

3.3. Glutamate and gamma-aminobutyric acid (GABA)

Glutamate and Gamma-aminobutyric acid (GABA) participates actively in neuropathophysiology of depression and emotional trauma. Both of them participates actively to regulate neurocircuitry, neurotrophic factors, and circadian rhythms in combination with the stress hormones and neurotransmitters (serotonin, norepinephrine, dopamine etc.). GABA is the chief inhibitory neurotransmitter in the fully developed and mature mammalian central nervous system [43,44]. GABA acts at inhibitory synapses by binding to specific trans membrane receptors in the plasma membrane of both pre- and postsynaptic neuronal processes. This binding opens the ion channels and allow the flow of either negatively charged chloride ions into the cell or positively charged potassium ions out of the cell. Due to this process a negative change in the trans membrane potential, causes hyperpolarization. There are two types of GABA receptors known as GABA A (ligand-gated ion channel complex) and GABA B (metabotropic G protein-coupled receptors) GABA regulates the proliferation of neural progenitor cells, the migration and differentiation the elongation of neuritis and the formation of synapses [45]. Abundant evidences confirmed that the GABA mediates a prominent role in the control of stress by affecting the brain as a vulnerable factor in mood disorders. It reduced brain concentration of the inhibitory neurotransmitter GABA as well as alterations in the subunit composition of the principal receptors (GABAA receptors) that mediating GABAergic inhibition, which is quite common in depressive disorders [46,47].

In contrast to GABA, glutamate is the chief excitatory neurotransmitter in the mammalian central nervous system. Glutamate is anabolized from glucose-derived pathways and almost all the glucose that enters inside the brain is ultimately converted to glutamate [48]. During the completion of tricarboxylic acid (TCA) cycle glutamates formed as intermediates from glucose and then packaged into synaptic vesicles via vesicular glutamate transporters (vGLuTs). The role of glutamate in brain physiology and metabolism is unique and vital [49]. Various techniques including immunoblotting, immunohistochemistry and positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) based neuroimaging studies justify the possible correlation between glutamate regulation and depression progression [50,51].

3.4. Cortisol

Cortisol is an important glucocorticoid steroid broadly regarded "stress hormone". It is the produced by zona fasciculata of the adrenal cortex as a final product of the hypothalamus-pituitary-adrenal axis

(HPAA) function. Corticosterone or cortisol activates the autonomic nervous system. Cortisol serves many functions including glucose utilization, blood pressure regulation and immune functions. During emotional trauma, prolonged stress and depression an alarm reaction is initiated due to higher level of the glucocorticoid cortisol initiates the alarming response. The levels of cortisol are usually under strict control of the neurons of hypothalamus as well as anterior pituitary secretion named adrenocorticotropic hormone (ACTH). Cortisol acts in a slow, genomic manner as transcriptional regulators of glucocorticoid responsive genes. Salivary Cortisol (C) sampling has been used as a measure of Hypothalamus Pituitary Adrenal (HPA) axis activity for some time, as there is a high correlation between salivary C levels and unbound free C levels in plasma and serum which remain high during the circadian cycle. The role of these molecules is a well-established factor in depression management and etiology [52–55].

3.5. Catecholamines

The adrenal medulla produces a hormonal cascade that modulate the secretion of catecholamines, especially norepinephrine and epinephrine to controls fight-fright-or-flight response. These hormones quickly elevate basal metabolic rate, blood pressure and respiration, and increase blood flow to the more vital organs [56,57].

3.6. Brain-derived growth factor (BDNF)

Brain-derived growth factor (BDNF) is a protein marker of nerve injury within the central and peripheral nervous system. This growth factor belongs to the neurotrophin family involved in survival, development, and function of nerve tissues. BDNF is an important protein coded by the BDNF gene, which helps the nervous system to cope up from existing stress, ischemia, neurodegeneration and excitotoxicity. It suppresses the apoptosis along with modulation in the synaptic activity by the involvement of various signaling cascades.

BDNF is synthesized as a 32–35 kDa precursor protein (pro-BDNF) form by endoplasmic reticulum (ER). During movement in trans Golgi network carboxypeptidase E (CPE) and convertase forms a 13 kDa biologically active and mature BDNF (mBDNF) [58,59]. During the neurological depression and other diseases such as Alzheimer, Parkinson's, epilepsy, multiple sclerosis NBDF levels diminished significantly [60–62]. Stress, depression and associated factors decrease the expression of BDNF in neuronal networks due to exposure of nervous system with the excess amount of corticosterone [63–66].

4. Oxidative stress biomarkers

During any kind of persistent stress, depression or mood disorder it is expected to identify the formation of reactive oxygen species, which leads the formation of oxidative stress within the body, which reduces the overall in vivo antioxidant pool [67,68]. In light of available literature, it is clearly evident that the markers of oxidative stress get alter during the depression. Higher levels of lipid peroxidation, peroxidases and malondialdehyde (MDA) along with low levels of glutathione peroxidase (GPx), superoxide dismutase enzymes (SOD) were reported in many such cases [69–72].

5. Non-invasive imaging markers

5.1. Computed tomography (CT)

All non-invasive methods are relatively new tools in comparison of biochemical markers to assist emotional stress and depression diagnosis but the accuracy and ease of interpretation makes them a potential candidate for future incorporation. Single-photon emission computed tomography (SPECT) identified lower metabolism in the left inferior parietal lobe and overall decreased bilateral cerebral blood flow (CBF) in

patients who had panic disorders compared with control subjects, and this decrease corresponded with the symptom severity [73,74].

5.2. Magnetic resonance imaging (MRI)

Electrical activity in brain neuronal network can be easily monitored by magnetic resonance imaging (MRI) techniques. Functional MRI is a popular identification tool, which helps the radiologists, psychologists, and clinicians to access normal and abnormal functional and networking such as changes in neuroanatomical structures of the brain, changes in fractional anisotropy within different regions of brain and quantification of nerve tracts present within the brain. In the similar connection for identification of anxiety and depression-like traits diffusion tensor imaging is also a relevant and unique approach to identify the white and grey matter integrities within various regions of the brains of normal subjects and the patients. However, these studies face various obstacles and get influenced by many factors such as caffeine consumption, nicotine consumptions, hypertension etc. but the unique outcome and future potential of the technique is bright in the diagnosis of mental and neurological health [5,75,76].

5.3. EEG

Electroencephalogram (EEG) is a promising and latest tool to access non-invasive pattern waves of brain. Investigating neurophysiological indices. EEG neurofeedback mechanism is one of the intelligent ways to determine the activity of neural circuits related to emotion, sadness, motivation, happiness and depression. EEG usually executes well in coordination with fMRI paradigms for diagnostic during resting and task-oriented phases. The activity of various brain regions can be easily accessed using EEG within fractions [77–79].

6. Conclusions

Apart from all scientific advancements and luxuries that we perceive today the physical and mental wellbeing is of most importance. The modern fast-tracked lifestyle puts everyone health at risk of high stress and associated neurodegeneration. The early and accurate diagnosis of emotional stress could work as a promising tool in the management of the social and personal wellbeing [80]. Present review is an effort to summarize the available biomarkers for determination of clinical emotional stress and depression that possibly give a better detection range if used in combination. Literature supports that there are potentially useful biomarkers exist nowadays, which could help the clinicians, psychiatrists, budding neurologists, researchers and students for designing and successful identification of patients of neuropsychiatry imbalance early and efficiently. However, selection of appropriate and most suitable marker for any particular type of study is still a challenging task for biologists and psychiatrist. With the availability of various markers many limitations also exist. The extend of emotional stress, progression and severity of neurological disorders gets affects by various co existing factors. While application and design of study various factors including past history, gender, age, cognitive ability, medications, heterogenicity should give appropriate considerations. For fulfilling the existing gaps, it is advisable to create the links between biomarker networks and interactions along with neuroimaging and cognitive function tests for a development of better and promising identification tools in future. The incorporation of latest and dynamic tools is an essential and advisable suggestion for better future.

Acknowledgements

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