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Review Article

Stress: Its Mechanism, Experimental Assessment and Diagnostic Markers

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Abstract

Stress is linked to the central nervous system. In addition to its primary function in the body, it also assists in body upkeep. As a result, its proper operation is critical for both health and sickness. When the central nervous system is out of equilibrium, the CNS system's mechanism changes. Understanding the mechanism of stress is crucial for developing pharmaceutical methods for its prevention. Among the common molecular pathways contributing to impaired brain function are inflammation, immunomodulation and oxidative stress. A variety of drugs and chemicals are used to experimentally induce stress of CNS, which are assessed in the laboratory by physiological, physically, emotionally and pathological biomarkers. The present review outlines some of the fundamental ideas in stress, as well as several preclinical screening methodologies and diagnostic markers.

Keywords: *Stress; Brain; Markers; Diseases*

Introduction

Stress is a generic response of the body to any demand imposed on it. It is a reaction of the body to stimuli that tends to upset its normal physiological equilibrium or homeostasis [1]. Also it is a sequence of metabolic and behavioural reactions that serves to strengthen the body in response to physical, chemical, biological, and emotional changes [2]. When stress is high, the organism's homeostatic processes become deficient, and the organism's life is jeopardised. Stress causes a wide range of body changes known as General Adaptation Syndrome in certain circumstances (GAS). The stressors that cause GAS range from physical to psychological elements such as cold, heat, illness, toxins, serious personal disappointment, and so on [2] (Figure 1).

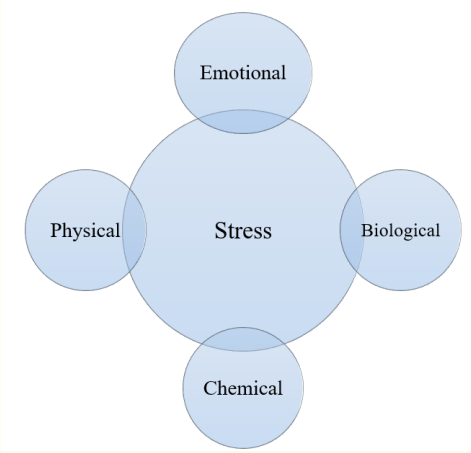

Figure 1

Stress disrupts the balance of several hormones, which has a substantial impact on the immune system's overall response. Immunological system functioning has been demonstrated to be affected by stress and depression, with immunosuppression and immune activation. Stress disrupts the organism's physiological balance, resulting in a variety of endocrine and visceral responses [3]. Stress is linked to a number of disease states, including psychiatric disorders such as depression and anxiety, immunosuppression, endocrine disorders such as diabetes mellitus, impotency, and cognitive dysfunction [4].

Mechanism of stress effect on brain

Stressors affect gene expression through a variety of mechanisms, including direct glucocorticoid effects on gene transcription and activation of epigenetic mechanisms in which histone modifications and methylation/hydroxy-methylation of CpG residues in DNA play a role in the repression and activation of genetic factors, including retro-transposons [5,6]. Like glucocorticoids some other excitatory amino acids and cellular mediators play crucial roles in these effects. Extracellular adhesion molecules, cytoskeletal components, and at least one nuclear pore complex protein are all influenced by these mediators. Some mechanism is as follows.

Role of excitatory amino acids

Excitatory amino acids, especially glutamate, are important in both morphological and functional changes in the brain. Initial studies of restraint stress, in which chronic stress causes the apical dendrites of hippocampal CA3 neurons to shrink, revealed that acute restraint stress raises extracellular glutamate levels via a process that is absent in adrenalectomized animals, implying that the adrenal cortex plays a role. Corticosterone does, in fact, promote glutamate release by acting directly on membrane related MR and GR. Importantly, blocking NMDA receptors and interfering with excitatory activation of ion channels, comparable to blocking adrenal steroid synthesis, prevents stress-induced dendritic remodeling in the hippocampus. In the medial PFC, stress-induced NMDA-dependent dendritic remodeling has also been observed. In the aftermath of trauma from convulsions, ischemia, or head trauma, excessive glutamatergic activity without appropriate absorption leads to irreversible neuronal death, a process worsened by glucocorticoids [7].

In this regard, the shrinkage of apical dendrites in CA3 pyramidal neurons as a result of stress can be viewed as a protective mechanism against permanent damage and neuron loss caused by the metastable dentate gyrus-CA3 feed forward and feedback circuitry, which is the foundation of its function but also makes it vulnerable to seizure-induced damage. Hibernation, a state of reduced energy supply to the brain accompanied by fast reversible (within hours) reduction of CA3 apical dendrites in the hippocampus, is a good example of this. This hypothesis is supported by studies showing that removing polysialic acid residues from the neural cell adhesion molecule (NCAM) causes significant increases in dendritic length and increased vulnerability to excitotoxic damage in CA3 neurons, implying that shorter dendrites reduce CA3 neurons' vulnerability to over-stimulation [7].

Role of glucocorticoids

Multiple locations and pathways in the brain induce both genomic and non-genomic effects from glucocorticoids. Furthermore, glucocorticoids exhibit biphasic effects that are dependent on the timing and degree of GR expression [7]. Both direct interactions with glucocorticoid response elements (GRE) and indirect effects via tethering to other transcription factors are involved in glucocorticoid activities via genomic pathways. Glucocorticoids can directly promote excitatory amino acid release via membrane-associated receptors, and they can also modulate glutamate and GABA release indirectly by inducing local endo-cannabinoid synthesis [8].

Furthermore, glucocorticoids and the anti-apoptotic protein B-cell-lymphoma 2 (Bcl-2) can translocate GR to mitochondria, where they promote Ca^{2+} sequestration, regulate mitochondrial oxidation and free radical formation, and regulate membrane potential, three independent measures of mitochondrial function. Bcl-2 inhibits the creation of Bax-containing holes on the mitochondrial outer membrane, lowering calcium and cytochrome C release from the mitochondria.

In the same way that the site of GR action is critical, the degree of GR expression is crucial. Overexpression of GR in the forebrain caused by genetics increases the lability of mood-related behaviours while simultaneously increasing antidepressant medication responsiveness [7], whereas knockdown of GR has the reverse effect. Increased CpG methylation within the GR promoter is related with a sub-optimal HPA stress response in rats and early childhood abuse in human suicide victims, implying that epigenetic modulation of GR activity has important functional ramifications [9,10].

A timely rise of glucocorticoids prior to the induction of stress, for example, inhibits PTSD-like delayed anxiety and traumatic stress-induced spine synapse development in the basolateral amygdala (BLA) in various animal models [11]. A protective role for appropriate glucocorticoid levels at the time of acute stress is supported by data on human PTSD [12,13]. However, sustained high-dose glucocorticoid therapy causes dendritic lengthening in BLA [14], highlighting the distinctions between acute and chronic glucocorticoid increases.

Mice that spontaneously showed increased anxiety had elevated expression of hippocampal MR, which mediated a stress-induced suppression of mGlu2 expression and increased levels of anxiety- and depression-like behavior. Mineralocorticoid receptors (MR) have both genomic and non-genomic actions to stimulate glutamate release. Blocking MR receptors and interfering with glucocorticoid-stimulated glutamate activity, for example, prevents stress-induced mood changes [7].

Involvement of secreted signaling molecules

Secreted signaling molecules, in addition to glucocorticoids, play a key role in the remodeling of brain tissue during stress. Corticotrophin releasing factor (CRF), best known for regulating ACTH and glucocorticoids release, is involved in stress-induced dendritic remodeling in the CA1 area of the hippocampus [15,16]. Over the last decade, additional actors have been implicated in the regulation of dendritic remodeling. Tissue plasminogen activator (tPA), for example, is a secreted signaling protein and protease that has been linked to stress-induced dendritic remodelling and spine loss in the medial amygdala and CA1 hippocampus. tPA-ko mice do not show any chronic

stress-induced memory impairment or spine loss in the CA1 [15,17]. When these two elements are combined, there is evidence that CRF [18] stimulates tPA release in the amygdala. Similarly, Lipocalin-2 is a new spine plasticity modulator with distinct effects in the amygdala and hippocampus [19,20].

Endocannabinoids are another type of signaling molecule that plays a significant role in the stress response. Endocannabinoids appear to be important for the regulation of structural plasticity under repeated stress, in addition to contributing to the termination of the acute response to stress and habituation to recurrent stress [7].

Stress effects on gene expression

The hippocampus is an essential gateway for understanding the effects of glucocorticoids and stress on gene expression in the brain since it was the first extra hypothalamic brain tissue to be discovered to have receptors for adrenal steroids. High-throughput study of gene expression changes in response to stress has become possible thanks to recent technical advancements. Microarray analysis of the whole hippocampus in mice after acute stress, chronic stress, and stress recovery revealed that both acute and chronic stress modulate a core set of genes, but that numerous changes are unique to each condition, highlighting how stress duration and intensity alter reactivity. Furthermore, corticosterone injections do not produce the same expression profile as acute stress, implying that *in vivo* stressors engage a distinct collection of pathways independent of GR activation.

Many of the genes changed in the hippocampus after glucocorticoid and chronic stress exposure are known epigenetic regulators, suggesting one plausible mechanism for the long-term changes in the expression response. Although stress-induced dendritic retraction in PFC neurons appears to be reversible in terms of dendritic length and branching, the recovered neurons differ in that dendrites that sprout after stress recovery are more proximal to the cell body than those that retracted [7].

Experimental evaluation models

Behavioral end points

The original description of the stress response as a "fight-or-flight" response, as well as evidence that arousal activation is invariably associated with it, suggests that general behaviour can dependably reveal stress symptoms. Exploratory activity is a commonly used behavioural descriptor of the reaction to stress in laboratory mice, and it is assessed using well-established measurable measures [21]. Because novelty is a stressor in most species, thorough baseline determination should precede observation of stress-induced effects in this experimental setting. Reduced exploratory activity is regarded to be a dependable behavioural result of stress exposure, while the outcome may vary depending on the nature and duration of the challenge. This response is described as "freezing" in its most extreme form, a period of time during which mobility and exploration are completely halted. In numerous stress paradigms, the freezing reaction may be reliably elicited, and techniques for quantifying it have been devised [22]. Acquired immobility, behavioural despair, and learned helplessness are behavioural abnormalities that are especially linked to acute stress; nevertheless, a learning component plays a key role in the expression of these symptoms.

Anxiety is commonly linked to behavioural reactions to stress, and there is a significant overlap between neurochemical processes triggered by stressful stimuli and those engaged in anxiety regulation. Anxiety testing is part of the usual toolkit for assessing stress's behavioural effects, and it provides a straightforward way to reveal stress's neuropathological implications. Because several experimental paradigms used to assess anxiety can quickly become habituated, caution should be exercised when using them repeatedly to examine long-term effects [21].

The stress reaction includes the elicitation of protective behaviour, which can be viewed as a continuum of changed anxiety. A recommended technique for monitoring stress effects is to assess the manifestation of aggression and changes in its pre-stress degree of expression [23] and a significant link between behavioural and neurochemical end points has been established. The analysis of audible and, in particular, ultrasonic vocalisation is a well-established approach for assessing stress in pain- and fear-based paradigms [24] particularly in young rats whose endocrine responses are inconsistent due to developmental inconsistency (see below). Ultrasonic vocalisation reliably predicts fear in juvenile animals, although it can be modified by maternal touch or predator cues [25].

The acquisition, retention, and retrieval of novel behavioural repertoire are all influenced by stress. Assessment of learning and memory can be used to evaluate the transitory and persistent effects of stress because this process is an intrinsic aspect of the establishment of stress coping strategies and connections with morphological and neurochemical measures have been found. The former phenomenon can be explained by the activation of monoaminergic transmission and arousal, while the biphasic effects of glucocorticoids, as well as their secondary influence on neurotransmission, have been implicated in the interpretation of shifts in learning and memory performance under stressful conditions [26].

Physiological end points

Cardiovascular reactions, such as variations in heart rate and arterial blood pressure, have long been recognised as important components of the stress response and are causally linked to autonomic nervous system activation. Monitoring of cardiovascular end points has become an important research tool in stress models, thanks to the growing use of telemetric recording technology [27].

The ability of stress to cause pain suppression has long been known, and the neurochemical mechanisms involved have been thoroughly investigated [28]. Stress-induced analgesia measurements are part of the standard toolkit for stress monitoring and pharmacological evaluation of the involved neurotransmitter and neuromodulator systems.

The physiological correlate of stress is a transient increase in body core temperature. Although the exact nature of stress-induced hyperthermia is still debated, its time course and multiple contributing neuropharmacological pathways have been thoroughly investigated, and the method's dependability has been demonstrated in a variety of experimental conditions [29]. Several stressful events have been shown to have a considerable impact on feeding behaviour, and investigations into the underlying neurochemical mechanisms have revealed that several stress-responsive systems are involved. Changes in food intake volume and pattern have been employed irregularly for stress monitoring, whereas stress exposure has progressed to a modelling method of eating disorders [30].

Endocrine end points

The limbic-hypothalamo-pituitary-adrenal neuroendocrine axis is not only the stress responses, but it also gives the most reliable neurohumoral substrate for assessing its magnitude, dynamics, and, ultimately, the organism's ability to overcome current and future benefit. Focus on the conclusiveness of individual measures of its activity in stress models because a thorough work of reference has addressed the structural and functional organisation and control of the LHPA axis under stressful conditions. The release of neuropeptide secretagogues of adrenocorticotropin is induced by input from stress-responsive neuronal circuits onto the hypothalamic paraventricular nucleus (PVN) (ACTH). Although stress-related changes in corticotropin-releasing hormone (CRH) blood levels have been shown, measuring CRH in the systemic circulation in laboratory animals has not gained general acceptance. Monitoring CRH concentrations in hypophyseal portal blood and, in particular, perfusates and dialysates from specific brain regions is thought to be more trustworthy, as it allows CRH release from unique neuronal populations to be distinguished.

Direct measurement of CRH neurons using either the "output" of the hypophyseotropic population to the median eminence or the "stationary state" of CRH gene expression is the most frequent method. Evidence indicating additional neurotropic effects of intra-cerebral

projections of CRH neurons, beyond those involved in the neuroendocrine response to stress, boosted the importance of the latter. Under basal and stress-related settings, CRH-coding transcripts in the PVN's parvocellular compartment are an excellent descriptor of LHPA axis activity. Because of the variability of the neuronal populations that create AVP in the circulation, measurements of circulating vasopressin (AVP) levels have been used to assess stress reactions. The involvement of these neuronal populations in the modulation of the LHPA axis is ambiguous. Peripheral AVP is mostly derived from the posterior pituitary terminals of magnocellular neurons of the supraoptic and posterior-lateral portions of the paraventricular nucleus. Stress-related increases in CRH and AVP expression in the PVN follow separate temporal patterns, with AVP "coming into action" with a specific delay or during chronic stress load, according to previous study.

As auxiliary peptidergic ACTH secretagogues, oxytocin and angiotensin should be included. Oxytocin, like AVP, is produced by a diverse range of neuronal populations and released in response to a variety of stresses in the systemic and adenohypophyseal portal circulations. Induction of oxytocin synthesis and secretion has been observed in a variety of stress scenarios, and its function appears to go beyond that of a simple "booster" of CRH and AVP. While oxytocin is unmistakably a stress hormone, interpreting its "net" effect necessitates taking into account the dissociated secretory activity of hypophyseotropic and intracerebral projections, the subject's sex and physiological condition, stress mode, and other interacting elements. Angiotensin secretion changes are a well-known part of the neuroendocrine response to stress, with diverse roles in various elements of allostasis.

Increased levels of ACTH in the systemic circulation and its precursor peptide pro-opiomelanocortin (POMC) in the anterior pituitary are common reactions to stress. While ACTH responses to acute stress closely follow CRH neuron activity, chronic stress and sustained CRH hypersecretion cause desensitisation of pituitary CRH receptors and reduced ACTH release. Stress-related neuroendocrine dysregulation is characterised by a decoupling between CRH hyperactivity and refractory corticotrophin response. The amplitude of the acute stress-induced rise, as well as the sensitivity of the hypothalamopituitary unit for glucocorticoids, characterise the status of the LHPA axis under quiescent settings [32].

Pharmacological models

Drug-induced changes in the initial "links" of stress-reactive chains could theoretically result in a wider range of "downstream" responses; however, because allostatic regulation systems are closed-loop, pharmacological changes that disrupt feedback circuits can also alter the activity level of several interconnected response cascades.

Individual stress-responsive systems can be activated by a variety of pharmacological stressors. However, because stress is such a complicated and multifaceted reaction, the number of pharmacological drugs that may affect many systems at the same time is limited. The effects of ether inhalation demonstrate the simultaneous occurrence of pharmacologically produced reactions in various systems involved in adaptation. This stressor causes behavioural agitation and alters brain monoamine metabolism, as well as the production and release of CRH and AVP. Similarly, glucoprivation induced by insulin or 2-deoxyglucose injection causes behavioural, neurochemical, and neuroendocrine changes similar to stress.

Several behavioural and endocrine responses to stress can be mimicked by pharmacological regulation of the key neurotransmitter systems that initiate the response to stressful stimuli, according to a large body of experimental research [33]. The established role of GABA-ergic signaling as a major tonic inhibitor of stress responses provides plausible explanation for the capacity of GABA/benzodiazepine antagonists to induce several behavioral and endocrine correlates of stress or augment the responsiveness to systemic and emotional challenges [34].

Despite the fact that endogenous opioids play a role in several aspects of the stress response, the divergent effects of opioid administration on neuroendocrine parameters, which may be due to complex interactions with other neurotransmitter systems, appear to be at odds

with the widely held belief that opioids tonically suppress the LHPA axis [35]. It's so useful to remember that the topic at hand is pharmacological effects with a sudden onset that aren't expected to cause major changes in what's known as "opioidergic tone" right away.

Exogenous CRH reliably duplicates various effects of stressful stimuli due to its critical role in the start and integration of behavioural, autonomic, and endocrine responses to stress. However, the stressogenic action of CRH is warranted after intracerebral injection, although some variation may occur after systemic administration. Despite overwhelming evidence that vasopressin has a role in various elements of the stress response, exogenous vasopressin treatment has only generated minor stress-like symptoms. These findings support the auxiliary role of vasopressin in the modulation of the LHPA axis in terms of the endocrine response. The growing interest in the role of neuropeptides other than ACTH secretagogues in stress, as well as the increasing availability of selective analogues, implies that such compounds could be useful in pharmacological stress modelling. The neuroendocrine pathways that control the LHPA axis's baseline activity and reactivity to stressful events have been demonstrated to deteriorate as a result of persistent hypercorticalism.

Peptide mediators/integrators of the inflammatory and immunological responses are a good example of pharmacologically induced activation of numerous stress-reactive systems. TNF, interleukin-1, and interleukin-6, as well as their sequential releaser, bacterial lipopolysaccharide, are the most commonly employed agents (LPS). Endotoxin or cytokine-induced effects are characterised by a combination of normal defensive behavioural reactions known as "illness behaviour," in which vagal afferentation plays a key part. Physical and neurogenic stress modalities elicit similar changes in central and peripheral neurotransmission, and activation of the LHPA axis is a well-known result. It has been demonstrated that cytokine-mediated disruption of the gonadal axis employs mechanisms that are independent of those involved in the general stress response as part of "sickness behaviour" and in terms of endocrine secretions; it appears that cytokine-mediated disruption of the gonadal axis employs mechanisms that are independent of those involved in the general stress response. Changes in growth hormone and prolactin release in response to cytokine exposure have received mixed reviews. However, solid proof that these agents can induce a full-scale stress response is currently absent [31].

Diagnostic markers of stress

Stress or depression like symptoms triggers the inflammatory immune system, particularly pro-inflammatory cytokines, which are signalling molecules produced by immune cells. As a result, increased cytokine levels in the circulation and brain areas serve as a biomarker for the diagnosis of depression or stress [36].

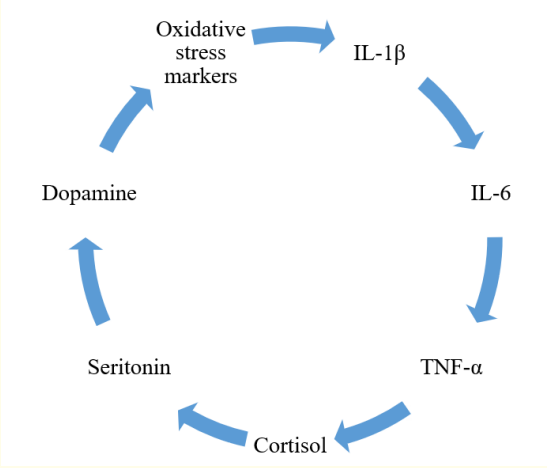

Figure 2

Interleukine-1 (IL-1β)

IL-1 is a crucial mediator in a number of stress and depression-related behavioural behaviours. The hypothalamus, hippocampus, cerebral cortex, and thalamus are all known to produce this cytokine. The cytokine IL-1 is a major pro-inflammatory cytokine that plays a role in depression. It is controlled by the P2X7 receptor, a purinergic, ATP-gated cation channel of the P2X family. The levels of IL-1 and IL-6 were found to be linked to feelings of anger and anxiety. IL-1 and IL-6 plasmatic and salivary levels are linked to an emotional difference during stress. *In vivo*, cytokine fluctuations boost the enzyme indoleamine 2,3- dioxygenase (IDO) and accelerate the release of neurotoxic metabolites (kynurenic acid, quinolinic acid, or 3-hydroxykynurenine) and cause oxidative stress during depression [37].

Interleukin 6 (IL-6)

The IL-6 gene encodes a pro-inflammatory cytokine as well as an anti-inflammatory myokine. Overexpression of IL-6 has been linked to a variety of depressive symptoms [38,39]. Overexpression of IL-6 during depression may have a direct impact on brain function and neurotransmitter synthesis.

The expression of brain-derived neurotrophic factor (BDNF) in the brain mediates the functions of IL-6 during depression and mood disorders. IL-6's epigenetic effects are mediated by hypermethylation of the BDNF promoter, resulting in a decrease in the neuronal network in the hippocampus and adjacent brain regions during depression [40,41]. IL-6 is a pro-inflammatory and immunoreactive cytokine. IL-6 has been identified as a significant proinflammatory component in the aetiology of depression in a number of studies. During the systemic repercussions of psychological stress mediating with stress through the hypothalamic pituitary-adrenal (HPA) axis, elevated serum levels are being considered as a future diagnostic sign and a predictive parameter of response to treatment.

Increased circulating IL-6 levels drive HPA axis activation and metabolic repercussions such as catecholamine release, which leads to insulin resistance, coagulation problems and endothelial dysfunction [42].

Tumor necrotic factor (TNF-α)

The TNF superfamily includes tumour necrosis factor alpha (TNF), also known as cachexin or cachectin. TNF is also produced by CD4+ lymphocytes, natural killer cells, neutrophils, mast cells, eosinophils, and neurons, but macrophages are the primary producers. TNF is a type II transmembrane protein that is first produced. By proteolytic cleavage, this integrated form of 233-amino acid transforms into soluble homotrimeric cytokine (sTNF). TNF alpha converting enzyme (TACE), a metalloprotease, mediates the synthesis of physiologically active forms in humans, which have a triangular pyramid structure and weigh roughly 17 kDa. This cytokine is a cell signalling protein that can function as an endogenous pyrogen and mediates acute phase reactions in systemic inflammation. TNF- is a pleiotropic cytokine that stimulates cells in both normal and pathological situations. In individuals with mood disorders and depression, a high level of TNF- is an active sign of neuropsychic symptoms. TNF-levels beyond a certain threshold are thought to be a clinical sign for Bipolar disorder patients [37].

Neuroendocrine biomarkers

In mood disorders, a variety of neurotransmitters and neuropeptides show changes. Depletion of the neurotransmitters serotonin, norepinephrine, or dopamine in the central nervous system is the fundamental pathophysiological basis of depression, according to the monoamine-deficiency theory [37].

Cortisol

Cortisol is a glucocorticoid steroid that is commonly referred to as the "stress hormone." It is created by the adrenal cortex's zona fasciculata as a byproduct of the hypothalamus-pituitary-adrenal axis' (HPAA) function. Corticosterone, often known as cortisol, is a hor-

mone that stimulates the autonomic nervous system. Cortisol is involved in a variety of processes, including glucose consumption, blood pressure regulation, and immunological function. A higher level of the glucocorticoid cortisol is released during emotional trauma, persistent stress, and depression, which triggers an alarm response. The neurons of the hypothalamus, as well as anterior pituitary secretion known as adrenocorticotropic hormone, are normally in charge of cortisol levels (ACTH). Cortisol functions as a transcriptional regulator of glucocorticoid responsive genes in a gradual, genomic manner. Salivary Cortisol (C) sampling has been employed as a marker of Hypothalamus Pituitary Adrenal (HPA) axis activity for a long time because salivary C levels are highly correlated with unbound free C levels in plasma and serum, which stay high throughout the circadian cycle. The involvement of these molecules in depression management and pathogenesis is well-established [43-45].

Serotonin

Serotonin is a complex monoamine neurotransmitter that has been widely investigated in the context of depression. It is in charge of expressing a wide range of sensations and emotions. The tryptophan-derived indoleamine serotonin affects cognition, reward, learning, memory, and emotional stability. Low serotonin levels have been linked to depression and emotional stress. Studies utilising tryptophan deprivation, which inhibits central serotonin synthesis, provide the clearest direct evidence for abnormally reduced central serotonergic system function. Selective serotonin reuptake inhibitors are most frequently used. They help to the management of wellbeing by increasing monoamine concentration in the brain [37].

Dopamine

Dopamine, or 3,4-dihydroxyphenylethyl amine, is a neurotransmitter with a chemical formula of 3,4-dihydroxyphenylethyl amine. Dopamine is produced infrequently during the production of noradrenaline. When tyrosine is hydroxylated to DOPA (3,4-dihydroxyphenylalanine), dopamine is produced by decarboxylation. The functioning of several key activities such as emotion, mood, sleep, memory, learning, focus, and motor control are all dependent on dopamine concentration balance. A decrease in the manufacturing of this neurotransmitter or a disruption in the dopamine receptors in the brain might cause emotional instability or depression. Down regulation of dopamine activity is a key sign of anhedonia, which is a core symptom of Major depressive disorder [37].

Oxidative stress biomarkers

It is expected to identify the creation of reactive oxygen species during any kind of prolonged stress, depression, or mood disorder, which leads to the formation of oxidative stress inside the body, which diminishes the overall *in vivo* antioxidant pool [46,47]. Based on the current evidence, it is obvious that during depression, the markers of oxidative stress change. In several of these cases, higher levels of lipid peroxidation, peroxidases, and malondialdehyde (MDA) were found, along with low levels of glutathione peroxidase (GPx), superoxide dismutase enzymes (SOD) [37].

Herbal medicinal plants

Herbal medicines are widely used as disease treatments, and they play an important role in the human health care of the great majority of the world's population. Traditional medicine, which is mostly based on plant material, is used by the majority of the world's populations. Traditional medicine refers to a wide range of ancient natural health care practises. These medicinal practises have existed since the beginning of time and have evolved gradually, to a large extent, by relying on or based on practical experiences, with little or no reference to modern scientific principles. Although herbal remedies are beneficial in the treatment of a variety of ailments, they are frequently misused or exploited without scientific backing. As a result, in the light of modern science, these plant medications need to be further investigated.

Traditions are living, breathing, unchangeable bodies of knowledge. Traditional medicine is evolving as communities and people find new strategies that have the potential to revolutionise traditions. In the current target-rich, lead-poor scenario, ethnopharmacology and natural product drug development remain critical challenges [48]. Ethnopharmacology is the source of many contemporary medications. Despite technical advancements, however, the drug discovery process is experiencing a significant innovation deficit, which is negatively impacting the pharmaceutical business. Many recent researches imply that entry barriers for new drug introductions have decreased over time [49]. The ethnopharmacology knowledge and experimental background enables drug research to be carried out from "Clinics to Laboratories" - a real Reverse Pharmacology Approach [50]. The most important beginning point in this procedure is "safety," and efficacy becomes a question of validation. Traditional knowledge, modern medicine, and modern science will combine in a golden triangle with a systems orientation to produce an innovative discovery engine for newer, safer, more inexpensive, and effective remedies [51]. The medicinal plants are shown in table 1.

Botanical name	Chemical constituents	Uses	References
Hypericum perforatum	Hypericin, hyperforin	Anti-depressant, anxiety, sedative, insomnia	[52]
Matricaria recutita	Apigenin	Anxiety	[53]
Albizia lebbeck Benth	Pindolol	Free radical scavenging activity, anti-oxidant	[54]
Centella asiatica Linn	Asiaticoside	Anti-stress, anti-depressant,	[55]
Coptis chinensis Franch	Berberine	Immunomodulatory, antiinflammatory	[56]
Galphimia glauca Cav	Nor-secotriterpene	Cytotoxic, sedative, anti-anxiety	[57]

Table 1

Conclusion

Central nervous system diseases are among the top degenerative, causing different problems per year. Besides, there are those who suffer from chronic CNS problems, needing recurrent hospitalization and prolonged medical attention, which leaves them physically, mentally, emotionally and financially devastated. Therefore, an attempt has been made in this review to give details about the mechanisms of stress, diagnostic markers of stress function which can be used for the diagnosis of the CNS. The present review also gives an account of some of the experimental models to evaluate new drugs/compounds and tabulate some of the important anti-stress plants with their parts used and chemical constituents which can be further validated using the modern scientific methodology.

Authors' Contributions

Mohd Rafi Reshi and Nusrat Nabi created the concept and designed the structural of the manuscript and involved in the preparation of the manuscript. Afshana Bashir Reshi and Aabida Majid also added some part in this article. Saman Anees, Maaz Naqvi, Nafaa Hassan and Jamal Akhtar also making some changes and adding some study material. Mohd Rafi Reshi and Nusrat Nabi make all over review, design and abstract of manuscript.

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