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An Overview of Stress: Insights from the Stress System, Posttraumatic Stress Disorder and Recent Approaches

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Abstract

Stress is an excessive, improper, or exaggerated response to a circumstance. Stress is a common occurrence in a rapidly expanding global population, with most people experiencing stress as a result of daily issues such as financial problems, family problems, educational problems, and so on. Despite the fact that the entire CNS has a direct or indirect function in maintaining general body homeostasis, several regions of the brain play crucial, unique roles in coordinating the stress response. The stress system plays a major role here via two different pathways, i.e., the HPA axis pathway and the sympatho-adreno-medulary (SAM) axis pathway. These two pathways work in response to stress by releasing different neurotransmitters in the brain and managing stress with positive and negative feedback mechanisms. This long-term exposure to chronic stress increases the chances of developing stress-related disorders like PTSD. Post-traumatic stress disorder (PTSD) is a disabling condition that often arises after exposure to a stressful event and affects around 8% of the population during their lifetime. To date, there is no effective treatment available for PSTD other than some antidepressants. Recently Ketamine has gained popularity in recent PSTD approaches as a good candidate for treating PTSD. In this review, we focus on the entire stress system, its treatments, and recent approaches.

Keywords

Reactive Oxygen species, free radical, Neurodegenerative disorder, Parkinson Disease, Alzheimer's disease.

Introduction

A broad definition of stress is an excessive, improper, or exaggerated response to a circumstance. When environmental demands exceed a person's ability to meet those needs, stress results. It can be evaluated according to its duration, amount, and quality. Selye was the first researcher to define stress as "a nonspecific response of the body to any demand." Hans Selye adopted the term "stress" from physics in the 1930s and defined it as the mutual actions of forces that occur over any portion of the body. He hypothesized that the occurrence of a constellation of stereotypical psychological and physiological events in gravely ill patients represented the consequence of a severe and extended application of adaptational reactions. Stress is regarded as a significant issue in both basic and clinical neuroscience research. Although this physiological phenomenon is essential for survival, it is also strongly associated with a number of brain disorders, such as depression, anxiety, and post-traumatic stress disorder.[1] Numerous Scientists have demonstrated that the response to stressful stimuli is elaborated and driven by the stress system, which integrates a wide variety of brain structures capable of detecting events and interpreting them as an actual or prospective threat: stressor.[2] Physiological and behavioural changes occur in conjunction with the perception of stresses and the adaptation to them.[3] Thus, the perception of actual or potential threats results in the production of molecules that serves as mediators. The interaction of these molecules with their appropriate receptors in the periphery and brain results in the stress response, which regenerates homeostasis and promotes adaptation through physiological and behavioural mechanisms (Fig. 1).[4] All living organisms aim for a dynamic equilibrium known as homeostasis. According to the traditional stress theory, this equilibrium is disrupted by specific physical and psychological occurrences known as "stressors." Additionally, stressors elicit physiological and behavioural reactions that try to restore balance.[5] If the stress response is insufficient or severe and prolonged, the cost of reestablishing homeostasis may become too great, a condition known as allostatic load.[5] There are individual variances in how people react to the same stressful circumstance, despite the fact that different kinds of stressful situations have a tendency to evoke diverse patterns of stress responses. The tendency to demonstrate a consistent pattern of stress responses in the face of a variety of stressors is known as "response stereotypy''.[6]

Types Of Stress

Stress can be beneficial for stimulating the body, mind, and energy of a person. It is the capacity of an individual to mobilise all of the body's resources in order to respond immediately and appropriately to any particular circumstance. However, if stress lasts too long, the body's resources get depleted and the individual develops detrimental or negative stress responses. To effectively manage the impacts of stress, it is helpful to identify its many types, symptoms, and causes.there are different types of stress according to situations and properties as follows

1. **Acute Stress**

The majority of people experience stress in this way. It might be traced back to recent happenings or be based on anticipation of things to come. Acute stress might make you feel excited and exhilarated, but prolonged exposure to it results in more negative effects than positive ones. As a result of its short duration, it does not have the chance to cause any harm, unlike the damage that longer-term stress will cause. It is very curable and incredibly easy to control.[7]

2. **Chronic Stress**

This is the form of stress that results from long-lasting, uncontrollable events and conditions. It is long-lasting, incapacitating, and manifests in those trapped in disastrous conditions, such as a disdained vocation, everlasting poverty, an unhappy marriage, a weird relationship, etc,[8, 7] On the other hand, chronic stress produces persistent and long-term harm to both physical and mental health through abnormalities in the physiological, behavioural, and psychological reactions in body. Chronic stress has remained relatively unfamiliar, although acute stress is gradually becoming a part of life. On both the individual and societal levels, chronic stress is recognized to result in a number of major health-related physical, financial, and emotional consequences.[8] The development of metabolic syndrome has been shown to be linked to chronic stress, which has also been shown to be connected with cardiovascular disease. Epidemiological data shows that chronic stress plays a big role in the development of coronary heart disease. Chronic stress also makes it much more likely for men over 65 to have a fatal stroke.[9] Because of immunosenescence, or the steady decline in immunological function that comes with ageing, elderly persons are more vulnerable to the negative effects of chronic stress. The production of antibody responses to immunisations and the ability to resist viral infections are impaired in older persons.[10, 6]

Physiology of Stress

Despite the fact that the entire CNS has a direct or indirect function in maintaining general body homeostasis, several regions of the brain play crucial, unique roles in coordinating the stress response.[11] Certain regions of the brain play essential roles in the mechanisms being discussed here, Modulation of the activity of the stress system at the level of both the hypothalamic-pituitary-adrenal axis and the central and peripheral components of the autonomic nervous system is essential for a successful adaptive response to stressors. Although In the human stress response, neurons and somatic cells are involved in a complex HPA and other axis. A variety of hormones, including cortisol, catecholamines, prolactin, oxytocin, and renin, are secreted by the body in response to exposure to hostile situations. These are regarded as survival mechanisms. This hormone is often called "stress hormones".[12]

Stress System

The stress response is a sophisticated, efficient, and evolutionarily conserved system whose modulation in various contexts requires the activation of mechanisms that link the brain and the body. The reaction to stressful stimuli is defined by a variety of brain areas capable of

detecting or interpreting events as either actual or potential dangers (stressors).[13] Depending on whether the event is physical or psychological, different networks are involved in the perception of it as a stress. The identification of a stressor results in the activation of two primary stress system components and the release of the system's final mediator molecules. The hypothalamus-pituitary-adrenal (HPA) axis secretes glucocorticoids, while the sympathetic-adreno-medullar (SAM) axis secretes noradrenaline and norepinephrine.[14] Once these axes are activated in response to a specific stressor, they will provide a coordinated reaction that begins within seconds and lasts for days, giving rapid responses that enable both the adoption of an optimal strategy and the restoration of homeostasis. To provide it, the stress response systemically stimulates energy mobilisation, metabolic alterations, immune system activation, and digestive and reproductive system repression. The stress response specifically generates short- and long-term consequences in the brain via non-genomic, genomic, and epigenetic processes (fig-1).[1]

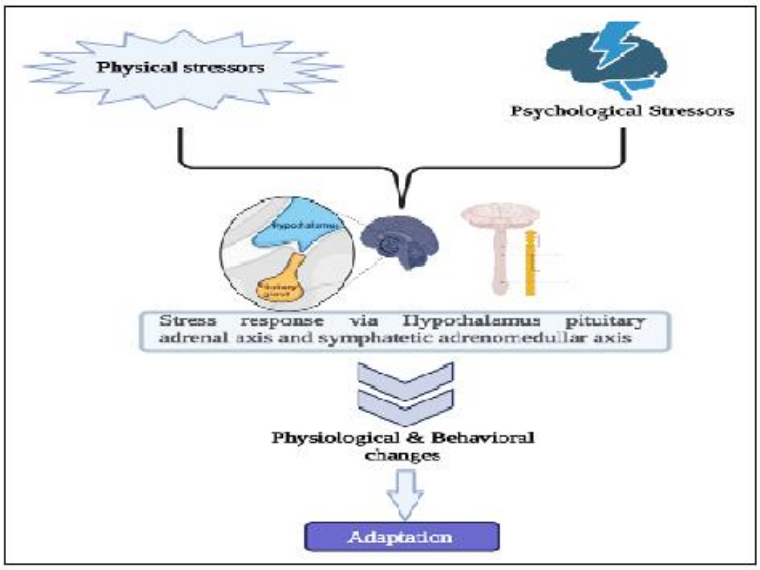

Figure No.1: Stress System[1]

ACTH/ HPA Axis

The principal regulator of the HPA axis, corticotropin-releasing factor (CRF), is synthesized and secreted by hypophysiotropic neurons in the medial parvocellular subdivision of the PVN. CRF is secreted into the hypophysial portal vessels that reach the anterior pituitary gland in response to physiological and psychological stress.[15] Adrenocorticotropic hormone (ACTH) is released into the systemic circulation as a result of the binding of CRF to its receptor on pituitary corticotropes. The adrenal cortex is the primary target of circulating ACTH, which causes it to increase glucocorticoid production and release from the zona fasciculata of the adrenal cortex.[16] Through widely dispersed intracellular receptors, glucocorticoids, which

are the HPA axis' downstream effectors, control physiological changes. However, insufficient or excessive activation of the HPA axis may lead to the development of diseases.[17, 15]

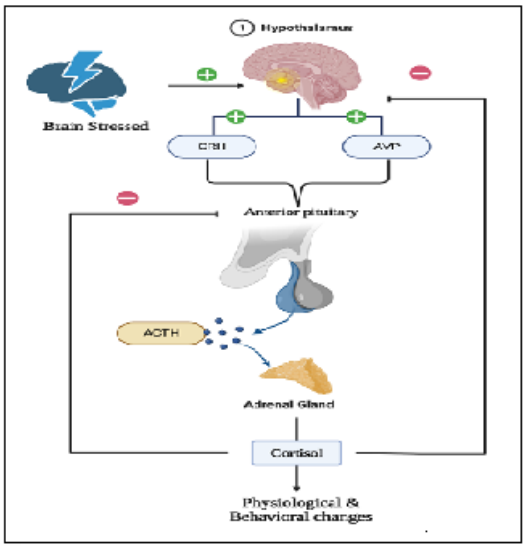

Figure No.2: systematic illustration of HPA axis

SAM Axis

The initial stress response pathway is known as the sympatho-adrenomedulary (SAM) axis. This is because it responds quickly to stressors by acting through the sympathetic nervous system (SNS) and the adrenal medulla.[18] Exposure to a stressor activates preganglionic sympathetic neurons in the intermediolateral cell column of the thoracolumbar spinal cord. These preganglionic neurons send out projections to the pre- or paravertebral ganglia, which further send out projections to the end organs and into the chromaffin cells of the adrenal medulla, which causes the medulla to secrete adrenaline into the circulation. Adrenaline has substantial and widespread impacts on the body, and it helps the body respond more quickly to stressful stimuli. As a result, several target organs, including the heart, are stimulated, blood vessels constrict, blood pressure rises, and salivary gland activity and digestion are inhibited.[19] The "fight or flight" response, which Walter Cannon and his colleagues first described in the early 20th century, is a prime example of this sympathetic activation.

Management of Stress

Stress management is the process of overcoming, minimizing, or enduring life's stresses. Stress management is coping with stress successfully. It reduces tension. It alters the emotional and physical state to control and reduce traumatic stress; Stress management uses a variety of techniques and psychotherapies to help people deal with stress. Here are some strategies for stress reduction.[7, 8]

1) Positive Thinking
2) Meditation

3) Muscle exercise
4) Talking with reliance person
5) Diaphragmatic Breathing
6) Progressive Muscle Relaxation
7) Social Support

Post-Traumatic Stress Disorder (PTSD)

Post-traumatic stress disorder (PTSD) is a disabling condition that often arises after exposure to a stressful event and affects around 8% of the population during their lifetime. Apart from the fact that a large percentage of the general population is exposed to potentially traumatic events, between 80 and 90 percent of people who are exposed to trauma do not develop post-traumatic stress disorder. This finding suggests that susceptibility to developing PTSD varies by individual.[20] A traumatic experience is defined by the fact that it can make a person feel afraid, helpless, or horrified because of the possibility of physical harm or death. People who are subjected to such occurrences have a higher likelihood of developing post-traumatic stress disorder (PTSD), as well as significant depression, panic disorder, and generalised anxiety disorder.[21] Post-traumatic stress disorder, which is also called PTSD, is one of the most common mental illnesses.[22] This condition is characterised by a long-lasting duration and debilitating symptoms. Across many different populations, there is an alarmingly high prevalence of posttraumatic stress disorder (PTSD), a form of anxiety disorder that is triggered by the initial stages of exposure to a particularly traumatic stressor. Such stressors include conflict, physical and sexual abuse in childhood, motor vehicle accidents, rape, and natural disasters. Patients who suffer from post-traumatic stress disorder frequently experience one or more of the following symptoms: intrusive memories, flashbacks, hypervigilance, sleep disturbances, avoidance of traumatic stimuli, physiological hyperresponsivity, numbing of emotions, and social dysfunction.[23, 24]

Biological Aspect of PTSD

The fact that the cingulate and amygdala control peripheral markers of physiological responsiveness raises the possibility that changes in the ways these brain areas work may be linked to PTSD symptoms. These parts of the brain work together, and through pathways that go through the hypothalamus and the medial prefrontal cortex, they affect the peripheral stress response, which is an increase in heart rate, blood pressure, catecholamines, and cortisol.[25, 26] The amygdala gathers data on environmental stimuli and assesses their significance. This then sets off a chain reaction of emotional responses, including the "fight, flight, or freeze" response, as well as variations in stress hormones and catecholamine's. When it comes to defining the ultimate fear reaction, the amygdala is primarily responsible; nevertheless, the hippocampus and the medial prefrontal cortex both have an impact. Lesions in the hippocampus have been linked to a more intense fear response, and a reduced hippocampal volume has been linked to post-traumatic stress disorder. The enhancement of negative feedback in the hypothalamic-pituitary-adrenal axis has been one of the most persistent neurophysiological theories. Several studies have found that people suffering from

post-traumatic stress disorder have lower cortisol levels.[27]

Biochemical Mediators

The stress response involves a vast variety of neurotransmitters, neurohormones, and neuropeptides released by the brain. When an organism is threatened or attacked, the chemical messenger systems act centrally in the brain as well as in the periphery. As part of the survival mechanism, being exposed to adverse environments causes the release of many hormones, such as corticosterone/cortisol, catecholamines, prolactin, oxytocin, and renin. These kinds of situations are frequently referred to as "stressors,"[28] and they can be broken down into three distinct categories: external conditions that result in pain or discomfort, internal homeostatic interruptions, and learned or associative reactions to the perception of impending endangerment, and psychological stress. The hormones secreted in reaction to stressors are commonly referred to as "stress hormones," and their production is controlled by neuronal circuits impinging on hypothalamic neurons, which are the final output to the pituitary gland and the kidneys.[29] They are essential for the survival response, which causes an increase in heart rate and blood pressure, respiration, alerting and vigilance behaviours, and the shunting of energy to the parts of the body that need it most for survival, specifically the brain and the muscles. These systems comprise endogenous benzodiazepines and opiates, dopamine, serotonin, norepinephrine, cortisol, and other neuropeptides. As per many studies there are certain types of biochemical mediators associated with PTSD; in this review, we summarise a few of them as follows:

Norepinephrine

Norepinephrine, commonly known as noradrenaline, is a brain neurotransmitter that regulates arousal, attention, cognitive functions, and stress responses. Additionally, it works as a hormone in the periphery of the sympathetic nervous system during the "fight or flight" reaction. The noradrenergic system stems from a small number of cells in the locus coeruleus (LC) and other cell groups in the medulla and pons that use norepinephrine (NE) as a neurotransmitter.[30] A variety of brief sensory inputs can temporarily excite noradrenergic neurons. This shows that the noradrenergic system gets information from both the internal and external environment that has been processed by a number of sensory systems.

In the pathophysiology of posttraumatic stress disorder (PTSD), increases in the quantity or effect of noradrenergic signalling have been suggested as a contributing factor. This perhaps enhanced signalling is the result of an increase in the release of norepinephrine (NE).[31] Certain PTSD phenotypes and symptoms, such as agitation, hyperarousal, and sleep disturbance, have been directly linked to alterations in noradrenergic function.[32] In addition, some clinical studies suggest that elevated NE levels in plasma and urine are seen in PTSD patients.[33]

Dopamine

Dopaminergic innervations are the most prominent in the brain. Most dopaminergic

neurons have their cell bodies in the ventral tegmental region of the midbrain and release neurotransmitters throughout the brain.[20] The mammalian brain has four main dopaminergic pathways: the nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular systems.[34] This pathway has numerous essential central nervous system processes, such as voluntary movement, eating, mood, reward, sleep, attention, working memory, and learning that heavily depend on these neurons. While in the periphery, dopamine regulates olfaction, retinal processes, hormonal regulation, cardiovascular functions, sympathetic regulation, immune system functions, and renal functions, among several others.[34, 35]

The dopaminergic innervation of the medial prefrontal cortex (mPFC) is especially susceptible to stress. In addition the mPFC is more prone to stress-induced dopamine release than other parts of the brain with dopaminergic connections. Dopamine turnover in the PFC and nucleus accumbens increases as a result of chronic stress and stressful events.[36, 37] In addition the discovery of elevated dopamine levels in the plasma or urine of PTSD patients, as well as an uptick in their dopamine beta-hydroxylase activity, has verified dopamine metabolic changes.[38]

Three perspectives can be used to evaluate the evidence supporting its involvement in PTSD: a molecular perspective, which includes genetic, ligand-receptor, and metabolic abnormalities; a geographical perspective; and a clinical perspective, which focuses on particular clinical symptoms.[20] Despite the fact that a number of studies investigating the relationship between specific dopamine receptor genes (DRD2) and PTSD have identified associations.[39]

Serotonin

Serotonin, one of the key neurotransmitters with the longest evolutionary history, (5-HT) is responsible for the regulation of the most extensive behavioural modulation system in the brains of vertebrates. 5HT projections are altered by extrinsic and intrinsic impulses from various cortical brain areas. These impulses travel through feedback loops to reach the raphe nuclei, which contain information about the external and internal workings of the body, such as planning, evaluation, motivation, or elicitation.[40] The serotonin is involved in the regulation of a wide range of behaviours and physiological activities, some of which are relevant to stress-related mental disorders like post-traumatic stress disorder (PTSD).[36] The neurotransmitter serotonin plays a role in the control of a variety of behaviours, including anxiety, alertness, vigilance, aggression, mood, and impulsivity, as well as food intake and sleep.[41] In addition to this, it plays a role in the regulation of physiological processes that are involved in the stress response. These processes include cardiovascular function, respiratory activity, motor output, neuroendocrine secretion, and analgesia.[41, 36] Also Studies on humans suggest that impaired serotonergic activity is linked to PTSD-related symptoms and behaviours such as impulsivity, aggressiveness, depression, and suicidal thoughts.[42] Clinical and theoretical evidence supports serotonergic drugs for PTSD. Serotonergic systems fundamentally incorporating 5-HT2 pathways may be

particularly significant for avoidance behaviours in PTSD animal models. Finally, open-label and controlled trials of 5-HT-selective medicines and other serotonergic medications (e.g., tricyclic antidepressants, monoamine oxidase inhibitors, and others) support the idea that modulating serotonergic function has a significant therapeutic effect in PTSD.[43]

Gamma-Aminobutyric Acid (GABA)

GABA is the primary inhibitory neurotransmitter of the central nervous system (CNS) and one of the most common neurotransmitters in mammals. It is present in 40% of the inhibitory synapses of adult vertebrates and is widely distributed throughout the brain. It is synthesised in the central nervous system (CNS) through the decarboxylation of glutamic acid, which is facilitated by glutamic acid decarboxylase (GAD). GABA exerts its inhibitory impact via two distinct receptor types, GABAA (ionotropic) and GABAB (metabotropic), which display distinct pharmacological, structural, and molecular distinctions.[44] The most important agonists that bind to GABA-A receptors are called benzodiazepines, and they include: There is a correlation between stress and alterations in benzodiazepine receptors. In some studies, it was found that exposure to unavoidable stressors, such as footshock or forced swimming, reduced benzodiazepine receptor binding in the prefrontal cortex by 20–30%.[45, 46] In human investigations, proton magnetic resonance spectroscopy (MRS), a non-invasive and non-radioactive neuroimaging method, has provided the majority of empirical evidence showing GABAergic and glutamatergic brain abnormalities in PTSD. Given its function in fear conditioning and extinction, GABA levels are of substantial interest in PTSD research.[47] Consistently, clinical trials have shown that GABAergic medications can boost neuronal activity by combining GABAergic receptors. Furthermore, patients who receive regular treatment with these medicines could minimise the anxiety-like behaviours that are associated with their condition.[48]

Treatment

Posttraumatic stress disorder (PTSD) is a complicated condition characterised by numerous neurological changes. In the last two decades, only two drugs (paroxetine and sertraline) with poor efficacy have been approved for the treatment of PTSD. In the meantime, the search for and development of new medication modes of action have stopped.[49] Due to the limited effectiveness of pharmacotherapeutic therapies, the PTSD treatment guidelines have selected exposure-based psychotherapy as the first-line treatment for PTSD. Despite many psychotherapeutic modalities, PTSD frequently persists as a chronic disorder with high rates of psychiatric and medical comorbidity. The U.S. Food and Drug Administration (FDA) has only approved two drugs for the treatment of PTSD: sertraline and paroxetine. Although numerous adjuvants have been demonstrated to be helpful, the majority of them are still contraindicated according to U.S. federal standards.[44] In regarding the use of pharmacotherapy, current professional practise guidelines for the treatment of posttraumatic stress disorder

provide conflicting recommendations. Concerning the role of pharmacotherapy in the treatment of posttraumatic stress disorder, there is controversy in the clinical setting. While some guideline authors consider pharmacotherapy to be the first-line treatment option, others endorse psychotherapy as a prerequisite to pharmacotherapy. When pharmacotherapy is chosen, selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors (specifically sertraline, fluoxetine, paroxetine, and venlafaxine) are regarded as first-line options.[44, 49] Utilization of antipsychotics and mood stabilisers should be a last option. Although There is a lack of direct head-to-head assessments of medication, and judgments are based on meta-analyses and limited studies.[50] In contrast, the Veterans Affairs/Department of Defense (VA/DoD) and the National Institute for Clinical Excellence consider trauma-focused psychotherapies (TFPs) to be superior to pharmacotherapy. In addition to this, they advise using TFPs rather than pharmacotherapy as the initial course of treatment whenever possible, since patients tend to favour TFPs. Non-drug treatments for post-traumatic stress disorder (PTSD) include brief eclectic psychotherapy (BEP), narrative exposure therapy (NET), prolonged exposure therapy (PE), eye movement desensitisation and reprocessing (EMDR), and cognitive processing therapy (CPT).[51]

Pharmacotherapy

Antidepressant medications are currently the only medications that have been approved by the Food and Drug Administration (FDA) for the treatment of post-traumatic stress disorder (PTSD). In particular, antidepressants like sertraline and paroxetine, which are called selective serotonin reuptake inhibitors (SSRIs), are thought to be the best drugs for treating PTSD. However, a significant number of patients continue to be unresponsive to antidepressants, either on their own or in combination with psychotherapy.[52]

The most recent evidence suggests that monotherapy with fluoxetine, venlafaxine, or paroxetine is best for posttraumatic stress disorder symptoms. The adverse effect profiles of selective serotonin reuptake inhibitors (SSRI) and selective norepinephrine reuptake inhibitors (SNRI) are generally well tolerated, which is one of the relative advantages of using these medications. A psychiatrist may switch SSRI or SNRI drugs based on patient response, tolerability, or metabolism concerns.[53]

In addition Several TCAs have been explored as potential treatments for post-traumatic stress disorder (PTSD). Even though some trials have shown that these drugs work, most treatment guidelines don't recommend them as the first choice because they have a number of undesirable side effects. In a similar manner,

monoamine oxidase inhibitors (MAOIs) like

phenelzine may be beneficial in treating PTSD; however, the use of these medications is restricted because of the safety and tolerability concerns they raise.[54]

Novel Approaches for Posttraumatic Stress Disorder

Even though PTSD is common, lasts a long time, and is very serious, current drug treatments are often ineffective or not good enough. It has been called a "PTSD pharmacotherapy crisis" because there aren't enough effective medicines for people with this disorder. That's why there is an urgent need to address a critical lack of advancement in the psychopharmacologic Treatment of posttraumatic stress disorder (PTSD).

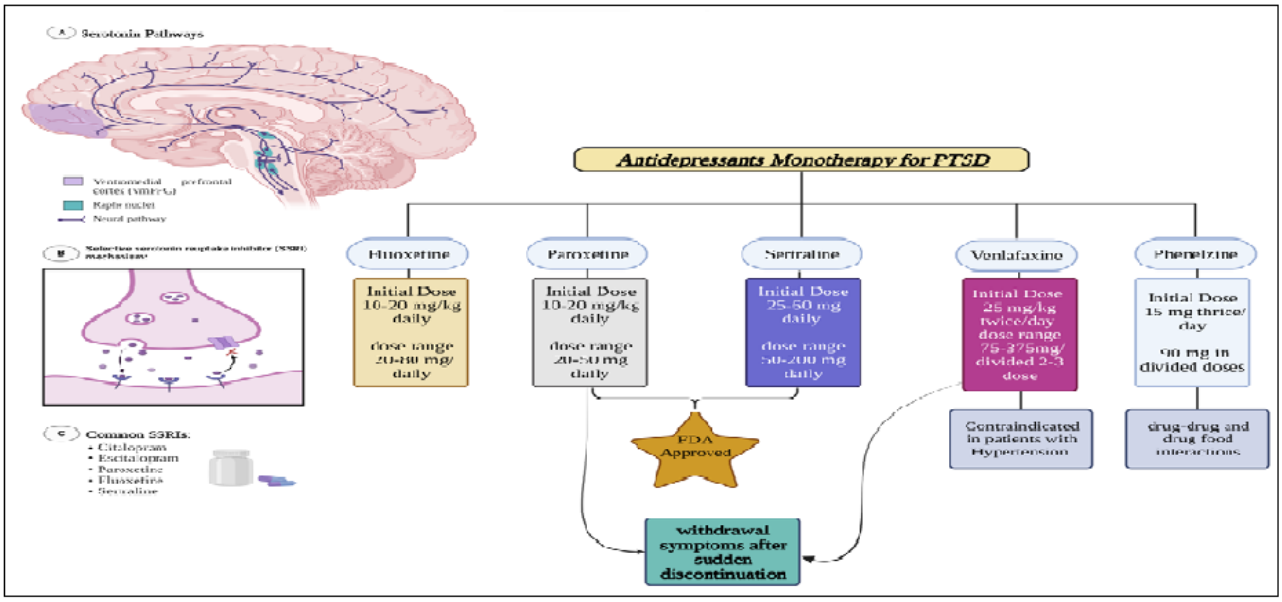

Figure No.3: Systematic Illustration of

Treatment on PTSD

Research on new interventions based on growing knowledge of fear conditioning, reconsolidation, and extinction, as well as anomalies in attention to threat and emotional problems and new insights on neural irregularities from brain imaging studies, will lead to new ways to improve adaptability, prevent or reduce the emergence of PTSD symptoms after trauma exposure, and lessen the severity of PTSD symptoms in people with chronic PTSD. The next ten years of clinical research are anticipated to produce innovative pharmacological treatments for post-traumatic stress disorder (PTSD).[55] These treatments will focus on lowering dysfunction in neurotransmitter, hormone, and neuropeptide systems that are implicated in the stress response. These systems include glutamate, NPY, endocannabinoids, the HPA axis, and oxytocin, among others. These treatments will also target immune system abnormalities that might cause PTSD symptoms to become chronic.[56]

Novel prevention agents

A new agent that helps prevent post-traumatic stress disorder (PTSD) is called a preventive agent.

1. Glucocorticoids

As has already been discussed above, the HPA axis is an important component of the neuroendocrine response to both short-term and long-term stress. To reduce the effects of stress and prevent the development of post-traumatic stress disorder (PTSD), it is possible to intervene within the HPA axis or at the level of glucocorticoid receptors. Hydrocortisone is a synthetic glucocorticoid that is often used in medicine to reduce inflammation. Findings show that glucocorticoids help extinction learning by improving the effects of glutamatergic N-methyl-D-aspartate (NMDA) receptors in the amygdala better.[57] This supports the idea that glucocorticoids might increase the therapeutic effect of prolonged exposure (PE). Some studies have found that the administration of glucocorticoids is associated with reduced recall of fear experiences in animals.[58] Through their interactions with the brain's noradrenergic systems, glucocorticoids also improve memory consolidation and reconsolidation. This may help with the re-framing of memories, which is a key part of posttraumatic recovery. In addition, it was found that patients who were treated for septic shock with large doses of glucocorticoids had a considerably lower risk of developing post-traumatic stress disorder (PTSD). Subsequent randomised clinical tests demonstrated that the effect of glucocorticoids like hydrocortisone on the prevention of post-traumatic stress disorder (PTSD) was due to a reduction in the potentially traumatic effects of memory.[59]

1. Propranolol

According to the research from the literature cited, propranolol treatment given before trauma memory reactivation decreased the severity of PTSD symptoms, decreased physiological reactions, and enhanced cognitive function in PTSD patients.[60] In addition it has been proposed that the beta-adrenergic antagonist propranolol can prevent the consolidation of recently acquired emotional memories in the basolateral nucleus of the amygdala by blocking post-synaptic betanoradrenergic receptors.[61]

Novel Treatment Agent

Drugs have been used to treat either the core symptoms of PTSD as a whole or the core symptoms of PTSD in a focused manner called as novel treatment agent.

1. Ketamine

In 1970, the Food and Drug Administration (FDA) granted ketamine its initial approval as an anaesthetic agent. Ketamine is a noncompetitive glutamate N-methyl-D-aspartate (NMDA) receptor antagonist. In addition to its usage as an anaesthetic, ketamine has been used in clinical practise for analgesia, sedation, and the treatment of certain forms of persistent pain in burn damage survivors.[62] In this regard, experimental and clinical evidence suggests that novel pharmacological compounds targeting the NMDA receptor may be good candidates for new anti-PTSD treatments.[63]

Interest in ketamine's potential fast-acting effects in PTSD was sparked by the drug's initial success in trials of patients with treatment-resistant depression. In a randomised controlled trial using a single dose of intravenous ketamine (versus midazolam), depressive and post-traumatic stress disorder (PTSD) symptoms were found

to decrease rapidly by 24 hours post-infusion. These results, along with those from structural and functional imaging studies, support the idea that PTSD is a "synaptic disconnection syndrome." Prefrontal connectivity, thought to be disrupted in PTSD, is increased by ketamine in depressed patients.[64] Initial results from published research seem promising, but definitive answers are anticipated following the conclusion of ongoing clinical trials of repeated ketamine treatment for PTSD.

1. Endocannobinoids (eCBs)

Endocannabinoids, also known as eCBs, are essential activity-dependent signals that control synaptic transmission throughout the central nervous system. This means that eCBs have a role in a wide variety of cognitive and behavioural processes in the brain, from regulating the body's ability to maintain a steady supply of food.[65] Even though the eCB system is quite prevalent in the CNS, not every synaptic connection has a fully operational copy of it. The expression of CB1R is a strong indicator of the presence of eCB signalling at a given synapse. This is because CB1R is the most important component of the eCB system. All brain areas that are significant for processing anxiety, fear, and stress express the eCB system at some synapses, including the hippocampus, the PFC, the bed nucleus of the stria terminalis (BNST), the basolateral amygdala (BLA), the central amygdala (CeA), and different hypothalamic nuclei.[66] Since the revelation that the endocannabinoid (eCB) system is involved in the processing of emotional memories, pharmacological modification of eCB signalling has become a potential treatment for PTSD. Among the potential alternative methods, the use of Cannabis sativa components such as CBD is the most promising.[67] A number of recent studies have revealed encouraging outcomes from the use of CBD in the treatment of a variety of neuropsychiatric disorders, including PTSD. Some evidence suggests that PTSD patients' brains have lower levels of endocannabinoids and higher levels of cannabinoid receptor type 1 (CB1) receptors. As a result, the utilisation of cannabidiol (CBD) and 9-tetrahydrocannabinol (9 -THC), both of which are derived from Cannabis sativa, has attracted an increasing amount of interest as a potential alternative method of treating PTSD.[63, 68]

Future Prospect and Conclusion

Post-traumatic stress disorder, also known as PTSD, is a mental health disease that can be brought on by either personally experiencing a horrific incident or witnessing another person going through it. In addition to having uncontrollable thoughts about the traumatic event, symptoms may include having flashbacks, nightmares, and acute anxiety. There are numerous PTSD management strategies, including optimistic thinking. Meditation, muscle exercise, progressive muscle relaxation, and social support however, it is just effective for stress management and does not cure stress-related diseases such as PTSD. As stated above, there are few effective treatments for stress and PTSD. We need to comprehend the fundamental pathophysiology of stress and develop novel treatments for PTSD patients. Several hypotheses are being established for the treatment of post-traumatic stress disorder (PTSD) based on clinical trials and recent

studies. One of these, the ketamine hypothesis, is growing rapidly, and many scientists believe that ketamine is an effective treatment for PTSD.

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