IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

ASSESSING THE SIGNIFICANCE OF HYPOTHALAMIC–PITUITARY–ADRENAL (HPA) AXIS MARKERS AND THEIR ACTIVITIES IN THE DEVELOPMENT OF MAJOR DEPRESSIVE DISORDERS (MDD)

[1]Remya Joy,[1] Chandrika Rao,[2] Suchetha Kumari N,[2] Suresh Babu S V,[2] Shrinivasa Bhat

[1]Associate Professor,[1]Associate Professor,[2]Professor,[2]Principal,2Professor

Biochemistry

Padmashree Institute of Medical Laboratory Technology,Bangalore,India

Abstract: People with Major Depressive Disorder have problems with the hypothalamic-pituitary-adrenal (HPA) axis and inflammatory systems that do not go away. Common methods of gauging cortisol include measuring diurnal fluctuations and assessing the cortisol awakening response (CAR). Activation of the hypothalamic-pituitary-adrenal (HPA) axis in certain people with severe depressive illness is one of the most robust and often seen discoveries in biological psychiatry. Some of these discoveries relevant to evaluating and treating depressed people will be discussed below. Understanding the cause and effects of HPA axis activation in depressed individuals will be a priority for future researchers. To add, there are drugs in development that target the HPA axis, which might one day be a standard component of a psychiatrist's or family doctor's toolkit for treating mental health issues. For a long, psychiatrists and neuroscientists have worked toward a deeper understanding of the biological roots of MDD and other mood disorders. The effects of neurotransmitters like norepinephrine and serotonin on major depressive disorder have been the subject of a great deal of research. There has also been research on the relationship between MDD and hormone levels and stress response.

Index Terms - Major depressive disorder, HPA axis, neurotransmitters, TAAR, immune system, cortisol awakening response, inflammation

1. Introduction

Roughly 17% of the population may experience major depressive disorder (MDD) at some time in their life, making it one of the most common mental health conditions. For a long, psychiatrists and neuroscientists have worked toward a deeper understanding of the biological roots of MDD and other mood disorders (Pochigaeva, 2017). The effects of neurotransmitters like norepinephrine and serotonin on major depressive disorder have been the subject of a great deal of research. There has also been research on the relationship between MDD and hormone levels and stress response. The hypothalamic-pituitary-adrenal (HPA) axis will be examined since it is aberrant in a subgroup of persons with the major depressive disorder during the last 30 years (Doolin, 2017). These results sparked hope that so-called neuroendocrine challenges, which boost or dampen HPA axis activity, may provide a "window to the brain" and reveal more about the etiology of major depressive disorder. The involvement of the HPA axis in mood disorders is still a hot topic of study, even though research interests and methods have shifted dramatically over the last four decades (Rhebergen, 2015).

Suicide is the second greatest cause of death among young adults, and the mental disease Major Depressive Disorder (MDD) is very common, with a prevalence estimate of 16% over a lifetime. Although depression is very common, its biological origins are still poorly understood. Further study of stress-related biochemical pathways in a depressed population may provide light on the stress-related etiology of depression, and this is supported by the observation that stress is a key risk factor in developing depression (Martinac, 2017).

One of the key components of the neuroendocrine system is the hypothalamic pituitary adrenal (HPA) axis, which regulates the body's response to stress. One constant result in the research into the biological basis of MDD is hyperactivity of the HPA axis, as seen by increased cortisol levels. An underactive HPA axis may be to blame for this hyperactivity (Francisco Juruena, 2015). The fast spike in cortisol production that typically happens daily during the first 30 minutes of waking, reflecting the physiological stress reaction to waking, is one metric often used to evaluate HPA axis activity and is known as the cortisol awakening response (CAR). Past research has shown that people with MDD had reduced waking reactions and higher cortisol levels upon awakening (Becking, 2015).

Concentrations of cortisol are often incorrectly assessed in enzyme-linked immunosorbent assays (ELISA) and other techniques of cortisol measurement because of the mistaken identification of glucocorticoids like cortisone. Hypercortisolemia is linked to a failure to regulate inflammatory reactions, although cortisone is an inert glucocorticoid that has a low affinity for both glucocorticoid and mineralocorticoid receptors. While cortisone is inactive outside of cells, the enzyme 11-HSD1 may easily convert it to the active steroid cortisol inside cells. Injections of cortisone are used to treat inflammatory disorders like arthritis by increasing the amount of cortisone available to be converted into cortisol in peripheral tissue. Anxiety and depression are recognized adverse effects of cortisone injections, which are used to treat inflammatory diseases. This suggests that cortisone may also have a role in the pathophysiology of depression (Foland-Ross, 2014).

2. Objective of the study

The main objectives of the study are to examine the significance of Hypothalamic–Pituitary–Adrenal (HPA) axis markers the significance of Hypothalamic–Pituitary–Adrenal (HPA) axis markers. The study also focuses on:

- To examine diurnal Hypothalamic-Pituitary-Adrenal Axis Measures and Inflammatory Marker Correlates in Major Depressive Disorder
- To make focus on major Depressive Disorder and Hypothalamic-Pituitary-Adrenal Axis Activity
- To examine the role of remission status concerning the Hypothalamic-pituitary-adrenal axis activity and cognition in major depression

3. Literature Review

3.1 Diurnal Hypothalamic-Pituitary-Adrenal Axis Measures and Inflammatory Marker Correlates in Major Depressive Disorder

According to Doolin, (2017) suicide is the second greatest cause of death among young adults, and the mental disease Major Depressive Disorder (MDD) is very common, with a prevalence estimate of 16% over a lifetime. Although depression is very common, its biological origins are still poorly understood. Considering that stress is an important contributor to the onset of depression, it stands to reason that studying the biochemical processes involved in stress in a depressed population could shed light on the etiology of depression as it relates to stress. Jairaj, (2020) stated that the hypothalamic pituitary adrenal (HPA) axis is one of several parts of the neuroendocrine system that is crucial in controlling how the body responds to external stress. Hyperactivity of the HPA axis, shown in elevated cortisol levels, is a consistent finding in the search for a biological etiology in MDD. An underactive HPA axis may be to blame for this hyperactivity. The fast spike in cortisol production that typically happens daily during the first 30 minutes of waking, reflecting the physiological stress reaction to waking, is one metric often used to evaluate HPA axis activity and is known as the cortisol awakening response (CAR). Past research has shown that people with MDD had reduced waking reactions and higher cortisol levels upon awakening.

According to Fong, (2022) concentrations of cortisol are often incorrectly assessed in enzyme-linked immunosorbent assays (ELISA) and other techniques of cortisol measurement because of the mistaken identification of glucocorticoids like cortisone. Hypercortisolemia is linked to a failure to regulate inflammatory reactions, although cortisone is an inert glucocorticoid that has a low affinity for both glucocorticoid and mineralocorticoid receptors. While cortisone is inactive outside of cells, the enzyme 11-HSD1 may easily convert it to the active steroid cortisol inside cells. Injections of cortisone are used to treat inflammatory disorders like arthritis by increasing the amount of cortisone available to be converted into cortisol in peripheral tissue. Nees, (2019) examined that anxiety and depression are recognized adverse effects of cortisone injections, which are used to treat inflammatory diseases. This suggests that cortisone may also have a role in the pathophysiology of depression. Regulation of the HPA axis and vulnerability to depression in humans have been linked to 11-HSD1. High levels of cortisol and greater rates of depression were seen in those who had the rs11119328 polymorphism in the HSD11B1 gene. In addition, deletion of the gene encoding 11-HSD1 in mice has antidepressant effects as measured by the forced swim test. As a bonus, 11-HSD1 has been connected to many inflammatory diseases.

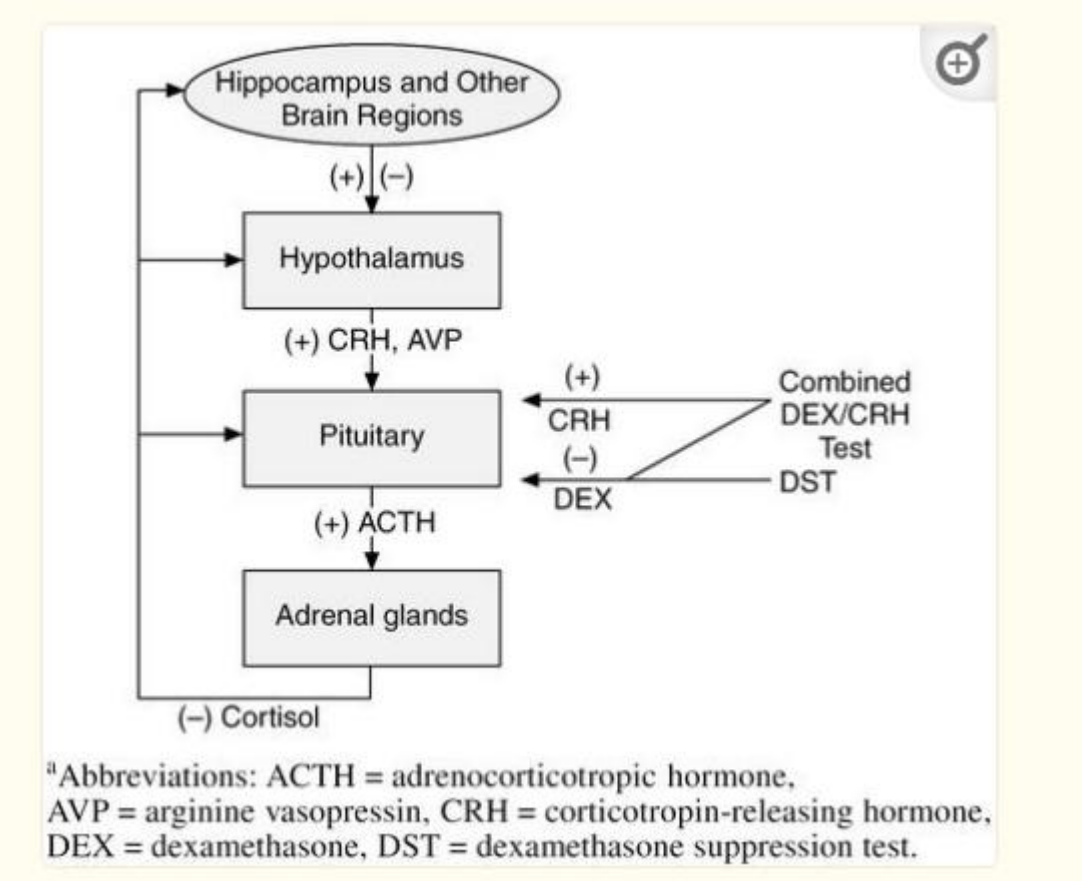
Gardhouse, (2021) stated that since glucocorticoids control inflammatory responses, and since increased inflammation is a well-established consequence of stress system activation, the HPA axis has a functional relationship with the immune system. Glucocorticoid resistance develops when the HPA axis is out of whack, and this prevents the immune system from being suppressed. Because of their functional interdependence, both of these pathways are probably disrupted in depressive disorders. Kinlein, (2020) analyzed that repeated studies have shown that people with MDD have activated inflammatory pathways, as shown by elevated levels of inflammatory cytokines. Interleukin (IL)-6 concentrations have been shown to rise steadily in the serum or plasma of depressed people. In addition, studies have shown that depressive individuals have higher levels of IL-1 and

TNF- in their plasma than those who are not sad. There is also evidence linking inflammation to a greater intensity of depressive symptoms.

3.2 Major Depressive Disorder and Hypothalamic-Pituitary-Adrenal Axis Activity

According to Ferrer, (2018), the hypothalamic-pituitary-adrenal (HPA) axis is thought to have an important role in the pathophysiology of depression. Since the 1960s, researchers have observed symptoms of hyperactivity of the HPA axis in depressed individuals, such as increased daytime cortisol levels, greater non suppression upon dexamethasone ingestion, and elevated corticotropin-releasing hormone and adrenocorticotropin hormone levels. . Salvat-Pujol, (2021) stated that unfavorable somatic health outcomes, such as cardiovascular disease or diabetes, may be explained by dysregulation of the HPA axis in depressed people. This theory is supported by findings that prolonged stress is linked to increased cortisol levels and that the most common type of hypercortisolism, Cushing's illness, is connected with both depression and cardiovascular issues.

According to Labad, (2018) salivary cortisol measurements are increasingly utilized to determine HPA axis activity because they are thought to be the least invasive on HPA axis control and accurately represent the active, unbound form of cortisol. Wang, (2020) analyzed that the cortisol awakening response is a biomarker of the HPA axis's innate reaction to waking up. Other common cortisol tests include the evening cortisol measurement (which can be interpreted as an indicator of baseline activity) and the dexamethasone suppression test (DST), which can shed light on the negative feedback mechanism of the HPA axis. Depression has been linked to measures of salivary cortisol like the CAR, although there are also contradicting findings.



[a]Abbreviations: ACTH = adrenocorticotropic hormone, AVP = arginine vasopressin, CRH = corticotropin-releasing hormone, DEX = dexamethasone, DST = dexamethasone suppression test.

3.3 Role of remission status concerning the Hypothalamic-pituitary-adrenal axis activity and cognition in major depression

Salvat-Pujol, (2021) stated that due to the chronic and intricate nature of the disease, major depressive disorder (MDD) imposes a heavy toll on society. Patients with MDD score worse than healthy controls on a battery of neuropsychological tests, including those that assess verbal and visual memory, attention, executive function, and speed of processing. The negative consequences of persistent cognitive impairment on quality of life and psychosocial functioning in people with MDD have been well-documented even in the absence of depressive symptoms, suggesting that this issue may be of relevance. According to Ferrer, (2020) previous research has shown that depression's emotional and cognitive symptoms are separate and likely progress independently of one another. Numerous studies have measured MDD patients' cognitive abilities, but the root causes of the resulting impairments remain unknown. Hypothalamic-pituitary-adrenal (HPA) axis hormones have been linked to the pathophysiology of depression, and hyperactivity in the HPA axis as well as poor negative feedback responses have both been reported in people with MDD, suggesting that these hormonal imbalances may exacerbate the cognitive deficits seen in people with MDD.

Labad, (2020) examined that the hippocampus is particularly susceptible to the consequences of hypercortisolemia because it is responsible for negative feedback on the HPA axis through glucocorticoid and mineralocorticoid receptors. By activating the glucocorticoid receptor, cortisol controls neuronal survival, excitability, neurogenesis, and memory formation and storage (GR). Cai, (2022) examined that in the hippocampus, dysfunctional GR activity (resulting in "glucocorticoid resistance") would trigger hyperactivity in the HPA axis, changes in neuronal functioning, and a decrease in neurogenesis, all of which may contribute to memory loss. High cortisol levels have been shown to reduce hippocampal volume and impair performance on hippocampus-

related cognitive activities in studies including healthy controls (HC). Also, the cognitive impairment and hippocampus shrinkage associated with Cushing disease, an endogenous source of hypercortisolism, improves with therapy and regulation of cortisol levels.

According to Yadav, (2020) in light of this speculation about the negative effects of glucocorticoids on cognitive function, various research has looked at the possibility that elevated levels of HPA axis activity are linked to cognitive impairment in MDD. Salivary cortisol levels are inversely linked with results on neuropsychological memory tests involving the hippocampus (both verbal and visual memory) and executive function. Soria, (2018) found a group-independent link between higher 24-hour plasma cortisol levels and worse verbal memory in a sample of MDD patients and HC, as well as an interaction effect between diagnosis and cortisol on inferior executive function in HC. Den The author demonstrated that people with MDD had slower processing speeds and a flatter cortisol curve over the day (change in cortisol levels between 8 a.m. and 9 p.m.) than HC patients. Trinetti, (2021) stated that additionally, the cortisol awakening response (CAR) and other markers of the HPA axis have been associated with worse cognition in people with MDD. For instance, Hinkelmann et al. (2013) discovered that abnormal (blunted) CAR was associated with worse verbal and visuospatial memory in patients with MDD but not HC. Contrary to these findings, however, other researchers have not linked the CAR to cognitive impairments in MDD. Studies using the dexamethasone suppression test (DST) to investigate defective negative feedback inhibition of glucocorticoids have also shown conflicting results regarding cognitive function.

According to Heaney, (2020), disruptions in the HPA axis and cognitive impairment have been linked to MDD, however, it is unclear whether these symptoms are states or traits. If hyperactivity of the HPA axis and reduced negative feedback were state indicators of depression, then improvements in depressed symptoms would be followed by a restoration of HPA axis status and cognitive ability. Although HPA axis activity has been studied extensively, there are conflicting findings. Lee, (2018) examined that a state-dependent marker, the dexamethasone/corticotropin-releasing hormone (DEX/CRH) test has been used to evaluate the HPA axis in certain investigations, with results showing increased pituitary-adrenocortical responses that were considerably decreased following therapy. It has been shown that HPA axis abnormalities are trait markers because studies using multiple salivary cortisol measures throughout the day, including the CAR, morning and evening cortisol samples, and DST, have failed to find differences according to remission status in severe depression. Some research suggests that cognitive symptoms may linger after an acute depressive episode has ended, but that they are not good predictors of future relapses.

According to Labad, (2018) some authors have postulated that subclinical hyperactivity of the endocrine stress system is connected with abnormalities in cognitive performance in recovered MDD patients, making disturbances in the HPA axis phenotypic indications of cognitive dysfunction in MDD. Increased cortisol after being exposed to DEX/CRH has been associated with worse performance on tests of verbal memory, attention, and executive function. Fischer, (2021) examined that no non-remitting MDD patients were included in that research sample, hence the results cannot be generalized to the population at large. Patients hospitalized with MDD who were given citalopram showed improved HPA axis reactivity (as measured by the DEX/CRH test). It was also linked to enhanced working memory function, but not to shifts in episodic memory, attention span, or overall depressive state.

According to Zhang, (2022) Whether or not remission alters the correlation between HPA axis measurements and cognitive function in people with MDD is uncertain. We hypothesize that abnormalities in the HPA axis are trait indicators of cognitive impairment in MDD because cognitive problems in MDD may continue after the depressive episode has finished. According to Andreescu (2019), researchers expect to find a correlation between HPA axis measurements and cognitive symptoms in individuals with MDD who have either remitted or not. The researcher hypothesizes that anomalies in the hypothalamic-pituitary-adrenal axis (HPA axis) would be related with lower cognitive performance in both the remitted and non-remitted groups due to the involvement of the prefrontal cortex and the hippocampus in visual, verbal, working memory and executive skills.

Serotonin

According to Mohammad-Zadeh, (2008) the monoamine neurotransmitter serotonin (5-hydroxytryptamine) is also known as 5-HT. Its biological role is intricate and multidimensional, affecting not just mood and cognition but also reward, learning, memory, and even vomiting and vasoconstriction. Most of the body's serotonin is found in the intestines, where around 90 percent of it is produced. Serotonin is made biochemically from indoleamine, which originates from the amino acid tryptophan through the (rate-limiting) hydroxylation of the 5 positions on the ring (producing the intermediate 5-hydroxytryptophan) and subsequently decarboxylation. Geyer, (2008) stated that the enteric nervous system, which is situated in the digestive tract, is where serotonin is largely concentrated (GI tract). It is also produced in the brainstem raphe nuclei, skin Merkel cells, lung neuroendocrine cells, and taste receptor cells. Serotonin is also an agonist to other platelets, and it is retained in blood platelets, where it is released during agitation and vasoconstriction. The enterochromaffin cells in the gastrointestinal tract house over 90% of the body's total serotonin and are responsible for controlling bowel motions. A few percent may be discovered in the central nervous system, while another 8 percent is located in platelets.

Dopamine

Wise, (2020) stated that dopamine acts as a neuromodulatory chemical and has several cellular roles. Simplified, it is an organic substance linked to phenethylamines or catecholamines. Most of the catecholamines in the brain are found in the dopamine system. Specifically, the brain and kidneys remove a carboxyl group from L-DOPA to make it. The majority of organisms, including plants, can produce dopamine via synthesis. Dopamine is a neurotransmitter, meaning it is used by neurons (nerve cells) to communicate with one another. Even though they are generated in distinct brain areas, the effects of neurotransmitters are felt all across the brain. Multiple dopamine pathways exist in the brain, with one being particularly important in driving reward-based actions. According to Iversen, (2007) dopamine is released in the brain in response to the expectation of most rewards, and many addictive substances either further boost dopamine release or prevent its absorption into neurons. Motor control and the regulation of hormone secretion are two further functions of the brain's dopamine circuits. Together, these circuits

and cell populations make up the neuromodulatory dopamine system. Though dopamine is widely portrayed as the primary chemical of pleasure in popular culture and media, the prevailing view in the field of pharmacology is that it confers motivational salience, or signals the perceived motivational prominence (i.e., the desirability or aversiveness) of an outcome, which then drives the organism's behavior toward or away from achieving that outcome.

Epinephrine levels in MDD

Pollack, (2021) examined that suicide, physical sickness, damaged relationships, missed employment, and drug misuse is just some of the negative outcomes that have been linked to depression. Although the precise pathophysiology of depression is not well understood, several biological, psychological, and social factors are known to contribute to the onset of depressed symptoms. Individuals with depression have been shown to have smaller hippocampal volumes compared to controls in imaging studies, suggesting a possible link between depression and the process of neurogenesis in the hippocampus. Hyperactivity in the hypothalamic-pituitary-adrenal axis, which has an effect similar to the neuroendocrine response to stress, has been associated to major depression, as stated by Jain (2020). There has been research on estrogen's potential involvement in both the cause and treatment of mental health problems. Greater blood concentrations of interleukin (IL)- and tumor necrosis factor (TNF)- have been found in depressed patients compared to controls, supporting the significance of pro-inflammatory cytokines in depression, according to meta-analyses of clinical data.

Syeda, (2018) analyzed that Other hypothesized illness processes include alterations in glutamatergic neurotransmission, reduced gamma-butyric acid neurotransmission, irregular circadian rhythms, impaired neurosteroid synthesis, impaired endogenous opioid function, an acetylcholine imbalance, thyroxine abnormalities, and malfunction of certain brain structures and circuits. Despite the discovery of different reasons for depression, the clinical development of new antidepressants is still driven by the monoamine hypothesis, which postulates a lack of serotonin (5-HT) and/or norepinephrine (NE) neurotransmission in the brain. MacDonald (2019) looked at how current antidepressants function and found that they inhibit 5-HT or NE reuptake, antagonize presynaptic inhibitory 5-HT or NE receptors, and inhibit monoamine oxidase. Enhanced neurotransmission of 5-HT and/or NE occurs as a result of many routes. The effectiveness of these medications in clinical settings lends credence to the monoamine hypothesis of depression.

The role and studies on TAAR 1 receptors in MDD

According to Dale, (2015), trace amines (TAs) are a large and varied class of aminergic chemicals that are produced in mammalian bodies via a variety of metabolic and enzymatic pathways, including those involved in the breakdown of foods like cheese and the manufacture of thyroid hormone and other neurotransmitters. Phenethylamine (PEA), tyramine, and tryptophan are produced from the aromatic amino acids phenylalanine, tyrosine, and tryptophan, respectively, by the enzymatic decarboxylation of these compounds. Espinoza, (2015) stated that these TAs, along with others, are found in much lower amounts in the brain and peripheral tissues compared to traditional monoamines like noradrenaline (NA) and serotonin (5-HT). Despite this, it seems that TAs play a key role in the regulation of mood, energy level, cognition, and other processes. It has also been postulated that a disturbance in their activity may have a role in the pathogenesis of a wide range of metabolic, neuropsychiatric, and even neurodegenerative illnesses, including severe depression and schizophrenia.

According to Leo, (2014) It is widely believed that TAs have sympathomimetic properties because they stimulate the reverse transport of monoamines from intraneuronal vesicles. Evidence for the notion that trace amines have neuromodulatory effects, themselves, through particular classes of receptors, was supplied by the discovery of receptors that bind TAs in rats, followed by the finding of a full family of G protein-coupled Trace Amine-Associated Receptors (TAAR), now simply called "TA" receptors. Thorn, (2014) analyzed that the olfactory epithelium expresses a large number of TAAR classes, and these TAARs detect volatile TAs. Whereas TAAR1 is mostly localized in the central nervous system and digestive organs. TAAR1 is expressed in corticolimbic projecting 5-HT neurons and dopamine (DA) neurons that originate in the cortex and the striatum. Additionally, TAAR1 is localized to the amygdala, hypothalamus, lateral parabrachial nucleus, and prefrontal cortex.

Di Pizio, (2014) stated that conventional, endogenous trace amines, amphetamine, methamphetamine, and MDMA all activate TAAR1, which is coupled to Gs and G13. Much of the TAAR1-related research has centered on the DAergic system because of its unique relationship with DA-releasing agents. Higher VTA neuron firing rates and increased behavioral sensitivity to psychostimulants are observed in TAAR1-deficient mice, suggesting that pharmacological TAAR1 activation may be useful in treating schizophrenia. Indeed, in some animal models, TAAR1 agonists show antipsychotic-like activity. Deficits in trace amine activity have also been linked to depression, and it has been found that TAAR1 agonists can have antidepressant effects when administered to rodents and nonhuman primates by boosting their effect.

4. Findings and Discussions

Previous research has revealed that unhappy people had higher waking cortisol and lower CAR reactivity. The current study demonstrated that elevated morning cortisol levels are the major cause of HPA axis dysregulation in MDD. There was no significant difference between groups in salivary cortisone levels or blood HSD11-1 mRNA levels. These findings provide further support for the hypothesis that increased inflammation coincides with the altered CAR in depression and indicate that glucocorticoid receptor downregulation may be to blame for ineffective HPA axis inhibition and an overactive immune response in individuals with major depressive disorder.

One of the major contributors to the development of depression is the HPA axis, namely its influence on cortisol secretion. Individuals with MDD had much higher cortisol levels than healthy subjects. In depressed patients, elevated cortisol levels have been shown to negatively affect verbal and working memory, leading to a general decline in mental capacity. Both HPA axis regulation and neurogenesis have been linked to the hippocampus, whose volume is considerably diminished in major depressive disorder. Complex relationships between HPA axis function and serotonergic transmission are suggested by data from a study of

meta-analyses and randomized clinical trials. This hyperreactivity of the HPA axis in schizophrenia has also been shown in more recent studies. To clarify the precise function of the HPA axis in the etiology of schizophrenia, high-quality randomized clinical studies are required; nevertheless, it should be highlighted that the results for schizophrenia are less definitive than for depression.

5. Conclusion and Recommendations

Major depressive disorder (MDD) is one of the most prevalent mental health problems, affecting around 17% of the population at some point in their lives. Researchers in the fields of psychiatry and neuroscience have been trying to learn more about the causes of major depressive disorder and other mood disorders for quite some time. There has been a lot of study on the role that neurotransmitters like norepinephrine and serotonin play in severe depressive illness. There has been a study on how MDD correlates with hormonal levels and the body's reaction to stress. Because the hypothalamic-pituitary-adrenal (HPA) axis is abnormal in certain people with severe depressive illness, it will be studied.

Major Depressive Disorder (MDD) is quite frequent, with a prevalence estimate of 16% over a lifetime, and suicide is the second leading cause of mortality among young people. The underlying molecular causes of depression remain poorly known despite the disease's prevalence. The finding that stress is a major risk factor in the development of depression lends credence to the idea that investigating the biochemical processes involved in stress in a depressed population may provide insight into the stress-related etiology of depression.

Enzyme-linked immunosorbent assays (ELISAs) and other methods of cortisol measurement often overestimate cortisol concentrations due to the inaccurate identification of glucocorticoids like cortisone. Hypercortisolemia is linked to an inability to regulate inflammatory responses, despite cortisone being a non-aggressive glucocorticoid with low affinity for both glucocorticoid and mineralocorticoid receptors. The enzyme 11-HSD1 in the cells can convert inactive cortisone into the active steroid cortisol. Injections of cortisone are used to treat inflammatory diseases like arthritis by raising the concentration of cortisone in the blood, where it can be converted into cortisol. Anxiety and depression are linked to the use of cortisone injections, which are used to treat inflammatory illnesses. Consequently, cortisone may be involved in both the genesis and the development of depression.

The mental illness Major Depressive Disorder (MDD) is quite frequent, with a prevalence estimate of 16% throughout a lifetime, and suicide is the second leading cause of mortality among young people. The underlying molecular causes of depression remain poorly known despite the disease's prevalence. Because of the strong correlation between stress and depression, it stands to reason that studying the biochemical processes involved in stress in a depressed population might provide light on the genesis of depression as it relates to stress. The neuroendocrine system, of which the hypothalamic-pituitary-adrenal (HPA) axis is a component, plays a vital role in regulating the body's reaction to stress. One constant result in the research into the biological basis of MDD is hyperactivity of the HPA axis, as seen by increased cortisol levels. It is possible that the HPA axis is underactive, which would explain this heightened state of activity. One measure often used to examine HPA axis function is the quick rise in cortisol production that generally occurs daily during the first 30 minutes of waking, representing the physiological stress reaction to waking (CAR). Previous studies have revealed that persons with MDD had diminished waking responses and elevated cortisol levels.

Misidentification of glucocorticoids like cortisone leads to inaccurate readings of cortisol concentrations in enzyme-linked immunosorbent assays (ELISA) and other methods of cortisol measurement. Although cortisone is a relatively innocuous glucocorticoid with a modest affinity for both glucocorticoid and mineralocorticoid receptors, hypercortisolemia is associated with a failure to control inflammatory responses. Inactive cortisone may be readily converted into the active steroid cortisol by the enzyme 11-HSD1 inside cells. By increasing the quantity of cortisone available to be converted into cortisol in peripheral tissue, cortisone injections are used to treat inflammatory illnesses like arthritis.

The hypothalamic-pituitary-adrenal (HPA) axis is thought to have an important role in the development and maintenance of depression. Evidence for hyperactivity of the HPA axis in patients with depression has been recorded since the 1960s. This includes increased daytime cortisol levels, more non suppression upon dexamethasone consumption, and raised corticotropin-releasing hormone and adrenocorticotropin hormone levels. Depressed people may be at a higher risk for cardiovascular disease and diabetes due to HPA axis dysregulation. Elevated cortisol levels are an indicator of long-term stress, and the most common type of hypercortisolism, Cushing's disease, has been linked to both depression and cardiovascular issues.

Major depressive disorder (MDD) has a significant societal impact owing to the complexity and length of time it takes to treat the condition. Patients with MDD score worse than healthy controls on a battery of neuropsychological tests, including those that assess verbal and visual memory, attention, executive function, and speed of processing. The negative consequences of persistent cognitive impairment on quality of life and psychosocial functioning in people with MDD have been well-documented even in the absence of depressive symptoms, suggesting that this issue may be of relevance.

The hippocampus is particularly susceptible to the effects of hypercortisolemia because it mediates negative feedback on the HPA axis through glucocorticoid and mineralocorticoid receptors. By activating the glucocorticoid receptor, cortisol controls cell survival, excitability, neurogenesis, and the formation and storage of memories (GR). Memory loss may be caused by hyperactivity in the HPA axis, alterations in neuronal functioning, and a reduction in neurogenesis in the hippocampus that occur from malfunctioning GR activity (leading to "glucocorticoid resistance"). In trials with healthy controls, high levels of cortisol have been demonstrated to decrease hippocampal volume and worsen performance on hippocampus-related cognitive tasks (HC). Cushing illness is an endogenous cause of hypercortisolism, and its cognitive impairment and hippocampal atrophy are reversed with treatment and management of cortisol levels.

It is unclear whether the symptoms of MDD related with abnormalities in the HPA axis and cognitive impairment represent states or characteristics. If increased negative feedback and decreased HPA axis hyperactivity were state markers of depression, then

the recovery from depression would be accompanied by normalization of the HPA axis and mental functioning. Extensive research has been done on HPA axis activity, although the results are inconsistent. Some studies have employed the dexamethasone/corticotropin-releasing hormone (DEX/CRH) test, a state-dependent marker, to assess the HPA axis; the test elicits heightened pituitary-adrenocortical responses, which are then markedly reduced after treatment. It has been shown that HPA axis problems are trait indicators since studies employing several salivary cortisol measurements throughout the day, including the CAR, morning and evening cortisol samples, and DST, have failed to find variations according to remission status in severe depression. Some research suggests that cognitive symptoms may linger after an acute depressive episode has finished, but that they are not good indicators of future relapses.

References

[1] Andreescu, C., Ajilore, O., Aizenstein, H. J., Albert, K., Butters, M. A., Landman, B. A., ... & Taylor, W. D. 2019. Disruption of neural homeostasis as a model of relapse and recurrence in late-life depression. *The American Journal of Geriatric Psychiatry*, *27*(12), 1316-1330.

[2] Becking, K., Spijker, A. T., Hoencamp, E., Penninx, B. W., Schoevers, R. A., & Boschloo, L. 2015. Disturbances in hypothalamic-pituitary-adrenal axis and immunological activity differentiating between unipolar and bipolar depressive episodes. *PLoS One*, *10*(7), e0133898.

[3] Cai, M., Park, H. R., & Yang, E. J. 2022. Nutraceutical Interventions for Post-Traumatic Stress Disorder in Animal Models: A Focus on the Hypothalamic–Pituitary–Adrenal Axis. *Pharmaceuticals*, *15*(7), 898.

[4] Doolin, K., Farrell, C., Tozzi, L., Harkin, A., Frodl, T., & O'Keane, V. 2017. Diurnal hypothalamic-pituitary-adrenal axis measures and inflammatory marker correlates in major depressive disorder. *International journal of molecular sciences*, *18*(10), 2226.

[5] Doolin, K., Farrell, C., Tozzi, L., Harkin, A., Frodl, T., & O'Keane, V. 2017. Diurnal hypothalamic-pituitary-adrenal axis measures and inflammatory marker correlates in major depressive disorder. *International journal of molecular sciences*, *18*(10), 2226.

[6] Ferrer, A., Costas, J., Labad, J., Salvat-Pujol, N., Segalàs, C., Urretavizcaya, M., ... & Soria, V. 2018. FKBP5 polymorphisms and hypothalamic-pituitary-adrenal axis negative feedback in major depression and obsessive-compulsive disorder. *Journal of Psychiatric Research*, *104*, 227-234.

[7] Ferrer, A., Labad, J., Salvat-Pujol, N., Monreal, J. A., Urretavizcaya, M., Crespo, J. M., ... & Soria, V. 2020. Hypothalamic-pituitary-adrenal axis-related genes and cognition in major mood disorders and schizophrenia: a systematic review. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *101*, 109929.

[8] Fischer, S., Schumacher, T., Knaevelsrud, C., Ehlert, U., & Schumacher, S. 2021. Genes and hormones of the hypothalamic-pituitary-adrenal axis in post-traumatic stress disorder. What is their role in symptom expression and treatment response? *Journal of Neural Transmission*, *128*(9), 1279-1286.

[9] Foland-Ross, L. C., Kircanski, K., & Gotlib, I. H. 2014. Coping with having a depressed mother: The role of stress and coping in hypothalamic–pituitary–adrenal axis dysfunction in girls at familial risk for major depression. *Development and Psychopathology*, *26*(4pt2), 1401-1409.

[10] Fong, T. C., Ho, R. T., & Yau, J. C. 2022. Longitudinal Associations Between Salivary Cortisol to C-reactive Protein Ratios and Psychological Well-being in Chinese Adults. *Psychoneuroendocrinology*, 105824.

[11] Francisco Juruena, M., Von Werne Baes, C., Castro Menezes, I., & Guilherme Graeff, F. 2015. Early life stress in depressive patients: role of glucocorticoid and mineralocorticoid receptors and hypothalamic-pituitary-adrenal axis activity. *Current pharmaceutical design*, *21*(11), 1369-1378.

[12] Gardhouse, K., Carcone, D., & Ruocco, A. C. 2021. Stressed, sick, and sad: Neuroendoimmune pathways between subjective lifetime stress and depression. *Brain, behavior, & immunity-health*, *14*, 100249.

[13] Heaney, J. 2020. Hypothalamic-pituitary-adrenal axis. *Encyclopedia of Behavioral Medicine*, 1127-1128.

[14] Jairaj, C., O'Leary, N., Doolin, K., Farrell, C., McCarthy, A., McAuliffe, F. M., ... & O'Keane, V. 2020. The hypothalamic-pituitary-adrenal axis in the perinatal period: its relationship with major depressive disorder and early life adversity. *The World Journal of Biological Psychiatry*, *21*(7), 552-563.

[15] Kinlein, S. A., & Karatsoreos, I. N. 2020. The hypothalamic-pituitary-adrenal axis as a substrate for stress resilience: Interactions with the circadian clock. *Frontiers in neuroendocrinology*, *56*, 100819.

[16] Labad, J., Salvat-Pujol, N., Armario, A., Cabezas, Á., de Arriba-Arnau, A., Nadal, R., ... & Soria, V. 2020. The role of sleep quality, trait anxiety, and hypothalamic-pituitary-adrenal axis measures in the cognitive abilities of healthy individuals. *International journal of environmental research and public health*, *17*(20), 7600.

[17] Labad, J., Soria, V., Salvat-Pujol, N., Segalàs, C., Real, E., Urretavizcaya, M., ... & Menchón, J. M. 2018. Hypothalamic-pituitary-adrenal axis activity in the comorbidity between obsessive-compulsive disorder and major depression. *Psychoneuroendocrinology*, *93*, 20-28.

[18] Labad, J., Soria, V., Salvat-Pujol, N., Segalàs, C., Real, E., Urretavizcaya, M., ... & Menchón, J. M. 2018. Hypothalamic-pituitary-adrenal axis activity in the comorbidity between obsessive-compulsive disorder and major depression. *Psychoneuroendocrinology*, *93*, 20-28.

[19] Lee, H. H., Chang, C. H., Wang, L. J., Wu, C. C., Chen, H. L., Lu, T., ... & Lee, S. Y. 2018. The correlation between longitudinal changes in hypothalamic–pituitary–adrenal (HPA)-axis activity and changes in neurocognitive function in mixed-state bipolar II disorder. *Neuropsychiatric Disease and Treatment*, *14*, 2703.

[20] Martinac, M., Babić, D., Bevanda, M., Vasilj, I., Bevanda Glibo, D., Karlović, D., & Jakovljević, M. 2017. The activity of the hypothalamic-pituitary-adrenal axis and inflammatory mediators in major depressive disorder with or without metabolic syndrome. *Psychiatria Danubina*, *29*(1), 39-50.

[21] Nees, F., Löffler, M., Usai, K., & Flor, H. 2019. Hypothalamic-pituitary-adrenal axis feedback sensitivity in different states of back pain. *Psychoneuroendocrinology*, *101*, 60-66.
[22] Pochigaeva, K., Druzhkova, T., Yakovlev, A., Onufriev, M., Grishkina, M., Chepelev, A., & Gulyaeva, N. 2017. Hair cortisol as a marker of hypothalamic-pituitary-adrenal Axis activity in female patients with major depressive disorder. *Metabolic brain disease*, *32*(2), 577-583.
[22] Rhebergen, D., Korten, N. C., Penninx, B. W., Stek, M. L., van der Mast, R. C., Voshaar, R. O., & Comijs, H. C. 2015. Hypothalamic–pituitary–adrenal axis activity in older persons with and without a depressive disorder. *Psychoneuroendocrinology*, *51*, 341-350.
[23] Salvat-Pujol, N., Labad, J., Urretavizcaya, M., De Arriba-Arnau, A., Segalàs, C., Real, E., & Soria, V. 2021. Childhood Maltreatment and Its Interaction with Hypothalamic–Pituitary–Adrenal Axis Activity and the Remission Status of Major Depression: Effects on Functionality and Quality of Life. *Brain sciences*, *11*(4), 495.
[24] Salvat-Pujol, N., Labad, J., Urretavizcaya, M., De Arriba-Arnau, A., Segalàs, C., Real, E., & Soria, V. 2021. Childhood Maltreatment and Its Interaction with Hypothalamic–Pituitary–Adrenal Axis Activity and the Remission Status of Major Depression: Effects on Functionality and Quality of Life. *Brain sciences*, *11*(4), 495.
[25] Soria, V., González-Rodríguez, A., Huerta-Ramos, E., Usall, J., Cobo, J., Bioque, M., & PNECAT Group. 2018. Targeting hypothalamic-pituitary-adrenal axis hormones and sex steroids for improving cognition in major mood disorders and schizophrenia: a systematic review and narrative synthesis. *Psychoneuroendocrinology*, *93*, 8-19.
[26] Trinetti, J., Sforzini, L., & Pariante, C. M. 2021. The hypothalamic-pituitary-adrenal axis in bipolar disorder. In *Neurobiology of Bipolar Disorder* ,285-292
[27] Wang, M., Dong, W., Wang, R., Xu, X., Wu, Y., Sun, G., & Sun, X. 2020. Gastrodiae Rhizoma Water Extract Ameliorates Hypothalamic–Pituitary–Adrenal Axis Hyperactivity and Inflammation Induced by Chronic Unpredictable Mild Stress in Rats. *BioMed research international*.
[28] Yadav, A. K. 2020. *Level of Serum Heat Shock Protein in Patients of Bipolar Disorders Having Hypothalamic Pituitary Adrenal Axis Dysfunction and Its Relation with Symptom Severity and Response to Treatment* (Doctoral dissertation, Central Institute of Psychiatry India.
[29] Zhang, Z. Q., Guo, Z. P., Lv, X. Y., Sörös, P., Wang, X. X., Wang, L., & Liu, C. H. 2022. Effect and neural mechanisms of the transcutaneous vagus nerve stimulation for relapse prevention in patients with remitted major depressive disorder: protocol for a longitudinal study. *BMJ open*, *12*(2), e050446.
[30] Mohammad-Zadeh, L. F., Moses, L., & Gwaltney-Brant, S. M. 2008. Serotonin: a review. *Journal of veterinary pharmacology and therapeutics*, *31*(3), 187-199.
[31] Geyer, M. A., & Vollenweider, F. X. 2008. Serotonin research: contributions to understanding psychoses. *Trends in pharmacological sciences*, *29*(9), 445-453.
[32] Iversen, S. D., & Iversen, L. L. 2007. Dopamine: 50 years in perspective. *Trends in neurosciences*, *30*(5), 188-193.
[33] Wise, R. A., & Robble, M. A. 2020. Dopamine and addiction. *Annual review of psychology*, *71*, 79-106.
[34] Pollak, C., Maier, H. B., Moschny, N., Jahn, K., Bleich, S., Frieling, H., & Neyazi, A. 2021. Epinephrine levels decrease in responders after electroconvulsive therapy. *Journal of Neural Transmission*, *128*(12), 1917-1921.
[35] Jain, R., Manning, S., & Cutler, A. J. 2020. Good, better, best: clinical scenarios for the use of L-methyl folate in patients with MDD. *CNS spectrums*, *25*(6), 750-764.
[36] Syeda, J. N., Rutkofsky, I. H., Muhammad, A. S., Abdalla, T. H. B., & Saghir, Z. 2018. The Psycho-cardiac Coupling, Myocardial Remodeling, and Neuroendocrine Factor Levels: The Psychosomatics of Major Depressive Disorder. *Cureus*, *10*(4).
[37] MacDonald, K., Krishnan, A., Cervenka, E., Hu, G., Guadagno, E., & Trakadis, Y. 2019. Biomarkers for major depressive and bipolar disorders using metabolomics: A systematic review. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *180*(2), 122-137.
[38] Dale, E., Bang-Andersen, B., & Sánchez, C. 2015. Emerging mechanisms and treatments for depression beyond SSRIs and SNRIs. *Biochemical pharmacology*, *95*(2), 81-97.
[39] Espinoza, S., Lignani, G., Caffino, L., Maggi, S., Sukhanov, I., Leo, D., & Gainetdinov, R. R. 2015. TAAR1 modulates cortical glutamate NMDA receptor function. *Neuropsychopharmacology*, *40*(9), 2217-2227.
[40] Leo, D., Mus, L., Espinoza, S., Hoener, M. C., Sotnikova, T. D., & Gainetdinov, R. R. 2014. Taar1-mediated modulation of presynaptic dopaminergic neurotransmission: role of D2 dopamine autoreceptors. *Neuropharmacology*, *81*, 283-291.
[41] Thorn, D. A., Zhang, C., Zhang, Y., & Li, J. X. 2014. The trace amine-associated receptor 1 agonist RO5263397 attenuates the induction of cocaine behavioral sensitization in rats. *Neuroscience letters*, *566*, 67-71.
[42] Di Pizio, A., & Niv, M. Y. 2014. Computational studies of smell and taste receptors. *Israel Journal of Chemistry*, *54*(8-9), 1205-1218.