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Effect of neurotransmitters in relationship of Depression and Anxiety

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Abstract

A growing body of researches support a role for dysfunction of serotoninergic, noradrenergic, and dopaminergic systems in the neurobiological processes involved in major depression disorder (MDD) and anxiety disorders. The physiological changes underlying abnormal signaling of 5-HT, NE, and DA may be due to either reduced presynaptic release of these neurotransmitters or aberrant signal transductions, and thus contributing to the alterations in regulation or function of receptors and/or impaired intracellular signal processing. Animal models demonstrate crucial responsiveness to disturbance of 5-HT, NE, and DA neurotransmissions. Post-mortem and biochemical studies have shown altered concentrations of 5-HT, NE, and DA metabolites in brain regions that contribute importantly to regulation of mood and motivation in patients with MDD or Anxiety. Neuroimaging studies have found abnormal 5-HT, NE, and DA receptors binding and regulation in regard to receptor numbers. Medications that act on 5-HT, NE, and DA neurons or receptors, such as SSRIs and SNRIs, show efficacy in both MDD and ADs. The overlapping treatment response presumably suggests a common mechanism underlying the interaction of these disorders. In this paper, we reviewed studies from multiple disciplines to interpret the role of altered neurotransmitters such as 5-HT, NE and DA in both MDD and Anxiety.

Keywords:

Major depressive disorder, anxiety disorders, mono-aminergic neurotransmitters, serotonin,norepinephrine, dopamine

Introduction

Depression, anxiety, and stress were seen in 29%, 32.2%, and 34.8% of adult residents respectively. The symptoms of the disorders were moderate, severe, and very severe in 18.2%, 20.2%, and 23.4% of the population, respectively. Also, a significant difference was found between the symptoms of depression, anxiety, and stress and sex, age group, education, employment, marriage status, and country of birth. Of the total population under study, 3.7% were depressed, 7.7% were anxious, 9.5% had stress alone and 16.4% had symptoms of all the 3 disorders. [1] This is a complex disease characterised by using depressed temper or loss of hobby and anxiety problems (commercials) are characterised by using excessive fear and tension.[2] Previous to the COVID-19 pandemic, prices of clinically sizeable generalized tension and depressive signs and symptoms in massive young people cohorts have been about 11.6%1 and 12.9%,2 respectively. Considering COVID-19 changed into declared an international public health emergency, youth around the sector have skilled dramatic disruptions to their regular lives. adolescents are enduring pervasive social isolation and overlooked milestones, together with faculty closures, quarantine orders, extended family pressure, and reduced peer interactions, all capacity precipitants of mental distress and mental fitness problems in teens. Indeed, in both cross-sectional and longitudinal studies amassed to date, the prevalence of youth mental illness appears to have increased during the COVID-19 pandemic. Certainly, in both cross-sectional and longitudinal research collected thus far, the prevalence of youngster's mental infection seems to have elevated at some stage in the COVID-19 pandemic. But, facts collected range appreciably. Particularly, levels from 2.2%12 to 63.8%13 and 1.8%12 to 49.5%13 for clinically improved depression and tension signs, respectively. [3] Increasing attention has been paid to the role of inflammation in a host of illnesses including neuropsychiatric disorders such as depression and anxiety. Activation of the inflammatory response leads to release of inflammatory cytokines and mobilization of immune cells both of which have been shown to access the brain and alter behaviour. The mechanisms of the effects of infection at the mind have turn out to be a place of in depth study. Information suggests that cytokines and their signalling pathways which include p38 mitogen activated protein kinase have good sized results at the metabolism of a couple of neurotransmitters such as serotonin, dopamine and glutamate through effect on their synthesis, release and reuptake. Cytokines also activate the kynurenine pathway which not only depletes tryptophan, the primary amino acid precursor of serotonin, however additionally generates neuroactive metabolites that could extensively have an effect on the regulation of dopamine and glutamate. Through their effects on neurotransmitter systems, cytokines impact neurocircuits inside the brain along with the basal ganglia and anterior cingulate cortex, leading to tremendous adjustments in motor interest and motivation in addition to anxiety. [4]

Patients receiving continual administration of the inflammatory cytokine, interferon (IFN) alpha. IFN-alpha is used to deal with most cancers and infectious diseases which includes hepatitis C,

however between 30–50% of patients administered IFN-alpha broaden substantial depressive signs in addition to tension relying at the dose. Certainly, almost 50% of Patients treated with high dose IFN-alpha for malignant cancer have been observed to satisfy symptom standards for important despair. A few of the depression and anxiety signs brought about by using IFN-alpha may be blocked by using pre-treatment with selective serotonin reuptake inhibitors (SSRI), indicating that these signs can be related to cytokine results on serotonin metabolism. [4]

The enteric nervous system, seemed because the human 2nd brain, produces and makes use of more than 30 classes of neurotransmitters which can be also identified in the central nervous system. It's well known that serotonin is a brain neurotransmitter, but more than 90% of the body's serotonin is synthesized inside the digestive tract. In addition to serotonin, the gut produces and store approximately 50% of the body's dopamine. Gut microbiota regulates the level of serotonin and dopamine in the host. An increasing number of evidences show that gut microbiota also produces or consumes other neurotransmitters, including norepinephrine, gamma-aminobutyric acid (GABA), histamine and acetylcholine. [5]

Preclinical and clinical evidences show that depression accompanied by the disturbance in serotonin, dopamine and norepinephrine transmission in the central nervous system. Serotonin network is the main target for most common classes of antidepressants. Serotonin also has a well-confirmed role in the regulation of eating behaviours and bipolar disorders. In addition, serotonergic, noradrenergic and GABAergic systems mediate the sleep cycle and some types of anxiety disorders. The imbalance of neurotransmitters is one reason that responsible for the distress or impairment of personal mental health.

The availability of NE appears to be essential for maintaining an antidepressant response to drugs that enhance the release of NE, and 5-HT appears to be vital for maintaining an antidepressant response to drugs that enhance 5-HT. These depletion study data tend to support the hypothesis that there is no single mechanism of antidepressant drug action: both the noradrenergic and serotonergic systems are important. [6]

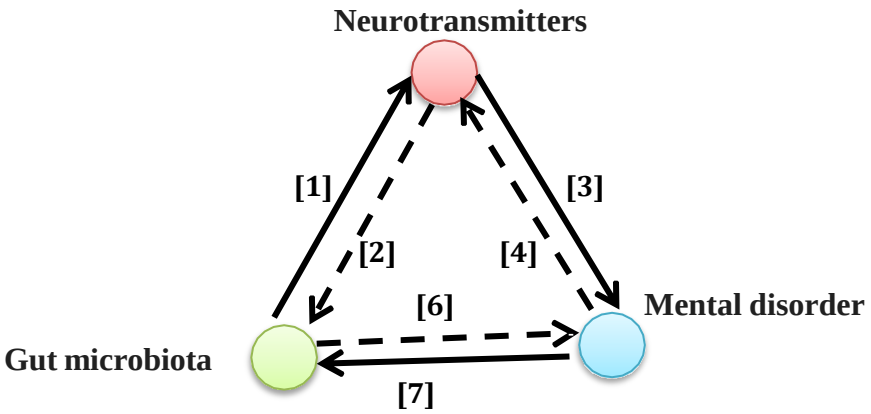

Fig no: - 01 Triangle relationship bet^{n} gut microbiota, neurotransmitters and mental disorders (1-Modulate level, 2- Affect growth, 3- Interruptions, 4-Imbalance, 5- Overgrowth of harmful, 6-Composition changes)

In the fig no 01 triangle relationship between gut microbiota, neurotransmitters and mental disorders. Gut microbiota modulates the level of neurotransmitters and conversely neurotransmitters affect the growth of gut microbiota. Disturbance of neurotransmitters involved in the mental problems and conversely mental disorders cause an imbalance of neurotransmitters in host. Mental disorder causes an overgrowth of bad microbiota and conversely changes the composition of gut microbiota cause mental disorders

The cocaine and amphetamine regulated transcript (CART) peptides are among the newest putative peptide neurotransmitters. It recently has been hypothesized to be an interesting neuropeptide that might be relevant to the treatment of depression. Brain-enriched neurotransmitter CART (cocaine- and amphetamine-regulated transcript) has multiple functions related to emotions. It is a potential neurotrophic factor and is involved in the regulation of hypothalamic-pituitary-adrenal axis and stress response as well as in energy homeostasis. CART is also highly expressed in limbic system, which is considered to have an important role in regulating mood. Notably, adolescents carrying a missense mutation in the CART gene exhibit increased depression and anxiety. Hence, CART peptide may be a novel promising antidepressant agent. [7]

CART performs an antidepressant effect through the regulation of certain cascades in the signal transduction pathway by modulating kinases, other neurotrophic factors and neurotransmitters such as BDNF, serotonin, dopamine, and GABA, respectively, resulting in increased neuronal survival and an alteration in the synaptic plasticity positive to a treatment of depression.(2)CART also enhances mitochondrial activity by acting as a partner of the key mitochondrial enzyme SDH, therefore CART increases cellular energy in the treatment of debilitating depression.(3)CART may regulate the HPA-axis feedback loop through the regulation of corticotropin-releasing factor (CRF or CRH), some pituitary corticotropes and adrenal hormones, at least partly via its transcription activity.

Effect of the various neurotransmitters and chemicals on Depression and anxiety

1. **Cytokine**

Activation of peripheral inflammatory responses were related to mood and anxiety problems and that peripheral immune activation can spread to the CNS, there has been tremendous interest within the effect of cytokines and their signaling pathways on neurotransmitter systems regarded to be associated with despair and tension along with serotonin, norepinephrine, dopamine and glutamate. From the fig.no 02 bottom left: Negative health behaviour's such as poor dietary habits, stress, and a sedentary lifestyle could trigger and/or enhance inflammatory responses. Below, we discuss two potential mechanisms mediating the effects of such behaviour's on inflammation; increased dietary n-6/n-3 ratio and dysbiosis. Subsequent pro-inflammatory signaling may trigger oxidative stress and lead to alterations in dopamine release, reuptake and synthesis. This in turn may generate symptoms of psychomotor retardation and motivational anhedonia, further reinforcing a state of

sickness behavior, and may induce, enhance, or maintain depression and more negative health behaviors. Abbreviations: omega-6 (n-6), omega-3 (n-3), arachidonic acid (AA), lipopolysaccharide (LPS), mitogen-activated protein kinases (MAPK).

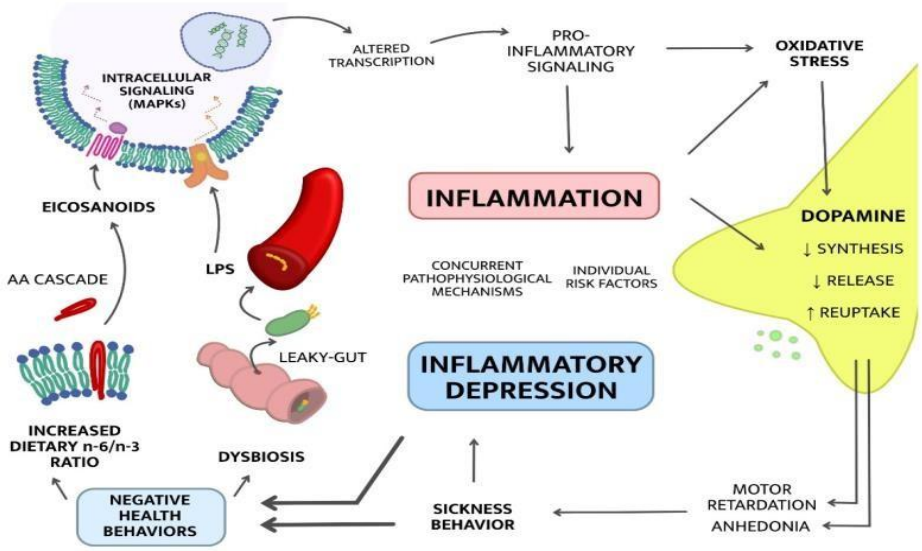

Fig no: - 02 Hypothetical model of bidirectional interactions between systemic low-grade inflammation and depression.

Results on neurotransmitter metabolism, inflammatory cytokines have profound stimulatory effects on HPA axis hormones in addition to CRH (mRNA and protein), in both the hypothalamus and the amygdala, a mind location that has a crucial position in worry and anxiety. These effects are, in huge element, mediated with the aid of a wealthy network of cytokines and their receptors inside HPA axis tissues which facilitate the integration of cytokine signals. Downstream cytokine signal transduction pathways, which include mitogen-activated protein kinases (MAPKs) and nuclear thing κB (NF-κB), also disrupt glucocorticoid receptor signaling, and for that reason may contribute to altered glucocorticoid-mediated feedback regulation of both CRH and further proinflammatory cytokine release. In addition, activation of p38 MAPKs would possibly make contributions to alterations in neurotransmitter function thru results at the serotonin transporter. [8]

2. Serotonin

A hyperlink among diminished serotonin and depression became first recommended within the 1960s, and broadly publicised from the 1990s with the arrival of the Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants. [9] Fourteen various kind of serotonin receptors had been identified, with maximum research on depression focusing on the 5-HT1A receptor. In fig no 03 mechanism of serotonin reuptake are explained but functions of different 5-HT receptors and their dating to depression have now not been well characterized, we limited our evaluation to facts on 5-HT1A receptors. 5-HT1A receptors, called auto-receptors, inhibit the discharge of serotonin pre-synoptically; consequently, if depression is the result of decreased serotonin activity due to

abnormalities inside the 5-HT1A receptor, humans with depression would be predicted to show extended interest of 5-HT1A receptors in comparison to the ones without. [10]

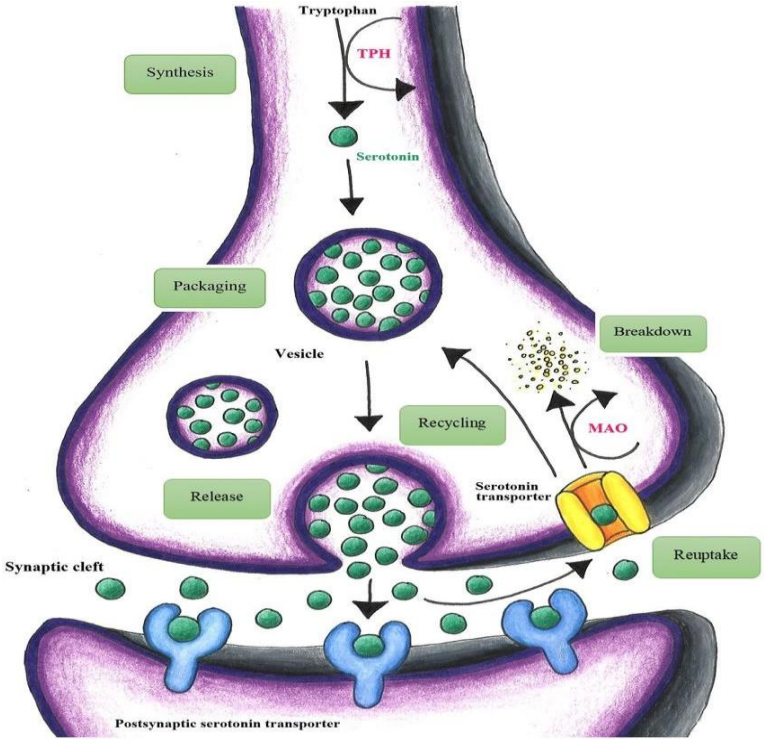

Fig no: - 03 the serotonin theory of depression

To evaluate the position of serotonin function in the improvement of panic anxiety, the behavioral and biochemical responses to the serotonin receptor agonist, m-chlorophenylpiperazine (MCPP) become tested in healthy topics and agoraphobic and panic ailment sufferers. MCPP had anxiogenic consequences in both the wholesome subjects and patients. [11]

The treatment of depression in senile patients with dementia is difficult with the drugs used formerly. The effects of a new anxiolytic drug, tandospirone, were investigated on depression symptoms in nine senile patients with dementia using Hamilton Depression Rating Scale (HAM-D) items. Tandospirone improved the symptoms, especially the depressive mood, agitation and anxiety, although a slight gastrointestinal symptom was found in one patient. The findings in the present study may suggest that tandospirone is a useful and comparatively safe drug for depression symptoms in senile patients with dementia. [12]

The selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline, paroxetine, citalopram, and escitalopram are contributors of the frontline class of antidepressant remedies and exert their number one pharmacological results through manipulation of the 5-HT gadget. Previous to the introduction of SSRIs, depression changed into dealt with using tricyclic pills which inhibit the reuptake of monoamines or monoamine oxidase inhibitors (MAOIs) which inhibit their enzymatic degradation. By comparison with these older pills, SSRIs have become clinically a success due to

the fact they reduced the frequency and severity of facet effects that were probably harmful and often required sufferers to withdraw from treatment. [13]

The serotonin transporter protein (SERT) transports serotonin out of the synapse, thereby decreasing the supply of serotonin within the synapse. Animals with an inactivated gene for SERT have better levels of extra-mobile serotonin within the mind than normal and SSRIs are thought to paintings by way of inhibiting the movement of SERT, and hence growing degrees of serotonin within the synaptic cleft. Despite the fact that modifications in SERT may be a marker for other abnormalities, if depression is because of low serotonin availability or hobby and if SERT is the foundation of that deficit, then the amount or pastime of SERT might be expected to be better in humans with melancholy as compared to those without. [14]

The dorsal raphe nucleus (DRN) innervates dopaminergic structures such as the corpus striatum and frontal cortex, both involved with motor activities. The median raphe nucleus (MRN) on the other hand innervates areas of the brain that are involved with sensory information and memory processing, for example the medial temporal lobe and the hippocampus. It is postulated that these serotonergic projections modulate different coping responses to acute and chronic aversive events. Acute events can be subdivided into proximal and distal events, according to how imminent the threat is. (Deakin JFW 1998) Experimental proof has cautioned that the irrelevant and immoderate activation of DRN-5-HT2 pathways performs a crucial function in anticipatory tension and within the pathogenesis of generalised tension disorders. Anxiolytic capsules were shown to decrease functioning in this system and experimental studies in volunteers display that 5-HT2 blockers and 5-HT2 agonists have the predicted effect on conditioned anxiety. [15]

Even though many serotonin (5-hydroxytryptamine; 5-HT) receptors had been recognized, our understanding of many of the subtypes is limited. But, we do understand that 5-HT1A agonists are concerned within the treatment of positive anxiety problems, that 5-HT1C and five-HT2 receptor antagonists can be indicated for the remedy of generalized anxiety ailment, and that five-HT1D receptor agonists are used within the remedy of migraine. Current research has recognized that various abnormalities in serotonergic characteristic are worried inside the pathogenesis of depression and anxiety, and has facilitated the improvement of new pharmacological sellers with superb therapeutic capability, for instance the selective serotonin reuptake inhibitors (SSRIs). These agents appear to be effective inside the treatment of many tension states and can have more efficacy than other agents inside the treatment of positive affective issues. As the critical serotonergic device continues to be "mapped", more recent and greater selective drugs are probably to be introduced, thereby likely improving the overall successful management of depression and anxiety disorders. [16]

Meta-chlorophenylpiperazine (mCPP), a 5-HT agonist with moderate affinity for 5-HT_2, 5-HT_{IC}, and a somewhat weaker affinity for 5-HT_{ID}, sites, [17] has been reported to produce elevated mood

in normal volunteer. There is, however, little evidence that other 5-HT agonists, e.g. buspirone (a 5-HT,, agonist), or MK-212, a 5-HT agonist with effects on various subtypes of 5-HTI and 5-HT, receptors, can produce elevated mood in normal controls or depressed patients (Meltzer, unpublished data). Charney et a1.I' reported a mood elevating effect of i.v. L-tryptophan in normals. However, Winokur et al. observed only sedative effects of an i.v. tryptophan load in normal subjects. [18]

Limitations of response to, current serotonine treatment strategies suggest an unmet need for efficacious, well tolerated treatments. Thus, from the various researches data it appears that blockade of noradrenergic and/or serotonergic activity may not be sufficient for optimal efficacy in some patients with MDD. A growing body of evidence exists to suggest that modulators of dopaminergic neurotransmission may have a role in the treatment of MDD. [19]

3. Dopamine

Dopamine (DA) is the most abundant catecholamine in the mammalian brain and is crucial for movement coordination, endocrine function, reward, mood, memory and emotions. [20] Symptoms of depression or anxiety are common in Parkinson's disease (PD) and are an important factor affecting quality of life. Treating symptoms of depression can improve not only mood but also physical symptoms, disability, and cognitive symptoms. Currently, dopamine agonists are recommended as an alternative to antidepressants in the treatment of Parkinson's disease depression. [21]

With regard to other catecholamines such as noradrenaline and dopamine, findings from various post-mortem brain studies and CSF studies in depressed patients have not been uniform. However, there has been one relatively consistent finding: reduced homovanillic acid (a primary dopamine metabolite) in CSF which suggests an important role of dopamine in the pathophysiology of depression.

A specific receptor for D9 -THC – termed cannabinoid type 1 (CB1) receptor – was identified in the brain, enabling the identification of the endogenous ligands in mammals, called endocannabinoids. As numerous investigations evidenced a role for endocannabinoids in anxiety- and depression-related behaviours in rodents. [22] CB1 receptors are widely distributed in the central nervous system, located mainly in presynaptic terminals of neurons. Brain regions with high CB1 receptor expression include the hippocampus, amygdala, prefrontal cortex, hypothalamus and basal ganglia.5 the presence of CB1 receptors in these structures explains why cannabis induces effects such as motor impairment, amnesia, and changes in mood and anxiety. [23] Endocannabinoids are synthesized 'on demand' at post-synaptic sites of neurons after increase in neural activity and calcium ion influx, and are then released into the synaptic cleft. Their main function appears to be the suppression of neurotransmitter release from the presynapse. [22]

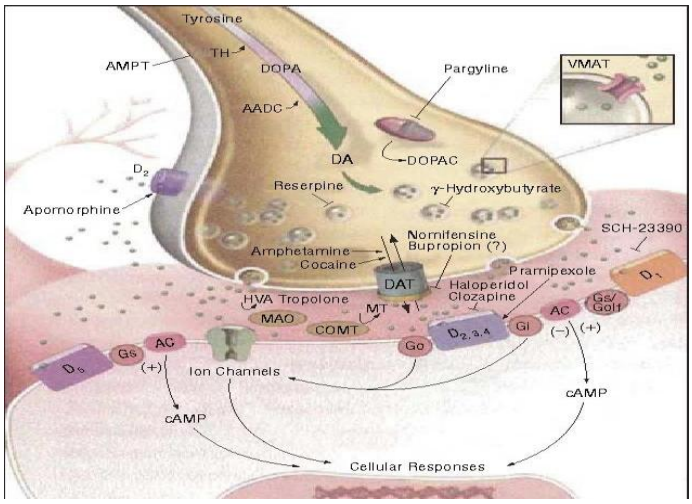

Fig no: - 04 Dopaminergic synaptic signalling.

In figure no. 04 AADC indicates aromatic acid decarboxylase; AMPT, alpha-methylparatyrosine; AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; COMT, catechol-O-methyltransferase; D1-D5, dopamine receptors 1 through 5; DA, dopamine; DAT, dopamine transporter; DOPA, 3,4-dihydroxyphenylalanine; DOPAC, dihydroxyphenylacetic acid; Gi, Go, and Gs, protein subunits; HVA, homovanillic acid; MAO, monoamine oxidase; MT, 3-methoxytyramine; TH, tyrosine hydroxylase; and VMAT, vesicular monoamine transporter.

Clinical studies have reported that CB1 receptor antagonism may lead to symptoms reminiscent of depression and anxiety related disorder. Further understanding the functioning of the endocannabinoid system will hopefully provide new therapeutic avenues that may avoid these psychiatric side-effects.

4. Adenosine

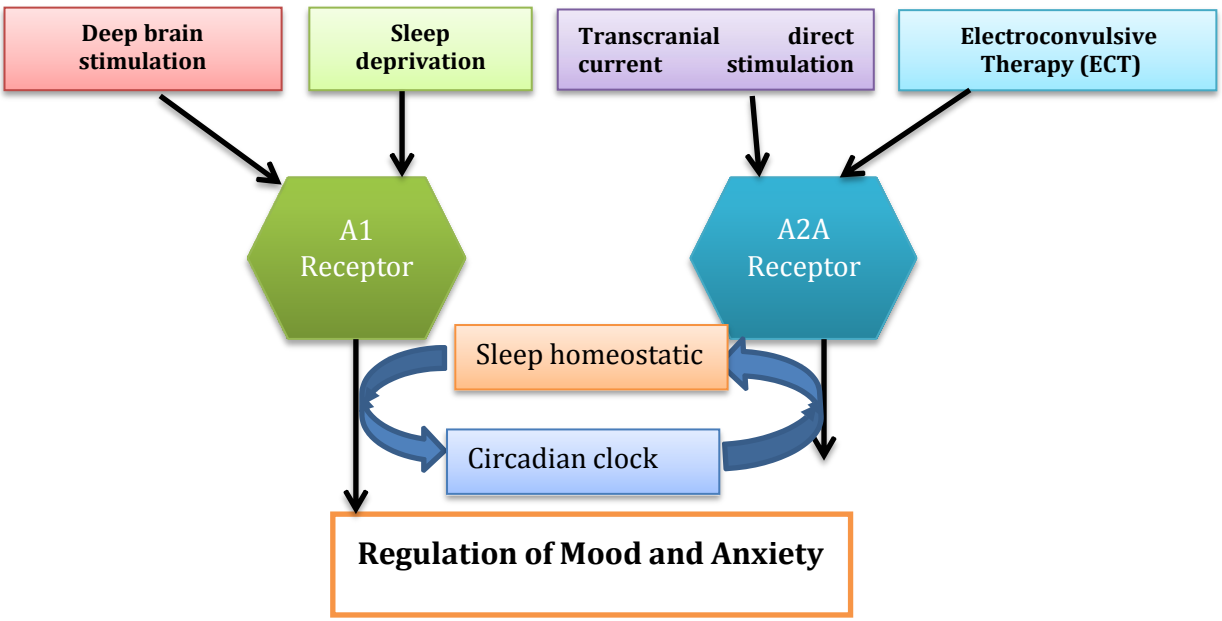

Fig no: - 05 the role of adenosine receptors in mood and anxiety disorders

In the fig no 05 explained that in brain, Adenosine receptors limit potentially dangerous over excitation, but also regulate mechanisms essential in sleep and psychiatric disorders. The role of adenosine receptors in mood and anxiety disorders is activation of A2A receptors is associated with increased depression-like symptoms, while increased A1 receptors signaling elicits rapid antidepressant effects. (Dietrich v. Knut B et.al. 2019)

5. Melatonin

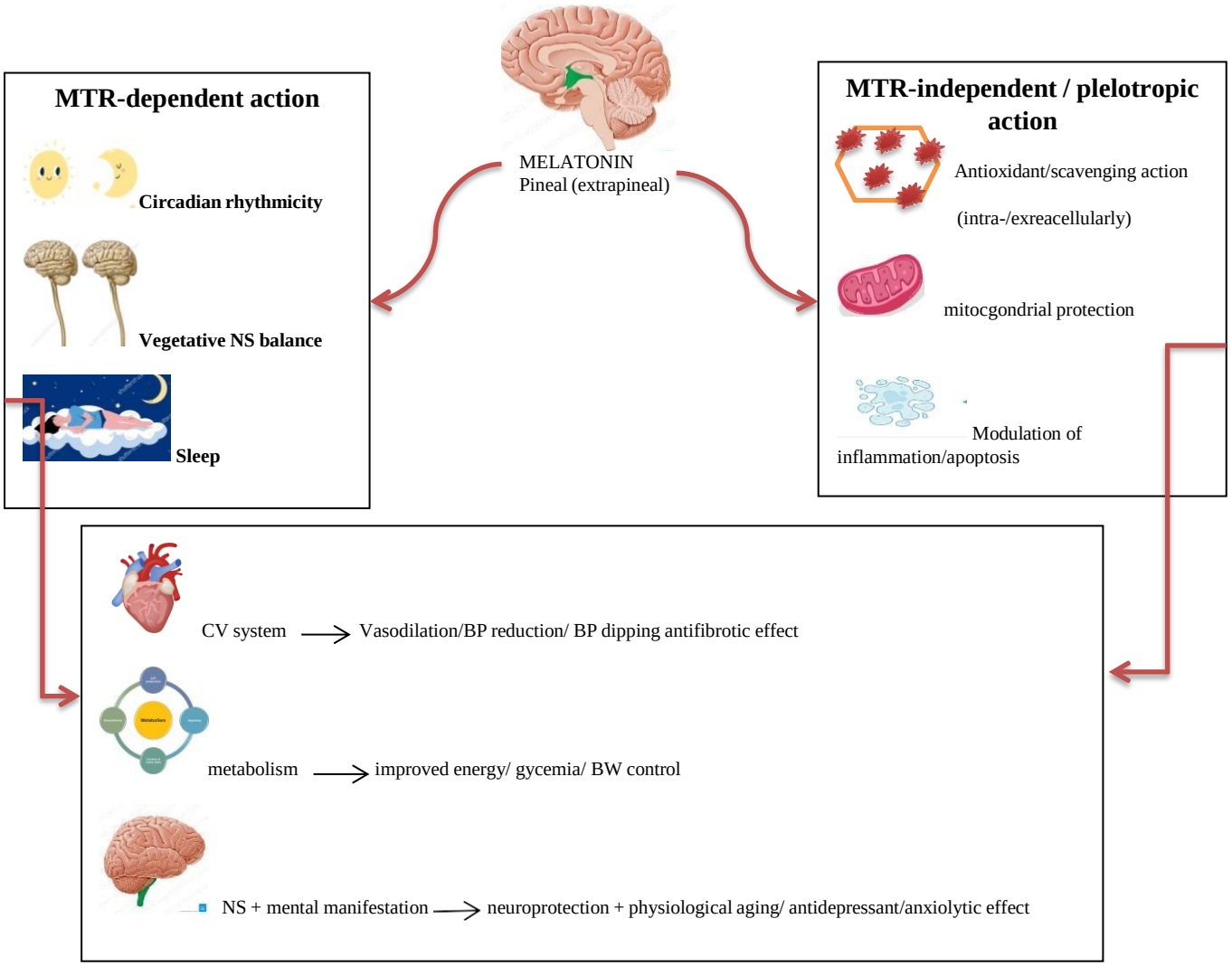

Fig no: - 06 Receptor-dependent and receptor-independent effects of melatonin.

In fig no 6, Melatonin is a neurohormone primarily synthesized by the pineal gland following a circadian rhythm with a high level during the night and a low level during the day. Alterations in the synthesis and secretion of melatonin have been reported in various mood disorders, including major depressive disorder. [24] The complex relationships between the endogenous circadian pacemaker and the development of depressive symptoms are far from being elucidated. The worsening of diurnal mood variation (DMV) with the early morning is a classic symptom of melancholic features of MDD and is one of the time-linked symptoms that have promoted speculation about the role of the circadian system in its pathogenesis. MDD seems to be related to a

disruption in the central circadian clock function and not to an alteration in a specific rhythm. In addition, the type of rhythm abnormality seems to be highly variable in depressed patients, including phase advance or phase delay of rhythms and increase or decrease in the rhythm amplitude. [25]

6. Neuropeptide

Neuroendocrine studies suggest that regulation of the hypothalamic-pituitary-adrenocortical (HPA) system plays an important role in development and depression. Neuropeptides are released by neurons as signalling molecules. [26] These signalling molecules affect the neurotransmitters or modulators of excitable cells. Therefore, neuropeptides are not only found in neurons; it also joins the cell and affects other cells by interacting with receptors with greater affinity. Neuropeptides are found in the brain and the environment. For example, corticotropin-releasing hormone is found in the endocrine and nervous systems and plays a role in regulating stress behavior. Currently, more than a hundred neuropeptides have been recognized and studied. Various methods have been proposed to classify different neuropeptides. For instance, neuropeptides are grouped into the following categories:

1. Gut-brain peptides (Substance P, Cholecystokinin, Galanin, Neuropeptide Y)
2. Hypothalamic releasing hormones (Corticotropin-releasing hormone, Melanin-concentrating hormone)
3. Pituitary hormones (Vasopressin, Adrenocorticotropic hormone)
4. Opioid peptides (Met-enkephalin, Leu-enkephalin, α-endorphin, Dynorphin)
5. Miscellaneous neuropeptides (Bradykinin) (Tarapati R. Tapan B.et.al.2022)

6.1 Vasopressin (VP) & Oxytocin

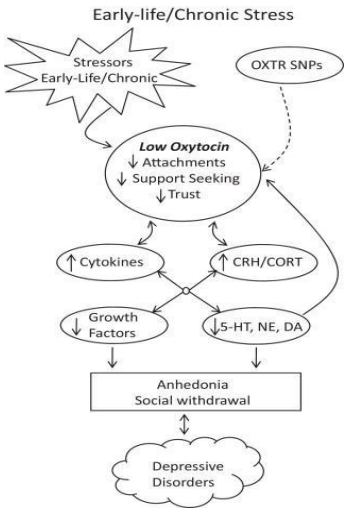

Fig no: - 07 A schematic depiction of the hypothesized interactions between oxytocin and other neurochemical and hormonal systems in response to an acute stressor.

Hypothesized interactions between oxytocin and other neurotransmitters are explained in the fig no 07 that Stimuli apprised as being stressful, as well as inflammatory cytokine challenges, elicit oxytocin and CRH release. In turn, oxytocin has inhibitory effects on both CRH and cytokine activity. Although stressors elicit growth factor variations, it is still unclear how oxytocin and neurotrophic factors interact (dashed line). In addition, oxytocin can elicit release of monoamines, and these neurotransmitters can have reciprocal effects to promote oxytocin release. Finally, stressor provoked oxytocin release may promote trust and affiliative behaviors as a compensatory mechanism aimed at attenuating stress responses. PFC = prefrontal cortex; Hipp = hippocampus.

VP is a nine-amino acid neuropeptide whose synthesis occurs mainly in the supraoptic nucleus and PVN of the hypothalamus, although significant amounts of VP are also found in the limbic region. Oxytocin and vasopressin are mediators of anxiety, stress-coping, and sociality. They are released independently from dendrites, axons and perikarya in the hypothalamus and limbic region or in cooperation with secretion from neurohypophyseal terminals. While central oxytocin exerts anxiolytic and antidepressant effects, vasopressin is prone to anxiolytic and antidepressant effects. Evidence from pharmacological and genetic studies confirms their involvement in individual differences in emotions and, by extension, psychopathology. Based on their negative effects on emotional behavior, we speculate that balanced activity of the two brain neuropeptides is important for appropriate behavior. Shifting the balance of the neuropeptide system to oxytocin through social stimulation and/or psychotropic medications may help improve emotional and mental health. [27]

6.2 Corticotrophin releasing factor

CRF is hyper secreted from hypothalamic as well as from extra hypothalamic neurons in depression, resulting in hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and elevations of cerebrospinal fluid (CSF) concentrations of CRF. This increase in CRF neuronal activity is also believed to mediate certain of the behavioural symptoms of depression involving sleep and appetite disturbances, reduced libido, and psychomotor changes. [28] In response to acute physical or psychological stress parvocellular neurons of the paraventricular hypothalamus PVN produce increased amounts of corticotropin releasing hormone which is released into portal vessels activating secretion of corticotropin (ACTH) from anterior pituitary cells In turn ACTH enters the circulation and elicits glucocorticoids from the adrenal gland. This rapid HPA activation can be life sustaining because of the metabolic effect of elevating blood glucose levels however other stress related responses needed for life sustaining adaptations encompass a number of behavioural reflexes elicited by activation of the HPA system presumably by an increase in CRH release.

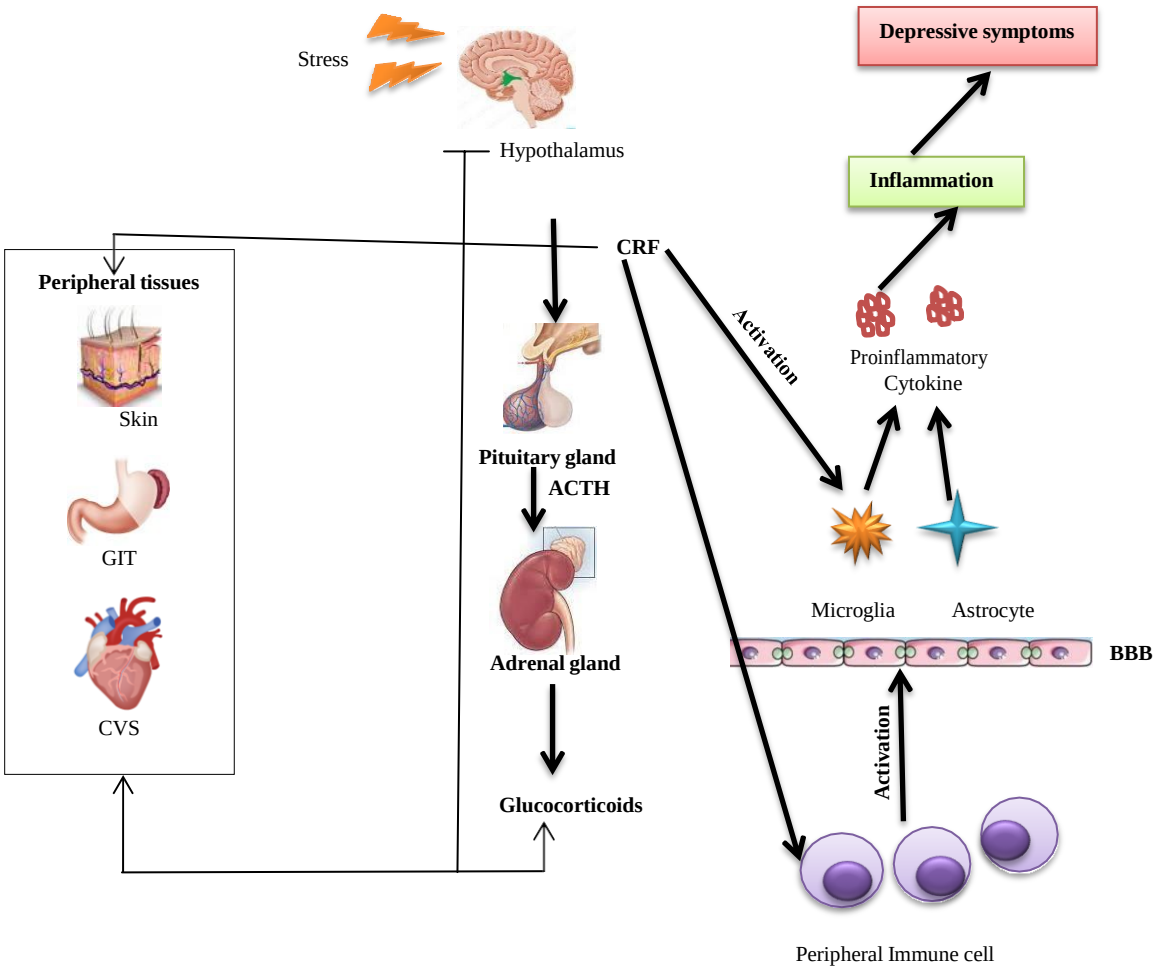

Fig no: - 08 CRF regulation of the endocrine and immune system in depression.

In the fig no. 8 CRF mediates the activity of the HPA axis and the neuroimmune system. It also exerts regulatory effect on other peripheral tissues such as skin, gastrointestinal tract and cardiovascular system. Chronic exposure to stress results in CRF hypersecretion and HPA axis hyperactivity. Elevated CRF level stimulates the production of pro-inflammatory cytokines by peripheral immune cells; these peripheral cytokines can cross the blood-brain barrier and activate astrocytes and microglia in the CNS. CRF can also directly activate astrocytes and microglia. The activated astrocytes and microglia secrete more pro-inflammatory cytokines. These astrocytes- and microglia-derived cytokines have a broad effect on the CNS, drive neuroinflammation and produce depression-like behavioral alterations. [29]

Data show that depression is characterized by activation of the central CRH system and hyperactivity of the pituitary-adrenal (HPA) axis. Atypical depression is characterized by hypoactivity of the central CRH system and accompanying hypoactivity of the hypothalamic-pituitary-adrenal axis. [30]

6.3 Substance P

Substance P (SP) is one of the most abundant peptides in the central nervous system and is involved in many physiological and pathophysiological processes, including the regulation of

stress, mood and anxiety, and highly reason-oriented behaviour. Studies show that P-like neurokinin-1 (NK1) receptors are highly expressed in brain regions important for regulating emotional behaviour and neurochemical responses to stress. [31] This classification provides many opportunities for interactions between substance P and the convergent norepinephrine and serotonin pathways of existing antidepressant drugs and suggests that substance P antagonists may play a role in mental illness. Some norepinephrine- and serotonin-containing cell bodies also coexpress P, providing an opportunity for direct neuronal modulation. [31]

6.4 Galanin

Galanin (GAL) is a neuropeptide widely distributed in neurons within the central nervous system. Three GAL receptor ($GAL_{1–3}$ receptors) subtypes with high affinities for GAL have been cloned. The $GAL_{1–3}$ receptors are involved in a number of central functions modulating neuroendocrine levels, pain control, cardiovascular functions, addiction, and food intake. GAL is also involved in mood regulation, including depression-related and anxiety-like behaviours.

6.5 Kappa-opioid receptors

Growing evidence suggests that kappa-opioid receptors (KORs) in the brain and dynorphin, an endogenous ligand that binds to these receptors, play a role in the regulation of motivation and emotion. These findings increased interest in the development of KOR-targeting ligands as therapeutic agents. For example, KOR antagonists may have a broad indication, including the treatment of depression, anxiety, and addiction, as well as conditions resulting from comorbidities of these diseases (e.g., post-traumatic stress disorder [PTSD]). [32])

There is accumulating evidence that brain kappa-opioid receptors (KORs) play an important role in transducing the effects of stress. Activation of KORs produces aversive and depressive-like states in humans and in laboratory animals. Stress and CRF are blocked by selective KOR antagonists who are consistent with other evidence that these agents have antidepressant-like and anxiolytic-like effects, including attenuation of fear-potentiated startle.

Treatment

The widely used tricyclic compound imipramine and the antituberculosis drug iproniazid were early treatments that effectively treated depression. Both drugs cause elevation of extracellular monoamine levels by either blocking monoamine oxidase (MAO) (like iproniazid) or by inhibiting the neuronal serotonin and/or noradrenaline transporter (like imipramine and its active metabolite desipramine). Later, the introduction of selective serotonin reuptake inhibitors (SSRIs such as fluoxetine) drove the “monoamine deficiency” hypothesis. Interestingly, serotonin is thought to regulate neurodevelopmental processes through maternal-fetal interactions that have long-term mental health implications, and recently, it has been discovered that there is a placental serotonin synthetic pathway from a maternal tryptophan precursor in both mice and humans. [33]

The recent global pandemic of COVID-19 has dramatically increased the incidence of depression

and has significantly increased the burden of mental health care worldwide. Since full remission of the clinical symptoms of depression has not been achieved with current treatments, there is a constant need to discover new compounds that meet the major clinical needs. Recently, the roles of sigma receptors, especially the sigma-1 receptor subtype, have attracted increasing attention as potential new targets and target-specific drugs due to their translocation property that produces a broad spectrum of biological functions. Even clinical first-line antidepressants with or without affinity for sigma-1 receptors have different pharmacological profiles. Thus, the regulatory role of sigma-1 receptors might be useful in treating these central nervous system (CNS) diseases. [34]

Discussion

This review summarizes the impacts of various neurotransmitters in anxiety and depression. Based on the data gathered to date, there is strong evidence that there is a link between depression and anxiety disorders with respect to various neurotransmitters and various chemicals. In general, the three mono-aminergic neurotransmitter systems are mutually interacting, each playing roles in the regulation of diverse human emotions. Depression and anxiety may be directly caused by dysfunction in brain areas including hippocampus, amygdala, and the prefrontal cortex. There is a clear dysregulation of various neurotransmitter activities contributing to these illnesses. The decrease in GABA+ concentrations may mediate the relationship between structural and functional alterations in the brain and depression scores. It has been found that GABA+ plays a role in the relationship between the gut microbiota and the central nervous system. Several studies indicate that effects of stress may be better related to localize than global changes within neurotransmitter systems.

Conclusions

Comorbid depression and anxiety are common and affect up to a quarter of patients attending general practice. In general, the three mono-aminergic neurotransmitter systems are mutually interacting, each playing roles in the regulation of diverse human emotions. Depression and anxiety may be directly caused by dysfunction in brain areas including hippocampus, amygdala, and the prefrontal cortex or by the neural systems modulated by mono-amine neurotransmitter systems in these brain regions.

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