IJPSR (2015), Vol. 6, Issue 7 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 October 2014; received in revised form, 03 February, 2015; accepted, 25 February, 2015; published 01 July, 2015

NEUROPHARMACOLOGY OF DEPRESSION: A REVIEW

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Keywords:

Depression, stress, cytokine, GABA, glutamate, monoaminergic transmitters, omega-3 fatty acid, T-cell, β-endorphine, synaptic plasticity, endocrine system and endocannabinoids.

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ABSTRACT: The selected theories are based on studies investigating the possible role of stress hormones and cytokine; gamma-aminobutyric acid (GABA); glutamate; monoaminergic transmitters such as serotonin, norepinephrine, dopamine; omega-3 fatty acid; T-cell; β-endorphine; synaptic plasticity; endocrine system and endocannabinoids in the pathophysiology of depression. Because all theories of depression apply to only some types of depressed patients but not others, and because depressive pathophysiology may vary considerably across the course of illness, the current extant knowledge argues against a unified hypothesis of depression. As a consequence, antidepressant treatments, including psychological and biological approaches, should be tailored for individual patients and disease states. Individual depression hypotheses based on neurobiological knowledge are discussed in terms of their interest to both clinicians in daily practice and clinical researchers developing novel therapies.

INTRODUCTION: Major depressive disorder (MDD) is a common and costly disorder which is usually associated with severe and persistent symptoms leading to important social role impairment and increased mortality [1, 2]. It is one of the most important causes of disability worldwide [3]. The high rate of inadequate treatment of the disorder remains a serious concern [1]. The World Health Organization (WHO) defines depression as a common mental disorder characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration [4].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(7).2696-08

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(7).2696-08

Affective disorders (depression) are recurrent and life threatening mental illness with high morbidity and mortality. The WHO estimates that depression is now the fourth most important cause worldwide of loss in human disability adjusted life years, and predicts that it will be the second by the year 2020. Although pharmacotherapy of depression includes a battery of drugs; their efficacies are unsatisfactory, they exert multiple unwanted side effects and also their antidepressant mechanism remains not clearly understood [5].

This review is aimed at summarizing the solid evidence on the etiology and pathophysiology of MDD.

Stress hormones and cytokines:

Corticotropin-releasing hormone (CRH) is released from the hypothalamus in response to the perception of psychological stress by cortical brain regions. This hormone induces the secretion of

pituitary corticotropin, which stimulates the adrenal gland to release cortisol into the plasma. The physiologic response to stress is partly gender-specific: women show generally greater stress responsiveness than men, which is consistent with the greater incidence of major depression in women [6]. Moreover, men show greater cortisol responses to achievement challenges, whereas women show greater cortisol responses to social rejection challenges [7]. Altered stress hormone secretion appeared to be most prominent in depressed subjects with a history of childhood trauma [8].

Elevated cortisol may act as a mediator between major depression and its physical long-term consequences such as coronary heart disease, type II diabetes, and osteoporosis [9]. The Hypothalamic pituitary axis (HPA) is regulated through a dual system of mineralocorticoid (MR) and glucocorticoid (GR) receptors. Decreased limbic GR receptor function [10, 11] and increased functional activity of the MR system [12] suggest an imbalance in the MR/GR ratio in stress-related conditions such as MDD. Epigenetic regulation of the glucocorticoid receptors has been associated with childhood abuse [13].

There is convergent evidence for CRH to play a major role in the pathogenesis of certain types of depression. Levels of CRH in the cerebrospinal fluid are elevated in some depressed subjects [14]. Post-mortem studies reported an increased number of CRH secreting neurons in limbic brain regions in depression [15], likely reflecting a compensatory response to increased CRH concentrations [16]. In addition, CRH produces a number of physiological and behavioral alterations that resemble the symptoms of major depression, including decreased appetite, disrupted sleep, decreased libido, and psychomotor alterations [17].

GABAergic transmission in depression:

γ-aminobutyric acid (GABA) transmission is present in interneuron's modulating local neuronal circuitry, including noradrenergic, dopamine and serotonin neurons. The potential role of GABAergic function in mood disorders was first proposed by based on efficacy of valproate, in the treatment of bipolar patients [18]. After Emrich's hypothesis, several animal and human studies have evaluated the potential role of GABAergic abnormalities in the pathophysiology of mood disorders [19]. Functional studies reported that the administration of vigabatrin, which increases brain GABA levels, inhibiting decreased the mesocortical dopamine release in mammalian animals and decreased D_2 receptor binding in human basal ganglia [20, 21, 22]. GABA may also activate the dopaminergic system, depending upon brain region and the duration of GABA stimulation [23]. It has been reported that musimol, which is a GABA agonist, may reduce the immobility time in the behavioural despair model of depression by activating the rat dopaminergic system, and that GABA may enhance dopamine release in rat striatum and frontal cortex [24, 25].

An important clue for the involvement of dopamine receptors in the regulation of GABA transmission comes from studies showing that D4 receptor, which is expressed at the highest levels in GABAergic neurons, modulates GABAergic signalling in prefrontal cortex [26].

The essential role of $GABA_A$ receptors in counteracting trait anxiety and depression-related behaviors, and research aimed at identifying individual $GABA_A$ receptor subtypes involved in physiological and pharmacological modulation of emotions [27].

GABA seems to decrease serotonin transmission. GABA agonists such as musimol or progabide and diproxylacetamide, a GABA-T inhibitor appeared to reduce the utilization rate and synthesis of 5-HT in rat brains, probably through GABA receptors located in the raphe nuclei [28, 29, 30, 31]. It has been reported that 5-HT release is increased by stimulation of GABA receptor in the suprachiasmatic areas [32].

It has shown that $GABA_{A/B}$ and $5\text{-}HT_{A/B}$ agonists decrease 5-HT and GABA release in the rat raphe nuclei, suggesting a reciprocal innervations between GABAergic and serotonergic neurons [33]. GABAergic transmission appears to be involved in the mechanism of action of antidepressant, mood stabilizers, and electroconvulsive therapy (ECT) in addition to benzodiazepines and newer antipsycotics (i.e.Olanzapine and clozapine) which

are tools used in the treatment of mood disorders [34, 35].

A series of magnetic resonance spectroscopy (MRS) studies consistently showed reductions in total GABA concentrations in the prefrontal and occipital cortex in acute depression [36]. This may reflect acute stress effects, since psychological stress seems to induce presynaptic down-regulation of prefrontal GABAergic neurotransmission [37]. Alternatively, low total GABA concentration may reflect reduction in the density and size of GABAergic interneurons [38].

Furthermore, clinical studies also highlight a loss of GABAergic interneurons in patients suffering from stress- related psychopatholgy e.g., depression [39] and a loss of GABAergic signals is apparent in imaging studies [40]. Another findings form clinical and preclinical studies have provided compelling evidence for an association between alterations in GABAergic transmission and stress-related psychiatric disorders including depression [41, 42, 43, 44, 45]. Abnormal GABA signalling in major depressive disorders was initially suggested following studies from the early 1980s that demonstrated reduced plasma and cerebrospinal fluid (CSF) levels of GABA in patients suffering from depressive disorders [46, 47], an observation subsequently confirmed by MRS studies of GABA levels [40, 48, 36]. Moreover, a reduction in the density of GABAergic interneurons has been reported in the cortex and amygdala of depressed patients [38, 39, 49].

Altered glutamatergic neurotransmission:

The serum levels of glutamate in patients with depression were significantly higher than those of healthy peoples [50]. There is a positive correlation between plasma glutamate levels and severity of depressive symptoms in patients with MDD [51]. Increased levels of glutamate in the frontal cortex implicate abnormality of glutaminergic neurotransmission as the pathophysiological features of MDD [52, 53]. The plasma levels of glutamate in patient with MDD is higher than in normal patients and significantly decreases after 5 weeks of treatment with antidepressants [54, 55]. The Proton MRS study revealed increase levels of glutamate in the occipital cortex of patients with MDD [48].

Novel therapeutic drugs are being developed targeting glutamate neurotransmission involved in depression e.g. Positive modulator of N-methyl-D-aspartate (NMDA) receptor: Non-competitive NMDA receptor antagonists such as ketamine have been demonstrated to have antidepressant effects in animal models of depression [56]. Several lines of evidence suggest a dysfunction of the glutamate neurotransmitter system in MDD: a single dose of the glutamate NMDA receptor antagonist ketamine produced rapid and large antidepressant effects in patients with treatment-resistant MDD [57]; inhibitors of glutamate release (e.g., lamotrigine, riluzole) demonstrated antidepressant properties [58]; abnormal glutamate levels were found in depressed subjects as determined by MRS [36]; and there is evidence for abnormal NMDA signaling in post-mortem tissue preparations [59]. Since glutamate is the major excitatory neurotransmitter involved in almost every brain activity, the characterization of the specific role of glutamate in depression deserves further investigation (e.g., there are promising leads that the metabotropic glutamate receptor 5 is specifically involved in MDD [60].

The mediating role of monoamines:

The first major hypothesis of depression was proposed that the main symptoms of depression are due to a functional deficiency of the brain monoaminergics transmitters norepinephrine, serotonin and/ or dopamine, whereas mania is caused by functional excess of monoamines at critical synapses in the brain [61, 62, 63].

The origin of noradrenergic, serotonergic and dopaminergic neurons in the brain and their projections into many areas of the brain, it is clear that monoaminergic systems are responsible for many behavioral symptoms, such as mood, vigilance, motivation, fatigue and psychomotor agitation and retardation. Abnormal function and the behavioral consequences of either depression or the manic state may arise from altered synthesis, storage or release of the neurotransmitters, as well as from disturbed sensitivity of their receptors or subcellular messenger functions [64]. Almost every compound that inhibits monoamine reuptake,

leading to an increased concentration of monoamines in the synaptic cleft, has been proven to be a clinically effective antidepressant [65]. Inhibiting the enzyme monoamine oxidase, which induces an increased availability of monoamines in presynaptic neurons, also has antidepressant effects. These observations led to the pharmacologically most relevant theory of depression, referred to as the monoamine-deficiency hypothesis.

The monoamine-deficiency theory posits that the underlying pathophysiological basis of depression is a depletion of the neurotransmitters serotonin, norepinephrine or dopamine in the central nervous system. Many attempts have been made to prove the hypothesis of reduced monoaminergics availability by measurements of neurotransmitter and/ or their metabolites in postmortem brain tissues and body fluids, such as cerebrospinal fluid (CSF), blood and urine [66]. Serotonin is the most extensively studied neurotransmitter in depression. The most direct evidence for an abnormally reduced function of central serotonergic system comes from studies using tryptophan depletion, which reduces central serotonin synthesis. Such a reduction leads to the development of depressive symptoms in subjects at increased risk of depression (subjects with MDD in full remission, healthy subjects with a family history of depression) [67, 68], possibly mediated by increased brain metabolismin the ventromedial prefrontal cortex and subcortical brain regions [68].

There is also evidence for abnormalities of serotonin receptors in depression, with the most solid evidence pointing to the serotonin- 1A receptor, which regulates serotonin function. Decreased availability of this receptor has been found in multiple brain areas of patients with MDD [69], however, there is no explanation for the mechanism of serotonin loss in depressed patients, and studies of serotonin metabolites in plasma, urine and cerebrospinal fluid, as well as post-mortem research on the serotonergic system in depression, have yielded inconsistent results. There is preliminary evidence that an increased availability of the brain monoamine oxidase, which metabolizes serotonin, may cause serotonin deficiency [70].

Dysfunction of the central noradrenergic system has been hypothesized to play a role in the pathophysiology of MDD, based upon evidence of decreased norepinephrine metabolism, increased activity of tyrosine hydroxylase, and decreased density of norepinephrine transporter in the locus coeruleus in depressed patients [71]. In addition, decreased neuronal counts in the locus coeruleus, increased alpha-2 adrenergic receptor density, and decreased alpha-1adrenergic receptor density have been found in the brains of depressed suicide victims post-mortem [72]. While the classical theories of the neurobiology of depression mainly focused on serotonin and norepinephrine, there is increasing interest in the role of dopamine [73].

Dopamine reuptake inhibitors (e.g., nomifensine) and dopamine receptor agonists (e.g., pramipexole) had antidepressant effects in placebo- controlled studies of MDD [74]. In the cerebrospinal fluid and jugular vein plasma, levels of dopamine metabolites were consistently reduced in depression, suggesting decreased dopamine turnover [75]. Almost all established antidepressants target the monoamine systems [76].

PET and other imaging methods enabled *in vivo* study of neurotransmitter receptors and transporters in human brain. These imaging studies focused on serotonin (5-HT1A, 5-HT2A, 5-HT1B), dopamine and norepinephrine receptors, serotonin or dopamine transporters, monoamine oxidase A, and muscarinic acetylcholine receptor 2 [77]. The role of these receptors and transporters in pathophysiology of depression are discussed with respect to results of animal studies, genetic studies and alterations in inflammation, endocrine function, and neurocircuitry e.g., acetylcholine neurotransmission has been linked to the regulation of mood, sleep, and neuroendocrine functions [78].

Omega 3-fatty acid in depression:

The role of omega-3 fatty acids is important in the neurobiology and treatment of major depressive disorder. A number of investigations have found a decreased omega-3 fatty acid content in the blood of depressed patients [79, 80, 81, 82]. Omega -3 fatty acids are essential component of central nervous system membrane phospholipid-acyl chains and as such are critical to the dynamic structure of

neuronal membranes [83]. Docasahexaenoic acid (DHA) is continuously secreted by astrocytes, bathing the neuron in omega -3 fatty acids [84]. Deficiency of omega-3 fatty acids also results in a 30-35% reduction in phosphatidylserine (PS) content in rat brain cortex, brain mitochondria and olfactory bulb [85]. Fish oil supplemented to rats can increased PS composition of the cerebral membrane [86]. This is an interesting finding given research showing that PS has antidepressant activity in adults [87, 88]. PS can activates various enzymes including Protein kinase C, Na^+ K^+ ATPase and tyrosine hydroxylase as well as regulating calcium uptake. It is therefore suggested that altering PS in cerebral membranes can alter neurotransmission [86].

A number of studies have specifically examined the effect of an omega-3 deficient diet on dopamine and serotonin levels in animals. Animals on such a diet have a decreased dopamine levels in the nucleus accumbens (NA) reduction in the dopaminergic vesicles pool along with a 40-60% decrease in the amount of dopamine in the frontal cortex and increase in the NA, alterations similar to the animal models of depression [89, 90, 91].

The frontal cortex dopamine reductions may be due to abnormalities of storage within the presynaptic terminals. The vesicular monoamine transporter (VMAT2) is present on the presynaptic vesicles membrane and allows for dopamine entry and storage in the vesicles. In omega-3 deficient rats, the levels of VMAT2 are significantly decreased in the frontal cortex. In addition, the pre- and post-synaptic dopamine receptor D_2 receptor is decreased in the frontal cortex and dramatically increased in the NA, alterations reflective of protein and mRNA expression [92]. Interestingly, fish oil supplementation in rats leads to a 40% increase in dopamine levels in the frontal cortex as well as an increase in binding to the D_2 receptor. In addition, fish oil supplementation (15 times greater than previously suggested minimum requirements) caused a decrease in the activity of monoamine-oxidase B, an enzyme responsible for breaking down dopamine [93, 86].

In healthy adults, higher concentrations of plasma DHA predict higher cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5HIAA), a metabolite that reflects serotonin turnover, particularly in the frontal cortex [94]. Numerous studies link low CSF 5 HIAA with psychiatric conditions, including violent suicide attempts during depression [95]. As further evidence of the research domain's importance, the National Institutes of Health conducted a workshop on the links between omega-3 fatty acids and psychiatric disorders in 1998 [96].

In an another study, the researcher compared 36 subjects with major depression, 14 with minor depression, and 24 nondepressed patients. Those with major depression had a significantly higher ratio of arachidonic acid to eicosapentaenoic acid in both serum cholesteryl esters and phospholipids and a significantly higher omega-6/omega-3 ratio than did the nondepressed subjects and those with minor depression. Such subjects also had significantly lower alpha-linolenic acid and lower total omega-3 in serum cholesteryl esters and lower EPA in both serum cholesteryl ester and phospholipid fractions [97].

In a study extending these results, the study done with 34 in patients with major depression and 14 normal volunteers. Major depression was associated with lower EPA and total omega-3 levels and a higher omega-6/omega-3 ratio in cholesteryl esters and phospholipids [81]. However, in this study there was no significant effect of antidepressant treatment on any of the polyunsaturated fatty acids. The authors suggested that major depression is associated with a deficiency of omega-3 fatty acids (which may act as a trait marker) and a compensatory increase of monounsaturated fatty acids and omega-6 fatty acids in phospholipids.

T-cells in depression:

Some studies have focussed the role of activated innate immune response and inflammation in neuronal integrity and neuropsychiatric disorder including depression [98, 99]. Depression and stress are associated with decrease in the percent of lymphocytes as well as the percent of T-cells, respectively [100]. One possibility that might explain increased T cell apoptosis in depression, especially in the context of increased immune activation, is tryptophan depletion. A number of cytokines and

cytokine signalling pathways have been shown to activate the enzyme, indoleamine 2, 3 dioxygenase (IDO), which breaks down tryptophan into kynurenine [98, 101]. Both activation of IDO and kynurenine are associated with the development of depression [102, 103, 98]. Tryptophan is an essential proliferative stimulus for effector T cells, and in a tryptophan-deprived environment T cells undergo apoptosis [104, 105].

Another mechanism that has been considered regarding reduced T cell responses in major depression is inhibition of T-cell function by glucocorticoids. Glucocorticoids have multiple effects on immune responses including inhibition of inflammation, mediation of cell trafficking and induction of apoptosis in multiple immune cell types including T cells, especially developing T cells in the thymus [106]. In addition, increased peripheral blood concentrations of the glucocorticoids, cortisol, is a hallmark of major depression [107].

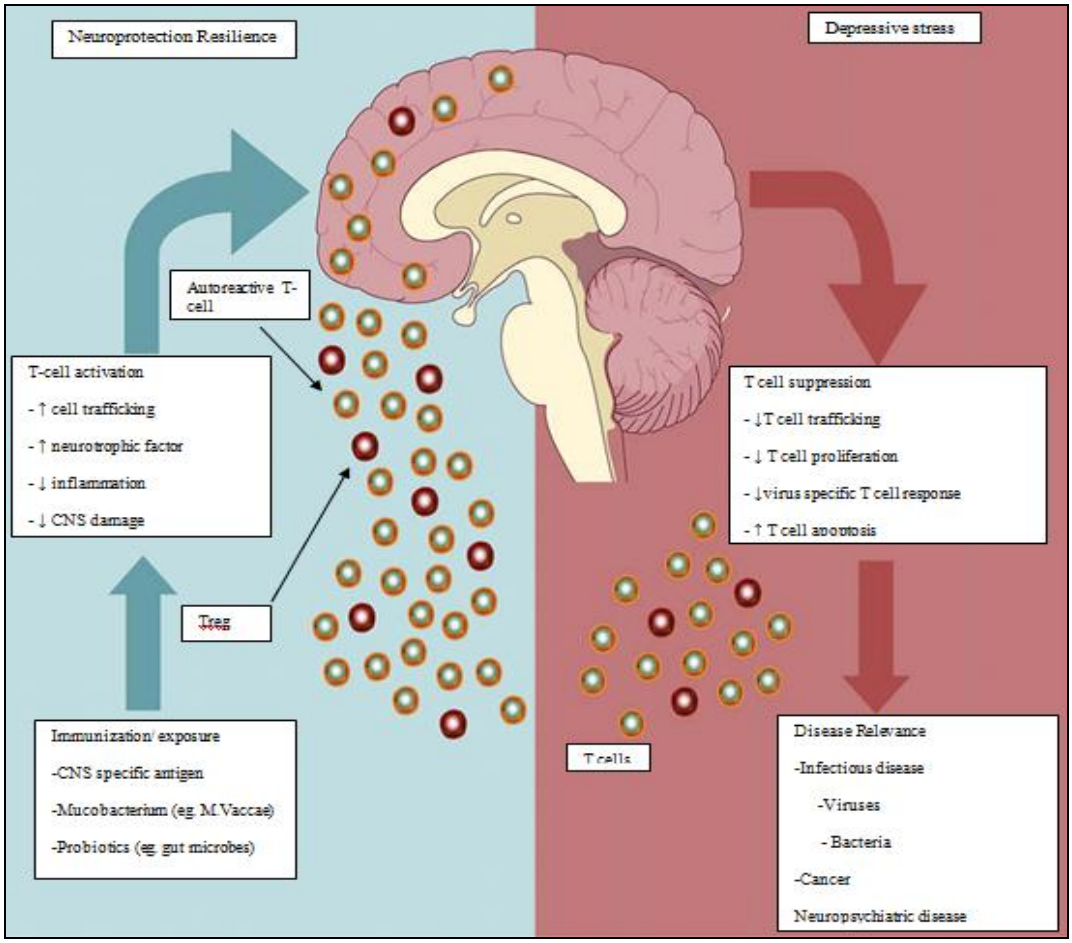

FIG. 1: BRAIN- T CELL INTERACTIONS IN HEALTH AND ILLNESS.

β-endorphin in depression

β-endorphin (β-END) is the most contributing endogeneous opioid, identified in etiology of MDD. Animal and humans research support, involvement of central opioid system in the pathophysiology of MDD. β-END has been the most studied and initials studies regarding β-END focused on peripheral and central transmission of pain stimuli and β-END's role on attenuation of nociception signalling. Increasing pain has become recognized as a very complex behaviour, encompassing sensory, affective and cognitive components [108]. Early reports suggested that β-END infusion had a temporary mood elevating effect in very small numbers of depressed patients [109]. Post-mortem evidence for increase in density of (μ) opioid receptor in the brain of depressed suicide victims [110] supports the hypothesis of β-END deficiency with a compensatory up-regulation of μ-opioid receptors in MDD [111]. Multiple opioids,

including β-END acting within specific brain region can modulate the information of memories and the regulation of emotional states [112]. Evidence supports that β-END influences processes related to reward and motivation, likely mediated though mesolimbic dopamine pathways [113, 114]. MDD is the female bias in the prevalence rates [115]. Animal studies have shown estrogen-induced changes in μ-receptor activity and density within limbic and hypothalamic nucleus [116].

The concept of synaptic plasticity in the pathophysiology of depression

Neurochemical imbalance underlies the pathophysiology of mood disorders. However, recent studies demonstrate that structural alterations also occur in response to stress and in patients with mood disorders [117, 118, 119]. Repeated stress is reported to cause atrophy of CA3 pyramidal neurons in the hippocampus, including a decrease in the number and length of apical dendrites [120]. In addition, exposure to acute stress decreases the proliferation of cells in dentate gyrus of the hippocampus [121]. Brain imaging studies demonstrated that the volume of the hippocampus is decreased in patients with depression or post-traumatic stress disorder [122]. There are also reports of alteration in cerebral cortex of patients with depression or bipolar disorder. These include a decrease in the volume of the subgenual prefrontal cortex and decrease in the number of neurons and glia [122, 123].

Administration of the antidepressant tianeptine is reported to block the atrophy of CA3 pyramidal neurones in response to long term stress [118, 120]. This effect was not observed with the 5-HT selective reuptake inhibitor like fluoxetine. Another reports demonstrate that antidepressant administration increase the proliferation of granule cell in hippocampus [118, 124].

Upregulation of cell proliferation has been observed with several different classes of antidepressant, including noepinephrine and 5-HT selective reuptake blockers indicating that it may be a common action of antidepressant. Antidepressant treatment is also reported to block the down regulation of neurogenesis that occur in response to stress [119]. These studies suggest that upregulation of neurogenesis could oppose the effect of stress and reverse the hippocampal atrophy that has been reported in depressed patients.

Endocrine process of depression

A variety of hormonal abnormalities, such as altered levels of cortisol, CRH, growth hormone or thyroid hormones indicate the existence of endocrine disturbances, especially dysfunction in HPA. The impaired corticosteroid receptor signalling is a key mechanism in the pathogenesis of depression [125]. Alterations in thyroid function have been repeatedly linked to depression and administration of Triiodothyronine (T_3) seems to be effective in the treatment for many patients [126, 127]. The relationship between thyroid hormone and neurotransmitters have mainly focused on the noradrenergic and serotonin system and it was shown that thyroid hormone application increase cortisol serotonin release and may act as cotransmitter to noradrenaline in the adrenergic nervous system [128, 129].

CRH is the principal mediator of the effects on the HPA axis and behaviour after stress [130]. Clinical studies demonstrated that this neuropeptide is implicated in depression and anxiety disorders [14, 16, 131]. Basic research studies have presented evidence that elevated central CRH levels are involved in the etiology of stress related physiological and behavioural disorder [122].

Estrogen is a potent neuromodulators and is known to alter the activities of multiple neurotransmitter system including those involved in MDD [132] as shown in **Fig. 2.**

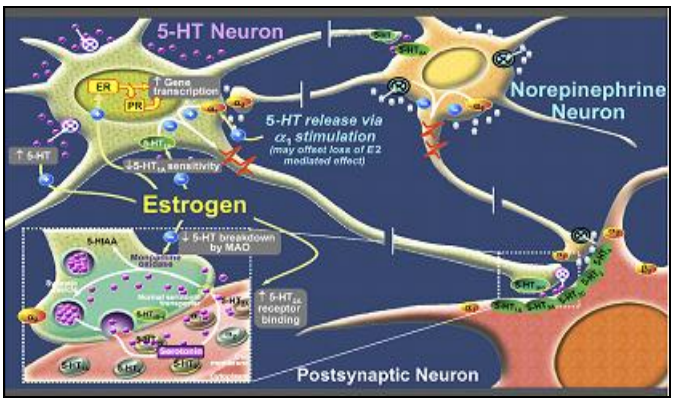

FIG.2: INTERACTIONS BETWEEN ESTROGENS, SEROTONIN AND NOREPINEPHRINE.

Endocannabinoids system and the hypothalamic-pituitary-adrenal axis in depression

Activation of the HPA axis by cannabinoids (CB) receptor has been observed in recent studies [133, 134, 135]. The CB receptor stimulated increase in corticotropin and cortisterone levels was attenuated by Rimonabent (selective CB1 receptor antagonist) [136, 137]. Cannabis dependence have been found to be associated with increase rates of psychotic and depressive system in addition to suicide attempts [138, 139, 140]. Besides cannabis an association among alcohol abuse, depression and suicidality has also been suggested [140, 141]. The deficient endocannabinoid signaling (disruptions in the signaling capacity of CB1 receptor) may produce a vulnerability to, or directly contribute to, the development of a depressive episode [142].

The endocannabinoid system is known to have positive effects on depression partly through its actions on neurotrophins, such as Brain-Derived Neurotrophic Factor (BDNF). As BDNF is also considered the major candidate molecule for exercise-induced brain plasticity [143].

Among the numerous of functions modulated by the endocannabinoid system [144], the control of emotions and the regulation of motivational behaviour appear to be of particular importance for the possible implication of this system in the pathogenesis of mental disorders such as drug addiction, depression, anxiety, and psychoses [145-149]. Studies aimed at investigating the role of the endocannabinoid system in the physiopathology of depression have demonstrated how both pharmacological activation of the endocannabinoid transmission [150] and blockade of CB1 receptors [151, 152] produce an antidepressant-like effect in animal models of depression that are predictive of antidepressant activity in humans.

Monoaminergic systems are regulated by CB1receptors by direct or indirect effects depending on their localization on monoaminergic, GABAergic, or glutamatergic neurons [153]. Inhibition of MAO by cannabinoids could contribute to their effect on monoaminergic systems [154,155].

Endocannabinoid signaling is an important stress buffer and modulates emotional and cognitive functions. Genetic polymorphisms in the human gene for CB1 receptor and fatty acid amide hydrolase (FAAH) have been found to contribute to occurrence of several mental disorders [156].

CONCLUSION: There are many theories of depression which suggest that depression is a clinically and etiologically heterogeneous disorder. There is no doubt that the monoaminergic system is one of the them, but any hypothesis for the pathophysiology of depression must take into account the many interactions with other brain systems and complexicity of the regulation of the CNS function. The discovery of antidepressant drugs and the investigation of their mechanism of action have revolutionized our understanding of neuronal functioning and possible mechanisms underlying depression.

ACKNOWLEDGEMENT: I would like to express my heartfelt thanks to my beloved parents for their blessings, encouragement, inspiration and everlasting love have helped me a lot for the successful completion of this review article.

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How to cite this article:
Khulbe A: Neuropharmacology of Depression : A Review. Int J Pharm Sci Res 2015; 6(7): 2696-08.doi: 10.13040/IJPSR.0975-8232.6(7).2696-08.