Tuijin Jishu/Journal of Propulsion Technology
ISSN: 1001-4055
Vol. 46 No. 4 (2025)

# Molecular (Neurotransmitter) Mechanism of Antidepressant Agents; A Signaling Approach

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***Abstract:*** Anxiety and depression are illnesses that impact a proportion of around 17-20 percent of world citizens. Antidepressants and anxiolytics are largely used in the management of depression and anxiety with antidepressants taking a series of weeks to develop clinical symptoms indicating that these drugs start any appropriate changes on brain structures affected by depression and anxiety. So that they may come up with more effective and shorter period to be used drugs in treating anxiety and depression, it is considerable to determine how antidepressants achieve the desired effects. Recent findings indicate that antidepressants have the ability of inducing neurogenesis in the adult brain; however, proposed mechanisms remained elusive. The paper outlines the differing neurotransmitter systems and receptors activation that is hindered by anxiety and depression including Serotonin, Noradrenalin, GABA, Orphan, mineralocorticoids, glucocorticoids receptors and the way they are modulated by antidepressant medication depending on the signaling molecules and pathways which are activated in neurogenic processes of neurotransmitter activated- receptors.

***Keywords:*** *Antidepressants; Receptors; Signaling Molecule; Neurogenesis; Treatment*

## 1. Introduction

Anxiety and depression are grave disorders that normally necessitate medical measures. Depression is typically a sad state of emotional and physical withdrawal whereas, anxiety refers to the state of fearing or terrified without the presence of a tangible object of stimulation (APA, 2012). Clinically, the two conditions are managed by use of antidepressants in combination with counseling. However, not every patient is always responsive to an antidepressant therapy, the effects of the treatment take several weeks and at times report some relentless effects of the side effects of the treatment. One has to comprehend the processes of anxiety and depression development as it will result in creating more targeted and more immediate forms of treatment. To conduct behavioral research on anxiety and depression, a raised plus maze, or the light-dark box experiment is used to investigate stress models in animals that belong to the anxiety category, and the forced swim or a conditioned suppression of motility experiment is used to study stress models that belong to depression (Filliol et al., 2010; Gordon and Hen, 2014). These publications also helped to explain antidepressant mechanisms and systems whose mechanisms become unstable during depressed/anxious states such as: hypothalamic-pituitary-adrenal (HPA) axis, monoaminergic system, y-aminobutyric acid (GABA) system and adult hippocampal neurogenesis. In this article, adaptations are given, and they occur in anxiety and depression and antidepressant treatment over these systems. It also documents on the findings on different types of transgenic mice and how the same can be used in order to develop new therapeutical models in order that anxiety and depression may be curable.

## 2. The Hypothalamic-Pituitary-Adrenal (HPA) Axis

Being one of the components of the HPA axis, the phenomenon of response of organisms to stress is weighty, and the emergence of the dysfunction of HPA axis is a significant feature of anxiety and depressive disorders. Once an individual is subjected to a stress situation, they will release a substance namely the corticotropin releasing substance/ hormone (CRH/CRF) which in turn stimulates 1) stimulation of the secretion of the adrenocorticotropic hormone (ACTH) by the pituitary and 2) the latter stimulates the secretion of the glucocorticoids by the adrenal cortex (Liberzon et al., 2007). The HPA axis is tightly regulated because the body lacks the ability to experience excessive doses of glucocorticoids because they are harmful to the organism (Liberzon et al., 2007). The feedback regulation is negative by primary use of the mineralocorti-coid and glucocorticoid receptors (Young et al., 2013). Cortisol is the primary glucocorticoids in human beings which regulate metabolism, thinking and feeling, particularly fear and anxiety (Mqller et al., 2012). Abnormalities in anxiety and depression of the HPA axis may entail elevated CRH levels (Nemeroff, 2006) or a misconstrued mechanism of negative cortisol feedback (Young et al., 2005). They are discussed as follows.

*Modulation by Corticotropin-Releasing Hormone (CRH)*

Other neuroendocrine, neurologic, and psychiatric pathologies that include chronic anxiety, melancholic and atypical depression have also been found to be considered in pathophysiology of CRH (Heinrichs and de Souza, 2009). The CRH activation along with other peptides will be under the exposure of some G-protein coupled receptors (GPCRs) which are also referred to as CRH-R1 and CRH-R2 (Grammatopoulos and Chrousos, 2012). The There is a diametric effect in the anxiety modulation since CRH-R1 had the anxiogenic effect and CRH- R2 has anxiolytic effect increasing stimulation of these receptors (Timpl et al., 2008; Kishimoto et al., 2010). CRH-R1 is a CRH and urocortin I receptor and they execute the fight or flight urging on stress. CRH-R2 forms a complex with urocortin I, II and III, the delayed component of adaptive response to a stress. The above leading one to think about the targeted disrupting research, led to the backing of earlier mentioned role of CRH-R1 in mediating normal response to stress (Timpl et al.,2008) and the role of CRH-R2 in fine tuning the response to stress (Kishimoto et al., 2010). Based on the impressed anxiogenic property of CRH and the anxiolytic property of urocortin II and III, the development of the anxiety and depression pathogenesis has been suggested to be associated with the CRH and urocortin peptide imbalance (de Kloet, 2014). Nonetheless, it is also recorded that there is hyperfunctioning of CRH-R1 or hypofunctioning of CRH-R2 in anxiety disorders (Keck et al., 2014). Because CRH-R1 receptor activation is associated with the development of anxiogenic and potentially depressogenic behavior, the presently observed behavioral effect of the agonist hence could be also reversed in a CRH-R1 antagonist administration, which is also accompanied by anxiolytic and non-depressogenic behavior. According to the studies, the studies have established that non-peptidic CRH-R1 receptor antagonists prevented the development of fear in rats or monkey, reducing the established fear responses and also potentiating the natural fear in the test animals and increasing the curiosity behavior (Keck et al., 2014).

*Modulation by Mineralocorticoid and Glucocorticoid Receptors*

In the case of stress responsive disorders like anxiety and major depression, a variation in corticoid receptors activity is one of the predeterminants of alteration in the pathophysiology process. These receptors act through the negative feedback regulation of the hypothalamo-pituitary-adrenal axis (Young et al., 2014) at the level of paraventricular nuclei of the hypothalamus, and at the anterior pituitary (Mqller et al., 2012). It is known that antidepressants and electroconvulsive shock treatment enhances mineralocorticoid and glucocorticoid receptors (Pariante and Miller, 2011).

In depression human, mineralocorticoid receptors, which were evident in the hippocampus, were also noted to be dysfunctional (Rubin et al., 2005; Heuser et al., 2010). But when the role of administration of antagonism (spironolactone in depressed patients) was determined; it was determined that the activity of the receptor was not greater in the depressed patients (Heuser et al., 2010). Depression does not seem to bias the total number of glucocorticoid receptors even though this was proven by some studies which showed that there is indeed a decrease (Pariante et al., 2005). The popular literature establishes that the cause which was influential was the receptor activity (the acceptance or the receptor to bind its partner or to transloca to the cell nucleus) and it was

not the change of the number of available receptors in the mood disorders (Pariante et al., 2011). Among all the possible speculations which can be made due to knowing the significant reduction in the functioning of the glucocorticoid receptor, the most appealing among them all is that it can be changed i.e. could be through ligand independent manners i.e. signal transduction, that is, non-corticosteroid related sports such as interleukin 1 and protein kinase A which also have been identified in the pathophysiology of major depression (Pariente et al., 2011).

Transgenic animals have been developed with particular genome modifications within the glucocorticoid or mineralocorticoid receptor to examine the regulatory components of the HPA axis, and behavioral impacts of genomic manipulation. Transgenic mice with diminished expression of the glucocorticoid receptor gene by antisense mRNA expression directed against the receptor have low levels of hypothalamic CRH expression (Dijkstra et al., 2008), a strengthened ACTH response associated with stress (Montkowski et a1., 2005; Barden et al., 2007; Defected spatial learning and glucocorticoid-mediated negative feedback efficacy (Dijkstra et al., 2008), and decreased effectiveness of glucocorticoid-mediated negative feedback (Pepin et al., 200 These mice also display impairments in spatial learning, an increase in responding to novel events and decreased locomotion in familiar conditions (Mqller et al., 2012). These mice exhibit changes as well in mesolimbic dopaminergic (Sillaber et al., 2008), and raphehippocampal serotonergic neurotransmission (Farisse et al., 2007; Linthorst et al., 2010), and defective long term potentiation in the hippocampal regions (Steckler, 2011). In addition, they are known to vary in the binding they assume towards 5- HT and hippocampus receptors 5- HT1 receptors where a combination of glucocorticoid and mineralocorticoids receptors exist (Cole et al., 2005). Deficient glucocorticoids in GR k/o mice causes death within the first days after birth owing to radical failure to develop the lungs (Cole et al., 2005). About 10 percent of the mice survived and possessed a high level of stratum of blood plasma and ACTH and corticosterone (Cole et al., 2005; Cole et al., 2011). First, long-term spatial memory is impaired whereas open field behavior is enhanced in these mice (Oitzl et al., 2007).

The glucocorticoids receptor (GR Nevre) inactivation in the nervous system of mice results in suffering of CRH in the hypothalamus, the inhibition of plasma ACTH, and amplification of plasma cortisol (Tronche et al., 2009; Gass et al., 2010). Such animals have a reduced level of the anxious-like behavior (Tronche et al., 2009; Gas et al., 2010). In mice where conditionally introduced knock-in of their inability to dimerize or activate the response to glucocorticoid response element (GRE)-driven genes is later (Feichardt et al., 2008; Tuckermann et al., 2009), the numbers of glucocorticoid receptors are preserved, and the impact of glucocorticoid does not become observed until the gene is deleted (Feichardt et al., 2008; Tuckermann et al., 2009). Another thing that was reported was that they had a compromised spatial memory but without any change in the anxiety-like behavior (Oitzl et al., 2011). Mice called YGR mice exhibit profound depletion of hypothalamic CRH and pituitary POMC, an increase in the plasma concentration of rational ACTH and lower plasma concentration of corticosterone in the overexpression of the glucocorticoid receptor (Reichardt et al., 2010). Up to date, there are no publications on behavioral research of such mice.

Finally, brain specific conditional overexpression of glucocorticoid receptors is displayed through transgenic mice, in addition to corticosterone aspects being apt to the basal levels of plasma. These animals portray high rates of anxiety behavior in dark-light box paradigm but normal rates of locomotor behaviour (Mqller et al., 2012). Mineralocorticoid receptor knock-out (MR k/o) will normally fail at about 10 days old and, following severe dehydration, show pseudohypoal- dosteronism (Berger et al., 2008). They have an increased level of plasma aldosterone and corticosterone. Remarkably, they show subdued hippocampal granule cell density and hippocampal neurogenesis upon exogenous provision of NaCl in a bid to rectify the syndrome of salt deficiency (Gas et al., 2010; Mqller et al., 2012).

*Modulation by Atrial Natriuretic Peptide (ANP)*

ANP prevents the work of HPA axis on all levels of its control. Production of ANP also occurs in atrial myocytes with the same also being present in the brain e.g. in the hypothalamus, the locus coeruleus and amygdala the location of ANP receptors has been identified. ANP will prevent the release of cortisol and ACTH stimulated by CRH (Strohle and Holsboer, 2013). Anxiolytic activity of ANP or a related hormone is acquired after intra-

cerebroventricular, intra-amydalar or intraperitoneal administration (Srohle and Holsboer, 2013). Anxiogenic effects of ANP receptor antagonist isoinatin is demonstrated by effects produced when it is tested on animals and is capable of blocking the anxiolytic effects of ANP applied intraventricularly (Bhattacharya et al., 2006).

## 3. Gabaergic and Monoaminergic Systems

*GABAergic System*

The other system that will be of utmost relevance on how we address the nature of anxiety and depression would be the GABA system. GABA neurotransmitter activates not only GABA receptors but GABA ionotropic receptors as well as metabotropic GABA receptors. They have theorized on the involvement of the GABAergic dysfunction in the condition of mood disorder as mood stabilizer-valproate proved beneficial in the treatment of bipolar patients (Emrich et al., 1990; Slattery et al., 2015). Due to the reason that valproate leads to an increase in the level of GABA concentration in the brain, the authors suggested that GABAergic deficiency is supposed to be the pathophysiology of mood disorders (Emrich et al., 1990; Brambilla et al., 2013). The outcomes of the procedure in which the GABA stages are measured in cerebrospinal fluid and plasma are also contradictory as they are observed to decrease in some of the cases and not change in others (Emrich et al., 1990). Nonetheless, the neuroimaging findings indicate that there is an implication in the major depressive disorder of impaired GABAergic neurotransmission (Sanacora et al., 2010). Otherwise, the gamma aminobutyric acid (GABA) performance is directly boosted by benzodiazepines, anxiety pills in depressive treatment protocol, which allosterically copies the subunits of GABA receptor (Emrich et al., 1990). Moreover, the selective GABA transporter GAT-1 selective re-absorption blockader, tiagabine, has proved useful in responding to anxiety-related behavioural states of mice or human beings (Gorman, 2013). The second piece of mentioning the role of the GABAergic system in anxiety and depression would be the GABA subunit knockout mice, which would demonstrate the antidepressants process whenever used during the forced swim test (Mombereau et al., 2014).

A point of interest may be observed whereby less GABA neurons is recorded in the orbitofrontal cortex of subjects with major depression when they are checked once they die (Rajkowska et al., 2009). The cause of what occurs behind the phenomenon is an enigma, but it can be linked to reduction in the brain derived neurotropic factor (BNDF) that deals with neurogenesis, and that reduction could be due to impact of stress (Rutherford et al., 2007). The other alternative concerns having fewer functional genes like bel-2 or less development of GABA cells neurogenesis in case they experience excessive turnover high degree (Krystal et al., 2012).

*Interaction with the Serotonergic System*

The links between GABAergic system and the serotonergic one are well-established. It is also described according to the findings of experiments that GABA receptors antagonists are antidepressants with an interaction of the serotoninergic system (GABA receptors) (Slattery et al., 20015). It is determined that 5-HT receptors are localized in the GABA inhibitory interneurons (Sarnyai et al., 2010) and stimulation of GABA receptors prevents firing of dorsal raphe nucleus (Mannoury et al., Secondly, the GABA, agonist, baclofen births the reduction of hyperpolarization and nerve cells firing at Sad dorsal raphe nucleus serotonergic cells in case of presence of 5-HT transporter (5-HT) knockouts (Mannoury et al., 2014). The inactivation of also 5-HTIA gene fulfills all these functions; namely, down-regulation of GABA and receptor alpha subunits and decreasing GABAA receptors and the benzodiazepine-resistant anxiety (Sibille et al., 2010). **Interactions with the Noradrenergic System**

Dynamics between GABAergic and the noradrenergic systems have been elucidated by the researchers known to induce anxiety and depression. The effect GABA has is that it may activate norepinephrine in the brains of rats (Emrich et al. 1990). Stimulation of GABA receptors has an enhanced ability to release the norepinephrine in hippocampus of rats and cortical regions (Suzdak and Gianutsos, 1995). Nevertheless, activation of GABA receptors leads to reduction of norepinephrine transmission in identical parts of the brain (Suzdak and Gianutsos, 1995). There is a loss of adrenergic binding sites in baclofen, and gain in GABA inhibitory transmission by norepinephrine, likely in that the chemical interacted with alpha adrenergic receptors in human cerebral cortex and rat cerebellar cortex (Ferraro et al., 2003; Mitoma and Konishi, 2009).

*Interaction with Neuroactive Steroids*

The borrowed neuropsychology of neuroactive steroids through neuropsychological disorders of GABAergic system with 30-reduced metabolites of progesterone and deoxycorticosterone has been researched by Rupprecht et al. (2011). The activities of the 30 degraded neuroactive steroids decrease depressives and anti-anxiety effects by working on the GABAergic system (Rupprecht et al., 2011). Neuroactive steroids are strong GABA receptor positive allosteric modulators since they raise. frequency or time surface opening of GABA-generated chloride channels (Paul and Purdy, 2002; Lambert et al., 2005). GABA chloride channels affect the expression of genes through intracellular progesterone receptors in tum (Rupprecht, 2013).

*The Monoaminergic System*

Monoamine oxidase inhibitors and tricyclic antidepressants were the first effective antidepressants that boost the level of serotonin and noradrenaline in the synapse (Hindmarch, 2012). This provided the pathophysiology hypothesis of depression via monoamine deficiency which presupposes lack of serotonin or noradrenaline regarding major sections of the brain of a depressed patient. However, this hypothesis is ignorant when it comes to explaining reasons when reasons must be given on why antidepressants work with anxiety disorders, and when there is need to explain why antidepressants such as tianeptine that enhance the reuptake of serotonin, are effective antidepressants (Hindmarch, 2012). In addition to the latter study, another research by Delgado et al. (Delgado and Moreno, 2010) pointed out that depletion procedures of 5-HT or NE also failed to induce clinical depression in healthy participants or worsen depression in un-medicated symptomatic patients having major depression. The role of the serotonergetic and noradrenergetic system with respect to the anxiety and depression is described in the following paragraph.

*The Noradrenergic System*

The noradrenergic one, like the serotonergic, has been a good candidate target of antidepressants, coincident with the serotonergic. Norepinephrine is also spread throughout the brain with some functions covering that of a general mood regulator and stimulus reaction stress regulator (Wang et al., 2009). Similar to the serotonergic system, the noradrenergic network is also anchored by intricate circuitry, which is endowed with numerous connections with the other systems of the neurology. Apparently, depression is perhaps related to the hypo-functioning of a noradrenergic system (Wang et al., 2009). and one of the parts of anti-depressants works like the modulators of the norepinephrine increase availability in the synapses (Brunello et al., 2013). The frontal and prefrontal cortex contains α2-adrenergic and Ãsh -adrenergic receptors which are believed to be directly associated with depression. Research studies have evidenced that there exist a down regulation in depression of a-2 adrenergic receptors (Brunello et al., 2013). Mirtazapine and robexetine affect at least partially, by way of alpha-2-autoreceptor to alleviate depressive symptoms (Brunello et al., 2013). Another factor that antidepressants attack is the norepinephrine transporters that carry out the reuptake of norepinephrine in the synapse. Investigation of the effects of administration of the norepinephrine reuptake inhibitor, desipramine, to rats indicated that reduction of norepinephrine transporter functions was due to reduction in transporter binding sites rather than gens (Bemansour et al., 2014). Investigating severity of correlation between serotonergic and norepinephrine systems has paid off as the efficacy of SNRIs is superior than the SSRIs or NRIs alone (Gimor et al., 2012). In knockout mice unable to translate norepinephrine and epinephrine, it was demonstrated that knockout animals never felt affected by the SSRI fluoxetine, sertraline and paroxetine, NRI desipramine and reboxetine, monoamine oxidase inhibitor (MAOI) pargyline and norepinephrine/dopamine reuptake inhibitor, bupropion (Cryan et al., 2 These findings were clear evidence that norepinephrine was implicated.

*Serotonergic System*

Serotonin system has been considered the system that is responsible in pathogenesis of anxiety and depression. Among the most convincing evidence, it is possible to mention the alleviation of serotonin selective reuptake inhibitor-induced depression that is associated with increased availability of the respective neurotransmitter at the synaptic level (Malagie et al., 2012). The links between serotonin and anxiety and depression were also confirmed based on the studies of tryptophan depletion (Gordon and Hen, 2014). Most Experiments have taken place to help in the unloading of how antidepressants work in the serotonergic system in a bid to ease mood disorders. To date, more than 15 types of serotonin receptors have been noted. The receptors are placed in seven families (5-HT) and

can be found in many different subtypes 5-HTA, 5-HT2, 5-HT3, and others, all of which are ligand-gated ion channels because the rest of the receptors are classified as a part of GPCRs superfamily (Gray and Roth, 2011). These receptors are dispersed to the major fear clusters of the brain such as hippocampus, cortex and raphe nuclei which after activation would promptly reverse the situation besides establishing irreversible changes (Gross et al., 2010; Gross et al., 2012). The 5-HTA is the most widely researched serotonin receptor. It is significant in the fear circuit where responses of the motor and the autonomic responses to the stress are controlled. The convention is that the resolution of anxiety and depression occurs in the repression of 5-HT receptor in the hippocampus along with the temporal lobe (Gross et al., 2010). The raphe nuclei have a presynaptic autoreceptor and postsynaptic heteroreceptor which have a negative regulation on the influence of serotonin and influence the effect of serotonin in a forebrain as a target tissue respectively (Gordon and Hen, 2014). The two types of receptors work to hyperpolarize membrane as well as to desensitize the neurons (Gross et al., 2010). These two types of receptors possess the agonists that are usually anxiolytic in a mouse (Gross et al., 2010). Some knockout strains of mice have been developed on 5-HT receptors with the purpose to further study the effect of serotonin in the context of stress response. 5-HTA knockout mouse exhibits an anxious phenotype, a low frequency of HPA activity and lower weight of adrenal glands (Gross et al., 2010). In tissue-specific rescues of the 5-HT knockout experiments, it was revealed that the wild type phenotype could only be recovered by expressing 5-HT1 receptors in the hippocampus and cortex but not the raphe nuclei at early postnatal stages only (and not during adulthood) (Gross et al., 2012). Nonetheless, to level the effect of chronic stress on learning and memory mediated through 5-HTIA receptors, experiments, which had been undertaken, showed that these mice lack hippocampal-dependent learning and memory. There was altered paired-pulse facilitation in the dentate gyrus, and increased limbie excitability (Sarnyai et al., 2010). This proved the effect of 5-HTLA receptors into reduced cognitive performance which is commonly considered in mood disorders (Sarnyai et al., 2010).

The other serotonin receptor studied widely is the 5-HT1B receptor. 5-HT1B receptors are found in superior colliculus within retinal ganglion cell axon terminals as well as in the hippocampus within terminal arms. The discharge of neural acetylcholine and glutamate is controlled with the usage of 5-HT receptors and serotonin (Malleret et al., 2009). They are similar to 5-HTA receptors in that they exert a cognitive behavioral mechanism. It turned out that knockouts are more inclined to either impulsive (Malleret et al., 2009) or aggressive (Knobelman et al., 2011) behavior. Efforts towards examining the interaction between 5-HTA and 5HTB receptors revealed that 5-HTB knockout contained elevated extracellular serotonin in the hippocampus and; thus, the combination of SSRI with a 5-HTLA antagonist would be a promising approach to anxiety and depression (Malagie et al., 2012). There is downregulation of 5-HT receptors when patient is treated with antidepressants (Gray and Roth, 2011). As per these findings, 5-HT receptor agonists are increased in their anxiogenic characteristics (Griebel, 2005). In postmortem frontal cortex of major depression patients, the measure of 5-HT and receptors demonstrated that untreated patients have a high receptor binding as compared to normal patients. There was also a reduced augmentation of 5-HT receptor binding in the latter of the medicated patients as well as in the people who escaped depression than the controls (Yates et al., 2000). It was shown by the study of knockouts of 5-HT that these mice have lower levels of anxiety and decrease in ACTH output in response to stressful conditions, low levels of vasopressin in the hypothalamus, and elevated CRIT mRNA levels in the amygdale (Bhatnagar et al., 2014), further, the 5-111, mCPP agonist is ansiogenic (Gordon and Hen, 2014).

Interpolations based on the data acquired in serotonergic system under the action of knockouts are to be handled with utmost care as they might fall under the influence of compensatory effect of other serotonergic receptors or any serotonergic closely related receptors. To illustrate, the frequency of firing of 5-4HT neurons in dorsal caphe of 5-Him knock out mouse increases almost twofold without the modulation of 5-HT 5-111 2- adrenergie receptors or alteration of 2-adrenoceptor on norepinephrine terminals (Richer et al., 2012). This means that the 5-HTm deficiency resulting receptors causes changes in 5-HT receptors. In several studies, interactions between serotonergic system and HPA had been established. The outcome is concomitant elevated serum levels of cortisol that under the depressed condition can deplete levels of /-tryptophan, lower 5-HT turnover, indirectly reduces the presynaptic 5-HT receptors, and indirectly up-regulates the presynaptic 5-HT -receptors. Conversely. Serotonin leads to the secretion of CRH and ACTH and may influence the negative feedback of HPA axis by glucocorticoids

(Maes et al., 2004). It was mentioned that the lack of CRH-R1 will result in the abundance of serotonin in relation to the situation within the basal condition as well as during the stressful scenario (Keck et al., 2014). Other than these, chronic stress downregulates the 5-HT receptor mRNA as well as the binding in the hippocampus (Lopez et al., 2008). All the research articles that are reflected in this part assert the significance of serotonergic system in the modulation of mood. They also indicate that none of the receptor subtype is represented as a disease on its own as anxiety and depression. Naturally, even the counterintuitive nature of serotonin behavior in circumstances where it is axiolytic along with axiogenic suggests the sheer sophistication of the brain response to stress (Gordon and Hen, 2014). In such a case, the serotonin system is at the basis of pathology of both anxiety and depression, further searching needs to be carried out intended to elucidate the processes of the signal transduction and receptor trafficking both in a healthy and a sick context.

*Orphan Receptors*

Examples of incompletely characterized genes are the so-called orphan GPCRs. The expressed proteins have an affinity of exhibiting homologous structural arrangement of seven transmembrane helixes with other GPCRs and are also termed as orphans due to the fact that they lack endogenous ligands currently. The recent data indicates that the orphan GPCRs (oGPRs) are the potential mediators of depression that could be considered an intended target of new drugs (Watkins and Orlandi, 2020; Albert, 2020). Crystal structures of the oGPRs have not been obtained to date, but homology depictions can be found in the GPCR database (Kooistra et al., 2021). GPR26 is a non-orphaned GPCR that is expressed, not just in the human hippocampus, amygdala and the thalamus in the human brain (Jones et al., 2007). GPR26 also promotes the adenylyl cyclase mechanism and triggers Gs. GPR26 knockout mouse is critical in the regulation of anxiety and depression like behavior as observed based on behavioral test (Zhang et al., 2011). GPR56 is a glycoprotein that subsidizes numerous biological processes like myelin, neurogenesis and development of oligodendrocyte. They conducted the in vivo experiments and detected the downregulation of GPR56 in prefrontal cortex (PFC) and dorsal hippocampus, but treatment response due to antidepressants eliminated that downregulation (Belzeaux et al., 2020). It has been observed that cells treated with GPR56 agonists including peptides P7: TYFAVLM-NH2; and P19: TYFAVLMQLSPALVPAELL-NH2 (Belzeaux et al., 2020) developed an increased level of depression. Overall, it can be proposed that GPR56 can be used as one of the possible molecular targets in depression treatment. The GPR158 transductions also have significant input into the PFC area that is central to the control of depression (Sutton et al., 2018). Ligand binding VFT domain is absent in GPR158, yet GPR158 has preserved G protein binding amino acids. Plasma membrane GPR158 G protein signaling regulator 7 (RGS7) complex anchor and as such may regulate other GPCRs signaling.

## 4. Molecular Genetic Approaches

This age has witnessed an enormous genetic potential and therefore researchers have gone into finding the cause of anxiety and depression at the genetic level. The given solution is very rational since relatives of depressed individuals are thrice as likely to develop a depression (Lesch, 2014). Factually, the individuals having never experienced psychiatric disorder, and belonged to families with high rates of depression depict aberrant reaction to combination of dexamethasone -CRH - challenge test, which is an indicator of HPA axis functioning (Modell et al., 2008). However since it is already emerging that there is no gene Q or b anxiety gene, the Q biochemical data alongside genetic technology, has opened up the new frontier of learning in the area of etiology of anxiety and depression.

As indicated in the introductory paragraph, some of the knock out animals have been covered because they are linked to relevant physiological systems that are said to form part of the symptoms of depression and anxiety. The latter are the analyses which are more accurately addressing the issue of heredity and genes of both anxiety and depression. The mismatches entailed the short and long alleles on the functional polymorphism in promoter area of the gene where 5-HT transporter is coded (Caspi et al., 2013). The allelic s type of the gene is associated with the reduced degree of transcription efficiency of the gene of 5-HT transporter as opposed to the dominating / allele. The existence of alleles of s// or s/s was a sign of increased depressive response to problems in life reactions to life pressure in persons with such genotype (Caspi et al., 2013). According to the study, the mere genotype is

merely a predisposition towards disease and its exposure only happens when that individual experiences stress through the issues of life (Caspi et al., 2013).

Additional doses discovered that the activation of neurons is greater when processing fearful stimuli among individuals who have copy of the s allele than among the participants who have a copy of the / allele (Hariri et al., 2012). In addition, one of the diseases, obsessive-compulsive disorder (Ozaki et al., 2013), had been experienced in six out of seven family members, possessing the same missense lle-425-Val substitution in a gene.

Gene expression changes can be detected upon exposure to antidepressants by microarray, which can be upregulated or downregulated. This has been utilized in establishing the adjustments in the expression of the mouse brain in unstressed mice on either mirtazapine or paroxetine. The mirtazapine effect was to modulate the cell cycle and brain development genes whereas paroxetine modulated the metabolism and cell structure genes (Langrebe et al. 2012). The receptors that may have been reviewed by such procedure include but are not limited to adenosine 2A and 5- HT and 5- HT because amelioration and etiology of panic disorder (Arnold et al., 2014) and 5- HT2A. Dopamine D4, 2B subunit of ionotropic N-methyl-d-aspartate associated with obsessive-compulsive disorder (Amold et al., 2014). So in one of the most interesting studies. To determine the mRNA of the hippocampal genes in animals that have been stressed and their unstressed counterparts, (Alfonso et al., 2014) adopted the polymerase chain reaction amplification. The four sequences revealed in the conducted investigation were those of nerve growth factor, membrane/ 6a glycoprotein, CDC- like kinase 1 and Gu, all being lesser in the stressed animals. It is assumed that all these genes contribute in the differentiation of the cells. Surprisingly, the application of the antidepressant; clomipramine in the stressed animals normalized the gene expression of all genes other than nerve growth factors (Alfonso et al., 2014). The findings of the current research are especially promising due to the fact that they support the recently emerging concept about neurogenesis influence during anxiety and depression and recovery process.

## 5. Neurogenesis

Studies carried out recently indicate that antidepressants can have their action through neurogenesis. The process of division, differentiation and maintenance in the neuronal stem cell is referred to as neurogenesis (Schaffer and Gage, 2014). The neuron progenitor cells in the subgranular zone invade the granule cell layer of the hippocampus and their processes develop on them and they differentiate into granule cells. Also, there has been an assumption that it develops in people gradually and visibly to a certain extent (Duman, 2014).

*Neurotransmitter Systems in Neurogenesis*

Duman et al. (2011) explain one of the means through which antidepressants could achieve effects on neurogenesis. The intensification of serotonin and/or NE is mediated by an up-regulation of key neurotransmitters by SSRIs or NRI which is enhancing their ability to stimulate activity of the CAMP cascade or the Ca% flat cascade leading to up-regulation of the level of CREB and BDNF, CREB (cAMP response element-binding protein) and (brain-derived neurotrophic factor) (Duman et al., 2011). Research has shown the CRH receptor antagonist inhibits the reduced neurogenesis that was found in the stressed-mice (Alonso et al., 2014). This is indicative of the participation of various receptor systems and cascades of protein signaling cascade in neurogenesis. Some of the other postulated molecules that are crucial in neurogenesis include the fibroblast growth factor (Duman et al., 2011; Schaffer and Gage, 2014), Sonic hedgehog (Shh), Noggins (Schaffer and Gage, 2014), epidermal growth factor (Duman et al., 2011), insulin-like growth factor1 (Cameron et al. 2008; Duman et al., 2011) and transforming growth factor Moreover, it is considered that glutamate, GABA, and opiates have an inhibitory effect on neurogenesis (Cameron et al., 2011). The reality of the presence of neurogenesis being relevant to the treatment of depression and anxiety was initially supported by evidence of lower hippocampal volume being found in those subjected to stress. The brains of PTSD patients were found to have an 8-percent smaller volume of right hippocampus than healthy individuals (Bremner et al., 2005). In another one, a 12 percent reduction of left hippocampal volume in those survivors of child maltreatments (which qualified to exhibit PTSD) was also identified (Bremner et al., 2007). Moreover, women who became victims of sexual abuse during childhood lost 5 percent of the volume of the left hippocampus (Stein et al., 2007). Conversely, evidence generated by a single

study did not identify notable distinctions in hollow volume of unmedicated depressed and undepressed patients (Vythilingam et al., 2014).

The association between depression and neurogenesis and the antidepressant pharmacology has supposedly been tested before by other researchers but Gould et al., 2002 has shown how corticosterone in adult dentate gyrus of rat affected neurogenesis. Nevertheless, the small size of hippocampus in patients with PTSD can be identified as the predisposing factor to the occurrence of the disease and not the result of neurotoxic activity of corticosteroids. The demonstration that antidepressants have a part in the adult hippocampal neurogenesis was shot by Santerelli et al. (2013), and it is admittedly beautiful. Antidepressants did not cause behavioral or neurogenic changes in mice whose hippocampus was exposed to X-irradiation. Besides, this experiment revealed the 5-HT knockout mice were not resistant, as well as, did not behave in response to SSRI, thus not demonstrating neurogenesis, which pointed to the involvement of these receptors in neurogenesis caused by antidepressants (Antarelli et al., 2013). These investigations give an idea of the fact that adaptive changes like neurogenesis that occur after antidepressant treatment within a week may be the reason behind the longer therapeutic action of such drugs. The drug intervention (venlafaxine or fluoxetine) in rats changed 33 proteins, indicating proteins involved in the neurogenesis process and out involved in the preservation of that neuronal process and neural regeneration/axonal guidance systems (Khawaja et al., 2014). Little is known about cascades of signal transduction during adult neurogenesis, although some of them have proposed that the CAMP-CREB signal transduction cascade might play any role in signal transduction in adult neurogenesis (Alonso et al., 2014). There are high chances that there exist certain other signaling pathways and cell systems of cells which is to be investigated yet.

*Cellular Signaling Molecules and Pathways in Neurogenesis*

The involvement of the 5-HTI receptor in neurogenesis and antidepressant induced cell proliferation has been demonstrated as explained above (Santarelli et al., 2013). Some of the experiments had done an exploration of the route and the molecules involved in a GPCR that had an involvement in neurogenesis. It is believed that the neuronal survival and outgrowth of the neurites is present when stimulation of a sub group of the G- protein coupled receptors is brought about. Indeed, a recent study had suggested that expression of the activated version of one of the members of the Gus family (Gas Q205L) leads to gain in elongation of neurites via a pathway implicating STAT-3 (Jordan et al., 2010) has triggered the work into signaling pathways that are central in elongation of neurites and survival of the neurons by a wide variety of Ga buttressed receptors that includes the 5-HTJA receptors. G-Rap1-Sre-STAT-3 is believed to contribute to neurite outgrowth in response to stimulation of a set of these receptors (Jordan et al., 2010; Fricker et al., 2011; Rios et al., 2014). It is consistent with the PC12 cells findings which have implicated Rap1 and STAT-3 (York et al., 2008; Wu et al., 2010). In addition, neurogenesis evoked by muscarinic receptor on the neural stem/progenitor cells is linked with the signaling pathway of CREB under the influence of Sre phosphorylation (Zhao et al., 2013). These findings together with our studies provide evidence that on activation, STAT-3 is phosphorylated on Sre and this is important in receptor-mediated neurogenesis.

## 6. Conclusion

The various systems involved in the pathophysiology of anxiety and depression have been explained in this review. It is apparent that the concept seems to interconnect the systems, pathways, and molecules which are believed to be involved in anxiety and depression. More than this is the fact that these processes also seem to be relevant to neurogenesis. Depression and anxiety exemplify a whole scope of abnormal neurological conditions. Hence, anxiety and depression have to be seen as global neurological aberrancy. Potentialities exist in various directions that are worth exploring to find out effective antidepressant and anxiolytic agents. There has been much potential area of researches in regard to the CRH receptor antagonist as antidepressants. As the effects of chronic stress and associated changes can be alleviated with the use of CRH-RI antagonists (Ducottet et al., 2013), on par with the antidepressant and fluoxetine, and lead to the neurogenesis (Alonso et al., 2014), it is valid to argue that CRH-R1 antagonists may form a new antidepressants cohort. In the deconstruction of signaling cascades triggered by SSRIs and other neurotransmitter systems (serotonin, adrenergic and GABA receptor), molecules, pathways

and networks used in neurogenesis will be required in enhancing more efficacious and faster acting antidepressants.

**ACKNOWLEDGEMENT**

My exclusive gratitude goes to Irinmwinuwa Eric of the department of Pharmacology and Toxicology Nnamdi Azikiwe University, Awka who inspired this work. I also dearly appreciate other co-authors who made a tremendous contribution

**Conflict of interest: Nil**

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