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GLUCOCORTIOCOID RECEPTOR- NEW TARGETS IN DEPRESSION

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ABSTRACT

Depression is very common mood disorder, which can affect person's behavior, feeling & sense of well- being. There are different biological mechanisms such as monoamine hypothesis, hormonal hypothesis, receptor sensitivity, neurogenesis which can causes depression in human. In this review we have targeted the glucocorticoid receptors (GR) which playing main role in depression. The impaired GR signaling may causes the hyperactivity of hypothalamic-pituitary-adrenocortical (HPA) system, resulting in overproduction & secretion of corticotropic releasing hormone (CRH) in various brain region which further leads to cause for depression. Thus, in this article we summarized searching of novel mechanism for depression beyond monoamine hypothesis and the antidepressant therapy which is based on impaired GR signaling as this is also key mechanism for pathogenesis of depression.

KEYWORDS: Glucocorticoid receptors (GR), Hypothalamic-pituitary-adrenocortical (HPA) axis.

1. INTRODUCTION

Depression is a common but serious mood disorder. It causes severe symptoms which can affects person's feeling, thinking, and handle daily activities such as sleeping, eating, or working[1] Without treatment, symptoms can last for weeks, month or years. Appropriate treatment, however, can help most of people who suffer from depression.[1] Depression affect mostly in women than men. Depression affect at least one in fifty children under the age of 12 years & one in twenty teenagers, mostly girls. There is increase in rate of depression among

the adolescent girl is due to physical changes that occur during puberty, suggestive of hormonal changes. Premenstrual syndrome (PMS) & postpartum depression are additional condition involving depression that specifically affect women and are suggestive of hormonal involvement in the pathogenesis of depression.[2]

Normal Mood Lowering

↕

Abnormal Mood Lowering

↕

Abnormal mood lowering and loss of function

1.1. Classification and Types of Depression

A. Major Depression Disorder

Major depression also called as unipolar depression is most serious type of depression. The term unipolar means the presence of one pole, i.e. mood- depressed mood. This may be compared with bipolar depression which has the two poles of depressed mood and mania. With this disorder person having combination of symptoms that interfere with the ability to work, sleep, eat and enjoy once-pleasurable activities; and may occur several times during a lifetime. Many people with this type of disorder cannot continue with their function normally. It can be run in families, which suggest that depressive illness can be inherited. Early signs of major depression include changes in brain function in those individuals having low self-esteem, who are readily overwhelmed by stress. The treatment for major depression are medication, psychotherapy, and in extreme cases, electroconvulsive therapy.[2]

B. Dysthymia

This is type of depression in that a level of depressed mood that doesn't reach the severity of depression is called dysthymia. It is also called as "bad state of mind." This depression must last for at least two years in adults and one year in children and teens before it can be diagnosed. If someone feels depressed most of the day but can still carry out daily responsibilities of living and work, this is dysthymia. Many of those with dysthymia also experience major depressive episodes at some point in their lives. To treat this Antidepressant and psychotherapy can help.[2][3]

C. Bipolar Disorder

a) Bipolar I Disorder

Bipolar I Disorder is the classic manic-depression. There are cyclic periods of mania, often

interspersed with periods of hypomania, depression, and times when there are no significant symptoms, i.e., remissions. The typical individual cycles one to two times a year. Those who have four or more mood episodes within one year are given the label "rapid cycling." About 0.6% of the population of adults have Bipolar I Disorder. The average age of onset of symptoms is 18, but onset occurs from childhood until the 60s and 70s for some people.

b) Bipolar II Disorder

Bipolar II Disorder is characterized by depressive episodes mixed with episodes of hypomania of a mild, nonpsychotic nature in periods of usually a week or less, but can be more. In hypomanic cycle, the individual may be overactive, overtalkative and have a great deal of energy. The hypomanic cycle often affect thinking, judgment and social behavior. Some mood stabilizing treatment can help in bipolar disorder. E.g. Lithium, carbamazepine valproic acid etc.[2][3]

D. Other Types of Depressive Disorder

Other type include seasonal affective disorder, which characterized as a type of depression which happen during particular season of the year. This disorder involves symptoms of depression that occur during fall and winter season, when the days are shorter and there is less exposure to sunlight. When spring & summer season are begin there is a greater exposure to longer hours of daylight, the symptoms of depression are disappear. Adjustment disorder with depressed mood is type of depression that results when a person has something bad happen that depresses them. (e.g. loss of one's job can cause this type of depression).[2]

1.2. Causes of Depression

Depression can be due to number of factors interacting with one another, which including biological factor such as genetic factors, hormones, brain chemicals and psychological factors such as thinking or stress which can range from mild to severe. Depression can occur along with other serious illnesses, such as diabetes, cancer, heart disease, and Parkinson's disease. Depression can make these conditions worse and vice versa. Sometimes medications taken for these illnesses may cause side effects that contribute to depression symptoms.[2][3]

1.3.Symptoms of Depression

Symptoms of depression can vary. They may manifest themselves differently from person to person. depression may occur during life time, usually people have multiple episodes of depression. During these episodes some symptoms are occur they are-Feeling bad about

yourself such as sadness, emptiness or hopelessness.

Depression may cause people to get easily frustrated or angered, irritable, feel guilty, anxious all time. People with depression may have a difficult time remembering, maintaining focus, or making decisions. Changes in sleep patterns such as sleep disturbances, insomnia or sleeping too much. Changes in appetite or weight i.e. reduced appetite & weight loss or gain.

Physical symptoms, such as body pain, headaches, cramps, and digestive problems also can occur. Younger children with depression commonly report physical pain symptoms. They may refuse to go to school or behave particularly clingy due to the worry about their aches and pains.[4]

1.4.BIOLOGICAL BASIS OF DEPRESSION[2][5][6]

A) Role of Monoamine

The monoamines are the neurotransmitter that include 5-HT(serotonin), dopamine, norepinephrine (NE), and epinephrine. The 'monoamine hypothesis' of depression, which describe that depression is caused by decreased monoamine function in the brain in post-synapses, many antidepressant drugs aims to correct these deficiencies. Norepinephrine may be related to alertness and energy as well as anxiety, attention, and interest in life. Serotonin related to anxiety, obsessions, and compulsions; and dopamine to attention, motivation, pleasure, and reward, as well as interest in life.

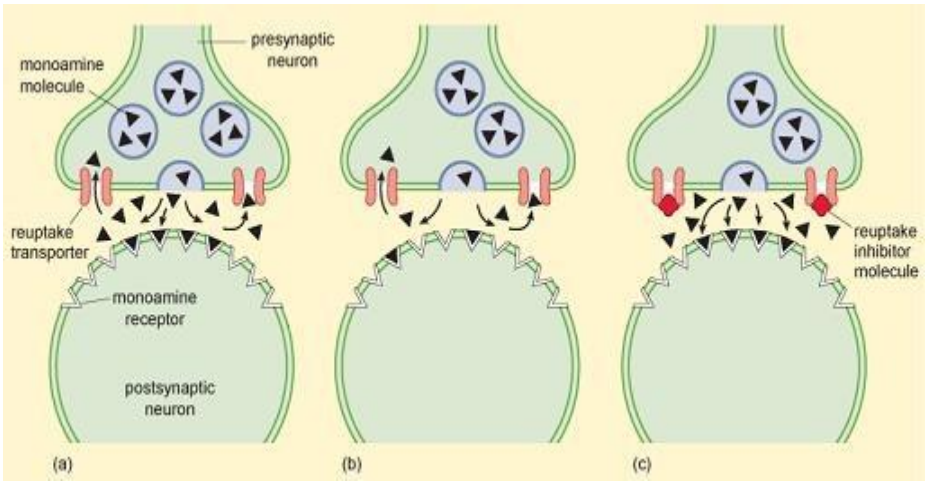

Fig. 1.

These deficiencies are corrected with the secondary amine TCAs (like desipramine or nortriptyline) inhibited the reuptake of NE into noradrenergic neuron & blocking the 5-HT

reuptake by tertiary amine TCAs (like clomipramine). Monoamine hypothesis suggests that monoamine oxidase A (MAO-A), an enzyme which metabolizes monoamines, may be active in depressed people. This would, in turn, cause the lowered levels of monoamine. This hypothesis received elevated activity of MAO-A in the brain of some depressed people. Thus, this enzymes are inhibited by some antidepressant called as MAO inhibitors (moclobemide, phenelzine). In genetic studies, the alterations of MAO-A-related genes have not been consistently associated with depression. Contrary to the assumptions of the monoamine hypothesis, lowered but not heightened activity of MAO-A was associated with the depressive symptoms in youth. This association was observed only in maltreated youth, indicating that both biological (MAO genes) and psychological (maltreatment) factors are important in the development of depressive disorders.

B) RECEPTOR SENSITIVITY HYPOTHESIS

The receptor sensitivity hypothesis proposes that the sensitivity of postsynaptic receptors to neurotransmitter is also important. Those with depression, possess postsynaptic receptors that have grown hypersensitivity to NE & 5-HT because of their depletion in synaptic cleft. Increase receptor sensitivity & increase in number of receptor on neuronal cell membrane are event that may correlate with the start with depression. According to this hypothesis, relief from symptoms of depression following chronic administration of antidepressant comes from normalization of receptor sensitivity by increasing concentration of NE & 5-HT in synaptic cleft. Therefore the use of reuptake inhibitors and MAOIs as antidepressant increase the concentration of NE &5-HTin synaptic cleft and, over time, causes the postsynaptic neuron to compensate by decrease in receptor sensitivity & number of receptor site.

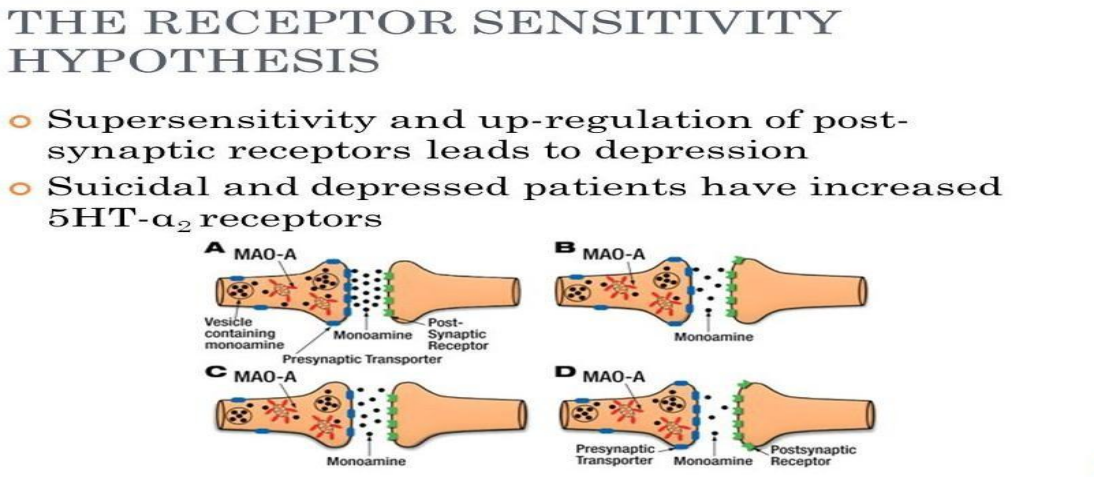

Fig 3.

C) HORMONAL HYPOTHESIS

The hormonal hypothesis suggests that changes in the hypothalamus-pituitary-adrenal axis (HPA). In event of stress, the hypothalamus produce a hormone in brain i.e. corticotrophin-releasing- hormone(CRH) which stimulate pituitary gland to secrete adrenocorticotropic hormone into blood, which stimulate adrenal gland to release cortisol, which prepare the body to deal with stress.

Stress is also directly stimulate the adrenal gland to secrete epinephrine and NE. Cortisol can cause the depression, especially when released in higher than usual amounts. The release of cortisol may push the individual over the edge into depression or contribute to component of anxiety, which can causes the depressive illness.

Antidepressant medication[2]

Sr. No.	Class	Drugs
1.	**Norepinephrine Reuptake Inhibitors (SNRIs)**	E.g.of secondary amine TCAs Desipramine, Nortriptyline, Amoxepine, Protriptyline.
2.	**Selective Serotonin(5-HT) Reuptake Inhibitors (SSRIs)**	Eg. of SSRIs drugs are Citalopram, Escitalopram, Fluoxetine, Paroxetine, Sertraline, etc.
3.	**Orepinephrine and Serotonin euptake Inhibitors (NSRI)**	E.g.The tertiary amine TCAs are amitryptline Imipramine Doxepin, Clomipramine, etc.
4.	**Monoamine Oxidase inhibitors**	The MAOIs can be classify as hydrazine (e.g. phenelzine) & nonhydrazine (e.g. tranylcypromine).
5.	**Mood stabilizer**	E.g. Lithium
6.	**Atypical antidepressant**	E.g tianeptine, bupropion, mirtazapine.

2. Glucocorticoid Receptor- New Targets In Depression

Major depression will be cause of disability. Studies on the molecular basis of depression has so far mainly focused on imbalances of neurotransmitter systems in the brain, especially depletion of the serotonin, norepinephrine and dopamine ("monoamine hypothesis"). However, depression is precipitated by long-term, chronic exposure to stress, and antidepressant treatment need to be administered chronically in order to elicit a therapeutic response in depressed patients. These long-term effects of both stress and antidepressants suggest that rather adaptive mechanisms may be involved in the pathogenesis of depression, which cannot be explain by imbalances of fast acting neurotransmitters alone. Brain regions, such as the hippocampus, undergo structural changes in depressed patients and it has been hypothesized that a loss of hippocampal volume may explain the long lasting mood and memory disturbances in depression. Although neuronal cell death, reduced neurogenesis and

alterations in neurotrophic proteins, such as brain-derived neurotrophic factor (BDNF), are hypothesized to contribute to hippocampal atrophy and depression. A growing body of evidence shows that depressed patients consistently exhibit hyperactivity of the hypothalamus–pituitary–adrenal (HPA) axis, which results in increased levels of the glucocorticoid hormone cortisol in patient. Cortisol is known to regulate neuronal survival, neuronal excitability, neurogenesis and memory acquisition, and high levels of cortisol may thus contribute to the manifestation of depressive symptoms by impairing these brain functions. On a molecular level, cortisol exerts its effects in part by activating the glucocorticoid receptor (GR). The GR has been shown to profoundly regulate the expression of neurotrophic factors such as BDNF. Impaired GR function has been suggested to be causal for HPA axis hyperactivity in depression, as glucocorticoids usually regulate the HPA axis through negative feedback inhibition and thereby reduce the production of glucocorticoids themselves. This effect is thought to be mediated in part by the GR. Therefore, hyperactivity of the HPA axis has been explained by an impaired feedback inhibition of glucocorticoids, possibly due to an impaired or dysfunctional GR (so-called "glucocorticoid resistance").

It thus seems that two opposing mechanisms may operate: on the one hand, depression is characterized by detrimental effects of excessive glucocorticoid signaling, which depend on a functional GR, whereas, on the other hand, GR function may be impaired in depression and thereby causing the high glucocorticoid levels. We will elaborate these below and we will discuss role of the GR in major depression and how GR function can be modulated by antidepressants and glucocorticoids. We will conclude by hypothesizing a partial impairment of GR function, which may contribute to depression and represent a future target for antidepressant treatment.[7][14]

2.1. Glucocorticoids

Glucocorticoids (GCs) are a class of corticosteroids, which are a class of steroid hormones. The name glucocorticoid (glucose + cortex + steroid) is composed from its role in regulation of glucose metabolism, synthesis in the adrenal cortex, and its steroidal structure. Glucocorticoid also refer as corticosteroids. Glucocorticoids are chiefly produced in the zona fasciculata of the adrenal cortex. Cortisol (or hydrocortisone) is the most important human glucocorticoid. Glucocorticoid synthesis is regulated by the HPA axis via ACTH. ACTH is synthesized by the posterior pituitary mainly in response to two synergistic factors – CRH and antidiueretic hormone (ADH or vasopressin), both of which produced in the paraventricular

nucleus of the hypothalamus. ACTH stimulates the synthesis of cortisol in the adrenal. Cortisol itself exerts negative feedback on the HPA axis by inhibiting both the release and actions of CRH. ACTH also exerts a short - loop negative feedback by inhibiting its own secretion.[8][9]

2.2. Glucocorticoid Receptors[8][9]

The glucocorticoid receptor (GR, or GCR) also known as NR3C1 (nuclear receptor subfamily 3, group C, member 1) is the receptor to which cortisol and other glucocorticoid are bind. The GR is expressed in almost every cell in the body and regulates genes controlling the development, metabolism, and immune response.

Like the other steroid receptors, the glucocorticoid receptor is modular in structure and contains the following domains (labeled A - F).

A/B - N-terminal regulatory domain C - DNA-binding domain (DBD).

D - Hinge region.

E - ligand-binding domain (LBD) F - C-terminal domain.

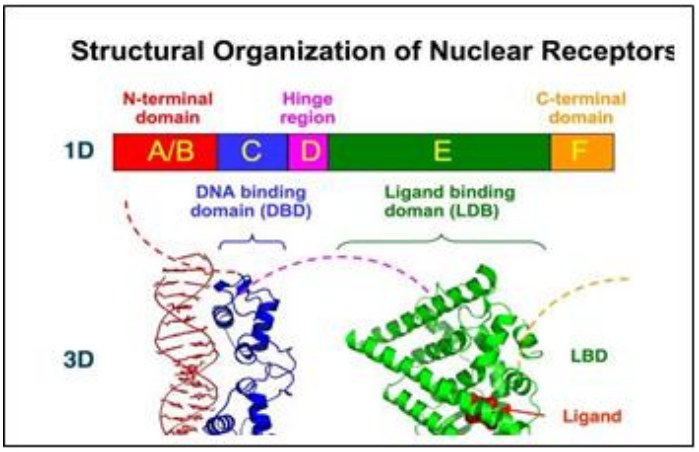

Fig. 4

2.3. Functions of Glucocorticoids & Glucocorticoids receptors[14]

When the GR binds to glucocorticoids, its primary mechanism of action is the regulation of gene transcription. The unbound receptor resides in the cytosol of the cell. After the receptor is bound to glucocorticoid, the receptor -glucocorticoid complex can take either of two paths. The activated GR complex up-regulates the expression of anti-inflammatory proteins in the nucleus or represses the expression of pro-inflammatory proteins in the cytosol (by preventing the translocation of other transcription factors from the cytosol into the nucleus.

Each receptor type forms a multiprotein complex with heat shock proteins and immunophilin, a protein that binds immunosuppressive drugs. The multiprotein complex is rapidly dissociated after binding of corticosteroid onto the receptor. The activated receptor is then dimerized and acquires a high affinity for nuclear domains. Both homo-and heterodimers of MR and GR can be formed. They attach as dimers to specific DNA sequences called glucocorticoid response elements (GREs) present in promoter regions of target genes, which, in turn, affects transcription. Regarding GR, both positive & negative regulations of target genes have been described. Activation of transcription occurs via well-conserved GREs, while negative regulation (transrepression) is mediated by less conserved inhibitory GREs. Dexamethasone and other corticosteroids are agonists, and mifepristone and ketoconazole are antagonists of the GR.

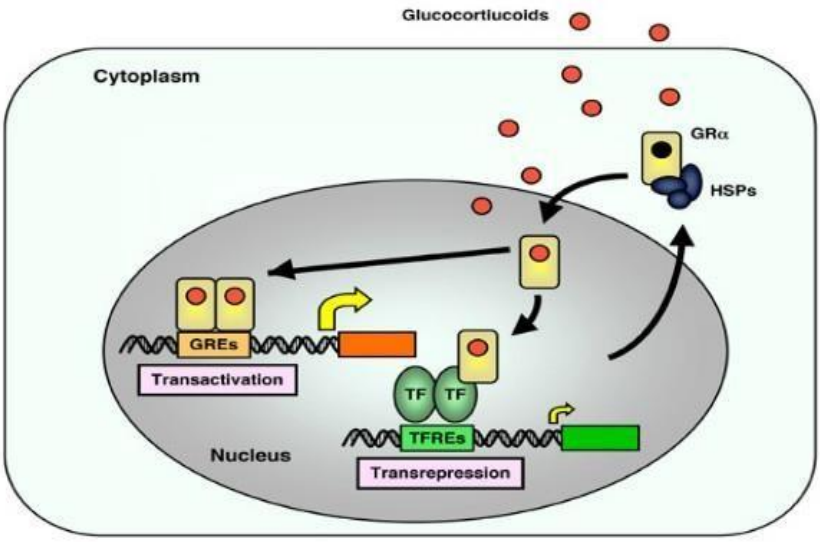

Fig 5: Transactivation and trans-repression of GR.

3. Glucocorticoid Receptor as Targets for Depression[12][13][14][15]

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It thus seems that two opposing mechanisms may operate: on the one hand, depression is characterized by detrimental effects of excessive glucocorticoid signaling, which depend on a functional GR, whereas, on the other hand, GR function may be impaired in depression and thereby causing the high glucocorticoid levels. We will elaborate these below and we will discuss role of the GR in major depression and how GR function can be modulated by antidepressants and glucocorticoids. We will conclude by hypothesizing a partial impairment of GR function, which may contribute to depression and represent a future target for antidepressant treatment.

3.1. Glucocorticoid (cortisol) in depression

It is a common found that depressed patients hyperactivity of the HPA axis.The HPA axis is a major part of the neuroendocrine system, which regulates the body's response to external stressors, e.g., by providing energy and by focusing attention The HPA axis is governed by the hippocampus, which controls the release of corticotrophin releasing hormone (CRH) and arginine-vasopressin (AVP) from the paraventricular nucleus (PVN) of the hypothalamus. CRH then induces the synthesis of adrenocorticotrophic hormone (ACTH) from the anterior

pituitary gland, ACTH in turn stimulates the production of glucocorticoids (cortisol in humans and corticosterone in rodents) in the adrenal cortex and their release into the blood stream.

Glucocorticoids have multiple functions in almost every tissue of the human body, as we previously seen. Glucocorticoid hormones can act back on the hippocampus, the PVN and the anterior pituitary, to exert GR-mediated negative feedback inhibition on the HPA axis and to inhibit the synthesis and secretion of CRH and ACTH. Ultimately, this regulatory feedback loop maintains low glucocorticoid levels under normal physiological condition. However, in some depressed patients this feedback inhibition is impaired, resulting in constant HPA axis hyperactivity, increased pituitary and adrenal gland volume, and high levels of glucocorticoids in saliva, cerebrospinal fluid, blood plasma and urine. Impaired negative feedback inhibition of glucocorticoids in depression can be examined indirectly by the dexamethasone suppression test (DST). Oral administration of the synthetic glucocorticoid dexamethasone, which specifically binds to the GR, activates HPA axis feedback inhibition in healthy subjects and thereby reduces cortisol secretion. In contrast, cortisol secretion cannot be inhibited by dexamethasone administration to depressed patients.

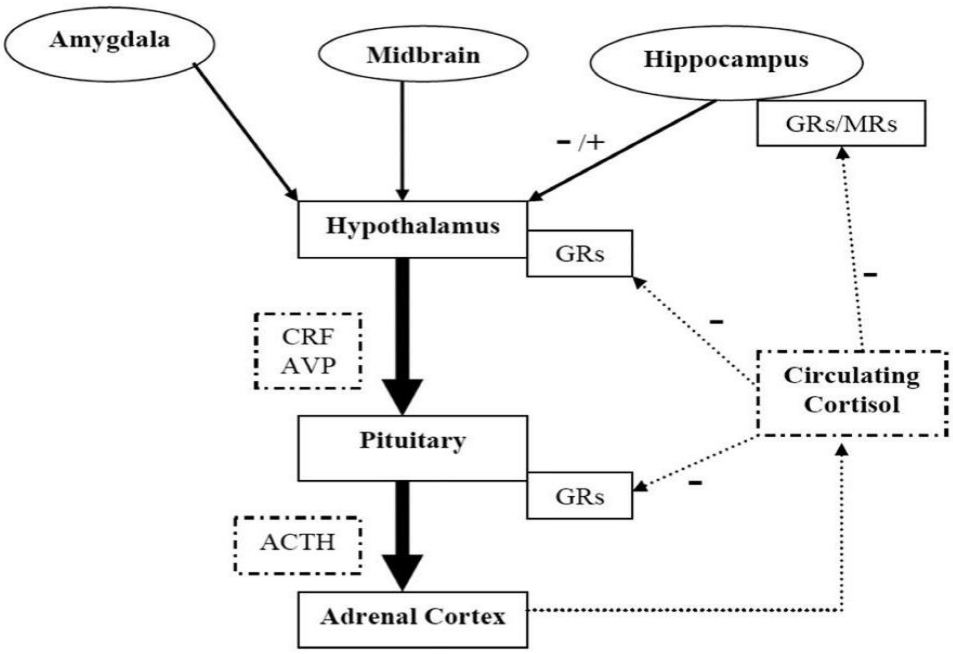

Fig 6: Schematic diagram of the Hypothalamis-Pituitary-Adrenal (HPA) axis, describing regulation and negative feedback (-) of cortisol via glucocorticoid receptors.

Thus, GR-mediated negative feedback on the HPA axis is impaired in this condition. The correlation between HPA axis hyperactivity, high glucocorticoid levels and depression, may

show that the high level of glucocorticoid are may cause of development of depression. The increase in glucocorticoid level also induce the decrease in neurogenesis. Reduced GR signaling (again, "GR resistance") can also impaired neurogenesis. And this in turn correlates with development of depressive symptoms. we have to discuss closer into the molecular mechanisms of GR signaling.

3.2. Glucocorticoid receptors and depression

Previously we have seen that what are the GR and what are their normal functioning. Now we will see the role of glucocorticoid receptors in depression.

- **Glucocorticoid Resistance**

Three major possibilities have been considered regarding GR resistance in depression. These include: 1) GR downregulation secondary to persistent hyper-cortisolism, 2) primary alteration in the genetic structure of the GR, and 3) a decrease in GR function secondary to alterations in ligand- independent pathways that regulate the GR. GR downregulation secondary hyper-cortisolism could overburden the recycling capacity of the GR, with consequent diminished capability of the cell to respond to further stimulation. Individuals with a high genetic loading for depression (i.e., euthymic subjects with high familiar risk for affective disorders) may carry a "trait" marker that manifests itself as impaired GR function (impaired HPA negative feedback as measured by the dexamethasone–CRH test).

A third consideration is that GR function is altered in major depression via ligand-independent mechanisms. The concept of "ligand-independent" regulation of GR function derives from findings that steroid receptor function is regulated not only by steroid ligand binding, but also by signal transduction pathway. Researcher also show that GR function can be influenced by a myriad of non-steroid compounds including proinflammatory cytokines, such as interleukin 1 and participants in the cyclic adenosine monophosphate (cAMP) cascade including protein kinase, a both of these factors have been implicated in the pathophysiology of major depression.

A second possible pathway involved in the pathogenesis of GR resistance is the cAMP/PKA cascade. There is now considerable evidence that phosphorylation of the GR and/or other steroid receptor coactivators by cAMP-dependent protein kinase has a relevant role in the regulation of GR function. For example, adenylate cyclase and PKA activators have been found to increase GR-mediated gene transcription, and b-agonists have been shown to

translocate the GR from cytoplasm to nucleus via the cAMP/PKA pathway. Therefore, it is possible that disruption in the cAMP/PKA pathway described in major depression is linked to GR resistance in this disorder and that antidepressants may overcome these receptor alterations via a direct effect on this pathway.

The complexity of the GR system, there is just one gene encoding for the GR, but several different mRNA splice variants are known. Whereas the GRα splice variant is the ligand-dependent nuclear transcription factor, which is abundant in almost every tissue and cell type, the GRβ splice variant does not have transcriptional activity. Alternative splicing of GR mRNA may result in tissue- and cell- type specific differences in transactivation and trans-repression potential. Thus, it has been shown that the GRα splice variant is decreased in the limbic brain and in peripheral blood mononuclear cells (PBMCs) of depressed patients without changes in GRβ.Such changes in GRα/GRβ ratio are likely to alter responsiveness to glucocorticoids and may thus contribute to glucocorticoid resistance in depressed patients.

- **Glucocorticoid Receptor in depression**

There is critical role of the GR in HPA axis hyperactivity and in mediating the effects of glucocorticoids on brain plasticity and mood. GR has been found to be a common mechanism for stress dependent changes in brain function and a potential target of antidepressant drugs. Changes in GR expression, nuclear trans-location, co-factor binding and GR-mediated gene transcription may play a fundamental role in altered HPA axis responsiveness to glucocorticoids in the HPA axis tissues, which may contribute to HPA axis hyperactivity.

Studies on immune cells from peripheral blood have shown that the capacity of glucocorticoids to inhibit proliferation of PBMCs in response to polyclonal mitogens is impaired in depressed patient. Mice witha GR deficiency only in the pituitary show impaired glucocorticoid mediate negative feedback inhibition and HPA axis hyperactivity without changes in GR expression in the central nervous system.

This gives that impaired GR function, specifically in the periphery, may account for glucocorticoid resistance and explain impaired feedback inhibition with resulting HPA axis hyperactivity. However, mice with a deletion of the GR specifically in the hippocampus, but not in peripheral tissues such as the pituitary, also display impaired feedback inhibition, HPA axis hyperactivity and depressive-like behavior These findings indicate that impaired GR function in both the periphery and also in the central nervous system are relevant for HPA

axis hyperactivity and behavioral abnormalities in depression.

4. GR – Target as Antidepressant

Antidepressants not only alter depressive symptoms and normalize HPA axis hyperactivity, they also protect from neuronal cell death and from reduction in adult hippocampal neurogenesis. Chronic antidepressant treatment, for example, dexamethasone-induced neuronal cell death and sub-lethal neuronal damage in the hippocampus and striatum of rats. These neuroprotective effects have been suggested to be mediated, at least in part, by elevated BDNF levels upon antidepressant treatment. Studies show that antidepressants and mood stabilizers increase hippocampal cell proliferation in healthy, non-depressed animals.

As the GR plays a crucial role in the effects of stress, depression and Glucocorticoid hormones on neurogenesis and HPA axis hyperactivity. Targeting the GR at key points for antidepressant treatment. Antidepressants of the class of monoamine re-uptake inhibitors regulate GR mRNA expression in primary neuronal cell cultures. More specifically, in neurons of the hypothalamus, the amygdala and the cerebral cortex, antidepressants increase GR mRNA levels after 48 h of treatment, independent of their ability to block monoamine re-uptake. These findings are supported by several other studies, which showed that treatment with tricyclic antidepressants increases GR binding affinity and GR mRNA expression. In hypothalamic and hippocampal neurons, suggesting that antidepressants enhance glucocorticoid sensitivity, specifically in the brain, and thereby may restore GR-mediated feedback inhibition on the HPA axis. However, both increased and decreased GR mRNA expression by antidepressants has been shown in the periphery, dependent on the duration of treatment.

Furthermore, studies have shown that antidepressants induce glucocorticoid-dependent and even glucocorticoid-independent nuclear translocation of the GR, and that they also facilitate glucocorticoid-dependent GR-mediated gene transcription.

4.1. How Antidepressant Regulate GR

The alterations in GR function described above may likely represent a point of several different chemical classes of antidepressants.

So far, no direct interaction of the antidepressant compound itself with the GR or any of its interacting proteins has been described. Thus, we will discuss how antidepressants actually

induce changes in GR function which would then have an effect on the biology of the cell, on changes in neuroplasticity, and ultimately on brain function and mood. Several mechanisms may be involved, including phosphorylation by protein kinases, membrane transporters like the MDR PGP, and miRNAs. In the following section, we will briefly describe each of them. There is considerable evidence for a cyclic AMP (cAMP) protein kinase A (PKA) dependent mechanism of GR regulation. PKA induces GR-transactivation in cells that lack endogenous cAMP response element binding protein (CREB) The phosphodiesterase type-4 inhibitor rolipram, which prevents the breakdown of cAMP to AMP and therefore enhances cAMP-dependent PKA activation, increases GR mediated gene transcription in vitro, and also potentiates the effects of antidepressants on increasing GR function.

Accordingly, β2-adrenergic receptor agonists have been shown to cause GR nuclear translocation via a cAMP/PKA-dependent pathway. These findings are intriguing in view of the fact that antidepressants are suggested to enhance neurogenesis via a cAMP/PKA-dependent effect. Antidepressants influence several other intracellular protein kinases such as protein kinase C (PKC) and calcium/calmodulin- dependent kinase, which seem to be specifically implicated in the antidepressant-induced decrease in GR-mediated gene transcription.

In particular, reduced GR expression may be a consequence of increased GR translocation, increased GR-mediated gene transcription and subsequent GR downregulation, and thus in fact reflect an increase, rather than a decrease in GR function Also, activation of different second-messenger pathways may result in differential phosphorylation of the GR, which in turn may cause changes in GR- dependent gene transcription but not completely abolish it.

- **CONCLUSION**

This review has concluded a brief study of depression with their types, causes, biological mechanism and medication generally based on monoamine hypothesis. We have targeted the glucocorticoid receptors as key mechanism for pathogenesis of depression. Thus, we have study that how the impaired GR signaling can causes the hyperactivity of HPA axis which leads to increase level of glucocorticoid which further give rise to development of depression symptoms. Thus, we have achieved some novel mechanism for depression and the new approach of antidepressant treatment base on glucocorticoid receptors beyond monoamine medication.

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