Review Article

Possible Targets Related to Connexins and Ceramides in the Treatment of Depression Using a Combination Approach

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Abstract

The novel targets considered in the recent research related to the treatment of depression include connexins, peroxisome proliferator activated receptor (PPAR), ω-3 fatty acids, ceramides, and renin–angiotensin–aldosterone system (RAAS). The major associated brain parts considered include hypothalamus, pituitary, and adrenal gland (HPA) axis in psychiatric disorders. The present review has proposed hypotheses such as combining PPAR (α/γ) agonist with noradrenaline dopamine reuptake inhibitor, gap junction channel modulator/hemichannel inhibitor with N-methyl-D-aspartate receptor antagonist like ketamine, ω-3 fatty acids derivatives like resolvin with tricyclic antidepressant like amineptine, RAAS-modifying drugs with serotonin reuptake inhibitors such as fluoxetine, ceramide synthase inhibitor/acid sphingomyelinase inhibitor with doxepin, and HPA axis-modifying drugs with bupropion. Further assessment of these combination approaches may help in availing better therapeutic options in the treatment of depression.

Keywords: *Ceramides, connexin, HPA axis, omega 3 fatty acids, PPAR, RAAS*

Introduction

According to the World Health Organization, "depression is a psychotic disorder characterized by anhedonia, persistent sadness and unable to perform regular locomotor activities for at least 2 weeks."[1] The recent novel targets considered for treating depression are peroxisome proliferator activated receptor (PPAR), connexins, omega-3 fatty acids, renin–angiotensin–aldosterone system (RAAS), ceramides, hypothalamus–pituitary–adrenal gland (HPA) axis, etc. The role of PPAR subunits in preventing depression-like behavior is well known by the PPAR alpha (PPARα)-cyclic adenosine monophosphate (cAMP) response element binding protein (CREB)-brain derived neurotrophic factor (BDNF) mechanism, but the link between noradrenaline (NA)/serotonin (5HT) reuptake inhibitors and PPAR subunit overexpression as antidepressant action is not well explained, and so the explanation regarding co-relation between same is needed.[2] The role of connexins in regulating depression-like behavior is explained in the present review article. Omega-3 fatty acids and its derivatives are responsible for the synthesis of secondary messenger molecules such as protein kinases, etc. and thus may help in treating depression.[3]

The pathophysiological role of angiotensin 2 (ATII) type 1 receptor and ATII type 2 receptor of RAAS in depression[4] is elaborated in the present review. Targeting ceramide is an essential approach for treating depression because the abnormal ceramide level may contribute to neurotoxicity and thus may be responsible for causing depression-like behavior.[5-7] The role of HPA axis in the pathophysiology of depression states that the inhibition of negative feedback mechanism of cortisol causes depression and other mood disorders such as anxiety.[8] The main focus of the present review is to discuss and elaborate the current novel targets and the related hypotheses in the treatment of depression.

Novel Targets for the Treatment of Depression

Peroxisome proliferator activated receptor

PPAR is expressed in the hippocampus of brain.[9] PPARα is a nuclear receptor,[10] which showed antidepressant-like effect through modulating transcription of the CREB gene, responsible for the synthesis of BDNF.[11-13] In the chronic unpredictable mild stress animal model of depression, the drugs such as venlafaxine and fluoxetine showed antidepressant action through increased levels of monoamines in brain, and there was also

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increase in the expression of PPARα and PPARγ in the hippocampal region of the brain.[2,9] Simvastatin showed antidepressant-like effect in the forced swim test (FST) animal model of depression by modulating K_{ATP} channel and PPARγ receptor.[14] Atorvastatin showed antidepressant-like effect, when it was administered with PPARγ agonist pioglitazone.[15] However, administration of atorvastatin with PPARγ antagonist GW-9662 failed to produce the antidepressant effect in the FST animal model of depression. Therefore, it was concluded that PPARγ is involved in the antidepressant action of atorvastatin.[15] A sesquiterpene beta-caryophyllene (BCP) showed neuroprotective, antidepressant, and anxiolytic activity through stimulation of cannabinoid receptor 2 (CBR2) and by agonism of PPARγ receptor.[16] The antidepressant effect of BCP was due to PPARγ-coactivator-1-alpha (PGC-1α) stimulation, which further elevated PPARγ and BDNF.[16] The CBR2 activation was responsible for the activation of PPARγ.[16] Rosiglitazone, a PPARγ agonist, showed antidepressant-like effect in the FST animal model of depression through increasing adiponectin in adipose tissue and so there exists a link between adiponectin and PPARγ.[17] Rosiglitazone is a substrate for P-gp, so the bioavailability of the drug was less for acting as antidepressant; also adiponectin was responsible for causing changes in mood.[17] PPARα agonists such as fenofibrate restored the dopamine level in nucleus accumbens (NACs) and restored the dopaminergic neurotransmission in the ventral tegmental area (VTA) of brain in FST and chronic unavoidable stress protocol in rats through PPARα modulation.[18] It also increased dopamine D_1 receptor signaling in VTA of brain.[18] Activation of PPARα caused inhibition of nitric oxide synthetase (NOS) enzymes and thus acts as anti-inflammatory and neuroprotective and so it was responsible for antidepressant action in FST. Thus, it also acts as medication for neuropathic pain.[19] However, the elaboration of pathway involved in modulating brain monoamines through PPAR activation is needed for carrying out further research for the development of better therapeutic option in the treatment of depression.

Connexin

Connexin, a protein molecule, is present in astrocyte immune cells.[20,21] Connexin43 (CX43) consists of two channels, comprising gap junction channel (GJC), which functions in communicating the neuroactive amines between neurons, and hemichannel (HC), which play an important role in the neurotransmitter uptake and its release.[20] When mice were treated with fluoxetine, the CX43 expression in the hippocampal region of brain was increased in the experimental models of depression and HC activity was inhibited, so the uptake of neurotransmitter was prevented.[22] Jeanson *et al.*[23] tested seven antidepressant drugs mostly belonging to 5HT and NA reuptake inhibitors and obtained variation in results concerning CX43 expression. Drugs belonging to tricyclic antidepressant (TCA) and selective serotonin reuptake inhibitor (SSRI) class showed strong inhibition of HC, whereas norepinephrine reuptake inhibitor (NRI) showed mild inhibition and serotonin NRI (SNRI) showed mixed inhibition, depending on efficiency.[23] The inhibitory action on HC activity of CX43 by antidepressant drugs supports the pathophysiology of major depressive disorder (MDD) mediated through glutamate release, which was due to the stimulation of HC. Further, it was responsible for neurotoxicity and decrease in the level of BDNF in the hippocampus, prefrontal cortex (PFC), and amygdala region of the brain.[23] Antidepressant drugs such as fluoxetine showed inhibition of corticosterone-induced depression in mice.[24] All antidepressant drugs do not inhibit the GJC functionality and CX43 expression, but they are likely to inhibit HC activity.[24] The gene analysis of the brain hippocampal region of patients suffering from MDD showed the dysfunctioning of the astrocyte gap junction and also hyperactivity of HC, and thus the new approach for treating depression would be reversing the intercellular GJC dysfunctioning and strategies for inhibiting HC hyperactivity. Astrocyte dysfunctioning is a mediator for impairment of synaptic neuronal transmission of neurotransmitter in the medial prefrontal cortex (mPFC) region of brain in the chronic social defeated stress mouse model of depression. There was imbalance in coordination of CX43 and CX30 in the mPFC and hippocampal region of brain in chronic stress-induced mouse model of depression, so depression-like behavior in mouse was observed.[25] Decreased CX43 GJC activity and increased HC activity were responsible for ATP release, glutamate release, release of inflammatory mediators such as tumor necrosis factor alpha (TNFα) and interleukin beta (IL-β), which further caused neurotoxicity and depression-like behavior.[26] Targeting connexin HC would be a good approach for antidepressant-like effect, and so there is a need to find new connexin antagonists which will specifically block HC rather than normal GJC.

Omega-3 fatty acids

Omega-3 fatty acid is a polyunsaturated fatty acid (PUFA), which is metabolized into eicosapentaenoic acid (EPA), and further EPA is converted into docosahexaenoic acid (DHA) by desaturases and elongases enzymes acting at different positions on respective fatty acid.[3] The role of PUFA in decreasing the morbidity and mortality in patients suffering from cardiovascular disorder is well elaborated.[3] PUFA is a precursor for the synthesis of phospholipids and other signaling molecules such as secondary messengers such as inositol phosphatases and several kinases such as protein kinase C.[3] In human subjects, the decrease in the erythrocyte DHA level caused depression-like behavior, whereas pre-treating the patient with EPA alone caused increase in the erythrocyte EPA and DHA level, thus preventing the depression-like behavior through inhibiting the inflammatory cytokines such as TNFα, IL-β, and IL-6.[27] EPA and DHA act as neuroprotective and so it plays a vital function in regulating the depression pathophysiology associated with inflammation.[27] Increase in inflammatory mediators and decrease in EPA and DHA caused dysregulation of the HPA axis and dysfunctioning of the serotonergic system.[28] n-3PUFAs is responsible for the

synthesis of various signaling molecules such as eicosanoids, among that n-3 LC PUFA showed anti-thrombotic, anti-inflammatory, and vasodilatory action.[29] n-3PUFAs deficiencies are noted in people suffering from psychiatric disorders such as bipolar disorder, depression, and attention deficit hyperactivity disorder.[29] DHA is a common n-3PUFA, which is found to be depleted in people suffering from depression.[29] A meta-analysis of post-mortem report of people who died because of psychiatric disorder showed a decrease in the peripheral level of PUFA.[29] One cause of perinatal depression is decrease in the level of EPA and DHA in pregnant women.[29] However, further studies did not conclude that the decreased level of EPA and DHA is responsible for perinatal depression, but there are reports suggesting that supplementing pregnant women with EPA and DHA play an important role in preventing perinatal depression.[29] The people with ultra-high risk for psychosis has decreased integrity of white matter and decreased NA, due to the decrease in the level of PUFA and hence there exists an association between PUFA and pathophysiology of depression.[30] The EPA is responsible for the synthesis of prostanoids and phosphatidylinositol and thus acts as a secondary signal messenger, which regulates migration, signal transmission, vasoconstriction, and vagus nerve stimulation, which further caused increase in the level of EPA and thus caused antidepressant-like action.[31] EPA also has anti-inflammatory action and thus it is related with pathophysiology of depression.[31] Resolvin is derived from omega-3 fatty acid; it showed antidepressant effect in the lipopolysaccharide (LPS)-induced murine animal model of depression and chronic unpredictable mild stress (CUMS) model of depression.[32] The exact mechanism of action of omega-3 fatty acid derivatives such as EPA and DHA as antidepressants is not well proven, and so further pharmacological biochemical study is needed to confirm the related antidepressant-like effect of EPA and DHA.

Renin–angiotensin–aldosterone system

The plasma renin activity (PRA) was increased in non-rapid eye movement sleep and vice versa, and the slow wave activity in sleep cycle increased the PRA.[33] Antidepressant drugs such as SSRI and TCA increased the mineralocorticoid receptor (MR) in the hippocampal region of the brain, but the monoamine oxidase inhibitor such as phenelzine does not increase hippocampal PRA.[33] Increase in MR caused inhibition of HPA axis, which was hyperactivated in patients suffering from depression.[33] The role of drugs such as MR antagonist, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin 2 (ATII) type 1 receptor blocker in depression was not elaborated.[33] When aldosterone was administered in rats for 2 weeks, the depression-like behavior was observed, which was reversed with RAAS-modifying drug treatment.[34] Decrease in antidepressant drug medication and subsequent increase in consumption of RAAS-modifying drug in patients suffering from diabetic nephropathy suggested that RAAS-modifying drugs may improve mood in diabetic nephropathy.[34] The sigma 1 receptor is expressed in brain, heart, and kidney and so the possible link of RAAS-modifying drugs in preventing depression-like behavior was due to activation of sigma 1 receptor, which leads to an increase in BDNF.[34] In patients suffering from depression, the high co-relation was observed among adrenocorticotropic hormone (ACTH)—aldosterone, ACTH—cortisol, and aldosterone—cortisol, whereas low co-relation was observed between renin–aldosterone and the sleep ACTH was mainly responsible for the release of aldosterone.[35] The activation of ATII type 1 receptor causes neurotoxicity, whereas activation of ATII type 2 receptor causes neurogenesis and hence increases BDNF, thus acting as antidepressant.[4] The ACE inhibitors such as lisinopril showed antidepressant-like effect by elevating mood in patients suffering from depression in clinical trials.[4] In the FST mice model of depression, the decrease in immobility time was observed after treating with losartan ventral infusion in the hippocampus. However, drugs such as captopril and enalapril did not reduce immobility time.[36] The observed antidepressant effect of losartan might be due to ATII type 1 blockade.[36] However, the exact pathophysiological role of RAAS in depression is not known, and further elaboration of RAAS in MDD is needed.

Ceramides

A comparative study carried out in normal control individuals and depressed patients suggested that the patients suffering with depression had elevated plasma ceramides level and imbalance in metabolism of ceramides.[5] The imbalance metabolism of the same may result in reduced affinity of agonists such as dopamine and serotonin receptors and thus may participate in the pathophysiology of depression.[5] The animal and cell cultured studies indicate that there was an increase in the activity of acid sphingomyelinase (ASM) and ceramide in depression.[5] The cell cultured study also indicated that treating the cell cultures with anti-depressant drugs such as amitriptyline and imipramine produced decreased activity of ASM.[5] The activity of p38 was increased by ASM, which further leads to depression-like behavior in the stress-induced mice model of depression.[37] Stress also causes elevation of p38K, thus it is responsible for causing inhibition of hippocampal neurogenesis.[37] Amitriptyline drug inhibits the activity of p38k, which is a mediator for stress-induced neurotoxicity. The stressed endothelial cells in the hippocampus release ceramides and thus cause inhibition of proliferation of neurons in the hippocampus, which may further lead to neurotoxicity.[6] However, the study failed to explain how the stressed endothelial cells along with ceramides releases ASM.[6] The stress-induced animal model of depression suggested an increased ceramide level in the hippocampus due to stimulation of hippocampal endothelial cell and was inhibited by a well-known antidepressant drug and ASM inhibitor amitriptyline.[6] The altered metabolism of ceramide was responsible for causing depression-like behavior, and abnormal ceramide concentration in brain was responsible for causing neuroinflammation and abnormal apoptosis.[7] The ceramide synthetase inhibitors may act as adjuvant therapy with standard antidepressant drugs for treating patients with MDD.[7] The lysosomal ASM, secretory ASM, and other metabolizing

enzymes which metabolize different types of sphingolipids may contribute to the pathogenesis of depression.[38] The secretory ASM (S-ASM) may serve as a biomarker for MDD, but still there is no enough evidence to support the role of S-ASM in the pathogenesis of depression but measures should be taken to validate the S-ASM hyperactivity as a biomarker for depression.[38] The study suggested importance and need of doing further research for S-ASM as a novel biomarker for diagnosing patients suffering from depression.[38] However, the exact role of ceramides in causing MDD is not known, and further biochemical study is needed.

HPA axis

The dysregulation of HPA axis was implicated in psychiatric disorders such as MDD and anxiety.[8] The components of HPA axis are hypothalamus, pituitary, and adrenal glands, which are responsible for glucocorticoid synthesis and regulation.[8] The release of cortisol was mediated by the HPA axis and the cortisol has high affinity to mineralocorticoid receptor (MR) in the hippocampal region of the brain, whereas development of MDD was more associated with the imbalance between glucocorticoid receptor (GR) and MR in the brain; further, the hypercortisolemia was indicated in reports of MDD patients with psychotic depression when compared with non-psychotic depression.[8] Drugs such as fludrocortisone inhibit MR stimulation in normal individuals, but this was not in the case of psychotic depression; hence, it indicates dysregulated functioning of MR.[8] In a study of psychotic depression patients and non-psychotic depression patients, hypercortisolemia was observed in psychotic patients, whereas cognition impairment was observed in both the groups of the patients.[8] HPA and 5-HT activity are stimulated by stress, and there is well-known evidence showing dysregulated neurotransmission of serotonin due to hyperactivity of HPA axis stimulated by stress.[39] The HPA axis is also responsible for regulation of neurotransmitters such as dopamine, glutamate, and gamma aminobutyric acid (GABA).[39] The GABAergic neurotransmission in the hypothalamus was decreased due to excessive release of corticotropin-releasing hormone (CRH) and also due to overstimulation of HPA axis in patients suffering from depression.[39] Imbalance in coordination of HPA axis causes hypersecretion of glutamate, which leads to excitotoxicity and is further responsible for neuronal death, thus contributing in the pathogenesis of depression.[39] The HPA axis plays an important role in regulating homeostasis, but chronically activation of HPA axis and inhibition of negative feedback mechanism of cortisol caused release of inflammatory mediator and decrease in BDNF; hence, it was involved in the pathogenesis of depression.[40] In MDD, the GR functioning was impaired, which caused excessive release of glucocorticoid and inhibition of negative feedback mechanism of cortisol.[40] GR antagonists such as mifepristone inhibit the HPA axis. Thus it was effective in treating patients suffering from bipolar disorder and also there are strong clinical data suggesting dysregulation of HPA axis in patients suffering from bipolar disorder, but still there is not any particular drug which modulates the dysregulated HPA axis, so targeting the HPA axis independently could not treat depression.[40] To assess the HPA axis activity, tests such as dexamethasone suppression test can be used.[40] The CRH_1 antagonist and GR antagonist can be used for the treatment of bipolar disorder, but CRH_1 antagonist is still unavailable.

Proposed Hypotheses

Synergistic antidepressant effect of PPAR (α/γ) agonist with noradrenaline dopamine reuptake inhibitor (NDRI) such as bupropion, etc.

PPARα agonists such as pioglitazone showed dose-dependent antidepressant-like effect in the FST model of depression.[41] The pioglitazone dose 30 mg/kg showed highest reduction in immobility time when compared with 10 and 20 mg/kg in the FST model of depression.[41] The reduction in immobility time was due to increased superoxide dismutase (SOD) and prevention of activation of HPA axis by pioglitazone.[41] Hence, pioglitazone has radical scavenging property and thus acts as neuroprotective.[41] Losartan is a partial PPARγ agonist, which inhibits inflammatory cytokines such as TNFα and IL-6 and thus acts as anti-inflammatory.[42] Losartan dosage 1 and 2 mg/kg did not reduce immobility time in the FST model of depression, and it also did not increase hippocampal BDNF.[42] However, the higher doses of losartan may increase hippocampal BDNF.[42] The PPARα agonist N-palmitoylethanolamine showed elevation of hippocampal BDNF and decreased immobility time in the FST and TST models of depression.[43] N-palmitoylethanolamine increased the allopregnanolone biosynthesis and thus further promoted GABAergic neurotransmission in brain; it prevents activation of HPA axis.[43,44] In clinical trials, the combination therapy of pioglitazone and citalopram showed improvement in depressive symptoms due to modulation of PPARα in brain.[45] When PPAR (α/γ) is activated by an agonist, there was activation of PGC-1α, which further caused increase in the PPAR (α/ γ) level in hippocampus.[16] The increased PPAR (α/γ) level causes inhibition of NOS enzyme, further causing inhibition of free radicals, and thus acts as neuroprotective and anti-inflammatory.[19] PPAR (α/γ) plays a significant role in enhancement of neuronal transmission of neurotransmitters such as dopamine, noradrenaline, etc. in brain, modulates the CREB gene and thus responsible for the synthesis of BDNF in hippocampus and prefrontal cortex, and hence prevents depression-like behavior.[2] Combining PPAR (α/γ) agonist with NDRI such as amineptine and bupropion may show synergistic antidepressant effect [Figure 1].[2,16-19]

Synergistic antidepressant effect of GJC modulator/HC inhibitor with N-methyl-D-aspartate receptor (NMDAR) antagonist drugs such as ketamine, etc.

Connexins play an important role in Glio-transmission across neurons.[46] Connexins are highly expressed in astrocyte and hippocampus.[46] The CX43 non-specific gap junction inhibitors

such as carbenoxolone and mefloquine have serious side effects such as amnesia and psychosis and hence CX43-specific gap junction inhibitors should be tested for better therapeutic options in treating depression.[46] Moreover, there is a need to develop CX43-specific gap junction inhibitors.[46] In depressed patients, dysregulation of neuronal plasticity between astrocytes and oligodendrocytes due to hyperactivity of HC was observed.[47] The above opinion clearly states the role of CX43 astrocyte in maintaining neuronal plasticity. Genistein showed antidepressant effect in the unpredictable, chronic mild stress-induced model of depression in mice.[48] The aforementioned antidepressant effect was accompanied by targeting the CX43-specific gap junction.[46] NMDAR antagonists such as ketamine produced antidepressant-like effect in animal models of depression by preventing excitotoxicity produced due to excessive activation of glutamate receptor.[49,50] The CX43-specific HCs blocker such as peptides like gap19 and polyamines may inhibit the NMDA channel and thus can act as antidepressant, as CX43 HCs activation was involved in producing depressive-like behavior in animal models of depression.[24,51] Ketamine should be preferably used in combination with HC inhibitor because this may block excessive glutamate release, thus preventing excitotoxicity and will help in preventing deterioration of BDNF in the hippocampus and cerebral cortex region of the brain. Hence, combining HC inhibitor with NMDAR antagonists such as ketamine may show synergistic antidepressant effect [Figure 2].[20,23,24,26,51]

Synergistic antidepressant effect of ω-3 fatty acids derivatives such as resolvin with tricyclic antidepressants such as amineptine, etc.

The dose ratio of EPA and DHA should be 2:1 g in humans for antidepressant activity in the Japanese population, but still a number of human subjects tested in a clinical trial were insufficient and hence, there is a need to carry out testing of the aforementioned dosage in huge population.[52] The Canadian Network for Mood and Anxiety Treatment recommended EPA and DHA as supplementary treatment for severe depression and monotherapy for mild depression.[53] EPA and DHA both regulate the serotonergic and dopaminergic neurotransmission

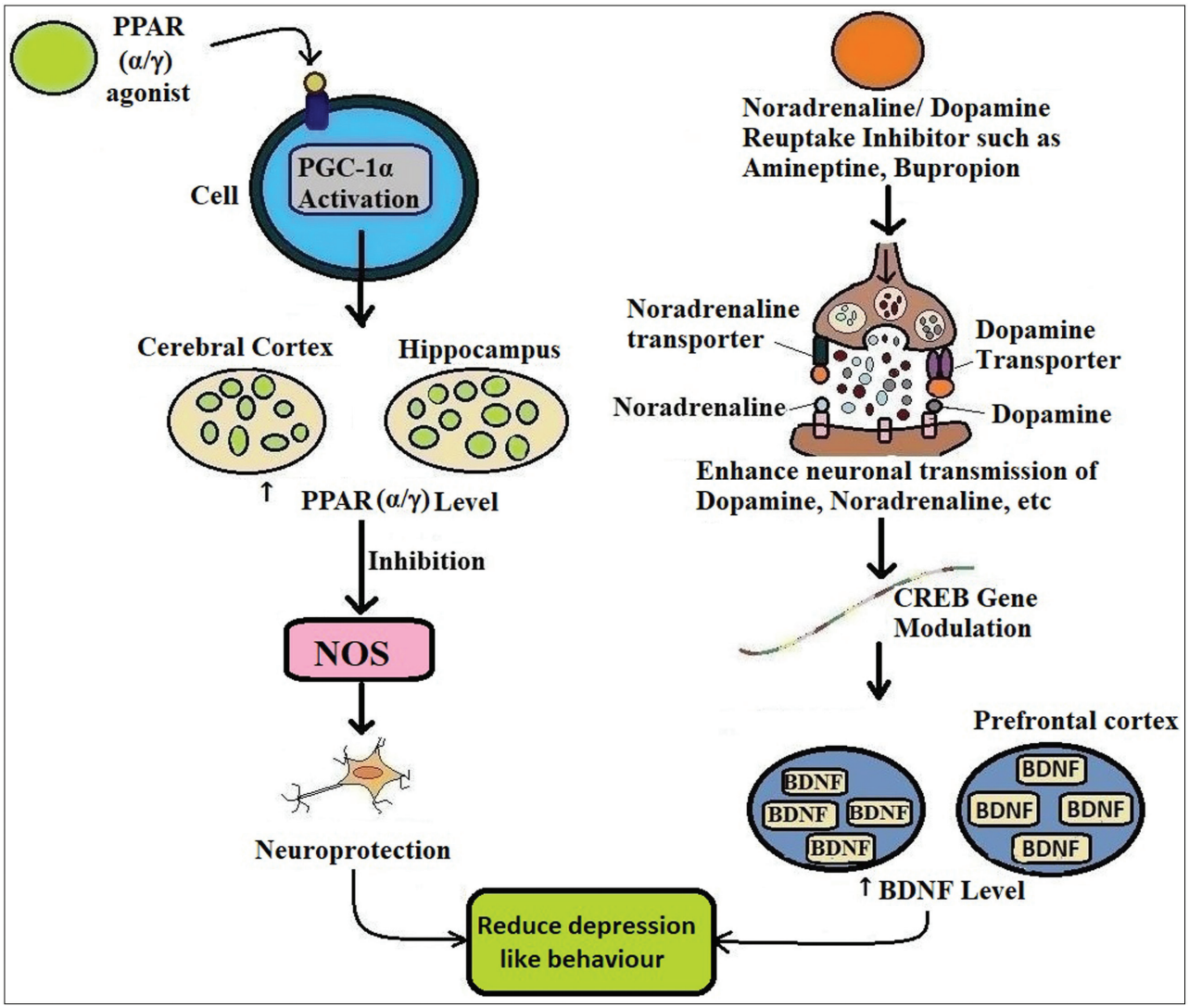

Figure 1: Possible synergistic antidepressant mechanism of PPAR (α/α) agonist[2,16,17,19] with noradrenaline dopamine reuptake inhibitor (NDRI)[18]

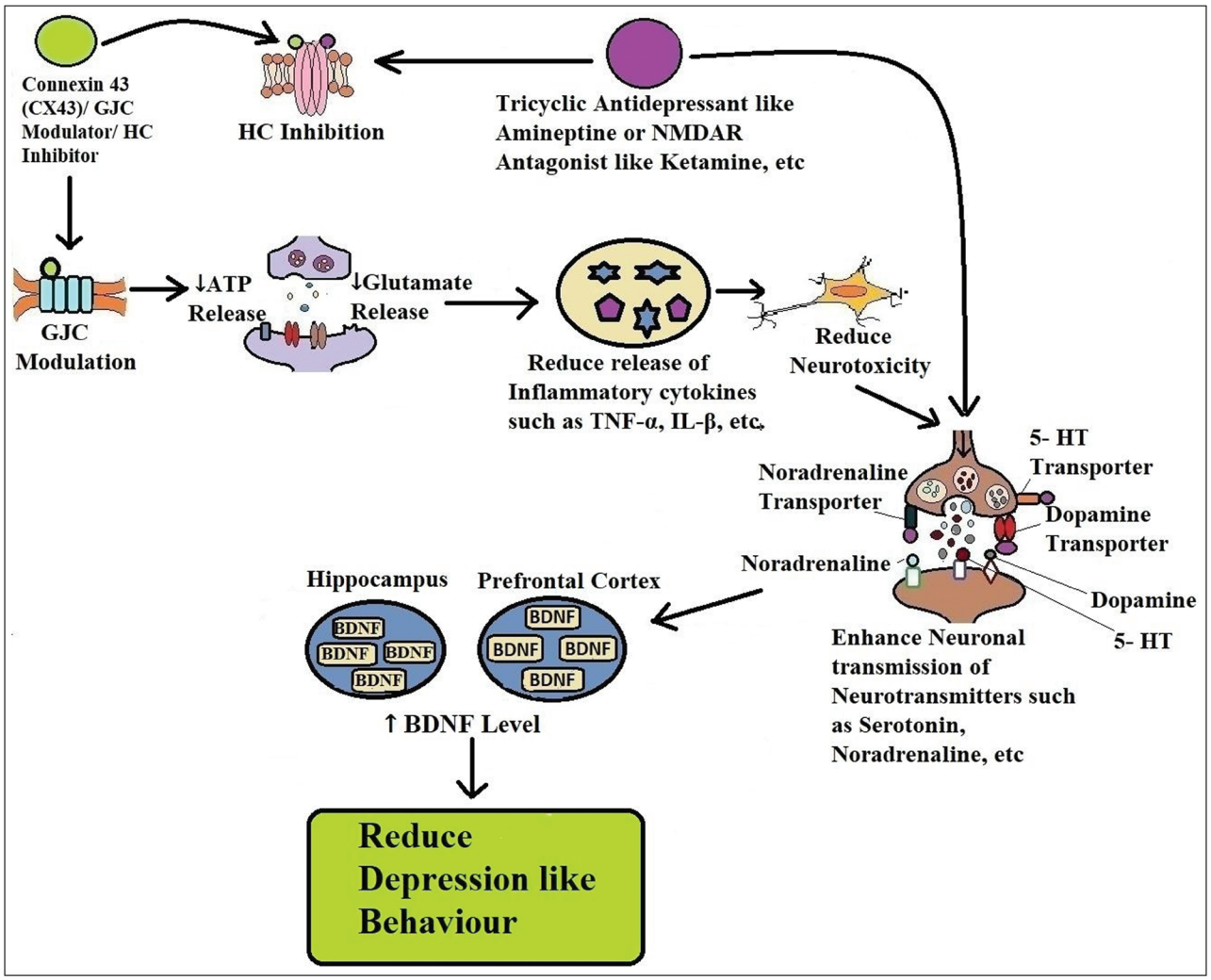

Figure 2: Possible synergistic antidepressant mechanism of GJC modulator/HC inhibitor[20,26] with NMDAR antagonist drugs such as ketamine, etc.[23,24,51]

in brain and also they plays an important role in regulating HPA axis.[53] ω-3 fatty acids derivatives such as resolvin, EPA, and DHA were involved in the neurotransmission of secondary messengers.[31,54] The role of ω-3 fatty acids derivatives such as resolvin, EPA, and DHA is explained in Figure 3.[31,54] The ω-3 fatty acids derivatives have a significant role in the synthesis of secondary messengers and thus may help in improving neurotransmission in depression.[3] The ω-3 fatty acids derivatives alone may not be as effective as in combination with standard antidepressant drugs and hence combining it with tricyclic antidepressants such as amineptine, etc. may potentiate the antidepressant effect [Figure 3].[3,30,31,54]

Synergistic antidepressant effect of RAAS-modifying drugs with SSRIs such as fluoxetine, etc.

The patient suffering from primary aldosteronism reported to have the highest prevalence of causing mood disorders.[55] The cross-sectional study carried out in primary aldosteronism patients showed a decrease in the prevalence of mood disorder when treated with MR antagonists.[55] The combination of losartan with nimesulide and ramipril with minocycline showed antidepressant effects in the chronic restraint stress-induced model of depression.[56] The losartan and ramipril block excessive corticosterone release and release of inflammatory mediator.[56] Activation of ATII type 1 receptor causes neurotoxicity, and activation of ATII type 2 receptor causes neurogenesis; hence, blocking ATII type 1 receptor and activating ATII type 2 receptor may show anti-depressant effect.[4] Activation of sigma 1 receptor in brain by RAAS-modifying drugs was responsible for BDNF synthesis in brain and thus it prevents depression-like behavior.[4] PRA activity is involved in mood disorders because variations in sleep cycle cause variations in PRA and thus RAAS-modifying drugs may help in treating mood disorders such as depression, anxiety, etc.[33] Alone ATII type 1 receptor blocker and ATII type 2 receptor agonist may not be effective, and hence it should be used in combination with SSRIs such as fluoxetine [Figure 4].[33-36]

Synergistic antidepressant effect of ceramide synthetase inhibitor/ASM inhibitor with tricyclic antidepressants such as doxepin, etc.

Stress inhibits autophagy in the hippocampus and thus caused depressive-like behavior in mice.[57] Amitriptyline induces autophagy in hippocampus in the stress-induced animal model

of depression by decreasing lysosomal ceramide concentration and thus preventing depressive-like behavior.[57] In MDD, there was an increase in ASM activity, further causing an elevation in inflammatory mediators such as TNFα and depletion in brain BDNF.[58] The standard antidepressant drug such as amitriptyline is an ASM inhibitor.[7] The ceramide synthetase inhibitor decreased the ASM activity in the stress-induced animal model of depression and thus it prevents

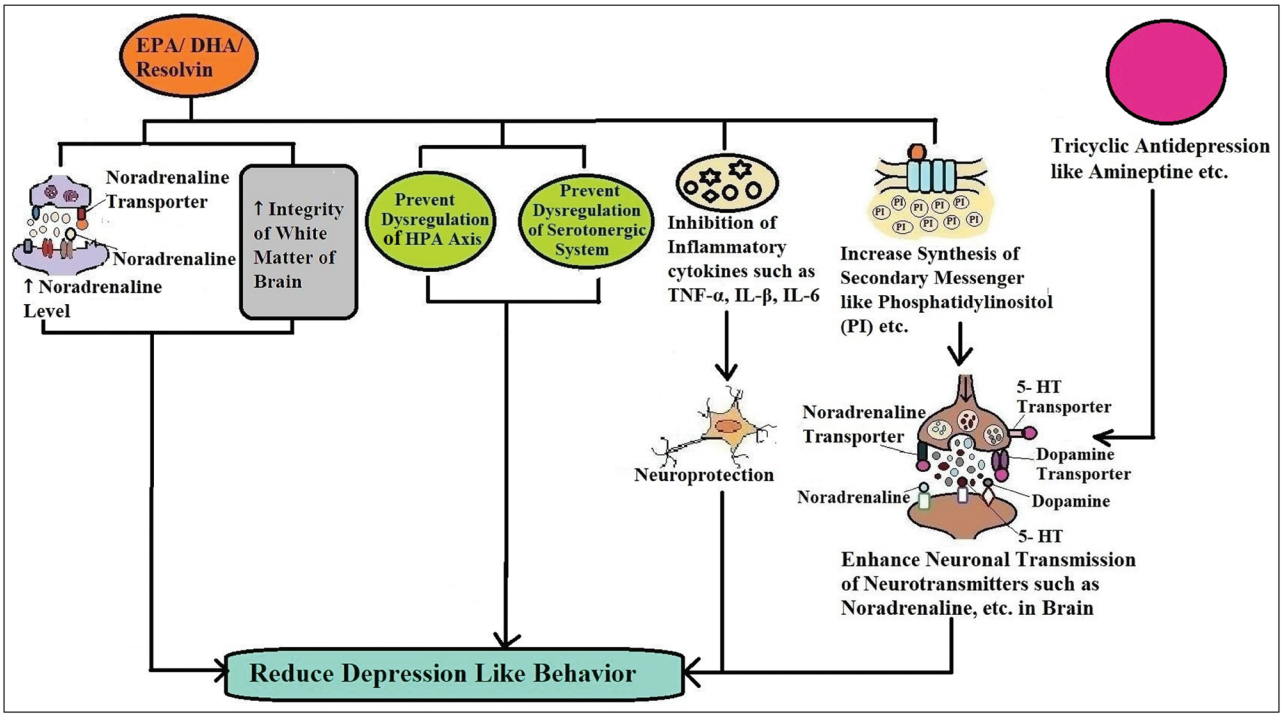

Figure 3: Possible synergistic antidepressant mechanism of ω-3 fatty acids derivatives such as resolvin[31,54] with tricyclic antidepressants such as amineptine, etc.[3,30]

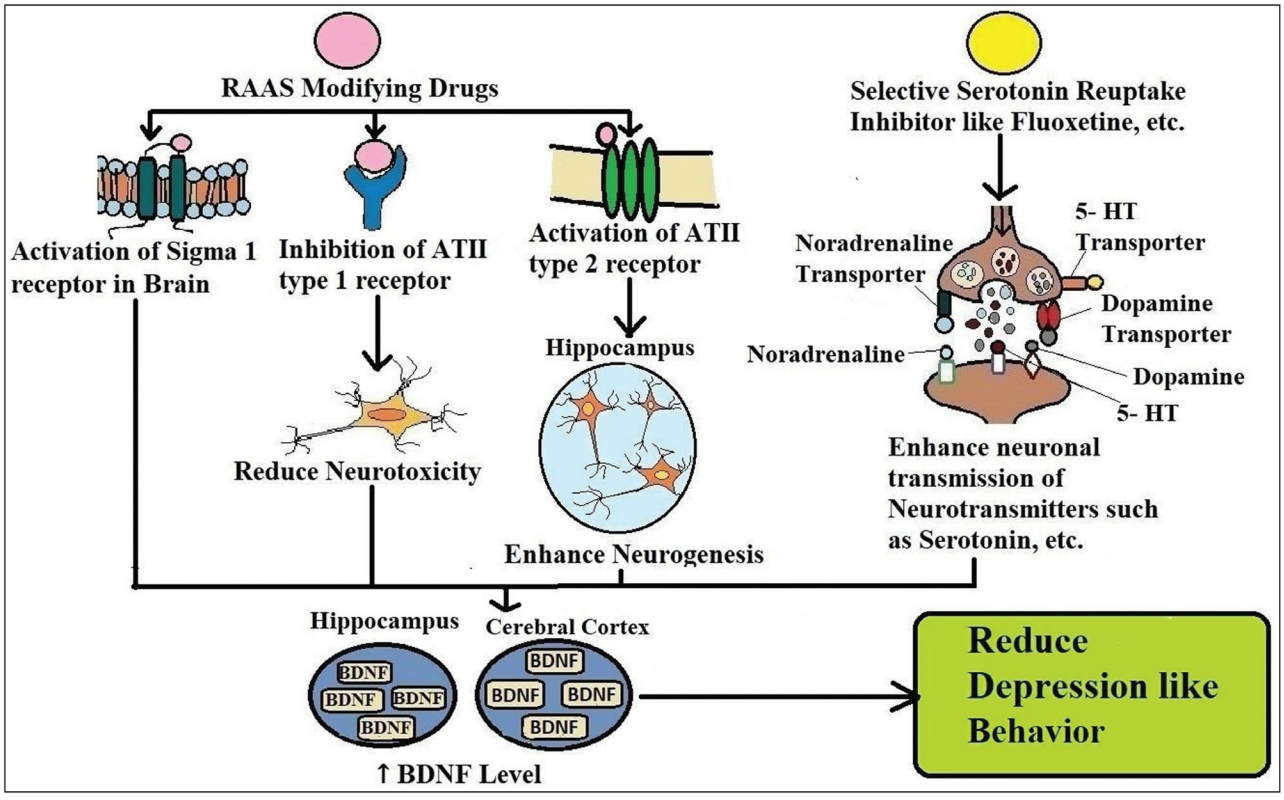

Figure 4: Possible synergistic antidepressant mechanism of RAAS-modifying drugs[33-35] with selective serotonin reuptake inhibitor such as fluoxetine, etc.[36]

neurotoxicity; further, it prevents deterioration of the BDNF level in hippocampus and prefrontal cortex.[7,59] Ceramide synthetase inhibitor also prevented inhibition of proliferation of neurons in hippocampus in the stress-induced animal model of depression and thus it prevented deterioration of the BDNF level in hippocampus and further benefited in reducing depression-like behavior.[59] Combining the ASM inhibitor/ceramide synthetase inhibitor with tricyclic antidepressant drugs such as doxepin may show synergistic effect [Figure 5].[5,7,37,59]

Synergistic antidepressant effect of HPA axis modifying drugs with NDRIs such as bupropion, etc.

HPA axis was dysregulated in patients suffering with from, so there was over secretion of CRH and cortisol synthesis, which further caused inhibition of negative feedback mechanism of cortisol and excessive release of inflammatory cytokines and glutamate. These may lead to neurotoxicity and occurrence of depression-like behavior.[39,40] The combination of NDRIs such as bupropion and HPA axis modifying drugs may show synergistic antidepressant effects [Figure 6].[8,39,40] There is a need to develop CRH antagonists, which would further help in treating depression.

Summary and Conclusion

The combination of PPAR (α/γ) agonists with NDRI, GJC modulator/HC inhibitor with NMDAR antagonist like ketamine, ω-3 fatty acids derivatives like resolvin with tricyclic antidepressants like amineptine, RAAS-modifying drugs with SRIs like fluoxetine, ceramide synthase inhibitor/ASM inhibitor with doxepin, and HPA axis modifying drugs with bupropion may show additive, augmentation, or synergistic antidepressant effect through multiple targets approach [Table 1]. These

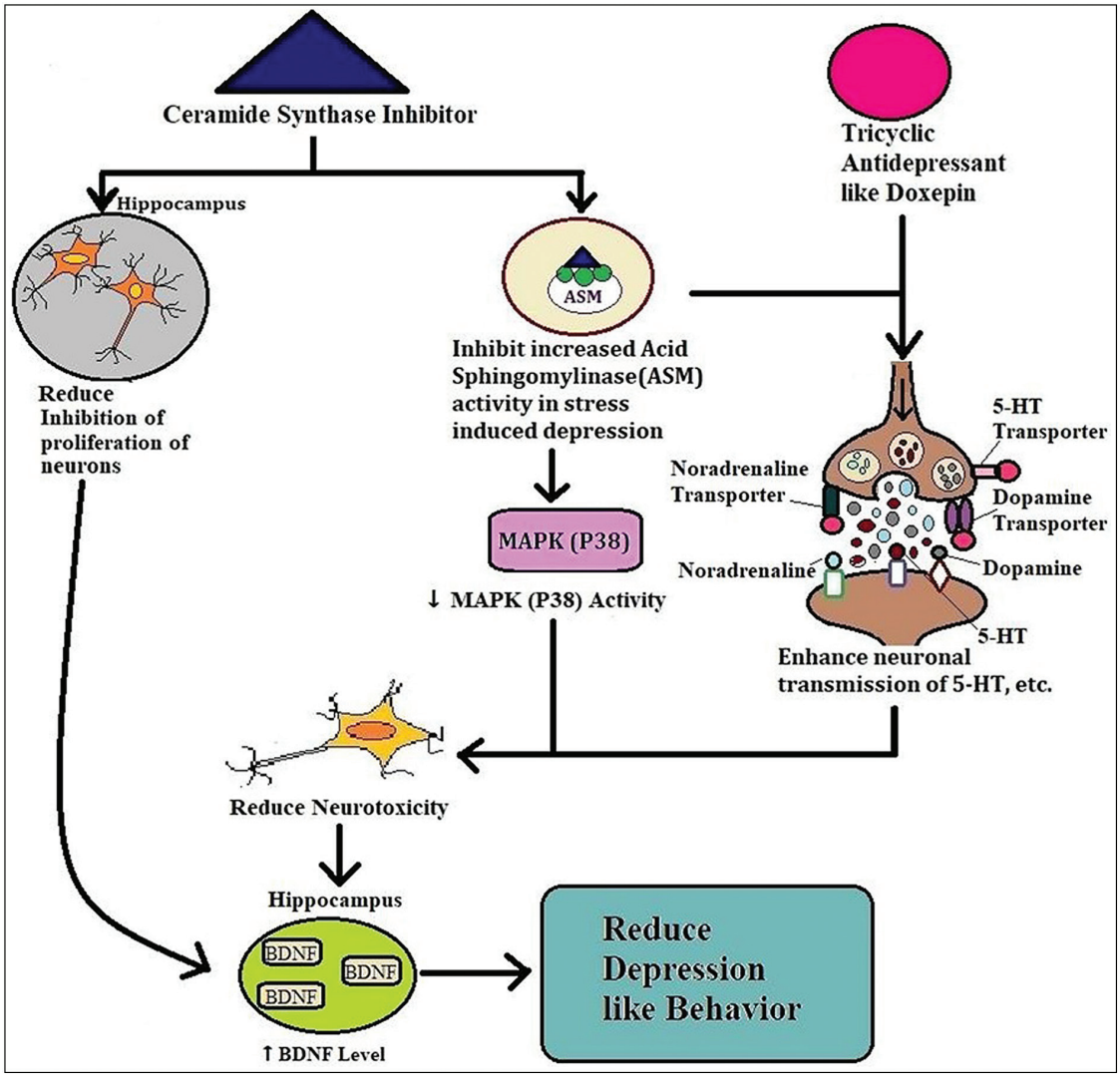

Figure 5: Possible synergistic antidepressant mechanism of ceramide synthetase inhibitor/ASM inhibitor[5,37,59] with tricyclic antidepressants such as doxepin, etc.[7,59]

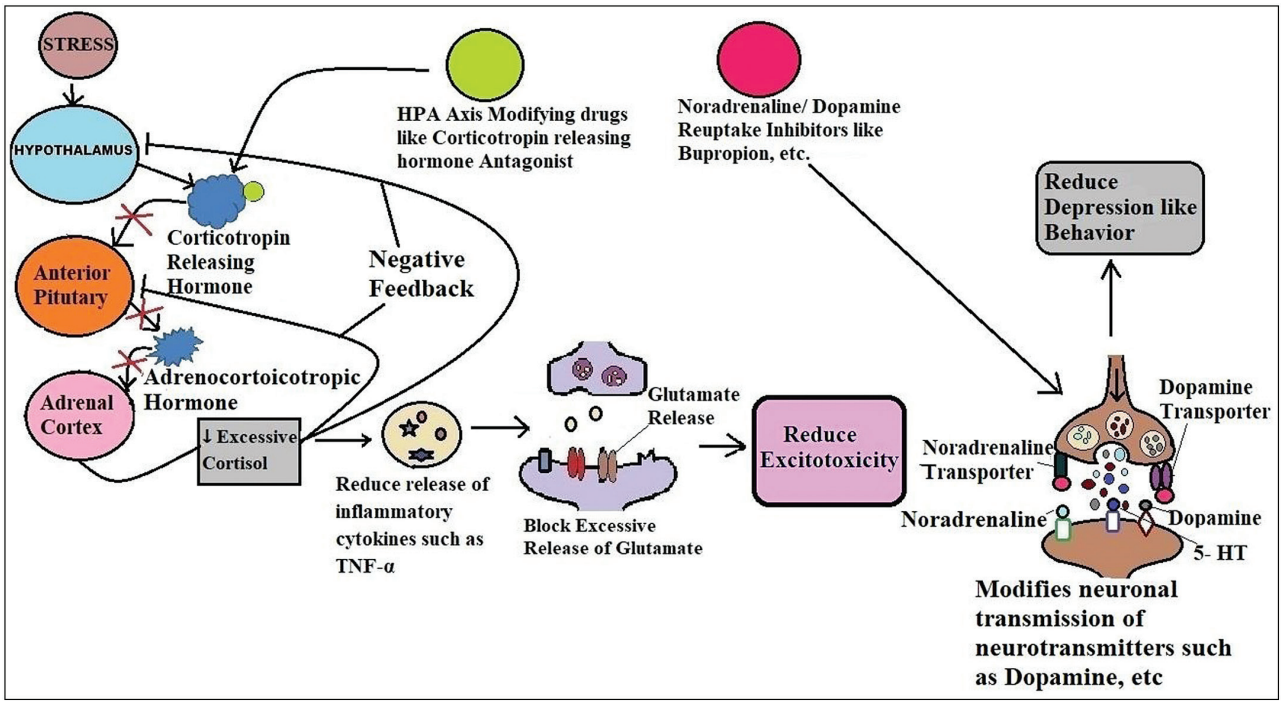

Figure 6: Possible synergistic antidepressant mechanism of HPA axis modifying drugs[8,40] with noradrenaline dopamine reuptake inhibitors such as bupropion, etc.[39]

Table 1: List of hypotheses consisting combination approach

Sr. no.	Combination approach
1	PPAR (α/γ) agonist[2,16,17,19] with noradrenaline dopamine reuptake inhibitor (NDRI)[18]
2	GJC modulator/HC inhibitor[20,26] with NMDAR antagonists like ketamine[23,24,51]
3	ω-3 fatty acids derivatives like resolvin[31,54] with tricyclic antidepressants like amineptine, etc.[3,30]
4	RAAS modifying drugs[33-35] with selective serotonin reuptake inhibitors such as fluoxetine, etc.[36]
5	Ceramide synthase inhibitor/ASM inhibitor[5,37,59] with tricyclic antidepressants such as doxepin, etc.[7,59]
6	HPA axis modifying drugs[8,40] with noradrenaline dopamine reuptake inhibitors such as bupropion, etc.[39]

therapeutic approaches need further assessment in different preclinical and clinical experimental settings.

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Conflicts of interest

The authors declare that they do not have any conflict of interest.

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