Potential Targets for the Development of Novel Antidepressants: Future Perspectives

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Abstract: Depression is an affective disorder characterized by hallucination, delusion and increased social risk and is estimated to affect approximately 20 % of the population at some point during the lifetime. As per World Health Organization (WHO) it is predicted to be the leading cause of burden of disease by 2030. Effects of currently available antidepressants have explained the monoamine hypothesis of depression, which proposes that impaired release of serotonin, noradrenaline and dopamine, are thought to be responsible for the development of depressive symptoms. However, these drugs are not specific for their action, as they also inhibit other enzymes; this explains the side effects/drug interactions associated with these agents. The present review will familiarize the readers with novel targets being identified for depression which will be certainly beneficial for researcher, academician for the development of drugs for the management of depression and related behavior.

Keywords: Cholinergic receptors, cocaine and amphetamine regulated transcript peptide, depression, histaminergic receptors, N-methyl-D-aspartate, oxidative stress, substance P.

INTRODUCTION

In early life, events substantially influence the brain development and consequent adult behaviors, may cause affective disorders like anxiety, depression and schizophrenia [1]. Depression is the affective disorder characterized by hallucination, delusion and increased social risk and is estimated to affect approximately 20 % of the population at some point during the lifetime. As per WHO, it is predicted to be the leading cause of burden of disease by 2030 [2]. In relation to this disorder, there is an increased explanation of negative information, difficulties disengaging from negative material, and deficits in cognitive control when processing negative information, which inter alia are responsible for negative thoughts and suicidal tendency in the individual [3]. Depression affects the mental performance along with impaired mood, cognition and other processes including sleep, appetite and libido [4]. Low mood is the most prominent clinical symptom of major depressive disorder and dispersion is often accompanied by significant impairments in neurocongnitive functioning that may be independent of depression, since cognitive impairment is seen in depression. In addition to cognitive disturbances, there are motoric, autonomic, and endocrine and sleep-wake abnormalities observed in depression [5-6].

Only one third of the patients receive adequate treatment and up to half of them relapse despite the increasing number of antidepressant drugs currently available [7]. Most of the symptoms of depression are interrelated and, thus, it may be complicated to exactly differentiate anxiety and depression. Anxiety and depression, as both dramatic and debilitating multi-facetic psychiatric illnesses, involve similar pathophysiological appearance and occurrences. Continuous and long lasting exposure to stressful circumstances results into anxiety, tension and finally depressive like symptoms. Pathophysiology of depression is presently documented with deficits in and/ impaired functioning of excitatory neurotransmitters viz serotonin and norepinephrine at post synaptic receptors [8-9]. The hypothalamic-pituitary-adrenal (HPA) axis dysfunction theory, based on hyperactivity of this system usually reflected in high levels of glucocorticoids, cognitive and behavioural theories and neurogenesis [10-11] also produce depressive like symptoms.

With such background information, we proposed various recent advances and novel targets that are certainly crucial in the management of depressive like symptoms. Hence, the present review will familiarize the readers with novel targets being identified for depression which will be certainly beneficial for researcher, academician for the development of drugs for the management of depression and related behavior.

CURRENT THERAPY OF DEPRESSION

The effects of presently used antidepressant drugs is based on the monoamine hypothesis of depression, which proposes that low levels or deficits in brain monoamines, such as serotonin, noradrenaline and dopamine, are responsible for the development of depression and or depressive like symptoms. The classes of these drugs include tricyclics and monoamine oxidase inhibitors (MAOI), noradrenaline reuptake inhibitors (NRI), selective serotonin reuptake inhibitors (SSRI), serotonin and noradrenaline

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reuptake inhibitors (SNRI), elicit antidepressants actions by potentiating or increasing the brain's monoaminergic system and elevating the monoamine levels [12].

The Tricyclic Antidepressants (TCAs)

All the tricyclic agents; imipramine, amitriptyline, doxepin and their metabolites potentiate the activity of noradrenaline and serotonin (5-HT) by blocking their reuptake results for the improvement of biological and emotional symptoms respectively. However, apart from these effects, TCA affects other receptor systems mainly, cholinergic, neurologic and cardiovascular and thus is responsible for their undesirable side effects [13].

Selective Serotonin Reuptake Inhibitors (SSRIs)

The SSRIs viz, fluoxitine, sertraline, citalopram, escitalopram, venlafaxine are common drugs demonstrating high selectivity for 5-HT reuptake and thus widely accepted as antidepressants. These agents inhibit selectively serotonin reuptake at a greater extent as that of noradrenaline, and induce lesser anticholinergic side effects, less dangerous at overdose too, and further in contrast to monoamino oxidase inhibitors, the SSRIs do not cause 'cheese reactions. Apart from their antidepressant action, the SSRIs are also prescribed in the management of obsessive compulsive disorder [14].

Monoamino Oxidase Inhibitors (MAOIs)

The MAOIs (phenelazine, tranylcypromine and iproniazid) produce irreversible inhibition of monoamino oxidase. Several studies have proposed a reduction in platelet MAO activity in certain groups of depressed patients, there is no clear evidence that abnormal MAO activity is involved in the etiopathogenesis of depressive like behavior. MAO-A is a substrate specific for serotonin and MAO-B is for phenylethylamine and both enzymes act on noradrenaline and dopamine. The MAO-A is the main target for antidepressant activity of MAOIs. The inhibition of MAO-A gene results into prevention of degradation of serotonin and thus concentration in synaptic cleft is increased [15]. In nerve terminals, MAO controls the free interneuronal level of serotonin or noradrenaline and therefore releasable stores of these neurotransmitters. Since MAOIs are not specific for their action, inhibit other enzymes too, this explains the side

FUTURE PERSPECTIVE IN DEPRESSION

Corticotropin-Releasing Hormone (CRH)

The key feature of the hypothalamus is to coordinate the nervous system through bridging to endocrine system *via* the pituitary gland and aid in secretion and release of hypothalamic-releasing hormones, and these in turn stimulate or inhibit the secretion of corresponding pituitary hormones. The CRH from the hypothalamus stimulates the release of adrneocorticotrophic hormone (ACTH), and subsequently higher cortisol concentration, the same was found to be high in depressed patients, treatment with amitriptyline reduces cortisol level significantly in these patients [16]. Supported with the fact that, depressed patients are more susceptible to suffer adrenal cortical hyperplasia, and the severity of depression was related to the density of cortisol as compared to non depressed patients [17]. The altered functioning of HPA axis is the most prominent and well-documented neuroendocrine abnormality observed in depression. The dysfunctional regulation of HPA axis could be a trait-rather than a state-related characteristic in depressed patients, leading to changes in hormonal responses [18]. The excessive cortisol release because of CRH resulted in impairment of functioning of hippocampus or locus ceruleus, and thus induced alterations in memory, attention, space perception, and behavior and finally development of affective disorders, including anxiety, depression and stress-related pathologies and dementia [19]. It also stated that the impairment of HPA axis during pregnancy may lead to symptoms similar to depression. The evidence supported with the findings of Burke and Roulet [20], the cortisol, ACTH, CRH and corticosterone binding globulin (CBG) levels were altered significantly during pregnancy and postpartum [20] and higher cortisol level during pregnancy and postpartum than during non-reproductive phases [21-22]. The CBG levels, increased during pregnancy and reduced with parturition [23-24] might responsible for the development of depressive symptoms in women. The aforementioned findings further supported that, administration of CRF, a positive modulator of alpha-melanocyte stimulating hormone, (α-MSH) elicited anxiogenic-and depressant-like behavior in experimental animals [25-26] and prevention/inhibition such behavior with Antalarmin, a CRF antagonist produced anxiolytic-and antidepressant-like effect [27-28]. Interactions of CRF with GABA and neuropeptide Y (NPY) on melanocortin receptors (MC) might play a probable role in the development of depression [29] suggesting the participation of NPY and MC receptors in the pathophysiology of depression. The HPA antagonists inhibit glucocorticoid synthesis and thus stress related behavior was abolished. Antagonist of corticosteroids, vasopressin or CRF, or blocking the actions of inflammatory cytokines, found to elicit antidepressant-like activity in animal models of depression [30].

Stress is characterized by physiological changes that occur in response to novel or threatening stimuli. These changes comprise a cascade of neuroendocrine events mediated by sympathetic nervous system and the HPA axis. Chronic exposure to stressful conditions results in impairment of the hippocampal inhibitory control on HPA axis *via* multisynaptic pathways projecting from the subiculum to the paraventricular nucleus (PVN), glutamatergic projections to the bed nucleus [31], the lateral septum, and different hypothalamic nuclei, all of them send GABAeric projections to the PVN Changes in these nuclei were restored/reduced with chronic antidepressant treatment [32-33]. With such effects during early life as well as in adulthood, it alters hippocampal neurogenesis and plasticity due to neuronal cell death and atrophy of neuronal process. Since, hippocampus neurogenesis has been implicated in cognitive function, therefore, reduction in neurogenesis by cortisol manifested into impaired cognitive symptoms in depression [35].

Substances P

Substance P is one of the groups of neuropeptides called as tachykinins. There are mainly 3 known members of this group: substance P, neurokinin (NK) A, and NK B. The receptors for these 3 neuropeptides are known as NK1, NK2, and NK3, respectively. Substance P is not only present in brain; it is also present in spinal cord tissue. Growing evidence suggest Substance P (SP) might play a significant role in depression and anxiety related disorders. Various experimental findings demonstrated the SP level was found to be increased in major depression [36], mice that cannot produce SP and NKA, or with a genetic ablation of the NK1 receptor gene, are less prone to show depression related behaviors in several animal models [37-38]. Studies mapping the expression of SP and NK1 receptors in neural circuits found large concentrations in the amygdala, hypothalamus and hippocampus, areas that are thought to be critical for regulating emotions [39]. SP is found to display the highest affinity for tachykinin; type 1 [NK1] receptors [40]. The behavioral studies evaluated by Kramer *et al.* (2004), by using brain-penetrant NK1 antagonists in a species (guinea pig) with NK1 pharmacology similar to that seen in humans provided evidence that selective blockade of the NK1 receptor was associated with an antidepressant-like profile. L-759274, a highly selective nonpeptide NK1 antagonist, is an efficacious and well tolerated antidepressant [38, 41]. Malkesman *et al.* (2007) suggested that it is unclear whether there is a complete involvement of substance P in depression; however, their findings reveal that NK1 receptors antagonists are effective in the relief at least with some symptoms of depression [42].

NK2 binding sites in several limbic structures viz hippocampus, septum, and the amygdala, hippocampus, cortex, dorsal raphe nucleus and thalamus and in periphery. The participation of the NKA/NK2 system could result in the intonation of emotional processes including depression. It is demonstrated that, modulation of NK2 is implicated in stress related anxiety and depression [40, 43] in various experimental animals. Furthermore, interactions of tachykinins with CRF increase noradrenergic population in locus coeruleus, and this action is antagonized by saredutant, NK2 receptor antagonist suggesting the involvement of NK2 receptors during CRF- mediated anxiety and depression [44]. These results are in agreement with the findings of Louis *et al.* that the effects of saredutant were comparable to those obtained under similar experimental conditions by fluoxetine or imipramine [45]. Pharmacological blockade of NK2 receptors results in a clear anxiolytic- and antidepressant-like effect in rodents [45]. The role of NK-2 receptor in depression is elucidated in Fig. (**1**).

NK3 receptors, located in periphery and, predominantly in striatum [46], might play a role in the modulation of excitatory neurotransmitter into the synaptic cleft and thus excitation of neuronal membrane. This proposal is in agreement with the findings of Stoessl *et al.* (1987), in which NK 3 receptors ligand increase the concentration of excitatory neurotransmitter 5 HT, and NA in synaptic cleft and thus induces antidepressant like activity [47]. This hypothesis is supported with the findings of NK3 receptor agonist aminosenktide which displayed antidepressant-like activity in the forced-swim test, a widely used model of depression, when a mouse line with over activity of the opioid system was used [48].

Calcitonin Gene Related Peptides (CGRPs)

The CGRP is a member of the calcitonin family of peptides that acts as a major neurotransmitter and exists in two forms, α-CGRP and β-CGRP. The α-CGRP formed from the alternative splicing of the calcitonin/CGRP gene located on chromosome 11 and β-CGRP differs in 3 amino acids is encoded in a separate gene. Both, CGRP-1 and CGRP-2, are selectively distributed in the CNS, often localized on the dopaminergic neurons [49-50] CGRP fibers are highly localized in the brain mainly in the frontal cortex, amygdala, and nucleus accumbens [51]. The CGRP through modulation of dopaminergic and noradrenergic neurons exerts various biochemical and behavioral effects in the CNS. The prime role of CGRP in CNS is known and in the dorsal horn of the spinal cord is responsible for the transmission of pain [52]. The interaction of CGRP with dopamine affects its release and metabolism in selected brain regions and thereby altered learning and memory process [53-54] in experimental animals and these are responsible for the development of depressive like symptoms. The CGRP acting within the bed nucleus of the stria terminalis (BNST) induced anxiety, and behavioral stress responses [55]. The administration of CGRP into the lateral ventricle, activate the HPA axis [56] through BNST results in anxiety and depression related behavior. Therefore, the HPA activation thorough CGRP might participate in the pathophysiology of depression. Although, there is no direct relation of participation of BNST in depression though the CGRP, however, indirectly through the activation of HPA axis and anxiety related behavior results in depressive like behavior [56].

Research findings reveals the CGRP-like immunoreactivity (CGRP-LI) in the CSF was increased in depressed patients as compared to healthy control [57], these effects are in agreement with the findings of Wortwein *et al.* (2006), where they demonstrated the CGRP-LI elevated in hippocampus and frontal cortex of "genetically depressed" Flinders Sensitive Line rats, and thus, these brain regions, hippocampus and frontal cortex are implicated in the neurobiology of depression [58]. The CGRP induces neurophysilogical reactions characterized by fear response which injected directly into amygdale [59]. The CGRP increased haloperidol-induced catalepsy and decreased apomorphine-induced hypermotility at the doses of 1 and 100 ng/rat and these behaviors are mainly due to the involvement of dopamine [60]. From this observation, CGRP's participation in the relation to release of neurotransmitters including 5HT, NA can not be ruled out. Further, in another study, CGRP/calcitonin concentration ratio was increased, which is consistent with a possibility of an altered splicing process favoring CGRP mRNA [61]. The increased depression-like behavior in the forced swim and sucrose preference tests, increased hippocampal expression of α-CGRP transcripts, and decreased methylation of the α-CGRP promoter compared with those gestated by cJ dams in adult hybrid mice gestated by B6 dams [62]. The differential expression of α-CGRP in adulthood did not result from the genomic imprinting, and differences between B6 and cJ mitochondrial DNA was not found to be responsible for

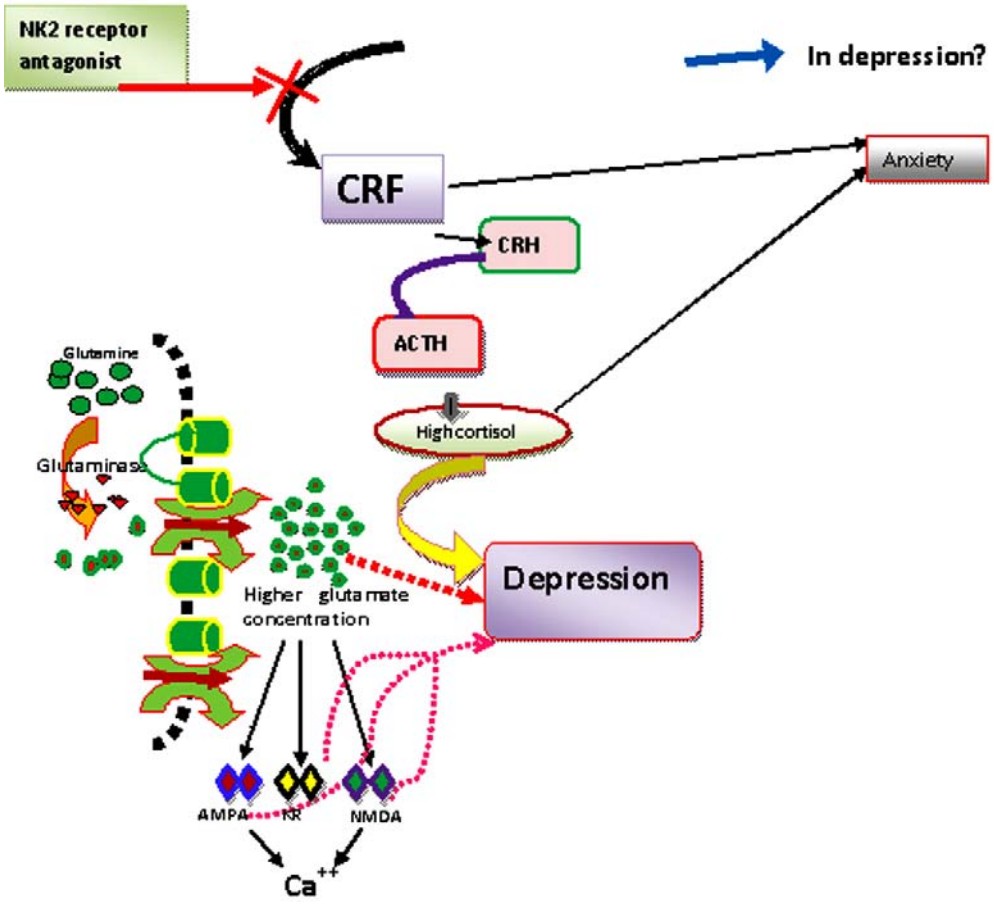


Fig. (1). Role of glutamate, cytokines, Tachykinins and cortisol level in depression. AMPA, (α-amino-3-hydroxy—5-methyl-4-isoxazole propionic acid; KR-Kinate receptor, NMDA-N-methyl-d-aspartate receptor, CRH-corticotropin releasing factor, ACTH-adrenocorticotrophic hormone.

behavioral phenotypes [62]. Administration of α-CGRP to adult hybrid mice induced depression-like behavior, the CGRP (1) receptor antagonist on other hand reduced depression-like behavior in the forced swim test. Furthermore, Jiao *et al.* (2012) confirmed gestational factors influence adult depression-like behavior through the methylation of the α-CGRP gene [59]. In contrary to these findings, intracerebroventricular administration of CGRP into the third ventricle in AKR and C57BL/6 mice decreases depression-like behaviors [63].

N-Methyl-D-Aspartate (NMDA)

The glutamate receptor channels mediate most of the fast excitatory synaptic transmission in the CNS and are classified into three major receptor channel subtypes, the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), the kainate, and N-methyl-D-aspartate (NMDA). Glutamate exerts its effects either ionotropic glutamate (iGlu) or metabotropic glutamate (mGlu) receptors. It is considered that depression might be related to impairment in the functioning glutamatergic system. The NMDA receptors are assembled from the two types of subunit, NR1 and NR2, each of them can exist in different isoforms in the brain. NR1 subunits co-assembled with varying expression of NR2 family of subunits, i.e. NR2 (A-D) and less commonly NR3 (A-B) subunits [64]. These subunits have different pharmacological properties and their presence in brain, and they play an important role in adjusting a cell's excitability threshold for synaptic modification. Depressed patients exhibit elevated levels of glutamate both in plasma and the limbic brain areas, which are believed to be involved in mood disorders [65]. Riluzole, an anticonvulsant agent produces antidepressant action through glutaminergic system [66]. Involvement of glutamate system in the depression is implicated and is demonstrated by administrations of D-cycloserine, a partial NMDA glutamate agonist, elicits antidepressant like activity [67]. Furthermore, alterations in glutamate signaling as well as changes in the expression of AMPA or NMDA receptors subunits also observed in experimentally induced depression [64]. Skolnick, (1999) suggested the inhibition of metabotropic glutamate subunit 5 (mGlu5) receptors, may produce a final effect similar to that exerted by NMDA receptor antagonists, which are known to display antidepressant-like effects [67]. Functional antagonists of NMDA receptors showed antidepressant-like effects in several screening methods [68-70]. These findings are in agreements with reports of Zarate *et al*. [66], in which they showed, acute administration of the NMDA receptor antagonist ketamine produced a rapid antidepressant response, lasting for several days. These data indicate the hyperfunction of NMDA (iGlu) may lead to a depression

and blockade of this NMDA receptors could be an approach [71-72]. Blockade of NMDA receptors produces more profound undesired reactions, such as psychotomimetic effects, memory dysfunctions, ataxia, neurodegeneration, and drug dependence [73], which makes them poor drug target. However, it is possible that substances acting / modulating the metabotropic glutamate receptors might be much safer antidepressants drugs, free of adverse effects, and with a reasonably fast onset of action. mGlu receptors, particularly subtypes mGlu5 receptors, which are mainly present postsynaptically, may play a role in affective disorders including depression. Although there is no evidence for the drugs or agents acting/modulating mGlu receptors demonstrate the antidepressant activity in clinical practice or in experimental animal. Further studies are required for the mGlu agonist or modulators for these receptors to prove the therapeutic target in the treatment of depression and associated symptoms.

Cholinergic Receptors

Acetylcholine is widely distributed in the brain, forebrain, midbrain and brain stem. Cholinergic neurons in the forebrain and brain stem send diffuse projection to many parts of cortex and hippocampus. *Septohippocampal pathway* is the main cholinergic input to the hippocampus and is involved in the memory process. The cholinergic system is known to be responsible for a number of CNS functions, including arousal, attention, learning and memory [74]. Dysfunctioning of *Septohippocampal pathway* may lead to poor attention, concentration and impaired memory and information processing [75]. Acetylcholine is known to exert excitatory effects, mediated through central cholinergic receptors (nicotinic and muscarinic). The response through these receptors contributes to both mood and cognitive symptoms of depression [74].

Various experimental findings demonstrated the participation of nicotinic cholinergic system in depression which includes : (a) rates of smoking in people with major depressive disorder range between 50% and 60%, far higher than smoking prevalence in the general population [76], (b) individuals with depression who smoke, have a greater likelihood to experience a major depressive episode upon smoking cessation [77] and (c) nicotine supplementation ameliorates depressive symptoms, even in non-smokers [78]. The cholinergic dysfunctions may account for the development of cognitive symptoms associated with depression, especially when the disease is long lasting and treatment resistant. It has also been suggested that the central cholinergic system plays an important role in the etiology of affective disorders, and depression was proposed to be a disease of cholinergic dominance (Fig. **2**). There is an ample evidence that cholinergic muscarinic agonists facilitate learning and memory whereas antagonists are associated with deficits in these processes [79-81]. The behavioral aspects of depression are a significant impairment in neurocongnitive function. Many of the behavioural effects associated with cholinergic pathway seem to be produced by acetylcholine through nicotinic receptor. However, Scarr (2009) suggested that the modulation of muscarinic system is known to reduce the depression associated symptoms [82]. Evidence of the involvement of acetylcholine in depression mainly arises from drug targeting nicotinic or muscarinic receptors [83], whether or not the nicotinic cholinergic receptor involved in the modulation of symptoms of depression is uncertain. The involvement of nicotinic cholinergic receptor was studied by Slotkin and Seidler, (2006); they demonstrated the down regulation of striatal α-7-nicotinic acetylcholine receptors (α7 nAChRs) in olfactory bulbectomised rat model of depression [84]. The experimental findings of Piccoto *et al.* both activation and desensitization of nicotine acetylcholine receptors have been suggested to contribute to behavior related to nicotine addiction and mood [85]. It is unclear that the exact role of either modulation of nicotinic or muscarinic receptors for the amelioration of depressive mood. Citalopram, a selective serotonin reuptake inhibitor has been demonstrated to improve memory impairment in depression by enhancing the acetylcholine level in hippocampus in laboratory animals [85]. Moreover, stress, the most important factor, is responsible for the impaired functioning of acetylcholine in CNS. As the stress response causes the release of acetylcholine in the forebrain and thus helps in activating the *Septohippocampal pathway* [86]. From this finding, one may certain to firm that acetylcholine likely to functions as a neurotransmitter and its modulation by various novel drugs might beneficial in the management of depression.

Histaminergic Receptors

Histamine is also an important neurotransmitter, has a role in arousal, alertness, learning, memory, appetite and the perception of pain. Therefore, histamine imbalances might result in alterations of mental illness, fatigue, eating disorders, self-mutilation, or addictive behaviors. Neuroanatomical studies demonstrated the direct hypothalamocerebellar pathways in the mammalian brain. The direct hypothalamocerebellar fibers that reach the cerebellar cortex and the cerebellar nuclei are comprised hypothalamocerebellar cortex and the hypothalamocerebellar nuclei projections, respectively and the histamine functions as a neurotransmitter in these pathways [87-88]. Cerebellar cortex plays an integral role in fine-tuning motor controls, apart from this function, it also contributes to cognition, language and emotion. Hence, cognition and emotion are the majority of symptoms that are noticed during depression. Therefore, possible role of cerebellar cortex in depression can not be ruled out. Histamine receptors are G-protein coupled receptors (GPCRs) and are classified into 4 distinct types (H1R, H2R, H3R, and H4R), the four histamine receptor subtypes are distinct in terms of their pharmacology and molecular biology and have been implicated in diverse biological effects of the neurotransmitter histamine [89]. The H1R are located in the brain stem hypothalamus, thalamus amygdala, septum hippocampus olfactory bulb and cortex, whereas, H2R is found in the basal ganglia, amygdala, hippocampus, and cortex. The endogenous histamine reduces the time of immobility in the forced swimming test, suggesting an antidepressant-like effect, *via* activation of H1 receptors [90-91]. The Tricyclic antidepressants also block H2R in brain suggesting the involvement of H2R in depression [92]. However, the implication of H2R in pathophysiology of gastric ulcer is predominant due to its abundant location in stomach as histamine controls gastric

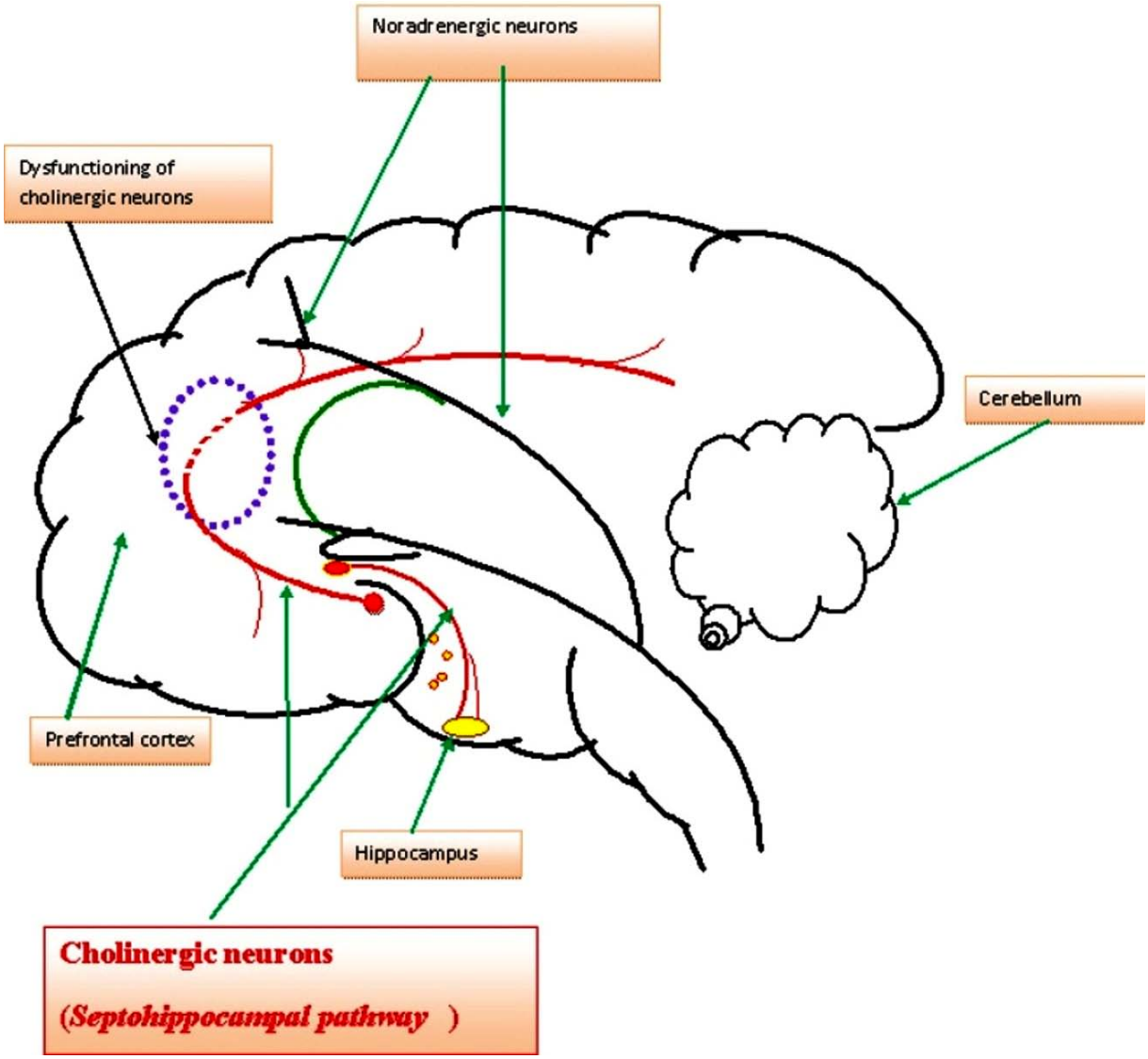
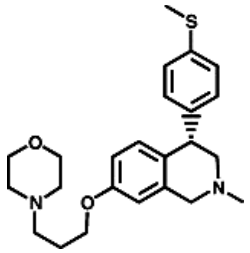


Fig. (2). Dysfunction of cholinergic innervations in prefrontal cortex.

acid secretion by activating the proton pump in parietal cells through H2R activation [93-94]. The H3R has been identified as a mainly presynaptic autoreceptor, regulating the release of histamine as well as a heteroreceptor on non-histaminergic neurons that is capable of regulating the release of many other important neurotransmitters, such as acetylcholine, norepinephrine, dopamine and serotonin [95-97], thus, an indirect release of these neurotransmitters through H3R might be beneficial for the management of depressive symptoms. Recently, JNJ-17216498 [chemically 2-Methyl-4-(4-methylsulfanyl-phenyl)-7-(3-morpholin-4-yl-propoxy)-1,2,3,4-tetrahydro isoquinoline], an H3R antagonist, is discovered and found to have *in vivo* functional activity at the histamine H_3 receptor. It also significantly increased cortical extracellular levels of serotonin at doses of 0.3 mg/kg (s.c.) and higher, showed antidepressant-like activity in the mouse tail suspension test at doses ranging from 3-30 mg/kg p.o. [98]. Experimental findings demonstrated, JNJ-28583867 is a combined histamine H_3 receptor antagonist-SERT inhibitor with *in vivo* efficacy in biochemical and behavioral models of depression and wakefulness useful in narcolepsy patient [98]. Furthermore, H4 receptors on human and rodent neurons highlight their implication in neuronal functions their location in the areas of CNS viz. hippocampus, thalamus, amygdala, cortex, striatum and spinal cord studied [99-100]. The role of H4R in depression was studied and experimental findings demonstrated the activation of cerebral H4 receptors was devoid of any effect on the mobility time in the mouse tail suspension test, indicating the lack of any antidepressant-like effect by this histamine receptor subtype [100].



JNJ-28583867- H_3 receptor antagonist

Cocaine and Amphetamine Regulated Transcript

Cocaine and amphetamine regulated transcript (CART) is a peptide expressed in the hypothalamus and major limbic structure [98-100] and various studies have been conducted for the presence and distribution of CART in brain and their behavioural/neurological effects. The CART is expressed in the olfactory bulb, sensory cortex, midbrain, thalamic nuclei, nucleus tractus solitarius, ambiguous, parabrachilis, lateral hypothalamus, raphe nuclei, hippocampus, paraventricular nucleus of hypothalamus (PVN), arcuate nucleus (ARC) etc [101, 104-105]. The CART found to modulate affective and anxiety behaviors [106]. Ma *et al.* (2007) suggested that an increase in 5-HT may contribute to antidepressant like effects of CART [107]. Various experimental findings reveal, CART elicited anti-depressant like actions and related neurodegenerative disorders [108-109], moreover, the CART immunoreactivity profile in different component that processes depression related information by use of Porsolt's forced swim test [110]. The participation of CART in the regulation of ethanol withdrawal induced anxiety like behavior within the framework of central nucleus of amygdala. Since amygdala is a center critical for the regulation of several psychological behavior including depression. The experimental outcomes of Dandekar *et al*., confirm that the endogenous CART may be involved in the regulation of depression like behavior possibly *via* central nucleus of amygdala [111] and this supported the observation that adolescents carrying a missense mutation in the CART gene exhibited anxiety and depression [112]. These findings also supported the fact that CART in the regulation of the HPA axis, is believed to be altered and is considered to be one of possible pathogeneses in major depression [113-114]. The therapeutic implication of CART in the treatment of depression and its antidepressant effects might be through the expression of excitatory neurotransmitters viz. 5-HT, noradrenaline and dopamine [107] or through the Brain-derived neurotrophic factor (BDNF), kinases (trkB) [108]. Antidepressant effect of CART might be due to increased level of extracellular signal-related kinase (ERK) phosphorylation that is associated with a variety of growth factors, hormones and neurotransmitters [115]. However, Dandekar *et al.* suggested the regulation of depression-like behavior might be due to anterograde transport of CART from the PVN and ARC neuronal cell bodies to the amygdala in olfactory bulbectomy as well as socially isolated rat models [111]. Taken into consideration, the possibility that endogenous CART system plays a major role in mediating symptoms of depression and could be a target for treating depression behavior by increasing the CART level/concentration. Fig. (**3**) depicted that the modulation of CART by novel activators might be beneficial in the management of depression.

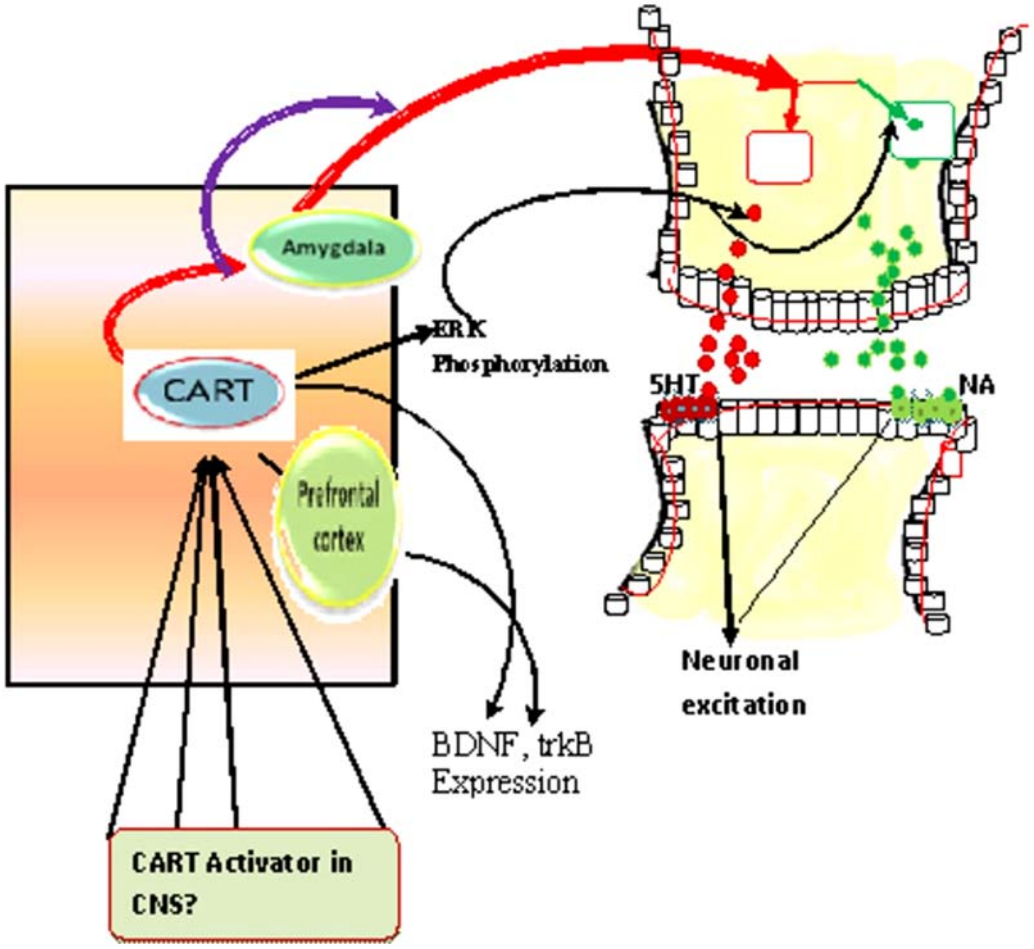


Fig. (3). Modulation of CART functioning in depression, CART-cocaine amphetime regulated peptide, BDNF- Brain-derived neurotrophic factor, trkB-tyrosine kinase B, 5HT-serotonin, NA- noradrenaline.

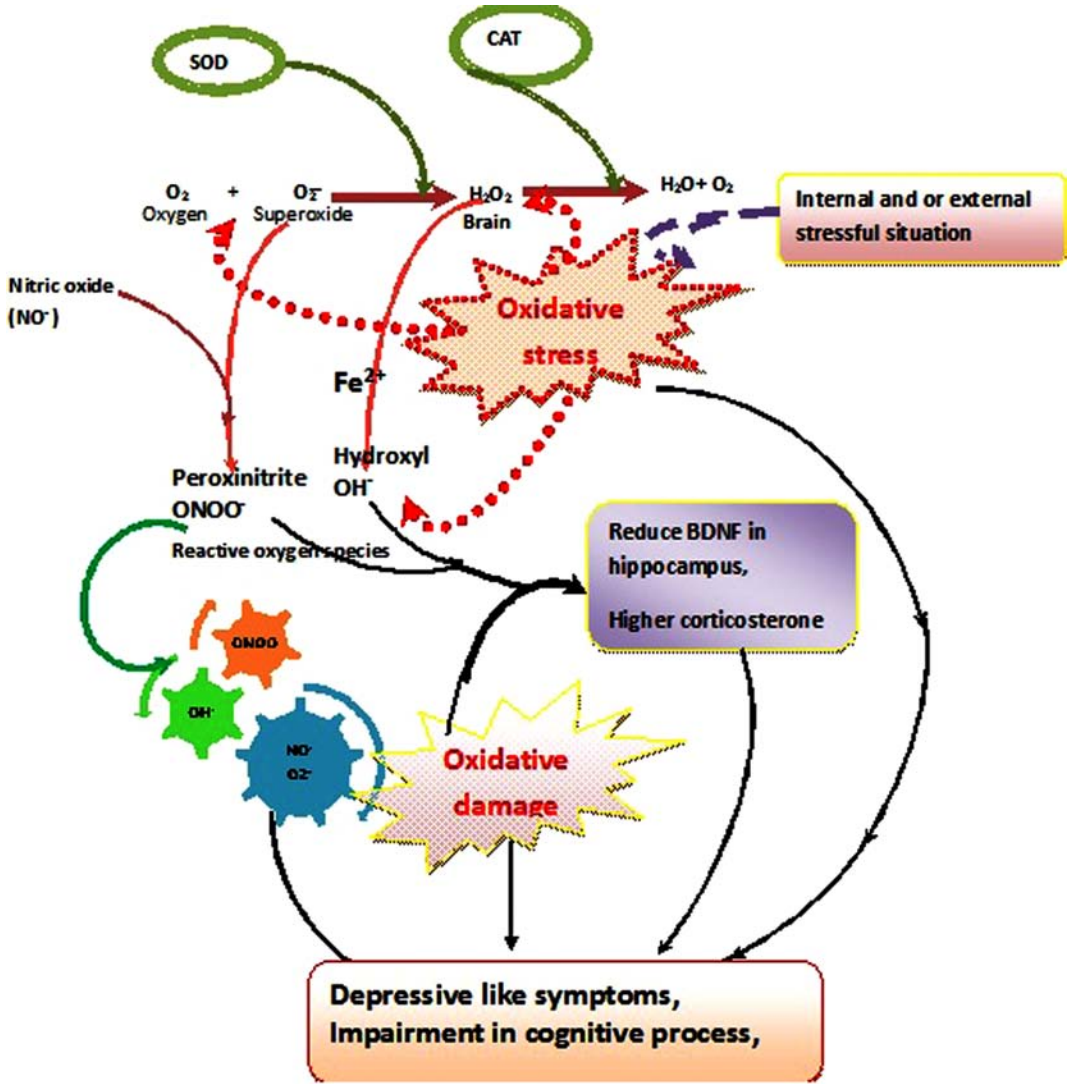


Fig. (4). Schematic representation of role of oxidative stress, production of free radicals, endogenous antioxidant enzymes; superoxide dismutase (SOD), and catalase (CAT); BDNF (brain derived neurotrophic factor) that collectively results in induction of depressive like symptoms and impairment in cognitive functions.

Oxidative Stress

The brain, being the master regulator of the body, suffers from the oxidative stress easily as compared to other organs. This might be due to either of these reasons: (a) presence of iron in brain which is responsible for higher free radicals formation, (b) low concentration of endogenous antioxidant enzymes in the brain and or (c) the presence of high amounts of lipids and fatty acids in the brain, makes the brain more susceptible to peroxidation process which manifests into increased oxidative stress and subsequently leading to increased formation of free radicals [116]. The lack of neuronal regeneration in all but certain stem-cell regions further renders the brain more vulnerable to oxidative stress. The generated free radicals are then produced damage to DNA, protein, neuronal membrane integrity, and mitochondrial dysfunction of neuronal cells (Fig. **4**). Oxidative stress is the imbalance between oxidant and anti-oxidants in favor of the oxidants, leading to a disruption of the redox signaling and control and/or molecular damage [117]. Use of an oxidative stress index, defined as the percent ratio of total peroxide plasma concentration to the total antioxidant potential, one can link between oxidative stresses with higher Hamilton Depression Rating Scales [118]. Stressful situations are believed to be important in the development of human psychopathologies including anxiety, depression, and impairment in the cognitive functions [119-121]. It is further demonstrated that, excessive oxygen free radicals production has been observed in patients with depression and anxiety due to oxidative stress [122] and simultaneous decrease in the endogenous antioxidant defense activity [123]. Experimentally induced depression in rats and mice supports oxidative stress which plays an important role in depression. Oxidative stress is measured in terms of estimation of superoxide dismutase (SOD) glutathione peroxidase (GSH-Px) and catalase (CAT) enzymatic activities, formation of malondialdehyde (MDA) and nitric oxide (NO) (mainly in hippocampus, prefrontal cortex, and amygdale).

Since, enzymatic functions lowered and increased MDA formation was observed in experimentally induced

depression in animals [124-125]. Currently used antidepressants, fluoxetine, citalopram, fluvoxamine or sertraline produce decreased NO, levels restored depleted SOD, GSH [126] and MDA formation and improved enzymatic activity of endogenous antioxidants [127]. In addition, venlafaxine, a serotonin-norepinephrine reuptake inhibitor, was shown to protect against stress-induced oxidative cellular and DNA damage, decreased the hippocampal MDA and NO and increased hippocampal GSH, total antioxidant levels in mice [127]. Therefore, the prevention and/or reduction in oxidative stress are one of the mechanisms involved in depression or its associated symptoms. This statement is agreements with various experimental findings, demonstrating antidepressant activity through antioxidant activity, by restoring depleted antioxidant enzymes and prevention of MDA formation due to oxidative stress [122-123, 126].

Moreover, neurotrophic factors are also involved in pathophysiology in the induction of depressive like symptoms [128], brain-derived neurotrophic factor (BDNF), one of the important neurotropic factors, and the reduced amount of BDNF in serum was demonstrated during oxidative stress in animals [129]. Chronic treatment with natural flavonoids, curcumin and resveratrol, increased hippocampal BDNF expression in mice [129-130].

CONCLUSION

Currently, several anti-depressants drugs are available for the management of depression, however, due to lack of specificity of presently used antidepressants and their side effects, it is requisite to discover and develop newer anti-depressants. Various targets like NMDA, SP, histaminergic receptors, cholinergic receptors, CART are now being investigated for their involvement in depression. Along with these targets, the most important being oxidative stress, is responsible for depressive like behavior, prevention of oxidative stress by antioxidants mainly from natural sources will be beneficial in augmenting such behavior. It is expected that having a better understanding of these targets and their insight pathophysiological implications in depression, a novel, safe and effective molecules would be made available for depression.

LIST OF ABBREVIATIONS

AMPA = α-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid

BDNF = Brain-Derived Neurotrophic Factor

CART = Cocaine and Amphetamine Regulated Transcript

CAT = Catalse

CGRPs = Calcitonin Gene Related Peptides

CRH = Corticotropin-Releasing Hormone

FST = Forced Swim Test

HPA = Hypothalamic-Pituitary-Adrenal

MAOI = Monoamine Oxidase Inhibitors

NK = Neurokinin

NMDA = N-Methyl-D-Aspartate

NPY = Neuropeptide Y

PVN = Paraventricular Nucleus

SOD = Superoxide Dismutase

SP = Substance P

SSRI = Selective Serotonin Reuptake Inhibitors

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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