

## **Depression: Current Therapy and Novel Anti-depressant Drug Targets**

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### **Summary**

Affective disorders such as depression and anxiety are a major cause of disability and place a burden on society from both economic and social perspectives. In spite of over 50 years of effort in drug discovery and development, a substantial increase in the efficacy of antidepressant therapies has not been achieved, although improvements in safety and tolerability have been observed in newer drug therapies. Despite the advances in the anti-depressant therapy with various serotonergic and noradrenergic agents, a substantial unmet medical need in the treatment of depressive illness remains. These needs range from efficacy in treatment resistant patients, to improved onset, to reductions in side effects such as emesis or sexual dysfunction. To address these needs, there are numerous combination therapies and novel targets that have been identified that may demonstrate improvements in one or more areas. At one end of the spectrum is combination therapies that maintain the benefits associated with standard anti-depressant drugs and at the other end more novel targets, such as neurotrophins (BDNF, IGF), based on recent findings that antidepressants induce neurogenesis could fit to the need of antidepressant therapy. This review summarizes the pathological detail of depression, current anti-depressant therapy and development of non-monoamine-based antidepressants, and provides a progress report on some of the most promising current strategies.

**Key words:** Depression, Anti-depressant, Novel targets, Anti-depressant assays

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**Introduction**

Depression is a chronic, recurring and potentially life-threatening illness that affects up to 20% of the population across the globe. It is one of the top ten causes of morbidity and mortality worldwide as per the survey of World Health Organization (WHO). The main behavioural changes in depression are low mood, negative evaluation of events, helplessness, decreased energy and concentration [1]. Most experts agree that depression should be viewed as a syndrome, not a disease. Therefore, the highly variable compilation of symptoms that is used to define depression (Table 1) and the highly variable course of the illness and its response to various treatments, indicates that depression subsumes numerous disease states of distinct etiology, and perhaps distinct pathophysiology [2].

**Table .1. Diagnostic criteria for depression [1,2]**

1. Depressed or irritable mood
2. Decreased interest in pleasure activities
3. Significant weight loss or gain
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feeling of worthlessness
8. Diminished ability to think or concentrate
9. Recurrent thought of suicide

(Depression (officially termed major depression) is diagnosed according to criteria in the Diagnostic Statistical Manual of Mental Disorders (DSM-IV) which defines a ‘major depressive episode’ as being characterized by at least five of the symptoms listed above).

The diagnosis of depression is based on the patient's self-reported experiences, behavior reported by relatives or friends, and a mental status exam. There is no laboratory test for major depression, although physicians generally request tests for physical conditions that may cause similar symptoms [3]. The course of the disorder varies widely, from one episode lasting months to a lifelong disorder with recurrent major depressive episodes. Depressed individuals have shorter life expectancies than those without depression, in part because of greater susceptibility to medical illnesses. Despite the high prevalence of depressive disorders in the population [4] our understanding of the mechanisms by which antidepressant drugs produce their effects are limited.

**Pathophysiology of depression**

The understanding of the nature and causes of depression has evolved over the centuries, though many aspects of depression remain incompletely understood and are the subject of discussion and research. Psychological, psycho-social, evolutionary and biological causes have been proposed [5]. Most biological theories focus on the monoamine chemicals serotonin, norepinephrine, and dopamine that are naturally present in the brain and assist communication between nerve cells [6]. This was consistent with the observation that reserpine, a drug used to control blood pressure and which depleted catecholamine, led to an increased rate of depression and suicide among patients. The second approach to understanding the pathophysiology of depression came about through the observation that stress appears to play a role in depression and that depressed patients often exhibit altered activity in the hypothalamic-pituitary-adrenal (HPA) axis [7]. When the HPA axis is stimulated with the dexamethasone/cortisol-releasing-hormone stimulation test (Dex/CRH-test) up to 85% of depressed patients show abnormalities, with a lack of suppression through dexamethasone (Heuser, et al. 1994). These data suggest HPA axis abnormalities could play a role and the glucocorticoid receptor (GR) within the axis is a favorite target for new antidepressants targeting the axis [8,9] have altered the focus of the discussion of the pathophysiology of depression from the receptor level to the level of gene activation. In going beyond the cell membrane, they have looked for consequences of the alterations in NE, 5HT and GR receptor function and showed that the cyclic AMP response element binding (CREB) protein could be crucial for antidepressant action [10].

One key factor in the lack of objective diagnostic tests for depression is our still limited knowledge of the brain regions and neural circuits that are involved in the condition. Moreover, given the heterogeneity of the illness, different regions might well be involved in different individuals [11]. The hippocampus and frontal regions of the cerebral cortex have received the most attention, particularly in animal studies of depression [12,3,13]. Other research has explored potential roles of molecules necessary for overall cellular functioning: cytokines and essential nutrients. Major depressive disorder is nearly identical to sickness behavior, the response of the body when the immune system is fighting an infection [14]. This raises the possibility that depression can result from a maladaptive manifestation of sickness behavior as a result of abnormalities in circulating cytokines.

In this review, we provide an overview of the depression pathology, currently available antidepressant treatments and provide a progress report on some of the most promising strategies used in today's antidepressant drug discovery efforts.

**Current Anti-depressant treatment**

Almost all of the available medications for depression are based on chance discoveries that were made more than half a century ago. Although the first drugs discovered to treat depression were serendipitous in nature, the foundation for further development of drugs that modulate monoaminergic neurotransmission was established. The chemical underpinnings of depression for the last 50 years have been referred to as the monoamine hypothesis that postulates that the debilitating and often chronic symptoms of depression result from perturbations in serotonin, norepinephrine and/or dopamine transmission. The current generation of antidepressant drugs primarily modulates neurotransmitter systems by indirectly elevating levels of monoamines [15]. There are four classes of standard antidepressants, monoamine oxidase inhibitors (MAOIs),

tricyclic antidepressants (TCAs), serotonin reuptake inhibitors (SSRIs) and norepinephrine (NE)-serotonin (5HT) reuptake inhibitors and some more class of drug affecting neurotransmitter are (Table 2).

**Table . 2: Anti-depressants and their common side-effects**

S. No.	Class	Specific Re-uptake Inhibitor (NRI)	Reboxetine Marketed drugs	Common side-effects
1	Tricyclic anti-depressants (TCAs)		Imipramine, Desipramine Trimipramine, Clomipramine	Dry mouth, constipation, headache, drowsiness, dizziness, excessive sweating, blurred vision, dry insomnia, orthostatic hypotension, seizures, weight gain, sexual disturbances
10	5-HT Re-uptake Enhancer		Tianeptine, Amisulpride, Nortriptyline	Sexual disturbances, anal pain, dry mouth, anorexia, nausea, vomiting,
2	Tetracyclic ADs		Amoxepine, Mianserin Maprotiline	Somnolence, insomnia, drowsiness, nightmares, asthenia, and tachycardia
3	Monoamine Oxidase Inhibitors (MAOIs)		Tranylcypromine, Phenelzine, Moclobemide	Sleep disturbances, weight gain, sexual disturbance
4	5-HT Selective Re-uptake Inhibitors (SSRIs)		Fluoxetine, Sertraline Paroxetine, Fluvoxamine, Citalopram	Gastro-intestinal disturbances, sexual dysfunction, insomnia, anxiety
5	Dual 5-HT and NE Re-uptake Inhibitor (SNRI)		Venlafaxine, Duloxetine	Nausea, somnolence, sweating, dizziness, hypertension, anxiety
6	5-HT-2 Antagonist and Re-uptake Inhibitors (SARIs)		Nefazodone, Trazodone	Drowsiness, dizziness, insomnia, nausea, agitation, priapism
7	NE and DA Re-uptake Inhibitor (NDRI)		Bupropion	Dizziness, dry mouth, sweating, tremor, agitation, aggravation of psychosis, seizures (High doses)
8	Noradrenergic and Serotonergic AD (NaSSAs)		Mirtazapine	Somnolence, increased appetite, weight gain, dizziness

Despite the prevalence and societal cost of depression of an estimated US\$50 billion [16], although antidepressants are widely prescribed, their mechanism of action is not yet understood. Therapeutic responses are delayed for weeks and accompanied by numerous unpleasant side-effects, posing significant clinical problem for the millions who suffer with Major Depression.

### **Novel antidepressants Targets**

However, despite billions of dollars of research in both academia and industry, this approach has not yet succeeded in bringing any fundamentally new medications to the market. At the same time, there has been an impressive accumulation of knowledge about non-monoamine systems that might contribute to the pathophysiology of depression in animal models, and some human evidence is also available. However, none of these discoveries has so far been translated into a new bona fide treatment for depression. Despite the advances that have been made in the development of antidepressants, there are clearly still unmet clinical needs that need to be addressed (Table 3).

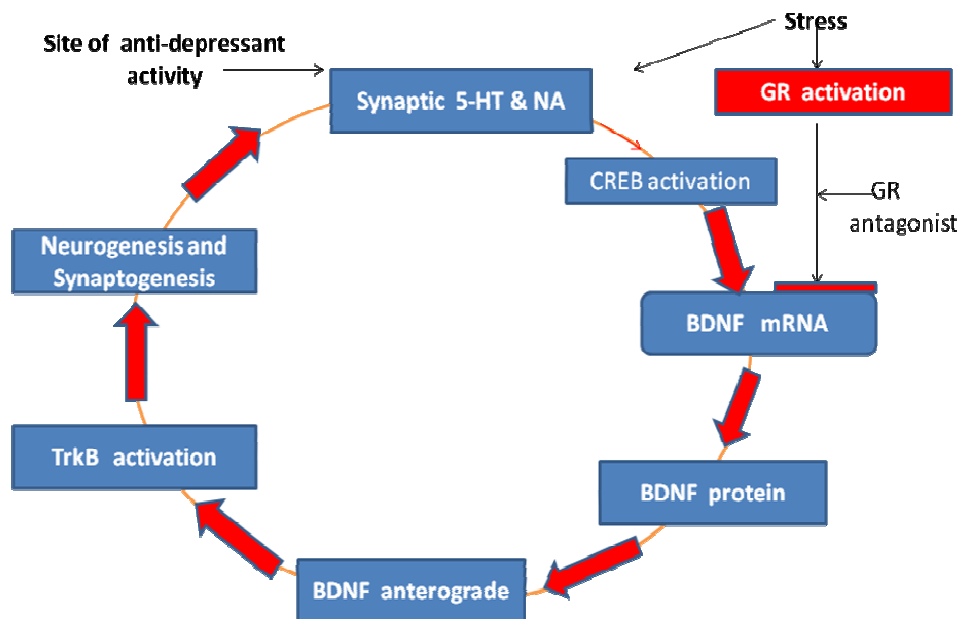
**Table .3 Clinical Needs for Novel Drug Targets**

<ul style="list-style-type: none"><li>➤ Decrease in side effect profile (sexual dysfunction and gastrointestinal events)</li><li>➤ Efficacy in refractory patients</li><li>➤ Treatment remission (recovery, relapse and recurrence)</li><li>➤ Weight gain</li><li>➤ Faster onset of antidepressant action</li><li>➤ Return of normal sleep patterns</li><li>➤ Reduction of cognitive deficits</li></ul>
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The future generation of successful antidepressants will need to address multiple efficacy parameters. The innovative approaches are targeting excitatory or inhibitory amino acids and receptors peptidergic systems, and neurotrophins. This review will bring to light the current progress in these areas with emphasis on the background, rationale and potential advantages, which may arise from these approaches.

### **1. Brain-derived nerve growth factor (BDNF)**

Plasticity in the nervous system is sub served by a variety of neurotrophins and growth factors. One well-characterized neurotrophic factor involved in activity-dependent neuronal plasticity, survival and differentiation of peripheral and central neurons is brain-derived nerve growth factor (BDNF) [17, 18] . By promoting neurogenesis, synaptic plasticity and cell survival, BDNF plays a pivotal role in the development and plasticity of the brain as shown in fig.1. During development of the cerebral cortex and hippocampus, BDNF induces the differentiation of neural stem cells into neurons and promotes the survival of newly generated neurons [19].



**Fig. 1** The structural hypothesis of depression suggests that in vulnerable individuals stress can inhibit the catecholamine systems and HPA axis in such a way as to inactivate CREB. Antidepressants have the opposite effect and these results in the synthesis of neurotrophins, such as BDNF, which activate receptors such as TrkB leading to synthetic cascades which result in either new synapse formation or new cell formation. These new structures then alter depressive behavior. (HPA, hypothalamic-pituitary-adrenal; CREB, cyclic AMP response element-binding protein; BDNF, brain-derived neurotrophic factor; TrkB, tyrosine receptor kinase B; mRNA, messenger ribonucleic acid; 5HT, 5-hydroxytryptophan (serotonin); NA, noradrenalin; GR, glucocorticoid receptor)

Several studies suggest that BDNF is a target of antidepressant action. Robust increases in the levels of BDNF mRNA in cortical and hippocampal regions have been reported following chronic antidepressant drug administration in rats [20, 21]. BDNF has also been shown to be regulated by exposure to stress [22], and antidepressant treatment can block this downregulation [20, 22]. BDNF is not only a putative target of antidepressant action but BDNF itself produces antidepressant-like effects and might thus be one of the molecular mediators of antidepressant drugs [23]. Nevertheless, BDNF signaling pathways seem to be attractive targets for interventions in depression and neurodegenerative disorder.

## 2. cAMP response element-binding protein (CREB)

CREB is a protein that is a transcription factor. It binds to certain DNA sequences called cAMP response elements (CRE) and thereby increases or decreases the transcription, and thus the expression, of certain genes [24]. Expression and activity of the transcription factor CREB have been implicated in the molecular and cellular mechanisms of pathogenesis and therapy of affective disorders [25,26]. Thus, human postmortem studies demonstrate decreased CREB levels in the temporal lobe of untreated depressed patients, but not in patients under antidepressant therapy [27, 28]. CREB is constitutively expressed in all CNS neurons and

activated by a variety of cellular signaling pathways that act via cAMP- or Ca<sup>2+</sup>-activated kinases, or by tyrosine kinases [29]. This activation resulting in CRE-mediated transcription of target genes such as brain-derived neurotrophic factor (BDNF). BDNF is mainly effective by activation of a specific receptor: tyrosine receptor kinase B (trkB). Mice with decreased CREB activity in the forebrain due to expression of a dominant-negative CREB-mutant polypeptide show reduced depression-like behaviours in the learned-helplessness paradigm [30]. Basic and clinical studies indicate that this CREB–BDNF–trkB pathway plays a crucial role in the pathogenesis and therapy of depression [31, 32].

### **3. Insulin like growth factor (IGF)**

Despite the high prevalence of depressive disorders in the population [4; 33, 34], our understanding of the mechanisms by which antidepressants produce their effects are limited. The current generation of antidepressant drugs primarily modulates neurotransmitter systems by indirectly elevating levels of monoamines [15]. More recent clinical and preclinical research in depression [9, 12] has begun to focus on the role of growth factors and neurotrophic factors in depression and antidepressant action. Insulin-like growth factor-1 (IGF-I) has a number of growth-promoting effects in the central nervous system (CNS), which qualify this molecule as a neurotrophin [35,36]. The insulin-like growth factors (IGFs) are polypeptides with high sequence similarity to insulin. Its primary action is mediated by binding to specific IGF receptors present on many cell types in many tissues. The signal is transduced by intracellular events. IGF-I has a number of growth-promoting effects in the central nervous system (CNS), which qualify this molecule as a neurotrophin [35,36]. In addition to the insulin-like effects, IGF-1 can also regulate cell growth and development, especially in nerve cells. Both central (icv) and systemic administration of IGF-I increases hippocampal cell proliferation and neurogenesis in the adult rat [37, 38]. IGF-I signals through the IGF-IR via a multiprotein signaling complex [39]. This receptor signaling pathway activates both the Ras/mitogen-activated protein kinase pathway and the PI3 kinase–AKT pathways [40,39]. These pathways share a high degree of overlap with the signaling pathways of 5-HT and BDNF, which are also implicated in antidepressant action [41]. It has also been shown that chronic (icv) infusion of IGF-I increases hippocampal 5-HT levels [34]. Therefore, IGF-IR activation may involve other growth factors as well neurotransmitter release. Clinically, reduced serum IGF-I levels are seen in patients with growth hormone (GH) deficiency and depressive symptoms have been reported in these populations. Previous studies in rats have identified, a neurotrophic factor, IGF-1, antidepressant action and neurogenesis. Central administration of IGF-1 produces antidepressant-like effects in the forced swim tests in rats [42], which indicates that IGF-1 and IGF-1-induced signal transduction pathways might be another mechanism by which antidepressants exert their behavioural effects [42]. Currently, there is little information available with respect to the behavioural effects of antidepressants in IGF-1. Increasing IGF-I levels directly or indirectly may represent a novel treatment for depression.

### **4. Glucocorticoid receptor antagonists (GR-A)**

The glucocorticoid receptor (nuclear receptor subfamily 3, group C, member 1) is the receptor that cortisol and other glucocorticoids bind to [43]. Glucocorticoids (GC) (cortisol in humans and corticosterone in most laboratory rodents) exert potent actions in the brain, influencing brain structure and function. In major depression there are two well-documented biochemical abnormalities: hypercortisolism, and its resistance to dexamethasone suppression. Stressful stimuli appear to be prime causal factors in the precipitation of depression; their impact on the

brain is primarily mediated by adrenocortical secretions (Fig. 2). The clinical evidence that hypersecretion of corticosteroids is causal to depression is overwhelming. Firstly, a sizeable proportion of depressives display hypercortisolism, secondly, pharmacological blockade of Glucocorticoid receptor (GR) activity can ameliorate symptoms and thirdly, the therapeutic efficacy of antidepressants usually follows normalization of the hypercortisolism [43]. It therefore seems reasonable to see if giving drugs which interfere with cortisol biosynthesis might bring about a remission. Glucocorticoids such as dexamethasone are hazardous if used for long periods but may have a place if used only briefly as described here. Combinations of the agents used in the above studies with tricyclic antidepressants or selective inhibitors of serotonin re-uptake may also be beneficial. Investigation of the neuroactive steroids, though difficult, should be pursued to determine how they act at physiological levels and what role they may play in depression.

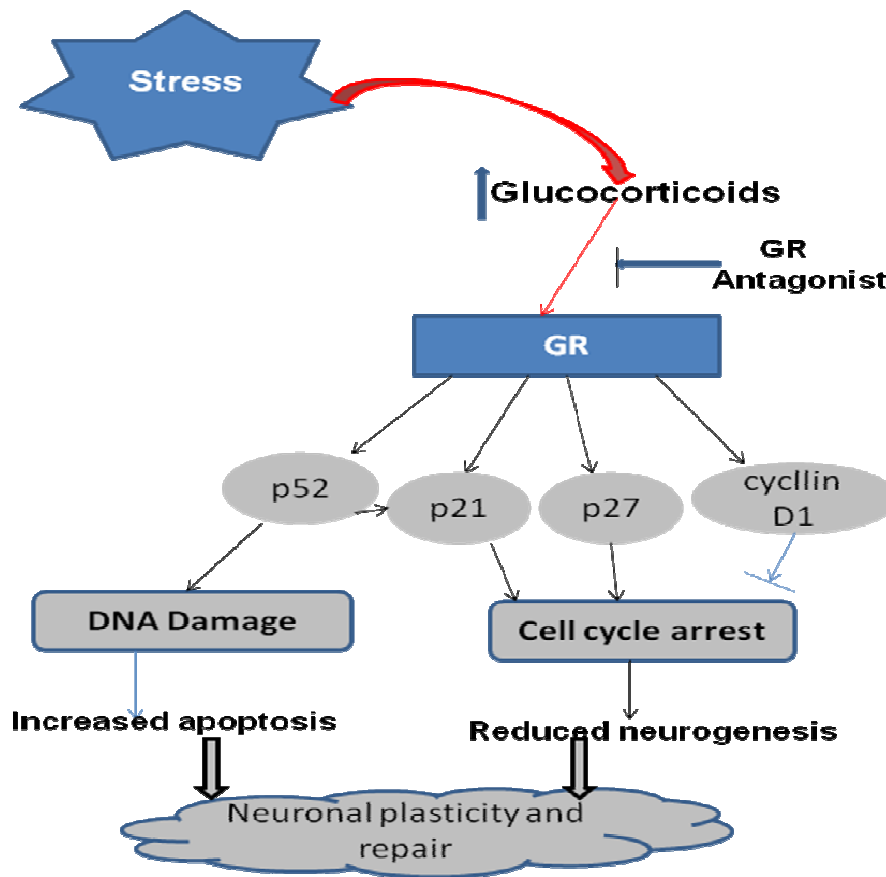
### **5. Vascular endothelial growth factor (VEGF)**

One of the most reproducible findings in antidepressant research is that different classes of antidepressants increase hippocampal cell proliferation and neurogenesis [44, 45, 46] and this effect is thought to contribute, in part, to the actions of antidepressants [47, 44]. VEGF was first characterized for its role in vascular permeability and was later described as a potent endothelial cell mitogen and survival factor. In addition to its regulation of endothelial cells and blood vessel formation/permeability, it is clear VEGF has taken a new role in the brain, as a true neurotrophic factor. Most well known for its role in tumor angiogenesis [48, 49] a role for VEGF has been identified in a wide variety of conditions and diseases including stroke, Amyotrophic Lateral Sclerosis [50, 51], Parkinson's disease [52] and Alzheimer's Disease [53, 54]. It has also not yet been determined which cells in the brain are most affected by antidepressant-induced VEGF which mediate the behavioural effects of VEGF delivery, however some studies cells in the hippocampus are involved [55]. In addition, characterization of the signaling pathway involved in the neurogenic and behavioural effects of VEGF will provide additional therapeutic targets. Further characterization of the signaling pathway that mediates the antidepressant effects of VEGF could identify upstream or downstream regulators that could be more specific targets.

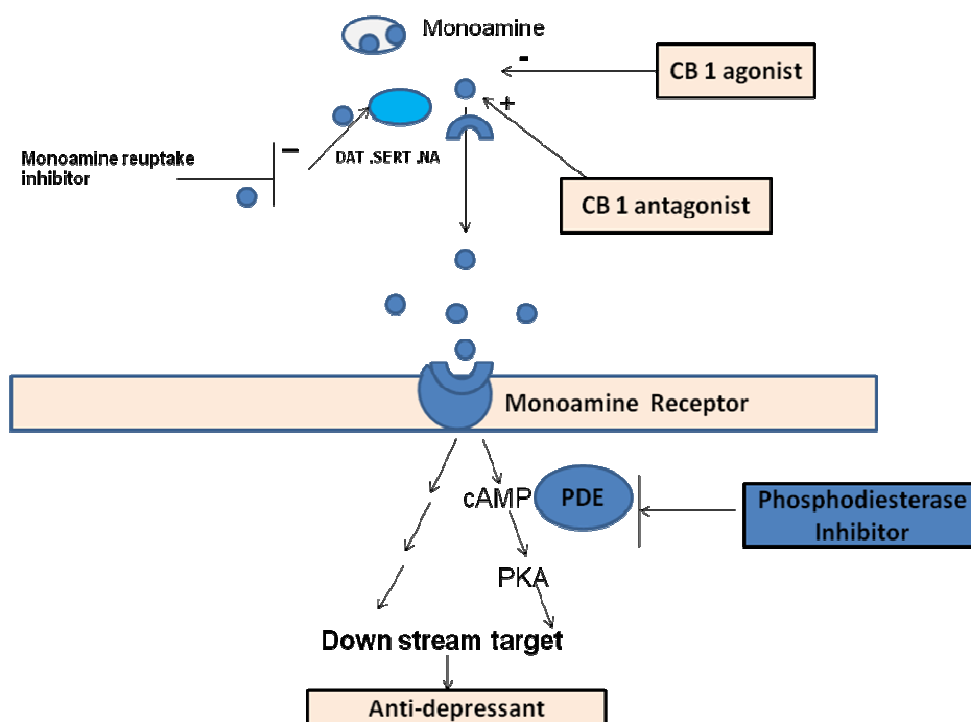
### **6. Phosphodiesterase (PDEs)**

Phosphodiesterases (PDEs) are a class of key enzymes within the intracellular signal transduction cascade that follow activation of many types of membrane-bound receptors. PDEs degrade cyclic Adenosine Mono Phosphate (cAMP) and/or cyclic Guanosine Mono Phosphate (cGMP) by hydrolysis of phosphodiester bonds. Thereby, they regulate intracellular levels of these ubiquitous second messengers. Impairments in signal transduction have also been implicated as possible mechanisms of reduced plasticity and neuronal survival in major depressive disorders [56]. This hypothesis provides a framework in which the pathophysiology and pharmacotherapy for depressive illness converge on cAMP-mediated signaling rather than being organized by receptor or neurotransmitter systems (Fig. 3). In animal models, elevated intracellular cAMP levels have been shown to possess antidepressant-like effects. This can be achieved by PDE inhibition or by the stimulation of adrenergic receptors and numerous studies have focused on the PDE4 subtype for therapeutic interventions [57, 58, 59]. Previous studies indicate that PDE4 knockout mice display decreased immobility in tail-suspension and forced-swim tests, which have positive predictive value for an antidepressant-like effect in humans [60,59, 61].





**Fig. 2** Glucocorticoid regulation of neuronal fate. GR seem to be important for neuronal survival and to have a neuroprotective function and these GR-mediated actions can be blocked with GR antagonists. Under stressful conditions, GC secretion is increased, resulting in the activation of low-affinity GR. Activated GR induce apoptosis and exert an inhibitory effect on neurogenesis in the hippocampus, effects that are sensitive to GR antagonists.



**Fig. 3** A simplified schematic of the general biogenic amine targets for conventional antidepressant therapies and cannabinoid (CB1) receptor antagonists, and a proposed mechanism of action of CB1 receptor antagonists and Phosphodiesterase inhibitor (PDE). (DAT, dopamine transporter, SERT, serotonin transporter) NE, Norepinephrine).

## 7. Cannabinoid receptors

The cannabinoid receptors are a class of receptors under the G-protein coupled receptor super family. There are currently two known subtypes, CB<sub>1</sub> [62] which is expressed mainly in the brain, but also in the lungs, liver and kidneys and CB<sub>2</sub> which is mainly expressed in the immune system and in hematopoietic cells. The cloning and neurobiological profiling of the two G-protein-coupled receptors (GPCRs) for cannabinoids (CB<sub>1</sub> and CB<sub>2</sub>) was reported in the 1990s [63]. CB<sub>1</sub> receptors are thought to be the most widely expressed G-protein coupled receptors in the brain and mediate the majority of the central effects of exogenous and endogenous cannabinoids, including effects on mood [64]. In the CNS, CB<sub>1</sub> receptors are expressed at high levels compared with other GPCRs and are particularly abundant in the cerebellum, basal ganglia, extended amygdala, cerebral cortex and hippocampus, regions that are associated with movement, memory and the perception of emotional valence [63]. Indeed, in all brain regions, cannabinoid receptor agonists pre-synaptically inhibit the release of most known neurotransmitters in a CB<sub>1</sub> receptor-dependent manner [65]. Furthermore, endogenous cannabinoids act as retrograde signaling molecules to homeostatically inhibit pre-synaptic activity and neurotransmitter release [66]. CB<sub>1</sub> receptor antagonists are thus predicted to shift the intracellular transduction equilibrium towards a more activated state and consequently to enhance neurotransmitter release (fig.3.). Enhancement of presynaptic activity in frontal structures (like hippocampus [67, 68], frontal cortex [69]) might be an important link to antidepressant activity. CB<sub>1</sub> receptor antagonists affect intracellular signaling that is relevant to

mood by increase cAMP production in addition to [3H] dopamine release in human cortical slices [70,71]. Selective CB1 receptor antagonists are in development for the treatment of obesity and tobacco smoking, and could be tested for antidepressant efficacy. Further, evaluations of the effects of CB1 receptor antagonists on intracellular signaling cascades and downstream mechanisms that are currently used as neurochemical markers of antidepressant drug action are clearly warranted.

### **8. Vasopressin receptor antagonists**

Vasopressin is a cyclic nonapeptide that is synthesized centrally in the hypothalamus. Although it participates in the hypothalamic-pituitary-adrenal axis, regulating pituitary ACTH (corticotropin) secretion by potentiating the stimulatory effects of corticotropin releasing factor (CRF), extra hypothalamic AVP-containing neurons have been characterized in the rat, notably in the medial amygdala, that innervate limbic structures such as the lateral septum and the ventral hippocampus [72-75]. There has been particular interest in the role of vasopressin in social behavior. The limbic localization of the vasopressin V1b receptor has prompted speculation as to a potential role of this receptor in the control of emotional processes. The neuropeptide vasopressin, which is synthesized in the paraventricular and supraoptic hypothalamic nuclei, is well known for its role in fluid metabolism. It also regulates the HPA axis: stress stimulates the release of vasopressin, which then potentiates the effects of CRF on ACTH release [76]. Vasopressin levels are reportedly increased in some patients with depression and might contribute to HPA axis abnormalities observed in these individuals. Furthermore, in postmortem studies, SSRI treatment has been reported to normalize vasopressin levels [77]. Non-peptide V1b antagonists show antidepressant-like effects in rodents, partly through amygdala-dependent mechanisms [76]. This is in contrast to V1b-knockout mice, which show normal stress responses [78].

### **9. Galanin Antagonist**

A large body of evidence suggests that dysfunctions of brain serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline (NA) neurones are involved in the aetiology of depressive disorders [79]. However, indirect and direct evidence suggest a role of the neuropeptide galanin [80], in the regulation of brain 5-HT and NA systems implicated in depression [81]. In the CNS, galanin coexists with NA in the locus coeruleus (LC) and 5-HT in the dorsal raphe (DR) nuclei [82], which extensively innervate the limbic forebrain and cortex [83]. Galanin signalling can affect NA and 5-HT neurotransmission, since galanin receptors GalR1-GalR3 [84], are expressed in the LC and DR, as well as in their projection areas [58]. Recent studies demonstrated that i.c.v. galanin administration increased the duration of immobility in rat FST, which was significantly reversed by galanin antagonist M35 [85]. Galanin receptor selective compounds may represent a new class of antidepressant drugs.

### **10. Neuropeptide Y**

Neuropeptide Y (NPY) is the ancestor of a peptide family that in mammals also includes pancreatic polypeptide (PP) and peptide YY (PYY). Neuropeptide Y mediates its physiological effects through at least four receptors known as Y(1), Y(2), Y(4), and Y(5). This peptide is one of the most abundant peptides in the central nervous system and is highly conserved throughout evolution. The most abundant receptors of the NPY family, the Y(1) and Y(2) receptors, are

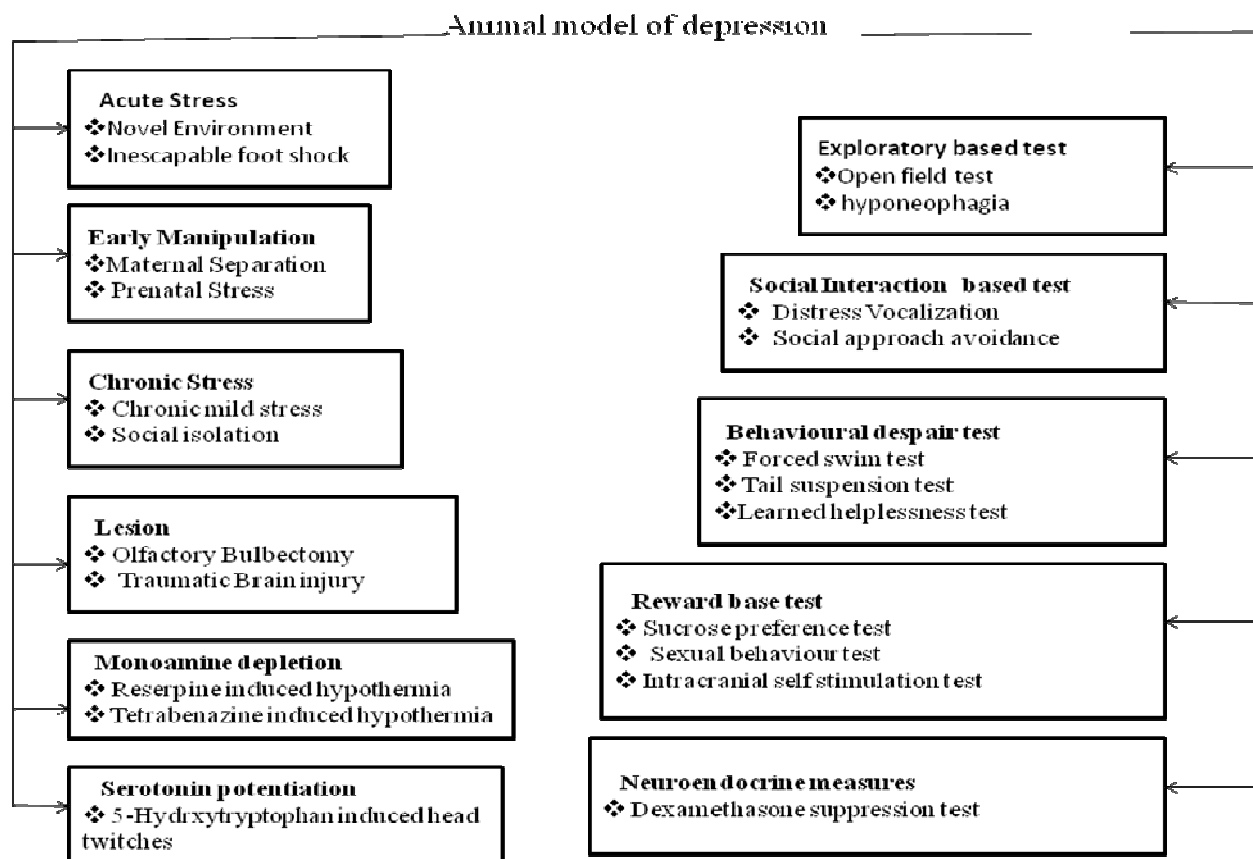
densely expressed in the cortex, hippocampus, and amygdale[86]. These receptors has been considered to be involved in the pathogenesis of affective disorders, and chronic treatment with lithium or electroconvulsive stimuli (ECS) has been shown to increase mRNA and peptide levels of NPY in rat brain tissue. Furthermore, studies in humans have suggested a link between low levels of NPY and increased risk for mood and anxiety disorders, a suggestion supported by data from preclinical experiments. A great body of evidence suggests that the reduction of 5-HT and NPY neurotransmission or receptor expression enhances or leads to depression [86, 87, 88].

### **Anti-depressant Assays**

Improved strategies for genetic modeling of depression-like syndromes in animals may, therefore, require a simultaneous targeted dysregulation of several genes involved in the pathogenesis of depression. This approach can be complemented Animal models of depression have been utilized vigorously to screen novel compounds with anti-depressant potential [89]. Ideally an animal model in psychopharmacology should be similar to human psychiatric pathology including its underlying neurobiological mechanism, its induced behavioural states and the answer to treatment habitually observed in the clinic. More specially in order for a model to be considered of any value\ it must possess predictive validity "does drug action in the model correspond to that in the clinic face validity "are there (phenomenological similarities between the model and the clinic) and construct validity "does the (model possess a strong theoretical rationale [90]. Of all behavioural tests FST, TST (tests of immobility), foot shock (learned helplessness test), and reversal of olfactory bulbectomy induced behavioural deficits have been bested suited to assess the antidepressant-like effects (Fig. 4). The earliest pharmacological models of antidepressant-like activity had significant impact on establishing the monoamine theory of depression, which assumes that an elevation of serotonin and norepinephrine levels will improve depressive symptomatology. These models offer good predictive validity in terms of monoamine-based antidepressant activity albeit they do not model core symptoms of depression. The reserpine model is based on the capability of antidepressants to reverse the inhibitory effects of reserpine on motility in rats and mice [91]. A similar approach is underlying the 5-hydroxytryptophan (5-HTP)-induced behavioral syndrome [92]. Genetic approaches offer both the possibility to identify the genetic determinants of depression and to generate models that meet more closely the clinical expectations and demands [93]. Genetically engineered mice have been successfully used to validate hypotheses illuminating the etiology of depression [33].

Improvements to animal models are often poorly validated due to the heterogeneity of depression. It is exceedingly difficult to envision an animal model that perfectly recapitulates the symptoms of depression in human patients. Animals not only lack consciousness of self, self reflection and consideration of others but also hallmarks of the disorder such as depressed mood, low self-esteem or suicidality are hardly accessible in non-humans [1]. Animal models of depression in the broadest sense have been designed either as tests of antidepressant drug action (fig.4) or as models that attempt to reproduce the underlying disease etiology and symptomatology. Hence, the choice of paradigm largely depends on the experimental intention, since both types of paradigms have their strengths but, also innate shortcomings. Despite the fact that none of the presently available animal models is able to model all aspects of depression and most likely never will, existing paradigms have proven extremely useful not only in the identification and improvement of antidepressant substances, but also in the validation of

neurobiological concepts. However, there is still a need for animal models of anti-depressant drug action that selectively screen and support the involvement of the novel targets like BDNF, CREB, PDE and IGF etc. The genetic dissection (knock out or knock in mice) of the organism's could be the answer for the neurobiological role of these targets in depression and anti-depressant assessment [94].



**Fig. 4 Anti-depressant screening methods**

**Conclusion**

Despite efforts to modernize the process of identifying novel drug targets (e.g. transgenic animals and gene chips), sometimes the most important information still comes from serendipitous clinical observation. Progress with some of these targets (for example, BDNF) has been hampered by the difficult chemistry involved. Nevertheless, this research has suggested numerous biomarkers or endophenotypes for depression for example, (BDNF expression, CREB, GR, IGF) hippocampal neurogenesis, neuronal morphology and CREB activity. A considerable leap forward in the field will require identification of genes that confer risk for depression in humans, and understanding how specific types of environmental factor interact synergistically with genetic vulnerability. This will make it possible to look more novel target and development of valid animal models of human depression. Important advances will also require the development of ever more penetrating brain imaging methodologies to enable the detection of molecular and cellular biomarkers in living patients.

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