Depression – emerging insights from neurobiology

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An emerging hypothesis suggests that the pathogenesis and treatment of depression is likely to involve a plasticity of neuronal pathways. The inability of neuronal systems to exhibit appropriate, adaptive plasticity could contribute to the pathogenesis of depression. Antidepressant treatments may exert their therapeutic effects by stimulating appropriate adaptive changes in neuronal systems. Recent studies have demonstrated that chronic antidepressant administration up-regulates the cAMP signal transduction cascade resulting in an increased expression and function of the transcription factor CREB. Enhanced CREB expression leads to an up-regulation of specific target genes, including the neurotrophin BDNF. Chronic antidepressant treatments enhance BDNF expression within hippocampal and cortical neurons and can prevent the stress-induced decrease in BDNF expression. Stress has been shown to: (i) induce neuronal atrophy/death; and (ii) decrease neurogenesis of hippocampal neurons. Clinical studies indicate significant hippo-campal damage in cases of major, recurrent depression. It is possible that anti-depressant treatments through enhanced expression of growth and survival promoting factors like BDNF may prevent or reverse the atrophy and damage of hippocampal neurons. Indeed, studies have indicated that chronic antidepressant treatments enhance hippocampal neurogenesis, promote neuronal sprouting and prevent atrophy. The molecular mechanisms underlying the effects of antidep-ressant treatments including adaptations in the cAMP transduction cascade, CREB and BDNF gene expression, and structural neuronal plasticity are discussed.

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Depression is a complex, heterogeneous disorder and several neuro-transmitter and neurohormonal pathways have been implicated in the pathophysiology of depression. The mechanisms underlying the pathogenesis of depression are not well understood. The serendipitous discovery of antidepressant treatments in the 1950s provided the first evidence of an inherent biochemical abnormality underlying the disorder. In the following 30–40 years research efforts concentrated on studying the mechanisms underlying antidepressant action thus attempting to gain insight into the dysfunction that results in depression.

These studies have led to the establishment of several theories not only for the mechanism of action of antidepressant drugs but also for the pathophysiology of depression. Amongst these has been the monoamine theory of depression. Both preclinical and clinical studies have clearly implicated the serotonin and norepinephrine neurotransmitter systems in antidepressant action. Although these studies have fuelled research efforts in the field and guided the development of novel therapeutic agents they have not been able to provide a clear model for the pathogenesis of depression. The monoaminergic hypothesis does not provide an adequate explanation for the number of patients who do not respond to current therapeutic agents and also does not solve the puzzle of the lag period in the therapeutic actions of antidepressants. Observations that monoamine depletion does not produce depressive symptoms in healthy individuals and that rapid elevation in monoamines is not correlated with quick antidepressant action has led to the need to revise the framework of existing theories[1,2].

An emerging hypothesis suggests that the pathogenesis and treatment of depression is likely to involve a plasticity of neuronal pathways[3,4]. Depression may arise when neuronal systems do not exhibit appropriate, adaptive plasticity in response to external stimuli such as stress. The dysfunction of adaptive pathways that control neuronal plasticity could contribute to the pathogenesis of depression. Antidepressant treatments may exert their therapeutic effects by either reversing this dysfunction or by independently stimulating an adaptive neuronal plasticity within the system. Despite the relatively rapid effects of antidepressant treatments on the monoamine system, their therapeutic actions emerge only after chronic administration. This supports the hypothesis that a plasticity or adaptation of neuronal systems following the acute effects of antidepressants underlies the therapeutic actions of these treatments. Initial research efforts focused on changes in monoamine neurotransmitter levels, receptors or receptor-coupled second messenger systems. Recent studies have demonstrated that the activation of intracellular cascades and the regulation of gene expression are likely to exert powerful effects on structural plasticity and neuronal survival. Our hypothesis is that these adaptive responses induced by antidepressant treatments may serve to reverse the underlying dysfunction induced by a genetic vulnerability or through exposure to stress and other aversive stimuli. In this review, we will discuss the recent advances that demonstrate a role for specific intracellular cascades, regulation of select target genes and structural neuronal plasticity in the action of antidepressants, as well as in the pathogenesis of depression.

Intracellular messenger cascades and depression

Regulation of intracellular messenger cascades exerts a powerful control on almost all aspects of neuronal function, inclusive of neuronal
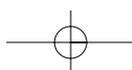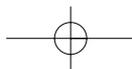
morphology, gene expression, activity and survival. It is these cascades that ultimately mediate the ability of neuronal systems to adapt in response to pharmacological and environmental stimuli[5]. Broadly, the intracellular signal transduction pathways can be classified into two categories, those that are regulated by G-protein receptor coupled second messengers (*e.g.* cAMP, Ca^{2+}, *etc*) and those that are regulated by receptors coupled directly or in close interaction with protein tyrosine kinases[6]. The former category is primarily regulated by neurotransmitters including the monoamines and neuropeptides, whereas the latter category is controlled by cytokines and growth factors including the neurotrophin family. It is our hypothesis that adaptations within these molecular cascades are likely to contribute eventually to the effects of antidepressant treatments on the plasticity of target neuronal populations within the brain.

Studies of cellular models of learning and activity-dependent plasticity have indicated that adaptations in response to stimuli include both enhanced synaptic strength as well as morphological changes, such as alterations in spine density, dendritic branching and axonal sprouting[7-9]. These forms of plasticity are mediated, in part, by underlying molecular adaptations in the intracellular signal transduction cascades[10,11]. Emerging insights from neurobiological research indicate that similar molecular and cellular adaptations arise in response to antidepressant treatments and may be relevant in the pathogenesis of depression.

Amongst the forms of molecular adaptations exhibited by intracellular signal transduction cascades are changes in functional status through alterations in phosphorylation state, changes in protein expression, or modified coupling to receptors. These forms of adaptations often result in either a positive or negative feedback. Positive feedback refers to the sensitization of a pathway leading to a stronger response in a system to the same stimulus. Negative feedback is observed when there is an enhancement or attenuation in the response of a cascade following decreased or increased stimulation, respectively. Antidepressants acting through diverse neurotransmitter systems may converge in their influences on adaptations within second messenger systems. Although these adaptations are complex and difficult to study, the realization of their importance has provided a strong incentive to examine their contribution to antidepressant action and in the pathophysiology of depression.

Antidepressant-induced adaptations of the cAMP signal transduction cascade

Amongst the second messenger cascades thought to play an important role in mediating the effects of antidepressant treatments is the cAMP cascade, which is regulated by both the serotonin and norepinephrine neurotransmitters. This signal transduction cascade represents a

common target for several classes of antidepressants that differentially influence these two neurotransmitters acutely. Receptor activation (*e.g.* β_1AR, 5-HT$_{4,6,7}$) leads to the generation of cAMP via the stimulation of adenylyl cyclase by the G-protein subtype Gsα[12]. In addition, intracellular Ca^{2+} levels can also regulate certain subtypes of adenylyl cyclase. The generation of cAMP then results in the activation of cAMP-dependent protein kinase (PKA). The catalytic subunits of PKA are responsible for mediating effects on cellular function through the phosphorylation of specific target proteins. Amongst the substrates of PKA is the transcription factor cAMP response element binding protein (CREB), which in the dephosphorylated form constitutively regulates gene transcription and, following phosphorylation, exhibits a dramatic increase in its ability to regulate transcriptional activity[13].

Although results from earlier studies indicated that chronic antidepressant treatment down-regulated β_1AR and cAMP production, more recently evidence has mounted for an up-regulation of the cAMP cascade following chronic antidepressant administration. Postreceptor components of the cAMP signal transduction cascade are regulated at several levels. The coupling of the stimulatory G protein Gsα to adenylyl cyclase is enhanced following antidepressant treatment[14]. This enhanced coupling leads to increased adenylyl cyclase activity in response to several different classes of antidepressant treatments[15]. Besides regulation of enzyme activity, the expression of adenylyl cyclase types I and II is also enhanced following chronic treatment with lithium[16]. In addition to regulation of cAMP production, another target is the metabolism of cAMP. Breakdown of cAMP is catalyzed by the phosphodiesterases (PDEs). There are several different isoforms of these enzymes and accumulating evidence suggests a role for PDE4A and PDE4B in antidepressant action[17–19]. Support for the hypothesis that enhanced cAMP signalling may produce antidepressant effects comes from studies with the phosphodiesterase inhibitor rolipram, which has been reported to have antidepressant effects in clinical trials. Although rolipram is not in clinical use because of its unpleasant side effects, a rational target for drug design are selective PDE inhibitors that lack these side effects. The potential for PDE inhibitors in the treatment of refractory patients and to accelerate the lag phase with antidepressant drugs when used in combination therapy needs to be more carefully examined.

Levels and activity of cAMP-dependent protein kinase are reported to be influenced by antidepressant treatment. Chronic, but not acute, treatment with antidepressants leads to enhanced PKA activity in cerebral particulate fractions[20]. Reports also indicate an increase of PKA levels within the crude nuclear fraction suggesting a translocation of this enzyme into the nucleus following antidepressant administration[21].
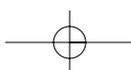
Nuclear translocation of PKA would suggest that antidepressant treatments recruit the cAMP cascade to regulate gene expression. Although there are differences in the results of these studies, these are likely to be due to the problems of being unable to obtain pure subcellular fractions. Evidence clearly indicates that antidepressant treatment up-regulates several components of the cAMP signal transduction cascade.

Although recent studies indicate an up-regulation of the cAMP cascade, this is in contrast to previous work, which reported βAR down-regulation and a decreased ability of the receptor to stimulate cAMP production. This led to the genesis of the βAR subsensitivity hypothesis which postulated that depression is a consequence of overexpression of βAR and that the mechanism underlying antidepressant action is a down-regulation of these receptors. Considerable evidence against this hypothesis has been generated in addition to the reports which clearly indicate an up-regulated cAMP second messenger system. The down-regulation of βAR does not follow the therapeutic time course of antidepressant drugs. In addition, βAR antagonists do not demonstrate antidepressant effects as would be predicted by the subsensitivity hypothesis. In addition, enhanced βAR expression induced by thyroid hormone administration is thought to be associated with the ability of thyroid hormone treatment to augment antidepressant medication. The up-regulation of the cAMP cascade but the decreased expression of βAR in response to antidepressant treatment, as well as an associated attenuation in the ability of βAR to stimulate cAMP production, appear to be contradictory. However, an inherent problem with these studies is the methodology employed for the cAMP assays which uses exogenous agonists in a brain homogenate or in an *in vitro* brain slice system. Based on these studies, one cannot truly draw a conclusion of the *in vivo* situation. It is possible that *in vivo*, even though levels of βAR are reduced, there is a residual population of available receptors that are sufficient to produce a response to the enhanced norepinephrine available at the synapse following antidepressant treatment. If this is the case, then even though the levels of βAR are decreased relative to control levels, the enhanced levels of norepinephrine following antidepressant administration would be sufficient to drive the remaining receptors to up-regulate the cAMP system in contrast to control (Fig. 1). This may provide an explanation to the paradoxical findings of decreased βAR and enhanced cAMP signal transduction cascades following chronic antidepressant administration. Further studies will be required to address this paradox and examine whether the above hypothesis is true.

Up-regulation of the cAMP cascade and nuclear translocation of PKA suggest that antidepressant treatments regulate specific target genes, *i.e.* those that are likely to contain a functional cAMP response element
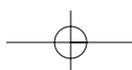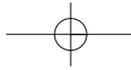
(CRE). A current area of research is to identify these candidate genes which are regulated in response to antidepressant treatment and to dissect out their significance in mediating the therapeutic effects of antidepressants.

Altered gene expression and depression

The property of neuronal plasticity which allows the brain to exert an adaptive response when faced with aversive stimuli is likely to arise through a programme of altered gene expression. It is these changes in gene expression which profoundly influence: (i) the metabolism of neurotransmitters; (ii) expression of receptors, channels, intracellular cascade components, growth factors and structural proteins; (iii) synaptic strength and neuronal activity;
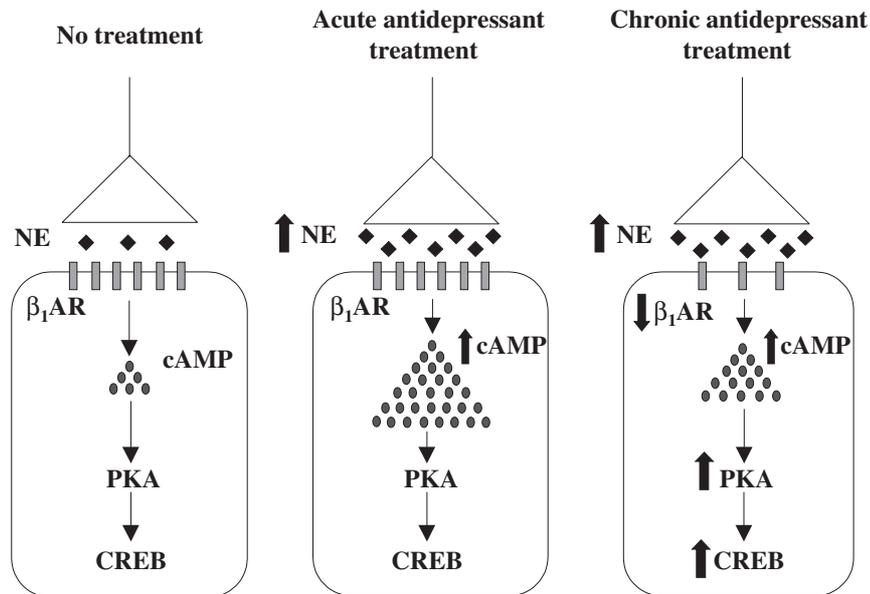

Fig. 1 A model explaining the paradoxical increase in the cAMP signal transduction cascade despite the down-regulation of βAR following chronic antidepressant treatment. In the absence of treatment, basal levels of norepinephrine (NE) stimulate the βAR-receptor coupled cAMP cascade, and levels of NE and cAMP are low. Following short-term administration of select antidepressants, there is an increase in NE levels leading to a corresponding increase in βAR-stimulated cAMP production. Chronic antidepressant administration leads to an increase in synaptic NE levels. Chronic treatment with several types of antidepressants results in a significant decrease in the β_1AR-binding sites available to stimulate cAMP production. This in turn causes a decrease in the maximal level of βAR-stimulated cAMP production. However, the residual population of βARs is sufficient to respond to the elevated levels of NE and drive an increase in cAMP production relative to the cAMP levels observed with no treatment. This model proposes a hypothetical mechanism, which requires further testing, to explain the enhanced cAMP cascade even though levels of βAR are decreased following chronic antidepressant treatment.
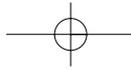
and (iv) morphology and survival of neurons, thus eventually contributing to an adaptive response being mounted by the brain in response to stimuli which perturb homeostatic balance. It is likely that aberrant programmes of gene expression, which lead to a dysfunction in neuronal plasticity, contribute to the pathogenesis of depression. Antidepressant treatments through their influence on intracellular signal transduction cascades serve to regulate specific transcription factors thus orchestrating long-term adaptations through the regulation of specific genes[22,23]. Adaptations resulting from antidepressant-induced changes in gene expression may then serve to reverse or ameliorate the dysfunction in neuronal plasticity. A major goal of current research efforts is to identify the target genes which are regulated by several classes of antidepressant treatments and to examine their role in the therapeutic effects of antidepressant action.

The regulation of transcription factors by different classes of antidepressants may serve as a common target for antidepressant drugs stimulating diverse receptor-coupled signal transduction cascades. Antidepressant induced regulation of transcription would then feed forward to the regulation of a number of target genes. Although this suggests that antidepressants may broadly influence the expression of several genes, it is likely that several additional factors would determine the target genes eventually regulated by antidepressant treatment. There is a differential regulation of intracellular cascades by antidepressant treatments within the brain, which would bring about a spatial restriction in the regulation of transcription factors and target genes. In addition, the control of gene expression will also depend upon a complex interplay between different transcription factors in the promoter region, eventually determining the influence of antidepressant treatment on a particular gene. The regulation of transcription factors by antidepressant treatments is of great interest since these factors may serve as common intracellular targets for different second messenger system cascades. Transcription factors are uniquely suited to integrate signals from distinct signal transduction cascades and mediate the effects of diverse classes of antidepressant treatments on gene expression. We will discuss the regulation of the transcription factor CREB as a potential common postreceptor target for antidepressant treatments. The regulation of CREB suggests that antidepressant treatments influence the regulation of specific genes containing CRE regulatory elements. We will describe the regulation of one such target gene of interest the growth factor brain-derived neurotrophic factor (BDNF).

Antidepressant regulation of CREB expression

Studies demonstrating an antidepressant-induced increase in (i) activity of the cAMP cascade and (ii) the nuclear translocation of PKA, suggest
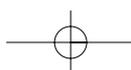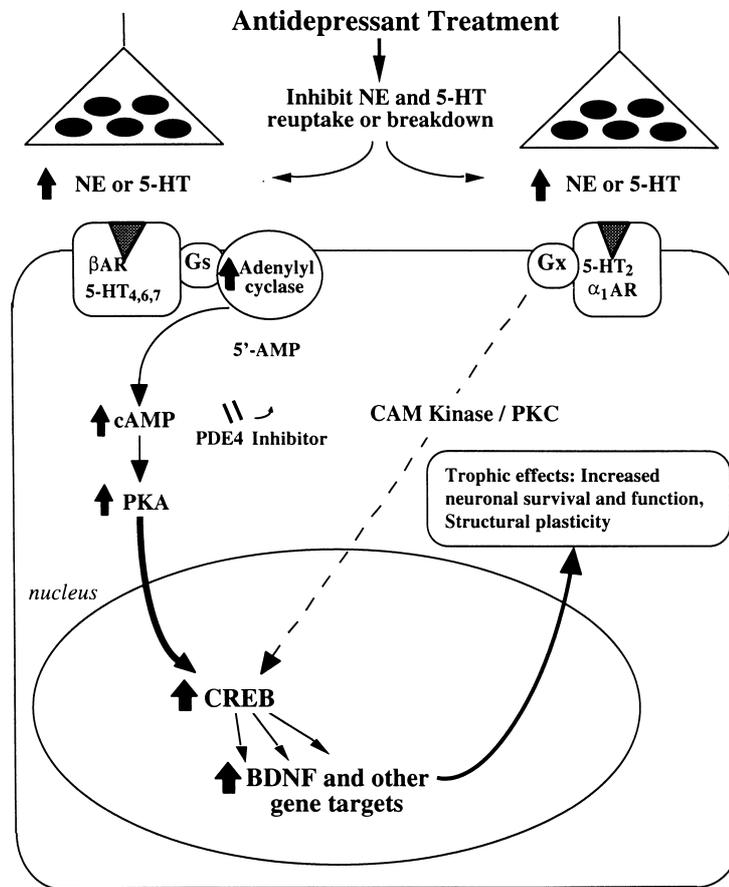
Fig. 2 A model describing the influence of antidepressant administration on the cAMP signal transduction cascade. Chronic treatment with different classes of antidepressants results in an up-regulation of the several postreceptor components of the cAMP cascade. Chronic antidepressant administration results in an increased coupling of Gs and adenylyl cyclase, increased expression of specific types of adenylyl cyclase, cAMP dependent protein kinase (PKA), and increased expression of cAMP response element binding protein (CREB). Taken together, these studies suggest that the cAMP cascade may serve as a common postreceptor target for diverse classes of antidepressant drugs. In addition, to up-regulation of CREB by norepinephrine (NE) and serotonin (5-HT) receptors (βAR, 5-HT$_{4,6,7}$) coupled to the cAMP intracellular pathway, CREB is also a target for calcium-dependent protein kinases and receptors coupled to activation of these pathways (5-HT$_2$, α_1AR). Up-regulation of the cAMP cascade may serve as a common target for different classes of antidepressants with diverse acute sites of action. Preclinical and clinical studies demonstrating the antidepressant effects of specific cAMP phosphodiesterase (PDE4) inhibitors support the possibility that up-regulation of the cAMP pathway may contribute to antidepressant action. Up-regulation of CREB by chronic antidepressant treatments suggests that specific target genes are likely to be regulated in response to antidepressant administration. Amongst these target genes is brain-derived neurotrophic factor (BDNF), which is known to play an important role in neuronal plasticity, survival and function.

that antidepressant treatment may regulate the cAMP responsive transcription factor CREB thus influencing gene expression. Recent studies clearly indicate that chronic, but not acute, administration of several distinct classes of antidepressant treatments up-regulates CREB mRNA expression within the hippocampus[24]. The antidepressants studied belong to diverse classes including selective norepinephrine and serotonin re-uptake inhibitors, non-selective tricyclic monoamine re-uptake inhibitors, monoamine oxidase inhibitors, and electroconvulsive seizure administration. This suggests that CREB may serve as a common target for antidepressant drugs with very different primary sites of action (Fig. 2). In addition to an up-regulation of CREB mRNA, corresponding increases in CREB protein as well as an increased level of CRE binding is observed following antidepressant treatment. CREB induction follows a time-course that is consistent with the therapeutic actions of antidepressant treatments (*i.e.* 10–21 days of treatment)[24]. In addition to these studies demonstrating an up-regulation of CREB expression, a recent study reports that the phosphorylation and transcriptional activity of CREB is also increased by antidepressant treatment[25]. This study used a transgenic mouse line that expresses a gene containing a tandem of CRE elements attached to a reporter (*LacZ*). Chronic antidepressant administration increased levels of CRE-mediated *LacZ* expression, as well as phosphorylation of CREB. Future studies are now needed to determine the functional consequences of altered CREB levels. This can be accomplished with inducible transgenic mice that express CREB, or a dominant negative mutant of CREB, in a region- and time-specific manner.

The mechanisms which underlie the enhanced expression of CREB mRNA and protein are not clearly understood *in vivo*. However, evidence from *in vitro* systems implicates activation of the cAMP system in this regulation[26]. This would reflect a positive feed-forward mechanism that controls expression of CREB in response to antidepressant treatments. It is likely that the cAMP system also plays a role in the antidepressant-mediated induction of CREB mRNA and protein. As has been described earlier, antidepressant treatments augment the functioning of the cAMP signal transduction cascade and PKA which is responsible for phosphorylation of CREB is translocated to the nucleus following chronic antidepressant administration. There are distinct CRE elements within the up-stream promoter region of the CREB gene, which have been shown to up-regulate CREB transcription[27,28]. However, studies in a cell culture system have demonstrated that activation of the cAMP signal transduction cascade leads to a down-regulation of CREB expression[29]. This suggests that the regulation of CREB by the cAMP cascade is likely to be region specific and will also be influenced by the tissue specific expression of cAMP response modulator (CREM) and inducible cAMP early repressor
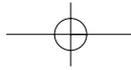
(ICER) proteins which bind to the CRE element and repress transcription.

Different classes of antidepressant treatments are likely to recruit distinct norepinephrine and serotonin receptor subtypes and evidence indicates that the signal transduction cascades activated by these diverse receptors may converge on CREB as a common postreceptor target (Fig. 2). Several norepinephrine and serotonin receptors (βAR, 5-HT$_{4,6,7}$) are coupled to the cAMP cascade and could contribute to up-regulation of CREB transcriptional activity through phosphorylation by PKA. In addition, specific classes of serotonin and norepinephrine receptors (α_1AR and 5-HT$_2$) are coupled to the phosphatidylinositol second messenger cascade inducing the release of Ca^{2+} from intracellular stores. The enzymes Ca^{2+}/calmodulin dependent protein kinase, and protein kinase C are both activated by Ca^{2+} and have been shown to phosphorylate and activate CREB[27]. Changes in Ca^{2+} signalling induced by ion channels may also eventually up-regulate CREB activity. CREB can also be phosphorylated and activated by an enzyme termed rsk or CREB kinase which is stimulated by signalling through the MAP kinase cascade. It is likely then that signalling through diverse signal transduction cascades in response to a variety of antidepressant treatments may converge to up-regulate CREB activity, which in a positive feed-forward mechanism would lead to an up-regulation of CREB mRNA expression.

Antidepressant treatments through adaptations in intracellular cascades induce a powerful regulation in gene expression of the transcription factor CREB. It is possible that an up-regulation in CREB may contribute to the actions of antidepressant treatments through effects on specific target genes. Inability to regulate expression or function of CREB and thus induce adaptive gene expression may contribute to the pathogenesis of depression. Support for this hypothesis comes from recent evidence that CREB expression is decreased within the temporal cortex of depressed patients and this decrease is reversed by antidepressant treatment in keeping with data from preclinical studies[30]. A goal of future studies is to determine the target genes that are regulated by CREB and to characterize their role in the actions of antidepressant treatments. One such candidate gene is the neurotrophic factor, BDNF.

Antidepressant regulation of BDNF expression

Brain derived neurotrophic factor, BDNF, belongs to the NGF family of growth factors referred to as the neurotrophins. BDNF is known to exert a powerful influence on the development, survival, maintenance
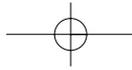
and plasticity of neurons within the immature and adult nervous system and has recently been shown to also elicit rapid action potentials thus influencing neuronal excitability[31,32]. Neurotrophic factors mediate their effects on cellular function and plasticity through the stimulation of specific tyrosine kinase coupled receptors, referred to as trks, which signal through MAP kinase signalling cascades. Studies have clearly indicated that BDNF serves as a target for antidepressant treatment (Fig. 2). Chronic, but not acute, administration of various classes of antidepressant drugs increases the expression of BDNF and its receptor trkB within the hippocampus[33]. This up-regulation follows the time course for the therapeutic action of antidepressant treatments. Pretreatment with antidepressants can also block the stress-induced down regulation of hippocampal BDNF mRNA[33].

Regions exhibiting an up-regulation of BDNF in response to antidepressant administration overlap closely with the regions that show an up-regulation of CREB. This spatial correlation suggests that CREB may contribute to the antidepressant induced increase in hippocampal BDNF expression. A role for the cAMP system in mediating the antidepressant-induced increase in BDNF expression is supported by studies with the PDE inhibitors papaverine and rolipram[24]. PDE inhibitors have been shown to enhance BDNF expression (Fig. 2) and to accelerate the induction of BDNF when co-administered with an antidepressant. In addition, culture studies indicate that activation of the cAMP or Ca^{2+} signalling systems up-regulates BDNF expression[34,35]. Studies indicate that there is a CRE-like element within the promoter region of exon III of BDNF. Further studies are required to dissect the role of CREB in mediating the up-regulation of BDNF expression following chronic anti-depressant treatment. In addition to regulation of BDNF expression through the cAMP/Ca^{2+} signalling and CREB system, an alternate pathway may involve βAR or 5-HT$_2$ receptor internalization. Receptor internalization recruits Ras and the MAP kinase intracellular cascade and may thus influence BDNF expression independent of the cAMP signalling cascade.

There are several lines of evidence that suggest a role for BDNF in the action of antidepressant treatment and in the pathogenesis of depression. First, chronic, but not acute, antidepressant treatment increases hippocampal BDNF mRNA with the induction following the time-course observed for the therapeutic effects of antidepressant treatments. In addition, pre-administration of antidepressants prevents stress-induced decreases in hippocampal BDNF mRNA. Second, direct infusion of BDNF protein into the midbrain exerts antidepressant effects in two models of depression, *i.e.* the forced swim and learned helplessness models[36]. Third, BDNF exerts a strong trophic effect on serotonergic and noradrenergic neurons regulating morphology, neurotransmitter metabolism and firing patterns of these neuronal populations[37,38]. Fourth, chronic stress is

known to result in neuronal damage and death. Decreased BDNF expression as a consequence of stress may play a role in stress-induced neuronal damage. We hypothesize that enhanced BDNF expression resulting from chronic antidepressant administration may play an important role in reversing or preventing neuronal damage that is a consequence of exposure to sustained stress or other aversive stimuli. Taken together, these studies indicate that antidepressants up-regulate BDNF expression and BDNF itself exerts an antidepressant effect. Moreover, antidepressant treatment can reverse the down-regulation of the BDNF expression induced by stress and antidepressant induced BDNF expression may serve to ameliorate stress-induced neuronal damage.

These studies provide evidence for a neurotrophic basis to the pathogenesis of depression. Further studies are required to characterize the role of CREB and BDNF in the influence of antidepressant treatments on neuronal plasticity including changes in neuronal structure and function. These studies will make it possible to design novel therapeutic agents for the treatment of depression rationally. A strategy for new drug development could focus on synthetic agonists for the trk receptors, as well as drugs that activate specific components of the cAMP pathway. We have described here only the cAMP cascade and gene expression likely to be regulated as a result of activation of the cAMP cascade. It is unlikely that only this intracellular pathway is involved. Preclinical and clinical studies are required to elucidate the role of other intracellular cascades, transcription factors and candidate genes in the pathophysiology and treatment of depression.

Structural plasticity and depression

Stress-induced neuronal atrophy and cell death suggest that antidepressants, through adaptive influences on neuronal plasticity, may serve to reverse or block the deleterious effects of stress on neuronal morphology and survival. Amongst the primary targets of stress is the hippocampus. Hippocampal CA3 neurons show neuronal atrophy or death following sustained exposure to stress[39]. Although mature dentate gyrus granule cell neurons are relatively resistant to stress-induced damage, stress is known to decrease on-going adult neurogenesis within the subgranular zone of the dentate gyrus[40]. Adult neurogenesis has been reported in rodents, tree shrews, non human primates and in humans[41]. The functional significance of neurogenesis is unclear, but studies indicate that hippocampal-dependent learning tasks and exposure to enriched environment enhance neurogenesis. These studies suggest that this form of structural plasticity may contribute to hippocampal

functions such as learning. Stress-induced neuronal atrophy, cell death and inhibition of neurogenesis may then serve to contribute to a functional deficit of the hippocampus.

Recent clinical studies have clearly indicated a decrease in hippocampal volume in patients suffering from recurrent, major depression. This decrease in hippocampal volume appears to be correlated with the duration of depressive episodes[42]. Hippocampal fast feedback inhibition of the hypothalamo-pituitary-adrenocortical (HPA) axis is deficient in depressed patients[43]. A decrease in feedback inhibition of the HPA axis would lead to elevated levels of cortisol and a further endangerment of hippocampal neurons through exposure to sustained high levels of stress steroids. Clinical and preclinical studies both suggest that exposure to prolonged stress and aversive stimuli can result in hippocampal damage. Hippocampal damage is seen in patients suffering from major depression, although the sites of damage within the hippocampus are as yet unclear. In addition, recent studies also report damage within the prefrontal cortex, through a reduction in neuronal and glial number, in patients suffering from depression[3,44]. Taken together, these studies suggest that the pathogenesis of depression may involve the atrophy and damage of specific neuronal populations. Antidepressants may mediate their therapeutic effects by exerting trophic actions on these vulnerable neuronal populations. The therapeutic effects of antidepressant treatments could arise from an ability to block/reverse neuronal damage or through direct influences on neuronal architecture, survival and function. In support of this hypothesis, several studies have indicated that antidepressants appear to block stress-induced damage and positively influence structural plasticity (Fig. 3). Most of these studies have focused on the hippocampus and need to be extended to examine the influence of antidepressants on other brain regions.

Antidepressant treatment, neuronal atrophy and sprouting

Chronic antidepressant treatment has been shown to block the stress-induced atrophy of CA3 hippocampal pyramidal neurons (Fig. 3)[3,39]. These studies demonstrated a blockade of stress-induced neuronal atrophy following chronic administration of the atypical antidepressant tianeptine, but not the serotonin selective re-uptake inhibitor fluoxetine. Tianeptine is known to enhance serotonin re-uptake. It is interesting to speculate that decreased availability of serotonin during stress may prevent the atrophy of hippocampal neurons. Our studies indicate that in part, stress decreases hippocampal BDNF expression through activation of the 5-HT_{2A} receptor[45]. It is possible that chronic
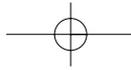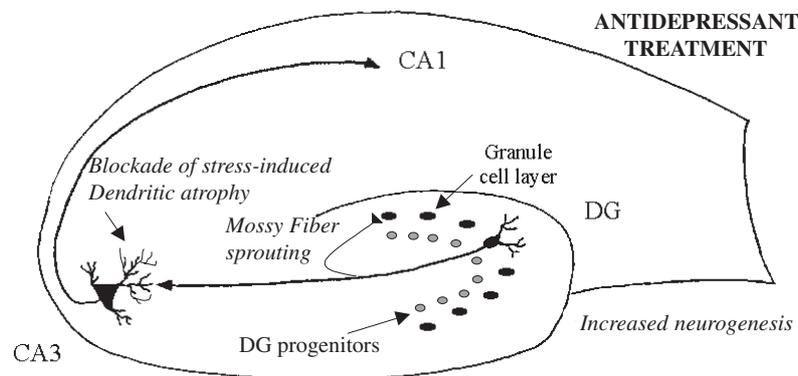
Fig. 3 Schematic diagram of the hippocampus and the influence of chronic anti-depressant treatment on different hippocampal subfields. The CA1, CA3 and dentate gyrus (DG) comprise the main hippocampal anatomical subfields. DG granule cell neurons project to the CA3 region via the mossy fibre pathway. Exposure to stressful stimuli leads to CA3 dendritic atrophy and in severe cases loss of CA3 pyramidal neurons. In addition, stress is known to suppress of on-going neurogenesis in the DG. Pretreatment with specific antidepressants blocks the ability of stress to induce CA3 dendritic atrophy. Chronic treatment with several classes of antidepressants results in an increased neurogenesis within the DG. This increase in neurogenesis is due to a marked increase in proliferation of DG progenitors. Chronic administration of a powerful antidepressant treatment (electroconvulsive seizure) results in sprouting of the mossy fibre pathway axons. Although the mechanisms underlying this form of structural re-organization are not clear, up-regulation of BDNF has been implicated. Structural plasticity within specific neuronal populations may play an important role in the therapeutic actions of antidepressant treatments.

pretreatment with tianeptine may act to block the decrease in BDNF and thus the atrophy of CA3 neurons. Based on these studies, one would predict that blockade of the 5-HT$_{2A}$ receptor, which is a known target of certain antidepressant drugs, would block the atrophy of CA3 neurons. Further studies are required to test this hypothesis and to examine the influence of different classes of antidepressant drugs on stress-induced hippocampal atrophy.

We have also found that chronic administration of a potent form of antidepressant treatment, namely electroconvulsive seizure (ECS), induces axonal sprouting of dentate granule cell neurons (Fig. 3)[46]. This effect is dependent on chronic administration and is fairly long-lasting, persisting 6 months after the last treatment. The increase in sprouting follows a time course that parallels the therapeutic effects appearing 10–12 days after chronic administration of ECS. This form of sprouting, in contrast to the mossy fibre sprouting seen in animal models of epilepsy, does not appear to arise as an adaptation to death of target neurons as there is no evidence of cell death following chronic ECS

treatment. ECS induced sprouting is significantly attenuated in BDNF heterozygote knockout mice, which show significantly decreased levels of BDNF in contrast to wild-type mice[46]. However, infusion of BDNF alone is not sufficient to induce mossy fibre sprouting suggesting that BDNF may be necessary, but not sufficient, to induce spouting of granule cell neurons. Chronic administration of antidepressant drugs does not produce sprouting of the mossy fibre pathway suggesting that this effect may be specific to ECS treatment. Further studies are required to examine the functional consequences of enhanced neuronal sprouting.

Antidepressant treatment and hippocampal neurogenesis

Antidepressant treatment could oppose the effects of stress on hippocampal neurogenesis through an increase in the proliferation of dentate granule cell neuron progenitors (Fig. 3). Recent studies have clearly demonstrated that chronic, but not acute, administration of several different classes of antidepressant treatments increases the proliferation of progenitor cells within the subgranular zone of the dentate gyrus (Fig. 4)[47]. Administration of non-antidepressant, psychotropic drugs did not enhance neurogenesis indicating that
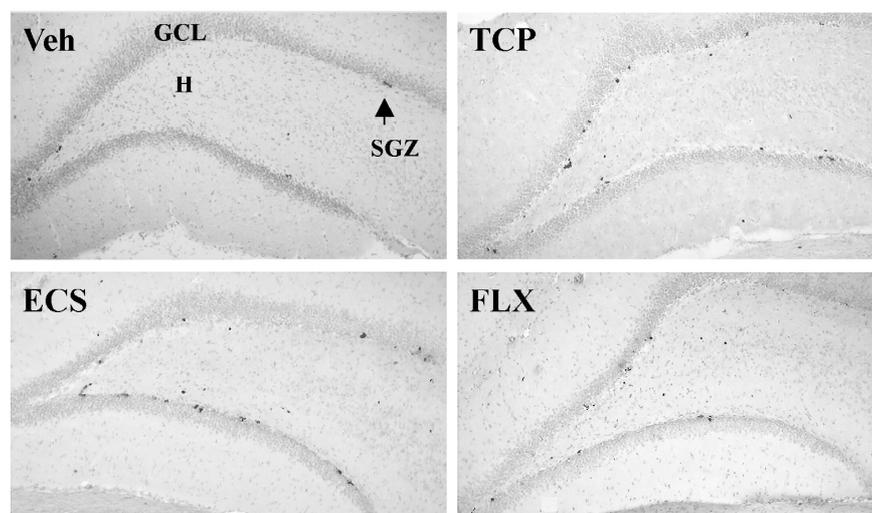

Fig. 4 Chronic antidepressant treatment increases the number of BrDU positive cells within the dentate gyrus region of the hippocampus. Rats received BrDU injection 4 days after the last electroconvulsive (ECS) seizure (10 days) or drug treatment (fluoxetine FLX or tranylcypromine TCP, 14–21 days) and were sacrificed 24 h after the last BrDU injection. Representative photomicrographs demonstrating the increase in BrDU immunolabelling following chronic ECS, FLX, TCP are shown. BrDU labelled progenitors are localised primarily within the subgranular zone (indicated by an arrow in the vehicle section) between the granule cell layer (GCL) and the hilus (H) of the dentate gyrus.
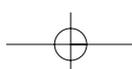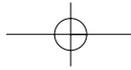
neurogenesis appears to be a common, selective target for diverse classes of antidepressant treatments. Proliferating progenitors mature and become neurons, as determined by double labelling with neuronal- or glial-specific markers indicating an increase in hippocampal neurogenesis. Preliminary studies[48] suggest that the 5-HT$_{1A}$ receptor subtype may be important in mediating the influence of antidepressant treatments on hippocampal neurogenesis. The underlying mechanisms which contribute to the effects of antidepressant treatment on neurogenesis are not yet clearly understood. Enhanced cAMP signal transduction cascades and regulation of trophic factors like BDNF may play a role in increased proliferation of neuronal precursors in the hippocampus following antidepressant treatment. Overall, these studies suggest a possibility that enhanced neurogenesis may be a potential mechanism via which antidepressant treatments reverse stress-induced hippocampal neuronal damage/death and exert their therapeutic effects.

Conclusions

Emerging insights from neurobiology suggest that chronic antidepressant treatment leads to an augmentation of the cAMP signal transduction cascade. One of the functional consequences of enhanced cAMP signalling is an increase in the expression and activity of the transcription factor CREB. Studies indicate that enhanced CREB function regulates diverse target genes one of which is the trophic factor BDNF. Several lines of evidence support a role for the growth factor BDNF in antidepressant action, and BDNF itself appears to exert antidepressant effects in certain animal models. Extensive preclinical and clinical studies have indicated a damage of hippocampal neuronal systems in animal models of chronic stress and in patients suffering from recurrent, major depression. This has lead to the model that neuronal atrophy and cell death of specific neuronal populations, within the hippocampus and prefrontal cortex, may play a role in the aetiology of depression. Individual variability in the vulnerability to stress and depression may arise from inherent genetic or environmental exposure differences that could predispose certain individuals to an enhanced susceptibility to depression, in response to stress or other precipitating factors. Chronic antidepressant treatments, through regulation of the cAMP cascade, CREB and BDNF, could exert their therapeutic effects by reversing or preventing neuronal damage and atrophy of damaged or vulnerable neuronal populations. Although the initial acute targets for antidepressants are distinct, these treatments could converge following chronic administration on specific signalling cascades and candidate genes to stimulate an adaptive form of neuronal plasticity. The validity

of this unifying hypothesis needs to be tested through preclinical and clinical studies.

Although the regulation of CREB and BDNF may be important to antidepressant action, it would be naive to imply that these are unique targets of antidepressant treatment. Mechanisms underlying antidepressant action are likely to involve a complex interplay between different signal transduction pathways and different target genes. Further studies are required to elucidate the interactions of different signalling pathways and candidate genes, which play an important role in mediating neuronal plasticity in response to antidepressant treatments.

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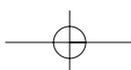
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