New insights into the mechanisms of antidepressant therapy

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Abstract

Depressive disorders are among the most frequent psychiatric diseases in the Western world with prevalence numbers between 9% and 18%. They are characterized by depressed mood, a diminished interest in pleasurable activities, feelings of worthlessness or inappropriate guilt, decrease in appetite and libido, insomnia, and recurrent thoughts of death or suicide. Among other findings, reduced activity of monoaminergic neurotransmission has been postulated to play a role in the pathogenesis of depression. Consistent with this hypothesis, most antidepressive drugs exert their action by elevating the concentration of monoamines in the synaptic cleft. However, it is not the enhancement of monoaminergic signaling per se, but rather long-term, adaptive changes that may underlie the therapeutic effect. These include functional and structural changes that are discussed later. In addition, in the last years, evidence has emerged that remissions induced in patients using lithium or electroconvulsive therapy are accompanied by structural changes in neuronal networks thereby affecting synaptic plasticity in various regions of the brain.
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1. Introduction

1.1. Background

Behind cardiovascular diseases depression is the second most important disease in the Western world. If one takes into account the years of suffering from a given illness together with the severity of the respective disease, unipolar depression is ranked number 1 before all other somatic and psychiatric illnesses (Lopez & Murray, 1998). Strengthening the significance of depression is the fact that its incidence has steadily increased in the last years. Depression therefore is a serious psychiatric illness with a lifetime prevalence of 5% (Klerman & Weissman, 1988). An even higher number, up to 20%, of individuals suffer from a depressive episode once in their lifetime. Typical symptoms of depression include depressed mood, diminished interest of pleasure (anhedonia), feelings of worthlessness or inappropriate guilt, decrease in appetite and libido, insomnia, and recurrent thoughts of death or suicide. Depression is potentially fatal since most patients think about suicide, about 50% try to commit suicide and up to 15% of patients with severe depression die from suicide (Disalver et al., 1994; Strakowski et al., 1996). In addition, in the last years, depression has been found to be a risk factor in diseases such as diabetes and cardiovascular disease (Musselman et al., 1998; Ciechanowski et al., 2000). Depression most often occurs in defined episodes, which can last from weeks to months, in severe cases for years. Many patients suffer from several relapses and/or chronification, which then often leads to severe cognitive and functional impairment as well as psychosocial disability (Coryell et al., 1993; Zarate et al., 2000). Treatment of depression includes various forms of psychotherapy as well as pharmacotherapy with antidepressants. In severe cases or in treatment-resistant depression, electroconvulsive therapy (ECT) is also applied. Depression is also a remitting disease in which normal clinical studies show a placebo response rate of about 40%. It is of interest that the rate of improvement under placebo treatment is identical to that seen in drug studies suggesting that the underlying mechanisms are very similar (Stassen et al., 1999). In view of the efficacy of drugs (about 60%) and ECT (80–90%) (Nobler & Sackheim, 2001; Shergill & Katona, 2001), it is clear that we still have a need to better understand the pathophysiology in order to develop effective medications.

Neurobiological basic research as well as clinical studies have revealed that 2 monoaminergic systems are involved in the etiology and therapy of affective disorders, namely serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (Coppen, 1967; Meltzer & Lowy, 1987; Charney, 1998). Thus, the common basis of pharmacotherapy is based on the enhancement of serotonergic and/or noradrenergic neurotransmission by either inhibiting the intracellular degradation of the monoamines with monoamino oxidase inhibitors or blocking their reuptake back into the synaptic cleft by selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNRI), or tricyclic antidepressants (TCA) (Nemeroff, 1998). SSRI and SNRI bind with high selectivity and affinity to the monoamine transporter proteins and thereby block the neurotransmitter translocation process that, in turn, leads to an increase of synaptic monoamines (Schloss & Williams, 1998; Iversen, 2000).

1.2. Monoamine transporter proteins

In contrast to cholinergic neurotransmission where acetylcholine is inactivated by enzymatic degradation, the principal means of terminating monoaminergic signaling is the rapid reuptake of these transmitters back into the presynaptic terminal. There, monoamines are either degraded by monoamino oxidases or they can be reloaded into synaptic vesicles via vesicular monoamine transporter proteins, which differ from the plasma membrane-bound transporters. The identification of the cDNA of the rat γ-aminobutyric acid (GABA) transporter GAT1 and the human norepinephrine transporter (NET) revealed that the encoded proteins share a high degree of amino acid identity (Guastella et al., 1990; Pacholczyck et al., 1991) and following homology screening led to the cloning of the related cDNA sequences of the selective transporters for dopamine, glycine, and serotonin. In the following years, several transporter isoforms were identified for GABA and glycine; however, up to now, only one form has been found for the transport of each of the monoamines dopamine, norepinephrine, and serotonin. All these plasma membrane-bound transporters exhibited highly related polypeptides that share a common, putative 12 transmembrane domain topological structure as shown by hydrophobicity analysis or antibody mapping (Guastella et al., 1990; Pacholczyck et al., 1991; Schloss et al., 1994; Brüss et al., 1995; Clark, 1997; Chen & Reith, 2002). Using various biochemical techniques, it has been shown that the transporters for GABA, dopamine, and serotonin assemble into dimeric or tetrameric quaternary forms (Milner et al., 1994; Jess et al., 1996; Chang et al., 1998; Kilic & Rudnick, 2000; Schmid et al., 2000; Hastrup et al., 2001; Horschitz et al., 2003; Kocabas et al., 2003). The cytoplasmic regions of all transporters contain phosphorylation sites, which can be used for regulation of transporter activity. Indeed, it has been shown that activation of protein kinase C in cells expressing the monoamine transporters and also the transporters for glycine and GABA results in a down-regulation of transporter activity (Kitayama et al., 1994; Osawa et al., 1994; Sato et al., 1995a, 1995b; Huff et al., 1997; Quian et al., 1997; Apparsundaram et al., 1998; Blakely et al., 1998; Bonisch et al., 1998; Zahniser & Doolen, 2001). It is thought that this effect results from a redistribution of the transporter proteins from the cell surface to intracellular compartments. Thus, subcellular distribution of trans-

porter proteins upon activation of second messenger systems obviously is a very effective process to control transporter activity and thereby the efficiency of neuronal signaling.

TCA, SSRI, and SNRI block their respective norepinephrine and/or serotonin transporter (SERT) protein thereby causing an increase of the neurotransmitter concentration in the synaptic cleft. Inhibition of uptake is achieved rapidly and efficiently. However, mood improvement occurs only after more than 1 week of antidepressant therapy. This finding suggests that it is not the reuptake inhibition per se but rather long-term neuroadaptive changes that may underlie the therapeutic effect. Here, it is feasible to consider that the efficiency of monoaminergic signaling can be enhanced by molecular changes at single synapses such as up-regulation of post-synaptic receptors and/or down-regulation or desensitization of presynaptic autoreceptors that are negatively coupled to exocytotic neurotransmitter release. Additional possibilities include enhanced neurotransmitter synthesis/release or down-regulation/desensitization of transmitter transporters. A different possibility takes into account that the efficiency of monoaminergic signaling is not only modulated at single synapses but also by the density of synaptic contact sites. This idea implies that long-term antidepressant treatment induces sprouting of monoaminergic fibers and the formation of new synapses or even neurogenesis.

Both ideas suppose that acute effects of antidepressant treatment strongly differ from the effects observed upon chronic administration. In the last years, many pieces of evidence have been found suggesting that indeed chronic antidepressant treatment induces long-lasting changes on proteins at single synapses as well as in the density of synapse formation.

2. Molecular effects of long-term antidepressant treatment

2.1. Regulation of post-synaptic receptors

The finding that increasing catecholamine concentrations in the synapse led to an antidepressant response with a delay of 1–3 weeks suggested that some downstream process must be responsible. For over 2 decades, theories were formulated concerning the down-regulation or desensitization of specific receptors. In general, neither of these processes takes place in a time scale consistent with antidepressant action. Desensitization is a general phenomenon for most receptors and results in decreased efficacy of an agonist following agonist exposure. This process occurs within minutes and often involves phosphorylation of the receptor. Receptor down-regulation was felt to be more consistent with the time needed for antidepressant response. Multiple theories were developed involving both noradrenergic and serotonin receptors to explain antide-

pressant action. The first and probably the most consistent is the view that all antidepressants cause the down-regulation of the β-adrenergic receptor. This was certainly true for the tricyclics, but with the advent of mianserin and subsequently the SSRI, this theory fell into disrepute. However, data using the animal model of depression, learned helplessness, showed that, in helpless animals, SSRI and mianserin cause a down-regulation of the β receptor (Henn et al., 1993). That is, the pharmacological response seen in wild-type animals is altered in animals showing depressive like features. Multiple studies using postmortem tissue also showed an up-regulation of the β receptor in suicide victims (Biegon & Israeli, 1988; Sastre et al., 2001). Nonetheless, the time scale for down-regulation of receptors is only a matter of hours after exposure to an agonist. The mechanism involves the internalization of the receptor and not a metabolic response and is clearly too rapid to be the final effector mechanism in the action of antidepressants.

There are several important points in considering the role of post-synaptic receptors in the etiology of depression. The lag time seen in antidepressive responses to medications is not always reflected in the rate of onset of the illness. The data on learned helplessness make it clear that the pharmacological effect of a given medication is different in wild-type tissue and pathological tissue. This is potentially an important distinction in that almost all of the studies on the mechanism of action of psychoactive drugs take place on wild-type animals, and we have only a few animal models that allow an investigation of the pharmacology in pathological tissue. In those cases where it has been studied, differences in post-synaptic receptor regulation have been observed in models where long-term behavioral changes are present. Thus, the major data we have on post-synaptic receptor regulation may be inapplicable to the action of these compounds in depression. Finally, a simplistic view of receptor regulation that postulates up-regulation with a decreased concentration of the receptor in the synaptic cleft and down-regulation with an increased concentration may also be incorrect. The effects of other circuits and modulators may lead to very different results. An example of this is the case of the 5-HT$_{1A}$ receptor, which is differentially regulated in the hippocampus and hypothalamus. The 5-HT$_{1A}$ receptor has been implicated through a variety of studies in affective disorders. It is present both pre- and post-synaptically. In the raphe, the receptor is located on cell bodies of 5-HT cells and slows the firing rate in a direct feedback loop (de Montigny et al., 1984; Aghajanian et al., 1990). In the terminal field areas of the 5-HT system including limbic and cortical areas, the receptor is located post-synaptically (Vergé et al., 1986; Hensler et al., 1991; Riad et al., 2000). The receptors in the hypothalamus, which control the reaction to stress, are rapidly down-regulated by agonist or antidepressant administration and this appears to occur acutely (Larsson et al., 1990). On the other hand, the receptors in the hippocampus are not altered even after

chronic administration of agonists or SSRI (Hensler, 2003). This suggests post-synaptic regulation is a complex phenomenon and is differently regulated in different brain areas and by different pharmacological means.

2.2. Regulation of presynaptic auto and heteroreceptors

Several pieces of evidence have suggested that 5-HT autoreceptors that negatively control Ca^{2+}-dependent 5-HT release are involved in long-term adaptive changes induced by chronic SSRI treatment. Activation of autoreceptors with the selective 5-HT$_{1A}$ receptor agonist 8-OH-DPAT and the 5-HT$_{1B}$ receptor antagonist RU24969 and CP-93,129 result in decreased 5-HT release (Hiorth & Magnusson, 1988; Sharp et al., 1998a, 1998b). In addition, it has been shown that the firing activity of some serotonergic neurons is attenuated upon acute SSRI treatment but returns to basal levels and elevates over basal levels after 2 weeks of treatment (Auerbach & Hjorth, 1995). In another report, acute SSRI treatment produced only a small increase in extracellular 5-HT as measured by microdialysis, whereas long-term application (2 weeks) caused a 6-fold increase in synaptic 5-HT (Blier & de Montigny, 1994). One possible explanation for this delayed effect is that acute inhibition of 5-HT reuptake first increases synaptic 5-HT concentration, which, in turn, activates inhibitory somatodendritic 5-HT$_{1A}$ and/or terminal 5-HT$_{1B}$ autoreceptors. Thus, acute administration of SSRI primarily leads to a reduction in transmitter release. Long-term treatment may then induce adaptive changes such as desensitization or down-regulation of autoreceptors, finally resulting in potentiated synaptic serotonergic activity underlying the therapeutic effect of antidepressant treatment. Supporting this hypothesis, pretreatment with the selective 5-HT$_{1A}$ receptor antagonist, (−)pindolol, has been shown to prevent the suppressing effect of paroxetine on 5-HT release of neurons of the dorsal raphe nuclei (Artigas et al., 1996). These findings go along with clinical studies, in which it has been shown that in some patients a combined therapy with an SSRI together with pindolol shortened the latency of the onset of antidepressant therapy (Artigas et al., 1994; Blier & Bergeron, 1995).

In animal experiments, the administration of the 5-HT$_{1A}$ receptor selective antagonist WAY 100635 and the SSRI fluoxetin also induced a strong increase in extracellular hypothalamic 5-HT, indicating the synergistic effect of combined blockade of autoreceptors and reuptake. Interestingly, in this set of experiments, subsequent administration of the serotonin precursor 5-hydroxytryptophan (5-HTP) led to a further increase of 5-HT release (Dreshfield-Ahmad et al., 2000). Down-regulation of 5-HT$_{1B}$ receptors upon long-term SSRI treatment has been shown using in situ hybridization. In this study, the SSRI paroxetine and fluoxetine, but not the SSRI sertraline, induced a significant decrease of 5-HT$_{1B}$ receptor mRNA in the dorsal raphe nucleus but not in the hippocampus (Anthony et al., 2000). After several days of washout, the 5-HT$_{1B}$ receptor mRNA levels then

returned to basal levels. The involvement of terminal 5-HT$_{1B}$ autoreceptor in regulating 5-HT release has also been demonstrated in transgenic mice, which lack the gene of this receptor. Microdialysis experiments revealed that whereas basal 5-HT release in the frontal cortex and the ventral hippocampus did not differ between wild type and the mutants, application of the 5-HT$_{1B}$-selective agonist CP-93,129 significantly decreased K^+-evoked release in these brain areas only in the wild-type mice but exhibited no effect in the mutants (Trillat et al., 1997).

Also, in the noradrenergic system, different effects of long-term versus acute SNRI application on presynaptic adrenoceptors have been reported. Early functional studies in the rat vas deferens had shown that antidepressants through inhibition of monoamine uptake induce effects on presynaptic α_2-autoreceptors that differ depending on the duration of antidepressant application: receptor activation after acute treatment followed by desensitization with long-term treatment (Garcia-Sevilla & Zubieta, 1986). In the rat brain, the responsiveness of neurons from the locus coeruleus (LC) to administration of the α_2-adrenoceptor antagonist idazoxan has been studied in the frontal cortex after short- and long-term imipramine treatment. Combined single-cell recording and microdialysis revealed that (i) the firing rate of the neurons was significantly lower in rats receiving acute imipramine application compared with rats with long-term treatment, (ii) noradrenaline release was higher in all imipramine treated animals compared with control rats, and (iii) the enhancing effect of idazoxan on the firing rate as well as on noradrenaline release was higher after long- than after short-term imipramine treatment of the animals (Linner et al., 1999). These data are thought to be indicative for a functional down-regulation of α_2-autoreceptors on LC neurons upon long-term noradrenaline reuptake inhibition and might suggest that addition of α_2-adrenoceptor antagonists to SNRI treatment may augment the clinical effect in SNRI-based pharmacotherapy in major depression. In another study, the effect of administration of the α_2-adrenoceptor agonist clonidine has been investigated in rats chronically treated with the SNRI desipramine. Here, clonidine at 10 μg/kg significantly reduced extracellular noradrenaline in control rats but not in desipramine treated animals. At higher doses, however, clonidine exhibited similar effects in both rats. Because radioligand binding studies in the LC did not show any differences between the animals investigated, it was concluded that long-term treatment with desipramine induces adaptive changes involving the desensitization of α_2-autoreceptors with no change in their density on noradrenergic neurons (Sacchetti et al., 2001). In addition, a significant reduction in noradrenaline uptake was measured in synaptosomal preparations from the dorsal hippocampus suggesting an effect of long-term antidepressant treatment not only on autoreceptors but also on the overall activity of transporter proteins (Fig. 1). This aspect will be discussed later.
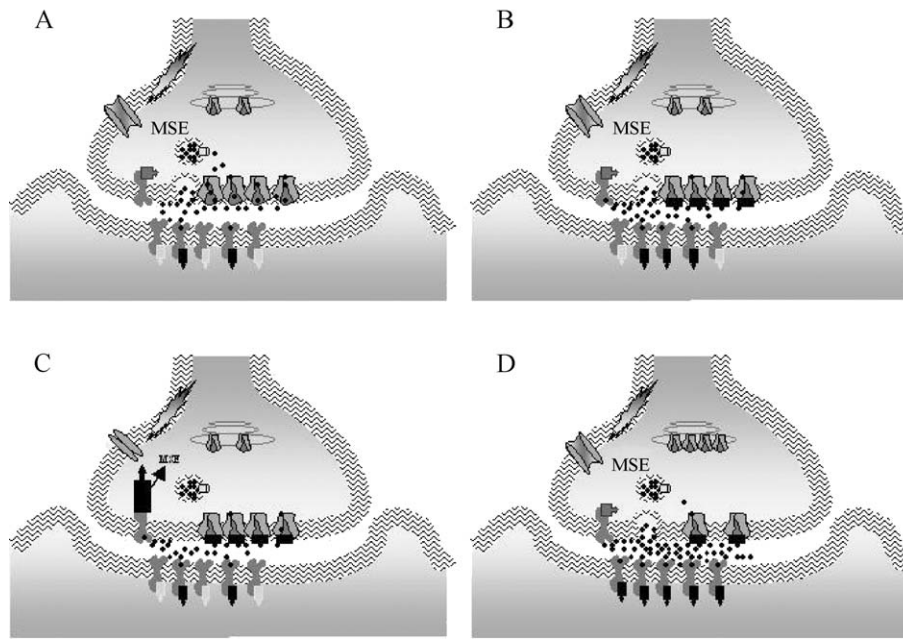
Fig. 1. Possible regulation of the efficiency of monoaminergic signaling at the synaptic level. Acute antidepressant administration shortly enhances the transmitter concentration in the synaptic cleft (**A**, **B**). This will result in an activation of presynaptic autoreceptors, which are negatively coupled to monoamine synthesizing enzymes (MSE) and/or exocytotic release (**C**). As a consequence, synaptic monoamine concentration will be lowered. Long-term activation of these receptors, however, induces their desensitization, which then allows new transmitter synthesis and release (**D**). In addition, chronic exposition to antagonists induces an internalization of transporter proteins into intracellular compartments, which causes a reduction of uptake capacity thereby additionally enhancing the efficiency of monoaminergic signaling.

Comparable to the effect of long-term antidepressant application, a desensitization of α_2-adrenoceptors has also been shown to occur after chronic administration of the monoamino oxidase inhibitor clorgyline (Prieto & Giralt, 2002). In hippocampal and cortical synaptosomal membrane preparations, a reduction in the sensitivity of α_2-adrenoceptors was measured upon chronic treatment with clorgyline. Accordingly, clonidine induced a decrease in tyrosine hydroxylase (TH) activity in control rats and animals subjected to an acute clorgyline treatment, but failed to do so after chronic treatment.

2.3. Regulation of monoamine synthesis

One mechanism by which autoreceptors control neurotransmitter release is that following activation of the receptor the β- and γ-dimer is released from the trimeric G-protein. This peptide binds with high affinity to voltage-gated calcium channels, thereby reducing their opening frequencies. This in turn leads to a diminished exocytosis process. Actually, in chick sympathetic neurons, it had been shown that this is the only mechanism by which presynaptic α_2-autoreceptors control noradrenaline release (Boehm & Huck, 1996). On the other hand, presynaptic inhibitory receptors also inhibit the synthesis of monoamines via down-regulation of the rate limiting enzymes TH and tryptophan hydroxylase (TPH) (Esteban et al., 1996).

Post-translational up-regulation of TH and TPH activity is known to be achieved through phosphorylation by various kinases (Ehret et al., 1989; Johansen et al., 1995; Banik et al., 1997; Lindgren et al., 2002; Stenfors & Ross, 2002; Stultz et al., 2002; Bevilaqua et al., 2003). The activation of both presynaptic α_2-adrenoceptors and 5-HT$_{1A}$ and 5-HT$_{1B}$ autoreceptors results in an inhibition of adenylyl cyclase, and thus, the molecular mechanisms of autoreceptor induced inhibition of TH and TPH may result from a down-regulation of Ca^{2+}/calmodulin-dependent protein kinases and cAMP-dependent protein kinase A (PKA), which attenuates after autoreceptor desensitization.

TH can also be inactivated by the binding of noradrenaline to its active site, which provides a direct negative feedback loop (Hufton et al., 1995). A comparable direct autoregulation is not known for TPH. Here, autoregulation seems to occur indirectly on the transcriptional level. In the TPH-expressing CA77 thyroid C-cell cell line, it has been shown that expressing the 5-HT1 selective agonist CGS12066A down-regulates TPH by repressing the TPH promotor activity as revealed by Northern blot analysis (Wood & Russo, 2001). Based on the results from transfection reporter gene assays, the authors present a model of autoregulation of the TPH promotor by 5-HT. In this model, the transcription of TPH is stimulated by MAP kinases, which leads to increased 5-HT synthesis. When synaptic 5-HT increases, stimulation of 5-HT1 autoreceptors increases MAP kinase phosphatase-1. As a consequence, MAP kinases are dephosphorylated and the activation of the TPH promotor following TPH transcription is reduced (Fig. 1).

To estimate the in vivo rates of TH and TPH, the accumulation of 3,4-dihydroxyphenylalanine (DOPA) and 5-HTP is measured after inhibition of the aromatic L-amino acid decarboxylase. It has been shown that in vivo application of α_2-adrenoceptor agonist leads to significant decreases of TH activity, whereas α_2-adrenoceptor antagonists induce an increase of DOPA (Pi & Garcia-Sevilla, 1992). This assay system has also been used to investigate the effect of acute and chronic antidepressant application on the in vivo sensitivity of α_2 adrenoceptors and 5-HT$_{1A}$ autoreceptors (Esteban et al., 1999). In these studies, acute inhibition of noradrenaline uptake but not of 5-HT uptake resulted in activation of α_2-autoreceptors indicated by reduced DOPA synthesis. Interestingly, acute application of the SNRI desipramine also reduced 5-HTP synthesis in the hippocampus, but not in the cortex. This effect is thought to be mediated through endogenous noradrenaline onto α_2-heteroreceptors located on hippocampal serotonergic nerve terminals. Conversely, acute inhibition of 5-HT reuptake resulted in a decrease of 5-HTP synthesis but did not affect DOPA synthesis. Chronic treatment with desipramine or the SSRI fluoxetine then resulted in a time-dependent loss in the ability of these drugs to reduce monoamine synthesis. This is most likely due to an ongoing desensitization of presynaptic α_2-autoreceptors, α_2-heteroreceptors, and 5-HT$_{1A}$ receptors as shown before.

In the studies discussed above the rate of DOPA and 5-HTP has been measured to monitor the activity of TH and TPH, respectively. This kind of assay, however, does not allow to distinguish between pre- and post-translational effects of autoreceptor activation. In another approach to investigate whether long-term antidepressant administration affects gene expression, Kim et al. (2002) have analyzed the effect of chronic sertraline (SSRI) on the mRNA and protein levels of TPH in vivo and in vitro. As determined by in situ hybridization and immunocytochemistry, injections of sertraline for 2 weeks resulted in a significant up-regulation of TPH mRNA and protein levels in the dorsal raphe nucleus of the rat brain. In vitro, sertraline application to the basophilic cell line RBL-2H3 also increased TPH mRNA and protein as revealed by Northern and Western blot analysis. When treating the cells with the selective PKA inhibitor H-89, the sertraline-induced up-regulation of TPH gene expression was attenuated but not abolished. It is known that long-term antidepressant administration increases the expression of cAMP-dependent PKA and thereby the activity of the transcription factor cAMP response element binding protein (CREB), which leads to enhanced transcription of genes containing a cAMP-responsive element in their promotor (Duman et al., 1999). It is known that the TPH gene contains a cAMP-responsive element (Valenciano et al., 2000), and because PKA inhibition does not completely block TPH induction, one might speculate that sertraline exerts a long-term effect on serotonergic neurotransmission by increasing the TPH expression partly by the cAMP/PKA pathway, but also by other mechanisms. Actually, it should be mentioned here that many results concerning the regulation of TPH have been obtained in non-raphe cells that might contain other noradrenergic or serotonergic receptors than original serotonergic neurons. In addition, one must not forget that chronic blockade of monoamine reuptake induces an intracellular deficit of neurotransmitters to be loaded back into the synaptic vesicles, which, to compensate for monoamine depletion, urges an up-regulation of monoamine synthesis.

2.4. Regulation of neurotransmitter transporter activity

In addition to effects on presynaptic autoreceptors and monoamine synthesizing enzymes, the effects of acute and chronic application of antidepressants on the activity of the NET and SERT have been thoroughly investigated in the last years. This resulted in contradictory findings. Using quantitative Northern blot analysis, Lesch et al. (1993) found in vivo that long-term treatment with the nonselective noradrenaline/serotonin uptake inhibitor imipramine or the SSRI fluoxetine strongly decreased SERT mRNA in the rat midbrain raphe complex. In contrast, when analyzing the effect of chronic imipramine and fluoxetine on the expression of SERT also by Northern blot analysis, Koed and Linnet (1997) report that "the serotonin transporter messenger RNA level in rat brain is not regulated by antidepressants." Using quantitative in situ hybridization, Lopez et al. (1994) report that chronic imipramine significantly increases SERT mRNA in the dorsal raphe nucleus, whereas Neumaier et al. (1996) state that chronic fluoxetine transiently reduces SERT mRNA in this brain region with a return to basal levels after about 3 weeks.

On the protein level, down-regulation of SERT following long-term SSRI application has been described (Pineyro et al., 1994). Here, in vitro uptake measurements in hippocampal and dorsal raphe slices revealed a 50–60% reduction in [^{3}H]5-HT transport in preparations from animals that were chronically treated with paroxetine accompanied by a 50% reduction in the number of cell surface expressed transporter molecules as estimated by determining [^{3}H]paroxetine binding parameters. In another approach, it has been shown that long-term SSRI application also reduces SERT density in the CA3 region of the hippocampus by 80–90% as assessed by quantitative autoradiography with [^{3}H]cyanoimipramine (Benmansour et al., 1999). As measured with high-speed in vivo electrochemical recordings, in this area, SSRI did not further diminish the clearance of serotonin as usually observed in nontreated animals. These findings suggest that serotonin clearance in vivo is altered to a greater extent by antidepressant-induced down-regulation of the SERT than by acute blockade of the protein (Benmansour et al., 2002).

In addition, reports on the regulation of the noradrenaline transporter are not consistent. In vivo, elevation of NET mRNA in the LC following short- and long-term SNRI treatment has been described (Szot et al., 1993) as well as that NET mRNA initially decreases upon acute desipramine treatment but increases after chronic drug treatment (Zhu et al., 2002; Zavosh et al., 1999). In the latter report, comparable investigations also have been performed in vitro using cultured SK-N-BE(2)M17 cells. As revealed by Northern blot analysis, NET mRNA levels are first reduced and then increase after longer drug incubation. Interestingly, NET protein levels decreased after the third desipramine treatment, but did not increase later. These opposite effects in NET mRNA and protein levels suggest noncongruent regulatory mechanisms induced upon chronic antidepressant treatment. Actually, in vitro, it has consistently been shown that SNRI treatment reduces the reuptake activity of endogenous NET proteins in PC12 cells as well as of NET proteins heterologously expressed in HEK293 cells (Zhu & Ordway, 1997; Zhu et al., 1998). Comparably, SSRI treatment induces a down-regulation of recombinant SERT (Horschitz et al., 2001). These modulations are selective, that is, longer incubations with an SNRI do not affect SERT expression and SSRI do not alter NET activity. It is hypothesized that similar to phosphorylation-induced subcellular distribution of transporters, ongoing occupation with antagonist may lead to internalization of the proteins thereby altering their cell surface expression and reduced transport activity independent of regulation processes on mRNA level (Fig. 1). As a physiological consequence, this would result in prolonged synaptic monoamine action.

Here a very important question arises: what physiological consequences does one expect upon measuring enhanced/decreased transporter mRNA or protein level? In cell culture experiments, a reasonable conclusion is that a drug-induced decrease of transporters on the cell surface goes along with a reduced transport activity and will result in enhanced monoaminergic neurotransmission. Thus, this could be indicative of the physiological antidepressant effect underlying long-term antidepressant therapy. This would for example explain that in an animal model of depression an increase of SERT has been found in hippocampal membrane preparations as compared with control animals (Edwards et al., 1991). On the other hand, in vivo, lower levels of transporter mRNA or protein concentration may also reflect a down-regulation of the density of synaptic contact site and consequently a reduction in monoaminergic signaling. With this interpretation, an increase of monoamine transporter protein would suggest higher monoaminergic signaling and would contradict the observation by Edwards et al. (1991).

In summary, chronic antidepressant therapy can modulate the activity and expression pattern of autoreceptors, which regulate neurotransmitter synthesis and release, as well as of their direct targets, the transporter proteins for noradrenaline and serotonin, respectively. Thus, in contrast to acute effects, chronic antidepressants can enhance the activity of single synapses on the molecular level by a variety of mechanisms that might differ in different brain regions.

3. Cellular changes upon long-term antidepressant treatment

In addition to changes in specific molecules, effects at the cellular level (e.g., the density of monoaminergic synapses) have been reported. Here, antidepressants not only affect single molecules, but also are thought to induce signaling cascades, which lead to the formation of new synapses (synaptogenesis), thereby enhancing monoaminergic signaling. This means that antidepressant therapy in addition to influencing functional parameters of receptors, transporters, and enzymes also induces anatomical-structural modifications in the brain and thus affects long-term neuronal plasticity.

3.1. Neurotrophins/glucocorticoids

In recent years, it has been hypothesized that antidepressant therapy is based on the activation of neurotrophic factors, which induce the sprouting of neurons, that is formation of new synapses, and stabilize already existent synapses. Long before a connection among neurotrophins and depression and antidepressant therapy had been presumed, the involvement of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor, and neurotrophin-3 has been investigated in the differentiation of the nervous system (Thoenen, 1995). Here, reciprocal interactions were found between BDNF and the serotonergic system, only some of which are listed below:

- In vivo, chronic infusion of BDNF into the neocortex induces sprouting of serotonergic fibers and the formation of new serotonergic synapses in the rat brain (Mamounas et al., 1995, 2000).
- Infusion of BDNF into the midbrain adjacent the dorsal and median raphe nuclei leads to an increase of the mRNA encoding the TPH (Siuciak et al., 1998).
- BDNF-deficient mice exhibit premature decrements of forebrain serotonergic fiber density. Interestingly, this anatomical serotonergic abnormality is associated with enhanced aggressive behavior (Lyons et al., 1999).
- In vitro, application of BDNF, that is, activation of its receptor TrkB up-regulates serotonergic phenotype in cell culture (Galter & Unsicker, 2000; Rumajogee et al., 2002).
- Activation of 5-HT$_{2A}$ receptors regulates the expression of BDNF in vitro and in vivo (Meller et al., 2002).

The specific interactions between neurotrophic factors and the activity of monoaminergic systems suggested the involvement of neurotrophins in molecular processes un-

derlying the etiology and therapy of depression. Important investigations had been performed in various animal models of depression and animals exposed to various kinds of stress. Stress is known to elevate glucocorticoid levels, which in turn induce molecular and structural changes in various brain regions (Holsboer, 2000). Interestingly, in many studies, chronic antidepressant administration has been shown to counteract or even revert stress-induced neuronal damage. In the rat cerebral cortex, it has been shown that stress induces degeneration, but imipramine induces regeneration of noradrenergic axons (Kitayama et al., 1997), and in the hippocampus formation, stress-induced decrease of cell proliferation is reversed upon treatment with an SSRI (Malberg et al., 2000; Malberg & Duman, 2003). Actually, it is postulated, that the therapeutic effect of antidepressant treatment requires neurogenesis of hippocampal cells (Santarelli et al., 2003). Both stress- and antidepressant-induced molecular and behavioral changes are accompanied by significant changes in the expression level of neurotrophins. Long-term stress via enhanced glucocorticoids down-regulates, whereas chronic antidepressant treatment up-regulates, BDNF expression in the rat brain (Nibuya et al., 1995; Smith et al., 1995). Interestingly, an inbred strain of rats, which exhibit congenital helplessness, react to stress with increased corticosterone levels but no decrease in BDNF (Vollmayr et al., 2001). Since these rats still respond to stress with elevated glucocorticoid levels, it is hypothesized that this strain has lost its behavioral plasticity with respect to the coupling of BDNF expression and glucocorticoid- and monoaminergic-mediated molecular signaling. Based on these finding, one might build up a simplified model in which long-term stress can disturb a given balance among monoamines, neurotrophins, and glucocorticoids (Altar, 1999). Here, the efficiency of monoaminergic signaling is positively coupled to the synthesis of BDNF, and increased glucocorticoid levels lead to a decrease of both neurotransmitter and neurotrophin. Most likely, reduced monoaminergic signaling results from a reduced transmitter concentration in the synaptic cleft as well as reduction of the total number of noradrenergic and/ or serotonergic synapses. Recently, it has been shown that glucocorticoids increase the expression of SERT in immortalized human B-lymphoblastoid cells (Glatz et al., 2003). Thus, one might speculate that reduced monoaminergic signaling results from both reduced monoamines in the synaptic cleft (due to enhanced reuptake) and reduced number of monoaminergic synapses. The effect of antidepressant will then include molecular changes at single synapses as discussed in Section 2.4, such as down-regulation of noradrenaline and SERT as well as the formation of new synapses. Antidepressant-mediated enhanced activation of adrenoceptors and 5-HT receptors is thought to trigger intracellular signaling cascades, which result in an increase of gene expression, protein synthesis, and release of BDNF (Altar, 1999). Activation of the TrkC by released BDNF will then trigger intracellular signaling pathways that induce the

formation of new synapses and/or the strengthening of already existent synapses. Recently, it has been shown that infusion of BDNF into the dentate gyrus of the hippocampus produced antidepressant effects in different animal models of depression (Shirayama et al., 2002). This was comparable with chronic administration of antidepressants, and thus, these findings suggest that antidepressants exert their behavioral effects through neurotrophin-dependent mechanisms.

3.2. Intracellular pathways

The induction of BDNF transcription again is thought to be based on the activation of the cAMP cascade in response to chronic antidepressant treatment. Here, long-term activation of 5-HT_{2A} receptors and β-adrenoceptors enhances the functional coupling of the stimulatory G-protein to adenylyl cyclase, which, in turn, leads to elevated levels of cAMP, the cAMP-dependent PKA, and finally the phosphorylated form of the CREB protein (for detailed reviews, see Duman et al., 1999; Duman, 2002; Nestler et al., 2002). Enhanced transcriptional activity of phosphorylated CREB then induces the synthesis and release of BDNF, which, in hippocampal pyramidal neurons, increases dendritic arborizations, and in the frontal cortex, promotes the sprouting of serotonergic fibers (Mamounas et al., 2000; Nestler et al., 2002).

On the other hand, the effect of antidepressants and stress on synaptic changes in the hippocampus and behavior do not by all means have to include the cAMP-CREB pathway. In this line, it has been shown that CREB knock-out mice still normally respond to antidepressant treatment in the forced swimming test without exhibiting elevated BDNF expression in the hippocampus (Conti et al., 2002). In addition, it has been reported that chronic stress produces an atrophy of apical dendrites in the CA3 region of the hippocampus with no change of BDNF or neurotrophin-3 expression levels (Kuroda & McEwen, 1998). Interestingly, this neuronal atrophy was reversible by the atypical antidepressant tianeptine.

In this context, one should point out that many incongruent results with regard to the molecular mechanisms underlying the late onset of antidepressant therapy have often been obtained either in cell culture systems or in "normal" animals, that is, animals that do not reflect the rodent equivalent of human depression. In addition, many studies have focussed on certain brain areas especially the hippocampus or frontal cortex, thereby neglecting possible changes occurring in the amygdala, the midbrain, or other areas.

Originally, it was thought that neurotrophins are secreted from their target tissues (e.g., post-synaptic dendrites) to increase the number of contact sites to the presynaptic innervation or to sustain already existent synapses. In this model, neurotrophin (NT) bind to and activate their opposite presynaptic tyrosine kinase receptors. NT/Trk complexes are then internalized by the nerve terminal and are retro-
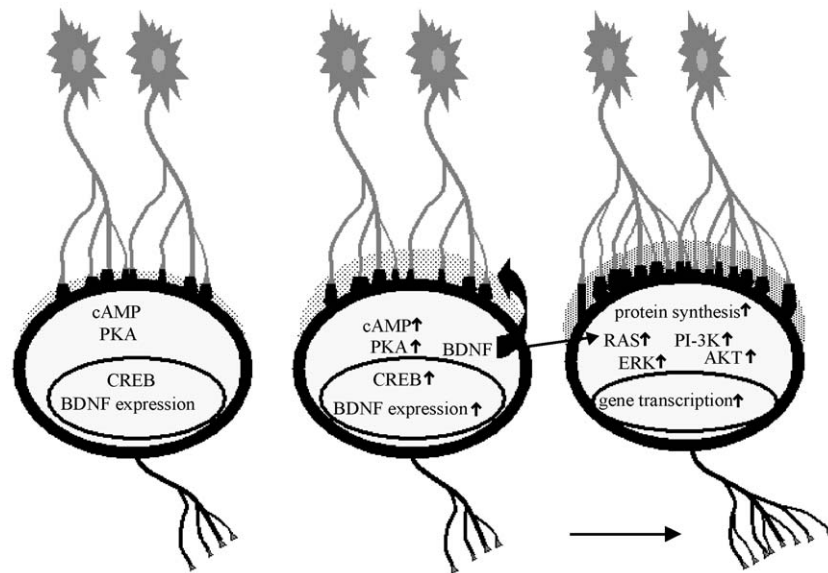
Fig. 2. Possible regulation of the efficiency of monoaminergic signaling on the cellular level. Chronic, but not acute, antidepressant treatment results in enhanced monoaminergic activation of G-protein-coupled receptors, which leads to an up-regulation of adenylyl cyclase and cAMP. PKA-mediated phosphorylation of CREB then induces the expression of BDNF. By activating the RAS/MAPK/ERK or PI3K/AKT pathways, BDNF switches on molecular mechanisms that are necessary for cell survival and/or cell growth. In addition, released BDNF can act paracrine on adjacent nerve terminals. Thus, BDNF can induce dendritic arborizations and the sprouting of nerve terminals, which results in increased synaptic connectivity not only of monoaminergic neurons.

gradely transported as so-called signaling endosomes. In the cell body, they signal through RAS-mediated activation of mitogen-activated protein kinases (MAPK) and/or the phosphatidylinositol-3-kinase (PI3K) (Heerssen & Segal, 2002; Coyle & Duman, 2003). The MAPK cascade triggers activation of the extracellular signal-regulated kinases (ERK), whereas PI-3K activation results in activation of AKT, also referred to as protein kinase B (PKB), which, in turn, inactivates glycogen synthase-3β. Because activated glycogen synthase-3β inhibits the transcription of CREB and, in addition, induces apoptosis, activation of the PI3K/AKT cascade is important for cell survival and the consolidation of synaptic contact sites (Jope & Bijur, 2002). The RAS/MAPK/ERK cascade is involved in the regulation of transcription, protein translation, and arrangement of cytoskeletal proteins and thus is believed to contribute to synaptogenesis. Besides signaling in the soma, activated Trk also exerts its stimuli within the axon, where it induces axonal elongation and outgrowth (Heerssen & Segal, 2002). In addition, it has been shown that upon CREB-mediated transcription, the translated BDNF protein is also anterogradely transported to the axon terminals. Here, after secretion BDNF can act paracrine or autocrine, depending on the site of Trk expression (see Fig. 2).

4. Electroconvulsive therapy

4.1. General background

ECT is the most effective form of antidepressant therapy available. It is effective in between 85% and 90% of cases of major depression compared with antidepressant medications, which are effective in 60–65% of cases (Nobler & Sackheim, 2001; Shergill & Katona, 2001). Thus, understanding the mechanism of ECT might be a major clue to understanding the etiology of depression. ECT treatment requires the induction of a series of convulsions, usually induced 3 times a week by the application of either bilateral or unilateral electrical shocks. The response is usually seen after 4–8 treatments and usually results in decided reduction in the symptoms of depression with the fourth to sixth treatment. Thus, repeated convulsions are necessary for the therapeutic effect (Franco-Bronson, 1996), and the drop in symptoms can occur in 1–2 weeks.

4.2. Molecular changes

ECT causes a widespread release of neurotransmitters with the resultant increase in the concentration of monoamines, among other transmitters. This results in a down-regulation of a variety of receptors including those felt to be up-regulated in depression such as the β-norepinephrine receptor and the 5-HT$_{1A}$ receptor (Nutt et al., 1989; Gur et al., 2002). There are also strong effects on the release of GABA and, of course, glutamate (Bajkowska et al., 1999; Sanacora et al., 2003). The widespread effects secondary to a generalized seizure make it difficult to isolate those events that are specific to the therapeutic effect of ECT. However, aside from the numerous receptor changes seen with chronic ECT, there are also changes along signal transduction pathways that are thought to play a role in the action of other antidepressants (Duman & Vaidya, 1988). Since ECT requires chronic administration and the therapeutic effect

lasts for a considerable time suggesting stable central nervous system changes, it may be that it acts through changes in gene expression patterns. Such patterns appear stable and may provide new clues to antidepressant action (Altar, personal communication). Transcription factors could be induced through ECT, and this is felt to be a key mechanism in triggering neural plasticity (Nestler et al., 2002).

In going downstream from the catecholamine receptors, one transcription factor appears to play an important role, namely the CREB. CREB has been implicated in the action of antidepressants (Nibuya et al., 1996; Thome et al., 2000). Both the level of CREB and transcription mediated by CREB are increased in both the hippocampus and the cerebral cortex by a variety of antidepressant treatments, including ECT (Nibuya et al., 1996; Koch et al., 2002; Nakagawa et al., 2002). In addition, low levels of CREB have been reported in depressed patients (Dowlatshahi et al., 1998) who committed suicide, though these findings are not significant by diagnosis alone. Recently another transcription factor has been implicated in the action of antidepressants Δ fosB. Hope et al. (1994) have shown that the AP-1 complex is induced with chronic ECT involving the induction of Δ fosB. The delta form of fosB is an alternatively spliced form, which complexes with JunD and binds to AP-1 sites. This form of fosB is a weak transcriptional factor and gradually accumulates in cells during chronic ECT. Using transgenic fosB mice Chen et al. (2004) have recently shown that it down-regulates the CCAAT-enhancer binding protein β. Since the delta form of fosB is a weak transcriptional activator, it has been suggested that it may act as a repressor in some circumstances (Nakabeppu & Nathans, 1991). CCAAT-enhancer binding protein β appears to play a role in memory consolidation (Taubenfeld et al., 2001) and apparently can be induced by serotonin (Alberini et al., 1994). The significance of these findings is not clear, but they suggest that ECT can play a role in the regulation of various transcription factors.

4.3. Cellular changes

There are a variety of cellular changes induced by ECT. These include both changes in cell morphology and presumably cell function as well as the induction of new cells or neurogenesis. Initially, studies showed that a chronic course of ECT could promote synaptic spine formation. Vaidya et al. (1999) reported that chronic ECT induced mossy fiber sprouting in the hippocampus. This finding is not seen with other antidepressants (Lamont et al., 2001), and indeed, information on the effect of various antidepressant treatments on spine formation and formation of new synapses is generally inconsistent. One problem may be similar to that which we saw in looking at the effect of antidepressants on post-synaptic densities, namely, that pathological tissue acts differently from wild type. On clue that this might be the case is the role of BDNF in synapse

formation. Vollmayr et al. (2001) have shown that BDNF reacts differently in learned helpless animals and in wild type, suggesting that the entire downstream actions of neurotrophins may be different in depression. Studies by Vaidya et al. (1999) show that ECT can robustly induce neurogenesis and can lead to increased neuron formation in the hippocampus. This suggests another possible pathway for antidepressant action. The article by Santarelli et al. (2003) using X-rays to halt neuron formation by progenitor cells suggests that this is the mechanism by which antidepressants may act. Their data suggest that active neurogenesis is necessary for antidepressant action. In another article, Vollmayr et al. (2003) suggest that neurogenesis is a general reaction to stress and not associated with depressed affect. These data on learned helpless animals show that one can dissociate the effect of stress that decreases neurogenesis but does not necessarily lead to helplessness. It still may be that antidepressants act through a pathway involving neurogenesis, but it is unlikely that this mechanism underlies depression. In conclusion, it appears that the final common pathway of antidepressants involves the induction of gene expression and structural as well as functional alterations. However, the exact nature of these changes remains to be elucidated.

5. Conclusions

This review examines the role of monoamines and subsequent downstream actions that result from alterations in these systems. This appears to be a reasonable approach to understanding the basis of antidepressant action, since all the currently effective antidepressants appear to act on aminergic systems. It must be remembered that a variety of peptide systems also play a role in depression including corticotropin-releasing hormone, substance P, and neuropeptide Y. In addition, the involvement of melatonin in mood disorders, especially its implication in the etiology of seasonal affective disorder, is also in discussion (Mendlewicz et al., 1979; Thompson et al., 1990). All of these systems are currently being investigated as possible avenues for new antidepressant medications. Nonetheless, even in these cases, it appears that the final pathway of change in antidepressant actions must be functional changes in how information is evaluated and processed. Clearly, the core of clinical depression is the negative evaluation patients have of themselves and the hopelessness they feel. What antidepressants do is alter this negative information processing. Current thinking suggests that this can only occur with some type of structural change that involves the activation of genes. This review, by concentrating on the differences between acute and chronic changes on signal transduction systems, gene activation of neurotrophins, and changes in synaptic connectivity and neurogenesis, aims to focus on the final common pathways that control affect. The data, even in this limited review, suggest that there are multiple inputs

to such final pathways. Clearly, one must conclude that different brain areas may be differently affected by antidepressants, that in vitro data may not mirror the changes seen in vivo, and that experiments on wild-type animals may not reflect what happens in pathological tissue. Even with these caveats, one must conclude that a study of the factors controlling synaptic efficacy, synaptogenesis, and neurogenesis clearly offer the most promise in understanding antidepressant action and insights into how to design more effective medications. The roles of 5-HT and norepinephrine are central to both induction of synaptogenesis and neurogenesis and they may well act through independent pathways (Delgado et al., 1999). Thus, an understanding of the acute and chronic adaptations of these systems to antidepressant modulation may give us an understanding of the factors that control the final common pathways of change due to these medications.

Acknowledgments

References

Aghajanian, G. K., Sprouse, J. S., Sheldon, P., & Rasmussen, K. (1990). Electrophysiology of the central serotonin system: receptor subtypes and transducer mechanisms. *Ann N Y Acad Sci 600*, 93–103.

Alberini, C. M., Ghirardi, M., Metz, R., & Kandel, E. R. (1994). C/EBP is an immediate-early gene required for the consolidation of long-term facilitation in *Aplysia*. *Cell 76*, 1099–1114.

Altar, C. A. (1999). Neurotrophins and depression. *TIPS 20*, 59–61.

Anthony, J. P., Sexton, T. J., & Neumaier, J. F. (2000). Antidepressant-induced regulation of 5-HT(1b) mRNA in rat dorsal raphe nucleus reverses rapidly after drug discontinuation. *J Neurosci Res 61*, 82–87.

Apparsundaram, S., Schroeter, S., Giovanetti, E., & Blakely, R. D. (1998). Acute regulation of norepinephrine transport: II. PKC-modulated surface expression of human norepinephrine transporter proteins. *J Pharmacol Exp Ther 287*, 744–751.

Artigas, F., Perez, V., & Alvarez, E. (1994). Pindolol induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors. *Arch Gen Psychiatry 51*, 248–251.

Artigas, F., Romero, L., de Montigny, C., & Blier, P. (1996). Acceleration of the effect of selected antidepressant drugs in major depression by 5-HT$_{1A}$ antagonists. *TINS 19*, 378–383.

Auerbach, S. B., & Hjorth, S. (1995). Effect of chronic administration of the selective serotonin (5-HT) uptake inhibitor citalopram on extracellular 5-HT and apparent autoreceptor sensitivity in rat forebrain in vivo. *Naunyn-Schmiedeberg's Arch Pharmacol 352*, 597–606.

Bajkowska, M., Branski, P., Smialowska, M., & Pilc, A. (1999). Effect of chronic antidepressant or electroconvulsive shock treatment on mGLuR1a immunoreactivity expression in the rat hippocampus. *Pol J Pharmacol 51*, 539–541.

Banik, U., Wang, G. A., Wagner, P. D., & Kaufman, S. (1997). Interaction of phosphorylated tryptophan hydroxylase with 14-3-3 proteins. *J Biol Chem 272*, 26219–26225.

Benmansour, S., Cecchi, M., Morilak, D. A., Gerhardt, G. A., Javors, M. A., Gould, G. G., & Frazer, A. (1999). Effects of chronic anti-depressant treatments on serotonin transporter function, density, and mRNA level. *J Neurosci 19*, 10494–10501.

Benmansour, S., Owens, W. A., Cecchi, M., Morilak, D. A., & Frazer, A. (2002). Serotonin clearance in vivo is altered to a greater extent by antidepressant-induced downregulation of the serotonin transporter than by acute blockade of this transporter. *J Neurosci 22*, 6766–6772.

Bevilaqua, L. R., Cammarota, M., Dickson, P. W., Sim, A. T., & Dunkley, P. R. (2003). Role of protein phosphatase 2C from bovine adrenal chromaffin cells in the dephosphorylation of phospho-serine 40 tyrosine hydroxylase. *J Neurochem 85*, 1368–1373.

Biegon, A., & Israeli, M. (1988). Regionally selective increases in beta-adrenergic receptor density in the brains of suicide victims. *Brain Res 442*(1), 199–203.

Blakely, R. D., Ramamoorthy, S., Schroeter, S., Quian, Y., Appasundaram, S., Galli, A., & DeFelice, L. J. (1998). Regulated phosphorylation and trafficking of antidepressant-sensitive serotonin transporter proteins. *Biol Psychiatry 44*, 169–178.

Blier, P., & Bergeron, R. (1995). Effectiveness of pindolol with selected antidepressant drugs in the treatment of major depression. *J Clin Psychopharmacol 15*, 217–222.

Blier, P., & de Montigny, C. (1994). Current advances and trends in the treatment of depression. *TIPS 15*, 220–226.

Boehm, S., & Huck, S. (1996). Inhibition of N-type calcium channels: the only mechanism by which presynaptic alpha 2-autoreceptors control sympathetic transmitter release. *Eur J Neurosci 8*, 1924–1931.

Bonisch, H., Hammermann, R., & Bruss, M. (1998). Role of protein kinase C and second messengers in regulation of the norepinephrine transporter. *Adv Pharmacol 42*, 183–186.

Brüss, M., Hammermann, R., Brimijoins, S., & Bönisch, H. (1995). Anti-peptide antibodies confirm the topology of the human norepinephrine transporter. *J Biol Chem 270*, 9197–9201.

Chang, A. S., Starnes, D. M., & Chang, S. M. (1998). Possible existence of quaternary structure in the high-affinity serotonin transport complex. *Biochem Biophys Res Commun 249*, 416–421.

Charney, D. S. (1998). Monoamine dysfunction and the pathophysiology and treatment of depression. *J Clin Psychiatry 59*(Suppl. 14), 11–14.

Chen, N. -H., & Reith, M. E. A. (2002). Structure-function relationships for biogenic amine neurotransmitter transporters. In M. E. A. Reith (Ed.), *Neurotransmitter Transporters. Structure, Function and Regulation* (2nd ed.) (pp. 27–40). Totowa, NJ: Humana Press.

Chen, J., Newton, S. S., Zeng, L., Adams, D. H., Dow, A. L., Madsen, T. M., Nestler, E. J., & Duman, R. S. (2004). Downregulation of the CCAAT-enhancer binding protein beta in deltaFosB transgenic mice and by electroconvulsive seizures. *Neuropsychopharmacology 29*, 23–31.

Ciechanowski, P. S., Katon, W. J., & Russo, J. E. (2000). Depression and diabetes: impact of depressive symptoms on adherence, function and costs. *Arch Intern Med 160*, 3278–3285.

Clark, J. A. (1997). Analysis of the transmembrane topology and membrane assembly of the GAT-1 gamma-aminobutyric acid transporter. *J Biol Chem 272*, 14695–14704.

Conti, A. C., Cryan, J. F., Dalvi, A., Lucki, L., & Blendy, J. A. (2002). CREB is essential for the upregulation of BDNF transcription, but not the behavioural or endocrine responses to antidepressant drugs. *J Neurosci 22*, 3262–3268.

Coppen, A. (1967). The biochemistry of affective disorders. *Br J Psychiatry 113*, 1237–1264.

Coryell, W., Scheftner, W., Keller, M., Endicott, J., Maser, J., & Klerman, G. L. (1993). The enduring psychosocial consequences of mania and depression. *Am J Psychiatry 150*, 720–727.

Coyle, J. T., & Duman, R. S. (2003). Finding the intracellular signaling pathways affected by mood disorder treatments. *Neuron 38*, 157–160.

Delgado, P. L., Miller, H. L., Salomon, R. M., Licinio, J., Krystal, J. H., Moreno, F. A., Heninger, G. R., & Charney, D. S. (1999). Tryptophan-depletion challenge in depressed patients treated with desipramine or fluoxetine: implications for the role of serotonin in the mechanism of antidepressant action. *Biol Psychiatry 46*, 212–220.

de Montigny, C., Blier, Pl., & Chaput, Y. (1984). Electrophysiologically-identified serotonin receptors in the rat CNS. Effect of antidepressant treatment. *Neuropharmacology 23*, 1511–1520.

Disalver, S., Chen, Y. -H., Swann, A. C., Shoaib, A. M., & Krajewski, K. J. (1994). Suicidality in patients with pure and depressive mania. *Am J Psychiatry 151*, 1312–1315.

Dowlatshahi, D., MacQueen, G. M., Wang, J. F., & Young, L. T. (1998). Increased temporal cortex CREB concentrations and antidepressant treatment in major depression. *Lancet 352*, 1754–1755.

Dreshfield-Ahmad, L. J., Thompson, D. C., Schaus, J. M., & Wong, D. T. (2000). Enhancement in extracellular serotonin levels by 5-hydroxy-tryptophan loading after administration of WAY 100635 and fluoxetine. *Life Sci 66*, 2035–2041.

Duman, R. S. (2002). Synaptic plasticity and mood disorders. *Mol Psychiatry 7*, S29–S34.

Duman, R. S., & Vaidya (1998). Molecular and cellular actions of chronic electroconvulsive seizures. *J ECT 14*, 181–193.

Duman, R. S., Malberg, J., & Thome, J. (1999). Neural plasticity to stress and antidepressant treatment. *Biol Psychiatry 46*, 1181–1191.

Edwards, E., Harkins, K., Wright, G., & Henn, F. A. (1991). Modulation of [^{3}H]paroxetine binding to the 5-hydroxytryptamine uptake site in an animal model of depression. *J Neurochem 56*, 1581–1586.

Ehret, M., Cash, C. D., Hamon, M., & Maitre, M. (1989). Formal demonstration of the phosphorylation of rat brain tryptophan hydroxylase by Ca2+/calmodulin-dependent protein kinase. *J Neurochem 52*, 1886–1891.

Esteban, S., Llado, J., & Garcia-Sevilla, J. A. (1996). α2-Autoreceptors and α2-heteroreceptors modulating tyrosine and tryptophan hydroxylases in vivo: an investigation into the α2-adrenoceptors subtypes. *Naunyn-Schmiedeberg's Arch Pharmacol 353*, 391–399.

Esteban, S., Llado, J., Sastre-Coll, A., & Garcia-Sevilla, J. A. (1999). Activation and desensitization by cyclic antidepressant drugs of α2-autoreceptors, α2-heteroreceptors and 5-HT$_{1A}$ autoreceptors regulating monoamine synthesis in the rat brain in vivo. *Naunyn-Schmiedeberg's Arch Pharmacol 360*, 135–143.

Franco-Bronson, K. (1996). The management of treatment-resistant depression in the medically ill. *Psychiatry Clin N Am 19*, 329–350.

Galter, D., & Unsicker, K. (2000). Sequential activation of the 5-HT1(A) serotonin receptor and TrkB induces the serotonergic neuronal phenotype. *Mol Cell Neurosci 15*, 446–455.

Garcia-Sevilla, J. A., & Zubieta, J. K. (1986). Activation and desensitization of presynaptic a2-adrenoceptors after inhibition of neuronal uptake by antidepressant drugs in the rat vas deferens. *Br J Pharmacol 89*, 673–683.

Glatz, K., Mossner, R., Heils, A., & Lesch, K. P. (2003). Glucocorticoid-regulated human serotonin transporter (5-HTT) expression is modulated by the 5-HTT gene-promotor-linked polymorphic region. *J Neurochem 86*, 1072–1078.

Guastella, J., Nelson, N., Nelson, H., Czyzyk, L., Keynan, S., Miedel, M. C., Davidson, N., Lester, H. A., & Kanner, B. I. (1990). Cloning and expression of a rat brain GABA transporter. *Science 249*, 1303–1306.

Gur, E., Dremencov, E., Garcia, F., Van de Kar, L. D., Lerer, B., & Newman, M. E. (2002). Functional effects of chronic electroconvulsive shock on serotonergic 5-HT(1A) and 5-HT(1B) receptor activity in rat hippocampus and hypothalamus. *Brain Res 952*, 52–60.

Hastrup, H., Karlin, A., & Javitch, J. A. (2001). Symmetrical dimer of the human dopamine transporter revealed by cross-linking Cys-306 at the extracellular end of the sixth transmembrane segment. *Proc Natl Acad Sci USA 98*, 10055–10060.

Heerssen, H. M., & Segal, R. A. (2002). Location, location, location: a spatial view of neurotrophin signal transduction. *Trends Neurosci 25*, 160–165.

Henn, F. A., Edwards, E., & Muneyyirci, J. (1993). Animal models of depression. *Clin Neurosci 1*, 152–156.

Hensler, J. G. (2003). Regulation of 5-HT$_{1A}$ receptor function in brain following agonist or antidepressant administration. *Life Sci 72*, 1665–1682.

Hensler, J. G., Kovachich, G. B., & Frazer, A. (1991). A quantitative autoradiographic study of serotonin1A receptor regulation: effect of 5,7-dihydroxytryptamine and antidepressant treatments. *Neuropsychopharmacology 4*, 131–144.

Hiorth, S., & Magnusson, T. (1988). The 5-HT$_{1A}$ agonist 8-OH-DPAT preferentially activates cell body 5-HT autoreceptors in rat brain in vivo. *Naunyn-Schmiedeberg's Arch Pharmacol 338*, 463–471.

Holsboer, F. (2000). The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology 23*, 477–501.

Hope, B. T., Kelz, M. B., Duman, R. S., & Nestler, E. J. (1994). Chronic electroconvulsive seizure (ECS) treatment results in expression of a long-lasting AP-1 complex in brain with altered composition and characteristics. *J Neurosci 14*, 4318–4328.

Horschitz, S., Hummerich, R., & Schloss, P. (2001). Down-regulation of the rat serotonin transporter upon exposure to a selective serotonin reuptake inhibitor. *NeuroReport 12*, 2181–2184.

Horschitz, S., Hummerich, R., & Schloss, P. (2003). Functional coupling of serotonin and norepinephrine transporters. *J Neurochem 86*, 958–965.

Huff, R. A., Vaughn, R. A., Kuhar, M. J., & Uhl, G. R. (1997). Porbol esters increase dopamine transporter phosphorylation and decrease transport Vmax. *J Neurochem 68*, 225–232.

Hufton, S. E., Jennings, I. G., & Cotton, R. (1995). Structure and function of the aromatic amino acid hydroxylases. *Biochem J 311*, 353–366.

Iversen, L. (2000). Neurotransmitter transporters: fruitful targets for CNS drug discovery. *Mol Psychiatry 5*, 357–362.

Jess, U., Betz, H., & Schloss, P. (1996). The membrane-bound rat serotonin transporter, SERT1, is an oligomeric protein. *FEBS Lett 394*, 44–46.

Johansen, P. A., Jennings, I., Cotton, R. G., & Kuhn, D. M. (1995). Tryptophan hydroxylase is phosphorylated by protein kinase A. *J Neurochem 65*, 882–888.

Jope, R. S., & Bijur, G. N. (2002). Mood stabilizers, glycogen synthase kinase-3β and cell survival. *Mol Psychiatry 7*, S35–S45.

Kilic, F., & Rudnick, G. (2000). Oligomerization of serotonin transporter and its functional consequences. *Proc Natl Acad Sci USA 97*, 3106–3111.

Kim, S. W., Park, S. Y., & Hwang, O. (2002). Up-regulation of tryptophan hydroxylase expression and serotonin synthesis by sertraline. *Mol Pharmacol 61*, 778–785.

Kitayama, S., Dohi, T., & Uhl, G. R. (1994). Phorbol esters alter functions of the expressed dopamine transporter. *Eur J Pharmacol 268*, 115–119.

Kitayama, I., Yaga, T., Kayahara, T., Nakano, K., Murase, S., Otani, M., & Nomura, J. (1997). Long-term stress degenerates, but imipramine regenerates noradrenergic axons in the rat cerebral cortex. *Biol Psychiatry 42*, 687–696.

Klerman, G. L., & Weissman, M. M. (1988). The changing epidemiology of depression. *Clin Chem 34*, 807–812.

Kocabas, A. M., Rudnick, G., & Kilic, F. (2003). Functional consequences of homo- but not hetero-oligomerization between transporters for the biogenic amine neurotransmitters. *J Neurochem 85*, 1513–1520.

Koch, J. M., Kell, S., Hinze-Selch, D., & Aldenhoff, J. B. (2002). Changes in CREB-phosphorylation during recovery from major depression. *J Psychiatr Res 36*, 369.

Koed, K., & Linnet, K. (1997). The serotonin transporter messenger RNA level in rat brain is not regulated by antidepressants. *Biol Psychiatry 42*, 1177–1180.

Kuroda, Y., & McEwen, B. S. (1998). Effect of chronic restraint stress and tianeptine on growth factors, growth-associated protein 43, and microtubule-associated protein 2 mRNA expression in rat hippocampus. *Mol Brain Res 59*, 35–39.

Lamont, S. R., Paulls, A., & Stewart, C. A. (2001). Repeated electroconvulsive stimulation, but not antidepressant drugs, induces mossy fibre sprouting in the rat hippocampus. *Brain Res 893*, 53–58.

Larsson, L. G., Renyi, L., Ross, S. B., Svensson, B., & Angeby-Moller, K. (1990). Different effects on the responses of functional pre- and postsynaptic 5-HT1A receptors by repeated treatment of rats with the 5-HT$_{1A}$ receptor agonist 8-OH-DPAT. *Neuropharmacology 29*, 85–91.

Lesch, K. P., Aulakh, C. S., Wolozin, B. L., Tolliver, T. J., Hill, J. L., & Murphy, D. L. (1993). Regional brain expression of serotonin transporter mRNA and its regulation by reuptake inhibiting antidepressants. *Mol Brain Res 17*, 31–35.

Lindgren, N., Goiny, M., Herrera-Marschitz, M., Haycock, J. W., Hokfelt, T., & Fisone, G. (2002). Activation of extracellular signal-regulated kinases 1 and 2 by depolarization stimulates tyrosine hydroxylase phosphorylation and dopamine synthesis in rat brain. *Eur J Neurosci 15*, 769–773.

Linner, L., Arborelius, L., Nomikos, G. G., Bertilsson, L., Svensson, T. H. (1999). Locus coeruleus neuronal activity and noradrenaline availability in the frontal cortex of rats chronically treated with imipramine: effect of alpha 2-adrenoceptor blockade. *Biol Psychiatry 46*, 766–774.

Lopez, A. D., & Murray, C. C. (1998). The global burden of disease, 1990–2020. *Nat. Med. 4*, 1241–1243.

Lopez, J. F., Chalmers, D. T., Vázquez, D. M., Watson, S. J., & Akil, H. (1994). Serotonin transporter mRNA in rat brain is regulated by classical antidepressants. *Biol Psychiatry 35*, 287–290.

Lyons, W. E., Mamounas, L. A., Ricaurtre, G. A., Coppola, W., Reid, S. W., Bora, S. H., Wihler, C., Koliatssos, V. E., & Tessarollo, L. (1999). Brain-derived neurotrophic factor-deficient mice develop aggressiveness and hyperphagia in conjunction with brain serotonergic abnormalities. *Proc Natl Acad Sci U S A 96*, 15239–15244.

Malberg, J. E., & Duman, R. S. (2003). Cell proliferation in adult hippocampus is decreased by inescapable stress: reversal by fluoxetine treatment. *Neuropsychopharmacology 28*, 1562–1571.

Malberg, J., Eisch, A. J., Nestler, E. J., & Duman, R. S. (2000). Chronic antidepressant treatment increases neurogenesis in the hippocampus. *J Neurosci 20*, 9104–9110.

Mamounas, L. A., Blue, M. E., Siuciak, J. A., & Altar, C. A. (1995). Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. *J Neurosci 15*, 7929–7939.

Mamounas, L. A., Altar, C. A., Blue, M. E., Kaplan, D. R., Tessarollo, L., & Lyons, W. E. (2000). BDNF promotes the regenerative sprouting, but not survival of injured serotonergic axons in the adult rat brain. *J Neurosci 10*, 771–782.

Meller, R., Babity, J. M., & Gravame-Smith, D. G. (2002). 5HT2A receptor activation leads to increased BDNF mRNA expression in C6 glioma cells. *Neuromol Med 1*, 197–205.

Meltzer, H. Y., & Lowy, M. T. (1987). *The serotonin hypothesis of depression. Psychopharmacology.* New York: Raven Press.

Mendlewicz, J., Linkowski, P., Branchey, L., Weinberg, U., Weitzmann, E. D., & Branchey, M. (1979). Abnormal 24 hour pattern of melatonin secretion in depression. *Lancet 2*, 1362.

Milner, H. E., Béliveau, R., & Jarvis, S. M. (1994). The in situ size of the dopamine transporter is a tetramer as estimated by radiation inactivation. *Biochim Biophys Acta 1190*, 185–187.

Musselman, D. L., Evans, D. L., & Nemeroff, C. B. (1998). The relationship of depression to cardiovascular diseases: epidemiology, biology and treatment. *Arch Gen Psychiatry 55*, 580–592.

Nakabeppu, Y., & Nathans, D. (1991). A naturally occurring truncated form of FosB that inhibits Fos/Jun transcriptional activity. *Cell 64*, 751–759.

Nakagawa, S., Kim, J. E., Lee, R., Chen, J., Fujioka, T., Malberg, J., et al. (2002). Localization of phosphorylated cAMP response element-binding protein in immature neurons of adult hippocampus. *J Neurosci 22*, 9868–9876.

Nemeroff, C. B. (1998). Psychopharmacology of affective disorders in the 21st century. *Biol. Psychiatry 44*, 517–525.

Nestler, E. J., Barrot, M., DiLeone, R. J., Eisch, A. J., Gold, S. J., & Monteggia, L. M. (2002). Neurobiology of depression. *Neuron 34*, 13–25.

Neumaier, J. F., Root, D. C., & Hamblin, M. W. (1996). Chronic fluoxetine reduce serotonin transporter mRNA and 5-HT1B mRNA in a sequential manner in the rat dorsal raphe nucleus. *Neuropsychopharmacology 15*, 515–522.

Nibuya, M., Morinobu, S., & Duman, R. S. (1995). Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J Neurosci 15*, 7539–7547.

Nibuya, M., Nestler, E. J., & Duman, R. S. (1996). Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J Neurosci 16*, 2365–2372.

Nobler, M. S., & Sackheim, H. A. (2001). Electroconvulsive therapy. In Henn, F. A., Sartorius, N., Helmchen, H., & Lauter, H. (Eds.), *Contemporary Psychiatry, vol. 3* (pp. 425–433). Berlin: Springer.

Nutt, D. J., Gleiter, C. H., & Glue, P. (1989). Neuropharmacological aspects of ECT: in search of the primary mechanism of action. *Convuls Ther 5*, 250–260.

Osawa, I., Saito, N., Koga, T., & Tanaka, C. (1994). Phorbol ester-induced inhibition of GABA uptake by synaptosomes and by *Xenopus* oocytes expressing GABA transporter (GAT1). *Neurosci Res 19*, 287–293.

Pacholczyck, T., Blakely, R. D., & Amara, S. G. (1991). Expression cloning of a cocaine- and antidepressant-sensitive human noradrenaline transporter. *Nature 350*, 350–354.

Pi, F., & Garcia-Sevilla, J. A. (1992). Alpha 2-autoreceptor-mediated modulation of tyrosine hydroxylases activity in noradrenergic regions of the rat brain in vivo. *Naunyn-Schmiedeberg's Arch Pharmacol 345*, 653–660.

Pineyro, G., Blier, P., Dennis, T., & de Montigny, C. (1994). Desensitization of the neuronal 5-HT carrier following its long-term blockade. *J Neurosci 14*, 3036–3047.

Prieto, M., & Giralt, M. T. (2002). Desensitization of alpha(2)-adrenoceptors which regulate noradrenaline synthesis and release after chronic treatment with clorgyline in the rat brain. *Pharmacology 65*, 49–56.

Quian, Y., Galli, A., Ramamoorthy, S., Risso, S., DeFelice, L. J., & Blakely, R. D. (1997). Protein kinase C activation regulates human serotonin transporters in HEK-293 cells via altered cell surface expression. *J Neurosci 17*, 45–57.

Riad, M., Garcia, A., Watkins, K. C., Jodoin, N., Doucet, Wl., Langlois, X., El Mestikawy, S., Hamon, M., & Descarries, L. (2000). Somato-dendritic localization of 5-HT$_{1A}$ and preterminal localization of 5-HT$_{1B}$ serotonin receptors in adult rat brain. *J Comp Neurol 417*, 181–194.

Rumajogee, P., Madeira, A., Verge, D., Hamon, M., & Miquel, M. C. (2002). Up-regulation of the serotoninergic phenotype in vitro: BDNF and camp share TrkB-dependent mechanisms. *J Neurochem 83*, 1525–1528.

Sacchetti, G., Bernini, M., Gobbi, M., Parini, S., Pirona, L., Mennini, T., & Samanin, R. (2001). Chronic treatment with desipramine facilitates its effect on extracellular noradrenaline in the rat hippocampus: studies on the role of presynaptic alpha2-adrenoceptors. *Naunyn-Schmiedeberg's Arch Pharmacol 363*, 66–72.

Sanacora, G., Mason, G. F., Rothman, D. L., Hyder, F., Ciarcia, J. J., Ostroff, R. B., Berman, R. M., & Krystal, J. H. (2003). Increased cortical GABA concentrations in depressed patients receiving ECT. *Am J Psychiatry 160*, 577–579.

Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Duman, R., Arancio, O., Belzung, C., & Hen, R. (2003). Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science 301*, 805–809.

Sastre, M., Guimon, J., & Garcia-Sevilla, J. A. (2001). Relationships between beta- and alpha2-adrenoceptors and G coupling proteins in the human brain: effects of age and suicide. *Brain Res 898*(2), 242–255.

Sato, K., Adams, R., Betz, H., & Schloss, P. (1995a). Modulation of the recombinant rat glycine transporter GLYT1b by protein kinase C. *J Neurochem 65*, 1967–1973.

Sato, K., Adams, R., Betz, H., & Schloss, P. (1995b). The recombinant GABA transporter GAT1 is down-regulated upon activation of protein kinase C. *FEBS Lett 375*, 99–102.

Schloss, P., & Williams, D. C. (1998). The serotonin transporter: a primary target for antidepressant drugs. *J Psychopharmacol 12*, 115–121.

Schloss, P., Püschel, A., & Betz, H. (1994). Neurotransmitter transporters: new members of known families. *Curr Opin Cell Biol 6*, 595–599.

Schmid, J. A., Scholze, P., Kudlacek, O., Freissmuth, M., Singer, E. A., & Sitte, H. (2000). Oligomerization of the human serotonin transporter

and of the rat GABA transporter 1 visualized by fluorescence resonance energy transfer microscopy in living cells. *J Biol Chem 276*, 3805–3810.

Sharp, T., Bramwell, S. R., Clark, D., & Grahame-Smith, D. G. (1998a). In vivo measurement of brain extracellular 5-hydroxytryptamine using microdialysis: changes in relation to 5-hydroxytryptaminergic neuronal activity. *J Neurochem 53*, 234–240.

Sharp, T., Bramwell, S. R., & Grahame-Smith, D. G. (1998b). 5-HT1 agonists reduce 5-hydroxytryptamine release in rat hippocampus in vivo as determined by brain microdialysis. *Br J Pharmacol 96*, 283–290.

Shergill, S. S., & Katona, C. L. E. (2001). Pharmacotherapy of affective disorders. In Henn, Sartorius, Helmchen, & Lauter (Eds.), *Contemporary Psychiatry, vol. 3* (pp. 317–336). Berlin: Springer.

Shirayama, Y., Chen, A. C. -H., Nakagawa, S., Russel, D. S., Duman, R. S. (2002). Brain derived neurotrophic factor produces antidepressant effects in behavioural models of depression. *J Neurosci 22*, 3251–3261.

Siuciak, J. A., Clark, M. S., Rind, H. B., Whittemore, S. R., & Russo, A. F. (1998). BDNF induction of tryptophan hydroxylase mRNA levels in the rat brain. *J Neurosci Res 52*, 149–158.

Smith, M. A., Makino, S., Kvetnansky, R., & Post, R. M. (1995). Stress and glucocorticoids affect the expression of brain-derived neurotropic factor and neurotrophin-3 mRNAs in the hippocampus. *J Neurosci 15*, 1768–1777.

Stassen, H., Angst, J., & Delini-Stula, A. (1999). Fluoxetine versus moclobemide: cross-comparison between the time courses of improvement. *Pharmacopsychiatry 32*, 56–60.

Stenfors, C., & Ross, S. B. (2002). Evidence for involvement of protein kinases in the regulation of serotonin synthesis and turnover in the mouse brain in vivo. *J Neural Transm 109*, 1353–1363.

Strakowski, S. M., McElroy, S. L., Keck Jr., P. E., & West, S. A. (1996). Suicidality among patients with mixed and manic bipolar disorder. *Am J Psychiatry 153*, 674–676.

Stultz, C. M., Levin, A. D., & Edelman, E. R. (2002). Phosphorylation-induced conformational changes in a mitogen-activated protein kinase substrate. Implications for tyrosine hydroxylase activation. *J Biol Chem. 277*, 47653–47661.

Szot, P., Ashlieg, E. A., Kohen, R., Petrie, E., Dorsa, D. M., & Veith, R. (1993). Norepinephrine transporter mRNA is elevated in the locus coeruleus following short- and long-term desipramine treatment. *Brain Res 618*, 308–312.

Taubenfeld, S. M., Milekic, M. H., Monti, B., & Alberini, C. M. (2001). The consolidation of new but not reactivated memory requires hippocampal C/EBPbeta. *Nat Neurosci 4*, 813–818.

Thoenen, H. (1995). Neurotrophins and neuronal plasticity. *Science 270*, 593–597.

Thome, J., Sakai, N., Shin, K., Steffen, C., Zhang, Y. J., Impey, S., Storm, D., & Duman, R. S. (2000). cAMP response element-mediated gene transcription is upregulated by chronic antidepressant treatment. *J Neurosci 20*, 4030–4036.

Thompson, C., Stinson, D., & Smith, A. (1990). Seasonal affective disorder and season-dependent abnormalities of melatonin suppression by light. *Lancet 360*, 703–706.

Trillat, A. C., Malagie, I., Scearce, K., Pons, D., Anmella, M. C., Jacquot. C., Hen, R., & Gardier, A. (1997). Regulation of serotonin release in the frontal cortex and ventral hippocampus of homozygous mice lacking 5-HT1B receptors: in vivo microdialysis studies. *J Neurochem 69*, 2019–2025.

Wood, J. L., & Russo, A. F. (2001). Autoregulation of cell-specific MAP kinase control of the tryptophan hydroxylase promotor. *J Biol Chem 276*, 21262–21271.

Valenciano, A. I., Alonso-Gomez, A. L., & Iuvone, P. M. (2000). Regulation of tryptophan hydroxylase activity in *Xenopus laevis* photoreceptor cells by cyclic AMP. *J Neurochem 74*, 1961–1967.

Vaidya, V. A., Du Siuciak, J. F., & Duman, R. S. (1999). Hippocampal mossy fiber sprouting induced by chronic electroconvulsive seizures. *Neuroscience 89*, 157–166.

Vergé, D., Daval, G., Marcinkiewicz, M., Patey, A., El. Mestikawy, S., Gozlan, H., & Hamon, M. (1986). Quantitative autoradiography of multiple 5-HT1 receptor subtypes in the brain of control or 5,7-dihydroxytryptamine-treated rats. *J Neurosci 6*, 3474–3482.

Vollmayr, B., Faust, H., Lewicka, S., & Henn, F. A. (2001). Brain-derived-neurotrophic-factor (BDNF) stress response in rats bred for learned helplessness. *Mol Psychiatry 6*, 471–474.

Vollmayr, B., Simonis, C., Weber, S., Gass, P., & Henn, F. A. (2003). Reduced cell proliferation in the dentate gyrus is not correlated with the development of learned helplessness. *Biol Psychiatry 54*, 1035–1040.

Zahniser, N. R., & Doolen, S. (2001). Chronic and acute regulation of Na^+/Cl^- dependent neurotransmitter transporters: drugs, substrates, presynaptic receptors, and signalling systems. *Pharmacol Ther 92*, 21–55.

Zarate Jr., C. A., Tohen, M., Land, M., & Cavanagh, S. (2000). Functional impairment and cognition in bipolar disorder. *Psychiatr Q 71*, 309–329.

Zavosh, A., Schaefer, J., Ferrel, A., & Figlewicz, D. P. (1999). Desipramine treatment decreases ^{3}H-nisoxetine binding and norepinephrine transporter mRNA in SK-N-SHSY5Y cells. *Brain Res Bull 49*, 291–295.

Zhu, M. Y., & Ordway, G. A. (1997). Down-regulation of norepinephrine transporters on PC12 cells by transporter inhibitors. *J Neurochem 68*, 134–141.

Zhu, M. Y., Blakely, R. D., Apparsundaram, S., & Ordway, G. A. (1998). Down-regulation of the human norepinephrine transporter in intact 293-hNET cells exposed to desipramine. *J Neurochem 70*, 1547–1555.

Zhu, M. Y., Kim, C. H., Hwang, D. Y., Baldessarini, R. J., & Kim, K. S. (2002). Effects of desipramine treatment on norepinephrine transporter gene expression in the cultured SK-N-BE(2)M17 cells and rat brain tissue. *J Neurochem 82*, 146–153.