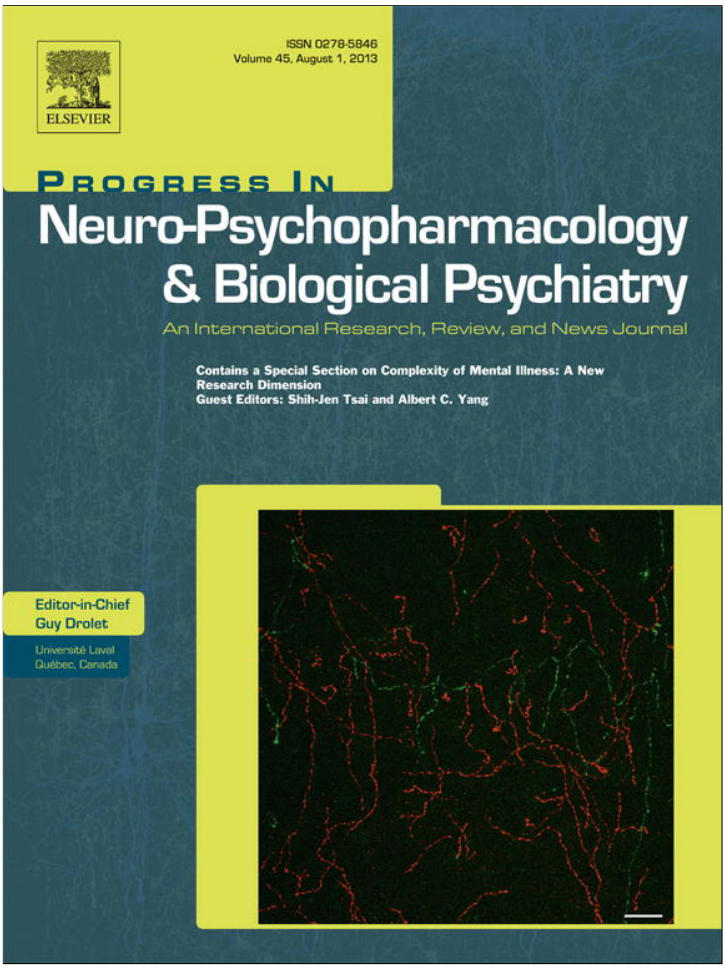

Progress in Neuro-Psychopharmacology & Biological Psychiatry 45 (2013) 54–63

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Review article

Monoamine neurocircuitry in depression and strategies for new treatments

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ARTICLE INFO

Article history:
Received 17 April 2012
Received in revised form 13 March 2013
Accepted 11 April 2013
Available online 19 April 2013

Keywords:
fMRI
Major depressive disorder
Monoamine neurocircuitry
Multimodal antidepressants
Serotonin receptors

ABSTRACT

Extensive studies showed that monoaminergic neurotransmission that involves serotonin (5-HT), norepinephrine (NE) and dopamine (DA) exerts major influence on brain circuits concerned by the regulation of mood, reactivity to psychological stress, self-control, motivation, drive, and cognitive performance. Antidepressants targeting monoamines directly affect the functional tone of these circuits, notably in limbic and frontocortical areas, and evidence has been provided that this action plays a key role in their therapeutic efficacy. Indeed, at least some of functional changes detected by functional magnetic resonance imaging in emotion- and cognitive-related circuits such as the one involving limbic-cortical-striatal-pallidal-thalamic connections in depressed patients can be reversed by monoamine-targeted antidepressants. However, antidepressants acting selectively on only one monoamine, such as selective inhibitors of 5-HT or NE reuptake, alleviate depression symptoms in a limited percentage of patients, and are poorly effective to prevent recurrence. Thorough investigations for the last 30 years allowed the demonstration of the existence of functional interactions between 5-HT, NE and DA systems, and the identification of the specific receptors involved. In particular, 5-HT systems were shown to exert negative influence on NE and DA systems through 5-HT_{2A} and 5-HT_{2C} receptor- mediated mechanisms, respectively. On the other hand, complex positive and negative influences of NE system on 5-HT neurotransmission are mediated through α_1- and α_2-adrenergic receptors, respectively. These data provided a rationale for the design of new, multimodal, therapeutic strategies involving drugs acting not only at the "historical" targets such as the 5-HT and/or the NE transporter, but also at other molecular targets to improve their efficacy and their tolerability.

Contents

Abbreviations: 5-HT, 5-hydroxytryptamine, serotonin; BDNF, brain derived neurotrophic factor; CA, catecholamines; Cg25, subgenual cingulate (Brodmann area 25); CNS, central nervous system; CO-MED, Combining Medications to Enhance Depression Outcomes; CRH, corticotropin-releasing hormone; DA, dopamine; DAT, dopamine transporter; DRN, dorsal raphe nucleus; fMRI, functional magnetic resonance imaging; HAM-D, Hamilton Depression rating scale; HPA, hypothalamo-pituitary-adrenal (axis); LCSPT, limbic-cortical-striatal-pallidal-thalamic (circuits); MADRS, Montgomery-Åsberg Depression Rating Scale; MAOIs, monoamine oxidase inhibitors; MDD, major depressive disorder; MRI, magnetic resonance imaging; NE, norepinephrine; NET, norepinephrine transporter; NMDA, N-methyl-D-aspartate; NRIs, selective norepinephrine reuptake inhibitors; OFC, orbitofrontal cortex; PET, positron emission tomography; PRL, prolactin; QIDS-SR, Quick Inventory of Depressive Symptomatology: Self Rated; ReHo, regional homogeneity; ROI, regions of interest; SERT, serotonin transporter; SNP, single nucleotide polymorphism; SNRIs, mixed serotonin and norepinephrine reuptake inhibitors; SR, sustained release; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; Tph2, tryptophan hydroxylase-2; VTA, ventral tegmentum area.

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http://dx.doi.org/10.1016/j.pnpbp.2013.04.009

1. Introduction

Major depressive disorder (MDD) is likely to comprise multiple disorders with overlapping symptoms and diverse etiologies (Belmaker and Agam, 2008; Trivedi et al., 2008). Currently, the symptoms of MDD are hypothesized to result from a combination of inherent and environmental factors that disrupt the reciprocal interactions of multiple neural circuits. Genetics play a substantial role in the risk of developing MDD. A large twin registry analysis showed that the heritability of MDD was approximately 38% in the overall population (Kendler et al., 2006). Inherited risk is likely to involve multiple genes, and it appears that any genetic propensity for MDD requires environmental influences to be actualized. Moreover, animal studies linking maternal behavior with changes in stress-related genes (Weaver et al., 2004) and results showing effects of antidepressants on DNA methylation patterns as well as other markers of epigenetic regulatory mechanisms (Baudry et al., 2010; Cassel et al., 2006; Massart et al., 2012) suggest a role for epigenetic processes in MDD and adaptive neurobiological changes induced by chronic antidepressant treatments. Preliminary data from postmortem analysis in humans are consistent with this hypothesis (McGowan et al., 2009). As a consequence, such diversity of underlying pathology combined with the complexity and plasticity of the central nervous system (CNS) has confounded the development of effective pharmacological treatments for this disabling syndrome.

Research over the second half of the 20th century was strongly influenced by the discovery that agents that alter monoamine metabolism, particularly that of serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE), relieved depressive symptoms. Those agents, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) are nonspecific, and hence their therapeutic benefits are associated with substantial side effects. Newer, more targeted agents such as selective serotonin reuptake inhibitors (SSRIs) and NE reuptake inhibitors (NRIs) are effective in relieving symptoms in a significant percentage of patients. Although cumbersome side effects may occur with these agents, they are generally better tolerated than TCAs and MAOIs. Nevertheless, side effects may be of sufficient intensity to cause discontinuation of treatment in up to 14.9% of patients under SSRI therapy, a proportion not so far from the 19% of patients who stop treatment by TCAs in short-term studies (Montgomery et al., 1994).

Despite half a century of research and the availability of numerous agents to treat MDD, the efficacy of currently available drugs remains inadequate, and no treatment is completely curative; approximately half of all patients with MDD fail to respond to first-line therapy, and more than 65% do not achieve remission. Even after sequential medication trials, between 10% and 20% of patients still do not achieve remission (Rush et al., 2006). In any case, a post hoc analysis of the Sequenced Treatment Alternatives to Relieve Depression trial data found that 90% of patients who achieved remission had at least one residual symptom (range 1–8) (Nierenberg et al., 2010). Some symptoms, such as cognitive dysfunction, consistently appear to take longer to resolve than mood symptoms and may persist for years (Brodaty et al., 1993; Hammar et al., 2010). Perhaps even more troubling than their persistence is the observation that residual symptoms were predictive of relapse, even among those who met the criteria for remission during the index episode (Judd et al., 2000; Nierenberg et al., 2010; Paykel et al., 1995).

Advances in imaging techniques, genetics and molecular biology have greatly expanded our view of the etiology of depressive disorders. The objective of the current review is to present the growing, but sometimes conflicting, body of evidence that provides a rationale for investigating new therapeutic targets for treatment of MDD.

2. Neural circuits in MDD

Advances in imaging techniques now allow the visualization of neural networks in the brain. In particular, the limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuits appear to play an important role in MDD (Drevets et al., 2008). Defined as histologically and immunocytochemically distinct areas, the LCSPT circuits connect the orbital prefrontal cortex, amygdala, hippocampus, ventromedial striatum, mediodorsal and midline thalamic nuclei, and ventral pallidum (Drevets et al., 2008; Ongür et al., 2003; Phillips et al., 2003). These pathways are involved in self-reference, fear, anxiety, visceral response, as well as stimulus assessment and reward (Price and Drevets, 2012).

Two networks have been delineated in monkeys that connect the prefrontal cortex with limbic systems and visceral control areas in the hypothalamus and periaqueductal grey. First, the orbital prefrontal network is involved in sensory integration as well as affect associated with reward and aversion (Drevets et al., 2008). Second, the medial prefrontal network connects the prefrontal cortex with the mid and posterior cingulate cortex, part of the anterior superior temporal gyrus and sulcus and the entorhinal and posterior parahippocampal cortex (Kondo et al., 2005; Saleem et al., 2008). The latter circuit is implicated in mood and emotion as well as visceral reactions to emotional stimuli (Drevets et al., 2008).

Important contributions to the present knowledge of functional alterations in brain circuits involved in mood and emotion have been made using positron emission tomography (PET) with [^{18}F]2-fluorodeoxy-D-glucose as a radioligand. In particular, Kennedy et al. (2001) noted that depression is associated with frontal hypometabolic activity accompanied by hypermetabolism in certain limbic regions. The relevance of these alterations to the disease is supported by the capacity of successful antidepressant therapy to normalize functional activity to levels observed in nondepressed subjects (Kennedy et al., 2001). Thorough structural equation modeling analyses of such PET data allowed the differentiation of drug treatment responders from nonresponders based on group specificities in limbic–cortical connections involving lateral prefrontal cortex, subgenual cingulate (Cg25), orbital frontal cortex, and hippocampus (Seminowicz et al., 2004). In particular, nonresponders showed additional abnormalities in limbic–subcortical pathways connecting the anterior thalamus to the anterior and subgenual cingulate cortex, orbital frontal cortex, and hippocampus. Accordingly, such neuroimage analyses might be a first step toward the phenotypical identification of depression subtypes at the neural systems level, and, hopefully, the optimization of treatment for individual patients (Seminowicz et al., 2004). Another important achievement derived from these PET data has been the development of deep brain stimulation to reduce metabolically overactive subgenual cingulate region (Brodmann area 25) in patients refractory to antidepressant drug treatments (Mayberg et al., 2005). The resulting successful alleviation of depression symptoms in at least some treatment-resistant patients provided support to the idea that disrupting focal pathological activity in limbic–cortical circuits using local electrical stimulation opens innovative therapeutic perspectives (Holtzheimer and Mayberg, 2011; Millet et al., 2010).

Connectivity of serotonergic, noradrenergic and dopaminergic neurons occurs through these neural circuits (Fig. 1). In the CNS, the primary source of 5-HT is the raphe nuclei. Serotonergic neurons

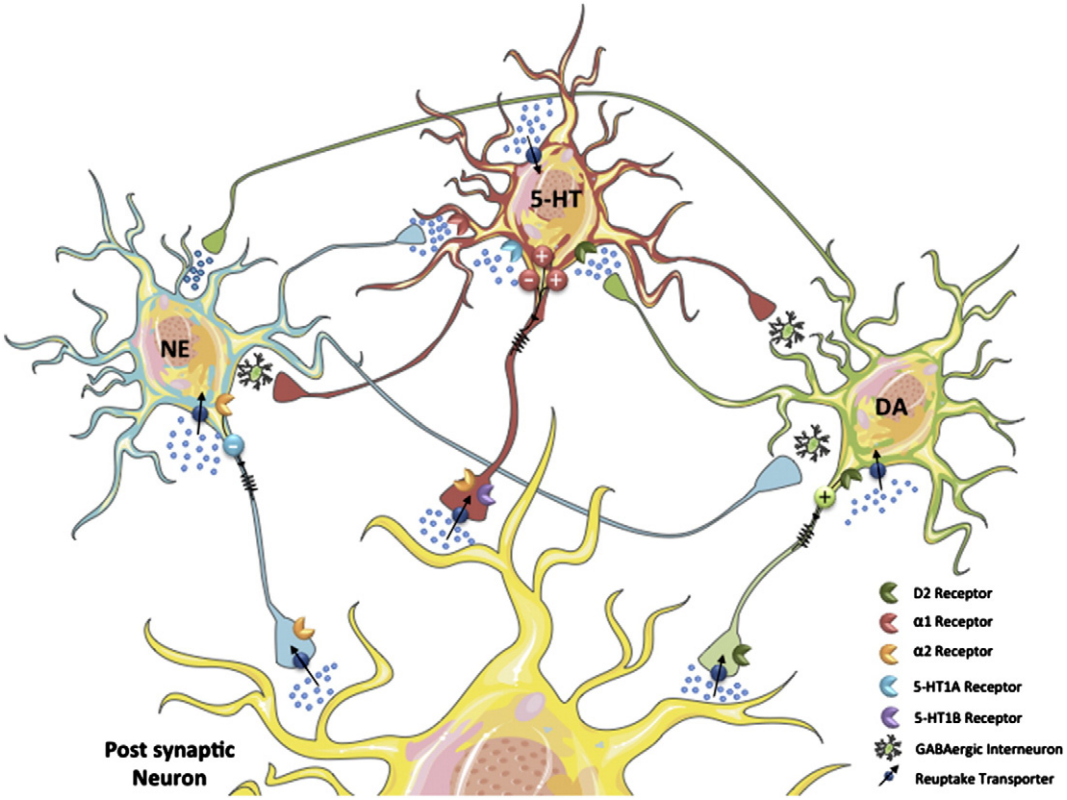

Fig. 1. Functional connectivity of monoaminergic neurons. Direct and indirect (through GABAergic interneurons) interconnections between 5-HT, NE and DA neurons are mediated through various receptor types which act both as autoreceptors controlling the activity of respective neuronal phenotype and heteroreceptors controlling the activity of the other two monoaminergic neuronal phenotypes. Combined pharmacological actions at reuptake transporters and selected auto/hetero-receptors allow finely controlled modulations of monoaminergic neurons reciprocal interconnections and impinging on post-synaptic neurons in brain circuits involved in depression. Multitargeted drugs acting at both reuptake transporters and selected monoamine receptors are especially promising as more effective and better tolerated antidepressants (see text).

project from the raphe to the caudate, putamen, pallidus, amygdala, limbic forebrain and neocortex (Steinbusch, 1981). Synthesis of NE occurs largely in neurons whose cell bodies are located within the locus coeruleus. Noradrenergic neurons project from the locus coeruleus to the lateral brain stem tegmentum, hippocampus, amygdala, entorhinal cortices, thalamus, and neocortex (Von Bohlen und Halbach and Dermietzel, 2006). DA is predominantly synthesized in neurons within the substantia nigra and ventral tegmentum area (VTA). Whereas dopaminergic neurons in the substantia nigra project to the caudate-putamen, those in the VTA project mainly to the nucleus accumbens and prefrontal cortex (Oades and Halliday, 1987).

Magnetic resonance imaging (MRI) studies have shown structural abnormalities in the brains of patients with MDD. Although results across individual studies have been highly variable, several meta-analyses have confirmed a small but significant loss of hippocampal volume in patients with MDD (Campbell et al., 2004; Cole et al., 2011; McKinnon et al., 2009; Videbech and Ravkilde, 2004). Predictors of volume loss were duration of illness >2 years and multiple depressive episodes (McKinnon et al., 2009). A recent meta-analysis of 7 studies involving 191 patients and 282 healthy controls found that individuals with early (first-episode) depression showed a mean volume decrement of 4% in the left and 4.5% in the right hippocampal regions compared with matched, healthy controls (Cole et al., 2011). The hippocampus is vulnerable to stress toxicity, and excessive hypothalamo-pituitary-adrenal (HPA) axis activity is often present in patients with depression (Mongeau et al., 2011). These results are therefore particularly intriguing because experimental evidence suggests that antidepressant-induced neurogenesis is a glucocorticoid receptor-dependent process (Funato et al., 2006; Paizanis et al., 2007; Pariante et al., 1997, 2003a, 2003b) and is critical to therapeutic efficacy (Santarelli et al., 2003). However, the latter assertion has been disputed (Bessa et al., 2009).

Many of the MRI studies have been performed in older patients, which have made it difficult to isolate abnormalities related to MDD from those that may result from age, treatment and environmental factors. To investigate treatment-independent brain abnormalities associated with early stages of MDD, Guo et al. (2011) used regional homogeneity (ReHo) analysis of resting functional MRI (fMRI) in 17 patients who had been diagnosed with a first major depressive episode and who were treatment naïve. Results were compared with those of a similar analysis of 17 matched controls. Patients had significantly lower ReHo in the left cerebellum posterior lobe, right fusiform gyrus, left parahippocampal gyrus, and the right post central gyrus. In contrast, higher ReHo was observed in the right inferior temporal gyrus in patients versus controls (Guo et al., 2011).

Recently, Zhu et al. (2011) used diffusion tensor imaging to investigate white matter changes in treatment-naïve patients experiencing a first major depressive episode. The analysis technique used in this study, like the ReHo analysis used by Guo et al. (2011), allowed for whole brain assessment rather than limiting analysis to predefined regions of interest (ROI). Compared with healthy controls, patients with MDD had lower fractional anisotropy in areas within the corticolimbic networks (anterior limb of the internal capsule, parahippocampal gyrus, and the posterior cingulate cortex). The fractional anisotropy was inversely correlated with the severity of depressive symptoms (Zhu et al., 2011). Results of these two studies are consistent with the presence of measurable pathology at diagnosis in young adult patients with MDD. Once reproduced and expanded, identification of abnormalities at early stages may be clinically useful in tailoring treatments.

Two small studies using unstimulated baseline fMRI showed differential functional connectivity in ROI between patients who respond to antidepressant therapy and those who do not. Kozel et al. (2011) found that baseline connectivity of both subcallosal cortices

to the left anterior cingulate gyrus was strongly correlated with outcome after an 8-week open-label treatment. Of the 13 patients enrolled in the study, 10 received bupropion sustained release (SR) 150 mg twice a day, 2 received escitalopram 20 mg once a day, and 1 took aripiprazole 5 mg once a day. Seven achieved response (≥50% improvement in the Quick Inventory of Depressive Symptomatology: Self-Rated [QIDS-SR] from baseline to week 8) (Kozel et al., 2011).

In a second trial (Lisiecka et al., 2011), orbitofrontal cortex (OFC) connectivity was established at baseline for 23 patients using an fMRI face-matching task. Patients were then randomized to treatment with mirtazapine (n = 10) or venlafaxine (n = 13). All patients were given a second fMRI face-matching task at the end of 4 weeks treatment. Twelve of the patients met the criteria for response (50% drop in the HAM-D score between the initial and follow-up assessments). Non-responders were characterized by higher OFC–cerebellum connectivity, with the strength of response positively correlated with functional coupling between left OFC and the caudate nuclei and thalami (Lisiecka et al., 2011). Interestingly, differences in longitudinal changes were detected between venlafaxine and mirtazapine treatment in the motor areas, cerebellum, cingulate gyrus and angular gyrus (Lisiecka et al., 2011). Although these trials were too small to draw definite conclusions, the fact that they were carried out with medications with different mechanism of actions makes them promising and bears repeating.

3. Neurotransmitter deficiency hypothesis

The monoamine deficiency hypothesis posits, as this wording implies, that depressive symptoms arise from insufficient levels of monoamine neurotransmitters 5-HT, NE, and/or DA (Delgado, 2006). This hypothesis grew out of observations that antidepressant therapies raise neurotransmission tone depending on one or more of these neurotransmitters. In addition, the association of depression with neurodegenerative disease of the basal ganglia such as Parkinson's and Huntington's implicated DA as well as GABA (Santamaría et al., 1986). Decreased levels of GABA measured in plasma, cerebrospinal fluid, and dorsal anterolateral prefrontal cortex neurons have been reported in patients with MDD. More recently, postmortem analyses and imaging studies found that compared with psychiatrically healthy controls, individuals with MDD had reduced densities of GABA neurons in the prefrontal and occipital cortices (Maciag et al., 2010; Rajkowska et al., 2007).

3.1. Monoamine depletion

Pharmacological blockade of 5-HT synthesis by the tryptophan hydroxylase inhibitor p-chlorophenylalanine was found to reverse the antidepressant effects of both MAOIs such as tranylcypromine and TCAs such as imipramine, indicating that 5-HT is required for the therapeutic action of these drugs (Shopsin et al., 1975, 1976). In contrast, blockade of catecholamines (CA) synthesis by α-methyl-p-tyrosine apparently did not reduce the antidepressant effect of imipramine (Shopsin et al., 1975). Subsequent studies that consisted of reducing 5-HT by dietary depletion of its precursor tryptophan or blocking CA synthesis also reported relapse in individuals with MDD who had been successfully treated with an SSRI (Delgado et al., 1999) or an NRI (Miller et al., 1996), respectively. However, convergent data showed that acute reduction in the synthesis of 5-HT, CA, or both combined does not cause depression in healthy adults. These findings show that serotonin levels above a certain threshold are necessary for antidepressant efficacy of SSRIs, and suggest that acute monoamine depletion is not sufficient to induce depression in otherwise healthy individuals.

3.2. Impaired synthesis

In contrast to that inferred from 5-HT depletion under acute or short-term conditions such as those used to demonstrate that intact levels of the indolamine is critical for the antidepressant effect of SSRIs, long-term inhibition of 5-HT synthesis may be associated with increased susceptibility to depression. Indeed, in a study by Zhang et al. (2005) a single nucleotide polymorphism (SNP) in the tryptophan hydroxylase-2 (tph2) gene, which results in loss of approximately 80% of this 5-HT synthesis rate-limiting enzyme capacity to convert tryptophan into 5-hydroxytryptophan in vitro (Zhang et al., 2005), has been identified in a subset of patients with unipolar depression. Furthermore, the same SNP change made by genetic knock-in produced depression-like alterations in mice (Jacobsen et al., 2012) strongly supporting the idea that 5-HT synthesis deficiency really contributes to the disease in patients with tph2 gene polymorphism.

3.3. Regulation of the activity of monoamines

The primary action of TCAs and monoamine reuptake inhibitors is to increase extracellular levels of neurotransmitters at the synapse by blocking neurotransmitter reuptake via their respective transporters. The efficacy of this therapeutic approach provides indirect support for the monoamine deficiency hypothesis. Moreover, evidence suggests that a common polymorphism in the promoter region of the serotonin transporter (SERT) gene is associated with a predisposition to depression with repeated life traumas, but the nature of the association remains unclear (Caspi et al., 2003; Lesch et al., 1996). Interestingly, Karg et al. (2011) recently confirmed the initial finding of Caspi et al. (2003) with a thorough meta-analysis of the 54 studies that have investigated this association published to date. In contrast, earlier meta-analyses with negative results were based on approximately 15 studies only (Levinson, 2006; Risch et al., 2009).

Postmortem and imaging studies indicate that the density of postsynaptic 5-HT_{1A} receptors is generally reduced in patients with depression, although some regional differences have been observed (Bhagwagar et al., 2004; Drevets et al., 2007). In line with a decreased density of postsynaptic 5-HT_{1A} receptors associated with severe depression, flesinoxan, a selective 5-HT_{1A} agonist that increases blood levels of adrenocorticotropic hormone, cortisol, prolactin (PRL), growth hormone and decreases body temperature in healthy volunteers through the activation of postsynaptic 5-HT_{1A} receptors (Pitchot et al., 2004; Seletti et al., 1995), has been reported to evoke blunted responses in MDD individuals who have attempted suicide compared with patients with depression who had not attempted suicide or nondepressed controls (Pitchot et al., 2005). However, whether "presynaptic" 5-HT_{1A} autoreceptors on the cell body of 5-HT neurons (Fig. 1) are at higher levels in MDD than in normal healthy subjects remains controversial (Boldrini et al., 2008; Parsey et al., 2006a, 2006b; Stockmeier et al., 1998). This is an important issue because autoreceptors, which indirectly regulate the balance of neurotransmitter uptake and release, play a pivotal role in depression and response to treatment (Piñeyro and Blier, 1999; Lanfumey and Hamon, 2004). Parsey and coworkers used PET scanning to assess [carbonyl-^{11}C]-WAY-100635 binding to 5-HT_{1A} receptors in the dorsal raphe nucleus (DRN). Binding was higher in antidepressant-naïve patients with MDD compared with patients treated with antidepressants and healthy subjects (Parsey et al., 2006b). These investigators also found an inverse correlation between 5-HT_{1A} binding and response to treatment (Parsey et al., 2006a). These results were consistent with an earlier postmortem study showing higher receptor binding in the DRN from patients who had committed suicide versus psychiatrically healthy controls (Stockmeier et al., 1998). The increased binding was more prominent in caudal regions of the DRN. In contrast, Boldrini et al. found lower overall levels of 5-HT_{1A} binding in DRN tissue from suicide victims compared with controls. In this study, binding was higher in the rostral regions from depressed subjects (Boldrini et al., 2008). Possible regional differences in the effects of glucocorticoids on the transcription of the 5-HT_{1A} receptor encoding gene might explain these variations and discrepancies (Lanfumey et al., 2008), especially because depression is apparently not always associated with tonic increase in cortisol secretion (Carroll et al., 2007). Thus, at

least in patients with hyperactive HPA axis, cortisol might decrease the transcription of 5-HT_{1A} receptor encoding gene in forebrain areas whereas the lack of such negative control on serotonergic neurons would allow an up-regulation of 5-HT_{1A} autoreceptors due to the G(-1019)allele in the repressor/enhancer region of the *5-HT1A* gene, which has been repeatedly found associated with major depression and suicide (Albert et al., 2011; Albert and Le François, 2010).

Evidence for alterations in 5-HT_{1B} receptor expression and signaling has also been consistently reported in validated animal models of depression (Lanfumey and Hamon, 2004; Lanfumey et al., 2008). 5-HT_{1B} receptors are autoreceptors on axonal terminals of serotonergic neurons (Fig. 1) and heteroceptors on axon terminals of nonserotonergic neurons of various phenotypes throughout the CNS (Riad et al., 2000). However, the density of 5-HT_{1B} autoreceptors represents only a very low percentage of all 5-HT_{1B} receptors in a given brain region (Sari et al., 1999), and the latter receptors are mainly involved in 5-HT-mediated inhibition of non-5-HT neurotransmitters' release from heterophenotypical terminals located postsynaptically to 5-HT projections. Expression of 5-HT_{1B} receptors is closely linked to expression of p11, a protein that has been claimed as enhancing 5-HT_{1B} receptor activity in brain regions receiving serotonergic projections. Levels of mRNA for 5-HT_{1B} and p11 were decreased in postmortem brain samples from patients with MDD relative to controls. Decreases were observed in the prefrontal cortex, OFC and hippocampus, where 5-HT_{1B} receptors are mainly located on GABAergic and glutamatergic terminals (Anisman et al., 2008). Similar changes were observed in animal models of depression and were to some degree reversed by antidepressant treatment (Svenningsson et al., 2006).

Conversely, the 5-HT_{2A} receptors have both excitatory and inhibitory roles depending on brain region and appear to be an important site of action of atypical antipsychotics. Interestingly, patients with depression who committed suicide show increased expression of 5-HT_{2A} receptors in the prefrontal cortex and, in contrast, lower expression and reduced 5-HT_{2A} receptor binding affinity in the hippocampus compared with matched controls (Anisman et al., 2008; Pandey et al., 2002; Rosel et al., 2000; Turecki et al., 1999).

Increased density of α_2-adrenergic autoreceptors (Fig. 1) has been measured in the locus coeruleus in postmortem samples from patients with MDD compared with those from controls whereas no differences were observed in α_2-adrenergic receptor density in raphe nuclei between the two groups (Ordway et al., 2003). As for the findings in the raphe nucleus for 5-HT_{1A} autoreceptors on serotonergic neurons, there is an increase in agonist binding at α_2-adrenergic autoreceptors on the cell body of these NE neurons, indicating an increased function of these autoreceptors and therefore suggesting a decreased noradrenergic transmission in MDD.

Deficient monoaminergic neurotransmission could result from altered second messenger response, even in the presence of adequate levels of monoamine neurotransmitters. Consistent with this possibility, levels of inositol and c-AMP are decreased in the brains of individuals with depression who died from suicide. Reduced inositol levels also have been measured in patients with depression using proton magnetic resonance spectroscopy (Coupland et al., 2005; Shimon et al., 1997).

Although these data are consistent with monoamine deficiency in patients with MDD, behavioral changes in monoamine-related knockout mice reveal a more complex picture. Mice lacking the NE transporter exhibit increased extracellular NE levels and less depressed behavior (Dziedzicka-Wasylewska et al., 2006). Transgenic mice with knockout of 5-HT_{1A} receptors (Zhuang et al., 1999) or α_{2A}-adrenergic receptors (Schramm et al., 2001) also are more resistant to depression than controls, possibly because part of these receptors act as inhibitory autoreceptors (Fig. 1), and their absence results in increased 5-HT and NE tone, respectively, in the mutants. However, other mechanisms might as well be involved because these knockout mice are also deficient in postsynaptic 5-HT_{1A} and α_{2A} adrenergic receptors, which normally exert modulatory influences on numerous non-5-HT, non-NE, cell types (Bonnavion et al., 2010; Milner et al., 1998). A further example emphasizing the complexity of knockout models is provided by mutant mice devoid of SERT, which can be considered as mice treated for their whole life with an SSRI blocking completely 5-HT reuptake. Indeed, paradoxically, SERT-/- mutants show more depressed behavior and lower tissue 5-HT levels in brain than paired wild-type mice (Fabre et al., 2000). These mutants also exhibit high levels of anxiety (Lira et al., 2003).

4. Multiple actions of antidepressants

Differences in the pharmacological properties of antidepressants, even those of the same class, contribute to their variable effects on primary and secondary targets (Hamon and Bourgoin, 2006). Sertraline, fluoxetine and paroxetine are nominally selective for SERT, with paroxetine having the highest potency (Kd ~0.1 nM). However, their – mostly limited – binding affinities for the NE and DA transporters vary widely, in concentration ranges at least two orders of magnitude higher than those effective at SERT (Hamon and Bourgoin, 2006). At their minimal effective doses, the so-called mixed SNRIs, venlafaxine (75 mg/day) and duloxetine (60 mg/day), largely act as SSRIs, but as the doses are escalated the NET is also progressively inhibited (Debonnel et al., 2007; Turcotte et al., 2001; Vincent et al., 2004). Milnacipran, in contrast, exerts a more potent action on NET than SERT *in vivo* (Koch et al., 2003). Paroxetine also demonstrates binding to muscarinic receptors, which sometimes leads to constipation in susceptible individuals and cholinergic discontinuation symptoms when switching abruptly to another SSRI at equivalent doses of SERT inhibition (Hamon and Bourgoin, 2006). In a similar vein, binding of sertraline to the DAT is thought to mitigate the impact of increased 5-HT on PRL release (Hamon and Bourgoin, 2006). Recognition that differential binding to multiple receptor subtypes could potentiate or mitigate beneficial and negative effects of selective reuptake inhibitors has slowly evolved into targeted multimodal therapies, where uptake inhibition is combined with targeted receptor activity (Hamon and Bourgoin, 2006; Narita et al., 1996; Owens et al., 2001; Richelson, 2010; Sánchez and Hyttel, 1999).

In vivo microdialysis to compare the effects of three different SSRIs, sertraline, fluvoxamine and paroxetine, in the medial prefrontal cortex, nucleus accumbens and striatum showed that these drugs actually affected not only the extracellular levels of 5-HT, but also, to different extents, those of DA and NE in rats (Kitaichi et al., 2010). Compared with vehicle infusion, drug treatments increased extracellular 5-HT levels in all three brain regions. NE levels also increased with all drugs in the nucleus accumbens, fluvoxamine being the least effective antidepressant in this respect. On the other hand, DA levels increased only in the nucleus accumbens and only with sertraline (Kitaichi et al., 2010). These findings suggest that although these effective antidepressants acutely increase levels of one neurotransmitter by selectively preventing its reuptake, they also exert important secondary effects on other neurotransmitters at least after a single administration.

4.1. Stress axis and neurotrophic effects

Plasma levels of cortisol and levels of corticotropin-releasing hormone (CRH) in cerebrospinal fluid are frequently higher in patients with MDD than in controls. Dysfunction of normal feed back control of HPA axis is measurable in approximately half of patients with severe depression (Carroll et al., 2007). Response to antidepressant treatment leads to restoration of normal cortisol and CRH levels through an increased brain expression of glucocorticoid receptors, which, in turn, restores normal feedback functioning. A growing body of evidence indicates that antidepressants stimulate hippocampal neurogenesis in humans and animals (Paizanis et al., 2007). This neurogenic effect has been found with antidepressants from different chemical classes, suggesting a common mechanism related to antidepressant activity. Interestingly, recent experimental data showed that the neurogenic

activity of antidepressants is dependent on glucocorticoid receptor function (Anacker et al., 2011).

4.2. Beyond transport inhibition

4.2.1. 5-HT$_{1A}$ receptors

These receptors are widely distributed throughout the brain, with high levels in the limbic system and raphe nuclei (Lanfumey and Hamon, 2004). Mice lacking expression of the 5-HT$_{1A}$ receptor exhibit higher levels of anxiety and do not respond to SSRIs. The delayed onset of action characteristic of SSRIs and SNRIs may reflect the time required to desensitize cell body 5-HT$_{1A}$ autoreceptor (Blier and de Montigny, 1983; Lanfumey et al., 2008). It is hypothesized that initially the autoreceptors compensate for inhibited 5-HT reuptake by decreasing the release of the indolamine from serotonergic neurons. Chronic SSRI treatment results in 5-HT$_{1A}$ autoreceptor desensitization, which inactivates this negative feedback mechanism, thereby allowing marked increase in extracellular 5-HT and activation of postsynaptic 5-HT receptors (Lanfumey and Hamon, 2004). The relationship of 5-HT$_{1A}$ receptor function to depression and antidepressant therapy was tested in a series of experiments in genetically engineered mice. In these animals, 5-HT$_{1A}$ autoreceptor expression in the raphe nuclei could be genetically manipulated to be low as compared with paired wild-type mice (Richardson-Jones et al., 2010). Under conditions of relatively high level of 5-HT1A autoreceptor expression, mice showed a blunted response to stress, greater behavioral despair, and no behavioral response to treatment with antidepressant agents. In contrast, lowering autoreceptor expression prior to antidepressant administration converted the mice from nonresponders to responders (Richardson-Jones et al., 2010). A marked down-regulation of 5-HT$_{1A}$ autoreceptors has successfully been achieved through internalization of anti-5-HT$_{1A}$ siRNA coupled to sertraline specifically in SERT expressing serotoninergic neurons in adult rats. Like that found in genetically manipulated mice (Richardson-Jones et al., 2010), si-RNA-treated rats were sensitized to the antidepressant effects of SSRIs, and expressed antidepressant-like behaviors in validated tests (Bortolozzi et al., 2012).

Pindolol, a bêta-adrenergic receptor partial agonist with 5-HT$_{1A}$ receptor antagonist properties, combined with SSRIs, results in a significant decrease in time to first response compared with SSRIs alone, probably through the resulting inactivation of 5-HT$_{1A}$-autoreceptor-mediated inhibitory feed back control of 5-HT neurons (Portella et al., 2011). Alternatively, a faster desensitization of 5-HT$_{1A}$ autoreceptors by a direct agonist might be another way to accelerate the therapeutic efficacy of SSRIs. This may be expected with vilazodone (EMD 68843), which acts both as a SERT blocker and a 5-HT$_{1A}$ receptor agonist (Owen, 2011; Page et al., 2002). Indeed, the 5-HT$_{1A}$ receptor agonists, buspirone, gepirone and ipsapirone, which are endowed with anxiolytic properties, also have efficacy in depression and/or in augmenting antidepressant therapy (Blier and Ward, 2003).

4.2.2. 5-HT$_7$ receptors

Another approach to shortening time of onset for effective therapeutic action involves the 5-HT$_7$ receptor, a less well-characterized Gs-protein-coupled receptor. 5-HT$_7$ receptors are involved in circadian cycles and depression. In a rat model of depression, 5-HT$_7$ receptor antagonists led to faster antidepressive-like actions compared with fluoxetine (Mnie-Filali et al., 2011).

4.2.3. 5-HT$_{2A}$ receptors

The 5-HT$_{2A}$ receptor, which is functionally coupled to Gq, is another potential target for multimodal interventions. Evidence suggests that antagonism of the 5-HT$_{2A}$ receptor potentiates NE release under SSRI treatment (Dremencov et al., 2007). In a series of ionophoretic experiments, Szabo and Blier (2002) identified a feedback loop involving 5-HT$_{1A}$ receptors on glutamatergic neurons and 5-HT$_{2A}$ receptors on GABA neurons that regulate noradrenergic tone. The latter interaction might contribute to the augmentation of the antidepressant efficacy of SSRIs and SNRIs by atypical antipsychotics, which are effective 5-HT$_{2A}$ receptor antagonists.

4.2.4. 5-HT$_{2C}$ receptors

The 5-HT$_{2C}$ receptors are also most often blocked by atypical antipsychotic drugs and are under investigation as targets for the treatment of schizophrenia, depression/anxiety disorders and Parkinson's disease. They are distributed throughout the corticolimbic networks and have been localized to glutamate decarboxylase-positive GABAergic interneurons in the DRN (Boothman et al., 2006). In rats, systemic exposure to WAY 161503, a 5-HT$_{2C}$ receptor agonist, suppresses serotonergic firing in the dorsal raphe nucleus (Boothman et al., 2006). These effects are antagonized by both 5-HT$_{2C}$ receptor antagonists and the GABA$_A$ receptor antagonist picrotoxin, suggesting that the 5-HT$_{2C}$ receptor-mediated suppression of 5-HT neurons has a GABAergic component (Boothman et al., 2006). Recently, clear-cut evidence has been reported that the negative influence of 5-HT$_{2C}$ receptor activation on central 5-HT tone is triggered at the early stage of SSRI treatment, thereby supporting the idea that combined treatment with an SSRI plus a 5-HT$_{2C}$ receptor antagonist might be more effective than the SSRI alone to enhance 5-HT neurotransmission (Mongeau et al., 2010). On the other hand, activation of 5-HT$_{2C}$ receptors in the VTA inhibits dopaminergic neurons (De Deurwaerdère et al., 2004), and this effect contributes to reduce the capacity of SSRI antidepressants to enhance DA neurotransmission. Consistent with these observations, sustained administration of the SSRI escitalopram suppresses the firing rate of DA neurons in the VTA, which is reversed by the selective 5-HT$_{2C}$ antagonist SB242084 (Dremencov et al., 2009). Accordingly, maintenance of DA neurotransmission in limbic areas can be expected in response to combined blockade of SERT and 5-HT$_{2C}$ receptors.

4.2.5. N-methyl-D-aspartate (NMDA) receptors

Intravenous infusions of subanesthetic doses of ketamine, an NMDA receptor blocker, provide rapid-onset antidepressant effects in patients with treatment-resistant depression (Berman et al., 2000; Diazgranados et al., 2010; Zarate et al., 2006). Animal studies showed that the rapid onset of antidepressant-like effects is underlain by activation of the mammalian target of rapamycin pathway, which, in turn, leads to increased synthesis of synaptic proteins and formation of synaptic spines in the prefrontal cortex (Li et al., 2010). Furthermore, as previously shown for monoaminergic antidepressants (Paizanis et al., 2007), ketamine and other NMDA antagonists produce these antidepressant-like actions in mice through BDNF-dependent neurotrophic/neuroplastic mechanisms, including hippocampal neurogenesis (Autry et al., 2011; Monteggia et al., 2012).

5. Basic studies and clinical trials of combination therapy

Guiard et al. (2011) measured the effect of treatment with triple monoamine reuptake inhibitors on neuronal activity in rat brain. Acute administration of SEP-225289 and DOV216303, which effectively inhibit 5-HT, NE and DA transporters in rats, was found to decrease the spontaneous firing rate of NE neurons in the locus coeruleus, DA neurons in the ventral tegmental area and 5-HT neurons in the dorsal raphe in a dose-dependent manner. The decrease was mediated by the activation of α -adrenergic-, D , and 5-HT$_{1A}$ autoreceptors, respectively (see Fig. 1). Moreover, in the presence of WAY100635, a 5-HT$_{1A}$ receptor antagonist, SEP-225289 increased the firing rate of 5-HT neurons. This neuronal excitatory action likely resulted from enhanced levels of NE and DA activating excitatory α_1-adrenergic- and D receptors on 5-HT neurons (Guiard et al., 2011). This observation suggests that combined administration of pindolol, which is endowed with antagonist properties at 5-HT$_{1A}$ autoreceptors (Portella et al., 2011), may be an effective augmentation strategy with triple reuptake inhibitors. In contrast, an antagonist which does not discriminate between

5-HT_{1A} autoreceptors and postsynaptic 5-HT_{1A} receptors was recently shown to be ineffective in enhancing the antidepressant efficacy of fluoxetine (Scorza et al., 2011), further emphasizing that only the selective blockade of 5-HT_{1A} autoreceptors could promote the therapeutic action of SSRIs.

To evaluate initial treatment of MDD with monotherapy or combination therapy, Blier et al. (2010) studied 105 patients suffering from moderate to severe MDD (mean HAM-D score of 23), with 63% of the patients having recurrent MDD. Patients in this double-blind study were randomized to treatment with fluoxetine monotherapy (20 mg/day) or mirtazapine (30 mg/day) in combination with fluoxetine (20 mg/day), venlafaxine (225 mg/day titrated in 14 days) or bupropion (150 mg/day) for 6 weeks. The primary end point, change from baseline HAM-D scores, was significantly greater for all combinations compared with fluoxetine monotherapy (Blier et al., 2010). However, response rates did not differ among the groups. At the end of the study, remission rates (defined as a HAM-D score of 7 or less) were 25% for fluoxetine, 52% for mirtazapine plus fluoxetine, 58% for mirtazapine plus venlafaxine, and 46% for mirtazapine plus bupropion. The remission rate was significantly different from monotherapy in the fluoxetine plus venlafaxine combination group (Blier et al., 2010). Of note, double-blind discontinuation of one agent produced a relapse in about 40% of cases with marked response to dual therapy (Blier et al., 2010).

The same group conducted a similar double-blind study in 61 patients with unipolar depression randomized to receive mirtazapine (30–45 mg/day), paroxetine (20–30 mg/day) or the combination of both drugs for 6 weeks (Blier et al., 2009). Change in baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score was significantly greater in the combination group versus the monotherapy groups. Remission rates at week 6 were 19% on mirtazapine, 26% on paroxetine and 43% on the combination (Blier et al., 2009).

In contrast, the Combining Medications to Enhance Depression Outcomes (CO-MED) trial (Rush et al., 2011), that included an open-label phase of one week followed by an 11-week single-blind phase, found no benefit with combination therapy. In this trial, 665 patients received escitalopram alone (≤20 mg/day), escitalopram (≤20 mg/day) plus sustained-release bupropion (≤400 mg/day), or extended-release venlafaxine (≤300 mg/day) plus mirtazapine (≤45 mg/day). There were no differences in response or remission rates or in change from baseline 16-item Quick Inventory of Depressive Symptomatology scores among the groups (Rush et al., 2011). It is noteworthy that the mean of the doses of venlafaxine was in its SSRI range (190 mg/day) and that of mirtazapine was not in its antidepressant range (20 mg/day). In the monotherapy escitalopram group, most patients received the higher dose, whereas in the bupropion combination group, most patients received the lower dose of escitalopram (Rush et al., 2011). Other differences between CO-MED and the two previously mentioned trials (Blier et al., 2009, 2010) may account for the poor performance of combination therapy in this trial.

Antidepressants with multitargeted activity combined into a single molecule would obviate the need for combining different drugs. Thus, agomelatine, which combines both agonist properties at melatonin MT1 and MT2 receptors and antagonist properties at 5-HT_{2C} receptors, is a multitarget agent whose antidepressant efficacy clearly involves these dual pharmacological actions (Kasper and Hamon, 2009). Results of a proof of concept clinical trial (Alvarez et al., 2011) evaluating the multimodal compound vortioxetine (LuAA21004: 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine) in patients with MDD provided further support to this approach. Vortioxetine is a novel compound under development as an antidepressant (Bang-Andersen et al., 2011) with affinity for the human 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_3 and 5-HT_7 receptors and the SERT (Bang-Andersen et al., 2011; Mørk et al., 2012; Pehrson et al., 2012; Westrich et al., 2012). The trial involved 429 patients and compared the efficacy of vortioxetine (5 and 10 mg/day) with placebo and a serotonergic-noradrenergic regimen of the SNRI venlafaxine (225 mg/day). The MADRS total score at week 6 versus placebo was highly statistically significant and similar in the three treatment arms, going from 34 to about 13, with fewer side effects compared with venlafaxine (Alvarez et al., 2011).

6. Conclusions

Research over the last 50 years has provided extensive evidence that abnormal monoamine neuronal function is an important underlying pathology in MDD. Designer molecules, molecular genetics, and imaging techniques have revealed much about brain connectivity and the neurochemistry of depression. In addition, these studies have shown that currently available antidepressant agents have effects on multiple neurotransmitter systems that account for their efficacy and their side effects. By understanding the synergy among neurotransmitter systems across different neural circuits, we may begin to develop multimodal therapies that more effectively target depressive symptoms and help minimize side effects. Research to identify different etiologies is critical to individualizing treatment.

Acknowledgments

M. Hamon and P. Blier both contributed to the collection and analysis of literature data, and the writing of this review article. In addition, editorial support was provided by The Medicine Group on behalf of Takeda Pharmaceutical Company, Ltd, as part of a joint clinical development program with H. Lundbeck A/S.

Disclosures

The two authors, M. Hamon and P. Blier, have fully approved the review article under its final, submitted form.

Dr. Hamon M. received grant funding and/or honoraria for lectures and/or participation in advisory boards from Bristol Myers Squibb, Esteve, Grünenthal, Lundbeck/Takeda, Merck, Pierre Fabre and Servier.

Dr. Blier P. received grant funding and/or honoraria for lectures and/or participation in advisory boards from Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Euthymics, Janssen, Lundbeck/Takeda, Merck, Pfizer, Sepracor, and Servier.

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