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Current Opinion in Pharmacology

5-HT and depression: is the glass half-full?

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Mood disorders such as major depression are common illnesses with considerable morbidity and significant mortality. A long-standing theory is that a breakdown in brain serotonin (5-hydroxytryptamine; 5-HT) signalling is critically involved in the symptoms and drug treatment of clinical depression. However, the nature of this 5-HT defect has proved to be frustratingly elusive, and it remains unclear how the 5-HT signalling effects of antidepressant drugs might alter neuropsychological mechanisms to bring about relief of depressed mood. This article highlights recent discoveries that advance our understanding of how 5-HT-evoked changes at molecular, cellular and neuropsychological levels might interact to alleviate the symptoms of clinical depression.

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Current Opinion in Pharmacology 2011, **11**:45–51

This review comes from a themed issue on
Neurosciences
Edited by Nicholas Barnes

Available online 4th March 2011

1471-4892/$ – see front matter

DOI 10.1016/j.coph.2011.02.003

Introduction

Major depression is a common and often severe psychiatric condition characterised by a complex syndrome of affective, vegetative and cognitive symptoms that show a relapse-remitting course over months and often years. All this adds up to a source of considerable morbidity and significant mortality. The World Health Organization forecasts that if current demographic trends continue, unipolar depression will be the greatest source of disability worldwide by the year 2030 [1]. Despite this worrying prediction, modern drug treatments are slow to act, with often poorly tolerated acute adverse effects including anxiety and insomnia, and up to 50% of patients fail to experience an adequate therapeutic response even after a treatment switch [2]. Moreover, only one novel antidepressant drug has been developed in the last 10 years, and major pharmaceutical companies are closing antidepressant drug development programmes [3].

The idea that the symptoms of depression are underpinned by a deficiency in brain 5-HT stretch back over 40 years to the discovery that the first generation of antidepressant drugs blocked 5-HT reuptake or metabolism as part of their pharmacological effect. Since then studies of the link between 5-HT and depression have continued to provide a rich source of discoveries including the development of selective 5-HT reuptake (SSRIs), which are currently the first choice antidepressant drug treatment. However, important questions remain. For instance, even though the interaction of an SSRI with the binding site of the 5-HT transporter (5-HTT; SERT) protein is now known with single amino acid resolution [4], it is unknown how the signalling events triggered by this interaction eventually translate into changes in mood. Equally, whilst the therapeutic effect of SSRIs illustrates how manipulations of 5-HT can have striking effects on mood [5••], it is unclear whether changes in brain 5-HT function are causally linked to the symptoms of depression. This article highlights recent discoveries that impinge on these and related questions.

5-HT abnormalities in depression

In the 1960s and 1970s it was reported that depressed patients had reduced 5-HT binding sites on platelets and low 5-HT metabolite levels in cerebrospinal fluid. These findings were not always reliable [5••], but they provided some of the first evidence for 5-HT changes in depression. This idea was strengthened by later more consistent findings of blunted neuroendocrine responses to 5-HT-selective pharmacological challenges in depressed patients. Interestingly, this effect was observed in patients with a history of depression even when recovered and off drug treatment [6], suggesting a link between reduced 5-HT function and depression vulnerability, and not just the acute depressive state [5••]. The neuroendocrine data accord with more recent findings from positron emission tomography (PET) studies [7], of a widespread decrease of 5-HT_{1A} receptors in the brains of acutely depressed patients as well as patients who have recovered [8,9].

Other PET studies have investigated the 5-HT_{2A} receptor and 5-HTT in depressed patients, but findings to date are inconsistent. If anything, 5-HT_{2A} receptor binding is increased in the cortex of both depressed and recovered subjects, and this neurochemical change correlates with measures of negative beliefs about the self and the world [10,11]. In contrast, some (although not all) imaging studies suggest reduced 5-HTT binding in brain stem regions, which resolves with clinical recovery [12,13]. However, the latter data raise the question of

why depressed patients respond to treatment with drugs like SSRIs that cause a further decrease in 5-HTT availability. It is possible that the drugs are in some way facilitating a prior neuroadaptive response to lowered 5-HT levels; however, this explanation does not seem altogether satisfactory.

The above imaging and neuroendocrine findings combined, provide tantalising evidence that impaired brain 5-HT function is indeed linked to depression and depression vulnerability. These data can be taken as evidence to suggest that the source of the 5-HT deficiency is at the level of postsynaptic 5-HT receptors as well as 5-HT release. In the latter context it should be noted that there are frequent reports of low circulating levels of the 5-HT precursor, L-tryptophan, in severely depressed patients [14]. This deficit has been linked to immune activation that is believed to often accompany the depressive state, and that leads to induction of indoleamine dioxygenase and increased tryptophan degradation [15].

In accord with the above findings, a significant body of data suggests that acute lowering of tryptophan using a tryptophan-free amino acid mixture, elicits a striking return of clinical depression in a high proportion of recovered depressed patients withdrawn from medication [16•]. These data do not speak directly to the question of whether depressed patients have low 5-HT release but certainly suggest that maintaining synaptic 5-HT levels is critical for the maintenance of mood in vulnerable individuals, and specifically those who have previously experienced depression and may have an already compromised 5-HT system. This idea accords with recent evidence that deep brain stimulation of the subthalamic nucleus that acutely decreases 5-HT transmission in experimental models [17], can elicit low mood in Parkinson's disease patients who are known to demonstrate preexisting 5-HT deficits at several levels [18].

Interestingly, in people at high familial risk of depression who have not themselves suffered from depression, tryptophan depletion produces a detectable but much milder lowering of mood [16•]. This observation suggests that the more profound clinical relapse in mood that follows tryptophan depletion in individuals with a history of depression, may be due to changes that occur as a result of recurrent illness. The nature of these changes, and whether they are best conceptualised at a psychological or neural level, are not known.

The key question of whether 5-HT release is decreased in depression may soon be tested with the development of PET imaging methods to monitor 5-HT release using the radioligand displacement approach, which has been so successful in the dopamine field [19]. There is an ongoing, intensive search for PET radiotracers that are sensitive to changes in synaptic 5-HT availability, with certain 5-HT_{1A} receptor agonist and 5-HT_{1B} receptor antagonist ligands already showing promise [20•], and other putative 5-HT-sensitive PET ligands are on the horizon. For example, studies in depression using the newly available 5-HT_4 receptor PET ligand [^{11}C]SB207145 [21] will be interesting given recent preclinical evidence that 5-HT_4 receptors adapt to enduring (although not acute) changes in synaptic 5-HT availability [22,23].

5-HT genes and depression

Studies of major depression in twins and families have shown moderate to high heritability, and much effort has been made to identify susceptibility genes linked to 5-HT. The 5-HTT gene (slc6a4) is one of the most intensively investigated genetic risk factors for depression. Levels of the 5-HTT vary up to sevenfold between individuals in the human population (e.g. [24]) and this may be due in part to the existence of functional 5-HTT gene variants, many of which continue to be discovered [25••,26]. Of particular interest is a 44 bp insertion/deletion polymorphism in the 5-HTT gene-linked polymorphic region (5-HTTLPR) of the 5-HTT gene promoter. This generates a low 5-HTT-expressing allele (s/s) that was found to be associated with factors linked to depression such as neuroticism [7] and increased responsiveness to fearful stimuli [27], as well as an actual increased risk of depression when accompanied by stressful life events in adult as well as early life [28••,29•].

Interpretation of these findings is complicated by failed replications [30,31•], and the view that the effect of individual polymorphisms on the phenotypic expression of complex traits is likely to be small [32]. In addition, PET studies do not indicate that 5-HTT genotype is linked to the density of 5-HTT sites *in vivo* [33]. Intriguingly however, investigations using genetic animal models observe striking phenotypic effects of altered expression of the 5-HTT. Specifically, 5-HTT knockout mice demonstrate anxiety-like behavioural phenotypes whereas 5-HTT overexpressing mice show the opposite [25••,34]. Moreover, heterozygote 5-HTT knockout mice lack a noticeable phenotype under baseline conditions but demonstrate a high anxiety phenotype in adulthood following exposure to environmental early life stressors [35,36]. These findings bear a close resemblance to human gene–phenotype association data [28••] and add further support to the idea that an interaction between the 5-HTT gene and early life events are a critical determinant of depression vulnerability [37••].

The neural mechanisms by which environmental adversity in early life might interact with the 5-HTT gene to influence emotionality in adulthood are not known, but likely to include epigenetic programming of gene expression. In this respect it is interesting that the promoter

region of the 5-HTT gene is rich in DNA methylation sites and that changes in the methylation status of these sites have been associated with altered stress sensitivity [38•,39].

Emerging evidence also associates depression vulnerability as well as antidepressant treatment response with a single nucleotide polymorphism (C(−1019)G) in the promoter region of the 5-HT_{1A} receptor gene, which determines the binding of certain gene repressors and is thereby functional [40•]. Interestingly, the putative risk (G/G) allele was recently modelled in mice through a targeted mutation that increased 5-HT_{1A} receptor expression specifically in midbrain raphe neurons [41••]. These mice demonstrated a suppression of 5-HT cell firing due to increased inhibitory 5-HT_{1A} autoreceptor tone. In addition, the mice showed increased sensitivity to stress as well as resistance to behavioural effects of SSRI treatment, thereby recapitulating the phenotype predicted by the human gene-association studies.

Molecular and cellular effects of 5-HT-targeted antidepressants

Although SSRIs rapidly enter the brain and block 5-HT reuptake, as evident in human PET studies of 5-HTT occupancy [42], a course of treatment of several weeks is required for the full antidepressant response. One early hypothesis put forward in the 1980s to explain this paradox was an adaptive desensitization of brain 5-HT_2 receptors and β-adrenoceptors, but this theory was later widely discarded in favour of one that emphasised the importance of 5-HT autoreceptor desensitization [43]. The latter theory posited that acute inhibition of 5-HT reuptake or metabolism evokes a rise in extracellular 5-HT which is immediately sensed by autoreceptors located on the somatodendrites (5-HT_{1A}) and nerve terminals (5-HT_{1B}) of 5-HT neurons to trigger a fall in 5-HT cell firing and synaptic 5-HT: evidence suggests that with continued antidepressant treatment, 5-HT_{1A} and 5-HT_{1B} autoreceptors desensitize allowing synaptic 5-HT to rise. Recent studies have identified additional mechanisms involved in the feedback control of 5-HT neurons that utilise postsynaptic 5-HT receptors including 5-$HT_{2A/2C}$ receptors [44•], which may also contribute to the acute adaptive response of 5-HT neurons to antidepressant treatment.

The 5-HT autoreceptor desensitization theory instigated drug development programmes that successfully identified molecules with combined 5-HT reuptake/5-$HT_{1A/1B}$ receptor antagonist properties [45]. Although little is currently known about the actions of these dual and triple action drugs in humans, clinical trials have demonstrated an overall beneficial clinical effect of using the 5-HT_{1A}/β-adrenoceptor ligand pindolol as an adjunct to SSRI treatment in terms of speed of onset of clinical effect [46]. Preclinical and clinical evidence of the SSRI augmenting properties of 5-HT_2 receptor antagonists (including risperidone) might link to 5-HT_2 receptor feedback mechanisms. For example, in patients who have failed to respond to SSRIs, the augmentation strategy with the best evidence base is the addition of atypical antipsychotic drugs at low doses that would preferentially antagonise 5-$HT_{2A/2C}$ receptors [47].

Recent evidence suggests that the response of 5-HT feedback mechanisms to SSRI administration is just part of a series of therapeutically relevant neuroadaptive events that occur during a course of antidepressant treatment. Current thinking is that increased synaptic 5-HT (presumably following 5-HT autoreceptor desensitization) activates a downstream gene programme that leads to enhanced neuronal plasticity which has failed because of the adverse effects of stress and other environmental and genetic factors [48••]. Much data, including that from genome wide analyses (e.g. see [49]), suggest that the gene programme is complex and likely includes a co-ordinated pattern of expression of many tens if not hundreds of genes involved in multiple processes ranging from synapse formation and strengthening to even neurovascular support. The net effect of these changes is thought to be an activity-dependent structural realignment and functional repair of neural circuitry, which is then better able to adapt to environmental challenges [50••,51].

The large diversity of 5-HT-sensitive genes influenced by a course of antidepressant treatment makes it difficult to attribute weight of importance to individual genes and their products, and specific downstream effects. However, there are much data in favour of a key role for brain-derived neurotrophic factor (BDNF) and its receptor TrkB in the actions of antidepressant drug treatment, if not depression pathophysiology [51,52•]. Equally, BDNF is a known mediator of neurogenesis, and there is a strong case for the importance of increased neurogenesis in the action of SSRIs although less so for other antidepressant drug classes [53••,54].

Identification of the 5-HT receptor subtypes and their signalling pathways that underpin the gene effects of 5-HT-targeted antidepressants is important to guide antidepressant drug development programmes. 5-HT receptor subtypes positively coupled to adenylate cyclase (5-HT_4, 5-HT_6, 5-HT_7) or stimulation of Ca^{2+}-dependent kinases (5-HT_{2A}, 5-HT_{2C}) are likely to activate the transcriptional regulator CREB and also MAP kinase, both of which are considered key nodal points in the signalling pathways underlying the gene expression and behavioural effects of SSRI and other antidepressants [55–57]. Interestingly, recent data show that 5-HT_4 and 5-HT_6 receptor agonists demonstrate early onset antidepressant-like molecular and behavioural effects in preclinical models [58,59]. Moreover, there are ongoing clinical trials into the antidepressant potential of psychedelic drug, psilocybin, reinforced by

evidence that a 5-HT_{2A} receptor agonist action may evoke changes in neural plasticity to produce long-lasting improvement in mood [60•].

5-HT and depression: neuropsychological approaches

Recently the idea that 5-HT might mediate adaptive changes in neural plasticity can be considered in the context of an emerging neuropsychological theory of antidepressant drug action (Figure 1). The latter theory emphasises that altered emotional processing is critical to the actions of drug treatments rather than a direct elevation in mood *per se*. In particular, it is proposed that at the neuropsychological level, antidepressants work by inducing a shift away from a cognitive state of negative affective bias, comprising negatively biased attention, memory and appraisal of internal and external emotional stimuli.

That 5-HT is important to this switch in emotional processing is supported by several lines of evidence, including findings that tryptophan depletion caused negative biases in the recognition of facial expressions [61] whereas the SSRI citalopram had the opposite effect [62]. Both effects occurr independent of changes in objective or subjective mood. Functional imaging studies suggest that the changes in biases produced by altered 5-HT neurotransmission are exerted via effects on limbic circuitry involving the amygdala [63••], which plays a key role in the very early nonconscious appraisal of negative emotional stimuli.

Interestingly, the ability of citalopram and other antidepressants to evoke a positive bias in emotional processing is detectable after a single dose [63••]. These observations have led to the idea that at the neuropsychological level antidepressants cause an immediate adjustment in negative affective bias and that this provides a platform for the relearning of new positive emotional associations brought about by the gradual exposure to social cues and reinforcement in this transformed emotional world [63••,64]. Over time this would be expected to lead to conscious improvement in subjective mood as new, positive, emotional contingencies are learned and experienced.

It is noteworthy that acute SSRI administration is also associated with enhanced startle responses and fear recognition [65]. These observations are interpreted as an early increase in threat processing, which is highly relevant to clinical findings of increased anxiety early during a course of SSRI treatment before the onset of anxiolytic effect (for further discussion see [63••]).

Figure 1

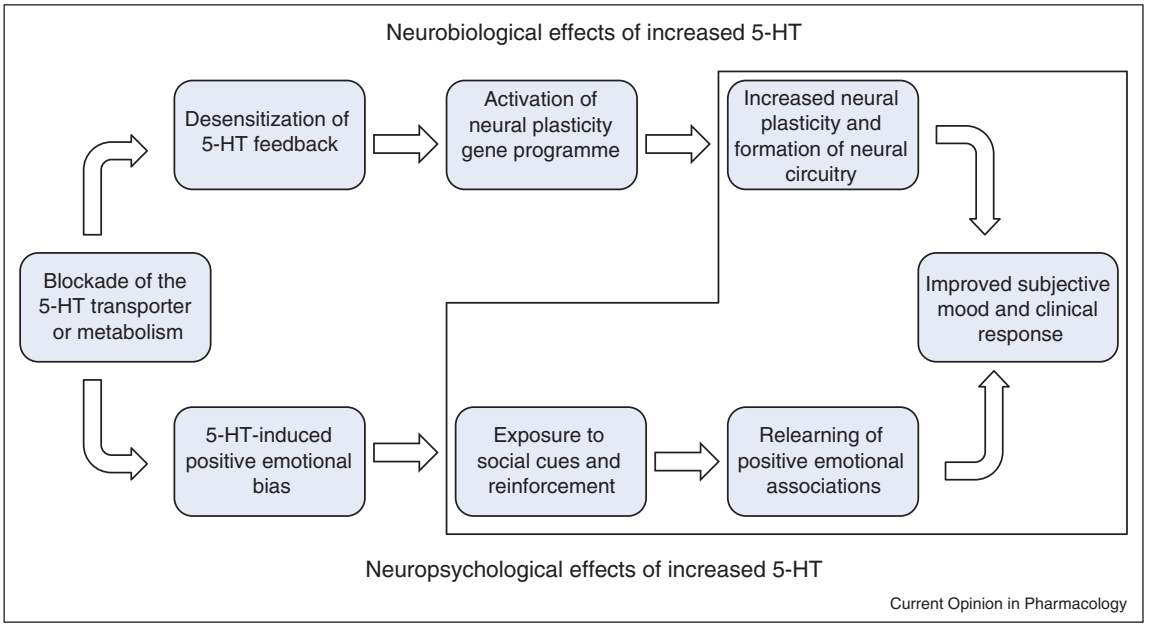

Illustration of the proposed sequence of 5-HT-mediated, adaptive neurobiological and neuropsychological processes that occur during a course of several weeks treatment with 5-HT-targeted antidepressant drugs (inhibitors of 5-HT reuptake and metabolism), leading up to the full therapeutic effect. The induction of positive emotional bias occurs after acute treatment and forms the basis for the gradual relearning of positive emotional associations. Similarly, activation and then desensitization of 5-HT feedback occur very early in the course of treatment and are required for the downstream changes in gene expression and increased neural plasticity. As indicated by the shadowed box, it is envisaged that the increase in neural plasticity and formation of neural circuits occurs within emotional processing networks to allow positive emotional stimuli (e.g. social cues) to act and to be relearned and bring about improved mood.

The effects of SSRIs on positive emotional bias and relearning, have an intriguing similarity to cognitive therapy approaches to depression where therapists use reflective discussion with patients to enable them to reframe negative perceptions and appraisals in a more 'realistic' that is, more positive, light. For this reason cognitive therapists are fond of quoting the Greek stoic philosopher, Epictetus (55–135 AD) who observed that, 'Men are disturbed not by things, but by the view which they take of them.' Of course, in contrast to drug treatment, cognitive therapy involves explicit and conscious reframing of experience presumably involving cortical mechanisms, whereas the ability of SSRIs to produce positive emotional bias appears to occur implicitly, probably through actions on non-conscious emotional processing at a limbic level.

The neural plasticity and neuropsychological hypotheses of antidepressant action are not mutually exclusive (Figure 1). Indeed, increased neural plasticity within critical neural circuits might provide the neural substrate through which acute increases in positive emotional processing lead to the relearning of positive emotional associations that ultimately bring about improvements in mood. This idea resonates with recent findings that repeated SSRI treatment brought about the functional (BDNF-dependent) recovery of circuitry of the visual cortex when combined with a visual stimulus operating through this circuitry [66••]. Thus, SSRI treatment may activate plasticity within visual circuits to allow a visual stimulus to act in the same way that SSRIs might activate plasticity within emotional processing circuits to allow a positive emotional stimulus to act and to be relearned. The application of animal models of negative bias [67•] should help provide an experimental means to test this hypothesis.

Conclusion

The evidence that brain 5-HT can influence the expression of depressive symptomatology is very strong, although impaired 5-HT function would appear to be neither necessary nor sufficient to cause clinical depression. In some patients increasing brain 5-HT function through blockade of the 5-HTT (SSRI treatment) seems sufficient to promote clinical recovery, though preclinical studies show that this simple pharmacological action is accompanied by a complex programme of molecular and cellular changes. The ability of SSRIs to both facilitate mechanisms of neural plasticity and remediate negative emotional biases, allows what might be an important convergence of neurobiological and psychological explanations of the role of 5-HT in antidepressant action and depression. Thus, the ability of 5-HT to alter both emotional experience and emotional learning could give this neurotransmitter a pivotal role in the treatment and pathophysiology of emotional disorders.

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