

# Depression and 5HT

J. F. W. DEAKIN

*Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK*

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5HT has been implicated in mechanisms of anxiety and depression for many years but the evidence is contradictory. Perhaps one error has been to think of 5HT as a unitary system when in reality it is highly differentiated. There has been an explosive increase in knowledge about different 5HT receptor subtypes and it has long been known that there are different anatomical subsystems. Evidence will be summarised that the different systems subserve different psychological functions and that dysfunction in the different systems results in depression, anxiety, panic and OCD in an understandable way.

Much evidence is compatible with the idea that 5HT systems reduce the impact of impending or actual aversive events. Anticipation of an aversive event is associated with anxiety and this motivates avoidance behaviour—a normal adaptive response. There is evidence that this is mediated by projections of the dorsal raphe nucleus and associated 5HT2 and 5HT3 receptors. Projections of the median raphe nucleus and associated 5HT1A receptors appear to mediate resilience to aversive events once they have occurred or if they persist. When this system breaks down depression results. It will be argued that all effective antidepressants act on 5HT1A, natural mechanisms of resilience.

## Introduction

There has been an explosive increase in knowledge and interest in the neurotransmitter, 5-hydroxytryptamine (5HT, serotonin). A large number of 5HT receptor subtypes have been delineated and the neurotransmitter has been implicated in an ever-widening range of conditions including anxiety, depression, dementia, eating disorders, and alcoholism. Yet it seems that the more we know about 5HT, the less we know. There are many contradictions and much confusion. For example, in the field of novel anxiolytic drugs the emphasis is on compounds which block 5HT neurotransmission—5HT2, 1C and 3 antagonists, but, in the field of antidepressants, the emphasis is on drugs which potentiate 5HT functioning. The contradiction is that 5HT seems to have an opposite involvement in two sets of symptoms which usually occur together—anxiety and depression.

The mistake is to think of the 5HT system as a unitary system. It is no longer possible to understand the role of 5HT in psychopathology without taking account of the anatomical and pharmacological complexity of the system.

## *5HT receptor subtypes*

While there are a large number of subtypes, 5HT receptors can be grouped into three families: the 5HT1 receptor family, the 5HT1C/2 receptor family, and 5HT3 receptors.

There is a great drive to develop drugs which have selective actions on these receptor subtypes; antagonists of the 5HT<sub>2</sub>/1C and 3 families are already available and agonists of the 1A receptor are in clinical use.

The key to understanding the role of these subtypes in depression and anxiety may be to take account of what is known about their basic psychological functions. There is a wealth of animal behaviour experimentation which offers many clues.

It is possible to discern a unitary function for 5HT systems. 5HT may function as a mediating system for adaptive or coping responses which deal with aversive events, or to use a looser terminology, a system for coping with stress, or unpleasant events. However, just as 5HT systems show a good deal of differentiation, so aversive events and stress are differentiated; there are different forms of aversion.

#### *Life events, anxiety and depression*

Finlay-Jones *et al.* (1981) divided life events into danger life events and loss life events. Danger life events contain the element of threat, for example, a woman discovering a lump in her breast with the possibility that this might indicate cancer. Loss life events include interpersonal losses such as bereavement or a close friend moving away. In a prospective study of women in the community, Finlay Jones *et al.* found that the occurrence of danger life events was significantly predictive of the development of anxiety states whereas loss life events were predictive of depressive illnesses. Two distinct forms of aversion were associated with distinct psychopathologies. Danger life events concern future or potential aversion. The normal and appropriate response to threat is anxiety. Anxiety is a drive which motivates avoidance behaviour so that the potential aversion is avoided completely or at least its impact is minimised, should it occur. In patients who develop anxiety states this normal adaptive response is excessively active, either because there are indeed many threats, or because the system is excessively responsive.

Loss life events, in contrast, refer to the present and there is an implicit chronicity and hopelessness. According to Brown *et al.* (1982), some mechanism keeps the hopelessness focused on the loss event in normal people, but in depression the sense of hopelessness becomes generalised.

#### *Two forms of aversion — two 5HT systems*

The two main forebrain 5HT systems may mediate coping responses to these two forms of aversive life event.

#### *Dorsal raphe nucleus and anxiety*

The dorsal raphe nucleus (DRN) in the brainstem sends widespread projections which strikingly correspond closely to the distribution of dopamine terminals in the brain. 5HT<sub>2</sub> receptors appear to be specifically associated with the terminals of the DRN. 5HT<sub>1B</sub> receptors (ID in humans) show the same correspondence but some of these are certainly pre-synaptic receptors on 5HT terminals. 5HT<sub>1C</sub> and 5HT<sub>3</sub> receptors are also present in the terminal fields of the DRN but it is less clear whether this is an exclusive association.

A great deal of evidence indicates that interference with functioning in dorsal raphe projections—by selective lesions or by micro-injecting antagonists into the amygdala—reduces behavioural signs of fear in animal experiments. Benzodiazepines and buspirone

shut off 5HT release from terminals of the DRN and this may contribute to their anxiolytic effect. Tricyclic antidepressant drugs may exert their anxiolytic actions through their shared ability to block or to down-regulate 5HT2 and 5HT3 receptors.

#### *Median raphe nucleus and resilience*

The median raphe nucleus (MRN) has a pattern of projections which is distinct from the DRN. The MRN projects to cortical structures including the hippocampus and associated areas of the cortex, and this distribution parallels the distribution of nor-adrenergic nerve terminals. 5HT1A receptors show the same distribution.

It is suggested that this system is concerned with adapting to aversive events once they occur; that is, it is a system which mediates tolerance or resilience to chronic adversity. When this system breaks down symptoms of depression develop in humans and learned helplessness develops in animal models of depression. The remainder of this article will consider evidence that the MRN resilience system does break down in depression, that this causes depression and that antidepressant drugs work by reversing the deficit.

#### *Impaired 5HT1A functioning causes depression*

##### *Reduced 5HT in depression*

Low CSF 5HIAA concentrations and reduced circulating plasma tryptophan contribute convincing evidence for the theory that defective 5HT functioning is responsible for depression. Neuroendocrine abnormalities in depression suggest that the 5HT1 system may be particularly affected. One of the most reproducible findings in biological psychiatry is that pituitary hormonal responses to the 5HT precursor tryptophan or to the 5HT releasing agent fenfluramine are blunted in depressed patients. These hormonal responses are thought to involve 5HT1 receptors. That the attenuation of 5HT1A functioning might cause the state of depression is suggested by our recent finding that the blunted hormonal responses to tryptophan are state dependent—when the patients get better, the hormonal responses normalise. It might, of course, be that the state of depression causes the blunted hormonal responses. However, the fact that antidepressant drugs all share the ability to enhance 5HT1A functioning suggests the reverse—that impaired 5HT1A functioning causes depression.

##### *Antidepressants enhance 5HT function*

De Montigny and Aghajanian (1984) have shown that all effective antidepressant drugs share the ability to enhance hippocampal 5HT neurotransmission—a 5HT1A mediated effect. Tricyclic antidepressants appear to work post-synaptically—the post-synaptic cells are more sensitive to the iontophoretic application of 5HT. The specific 5HT reuptake blockers such as fluvoxamine appear to work on the 5HT neurone and enhance synaptic concentrations of 5HT. This is not an immediate effect. 5HT neurones are sensitive to 5HT and this is mediated by autoreceptors. Autoreceptors on 5HT nerve terminals sense the synaptic concentration of 5HT, and when this begins to increase under the influence of a reuptake blocker there is an immediate negative feedback inhibition of further release. The cell body dendrites of 5HT cells are also sensitive to 5HT through 5HT1A autoreceptors. These autoreceptors influence the firing rate, and when extracellular 5HT begins to

increase under the influence of an uptake blocker, 5HT cells stop firing. Gradually, however, 5HT neurones learn to live with raised extracellular 5HT concentrations, and there is evidence that the autoreceptors become less sensitive, so the neurone tolerates a greater extracellular concentration of 5HT under the influence of 5HT reuptake inhibitors.

#### *Antidepressants work by enhancing 5HT function*

A crucial study by Delgado *et al.* (1990) suggests that the undoubtedly ability of antidepressant drugs to enhance 5HT functioning may cause their efficacy. This experiment involved administering a low tryptophan diet and a special cocktail of amino acids excluding tryptophan. This caused a very large fall in circulating plasma tryptophan concentrations, thus interfering with central 5HT synthesis. In a group of depressives who had recently recovered with various antidepressant drugs, the low tryptophan diet caused a doubling of Hamilton depression ratings; plasma tryptophan depletion temporarily reversed the effect of antidepressants. This result suggests that intact 5HT functioning is necessary for antidepressant drugs to work.

These studies suggest that impaired 5HT1A functioning occurs in depression and that this causes the state. Antidepressant drugs work by reversing this abnormality.

#### *The median raphe system and tolerance to aversion*

The idea that the median raphe system copes with chronic aversion comes from an animal model of depression developed by Kennett *et al.* (1985). The stress involved immobilising experimental rats for two hours by taping them to a wire grille. They were returned to their home cages and 24 hours later placed in an open field. The earlier immobilisation stress markedly reduced open-field activity compared with unstressed controls. These authors showed that when the stress was repeated on a daily basis open-field activity gradually returned to normal, so that after seven daily immobilisations there was no impairment of open-field exploration. The rats had become tolerant to immobilisation stress. The authors showed that the tolerant animals were behaviourally supersensitive to 5HT1A agonist drugs. It was further demonstrated that the acute effect of immobilisation stress could be blocked by pre-treatment with an antidepressant or with a large dose of a drug which stimulates 5HT1A receptors. These findings suggest that adaptation to chronic aversion is associated with an enhancement of 5HT1A functioning and that antidepressant treatments promote and accelerate adaptation to aversion in this animal model through 5HT1A systems.

#### *How does the median raphe system cope with chronic aversion?*

There is increasing evidence that 5HT plays an important role in the modulation of memory. Thus, some 5HT antagonists actually improve learning. This is compatible with an earlier hypothesis (Deakin, 1983) that the median raphe system operates as a disconnection mechanism, through which behaviours followed by an aversive outcome become progressively disconnected from the animal's repertoire. Such a disconnection mechanism in humans might underlie the defence of denial or dissociation. For example, a woman might well develop symptoms of anxiety because of unpredictable violence from an alcoholic husband. Nevertheless, she might well be able to continue her daily work and normal interactions with other people without developing a depressive illness. Some

mechanism of resilience disconnects her emotional state from the background threat of violence. However, should the disconnection mechanism break down, then symptoms of learned helplessness and depression would develop as the aversiveness of her husband regained its full impact.

#### *Risk factors for depression*

Apart from genetic and physical causes, depression appears to be psychosocially determined. Brown *et al.* (1982) have identified a number of risk factors which predispose people to developing depression. These are early loss of mother, chronic psychosocial stress (e.g. financial and housing difficulties), and social isolation including lack of a confiding relationship with spouse. Analogous factors in animal behavioural experiments appear to operate through the 5HT system.

#### *Chronic psychosocial stress and stress hormones*

Deakin *et al.* (1990) reported that depressed patients whose illnesses developed in the setting of chronic psychosocial stress had increased resting plasma cortisol concentrations, and this is in agreement with one other study. Remarkably, no other studies have investigated the relationship between cortisol secretion and psychosocial adversity. It is suggested that hypersecretion of cortisol is not a marker for biological vulnerability to depression but is a reflection of psychosocial adversity. Deakin *et al.* further observed that blunted prolactin responses to tryptophan infusion occurred in those depressives with raised basal cortisol secretion; and several studies with fenfluramine challenge have found the same. These and other studies suggest that glucocorticoids can impair functioning in 5HT1A systems. Thus chronic psychosocial stress may predispose to depression by undermining functioning in the median raphe 5H1A resilience system via stress hormone mechanisms.

#### *Social support and 5HT functioning*

It is well known that housing animals singly causes marked behavioural changes which in many cases are reversed by antidepressant treatment. It has further been shown that housing in isolation interferes with 5HT functioning in experimental animals. In the immobilisation stress model of depression it was found that two hours of immobilisation stress was completely without effect on subsequent open-field behaviour 24 hours later if the stressed animals recovered in group housing conditions. In other words immobilisation stress was only effective in altering open-field behaviour if the animals were singly housed. This is remarkably analogous to the Brown and Harris model in humans where life events increase the risk of depression only in the setting of vulnerability factors, which include social isolation (Brown and Harris, 1986).

The animal studies raise the important question of how social contact is detected and how this promotes resilience. In rats the two most likely modalities are smell and touch, since grooming and vigorous play are important in rodent and primate social groupings and hierarchies. Something about social contact in animals affects 5HT functioning. Could it be that in humans the resilience induced by social support and a confiding relationship with a spouse is built on a more primitive connection between touch and 5HT functioning?

### Conclusion

This article has argued that 5HT systems are concerned with coping with adversity. Threats of aversion elicit anxiety mediated by projections of the dorsal raphe system to amygdala and other limbic structures. This motivates avoidance behaviour which has the beneficial effect of reducing the chances of the feared event occurring. When this system goes wrong, symptoms of morbid anxiety develop.

When aversive events occur and become chronic, other adaptive mechanisms come into play. There is evidence that behavioural tolerance to repeated aversion involves 5HT mechanisms. This may involve projections of the median raphe nucleus to the hippocampus, a structure implicated in memory, which in some way disconnects associations between aversive cues and behavioural responses so that some aspect of the aversiveness becomes progressively reduced. When this adaptive mechanism breaks down, symptoms of learned helplessness and depression develop. With the exception of delusional depression and bipolar affective disorder, psychosocial factors appear to be important in the aetiology of most cases of depression. There is evidence that chronic psychosocial adversity and social isolation both interfere with 5HT neurotransmission and this causes the state of depression. Antidepressant drugs appear to work by reversing impaired functioning in 5HT neurotransmission.

This argument suggests that antidepressant drugs including the 5HT reuptake blockers do not cure illnesses. This is compatible with the evidence that there are no specific clinical predictors of response to antidepressant therapy which do not also predict placebo response rate. Thus delusional depression has a minimal placebo response rate and a poor response to antidepressant drugs. Similarly, chronic characterological depression is poorly responsive to medication and poorly responsive to placebo. Depressive illnesses with classic somatic disturbances show a high spontaneous remission rate and a good response to antidepressant drugs. It would therefore appear that antidepressant drugs work by acting on natural mechanisms of resilience—the median raphe 5HT1A system.

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**Audience Discussion***Audience*

One thing that puzzles me is that loss of appetite and loss of libido, which are a fundamental part of depression, are actually increased by the current antidepressants promoted for 5HT effect. One would have thought that buspirone would be an ideal drug in this situation. Why is it not effective as an antidepressant?

*Professor Deakin*

Buspirone's successor, gepirone, has been groomed as an antidepressant, and I think that fits perfectly because buspirone does two things: it switches off that dorsal raphe anxiety system by the autoreceptor action, and it stimulates the post synaptic 1As in the hippocampal system. I would not agree that buspirone is not an antidepressant. In fact in the Goldberg and Finnerty trial many years ago on a group of mixed anxiety depressed outpatient states, buspirone and diazepam were compared. They were equally effective in reducing anxiety, but buspirone was significantly better at alleviating depressive symptoms. I think that as the theory predicts, buspirone is an antidepressant drug and perhaps needs to be given in bigger doses. It remains to be seen how good gepirone is in relation to reuptake blockers.

*Audience*

What is your evidence for a desensitisation mechanism?

*Professor Deakin*

The evidence that the auto receptors become tolerant comes from electrophysiological studies of the raphe. If you squirt 5HT onto the 5HT cells they stop. In chronically antidepressant-treated animals, if you squirt 5HT onto the 5HT cells they carry on; they are not so inhibited by the 5HT, they are less sensitive to 5HT outside. However, I presented a very simplistic picture.

*Audience*

I believe it has been suggested that these drugs may lead to an increased suicide rate. Is this so for all of them? (Refer to paper by Baldwin—this volume—for full discussion of this question.)

*Professor Deakin*

There is evidence that symptoms of anxiety (it is not clear whether it is actually anticipatory anxiety or panic attacks) increase early on in treatment with many 5HT reuptake blockers. I believe this happens with fluvoxamine and fluoxetine, so that component of depressive symptomatology increases. There is very little objective evidence that signs of depression—depressed mood, suicide and suicidal ideation—increase early on in treatment with 5HT reuptake blockers. Consider the Delgado study involving a plasma tryptophan lowering drink. Patients only relapse after getting better on antidepressant drugs. If the tryptophan lowering agent is given while patients are depressed, before treatment, there is no exacerbation of depression. It might be that the 5HT system is already inactive, so if dropped any further it makes no difference.

*Audience*

Could this explain the delay in onset of effectiveness?

*Dr Montgomery*

In fact there is increasing evidence that the drugs do work at 1 to 2 weeks. It is not a very large effect, but there are already large studies showing a significant difference early on with the 5HT uptake inhibitors and also with imipramine.

*Professor Deakin*

Delay of onset is a bit of a myth. It is quite a digital thing sometimes. People suddenly get better over a few days, but if you add all the patients together you see a graph of improvement which does not reflect how people actually improve on an individual basis.

*Dr McCaskin*

There is a spectrum of 5HT and catecholamine uptake blockers with respect to blocking potency, but I am not aware of any evidence linking any other action with efficacy in depression.

*Professor Deakin*

I have only been able to present a fraction of an extremely complex system today. In addition there is the role of catecholamines in normal behaviour and how that goes wrong in depression; there is a great deal of evidence that dopamine and nor-adrenaline are involved in reward mechanisms in the brain, in how we learn actions which produce a favourable outcome. What mediates pleasure? Depression involves breakdown of hedonic mechanisms leading to the syndrome described in DSM III. The loss of interest in pleasurable activities associated with depression perhaps results from catecholamine reward systems which have been disrupted by circumstance or by biology. I think that it is the catecholaminergic effects of reuptake blockers and other antidepressants which reverse antedonism?

*Audience*

You talked about the 5HT neurones and their complete isolation from other neurones. Obviously normal bodies function as a single unit, but there is interaction between all the systems and there are roles for modulators. Can we take one system and concentrate on that system in isolation?

*Professor Deakin*

As I indicated, there are certain interactions with catecholamine systems. The dorsal raphe system seems to interact particularly with dopaminergic mechanisms. Certainly the dorsal raphe nucleus interconnects with such structures as the basal ganglia, and amygdala, whereas the median raphe nucleus innervates structures which are nor-adrenergic. There is much evidence that the indolamines and the relevant catecholamines oppose each other in those terminal areas, and I have evidence that hypersecretion of stress hormones interacts with this system and undermines 5HT1A functioning. By stress hormones I mean cortico-steroids of the type released in response to psycho-social stress. I do not think that dexamethasone suppression has anything to do with endogenous depression, but it is connected with depression of psychosocial origin. Then of course there are co-transmitters

in this system; there is a lot of cholecystokinin in this area and this is thought to be important in the aetiology of panic and anxiety disorders. I do not believe that it is just 5HT acting as an isolated system to cause depression.

*Audience*

Is it too simple to say depression is excess 5HT? How might 5HT1A agonists like buspirone work in this system?

*Professor Deakin*

It is interesting that buspirone stimulates 5HT1A receptors. Some of those receptors are auto receptors, particularly in the dorsal raphe nucleus, and buspirone is a very effective way of switching off this system by stimulating those auto receptors. The dorsal raphe system is fooled into thinking that there is too much 5HT around, and stops firing. I think that this mediates a path, so inhibition of DRN firing causes the anxiolytic effect by blocking this anticipatory anxiety mechanism. It seems fairly clear to me from the clinical trial evidence that the 5HT1A antagonists are not only anxiolytic but are also antidepressants. This may be a consequence of post-synaptic actions in hippocampal and other areas.