Title: BRIDGING THE GAP BETWEEN PSYCHOPHARMACOLOGY AND CLINICAL SYMPTOMS

Author: D. Healy

Address: North Wales Department of Psychological Medicine

University of Wales College of Medecine

Bangor LL57 2PW

Wales

UK

Tel. No.: To be inserted

Fax No. To be inserted

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Abstract

The monoamine hypothesis of depression postulates that depression is a biochemical disorder which arises because of a dysfunction in the monoamine systems in the brain. However, experimental evidence has not provided unequivocal support for this hypothesis. Efforts to identify patients with 'serotoninergic' or 'noradrenergic' depression and to boost their therapeutic responses by administering the appropriate selective agents have not been successful to date. It is now clear that depression is not due to a malfunction of only one neurotransmitter system. Hence, antidepressants which act on more than neurotransmitter systems are likely to have a wider spectrum of activity than agents which only affect one system.

Introduction

The monoamine hypothesis of depression postulates that depression is a biochemical disorder which arises because of a dysfunction in one of the monoamine systems in the brain (1, 2). According to this theory, antidepressants act upon a specific system to directly correct the lesion: for example, selective serotonin reuptake inhibitors (SSRIs) are assumed to remedy a defect in the serotonergic (5-HT) system which results in the development of depression. However, experimental evidence has not provided unequivocal support for this hypothesis. This paper will review current thinking on the likely mechanisms by which antidepressants improve depressive symptoms.

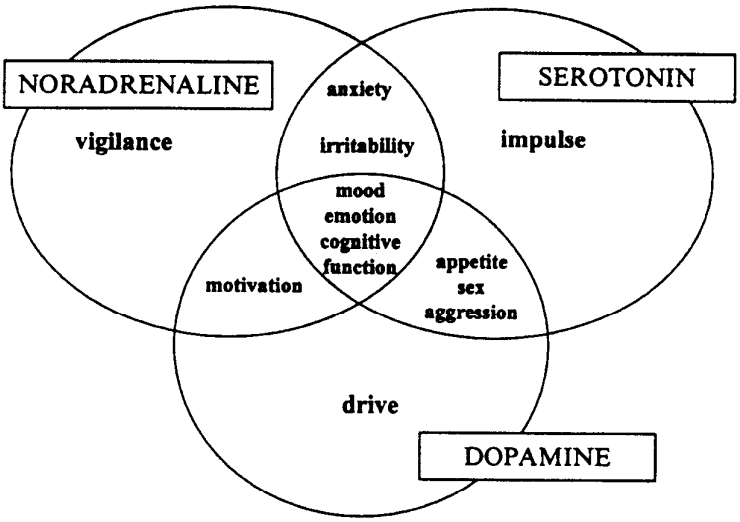
Role of monamine systems in depression

Traditionally, it has been suggested that the noradrenergic, dopaminergic and serotonergic systems are functionally different (3-6). It has been postulated that noradrenaline (NA) has a major impact on vigilance; 5-HT on impulse control and dopamine (DA) on the regulation of drive. Clinically significant consequences of stimulating 5-HT2 receptors include agitation, akathisia, anxiety, panic attacks, insomnia and sexual dysfunction (2). Administration of a SSRI (paroxetine) to normal volunteers resulted in a decrease in the focal indices of hostility: the psychometric assaultiveness and the negative affect were reduced relative to placebo (6). However, SSRI administration did not significantly alter the positive affect which indicates that the antidepressant was not acting as a sedative. In addition, it enhanced behavioural indices of social affiliation in a co-operative task. Changes in behaviour were significantly correlated with the plasma levels of paroxetine, suggesting that central

serotonergic function may modulate certain dimensions of personality in non-depressed individuals.

Certain functions are assumed to be influenced by two or three of the monoamine systems: anxiety and irritability is believed to be affected by both the 5-HT and NA systems while mood, emotion and cognitive function are influenced by all three systems. Appetite, sexual function and aggression are all thought to be affected by both the 5-HT and DA systems while motivation is influenced by the NA and DA systems.

Insert Figure 1 from Healy and McMonagle paper if copyright allows



If this model of monamine functioning is correct, drugs which act on the serotonergic system should reduce irritability, i.e. function as an anxiolytic. According to this schema, the mechanism by which the anxiety is reduced will differ from that by which benzodiazepines exert their anxiolytic effects. Benzodiazepines act by inhibiting the feedback loop between muscular tension and mental state. By contrast,

SSRIs inhibit the reuptake of 5-HT by serotonin neurons, which leads to the down regulation of the 5-HT1A autoreceptors and, eventually, a reduced inhibition of the impulse flow in the neuron.

'Serotonergic' and 'noradrenergic' depression – a redundant concept?

Over the past two decades, the concept that depressions could be classified as 'serotonergic' or 'noradrenergic' stimulated considerable research and discussion (1, 7-12). The hope was that, if the precise biochemical deficit could be identified for each patient with depression, therapy with a drug which selectively targeted the malfunctioning monoamine system would be exquisitely sensitive and successful (1). Levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) and other catecholamine metabolites were measured in samples of cerebrospinal fluid (CSF) from patients in order to identify whether they had 'noradrenergic' depression. Similarly, evidence of reduced 5-HT turnover, in the form of reduced CSF levels of 5-HIAA, was sought in an attempt to find patients with 'serotonergic' depression who would benefit from therapy with a SSRI.

However, to date, efforts to identify such patients or to boost therapeutic responses by treating patients with low levels of 5-HT or NA with the appropriate agents have not been successful (7, 9, 12, 13). For example, Montgomery and colleagues compared the effects of maprotiline (a NA uptake inhibitor) with those of zimelidine (a SSRI) in double blind, cross over study of patients with moderate to severe depression (7). CSF levels of MHPG and 5-HIAA were measured prior to the initiation of active therapy. No significant difference in overall response was found between the two treatment groups. Pre-treatment CSF levels of MHPG and 5-HIAA failed to predict

responses to the selective antidepressants. In addition, patients who did not derive benefit from one of the agents also failed to respond to the other antidepressant. Another double blind study, comparing the effects of lofepramine (a NA-specific reuptake inhibitor) and of fluoxetine (a SSRI) in patients with major depressive disorder, found no evidence to substantiate the existence of 'serotonergic' and 'noradrenergic' depressions (9). The data suggested that, although lofepramine was effective in patients with anxiety symptoms, it was less likely to result in a treatment response in patients with motor and energy deficits – the very patients who should have benefited from a 'NA-specific' agent, according to the 'serotonergic/noradrenergic concept of depression'. In truth, the clinical profiles of the affective disorders have never resembled the inborn error of metabolism disorders which this model suggests. It therefore appears that the concept of 'serotonergic' and 'noradrenergic' depressions should be consigned to the 'formerly useful but not proven' category.

A more useful approach may to consider depression as arising from perturbations of more than one neurotransmitter system. Homeostatic mechanisms may be triggered by the actions of an antidepressant in such a way that resolution of the condition can then occur via a myriad of pathways. Clinical data from studies with agents which act on more than one monoamine system, such as milnacipran which selectively inhibits both serotonin and noradrenaline reuptake, suggest that such multiple effects are very advantageous in the treatment of patients with severe depression (12, 14, 15). Drugs which act on the noradrenergic system, as well as on the serotonergic system, appear to increase drive and vigilance to a greater extent than the SSRIs and this may be

particularly beneficial for certain types of depression, e.g. severe depression in which psychomotor retardation is pronounced (12, 13).

It should not be assumed, however, that agents which act on the noradrenergic system are only useful in cases of severe depression: patients with mild to moderate depression who complain of 'lack of energy' or 'constant tiredness' may benefit from the more 'stimulating' actions of such agents, e.g. milnacipran or reboxetine (13). In addition, although SSRIs are noted for their anti-anxiety effects, milnacipran has been shown to reduce anxiety symptoms in patients to a greater extent than SSRIs and to a similar degree as the TCAs (16).

Visualising depression as a maze, which can be escaped from via multiple routes and not just by re-tracing the path by which one entered, provides us with a useful image when considering therapeutic options. Very few patients present with clear cut symptoms of one sub-type of depression or another. Thus, in most cases, we cannot 're-trace' the path by which they became depressed and remedy the precise biochemical lesion which triggered their depression. Prescribing an antidepressant which acts on more than one neurotransmitter system may provide multiple 'escape' routes which restores the patient to health, even if we are not entirely certain which component has been the most useful in achieving this outcome.

Symptoms versus syndromes

When one examines the list of symptoms which, according to the DSM-III-R, lead to a diagnosis of major depression, they bear a striking similarity to those which result in a diagnosis of dysthymic disorder (5, 17). Does this mean that our definitions of

depressive syndromes are incorrect or, as I believe, that specific neurochemical deficits lead to particular symptoms which occur in a range of syndromes? It is likely that a given biological variable, e.g. a 5-HT deficit, relates to a component of a disorder, i.e. a specific psychological dysfunction such as lack of impulse control, rather than being responsible for the total disorder (5). The data which supports this has been comprehensively reviewed by van Praag (5).

The effects of a deficit in 5-HT on behaviour are well characterised: heightened anxiety and dysregulated aggression are observed in both depressed and non-depressed individuals. Several observations support the concept that a 5-HT disturbance is associated with heightened anxiety. Firstly, SSRIs have been shown to have anxiolytic effects in both humans and animals (18). Secondly, a challenge of M-chlorophenylpiperazine (a 5-HT1 and 5-HT2 receptor agonist) induced anxiety in patients with panic disorder but not in those with major depression or in normal controls (5). Thirdly, a negative correlation has been observed between anxiety ratings and CSF levels of 5-hydroxyindoleacetic acid (HIAA) in patients with depression. Reduced CSF levels of HIAA have also been detected in depressed individuals exhibiting autoaggression; non-depressed suicide attempters; non-psychotic and psychotic persons; and individuals with uncontrolled outward directed aggression (5). Although the outward manifestation of the lack of impulse control is similar in all of these individuals, it does not mean that they are all experiencing the same underlying syndrome.

Similar findings have been reported in relation to DA dysfunction (5). Patients with Parkinson's disease are prone to depression in which motor retardation is a common

feature. This appears to be related to the disturbances in DA metabolism which occur in Parkinson's disease. CSF levels of homovanillic acid, a major DA metabolite, have been shown to be reduced in patients with both Parkinson's disease and depression as well as in patients with depression who exhibited symptoms of motor retardation. Levels of homovanillic acid in patients with non-motor retarded depression were similar to those in normal controls. Administering l-DOPA, which stimulates DA production, improved the motor condition of patients with psychomotor retarded depression but had no effect on their symptoms of depressed mood and anhedonia.

In the light of these experimental data and clinical observations, there appears to be a dimensional involvement of the neurotransmitter systems in the development of depression (5). Hence, deficits in individual systems can lead to symptoms which are common to a number of depressive and non-depressive syndromes.

Conclusions

Based on the evidence reviewed in this paper, it is clear that depression is not due to a malfunction of only one neurotransmitter system. Given the overlap in functions between the different monoamine systems and the complex homeostatic mechanisms which act within the brain, it is evident that antidepressants which have an effect on more than neurotransmitter systems are likely to have a wider spectrum of activity than agents which only affect one system (12, 13). Since patients rarely present with depressive symptoms which are clearly due to only one sub-type of depression, this simplifies the decision making process for the clinician as it is not necessary to evaluate the precise type of depression before choosing an antidepressant. Newer antidepressants such as milnacipran, which selectively inhibits both serotonin and

noradrenaline reuptake and is effective in patients with moderate to severe depression, provide therapeutic benefit for a wide range of patients and may off advantages over selective agents.

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