To: "David Healy", healy_hergest
CC: "Anne Sertillanges", INTERNET:Anne.Sertillanges@pierre-fabre.com
From: "Mike Briley", INTERNET:brileym@pierre-fabre.imaginet.fr
Date: 5/3/99, 12:48 AM
Re: ECNP satellite symposium - manuscript for supplement.

Dear David,

I am delighted that you are able to participate in our satellite symposium on milnacipran at the London ECNP meeting in September. We are planning to produce a supplement to this symposium which will be published in the International Journal of Psychiatry in Clinical Practice (Ed S. Kasper and D. Baldwin) with an article by each of the speakers.
In order to reduced your workload to a minimum we have had our ghostwriters produce a first draft based on your published work. I enclose it here as an attachement (it is in Word 6 format and ASCII format). We would be grateful if you could read through it and make whatever corrections you consider appropriate. You can either edit directly the file or annotate the manuscript and fax it to me at the following number (33 563 725 066). If you have any questions please don't hesistate to contact me by E-mail or by phone (33 563 714 567).

With best regards

Mike Briley

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To: "David Healy" <healy_hergest@compuserve.com>
Cc: "Anne Sertillanges" <Anne.Sertillanges@pierre-fabre.com>
Subject: ECNP satellite symposium - manuscript for supplement.
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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

Running title: Psychopharmacology and clinical symptoms

Key words: psychopharmacology, antidepressant, depression, milnacipran, depressive subtypes, serotonin, noradrenaline, dopamine

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

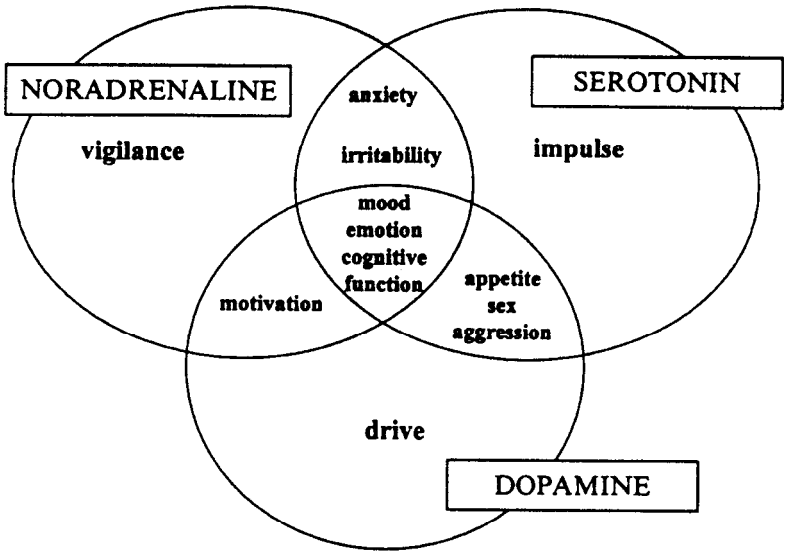
The monoamine hypothesis of depression postulates that depression is a biochemical disorder which arises because of a dysfunction in one of the monoamine systems in the brain (1, 2). According to this theory, antidepressants act upon a specific system to directly correct the lesion: for example, selective 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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To: "David Healy", healy_hergest
From: "Mike Briley", INTERNET:brileym@pierre-fabre.imaginet.fr
Date: 5/6/99, 5:04 AM
Re: Re: ECNP satellite symposium - manuscript for supplement.

David,
Thanks for your E-mail and the offer to improve the M/S. Please improve it all you can.

I confirm that milnacipran inhibits only NA and 5-HT reuptake. It has no effect on DA reuptake and no effect on any receptors or enzymes. It doesn't even down-regulate beta receptors.

I'll have to have a look to see if we have data similar to Organon.

We have slides on the basic description of milnacipran and we can make up whatever else you need. We'll probably use a powerpoint presentation from a portable PC to keep things flexible.

I'm not yet clear on my traverl plans but it is unlikely that I'll be attending any meetings before London. If necessary I could come over to see you however. We see how things go.

Many thanks

Mike
-----Message d'origine-----
De : David Healy <healy_hergest@compuserve.com>
À : Mike Briley <brileym@pierre-fabre.imaginet.fr>
Date : jeudi 6 mai 1999 13:28
Objet : ECNP satellite symposium - manuscript for supplement.

>Mike
>
>There's some excellent material in the draft you sent.
>But I think I can potentially improve on it.
>I'll be going to APA next week and on the plane might try and get something
>together.
>
>As regards scientific material, Organon produced a beautiful slide out of
>their mirtazapine-fluoxetine study
>showing that the better HAM-D responses on mirtazapine
>actually stemmed from a greater number of responders
>rather than from a similar number of responders responding to a greater
>extent.
>It features in their recent posters - a histogram of responders at Week
>0,1,4,6 or something like that
>
>Do you have anything similar?
>
>Also can you confirm milnacipran just inhibits NA and 5HT reuptake
>no receptor blocking and no dopamine uptake inhibition.
>I assume you guys have slides showing the active mechanisms - with lack of
>action on other systems etc.
>I'll probably need one or two of these.

>
>If you're at APA or BAP or WPA perhaps we should get together
>and I'll fill you in on where I thought I might take things
>
>David
>

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To: "David Healy" <healy_hergest@compuserve.com>
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To: "David Healy", healy_hergest
CC: "Charles Mackinnon", INTERNET:charles.mackinnon@cmc.co.uk
CC: "Anne Sertillanges", INTERNET:Anne.Sertillanges@pierre-fabre.com
CC: "Glenn Stanley", INTERNET:glenn.stanley@pierre-fabre.com
From: "Mike Briley", INTERNET:brileym@pierre-fabre.imaginet.fr
Date: 5/31/99, 1:39 AM
Re: Re: ECNP satellite symposium - manuscript for supplement.

David,

Have you had a chance to look at the draft M/S? Sorry to push you but the
deadline is June 23rd "on my desk in electronic form".

CMC (Complete Medical Communications) are helping us with the positioning of
the compound and we have contracted with them for the management of the
satellite symposium logistics. This includes slide preparation. I have
copied Charles Mackinnon in on this message so that he should be contacting
you very shortly concernig your presentation.

I look forward to hearing from you

Mike

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From: "Mike Briley" <brileym@pierre-fabre.imaginet.fr>
To: "David Healy" <healy_hergest@compuserve.com>
Cc: "Glenn Stanley" <glenn.stanley@pierre-fabre.com>,
        "Anne Sertillanges" <Anne.Sertillanges@pierre-fabre.com>,
        "Charles Mackinnon" <charles.mackinnon@cmc.co.uk>
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To: "David Healy", healy_hergest
CC: "Anne Sertillanges", INTERNET:Anne.Sertillanges@pierre-fabre.com
From: "Mike Briley", INTERNET:brileym@pierre-fabre.imaginet.fr
Date: 5/3/99, 11:04 PM
Re: Re: ECNP satellite symposium - manuscript for supplement.

David,
Lucky you for the bank Holiday - this year all our holidays in May fall on Saturday or Sunday (with no compensation)!!.

Yes please use me for any scientific matters concerning the ECNP. For logistics or financial issues you should deal with Anne Sertillanges.

I look forward to hearing from you.

Mike
-----Message d'origine-----
De : David Healy <healy_hergest@compuserve.com>
À : Mike Briley <brileym@pierre-fabre.imaginet.fr>
Date : lundi 3 mai 1999 23:30
Objet : ECNP satellite symposium - manuscript for supplement.

>Mike
>
>We've just had a bank holiday weekend here and i took my brain out of gear.
>Will print this off tomorrow and get back to you later in the week.
>
>There are a few bits of data, I'd hope to get to include in the talk
>Are you the best person to approach for this?
>
>David
>

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To: "David Healy" <healy_hergest@compuserve.com>
Cc: "Anne Sertillanges" <Anne.Sertillanges@pierre-fabre.com>
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To: "David Healy", healy_hergest
CC: "Anne Sertillanges", INTERNET:Anne.Sertillanges@pierre-fabre.com
CC: "Glenn Stanley", INTERNET:glenn.stanley@pierre-fabre.com
From: "Mike Briley", INTERNET:brileym@pierre-fabre.imaginet.fr
Date: 6/10/99, 2:32 AM
Re: Re: article

I've only had time for a quick read of your article but I like what I read.
I think, however, we need to bring out a bit more the relationship between symptoms (or even patients profiles) and neurotransmitter dysfunction.
I am taking a plane in a few minutes (it does happen - a one day trip to sunny Manchester!!!) and I'll reread it in detail and come back with more details and comments. I'll also send you milnacipran material that can be included.

Speak to you soon

Mike
-----Message d'origine-----
De : David Healy <healy_hergest@compuserve.com>
À : Mike Briley <brileym@pierre-fabre.imaginet.fr>
Date : lundi 7 juin 1999 23:16
Objet : article

Mike

Attached, hopefully in readable format
is a copy of
Antidepressant Psychopharmacotherapy: At the Crossroads.
It covers very similar ground to the draft piece sent to me
making similar points
but doing something quite different to stuff i've done for reboxetine
trying to avail of opportunities milnacipran offers.

Will be interested in your comments.
Am open to any additions you think could be added
especially where there is milnacipran data that can be added in.

File is called mikebriley
another one in powerpoint called mikebriley is also coming.
A second email will explain what that's all about

David

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From: "Mike Briley" <brileym@pierre-fabre.imaginet.fr>
To: "David Healy" <healy_hergest@compuserve.com>
Cc: "Glenn Stanley" <glenn.stanley@pierre-fabre.com>,
        "Anne Sertillanges" <Anne.Sertillanges@pierre-fabre.com>
Subject: Re: article
Date: Thu, 10 Jun 1999 11:29:52 +0200
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X-Priority: 3
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X-Mailer: Microsoft Outlook Express 4.72.3155.0
X-MimeOLE: Produced By Microsoft MimeOLE V4.72.3155.0

To: "David Healy", healy_hergest
CC: "Anne Sertillanges", INTERNET:Anne.Sertillanges@pierre-fabre.com
From: "Mike Briley", INTERNET:brileym@pierre-fabre.imaginet.fr
Date: 7/9/99, 7:35 AM
Re: And one became two...

Dear David,

Re-reading you m/s, Antidepressant psychopharmacology at the cross-roads, I felt that it was a pity to try to modify it since it reads so well. On the other hand we need to bring across one or two points that are not accentuated in your M/S. We have therefore decided to publish "crossroads" as it is in the supplement (I'm E-mailing it to the publishers today) but also to publish the other manuscript. Siegried Kasper has kindly agreed to author this one. We would however like your talk to be more on the first manuscript "Bridging the gap....." in order to bring out the main commerically important points. CMC, Anne or myself will be in contact with you concerning the slides in the weeks to come.
I hope this arrangement is acceptable.

best regards

Mike Briley
Scientific Director
Worldwide Operations
Pierre Fabre Médicaments
Parc Industriel de la Chartreuse
81100 Castres, France
tel. (33) 563714567
fax (33) 563725066
brileym@pierre-fabre.imaginet.fr
mike.briley@pierre-fabre.com

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Sender: brileym@pierre-fabre.imaginet.fr
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by hpamgaac.compuserve.com (8.8.8/8.8.8/HP-1.5) with ESMTP id KAA24922
for <healy_hergest@compuserve.com>; Fri, 9 Jul 1999 10:34:56 -0400 (EDT)
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From: "Mike Briley" <brileym@pierre-fabre.imaginet.fr>
To: "David Healy" <healy_hergest@compuserve.com>
Cc: "Anne Sertillanges" <Anne.Sertillanges@pierre-fabre.com>
Subject: And one became two...
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