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Pharmacology, Biochemistry and Behavior 71 (2002) 555–568

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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The medical benefit of 5-HT research

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Received 8 October 2001; received in revised form 25 October 2001; accepted 26 October 2001

Abstract

5-HT research is now more than 50 years old, and it has generated a wealth of therapeutic agents, some of which have had a major impact on disease management. The 5-HT reuptake inhibitors (SSRIs) are among the most widely prescribed drugs for treating depression and a variety of other disorders including anxiety, social phobia and premenstrual dysphoria (PMD). The other major success stories of 5-HT research are the discovery of 5-HT1B/D receptor agonists for treating migraine and 5-HT3 receptor antagonists for chemotherapy and radiation-induced emesis. The role of 5-HT in the mechanism of action of antipsychotic agents remains a topic of intense research, which promises better treatments for schizophrenia in the future. Compounds interacting with 5-HT1F, 5-HT2C, 5-HT6 and 5-HT7 receptors are currently under investigation and may prove to have important therapeutic applications in the future. © 2002 Published by Elsevier Science Inc.

Keywords: 5-HT reuptake inhibitors; 5-HT receptor antagonists; 5-HT receptor agonists; Therapeutic applications

1. Introduction

Since its discovery over 50 years ago, 5-HT has been the topic of intense research activity, which has led to the discovery of a range of potential drug targets: the receptors, the metabolising and synthetic enzymes, the uptake sites. Some have been exploited successfully and drugs are available and some have delivered compounds currently under preclinical or clinical evaluation. For others, the scientific evidence shows that they are unlikely to be of value as drug targets, and several others remain untried. The disorders treated by drugs modulating 5-HT function cover a wide range, from chemotherapy-induced emesis to depression.

The early research on 5-HT was focused on its functions in peripheral tissues (Gaddum and Hameed, 1954), and it was not until much later that its function as a neurotransmitter in the brain was demonstrated (Dahlström and Fuxe, 1964). This was a major turning point in the discovery of therapeutic agents that modify 5-HT function. There are some very important peripheral therapeutic applications of 5-HT research, but it is a fact that a large proportion of the research to exploit 5-HT pharmacology for therapeutic benefit has focused on its CNS functions. This is illustrated by a survey of the best-selling CNS drugs worldwide in 2000—the top five all modulate 5-HT function (Table 1).

5-HT has been shown to have a multitude of different physiological actions, and this is not surprising given the nature of the 5-HT neuronal system and the variety of different 5-HT receptors (Barnes and Sharp, 1999). The 5-HT neurones originate in the hindbrain in a relatively circumscribed area, but they send projections to most parts of the brain (Azmitia and Whitaker-Azmitia, 1991). Couple that with the multiple ways that 5-HT can exert its action through many different receptors and it becomes clear why the pharmacology of 5-HT in the CNS is so complex. Furthermore, 5-HT is known to interact with other neurotransmitter systems, and the literature is particularly rich in publications in the interactions of 5-HT systems with dopaminergic systems (Lieberman et al., 1998).

In this short review, we have looked at the disorders that benefit from 5-HT research currently and those that may benefit in the future. As the subject is so large, we have not been able to delve into the detail. Where possible,

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0091-3057/02/$ – see front matter © 2002 Published by Elsevier Science Inc.
PII: S0091-3057(01)00745-6

Table 1
Worldwide leading CNS products in 2000

Rank	Product	Generic name	Mechanism of action	Therapeutic class	2000 sales (mi USD)
1	Prozac	Fluoxetine	SSRI	Antidepressant	2875
2	Seroxat	Paroxetine	SSRI	Antidepressant	2416
3	Zyprexa	Olanzapine	DA2/5-HT2/other	Antipsychotic	2391
4	Zoloft	Sertraline	SSRI	Antidepressant	2248
5	Risperidal	Risperidone	DA2/5-HT2/other	Antipsychotic	1707

Source IMS: sales figures based on prescription sales.

we have quoted reviews on the topics so that the interested reader can proceed with further reading.

2. Depression

Drugs derived from the monoamine theory of depression have dominated the treatment of depression (Schildkraut, 1965). Indeed, the monoamine reuptake inhibitors and the monoamine oxidase inhibitors were shown to have antidepressant activity by chance, and the discoveries of their modes of action were instrumental in developing the monoamine theory.

In the days when the monoamine theory of depression was evolving, the focus was more on noradrenaline than 5-HT or dopamine. The theory developed from observations that reserpine depleted monoamines and caused depression, whereas the monoamine oxidase inhibitors and monoamine reuptake inhibitors enhanced monoamine function and thereby relieved depression. Unravelling which of the three monoamines was most important in this context was the subject of extensive research. It became clear that the compounds with the greatest selectivity for noradrenaline uptake, such as desmethylimipramine, had similar antidepressant activity. Against this background, there was limited optimism that a compound selective for 5-HT reuptake would be a major advance. The imipramine analogue clomipramine was reasonably selective for 5-HT reuptake but did not show any advantages as an antidepressant (but see Section 6). Subsequently, nontricyclic, highly selective 5-HT reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine and sertraline were discovered.

Although intellectually, the discovery of the selective SSRIs represented an incremental step in the development of antidepressant drugs, their clinical impact was much greater than anticipated, and they are now the drugs of choice in treating depression. Their efficacy is similar to that achieved by traditional tricyclic agents, but they have far superior side effect profiles and, in particular, they do not have the potentially dangerous cardiac liability of the tricyclics. They are among the most widely prescribed class of therapeutic agents and represent one of the biggest success stories of 5-HT research (Goodnick and Goldstein, 1998).

Like the tricyclic antidepressants, the SSRIs have a delayed onset of action of 2–6 weeks before the therapeutic effect becomes established. There is some evidence that this delay can be shortened by giving high doses in an aggressive, rapidly escalating dose regimen, but the relatively rapid onset is achieved at the expense of adverse effects (Stahl et al. 2001).

To discover an antidepressant that has an effect within days rather than weeks, researchers have been trying for decades to understand the reasons for the delay in onset of antidepressant action. The focus has been mainly on SSRIs. The most convincing theory is that inhibition of 5-HT reuptake initially causes activation of the presynaptic 5-HT1A receptors on the cell bodies in the dorsal and median raphe. This inhibits the firing of 5-HT neurones, so reducing rather than increasing the release of 5-HT at the terminals. (For an opposing view, see Kalsner, 2000.) The desired effect is an increased activation of the postsynaptic 5-HT receptors in the forebrain, but this is not achieved until the raphe 5-HT1A receptors become desensitized. The obvious conclusion to draw from this is that selective blockade of the presynaptic raphe 5-HT1A receptors, ideally with no effect on the postsynaptic forebrain receptors, should short circuit the need to achieve desensitization and thereby hasten the onset of antidepressant action of the SSRIs (Blier, 2001).

The problem with putting this into practice clinically is that there are no selective 5-HT1A receptor antagonists available for clinical use. However, Artigas et al. pioneered the use of pindolol as a 5-HT1A receptor antagonist for proof of this concept. Pindolol has a high affinity for beta-adrenoreceptors so its dose in depression trials has to be limited to avoid cardiovascular effects: 7.5 mg/day has been used in nearly all of the studies, considerably less than the doses used for treating hypertension (up to 45 mg). One feature of pindolol that may work in its favour is that it appears to have a selective action on presynaptic over postsynaptic 5-HT1A receptors (Romero et al., 1996).

The results of the initial open trials were very encouraging (Artigas et al., 1994). When double blind, placebo-controlled studies were undertaken, the results were less clear-cut, and some trials failed to show any advantage of the pindolol–SSRI combination (Artigas et al., 2001). However, the evidence from at least half of the trials favours the combination as providing a faster onset of action. Fewer cases showed an improved response rate, but there was no benefit in treating resistant depression (Perez et al., 2001).

It has been suggested that the limited improvements achieved with pindolol relate to the dose limitations and that higher doses would give greater benefit. With this in

mind, receptor occupancy studies have been undertaken using positron emission tomography in human volunteers with the selective PET tracer [11C]-WAY 100,635. A dose of 7.5 mg daily of pindolol achieved around 40% receptor occupancy of 5-HT1A receptors in the raphe region but only 20% receptor occupancy in a postsynaptic region such as the hippocampus. Furthermore, the intersubject variability was high (Martinez et al., 2001). It would seem unlikely that the dose of pindolol used in the interaction studies with SSRIs was high enough to truly test the hypothesis. The same conclusion was drawn from a study of the pindolol–paroxetine combination in guinea pigs using microdialysis to measure pindolol concentrations in brain (Cremers et al., 2001). The issue may therefore not be decided until a better 5-HT1A receptor antagonist becomes available for clinical use.

There is, however, an additional element to consider: The 5-HT1B terminal autoreceptors are probably also involved in the adaptive response to SSRIs, and it may require their desensitization to achieve the antidepressant action. If so, antagonists of the terminal 5-HT1B autoreceptors may be rapid-onset antidepressants. This mechanism does not rely on desensitization of somatodendritic 5-HT1A receptors and therefore bypasses the control of firing rate at the cell bodies (Roberts et al., 1997). Unfortunately, no selective 5-HT1B receptor antagonists have reached clinical trials to date, although tool compounds such as SB-224289 are available (Selkirk et al., 1998). It has been suggested that such compounds might be used in combination with SSRIs, or the properties combined into one compound for a rapid-onset antidepressant (Matzen et al., 2000). On theoretical grounds, if the somatodendritic 5-HT1A autoreceptor inhibition is important, the 5-HT1B receptor antagonist alone might have a more rapid onset than the combination. Reuptake inhibition would invoke somatodendritic autoinhibition, which would, in turn, reduce 5-HT release at the terminals and nullify the action of the 5-HT1B receptor antagonist.

It should be noted that the control of 5-HT neuronal function is undoubtedly more complex than the picture painted above. For instance, there are 5-HT1B and 5-HT1D receptors in the raphe region, and they appear to be involved in the control of 5-HT function. This area has been reviewed recently (Stamford et al., 2000).

The old question of "Why not simply use a postsynaptic receptor agonist instead of enhancing the action of 5-HT?" has not been answered satisfactorily. The problem is that the identity of the key postsynaptic 5-HT receptor(s) is not known with certainty, although the 5-HT1A receptor has been proposed (Blier and de Montigny, 1994). A selective postsynaptic 5-HT1A receptor agonist has not yet been discovered, and the history of 5-HT1A receptor research would suggest that it will be a very difficult objective: It has been easier to find agonists apparently selective at presynaptic receptors. This probably reflects the fact that the receptor reserve is much higher in the presynaptic regions, so partial agonists appear to be antagonists at the postsynaptic receptors and agonists at the presynaptic receptors (Meller et al., 1990; Yocca et al., 1992). A selective, full 5-HT1A receptor agonist will activate postsynaptic receptors, but it will also shut down the firing of 5-HT neurones. What impact this would have is difficult to predict, but it would obviously prevent activation of other postsynaptic 5-HT receptors.

Activation of a single 5-HT receptor type may not be the answer; reuptake inhibitors indirectly cause activation of all postsynaptic receptors, and it may be that this is what is needed to achieve an antidepressant action. There is also a current belief that activation of both 5-HT and noradrenaline receptors may be required, in effect reverting back to the original profile of the tricyclic antidepressants but without their limiting side effects. Venlafaxine is the archetype of this new generation of antidepressants referred to as serotonin–noradrenaline reuptake inhibitors (SNRIs). It has been reported that it can achieve a statistically significant antidepressant effect in a week with high-dose treatment (Rudolph et al., 1998).

In view of the strong link between 5-HT and mood, there may be new opportunities to exploit 5-HT pharmacology to treat depression in the future. For instance, it has been suggested that selective 5-HT2C receptor antagonists could have antidepressant properties by virtue of their ability to enhance mesolimbic dopaminergic function (Di Matteo et al., 1999).

3. Schizophrenia

This is an area of 5-HT research where there is still much to be learned about the role of 5-HT in the pathophysiology of schizophrenia and the action of antischizophrenic drugs. The story began when it was shown that the indole-containing hallucinogenic agents such as LSD interacted with 5-HT systems, although at the time it was believed to be an antagonist at 5-HT receptors (Woolley and Shaw, 1954). The general consensus now is that LSD and other hallucinogens like 2,5-dimethoxy-4-methylamphetamine (DOM) and 2,5-dimethoxy-4-iodoamphetamine (DOI) induce hallucinations by activating 5-HT2 receptors. Furthermore, experimental evidence in animals suggests that it is the 5-HT2A receptor rather than the 5-HT2C receptor that is involved: discriminative stimulus properties of DOM and DOI are blocked by selective 5-HT2A receptor antagonists but not 5-HT2C receptor antagonists (Schreiber et al., 1994; Winter et al., 1999). LSD and similar hallucinogens do not, in reality, induce a good representation of schizophrenia, particularly as they induce visual hallucinations rather than the auditory hallucinations characteristic of schizophrenia. The syndrome induced by the NMDA antagonist phencyclidine is regarded as a closer mimic of schizophrenia and, furthermore, its effects are inhibited by 5-HT2A receptor antagonists (Millan et al., 1999). The link between seroto-

nergic and glutamatergic systems may be a very important element in the pathophysiology of schizophrenia and is becoming prominent in modern thinking on the topic (Aghajanian and Marek, 2000).

The actions of antipsychotic agents offer a different perspective on the role of 5-HT in schizophrenia. Most antipsychotic agents are dopamine D2 receptor antagonists, but many of them, notably the atypical antipsychotic agents, also block 5-HT receptors, particularly 5-HT2A and 5-HT2C receptors. Interestingly, the ones with the strongest 5-HT receptor blocking activity tend to be the ones with the lowest extrapyramidal side effects (EPS), and there is preclinical evidence indicating that 5-HT2C receptor blockade is responsible for reducing EPS: 5-HT2C receptor antagonists but not 5-HT2A receptor antagonists inhibit haloperidol-induced catalepsy in rats (Reavill et al., 1999). However, the evidence that the 5-HT receptor blocking actions contribute to the antipsychotic effect is lacking. Nevertheless, the atypical antipsychotic agents are now preferred to the traditional agents and represent the most obvious target for designing potent antipsychotic agents with benign side effect profiles. The difficulty lies in understanding the contributions of the different elements of their pharmacology. If we accept that the interactions with 5-HT systems are critical, what are the most important interactions and how can we design better compounds?

Clozapine has been held to be the key to this riddle—it is the most effective agent in chronic schizophrenia, it has a low propensity for EPS and it does not induce tardive dyskinesia with prolonged treatment. Its use is limited by its propensity to induce agranulocytosis, so patients must be monitored closely. It is testimony to our poor understanding of the mechanisms underlying the action of clozapine that a drug with a serious side effect is an essential part of our armamentarium against psychosis.

So what is the secret of clozapine? It has a very wide range of pharmacological actions, and it is not clear which ones contribute to its unique clinical profile. It is a modest dopamine D2 receptor antagonist, but it also acts on several 5-HT receptors: Its highest affinity is for the 5-HT2A receptor but it also acts on 5-HT2C, 5-HT1A, 5-HT3, 5-HT6 and 5-HT7 receptors (Brunello et al., 1995). The observation that clozapine inhibits the psychotic symptoms induced by phencyclidine in normal volunteers suggests that 5-HT2A receptor antagonism may contribute to the antipsychotic properties of clozapine.

A further observation supporting the involvement of 5-HT2A receptors in antipsychotic actions was made by Varty and Higgins (1995), who were studying dizocilpine-induced prepulse inhibition. This is a test that has good face and construct validity as a model of the sensorimotor gating deficit in schizophrenia (for a comprehensive review, see Geyer et al., 2001). Whereas selective dopamine D1 and D2 receptor antagonists did not have any effect, risperidone, a combined D2/5-HT2 receptor antagonist, was effective. To confirm that this was a 5-HT2-mediated effect, the authors demonstrated that ketanserin and metergoline were also effective.

Whether blockade of 5-HT2A receptors alone is adequate for an antipsychotic action is still not clear. There is some evidence that ritanserin, a 5-HT2A/C receptor antagonist has efficacy in schizophrenia, but not all studies are in agreement (Lieberman et al., 1998). The outcome of trials in schizophrenia with M100907, which is a very selective 5-HT2A receptor antagonist, should make this clear. It has already been established that the drug gives high occupancy of 5-HT2A receptors in the brains of schizophrenics when measured with positron emission tomography (Talvik-Lotfi et al., 2000).

There is little doubt that 5-HT and dopaminergic systems have very strong interactions (Lieberman et al., 1998), and when we finally understand the mechanism of action of the atypical antipsychotics, one of the most likely outcomes is that a combined action at both dopamine and 5-HT receptors is required for optimal activity.

While the evidence for the role of 5-HT2 receptors in the mode of action of clozapine is reasonably strong, there is a suggestion that 5-H1A receptors may also be involved (Millan, 2000). There is good evidence that 5-HT1A receptor density is high in the frontal cortices of schizophrenics (Burnet et al., 1997), and the same phenomenon has been observed in the cerebellar vermis (Slater et al., 1998). Whether this is a common feature in schizophrenia or a characteristic of a subpopulation remains to be established. Clozapine is a partial agonist at 5-HT1A receptors (Newman-Tancredi et al., 1998), but other 5-HT1A partial agonists such as buspirone are anxiolytic rather than antipsychotic. Nevertheless, the observation that they inhibit the catalepsy induced in experimental animals by classical neuroleptic agents supports the belief that the 5-HT1A partial agonist property of clozapine contributes to its low EPS (Bantick et al., 2001). Whether full or partial agonism at 5-HT1A receptors is optimal in an antipsychotic agent is not clear and given the complexities around interpreting the impact of different levels of partial agonism of 5-HT1A receptor agonists (see Section 2), unravelling the role of this property in the action of clozapine will remain a considerable challenge.

5-HT3 receptor antagonists were predicted to have antipsychotic activity by experimental models (Costall and Naylor, 1994a), but the clinical experience with these compounds in schizophrenia has been disappointing (Greenshaw and Silverstone, 1997). In an open trial in patients with psychosis in advanced Parkinson's disease, ondansetron had a beneficial effect on the psychosis, particularly the visual hallucinations (Zoldan et al., 1995). The compelling evidence provided by the animal models does provoke thoughts that the therapeutic benefit of these compounds in psychosis has yet to be uncovered, and there may be other populations of psychotic patients that respond to 5-HT3 receptor antagonists. Considering the problems encountered with conventional antipsychotic agents, it would seem worthwhile to invest-

igate the 5-HT3 receptor antagonists further as most of them have benign side effect profiles. Of course, clozapine also possesses 5-HT3 receptor antagonist properties that possibly contribute to its unique therapeutic profile (see above).

The neurodevelopment role of 5-HT may be important in the pathophysiology of schizophrenia. It has a role in promoting appropriate connections between neurones and in the maintenance and remodelling of synapses (Lieberman et al., 1998). The neurodevelopmental theory of schizophrenia is becoming increasingly more compelling (Harrison, 1999). Although the prevailing belief is that prenatal neurodevelopment is disordered, the most common period for the emergence of symptoms is in the third decade of life. Perhaps the key is what happens in adolescence, when there is a rationalization of synapses to establish adult brain function. Dysfunction at this point could result in inappropriate connections and the disordered thinking that is characteristic of schizophrenia. Whether 5-HT is involved in this process is an intriguing topic for further research that could throw more light on the underlying cause of schizophrenia and could possibly lead to the discovery of preventative therapy.

4. Generalized anxiety disorder (GAD)

The most prevalent anxiety disorders are GAD, obsessive–compulsive disorder (OCD), posttraumatic stress disorder (PTSD), social anxiety disorder (SAD), phobias and panic attacks (see relevant sections below). Collectively, these are the most common of mental illnesses and are costing the US as much as depression. However, less than one-third of these people are receiving proper treatment, and 43% of people with anxiety disorders are also depressed and/or substance abusers (National Anxiety Association).

GAD is characterized by periodic anxiety that is not manifested into discrete panic attacks or phobias (Hidalgo and Davidson, 2001). Increased psychomotor tension, autonomic overactivity and hypervigilance are common. According to DSM-III-R criteria, documentation of several symptoms that include elements of motor tension, autonomic hyperactivity, vigilance and scanning are required for diagnosis over a 6-month period. More often than not, the disorder pursues an intermittent course with exacerbations and remissions over several years. However, in contrast to PD, patients with GAD do not present with cardiopulmonary and neurological symptoms. When patients consult with physicians, they present worries about their health, or that of their loved ones, low grade nervousness, insomnia, headaches and gastrointestinal and urinary complaints (Hoehn-Saric and McLeod, 1985).

Benzodiazapines have long been considered first-line therapy for the treatment of GAD, having effects on both psychic and somatic symptoms. However, major problems are associated with chronic use of benzodiazepine-type anxiolytics in the clinic, including the development of tolerance to their anxiolytic effects and a withdrawal anxiogenesis following cessation of chronic drug administration. Recent clinical studies have shown SSRIs and the SNRI venlafaxine (extended release) to be effective in the treatment of patients with GAD, particularly when GAD is associated with comorbid conditions such as depression (Ballenger, 2001; Silverstone and Salinas, 2001). A consensus group recently recommended SSRIs and SNRIs as first-line treatment in GAD in preference to benzodiazepines (Ballenger et al., 2001).

The 5-HT1A receptor partial agonists, notably buspirone, are also effective in the treatment of GAD. Buspirone is not recommended for first-line therapy because there is a belief that it does not treat the comorbid conditions such as depression (Ballenger et al., 2001). However, this may simply reflect the lack of sufficient data available from controlled studies (Apter and Allen, 1999).

Of the various compounds with antagonist properties at the 5-HT2A receptor tested in the clinic, serazepine (CGS-15040A) showed efficacy in a multicentre trial in GAD. Effects appeared primarily related to the psychic components of anxiety (Katz et al., 1993). However, no further clinical data are available on this compound. More recently, researchers at GlaxoSmithKline published on a series of compounds that are selective antagonists at the 5-HT2C receptor. Of these compounds, SB-243213 has been shown to be active in animal models of anxiety following acute and chronic administration (Wood et al., 2001). Additionally, Deramciclane (EGIS 3886), a novel 5-HT2C receptor antagonist, was originated by Egis and is currently in late phase II trials for the treatment of anxiety in Hungary and Finland. In animal models, the compound appeared nontoxic at low doses. It had a high affinity for 5-HT2A and 5-HT2C receptors in dogs. It appeared to have an anxiolytic effect in a variety of tests on animal models, including punished drinking tests, social interaction tests and maze tests in rats and marble burying tests in mice. It does not have a muscle relaxant effect but appears to improve the escape performance of rats in a learned helplessness model, indicating that it may also have potential for the treatment of depression (Pälvimäki et al., 1998).

Preclinical evidence indicated that 5-HT3 receptor antagonists would be potent inhibitors of anxiety with minimal side effects (Jones and Piper, 1994). Unfortunately, expectations were not fulfilled in the clinic (Olivier et al., 2000), although there may still be scope for investigating lower doses, because the animal studies showed that these compounds generated bell-shaped dose–response curves.

Thus, although it is clear that 5-HT drugs have an important place in the treatment of GAD, more research is needed to address issues such as whether SSRIs and SNRIs improve the rate of wellness or remission from GAD and whether prolonged therapy with these compounds for GAD protects against later emergent depression.

5. Social phobia

The high lifetime prevalence of social phobia (about 13%; Kessler et al., 1994) and its debilitating effects on the patient's life make it a much more significant health issue than was appreciated a decade ago. It is characterized by a high level of comorbidity with other disorders such as depression, alcohol abuse, eating disorders and other anxiety disorders (Liebowitz, 1999; Brunello et al., 2000). Consequently, the most successful treatments are those that will treat the social phobia and the comorbid conditions.

The first pharmacotherapeutic agents to be used successfully to treat social phobia were the MAOIs, whereas the tricyclic antidepressants were less effective (Schneier, 2001). Phenelzine in particular became the drug of choice. Trials with the reversible MAOIs have been disappointing (Davidson, 1998) and the need for dietary restrictions with the irreversible MAOIs has limited their usefulness.

In contrast to the tricyclic antidepressants, the SSRIs are effective in treating social phobia and are now recommended as first-line treatment, being much safer drugs than the MAOIs. Furthermore, they are also useful for treating comorbid depression and panic (Lydiard, 1998). SSRIs are also effective in treating agoraphobia, which may coexist with social phobia (Bakker et al., 2000).

As with other phobias, cognitive–behavioural therapy (CBT) has an important place in the treatment of social phobia. Pharmacotherapy can facilitate CBT and may physicians believe that the combination of the two is the optimal therapy (Brunello et al., 2000).

6. Obsessive–compulsive disorder (OCD)

Tricyclic antidepressants were shown to be effective in the treatment of OCD many years ago, but evidence emerged that clomipramine was the most effective of the tricyclics (Goodman, 1999). Its major differentiator from the other tricyclics is that it has greater 5-HT uptake inhibitory action, so it was no surprise when the SSRIs were shown to be effective. There is some evidence that clomipramine may be superior to the SSRIs in treating OCD, but the validity of the meta-analytical studies showing this has been questioned (Cartwright and Hollander, 1998). There is little doubt that the SSRIs are better tolerated than clomipramine and, as a result, they are now the drugs of choice (Vythilingum et al., 2000).

The treatment of OCD with SSRIs requires higher doses and longer treatments than are required in depression. It may take 8 weeks or more before significant benefits are attained and gradual improvement may continue over 6 months. Discontinuation of treatment causes relapse, therefore, long-term treatments are indicated (Cartwright and Hollander, 1998).

A mechanistic insight into OCD was achieved when it was demonstrated that the nonselective 5-HT receptor agonist meta-chlorophenylpiperazine (*m*-CPP) was shown to exacerbate the symptoms of OCD (Hollander et al., 1992). This does not accord with the known therapeutic benefits of SSRIs in OCD, since they are believed to enhance the functions of 5-HT. Further experiments with the 5-HT1B/D receptor agonist sumatriptan showed that it also exacerbated OCD symptoms, although this is not a consistent observation (see Moret and Briley, 2000). It should be noted that sumatriptan does not readily penetrate the blood–brain barrier (Humphrey et al., 1991). In contrast to these observations, patients have been reported to obtain relief from OCD by taking hallucinogenic agents, such as psylocibin or LSD, which activate 5-HT2A/C receptors. However, tryptophan depletion does not have any effect on OCD symptoms (Delgado and Moreno, 1998).

Related to OCD are the obsessive–compulsive spectrum disorders (OCSD) such as body dysmorphic disorder and pathological gambling. Autism (see Section 19) is also classified among the OCSDs. As in OCD, these disorders also respond to SSRIs (Hollander, 1998).

7. Panic disorder

Panic disorder is a significant health issue, having a lifetime prevalence of up to 4% and coexisting with depression in nearly half of the cases (Wade, 1999). Furthermore, patients with panic disorder and depression are at high risk of committing suicide (Sheehan, 1999).

Antidepressants are able to relieve both the panic and the depression but as with the treatment of depression, the therapeutic benefit is not evident for 3 weeks or more and may take considerably longer to reduce the panic attacks to zero (den Boer and Slaap, 1998). For this reason, high-potency benzodiazepines are often given in the early stages of treatment.

The tricyclic antidepressants and the MAOIs were first shown to be effective in treating panic disorder in the 1960s. The MAOIs are probably more effective than the tricyclics; clomipramine, the partially 5-HT selective reuptake inhibitor, is probably the most effective tricyclic. In accordance with this observation, the effectiveness of the SSRIs has been demonstrated in large-scale trials and the SSRIs now established as the treatment of choice in panic attacks (Goddard and Charney, 1998). The optimal therapy is probably a combination of SSRIs and exposure therapy (Bakker et al., 2000).

8. Posttraumatic stress disorder (PTSD)

Although this condition was probably familiar to our warlike ancestors centuries ago, it was only relatively recently, after veterans of the Vietnam war were studied, that PTSD gained official recognition. PTSD is now recog-

nized as a relatively common and treatable medical condition. It has a lifetime prevalence of 5–10% (Ballenger et al., 2000).

Psychotherapy is understandably a primary treatment approach, but MAOIs and SSRIs have been shown to be effective in a small number of trials (Friedman, 1997; Davidson et al., 2001). It appears from the limited data that the SSRIs and MAOIs are superior to the tricyclic antidepressants in PTSD (Friedman, 1997).

In spite of the limited evidence from clinical trials, SSRIs are emerging as the pharmacotherapy of choice, although a combination of SSRI and psychotherapy is probably the most effective strategy. A bonus associated with the use of SSRIs is that they reduce alcohol consumption (see Section 18); not surprisingly, many patients with PTSD self-medicate with alcohol and may become heavy drinkers or alcohol dependent.

Some of the trials show a potential differentiation of treatment response depending on the trauma, and it seems that the war veterans are relatively refractory to treatment, probably because they are severely impaired. Unfortunately, the majority of published trials have been undertaken on this cohort. This is clearly an area requiring further carefully controlled studies, particularly in relation to the nature of the trauma. A variety of drug types have been tried in PTSD with little success, and there are still questions over the methodology to assess the benefits (Friedman, 1997). This is complicated by the fact that PTSD is often comorbid with disorders in the anxiety–depression spectrum and is frequently associated with a variety of somatic symptoms (Davidson et al., 2001). This complex picture does not encourage the belief that the pathophysiology of PTSD will become clearer in the near future, but the benefit of SSRIs is perhaps an indicator that other 5-HT-modulating drugs should be tried (Davidson and Connor, 1999; Friedman, 2000).

9. Migraine

This is one of the major success stories of 5-HT research. Based on the vascular theory of migraine, which states that dilatation of extracranial vessels is responsible for the headache, colleagues (Humphrey and Feniuk, 1991) reasoned that selective 5-HT1 receptor agonists would constrict the dilated vessels and thereby relieve the headache. This led to the development of sumatriptan which, using current nomenclature, is a 5-HT1B/D receptor agonist. Clinical evaluation of sumatriptan proved the theory to be correct and thus began a new era of migraine therapy where migraneurs found long-awaited relief from their debilitating headaches.

Since that time, several other ''triptans'' have been developed and marketed (Deleu and Hanssens, 2000; Tfelt-Hansen et al., 2000), some having considerably longer durations of action than sumatriptan, which has a plasma half-life of about 2 h. The reasoning behind increasing the duration of action is to overcome headache recurrence, which occurs in about 30% of patients. The triptans may vary in their rates of headache recurrence, but it is evident that recurrence does not correlate with duration of action (Goadsby, 1999).

There is an additional component of the pathophysiology of migraine that is also inhibited by the triptans: the sterile neurogenic inflammation in the dura mater that gives rise to plasma extravasation (Goadsby, 1999). The triptans vary in their abilities to inhibit this response, although the effect is believed to be mediated by 5-HT1B receptors. Evidence that inhibiting the neurogenic inflammation alone is insufficient to relieve migraine was obtained with the compound CP-122,288. It is a conformationally restricted sumatriptan analogue that potently inhibits neurogenic inflammation without vasoconstrictor activity (Lee and Moskowitz, 1993). Disappointingly, in placebo-controlled trials at doses believed to be in excess of those required to inhibit neurogenic inflammation, the compound was ineffective in treating acute migraine (Roon et al., 1997).

On the basis of its activity in an animal model of neurogenic inflammation, LY334370, a selective 5-HT1F receptor agonist was evaluated clinically as a treatment for migraine. It was active, albeit at relatively high doses but with a clean side effect profile (Goldstein et al., 1999). The triptans also have activity at the 5-HT1F receptor, so a full exploration of the potential of 5-HT1F receptor agonists in the treatment of migraine is still required.

10. Pain

Tricyclic antidepressants have been used for many years in the treatment of chronic pain, particularly postherpetic neuralgia, facial pain and painful diabetic neuropathy. In contrast to the antidepressant effect, the analgesic effect is apparent within days and only requires relatively small doses. This is a case where the SSRIs are probably inferior to the tricyclics, although the evidence is limited (Smith, 1998; Lynch, 2001). It is unlikely that the tricyclics owe their antinociceptive effects to their ancillary receptor blocking properties because venlafaxine, which is a more selective 5-HT and noradrenaline uptake inhibitor, is at least as effective as the tricyclics at providing pain relief (Barkin and Fawcett, 2000). It seems therefore that combined inhibition of 5-HT and noradrenaline uptake provides the optimal profile for chronic pain relief.

5-HT applied to a blister base causes pain, and this has been used as a model in human volunteers. The effect can be blocked by 5-HT3 receptor antagonists (Fozard, 1994). The observation that the dorsal horn of the spinal cord contains a dense population of 5-HT3 receptors also prompted investigations of 5-HT3 receptors and nociception. However, it seems that in spinal analgesia, 5-HT probably stimulates GABA release through 5-HT3 receptors and this induces analgesia (Alhaider et al., 1991). In this case, 5-HT3 receptor antagonists block the analgesia.

5-HT3 receptor antagonists have not found a place as analgesic agents, although the initial evaluations in migraine were promising (Fozard, 1994). In irritable bowel syndrome (IBS), however, 5-HT3 receptor antagonists are effective in relieving the pain (see Section 15).

11. Cognitive disorders

There is no drug currently available that has unequivocal benefit in cognitive disorders such as Alzheimer's disease, although cholinesterase inhibitors are effective in some patients. 5-HT research provides some encouragement that valuable drugs may become available in the future.

There is experimental evidence in animals that 5-HT6 receptor antagonists are able to enhance cognitive function (Reavill and Rogers, 2001; Woolley et al., 2001). This may link to the apparent involvement of 5-HT6 receptors in the control of central cholinergic function (Bourson et al., 1998). Several pharmaceutical companies are developing novel 5-HT6 receptor antagonists and the hope is that these compounds will have therapeutic benefit in cognitive disorders.

Recently, the 5-HT6 receptor polymorphism C267T was associated with Alzheimer's disease, subjects with the 267C allele being more susceptible to the disease. Furthermore, this was independent of the coexistence of depression (Liu et al., 2001).

5-HT3 receptor antagonists were shown to enhance cholinergic function and this corroborated behavioural evidence that they had cognition-enhancing properties in experimental animals (Costall and Naylor, 1994b). Clinical results have been variable with both encouraging and disappointing results (Preston et al., 1992; Broocks et al., 1998).

A great deal of research has been undertaken on the role of 5-HT in cognition and further information can be found in two recent reviews (Meneses, 1999; Buhot et al., 2000).

12. Aggression

One of the few sustainable observations linking a biochemical marker of 5-HT function to a psychiatric manifestation is that low CSF 5-HIAA concentrations predict a higher risk of suicide in depressed patients (Asberg et al., 1976). Low CSF 5-HIAA has also been observed in subjects with aggressive and impulsive behaviours and Linnoila and Virkkunen (1992) have postulated a "low 5-HT syndrome," a disorder of impulse control observed in a subgroup of violent offenders. The subjects show hypoglycaemia, altered diurnal rhythms and increased alcohol consumption. There is, however, no definitive evidence to show whether low 5-HT functioning is either causal or just correlated with aggression (Berman et al., 1997).

A further link between 5-HT and aggression comes from the observation that the 5-HT1B receptor knockout mouse shows increased aggression (Ramboz et al., 1996), and this accords with earlier observations that "serenic" compounds, such as eltoprazine, which have 5-HT1A/5-HT1B receptor agonist and 5-HT2C receptor antagonist activity, decrease aggression in animal models (Olivier et al., 1986). Eltoprazine was tested clinically against aggression in mentally handicapped patients, but the results were disappointing (de Koning et al., 1994).

13. Premenstrual dysphoria (PMD)

PMD occurs in about 5% of women of child-bearing age and is characterized by irritability and anger during the luteal phase of the menstrual cycle. The strong link between 5-HT function and aggression, coupled with the observation that PMD sufferers are often depressed, prompted the suggestion that PMD is a disorder of the 5-HT system (Eriksson, 1999; Steiner and Born, 2000).

This theory is borne out by a trial showing that the SSRI paroxetine was more effective in treating PMD than the noradrenergic antidepressant maprotiline (Eriksson et al., 1995). Furthermore, the SSRIs provide relief in 1–2 days (Sundblad et al., 1992), in contrast to their delayed onset in depression. This offers the major advantage that only short periods of treatment to cover the luteal phase are required.

Further support for the 5-HT theory of PMD is that the 5-HT1A receptor partial agonist, buspirone, the nonselective 5-HT receptor agonist meta-chlorophenylpiperazine, the 5-HT-releasing agent fenfluramine and the 5-HT precursor tryptophan all have beneficial effects in PMD (Eriksson, 1999). Since these compounds are not antidepressants, it is clear that the relief of PMD is not equivalent to an antidepressant effect but depends specifically on the enhancement of 5-HT function. SSRIs enhance 5-HT function acutely in some regions of the brain where their effects are not counteracted by autoreceptor inhibition (Hjorth et al., 2000). This must give a pointer to the key regions involved in the manifestation of PMD.

14. Chemotherapy and radiation-induced emesis

The emesis induced by chemotherapy and radiation in cancer patients can be so severe that patients may withdraw from therapy. The discovery that 5-HT3 receptor antagonists inhibit the emesis revolutionised the treatment of cancer with chemotherapy and radiation.

The discovery arose from carefully reasoned experimental research. It was shown in animal studies that chemotherapeutic agents such as cisplatin released 5-HT in the gut in vast quantities. This, in turn, activated 5-HT3 receptors in the gut, firing off a vagally mediated response that resulted in emesis. Further animal studies showed that this response was blocked by 5-HT3 receptor antagonists (Andrews, 1994). The two leading 5-HT3 receptor antag-

onists, ondansetron and granisetron, were shown to be effective clinically, and both were marketed in a relatively short time. They are both effective by the intravenous or oral routes (Walton, 2000).

This is a case where tool compounds were available before clinical applications were defined. The 5-HT3 receptor was the "M" receptor on guinea pig ileum discovered by Gaddum and Picarelli in (1957), and several companies had been using the same preparation to discover selective agents that blocked the receptor. The discovery of tool compounds allowed the evaluation of potential therapeutic applications resulting in the success described above. Several other therapeutic applications were predicted from experiments in animal models, but, so far, the antiemetic application is the only one that has become firmly established (Greenshaw and Silverstone, 1997).

15. Irritable bowel syndrome (IBS)

IBS is associated with recurrent abdominal pain and abnormal bowel activity that may reflect hypersensitivity of the GI tract to normal stimuli. The mechanism underlying the hypersensitivity is not understood, but there is evidence that it is mediated by 5-HT, possibly through 5-HT3 and/or 5-HT4 receptors (Humphrey et al., 1999; Houghton et al., 1999). IBS is a complex disorder, and there may be a strong central component to the pathophysiology; in about half the patients with IBS, there is comorbid anxiety and/or depression (Farthing, 1999). It is likely that IBS is a cluster of related disorders rather than a single entity. It follows that one drug will not be effective in all cases of IBS and in practice, a wide range of drugs is used in its treatment (Farthing, 1998).

5-HT3 receptor antagonists were predicted to be effective in diarrhoea-predominant IBS, and this led to the development of the long-acting 5-HT3 receptor antagonist, alosetron (Humphrey et al., 1999). Although trials with ondansetron and granisetron showed a reversal in rectal hypersensitivity in IBS patients, alosetron gave an encouraging improvement in IBS symptoms, but only in women (Camilleri, 2000). Alosetron was approved for the treatment of IBS but has since been withdrawn because of rare reports of serious gastrointestinal adverse events among patients taking the drug.

The diversity of symptoms in IBS is reflected in the drugs acting on 5-HT4 receptors that are being developed for treating the condition: Tegaserod (HTF-919) and prucalopride (R93877) are 5-HT4 receptor partial agonists and piboserod (SB-207266) is an antagonist. (De Ponti and Tonini, 2001). The agonists are intended to have prokinetic activity, like the mixed 5-HT4 receptor agonist/5-HT3 receptor antagonist cisapride. They are therefore indicated for constipation-predominant IBS. On the other hand, the antagonist piboserod was indicated for diarrhoea-predominant IBS. Although it was shown to decrease rectal sensitivity (Houghton et al., 1999), the therapeutic benefit of piboserod in IBS was not considered sufficient to warrant further clinical studies.

16. Obesity and appetite disorders

There is preclinical evidence to support serotonergic enhancement as a way of reducing feeding (Curzon, 1995; Halford and Blundell, 2000), and for many years, dexfenfluramine, either alone or in combination with phentermine, was in widespread use as an appetite suppressant before it was withdrawn from the market because of an association with valvular heart disease (Curzon and Gibson, 1999). It is a 5-HT-releasing agent related to amphetamine but without stimulant properties. Presumably, dexfenfluramine indirectly activated postsynaptic 5-HT receptors to suppress appetite, but the receptors involved have not been elucidated, although recent evidence implicates 5-HT2C receptors (Vickers et al., 2001). This is supported by clinical evidence that meta-chlorophenylpiperazine reduces food intake (Sargent et al., 1997).

The other interesting link between 5-HT2C receptors and obesity is the observation that 5-HT2C receptor knockout mice become obese at about 5–6 months of age (Tecott et al., 1995). However, it is still unclear whether this represents a lead into novel antiobesity treatments because selective 5-HT2C receptor antagonists do not induce weight gain in experimental animals (Wood et al., 2001). The interpretation of phenotypic data on genetic knockouts of the 5-HT system is of course complicated by the fact that 5-HT has a crucial role in the development of neurones. Nevertheless, it will be interesting to see if selective 5-HT2C receptor agonists have any therapeutic value as appetite suppressants.

Sibutramine is one of the few recently launched treatments for obesity. It was originally developed as an antidepressant, being a nontricyclic, nonselective monoamine reuptake inhibitor (Lean, 1997). Venlafaxine is similarly a nontricyclic mixed noradrenaline and 5-HT uptake inhibitor that suppresses appetite, although it is marketed as an antidepressant. Whether the mode of action of these compounds in obesity is through 5-HT mechanisms is unknown but they clearly differ from the tricyclic antidepressants, which tend to increase body weight.

The current trend in seeking the next generation of antiobesity drugs is to move away from 5-HT research and investigate peptide mediators, such as leptin, and ways of stimulating energy expenditure, such as $\beta 3$ receptor agonists or inhibition of absorption, exemplified by orliststat (Bray, 1999).

17. Sexual dysfunction

Depressed patients often have sexual dysfunction, and it has been known for many years that antidepressants

themselves can cause sexual dysfunction (Rothschild, 2000). This side effect has been brought into sharp relief by the SSRIs, possibly because they do not have many of the other side effects of the tricyclic antidepressants so that sexual dysfunction becomes one of the most reported side effects. The most commonly reported changes are delayed ejaculation in males and absent or delayed orgasm in males and females.

The underlying mechanism is not clear, and various augmentation therapies have been shown to have beneficial effects in counteracting the sexual dysfunction (Rosen et al., 1999). Some may give insight into the 5-HT mechanisms involved. For instance, there have been reports that the 5-HT1A receptor partial agonist, buspirone, can reverse the sexual dysfunction induced by SSRIs (Norden, 1994). This combination has an additional advantage in that it may improve the therapeutic response in depression (Menkes, 1995). There is also a report that the 5-HT3 receptor antagonist granisetron has some beneficial effects in reversing the sexual dysfunction induced by fluoxetine (Nelson et al., 1997).

This particular effect of the SSRIs has been used therapeutically in men with premature ejaculation (Kara et al., 1996; Ludovico et al., 1996). Premature ejaculation has a very high prevalence rate, possibly occurring in up to 40% of adult males (Spector and Carey, 1990), so this is potentially a significant area of therapeutic benefit.

18. Alcoholism, drug dependence and abuse

The darker side of 5-HT pharmacology is that several drugs emerging from 5-HT research have become drugs of abuse. One that has achieved notoriety in the popular press because of its toxicity is 3,4-methylenedioxymethamphetamine (MDMA, ''Ecstasy''). Originally conceived as a potential appetite suppressant, it entered the recreational drug scene in the 1970s. Unfortunately, there have been several reported cases of fatalities that were not associated with excessive dosage. Why some individuals are so susceptible to MDMA toxicity is still not clear (Burgess et al., 2000).

In animals, the acute effect of MDMA is a typical amphetamine-like sympathomimetic response. MDMA releases 5-HT in the brain, and this results in a reversible depletion. However, chronic administration induces serotonergic neurotoxicity, and it is a major concern that regular Ecstasy users may be exposing themselves to this risk. There is already evidence of psychiatric syndromes and cognitive deficits that may have been caused by repeated use of Ecstasy (McGuire, 2000; Morgan, 2000).

On the positive side, some 5-HT drugs may be beneficial in treating drug and alcohol dependence. For instance, SSRIs are beneficial in reducing alcohol consumption in alcohol-dependent individuals (Pettinati et al., 2001). This is not an indirect effect on an underlying depression. 5-HT3 receptor antagonists may also be useful in treating alcoholism. They reduce alcohol consumption in animal models and in clinical subjects, although the clinical data are variable (Ye et al., 2001).

There is considerable experimental evidence that 5-HT plays a crucial role in impulsivity and craving and that uncontrolled drug-seeking behaviour is most likely in a state of lowered 5-HT function (Ciccocioppo, 1999). This argues for the use of SSRIs and/or 5-HT receptor agonists in the treatment of drug addiction.

19. Autism

One of the earlier biochemical findings in autism was an above-average concentration of 5-HT in the blood (Anderson et al., 1990), and this has been substantiated by other investigators. The meaning of this observation has never been put into context but has prompted trials of drugs that have effects on the 5-HT system. If the high blood concentration of 5-HT signifies an overactive serotonergic system, then 5-HT receptor agonists should be beneficial and SSRIs should exacerbate the symptoms. On the contrary, the SSRIs and the 5-HT1A receptor partial agonist buspirone have shown beneficial effects in several trials (Buitelaar and Willemsen-Swinkels, 2000). The effectiveness of these agents depends on the type of symptoms present in the patient.

Because of the similarities between autism and schizophrenia, it is not surprising that antipsychotic agents have been used to treat autism. The lower level of side effects in the atypical agents has prompted their wider investigation and risperidone seems to be emerging as a moderately effective agent (Hunsinger et al., 2000). It is tempting to speculate that the benefit is related to blockade of 5-HT receptors rather than dopamine receptors, but this remains an open question.

A multitude of different treatments has been tried for autism and the 5-HT-related drugs referred to above, like several other treatments, provide only modest benefit. However, the hyperserotonemia does provide an avenue of research that still requires much more investigation.

20. Other issues

There are other therapeutic areas where 5-HT-derived drugs may have some benefit that we have not covered. The interested reader might want to consult the following articles: asthma (Cazzola and Matera, 2000); glaucoma (Osborne et al., 2000); cardiovascular disease (Frishman and Grewall, 2000) and urinary incontinence (Wein, 2001).

The more recently discovered 5-HT6 and 5-HT7 receptors are still being evaluated for potential therapeutic applications (Branchek and Blackburn, 2000; Vanhoenacker et al., 2000), so it is too early to predict how much impact they may have in the future. Several 5-HT receptors such as

5-HT4, 5-HT7 and 5-HT2C have genetic variants, and these may influence the effectiveness of therapeutic agents or offer new opportunities for more selective management of disease. Recently, a potential link between a 5-HT2C receptor allele and vulnerability to affective disorders was reported (Lerer et al., 2001).

There is a further dimension to 5-HT receptors that may be exploitable for drug discovery in the future: the diversity of signalling that has been observed with several 5-HT receptors (Pauwels, 2000). By driving or inhibiting signalling along particular pathways, agonists or antagonists could have novel actions and possibly more selective actions in the treatment of disease.

21. Conclusion

There is little doubt from this brief review that 5-HT research has had an enormous impact on medicine. There are also many avenues that remain unexplored so there are undoubtedly further advances to be made. In the next few years, we may see compounds selective for 5-HT1F, 5-HT2C, 5-HT6 and 5-HT7 receptors being evaluated clinically and possibly making further significant impacts on the treatment of disease.

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