Buspirone And Anxiety Disorders: A Review With Pharmacological And Clinical Perspectives

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Citation


Abstract

The treatment of anxiety is one of the leading problems in medicine today. Buspirone, an azpirone derivative and a 5-HT-1A (5-hydroxytryptamine-1A) partial agonist, is the first nonbenzodiazepine anxiolytic introduced into medicine for the treatment of generalized anxiety disorder (GAD). It has a strong affinity for the 5-HT-1A receptor and does not appear to interact at the benzodiazepine receptor complex. Buspirone's distinctive mechanism of action helps to avoid pharmacological properties ancillary to the treatment of anxiety and contributes towards an apparently superior safety profile with generally fewer and more tolerable adverse effects than benzodiazepines.

This article provides a brief overview on the results of animals and clinical studies in which the potential for buspirone dependence or abuse and the effects of its withdrawal were assessed. The pharmacology of serotonin systems and its role in the management of anxiety, along with the review of the contemporary literature is also discussed.

INTRODUCTION

A role of central serotonin (5-hydroxytryptamine; 5-HT) in the pathogenesis of anxiety has been the subject of intensive research. Experimental evidence based primarily on drug therapy suggests that anxiolytic effects of benzodiazepines (BZs), the conventional anxiolytics, are manifested by the stimulation of BZ-GABA (Gamma amino butyric acid) receptor complex and a concomitant decrease in serotonergic neuronal activity. Despite a trend of reduced prescribing the BZs remain the most widely used psychotropic drugs and this is due to their considerable effectiveness as anxiolytic, hypnotic, and anticonvulsant. Although a large number of different BZs exist, they share a common property of binding with a high affinity to specific recognition sites in brain. Drugs that tend to increase 5-HT functions are anxiogenic while blockade of serotonergic neurotransmission produced anti-anxiety effects.

Serotonergic hypothesis of anxiety is complicated by recent awareness of heterogeneity of 5-HT receptors in the central nervous system. The advent of selective agonists and antagonists for 5-HT receptor subtypes has rekindled investigation of the role of 5-HT in anxiety mechanisms.

Serotonin agonists with selectivity towards 5-HT-1A sites have been shown to release suppression of behaviour in models of anxiety. These drugs decreased 5-HT turnover in rat brain. Serotonergic cell groups of the median raphe nucleus innervating the hippocampus have an important role in the anxiety mechanisms. Brain hippocampus, an important site of BZ action, possessing high density of 5-HT-1A binding sites. Pharmacological studies show that decreasing the availability of 5-HT at postsynaptic 5-HT-2A or 5-HT-2C sites is anxiolytic. 5-HT-1A agonists such as buspirone, ipsapirone and 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) showed anxiolytic profile. This may be due to their potent agonistic activity towards cell body autoreceptors. Since they reduce serotonin neural function by suppressing neuronal firing. It has been proposed that this is the basis of their anxiolytic action. Unlike the BZs, 5-HT-1A agonists have been reported to produce little sedation, do not potentiate the effects of ethanol, and do not show potential for dependence or abuse. They do not seem to interact with the GABA-benzodiazepine-Cl ionophore complex. Depression of 5-HT neuron function is, therefore, critically important for therapeutic effects of both 5-HT-1A and BZ anxiolytics. Taken together, these observations lead to the conclusion that different 5-HT mechanisms, mediated by different receptor subtypes, are involved in the genesis of anxiety.
ANXIETY

Anxiety is a normal reaction but when it is severe and disabling it becomes pathological. Anxiety is an almost ubiquitous component of mental illnesses. It is present in its purest form in the so-called anxiety disorders, but also found in depression, schizophrenia and personality disorders. Anxiety disorders are common psychiatric manifestations of the modern world. The phenomenon as a &disorder has travelled through medical history under various labels such as &anxiety neurosis; &agoraphobia; and &panic disorder; &obsessive-compulsive disorder (OCD) are discrete diagnostic entities (see Table 1).

Table 1: Treatments for Anxiety Disorders

<table>
<thead>
<tr>
<th>Drug Treatment Options</th>
<th>Cognitive-Behavioral Therapy</th>
<th>Other Non-Drug Therapies</th>
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<tbody>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>Cognitive-behavioral therapy, stress management, biofeedback</td>
<td></td>
</tr>
<tr>
<td>Panic Attacks</td>
<td>Cognitive-behavioral therapy</td>
<td></td>
</tr>
<tr>
<td>Phobias</td>
<td>Cognitive-behavioral therapy, stress management, biofeedback</td>
<td></td>
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<tr>
<td>Obsessive-Compulsive Disorder</td>
<td>Cognitive-behavioral therapy, electroconvulsive therapy</td>
<td></td>
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<tr>
<td>Performance Anxiety Disorder</td>
<td>Cognitive-behavioral therapy, stress management, biofeedback</td>
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Buspirone (BuSpar) is an azapirone, a class of drugs showing promise for generalized anxiety disorder. Unfortunately, it usually takes several days to weeks for the drug to be fully effective, and it is not useful against panic attacks. Unlike the benzodiazepines, buspirone is not addictive, even with long-term use, and it seems to have less pronounced side effects and no withdrawal effects, even when the drug is discontinued quickly. The drug does not produce any immediate euphoria or change in sensation, so some people believe, erroneously, that the drug doesn't work. Because it has a low potential for abuse, buspirone is useful in persons whose anxiety disorder coexists with alcoholism. Some experts also think it may be useful for adolescents and children. Common side effects include dizziness, drowsiness, and nausea. Patients who have recently been taking benzodiazepines may respond less well to buspirone than others. BuSpar should not be used with monoamine oxidase inhibitors (MAOIs).

Evidence supporting the involvement of central serotonin in the anxiety-related behaviour and in the mechanisms of action of anxiolytics is well documented. With the introduction of several new and more specific drugs that act on serotonin receptors there has been a resurgence of interest in the possible role of these pathways in the control of anxiety. The hypothesis that serotonin may be involved in the anti-anxiety originated from the early work by Geller and Blum. It was shown that administration of para-chlorophenylalanine (PCPA), a tryptophan hydroxylase inhibitor, produced anxiolytic effects in animal tests of anxiety. This study was confirmed by Stein and Colleagues in 1973. The anxiolytic effect of PCPA was reversed by the administration of 5-hydroxytryptophan (5-HTP; an immediate precursor of 5-HT). Neurochemical studies on the effects of BZs on brain 5-HT metabolism also support the hypothesis because systemic administration of BZs has been reported to decrease synthesis and release of 5-HT in many regions of rat brain.

Lesions of serotonergic pathways, resulting from the injection of neurotoxins 5,6 or 5,7-dihydroxytryptamine (5,7-DHT) have been reported to produce anxiolytic profiles in conflict paradigms. The dorsal raphe ascending pathways seems to be of particular importance. Small 5,7-DHT lesions of this nucleus produced anxiolytic effects in the social interaction test and a similar effect was also produced by injecting the toxin into the lateral septum. Thiebot et al also found that 5,7-DHT lesions of the dorsal raphe resulted in an anti-conflict effect in animal models. Microiontophoretic injections of 5-HT into the dorsal raphe were found by Thiebot et al to release punished responding. Because of evidence that these 5-HT injections may depress the firing rate of dorsal raphe neurons, probably through an action of autoreceptors, the results were interpreted as support for the hypothesis that decreased 5-HT activity results in an attenuation of behavioural suppression. The 5-HT agonist, -methyltryptamine suppressed punished responding in both the pigeon and the rat, but since unpunished responding was also decreased, the results may simply reflect a non-specific depressant effect of the drug. Another 5-HT agonist, 5-methoxy, N, N-dimethyltryptamine (5-MeODMT) had no effect on punished response rates in a
conflict procedure and reduced unpunished rates \textsuperscript{63}. However, in this study 5-MeODMT was unable to reverse the anti-conflict effects of chronic administration of PCPA. The effects of quipazine, a non-selective 5-HT agonist have been studied in the social interaction test \textsuperscript{56} (Nutt and Cowen 1987). The compound did not appear to be anxiogenic in this test but an anxiogenic action was shown by decreased social interaction without a concomitant drop in motor activity \textsuperscript{64}. Fenfluramine, which releases 5-HT, had no effect on punished responding, whereas the 5-HT precursor, 5-HTP did have pro-conflict effect \textsuperscript{65}. However, this effect was blocked by the addition of carbidopa, which blocks peripheral decarboxylation, indicating that a peripheral action of 5-HTP was responsible for the behavioural effect. It has been shown that administration of carbidopa, a 5-HTP decarboxylase inhibitor, did accumulate 5-HTP in the rat brain and contributes to the reduced 5-HT synthesis. The data, however, strongly supported the hypothesis that central serotonin may be involved in the anti-anxiety effects of BZs.

**SEROTONIN RECEPTORS IN THE MODULATION OF ANXIETY**

A substantial body of work in animals and some exciting recent findings in humans warrant a closer examination of the 5-HT/ anxiety relationship. Figure 1 gives a schematic overview of the localizations of the 5-HT receptor types and subtypes on a hypothetical 5-HT neuron. The present contribution focuses on the possible role of different 5-HT receptors in the modulation of anxiety. For example, anxiolytic behavioural effects (like exploratory behaviour, elevated plus maze etc.) of 5-HT-1A receptor agonists such as buspirone \textsuperscript{100} appear to be produced by the stimulation of presynaptic 5-HT-1A autoreceptors that inhibit the synthesis and secretion of serotonin. Alternatively, antagonists of 5-HT-1A, 5-HT-2, or 5-HT-3 receptors may exhibit anxiolytic effects by blocking postsynaptic serotonin receptors \textsuperscript{18} (Fig 1).

The 5-HT-2A receptors are also involved in anxiety. For example, animal studies have demonstrated that 5-HT-2 receptors can independently modulate the function of the hypothalamo-pituitary adrenocortical (H-PA) axis \textsuperscript{101}, although the respective role of 5-HT-2A receptors in the management of anxiety is highly complex. A number of commonly used antidepressants, such as amitriptyline, clomipramine and trazodone are potent antagonists of 5-HT-2A receptors and demonstrate anxiolytic effects in some animal models \textsuperscript{102,103}. Early evidence from clinical trials indicated that ritanserin, a selective 5-HT-2 receptor antagonist, may be an effective anxiolytic agent \textsuperscript{104} and is being tested in a variety of psychiatric syndromes, including anxiety disorders. Peroutka and Snyder \textsuperscript{105} have reported that cortical 5-HT-2A receptors are down-regulated by the long-term administration to rats a variety of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Behavioural studies with the X-maze anxiety model and punished responding suggest that 5-HT-2A receptor antagonists demonstrate anxiolytic effects in animal models \textsuperscript{102,103}.

One psychoactive drug, meta-chlorehenylpiperazine (m-CPP), has attracted considerable recent attention because it is a metabolite of the antidepressants trazodone and nefazodone and has a high affinity as an agonist for a number of 5-HT receptors. In a variety of animal models, m-CPP produces diverse behavioral changes (such as hypolocomotion, hypophagia, hypothermia etc.). Hypolocomotion, an axiogenic behaviour has been shown to
be mediated by the stimulation of 5-HT-2C receptors. Blockade of 5-HT-2C receptors with selective 5-HT-2C receptor antagonists can prevent anxiogenic effects of m-CPP. In addition, 5-HT-2C receptor antagonists given alone may produce anxiolytic effects. The functional effects of 5-HT-2C receptor activation are desensitized by the long-term administration of selective serotonin reuptake inhibitors (SSRIs) and MAOIs. It is possible that some of the effects produced by long-term administration of SSRIs and MAOIs on anxiety-related behaviours are involve in this common mechanism. Clinical studies have demonstrated that m-CPP can produce symptoms of anxiety in normal volunteers. This drug also augments symptoms of panic anxiety and OCD.

Ondansetron (Zofran), a 5-HT-3 receptor antagonist, currently marketed as an antiemetic agent for the treatment of chemotherapy-induced nausea and vomiting. Recent studies suggest that it might be an effective anxiolytic in a variety of animal models. A variety of other 5-HT probes have also been utilized in the patients with anxiety disorders like OCD. These include tryptophan (5-HT precursor), fenfluramine (5-HT releaser) and metergoline (5-HT antagonist).

The very recent development of compounds that interact in a specific manner with part of the 5-HT system and that possess anxiolytic properties in animals and human, has offered the possibility to elucidate the role of 5-HT in anxiety in more detail. The 5-HT receptors in the hippocampus and also other parts of the limbic systems are primarily of the 5-HT-1A type. It is therefore tempting to speculate that the drug which displays a high degree of selectivity towards 5-HT-1A receptor sites may selectively affects anxiety states. It has been suggested by Dourish that 5-HT-1A receptor agonists elicit their anxiolytic effects through stimulation of 5-HT-1A receptors located on the cell bodies and/ or dendrites of 5-HT neurons in the raphe nuclei. A breakthrough in that direction was the finding that, buspirone, a drug with anxiolytic activity in animals and humans, could displace [3H]-5-HT with relatively high potency from its hippocampal binding sites. Later discovery that buspirone and other 5-HT-1A receptor agonists produce anxiolytic and antidepressant activity directed attention to the 5-HT-1A receptor as the possible site of all the anxiolytic and antidepressant effects.

In the central nervous system (CNS), the 5-HT-1A receptors are broadly distributed, occurring as a somatodendritic autoreceptor on 5-HT cell bodies located in the raphe nuclei, and postsynaptically in other areas such as the hippocampus (see Fig 3). The distribution of 5-HT-1A receptor sites in the brain and pattern of buspirone binding to different brain structures has been established using radiolabelled 5-HT and buspirone. This evidence confirms that in regions of the brain implicated in the mediation of mood and emotion, buspirone acts in a similar fashion to 5-HT. Buspirone appears to exert its beneficial effects by binding specifically, and with a high affinity, to the 5-HT-1A receptor in the brain and thus altering serotonergic transmission.

**PRE-SYNAPTIC AND POST-SYNAPTIC 5-HT-1A RECEPTOR INTERACTION IN ANXIETY**

Buspirone, a nonbenzodiazepine anxiolytic, belongs to the azapirone family of drugs and differs from the BZs both chemically and pharmacologically. It was originally suggested that the proposed anxiolytic activity of buspirone involved action on dopamine systems in the brain. Buspirone was found to displace binding to 5-HT-1 sites in hippocampal membranes from the calf. Displacement of binding to a 5-HT-1 site in rat hippocampus was subsequently reported. Buspirone and related compounds (gepirone, ipsapirone and tandospirone) that are effective for the treatment of generalized anxiety disorder demonstrate a high affinity for 5-HT-1A receptors. The important pharmacologic actions of buspirone are (1) stimulating presynaptic 5-HT-1A receptors, (2) blocking postsynaptic 5-HT-1A receptors and (3) reducing the density of 5-HT-2 receptors during long-term or chronic administration. These effects act in concert to diminish serotonin neurotransmission and might underlie the actions of buspirone in anxiety and depression. The hypothesis is further supported by the reported observations that the complex behavioural syndrome observed following administration of serotonin agonists reflects activation of central serotonin receptors, particularly the 5-HT-1A receptors.
Various reported studies have shown that BZs and buspirone reduce the activity of serotonergic neurons in the dorsal raphe nucleus. The 5-HT-1A receptors in the dorsal raphe are considered presynaptic, while those located in the hippocampal formation and cortex are considered postsynaptic. Buspirone demonstrates varying agonistic activity at these regionally distinct receptors (Fig 2).

Electrophysiological studies of events in the dorsal raphe nucleus show that spontaneous firing of serotonergic neurons is attenuated or abolished by buspirone in a way similar to that of a serotonin agonist. Binding of buspirone to presynaptic 5-HT-1A receptors inhibits the activity of serotonergic neurons via a negative feedback mechanism. Thus, buspirone acts as a full agonist at presynaptic receptors. Studies in rat hippocampal membranes of the binding of buspirone to postsynaptic 5-HT-1A receptors showed it to have approximately half the intrinsic activity of 5-HT i.e. implying partial agonist activity of postsynaptic receptors. As a partial agonist, buspirone competes for the binding sites and displaces the more active full agonist from such sites. This allows buspirone to function like an antagonist in the presence of high concentrations of 5-HT. Thus, buspirone acts as a 5-HT agonist at presynaptic receptors and a partial agonist at postsynaptic receptors.

CLINICAL IMPLICATIONS

This article provides a brief overview of the pharmacology of serotonin systems and developments in research so that the relationship between serotonin compounds and anxiety can be better understood. There is convincing evidence that 5-HT brain pathways are involved in the mechanisms of action responsible for the alleviation of anxiety. Hence, the role of 5-HT in anxiety and other affective disorders is fundamental to the pharmacology of 5-HT-1A agonist buspirone. Evidence suggests that pre-synaptic 5-HT-1A receptors located on cell body dendrites are involved in the anti-anxiety effects of azapirones while post-synaptic 5-HT-1A receptors stimulated by serotonergics produce antidepressant effects. Because anxiety and depression often coexist, drugs of azapirone type may have clinical implications in the treatment of both anxiety and depression. The fact that anxiety can be treated with the novel serotonergic drugs buspirone, gepirone and ipsapirone sheds new light on the old hypothesis that BZ anxiolytics act in part via modulation of 5-HT neurotransmission. A common effect of the BZs and 5-HT-1A receptor-related anxiolytics is their inhibition of serotonergic impulse flow.

In conclusion, the study supports the suggestion that activation of somatodendritic 5-HT-1A autoreceptors play a critical role in the mechanisms underlying the anxiolytic effects of selective 5-HT-1A receptor agonists. Further clinical studies with more selective pharmacological agents are required to identify the specific contribution of the serotonergic systems in the pathophysiology of anxiety disorders and therapeutic strategies to combat the undesirable stressful situations in anxiety and depression. Unravelling the role of serotonin in anxiety and related disorders and parallel studies on animal models could hopefully provide better therapy and is likely to lead to new insights in our understandings of anxiety and depression.

References

94-129.
47. Barret JE, Vanover KE. 5-HT receptors as a target for the development of novel anxiolytic drugs: models.
57. File SE, Hyde JRG, MacLeod NK. 5-, 7-
82. McMenamy RH, Ordyle JL. The specific binding of L-
86. Kragh-Hansen U. Relations between high affinity
115. Dourish CT. Brain 5-HT-1A receptors and anxiety. In: Brain 5-HT-1A receptors and anxiety. (Dourish CT, Aghajanian GK, Price LH eds.) 1987; p 261.
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