Serotonin 5-HT₂ Receptor Antagonists
Potential in the Treatment of Psychiatric Disorders

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Summary

This review highlights recent pharmacological and clinical advances in the understanding of the potential use of serotonin 5-HT₂ receptor antagonists as treatments for a number of psychiatric disorders, namely anxiety, depression and schizophrenia.

5-HT₂ receptor antagonists have not yet been clearly demonstrated to be effective in humans as treatments for anxiety. Some preliminary clinical trials suggest that the 5-HT₂ receptor antagonist ritanserin may have a beneficial effect in patients with generalised anxiety disorder, but the evidence is far from compelling.

Upregulation of central 5-HT₂ receptors and an accompanying increase in phosphoinositide turnover appear to be predisposing biological factors in depression. A functional interaction between 5-HT₁A and 5-HT₂ receptors may be of particular importance, since 5-HT₂ receptor antagonism can ultimately result in a facilitation of 5-HT₁A receptor–mediated neurotransmission and this may be beneficial for the treatment of depression. Ritanserin appears to be more effective than placebo in alleviating the depressive symptoms of dysthymia. Nefazodone is a new antidepressant that combines 5-HT₂ receptor blockade with serotonin reuptake inhibition. Comparisons with imipramine favour nefazodone in terms of tolerability and suggest that both drugs are equally clinically effective.

In schizophrenia, 5-HT₂A receptor function appears to be altered. Modulation of dopaminergic function via 5-HT₂A receptors may provide a viable mechanism...
for enhancing the effect of antipsychotics. Risperidone, the first post-clozapine agent that has 5-HT2A and dopamine D2 receptor antagonist actions, is at least as effective as haloperidol and perphenazine in reducing acute psychotic symptoms. Its major clinical advantages are a greater efficacy in controlling the secondary negative symptoms and a lower incidence of extrapyramidal symptoms (EPS). The efficacy of ritanserin in alleviating both positive and negative symptoms in acutely psychotic patients seems to support the hypothesis that potent 5-HT2A receptor antagonism alone may contribute to the therapeutic action of several clinically effective antipsychotics that have reduced liability to induce EPS.

The role of the serotonin (5-hydroxytryptamine; 5-HT) system in the pathophysiology of various psychiatric disorders has become the focus of increasing attention. The effects of serotonin are likely to be mediated by a variety of serotonin receptor subtypes; at least 16 distinct types of serotonin receptor have been cloned from mammalian tissues. This review concentrates on serotonin 5-HT2 receptors. Several compounds with affinity for these receptors are currently under investigation for the treatment of anxiety, depression and schizophrenia.

1. Pharmacology of Serotonin 5-HT2 Receptors

On the basis of functional studies with agonists and antagonists, ligand binding affinities, molecular structure and intracellular transduction mechanisms, the 5-HT2 receptor family comprises 3 specific receptor subtypes: 5-HT2A, 5-HT2B and 5-HT2C.

All are G-protein-linked molecules that are positively coupled to phosphoinositide metabolism and display an overall sequence homology of about 60%. The presence of the same intron-exon junction structures in 5-HT2A, 5-HT2B and 5-HT2C receptor genes indicates that the pharmacologically, physiologically and molecularly defined family of 5-HT2 receptors is also defined by gene structure. The pharmacological properties of 5-HT2A, 5-HT2B and 5-HT2C receptors are summarised in tables I and II.

2. 5-HT2 Antagonists for the Treatment of Anxiety

2.1 Rationale for Development

Pharmacological manipulations of serotonin and serotonin receptor subtypes in the brain have recently received increased attention as possible means of finding alternatives to benzodiazepine anxiolytics. Interest in this approach has been stimulated by the reported clinical efficacy of 5-HT1A receptor partial agonists, such as buspirone and ipsapirone, in the treatment of generalised anxiety disorder.

When discussing serotonin and anxiety, variables which deserve separate discussion are:

- the different subtypes of serotonin receptors (e.g., 5-HT1A, 5-HT2 and 5-HT3), which may all play more or less prominent roles in some pathophysiological mechanisms underlying anxiety disorders;
- the different experimental models of anxiety;
- the different types of human anxiety disorders (e.g., generalised anxiety disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, phobias) for which certain animal experimental situations could serve as models.

Animal models of anxiety can be divided broadly into 2 classes: (i) exploratory activity and (ii) punished behaviour. Exploratory activity appears to be a function of general activity level, impulsivity (the need to become familiar with strange territory) and anxiety (the desire to escape from the unknown and unpredictable). Animal models used