5-HT\textsubscript{1A} Partial Agonists
What is Their Future?

Debra A. Glitz and Robert Pohl
Wayne State University, Detroit, Michigan, USA

Drugs that act selectively on the serotonergic system (e.g. fluvoxamine) are effective in a variety of psychiatric disorders including depression, panic disorder and obsessive compulsive disorder (OCD) [Den Boer et al. 1987; Goodman et al. 1989; Schatzberg et al. 1987]. Recently, multiple subtypes of serotonin (5-hydroxytryptamine, 5-HT) receptors have been identified, along with agents that act relatively selectively at the various 5-HT receptor subtypes. Increasingly, selective and specific psychotropic agents are of clinical interest because they generally have fewer side effects. Such agents may help determine whether there is any diagnostic specificity for abnormalities involving 5-HT receptor subtypes.

At present, 3 main classes of 5-HT receptor subtypes have been identified: 5-HT\textsubscript{1A}, 5-HT\textsubscript{2} and 5-HT\textsubscript{3}. Within the 5-HT\textsubscript{1} class of receptors, at least 4 different receptor subtypes have been identified: 5-HT\textsubscript{1A}, 5-HT\textsubscript{1B}, 5-HT\textsubscript{1C} and 5-HT\textsubscript{1D} (Peroutka & Snyder 1979; Peroutka et al. 1989).

Early studies with buspirone, a partial 5-HT\textsubscript{1A} receptor agonist, suggested a possible role for this receptor in the pathophysiology of anxiety disorders. Several other investigational drugs have also been developed which demonstrate high affinity for the 5-HT\textsubscript{1A} receptor, including 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), a highly selective 5-HT\textsubscript{1A} receptor agonist, gepirone and BMY 7378, ipsapirone, SM3997, WY47846 and MDL 72832. In this article the potential clinical applications of 5-HT\textsubscript{1A} partial agonists in the treatment of neuropsychiatric disorders are discussed.

1. Anxiety Disorders
1.1 Generalised Anxiety Disorder

The discovery that buspirone inhibited aggressive behaviour in rhesus monkeys (Tompkins et al. 1980) led to clinical trials in the treatment of anxiety. Several controlled studies in anxious patients have found buspirone to be superior to placebo and to have a similar therapeutic effectiveness in comparison with diazepam and chlor Diazepate (Böhm et al. 1990; Feighner & Cohn 1989; Goa & Ward 1986; Goldberg & Fintory 1979, 1982; Murphy et al. 1989; Pecknold et al. 1989; Rickels et al. 1982; Wheatley 1982). Gepirone has also been reported to be an effective anxiolytic agent (Casanolosi et al. 1987; Cott et al. 1988; Harto et al. 1988). Unlike benzodiazepines, but similar to antidepressants, the anxiolytic effects of 5-HT\textsubscript{1A} partial agonists may develop gradually over several weeks (Harto et al. 1988). This suggests that chronic modulation of 5-HT receptors may be necessary for their therapeutic activity.

The mechanism of the anxiolytic effects of these compounds is unclear. Although buspirone affects both dopaminergic (Taylor et al. 1982) and noradrenergic activity (Gower & Tricklebank 1988), there is evidence to suggest that the anxiolytic activity of 5-HT\textsubscript{1A} partial agonists is related to their effect on 5-HT neurotransmission (Eison et al.
However, the precise nature of the effect on 5-HT neurotransmission has not been fully elucidated. While there is evidence to suggest that 5-HT1A partial agonists inhibit 5-HT neurotransmission (VanderMaelen & Wilderman 1984a,b), most likely via 5-HT1A autoreceptor stimulation (Dourish et al. 1986), there is also evidence that these agents have postsynaptic 5-HT1A agonistic activity as well (Martin & Mason 1987; Rowan & Anwyl 1987). The overall balance between inhibitory and facilitatory effects on 5-HT neurotransmission may vary in different areas of the brain.

To further complicate matters, there is evidence to suggest that 5-HT has both anxiolytic and anxiogenic properties. Studies using animal models of anxiety generally suggest that 5-HT promotes anxiety (Geller & Blum 1970; Johnston & File 1986; Tye et al. 1977). In contrast, other evidence suggests that a 5-HT-deficient state might promote anxiety (Brody 1970; Mendels & Fraser 1974). Soubré (1986) has suggested that animal conflict paradigms may actually be investigating impulsivity rather than anxiety. 5-HT1A partial agonists similarly demonstrate both anxiolytic and anxiogenic properties in animal models of anxiety (Craft et al. 1988; Engel et al. 1984; Geller & Hartman 1982; Higgins et al. 1988; Sanger et al. 1985; Shimizu et al. 1987).

It is clear that no simple theory about 5-HT and anxiety can account for the findings reviewed above. The apparent contradictions may relate to complexities in the regulation of 5-HT neurotransmission.

### 1.2 Panic Disorder

In 2 collaborative published controlled trials of buspirone in the treatment of panic disorder (Pohl et al. 1989; Robinson et al. 1989a; Sheehan et al. 1990), the results were inconclusive. In the pooled data analysis, neither buspirone nor imipramine (a standard treatment with proven efficacy) was significantly better than placebo. However, there was a nonsignificant trend towards increased efficacy with buspirone. The failure to demonstrate a significant difference in efficacy may have been in part related to a robust placebo response in these studies.

Despite the lack of demonstrated efficacy, there is evidence to suggest that enhancement of the 5-HT system may reduce panic attacks. The locus coeruleus hypothesis of panic disorder suggests that activity in the brain noradrenergic neurons is increased during panic attacks (Charney & Redmond 1983). The dorsal raphe nuclei send 5-HT projections to the locus ceruleus (Morgane & Jacobs 1979) which are inhibitory (Segal 1979). Although buspirone increases the firing of neurons in the locus ceruleus acutely, its long term effect is unknown (Sanghera et al. 1983). Interestingly, Chignon and Lepine (1989) report a case of panic attacks precipitated by the addition of a single dose of buspirone to an existing tricyclic antidepressant regimen.

5-HT-selective reuptake inhibitors (e.g. fluvoxamine) are effective in treating panic attacks (Den Boer & Westenberg 1988; Den Boer et al. 1987). The 5-HT precursors, tryptophan and 5-hydroxytryptophan (5-HTP, oxtiriptan) also have weak antipanic activity (Hoes et al. 1981; Kahn et al. 1987). Furthermore, the antipanic effects of fluvoxamine may be unrelated to its 5-HT2 antagonism since 5-HT2 antagonists are ineffective as antipanic agents (Westenberg & Den Boer 1989). In addition, the therapeutic effect of fluvoxamine appears biphasic. After an initial exacerbation, the panic symptoms subsequently improve (Den Boer et al. 1987). This suggests that chronic modulation of 5-HT1 receptors may be necessary for its antipanic properties. Since the precise nature of the acute and chronic effects of 5-HT1A partial agonists on 5-HT neurotransmission has not yet been definitively established, additional clinical trials are needed to determine whether these agents are beneficial in the treatment of panic disorder.

### 1.3 Obsessive Compulsive Disorder

There is strong evidence to suggest serotonergic involvement in the pathogenesis of OCD. Clomipramine (chlorimipramine), an antidepressant with