The last few years have seen important advances in the understanding of 5-HT and its mechanisms of action in modulating responses to stress. Findings in a variety of animal models suggest that selective 5-HT_{1A} receptor antagonists/inverse agonists may have therapeutic effects in anxiety- or stress-related disorders.

5-HT_{1A} Receptor Blockers as Potential Drug Candidates for the Treatment of Anxiety Disorders

by Guy Griebel

Summary

Serotonin (5-HT) is an important neurotransmitter which regulates various biological responses, some of which are potentially important in the pathogenesis of stress-related diseases such as generalized anxiety. 5-HT produces its biological effects by stimulating specific 5-HT receptors. Among these, the 5-HT_{1A} receptor has been the focus of considerable research since the early 1980s. This receptor subtype is widely distributed in the central nervous system and is located both presynaptically, on 5-HT cell bodies in the raphe nuclei of the brainstem, and postsynaptically, in particular, in limbic structures. A considerable body of evidence indicates that the activation of presynaptic 5-HT_{1A} receptors yields anxiolytic activity. The recent availability of compounds that selectively block 5-HT_{1A} receptors has prompted speculation about their potential to modulate emotional behaviors. Studies in animals show that 5-HT_{1A} receptor antagonists display anxiolytic-like actions, but the magnitude of these effects is generally smaller than that of benzodiazepine anxiolytics. However, comparisons with 5-HT_{1A} receptor agonists such as buspirone, a compound currently used in the treatment of generalized anxiety disorders, suggest that the anxiety-reducing potential of 5-HT_{1A} receptor antagonists may be superior to that of full or partial agonists for this receptor. Clinical trials with 5-HT_{1A} receptor antagonists in patients with anxiety disorders will eventually determine whether such compounds may be useful in the treatment of these conditions.

During the last two decades significant progress has been made in understanding the function of the serotonin (5-HT) system, an important neurotransmitter network regulating various physiological functions and behaviors, including anxiety and affective states.[1] Several distinct 5-HT receptor subtypes, grouped into the seven main classes of 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 receptors, are known to mediate the physiological effects of the neurotransmitter.[2,3] Within the 5-HT_1 family, at least five subtypes

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have been recognized: 5-HT_{1A}, 5-HT_{1B} (formerly also termed 5-$HT_{1D\beta}$), 5-HT_{1D} (formerly 5-$HT_{1D\alpha}$), 5-HT_{1E} and 5-HT_{1F}.

The 5-HT_{1A} receptor has been the focus of considerable research effort since the early 1980s. This receptor subtype is widely distributed in the central nervous system. It is located both presynaptically (somatodendritic autoreceptors), on the 5-HT cell bodies in the raphe nuclei of the brainstem which innervate the forebrain, and postsynaptically, in particular, in limbic structures, such as the hippocampus, septum and amygdala.[4,5] Stimulation of the postsynaptic 5-HT_{1A} receptor in rats produces a variety of physiological, biochemical and behavioral effects, including hypothermia, elevations in plasma corticosterone and a characteristic 5-HT syndrome consisting of flat body posture, forepaw treading and headweaving. The activation of presynaptic 5-HT_{1A} receptors induces hyperphagia and anxiolytic-like activity in a variety of rodent models of emotional behavior.[6–8] This latter action is claimed to account for the clinical anxiolytic efficacy of the 5-HT_{1A} receptor agonists buspirone, gepirone and ipsapirone.[9–14]

5-HT_{1A} receptor agonists also demonstrated efficacy in the treatment of depressive disorders.[15–22] Although the development of selective agonists for 5-HT_{1A} receptors has facilitated investigations of their functional role in these pathophysiological states, full characterization of this involvement has been hampered by the lack of selective antagonists for these sites. In addition to their utility as research tools, it has been suggested that selective 5-HT_{1A} receptor antagonists may themselves have anxiolytic potential.[23] This article briefly reviews the evidence suggesting that selective 5-HT_{1A} receptor antagonists may have the potential to become effective antianxiety agents.

Search for selective 5-HT_{1A} receptor antagonists

Until recently, only nonselective 5-HT_{1A} receptor antagonists had been described. These include (–)-pindolol and (–)-propranolol, which have greater affinity for β-adrenoceptors than for 5-HT_{1A} receptors,[24–26] and spiperone, which displays high affinity for 5-HT_2 and dopamine D_2 receptors.[24,27] A number of compounds were initially designated selective 5-HT_{1A} receptor antagonists, for example, BMY-7378,[24] NAN-190[28] and MM-77,[29] but while demonstrating antagonistic-like activity in postsynaptic 5-HT_{1A} receptor models, these compounds showed partial agonist-like activity at presynaptic somatodendritic 5-HT_{1A} receptors.[24,29–31]

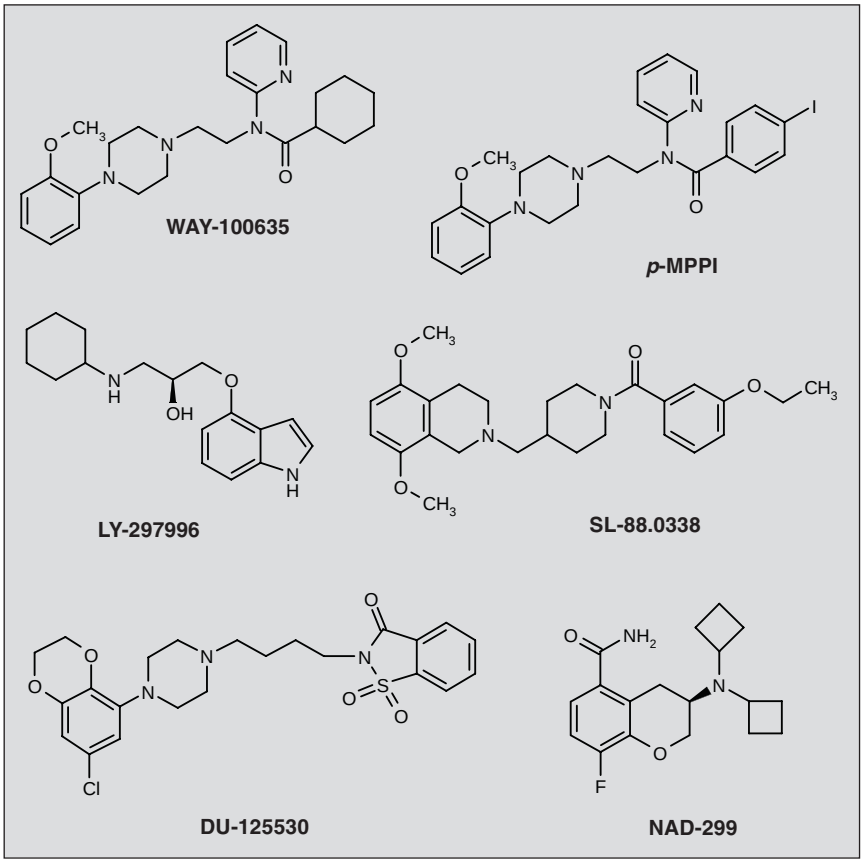

Fig. 1. Structures of several selective 5-HT_{1A} receptor blockers.

The first ligands that displayed consistent 5-HT_{1A} receptor antagonist properties were the (*S*)-enantiomer of 5-fluoro-8-OH-DPAT, (*S*)-UH-301,[32] the phenylpiperazine derivative WAY-100135[33] and the pindolol derivative pindobind-5-HT_{1A}.[26] However, (*S*)-UH-301 and pindobind-5-HT_{1A} have only eight- and ninefold selectivity for 5-HT_{1A} relative to D_2 receptors and α_1-adrenoceptors, respectively.[26,32] Furthermore, (*S*)-UH-301 was found to display D_2 agonist-like activity,[34] while WAY-100135 has demonstrated both 5-HT_{1A} receptor partial agonist activity[35,36] and α_1-adrenoceptor antagonism.[37]

It is only within the last few years that selective 5-HT_{1A} receptor antagonists have become available. These include the phenylpiperazine derivative WAY-100635[38–40] and its close structural analogue *p*-MPPI,[41–44] the pindolol analogue LY-297996 (also known as (–)-LY-206130),[45] the aminomethylpiperidine SL-88.0338,[46] DU-125530[47] and NAD-299[48] (Fig. 1). As shown in Table I, WAY-100635, SL-88.0338 and NAD-299 are the most selective. They display at least one hundred-fold selectivity for 5-HT_{1A} relative to other neurotransmitter receptors. LY-297996, DU-125530 and *p*-MPPI are moderately selective for

TABLE I: COMPARISON OF THE RECEPTOR-BINDING PROFILE OF SEVERAL 5-HT$_{1A}$ RECEPTOR BLOCKERS

COMPOUND	AFFINITY (K_i* or IC_{50}, nM)							
	5-HT$_{1A}$	5-HT$_{2A}$	α_1	α_2	β	D_1	D_2	REFERENCES
WAY-100635	1	>100	229	>1000	>100	>100	>100	38
p-MPPI	1	270	35		742		19	43
LY-297996	3.4				23			45
SL-88.0338	3.9	>1000	650	>1000		>1000	520	46
DU-125530*	0.7	240	6.4				5.2	47
NAD-299*	0.59		260	>1000	340	>1000	>1000	48

the 5-HT$_{1A}$ receptor and display high affinity for β, α_1 and D_2 receptors, respectively.

Functional characterization of selective 5-HT$_{1A}$ receptor antagonists

The 5-HT$_{1A}$ receptor antagonistic properties of drugs that interact with this binding site can be demonstrated in a variety of *in vitro* and *in vivo* models of both pre- and postsynaptic 5-HT$_{1A}$ receptor function. The activation of 5-HT$_{1A}$ autoreceptors attenuates the rate of firing of raphe 5-HT neurons and, consequently, the release of 5-HT from axonal terminals. The former effect can be monitored electrophysiologically using raphe brain slices. Endogenous 5-HT release in forebrain regions is measured by microdialysis. In the hippocampus, postsynaptic 5-HT$_{1A}$ receptors are linked to potassium channels and to adenylyl cyclase providing biochemical (inhibition of forskolin-stimulated cAMP synthesis) and electrophysiological models of postsynaptic function. Several *in vivo* responses are employed as functional models of presynaptic (hyperphagia) and postsynaptic (induction of 5-HT syndrome, hypothermia, elevation of plasma corticosterone or ACTH) 5-HT$_{1A}$ receptors.

In vitro electrophysiological studies demonstrated that WAY-100635 blocked the effects of agonists at both the postsynaptic 5-HT$_{1A}$ receptor in the CA1 region of the hippocampus and the somatodendritic 5-HT$_{1A}$ receptor located on dorsal raphe 5-HT neurons. *In vivo*, WAY-100635 also blocked the ability of 8-OH-DPAT to inhibit the firing of dorsal raphe 5-HT neurons, to induce the 5-HT syndrome, hypothermia and hyperphagia, and to elevate plasma ACTH levels.[38]

In the forskolin-stimulated adenylyl cyclase assay using rat hippocampus, *p*-MPPI showed no intrinsic agonist activity, but completely antagonized the inhibition of 5-HT turnover induced by the 5-HT$_{1A}$ receptor full agonist 8-OH-DPAT.[41] Furthermore, in the absence of intrinsic effects, *p*-MPPI antagonized the hypothermia, 5-HT syndrome and inhibition of 5-HT turnover induced by 8-OH-DPAT.[44,49]

LY-297996 was found to block 8-OH-DPAT–induced inhibition of forskolin-stimulated adenylate cyclase in rat hippocampus[45] and to prevent 8-OH-DPAT–induced elevations in serum corticosterone.[50] In addition, the drug antagonized the 8-OH-DPAT cue[51] and blocked 8-OH-DPAT–induced hyperphagia.[45]

In models of presynaptic activity, SL-88.0338 blocked 8-OH-DPAT–induced inhibition of dorsal raphe firing, reversed 8-OH-DPAT–induced reduction of 5-HTP levels in the rat hypothalamus, hippocampus and cortex, and antagonized 8-OH-DPAT–induced hypothermia in mice. In addition, SL-88.0338 potentiated 5-HTP–induced head twitches in mice, suggesting that it can enhance the effects of 5-HTP on 5-HT overflow via inhibition of presynaptic 5-HT$_{1A}$ receptors. In models of postsynaptic activity, SL-88.0338 antagonized 8-OH-DPAT– induced inhibition of forskolin-stimulated cAMP production in rat hippocampus and blocked 8-OH-DPAT–induced forepaw treading in rats. SL-88.0338 also antagonized the discriminative stimulus effects and the rate-decreasing effects of 8-OH-DPAT in an operant discrimination procedure in rats. Interestingly, SL-88.0338 exhibited inverse agonist effects, as it inhibited basal 5-HT$_{1A}$ receptor-mediated [^{35}S]-GTPγS binding in CHO-h5-HT$_{1A}$ membranes, unlike WAY-100635, which exhibited antagonist activity without any detectable agonist or inverse agonist effects in this model.[46]

DU-125530 was shown to act as a full antagonist on cloned human 5-HT$_{1A}$ receptor. *In vivo*, it antagonized the discriminative stimulus effects of the 5-HT$_{1A}$ receptor full agonist flesinoxan.[47]

NAD-299 behaved as a postsynaptic 5-HT$_{1A}$ receptor antagonist in both *in vitro* and *in vivo* experiments. It blocked 5-HT–induced inhibition of vasoactive intestinal peptide-stimulated cAMP production in GH_4ZD10 cells and had no intrinsic activity. Moreover, NAD-299 antagonized the 8-OH-DPAT–induced 5-HT syndrome effects, hypothermia and corticosterone secretion.[48]

Effects of selective 5-HT$_{1A}$ receptor antagonists in animal models of emotional behaviors

A bewildering diversity of animal procedures claim to model anxiety.[52,53] Most of them involve exposure of animals to external (e.g., cues previously paired with footshock) or internal (e.g., drug states) stimuli that are assumed to be capable of inducing anxiety in humans. The first of these categories can be grouped into two subclasses: the first subclass includes

TABLE II: EFFECTS OF SELECTIVE 5-HT$_{1A}$ RECEPTOR BLOCKERS IN ANIMAL MODELS OF ANXIETY.

TESTS	WAY-100635	*p*-MPPI	LY-297996	SL-88.0338	DU-125530
Geller-Seifter conflict	0	0		0	
Vogel conflict	0/+	+		+	
Pigeon conflict	0				
Fear-potentiated startle	+				+
Conditioned emotional response	0				
Ultrasonic distress vocalization	0				
Elevated plus-maze	0/+	+	0/+	+	
Light/dark	–/0/+			0	
Social interaction	0				
Defensive behaviors	+	+		+	

+, anxiolytic-like effect; 0, inactive; –, anxiogenic-like effects. See text for references.

ethologically based paradigms and involves animals' spontaneous or natural reactions to stressful stimuli that do not explicitly involve pain or discomfort (e.g., elevated plus-maze, light/dark, social interaction, defensive behaviors); the second subclass involves animals' conditioned or unconditioned responses to stressful and often painful events (e.g., exposure to electric footshock conflict tests).

WAY-100635 is the most studied 5-HT$_{1A}$ receptor antagonist in anxiety models. As shown in Table II, results obtained with this compound have been highly variable. In the elevated plus-maze test in mice, WAY-100635 has been shown to produce robust anxiolytic-like effects on both conventional (open arm activity) and ethological (risk assessment) measures.[54–56] Similarly, in a mouse defense test battery, where animals are directly confronted with a natural threat (i.e., a rat) as well as situations associated with this threat, WAY-100635 was found to modify defensive behaviors in much the same way as the benzodiazepine anxiolytic diazepam.[57] Furthermore, evidence for an anxiolytic-like action of WAY-100635 has also been reported in certain rat models of anxiety, such as the fear-potentiated startle,[58] the Vogel conflict[59] and light/dark exploration[60] tests. However, there are a significant number of reports indicating that WAY-100635 is inactive in anxiety models. Thus, negative findings have been obtained in rat and pigeon conflict,[59,61–66] rat ultrasonic vocalization,[67–71] rat conditioned emotional response,[61,72] mouse stress-induced hyperthermia,[73] mouse light/dark,[74] rat social interaction[75] and rat elevated plus-maze[64,75–77] tests.

Studies with *p*-MPPI and SL-88.0338 have also yielded differential profiles. Both drugs were found active in the elevated plus-maze and Vogel conflict tests and reduced defensive behaviors of mice confronted with a rat.[57,59,78] However, they failed to alter punished responses in a modified Geller-Seifter procedure.[59] In addition, SL-88.0338 did not change avoidance behavior of a brightly illuminated area in the light/dark test in mice.[59] The few studies with LY-297996 and DU-125530 showed that the former produced variable effects in the elevated plus-maze test,[79–81] whereas the latter was active in the fear-potentiated startle test in rats[58] but without effect against stress-induced hyperthermia in mice.[73]

While some of these negative data may be due to the use of limited dose ranges, the general pattern of inconsistency has yet to be adequately explained. On the basis of the finding that LY-297996 produces anxiolytic-like activity in the murine elevated plus-maze in the mid-dark, but not the mid-light phase, it has been suggested that circadian factors may be important in the detection of 5-HT$_{1A}$ receptor antagonist anxiolysis.[80,81] Interestingly, when the 5-HT$_{1A}$ receptor antagonists displayed anxiolytic-like effects, the magnitude of their effects was generally smaller than that of the benzodiazepine diazepam. However, comparisons with the 5-HT$_{1A}$ receptor agonist buspirone, a compound currently used in the treatment of generalized anxiety disorders, suggest that the anxiety-reducing potential of 5-HT$_{1A}$ receptor antagonists may be superior to that of full or partial agonists for this receptor. Clinical trials with 5-HT$_{1A}$ receptor antagonists in patients with anxiety disorders will eventually determine whether such compounds may be useful in the treatment of these disorders.

The precise mechanisms underlying the positive effects of 5-HT$_{1A}$ receptor antagonists in anxiety models remain to be determined. These compounds have all demonstrated antagonistic-like activity on pre- and postsynaptic 5-HT$_{1A}$ receptors. As a result of findings that exposure to aversive stimuli like those used in the above studies increases 5-HT release, we would expect a 5-HT$_{1A}$ receptor antagonist to attenuate this effect and thus display anxiolytic activity; however, further studies on this issue are clearly warranted.

Conclusion

In conclusion, the last few years have seen important advances in the understanding of 5-HT and its mechanisms of action in modulating responses to stress. Particularly, the findings that the blockade of 5-HT$_{1A}$ receptors may decrease anxiety-related behaviors in a variety of animal models suggest that selective 5-HT$_{1A}$ receptor antagonists/inverse agonists may have therapeutic effects in anxiety- or stress-related disorders. The development of such compounds as novel anxiolytics is

being actively pursued by a number of major pharmaceutical companies and data on the therapeutic potential of these compounds should become available soon.

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NOVARTIS R&D DAY 1999: INNOVATION DRIVES FUTURE GROWTH

Novartis has a rich R&D portfolio focused on seven key therapeutic areas and is in a position to launch three new products per year through 2003, according to company executives presenting September 21, 1999, at the Novartis R&D Investor Seminar in New York. The seven therapeutic areas being targeted by Novartis are transplantation and immunology; CNS; dermatology; cardiovascular/metabolic/endocrinology; respiratory diseases; oncology; and arthritis/inflammation/bone metabolism, with a total of 53 products (both new molecular entities and line extensions) in clinical trials or under regulatory review. The company also has a continuous stream of long-term projects going on, with 33 preclinical candidates reported to be in active development. In an ongoing process of portfolio prioritization, the development of seven investigational products has been terminated and four new projects have entered development since March 1999.

Near-term projects highlighted during R&D day include the photosensitizing agent **verteporfin** (*Visudyne*™), a novel treatment for age-related macular degeneration in development by the company's Ciba Vision subsidiary in collaboration with QLT PhotoTherapeutics. Registration dossiers for verteporfin have been submitted in the United States, Europe and Switzerland and priority review status has been granted by the FDA. The first approvals of the drug are expected to be received in the United States and Switzerland early next year, with product launches anticipated soon thereafter. Verteporfin will most likely be the first drug ever to reach the market for this indication.

Another significant near-term product is the insulin secretagogue **nateglinide** (*Starlix*®), an antidiabetic agent with a unique dual mechanism of action and excellent tolerability. Novartis has completed registration studies with nateglinide and expects to submit a New Drug Application (NDA) in December.

The company also has high hopes for the 5-HT_4 agonist **tegaserod maleate** (*Zelmac*®), a promising new treatment for irritable bowel syndrome. Three pivotal trials have been completed, and filing is slated for January 2000. Tegaserod is also in phase II testing for the indication of gastroesophageal reflux disease (GERD).

E25, an anti-IgE monoclonal antibody, represents a unique approach to the treatment of allergic asthma and rhinitis. In collaboration with development partner Tanox, Novartis has completed registration studies of E25 in allergic rhinitis and is nearing completion of registration studies in asthma. Filings will be made in mid-2000.

Four new products were mentioned for the first time during the presentation:

The COX-2 (cyclooxygenase type 2) inhibitor **COX-189** represents a new generation of compounds with a structure differing from those of celecoxib and rofecoxib. It is highly selective for COX-2 and has a quick onset of action, high potency, a broad spectrum of activity and an excellent tolerability profile.

KCO-912 is a potent and selective potassium K_{ATP} channel opener in development for asthma. It reduces the excitability of smooth muscle cells, neurons and secretory cells and decreases airways hyperreactivity, without producing the cardiovascular side effects seen with compounds such as cromakalim or bimakalim. KCO-912 demonstrated a wide therapeutic window in volunteer studies, and is now being evaluated in proof-of-concept studies in exercise-induced asthma.

ICL-670, a novel treatment for chronic iron overload, is in phase I testing. The appearance of this new product coincides with termination of **ICL-749**, a depot formulation of deferoxamine that was being developed for the same indication.

Finally, the company's CNS pipeline has been enhanced with the addition of **TCH-346**, a candidate antiparkinsonian that is in phase I testing.