Pergamon

0163-7258(94)00005-4

Pharmac. Ther. Vol. 66, pp. 339–368, 1995

0163-7258/95 $29.00

Specialist Subject Editor: F. MITCHELSON

SEROTONIN RECEPTORS: SUBTYPES, FUNCTIONAL RESPONSES AND THERAPEUTIC RELEVANCE

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Abstract—Recent, rapid progress in the molecular biology of serotonin (5-HT) receptors requires conceptual re-thinking with respect to receptor classification. Thus, based on operational criteria (agonist and antagonist rank order), as well as transduction mechanisms involved and the structure of the receptor protein, the *Nomenclature Committee of the Serotonin Club* has proposed the following classification and nomenclature: the main receptor types 5-HT_1 to 5-HT_4, recombinant receptors (e.g. 5-ht_5 to 5-ht_7) and 'orphan' receptors. The aim of the present review is to discuss the events leading to this classification, the criteria for and functional responses mediated by various 5-HT receptors, as well as the therapeutic possibilities with 5-HT ligands.

Keywords—Anxiety, cardiac disorders, central nervous system diseases, depression, gastric motility disorders, 5-hydroxytryptamine, 5-hydroxytryptamine receptors, hypertension, migraine, pain, serotonin, vomiting.

CONTENTS

Abbreviations—5-HT, 5-hydroxytryptamine, serotonin.

INTRODUCTION

Serotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter in the CNS, but is also present in particularly high concentrations in blood platelets and the enterochromaffin cells of gastrointestinal mucosa. Though the vasoconstrictor properties of defibrinated blood and blood serum were long known (Ludwig and Schmidt, 1868), it was only in 1948 that Page (1958) succeeded in isolating a crystalline complex 'serotonin' from the blood serum (Rapport *et al.*, 1948); the active moiety of this complex was found to be 5-HT (Rapport, 1949). In the 1930s, Erspamer and colleagues became involved in the characterization of 'enteramine' from the enterochromaffin cells in the gastrointestinal tract (see Erspamer, 1954). Subsequently, 'enteramine' was also identified as 5-HT and the chemical identity of the natural and synthetic serotonin was backed by the similarity of pharmacological profile, such as contraction of the sheep carotid artery, guinea-pig, mouse and rabbit jejunum, rat and cat uterus and cat nictitating membrane, triphasic blood pressure response and antagonism by yohimbine and potentiation by cocaine of the sheep carotid artery contraction (Erspamer, 1954; Page, 1958). Thus, the scene was set for the characterization of serotonin receptors.

2. EARLY SEROTONIN RECEPTOR CLASSIFICATIONS

2.1. Gaddum's 'M' and 'D' Serotonin Receptors

Woolley and Shaw (1953a,b) and Page and McCubbin (1953) reported that the vascular responses to serotonin could be antagonized by several drugs including some tryptamine derivatives. Gaddum (1953) found that the guinea-pig isolated ileum was selectively desensitized to serotonin or substance P by high concentrations of these substances, suggesting that the two compounds activated different receptor populations. The serotonin-induced contraction of the guinea-pig ileum was not affected by drugs such as diphenhydramine, nicotine (high doses), hexamethonium or decamethonium, but was partially suppressed by atropine and cocaine, as well as by its own repeated administration, at which time the responses to histamine, acetylcholine, pilocarpine or nicotine were unaffected (Feldberg and Toh, 1953; Rapport and Koelle, 1953; Rocha e Silva *et al.*, 1953). Gaddum and Hameed (1954) postulated that there must be two types of receptors on the enteric parasympathetic ganglia, which responded to either serotonin or nicotine. It was also reported that the vasoconstrictor effect of serotonin on the rabbit ear artery was not much affected by piperoxan, atropine or cocaine, was moderately antagonized by dibenamine and gramine, but was potently blocked by lysergide, dihydroergotamine or ergotamine.

A vital step towards characterization of serotonin receptors was undertaken by Gaddum and Picarelli (1957), who reported that the serotonin-induced guinea-pig ileum contraction was only partially blocked by either morphine or dibenzyline (phenoxybenzamine), but was completely antagonized by the combined use of the two compounds. Furthermore, lysergide, 2-bromolysergide and dihydroergotamine completely antagonized the response to serotonin in the morphine-treated ileum, and the same was true for atropine and cocaine in the dibenzyline-treated ileum. It was concluded, therefore, that serotonin activated two different types of receptors: an 'M' serotonin receptor, located on the parasympathetic ganglion and mediating acetylcholine release from postganglionic nerve endings, and a 'D' serotonin receptor, located on smooth muscles and directly contracting the muscle (Fig. 1). However, it may be noted that the interference of the contractile effect of serotonin by morphine and atropine was due to the inhibition of acetylcholine release (see Saxena, 1970) and its interaction with the muscarinic receptor, respectively; only cocaine proved to be a weak 'M' serotonin receptor antagonist (see Fozard, 1990), while phenoxybenzamine acted as an unspecific antagonist.

For a long time, no potent and selective antagonist at 'M' serotonin receptors was reported, but a number of compounds (e.g. cyproheptadine, lysergide, methysergide, pizotifen, mianserin) became known as 'D' serotonin receptor antagonists.

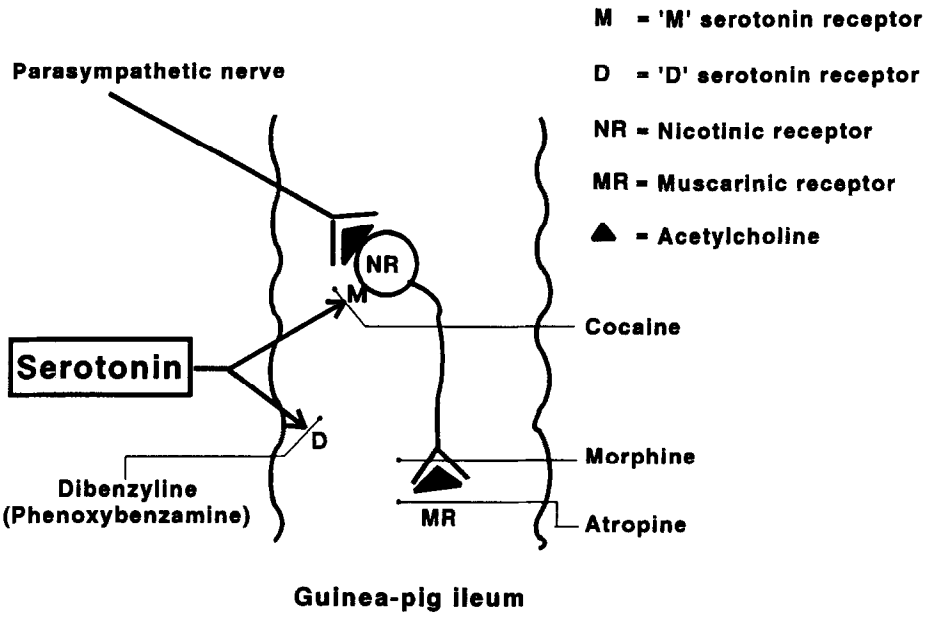

Fig. 1. Graphic illustration of the location of 'M' and 'D' serotonin receptors in the guinea-pig ileum.

2.2. Non-'M' and Non-'D' Serotonin Receptors

Despite the 'M' and 'D' serotonin receptor classification becoming widely accepted, there were some responses to serotonin which could not be placed within this scheme. For example, in the early 1970s, it was reported that the 'D' receptor antagonists, mianserin and cyproheptadine, failed to antagonize the vasoconstrictor effect of serotonin in the canine external carotid arterial bed (Fig. 2). Therefore, it was concluded that the serotonin receptors in the external carotid vascular bed of the dog were of a 'special' type and could not be categorized as either 'M' or 'D' type (Saxena *et al.*, 1971; Saxena, 1972; Saxena and De Vlaam-Schluter, 1974).

2.3. 5-HT_1 and 5-HT_2 'Receptors'

Bennett and Aghajanian (1974) reported the first successful radioligand binding study of serotonin receptors using D-[^{3}H]lysergide. [^{3}H]serotonin also showed a high affinity, but because of discrepancies between the binding of [^{3}H]lysergide and [^{3}H]serotonin, a recognition site with two different states was suggested (Bennett and Snyder, 1976; Fillion *et al.*, 1978). However, further studies with [^{3}H]serotonin, [^{3}H]spiperone and [^{3}H]lysergide enabled Peroutka and Snyder (1979) to suggest the existence of two distinct serotonin 'receptors'—a 5-HT_1 'receptor' (high nanomolar affinity for serotonin) and a 5-HT_2 'receptor' (high affinity for spiperone and low micromolar affinity for serotonin). Subsequently, Pedigo *et al.* (1981) reported that the 5-HT_1 binding site could be subdivided into 5-HT_{1A} and 5-HT_{1B} subtypes on the basis of high and low affinity, respectively, for spiperone. Soon, 8-OH-DPAT was recognized as a selective ligand for the 5-HT_{1A} subtype (Middlemiss and Fozard, 1983). This subdivision of the 5-HT_1 binding site continued into 5-HT_{1C} (Pazos *et al.*, 1984), 5-HT_{1D} (Heuring and Peroutka, 1987), 5-HT_{1E} (Leonhardt *et al.*, 1989) and 5-HT_{1F} (Amlaiky *et al.*, 1992; Adham *et al.*, 1993) subtypes; the 5-HT_{1D} subtype itself also appeared to be heterogeneous (Sumner and Humphrey, 1989).

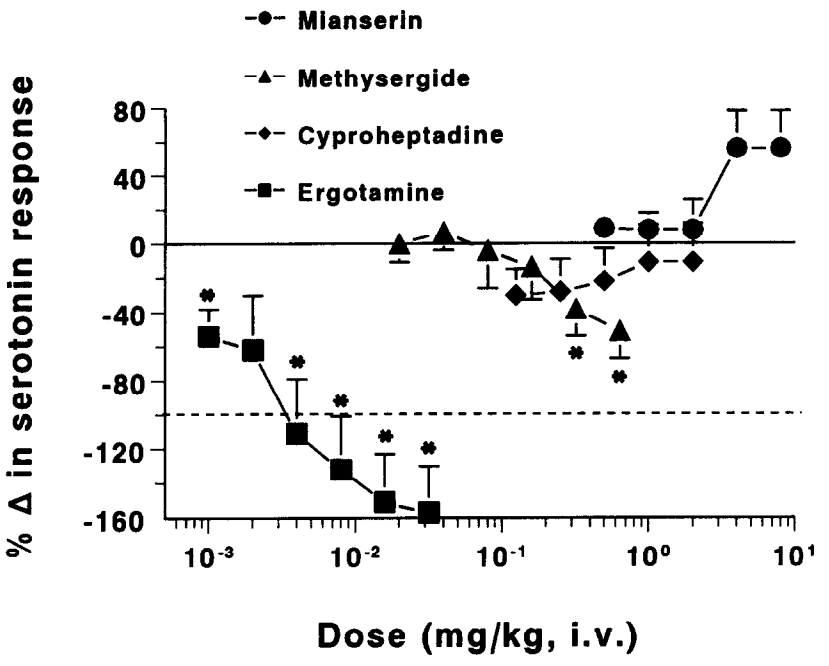

Fig. 2. Dog external carotid artery vascular bed. Effect of mianserin, methysergide, cyproheptadine and ergotamine on the vasoconstrictor response to serotonin. Values below the interrupted line (i.e. change more than 100%) mean that serotonin caused vasodilatation instead of vasoconstriction. Note that the apparent reversal of the response to serotonin by ergotamine may have been due to its strong vasoconstrictor property. *Significant ($p < 0.05$) change compared with parallel administration of saline. Data from Saxena *et al.* (1971) and Saxena (1972).

3. MODERN SEROTONIN RECEPTOR CLASSIFICATION

3.1. Development of a Framework

The need for a uniform terminology for serotonin receptors was apparent, since these receptors were being referred to by various names ('D', 'M', 5-HT_1, 5-HT_2, S_1, S_2 etc.) (Humphrey, 1983; Verdouw *et al.*, 1984). Indeed, it was suggested that the old serotonin receptor classifications "should give way to a new classification based on a 5-HT_1, 5-HT_2, 5-HT_n series... the 5-HT receptors subserving arteriolar dilatation, presynaptic inhibition of sympathetic transmission, autoinhibition in the brain and possibly constriction of arteriovenous anastomoses, could be termed 5-HT_1. The receptors mediating vaso- and broncho-constriction and platelet aggregation could be called 5-HT_2 receptors and those mediating ganglionic stimulation, the Bezold–Jarisch reflex and catecholamine release in the heart should be designated as 5-HT_3 receptors in place of 'M' receptors. As there are many effects of 5-HT which await classification... this series could, if needed, be extended by using both numbers and letters (as additional subscripts)" (Verdouw *et al.*, 1984).

In 1986, a group of scientists formulated criteria for the characterization, and a general framework for the nomenclature of serotonin receptors. From the beginning, it was obvious that either of the two previous classifications proposed by Gaddum and Picarelli (1957) and Peroutka and Snyder (1979) were incomplete, but did complement each other. Therefore, it was decided to build upon these two classifications, taking into account rank order and ligand binding affinities of the agonists and antagonists, with some consideration of the second messenger systems involved. Thus, serotonin receptors were classified into three main categories: 5-HT_1-like (corresponding to some 'D' receptors and 5-HT_1 binding sites), 5-HT_2 (corresponding to most 'D' receptors and 5-HT_2 binding sites) and 5-HT_3 (equivalent to 'M' receptors) (Bradley *et al.*, 1986). The important criteria for classification were: 5-HT_1-like receptors—5-carboxamidotryptamine, generally a more potent agonist than serotonin, high affinity for the antagonist methiothepin, but not for ketanserin or ICS 205-930 (tropisetron); 5-HT_2 receptors—high affinity for the agonist α-methyl-5-HT and antagonists

ketanserin and methiothepin, but not for tropisetron, coupling to phosphatidylinositol turnover; and 5-HT_3 receptors—high affinity for the agonist 2-methyl-5-HT and antagonist tropisetron, but not for ketanserin or methiothepin, part of cation channels. It was clearly pointed out that the 5-HT_1-like receptors were heterogeneous and that some serotonin responses, e.g. the tachycardia in the pig (Duncker *et al.*, 1985), still defied classification. Shortly thereafter, 5-HT_3 recognition sites were described in the brain (Kilpatrick *et al.*, 1987), and evidence in favour of 5-HT_4 receptors began to emerge (see Saxena, 1986; Bom *et al.*, 1988; Dumuis *et al.*, 1988, 1989).

3.2. Cloning of Serotonin Receptors

Since the original scheme of serotonin receptor classification was proposed (Bradley *et al.*, 1986), an enormous amount of new information on the molecular biology of serotonin receptors has become available. Several receptors have now been cloned and expressed in cells, and the amino acid sequence and structure of the receptor protein, as well as the gene involved, have been determined. Furthermore, using second messenger responses in the host cell, agonists' and antagonists' rank order of the recombinant serotonin receptors has been compared with that of the native receptors. This process has led to identification of several serotonin receptor clones (Table 1). In the case of 5-HT_4 receptors, the clones have two splice variants: a short form with 387 amino acids (5-ht_{4S}) and a long form with 407 amino acids (5-ht_{4L}) (Gerald *et al.*, 1994). Both these forms show similar pharmacology (Adham *et al.*, 1995), but the functional effects have not been established yet.

3.3. Approach to Receptor Classification

The knowledge accumulating from molecular biological work compels reconsideration of conceptual thinking behind receptor classification (Hoyer *et al.*, 1994), not only in the case of serotonin, but for other neurotransmitters. The Nomenclature Committee of the Serotonin Club, which evolved the Bradley Classification of serotonin receptors (Bradley *et al.*, 1986), once again assigned itself this task. After a brief report of its deliberations (Humphrey *et al.*, 1993), a detailed version approved by the main IUPHAR Committee for Receptor Nomenclature has been published recently (Hoyer *et al.*, 1994).

The IUPHAR receptor nomenclature committee has advocated a number of criteria for receptor classification (Kenakin *et al.*, 1992), and these have been extended by the Nomenclature Committee of the Serotonin Club (Hoyer *et al.*, 1994). As shown in Table 2, these criteria fall into three categories: operational (selective agonists, selective antagonists and ligand binding affinities), structural (molecular structure of the receptor protein and, thus, the extent of homology) and transductional (intracellular receptor–effector coupling mechanism). Together, these provide a 'finger-print' basis for identifying distinct receptors.

It is undeniably true that the structure of the receptor protein is the mark of true identity of the receptor. However, it is equally important to realize that substantial changes in the amino acid sequence may not affect (e.g. in the case of 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors), while little alteration may cause vast changes in the operational characteristics of a receptor (e.g. in case of species homologous 5-HT_{1B} and 5-$HT_{1D\beta}$ receptors) (Hartig *et al.*, 1992).

Two other important recommendations have been made by Hoyer *et al.* (1994). Firstly, in keeping with the earlier suggestion (Kenakin *et al.*, 1992), it has been advised to use lower case letters for recombinant receptors with little knowledge of operational characteristics (e.g. 5-ht_5 receptor) and upper case letters for reasonably well-characterized native receptors (e.g. 5-HT_2 receptor). Secondly, since not all necessary criteria, as outlined in Table 2, are always available, it is probably not possible to obtain a fully rationale classification scheme. Therefore, it is necessary to hold certain receptors provisionally in an 'orphan' category awaiting further characterization.

3.4. The Present Classification of Serotonin Receptors

Based on the general criteria mentioned in Table 2 and in keeping with the above recommendations, serotonin receptors can be subdivided into four main classes (5-HT_1, 5-HT_2, 5-HT_3

Table 1. *Cloned Serotonin Receptors*

Species	Receptor	nAA	Remarks	References
Human	5-HT_{1A}	421	G21 clone, intronless gene	Kobilka *et al.*, 1987; Fargin *et al.*, 1988
Rat	5-HT_{1A}	422	89% homology with the human receptor, intronless gene	Albert *et al.*, 1990
Rat	5-HT_{1B}	386	Probe derived from human 5-$HT_{1D\beta}$ clone	Voigt *et al.*, 1991; Aldman *et al.*, 1992
Mouse	5-HT_{1B}	386	Sequence slightly different from the rat receptor	Maroteaux *et al.*, 1992
Human	5-$HT_{1D\alpha}$	377	Primers derived from canine RDC4 receptor	Hamblin and Metcalf, 1991; Hartig *et al.*, 1992; Weinshank *et al.*, 1992
Rat	5-$HT_{1D\alpha}$	374	95% homology in transmembrane region with the human receptor	Hamblin *et al.*, 1992; Bach *et al.*, 1993
Human	5-$HT_{1D\beta}$	390	Pharmacologically as 5-$HT_{1D\beta}$, but is considered as a species homologue of the rat 5-HT_{1B} receptor	Hartig *et al.*, 1992; Jin *et al.*, 1992; Levy *et al.*, 1992a; Weinshank *et al.*, 1992
Human	5-ht_{1E}	365	AC1/S31 clone, intronless gene	Levy *et al.*, 1992b; McAllister *et al.*, 1992; Gudermann *et al.*, 1993
Human/rat	5-ht_{1F}	366	Intronless gene	Adham *et al.*, 1993; Lovenberg *et al.*, 1993b
Mouse	5-ht_{1F}	367	Previously mentioned as 5-HT_{1E}-like	Amlaiky *et al.*, 1992
Rat	5-HT_{2A}	449/471	80% homology in transmembrane region with 5-HT_{1C}	Pritchett *et al.*, 1988; Juluis *et al.*, 1990
Human	5-HT_{2A}	471	Sequence resembles the rat receptor	Saltzman *et al.*, 1991
Mouse	5-HT_{2B}	460	Partial sequence, previously mentioned as serotinin-like receptor	Foguet *et al.*, 1992a
Mouse	5-HT_{2B}	504	Full sequence, expressed in brain, heart, intestine	Loric *et al.*, 1992
Rat	5-HT_{2B}	479	Isolated from rat fundus cDNA	Foguet *et al.*, 1992b; Kursar *et al.*, 1992
Rat	5-HT_{2C}	460	Previously 5-HT_{1C}, gene has introns	Julius *et al.*, 1988; Lübbert *et al.*, 1987a,b
Human	5-HT_{2C}	458		Saltzman *et al.*, 1991
Human	5-HT_3	487	Part of channel complex; single subunit isolated from NCB-20 cells	McKernan *et al.*, 1990; Maricq *et al.*, 1991
Rat	5-HT_4	387/407	Splice varient: short (5-ht_{4S}) and long (5-ht_{4L}) forms	Gerald *et al.*, 1994
Mouse/rat	5-ht_{5A}	357	MR22 clone in rat	Plassat *et al.*, 1992; Matthes *et al.*, 1993; Erlander *et al.*, 1993
Mouse/rat	5-ht_{5B}	370/371	REC 17 clone in rat	Plassat *et al.*, 1992; Matthes *et al.*, 1993; Erlander *et al.*, 1993
Rat	5-ht_6	437/436	Cloned from rat striatal mRNA; gene has one intron	Monsma *et al.*, 1993; Ruat *et al.*, 1993a
Rat	5-ht_7	448/435/404	Intron-containing gene	Meyerhof *et al.*, 1993; Ruat *et al.*, 1993b; Shen *et al.*, 1993
Mouse	5-ht_7	448		Lovenberg *et al.*, 1993a; Plassat *et al.*, 1993
Human	5-ht_7	445		Bard *et al.*, 1993

Abbreviation—nAA, (predicted) number of amino acids.

Table 2. *Criteria for Receptor Characterization and Classification*

Operational	Structural	Transductional
Selective agonists • Agonists with unique or high selectivity as compared with their potency at other receptors • Relative equiactive concentration ratios • Specific rank order of potency of agonists *Selective antagonists* • Potent and specific antagonists • Dissociation constants and rank order for the receptor interaction *Ligand binding affinities* • Dissociation constants (affinity measures) for ligands (selective agonists and antagonists) should correlate with corresponding data from functional studies	*Molecular structure* • Amino acid sequence of the receptor protein provides definitive evidence of receptor identity • Receptors that are structurally different may not be different in operational terms and vice versa • Relative homologies of receptors can also provide useful data for receptor classification	*Intracellular transduction mechanisms* • Important information that further defines the receptor superfamily (i.e. ligand-gated ion channel or G-protein linked) • Helps define the nature of the G-proteins linkage (if any), which, in turn, relates to the nature of the intracellular protein structure of the receptor itself

The above data provide a 'finger-print' basis on which to identify and classify distinct receptors. Adapted from Hoyer *et al.* (1994).

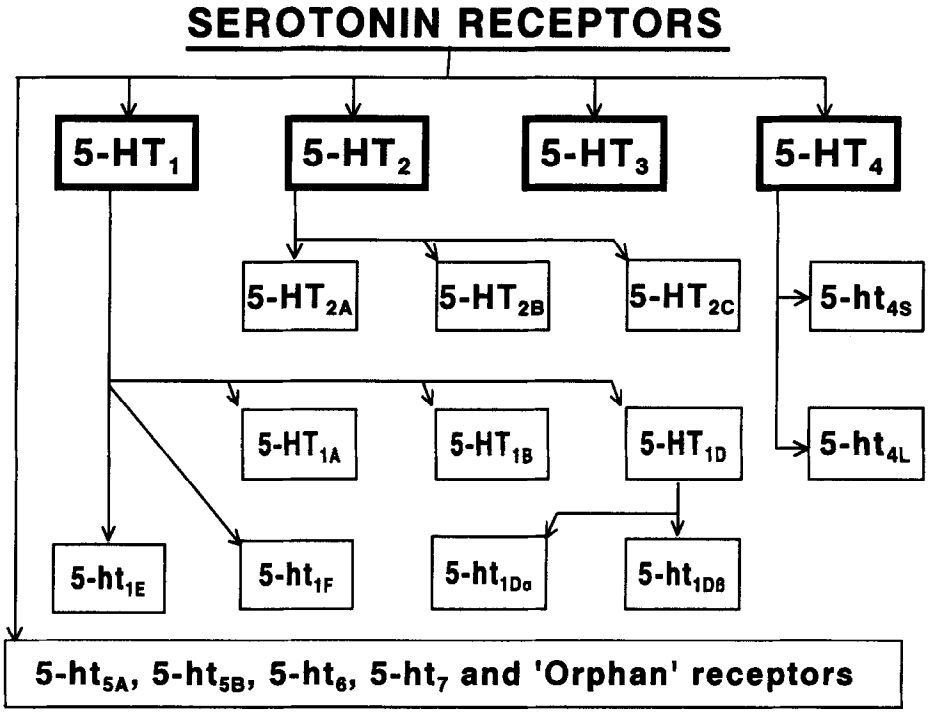

Fig. 3. Subclassification of serotonin receptors. The receptors denoted in lower capital (e.g. 5-ht$_6$) are recombinant receptors, which are not fully characterized yet. The 5-ht$_{4S}$ and 5-ht$_{4L}$ receptors are the short and long splice variants of the 5-ht$_4$ receptor.

and 5-HT$_4$ receptors), with certain recombinant (5-ht$_{1D\alpha}$, 5-ht$_{1D\beta}$, 5-ht$_{1E}$, 5-ht$_{1F}$, 5-ht$_{4S}$, 5-ht$_{4L}$, 5-ht$_{5A}$, 5-ht$_{5B}$, 5-ht$_6$ and 5-ht$_7$) and 'orphan' receptors (Fig. 3).

The specific operational, structural and transductional properties of the different serotonin receptors are shown in Table 3 (Hoyer *et al.*, 1994). Structurally, all serotonin receptors, except the 5-HT$_3$ receptor, which forms a part of cation channels, belong to the G-protein superfamily and contain the characteristic seven transmembrane regions. All 5-HT$_1$ receptors are negatively coupled to adenylyl cyclase; all 5-HT$_2$ receptors, including the previously called 5-HT$_{1C}$ receptor (hence renamed 5-HT$_{2C}$), are coupled to protein kinase C via increased phosphoinositide breakdown, while the 5-HT$_4$, 5-ht$_6$ and 5-ht$_7$ receptors are positively linked to adenylyl cyclase.

Except for the recombinant subtypes 5-ht$_{1E}$ and 5-ht$_{1F}$ (which have been placed in the group based on structural homology and transductional similarity), operationally all other 5-HT$_1$ receptors have high affinity for 5-carboxamidotryptamine as agonist and methiothepin as antagonist. It should be noted that such operational criteria also apply to the 'orphan' receptor mediating smooth muscle relaxation; indeed, it was known previously as the sumatriptan-insensitive 5-HT$_1$-like (or 5-HT$_{1Y}$) receptor (Bradley *et al.*, 1986; Saxena and Villalón, 1990a). However, in view of its positive coupling to adenylyl cyclase, this receptor, which may turn out to be identical to the recombinant 5-ht$_7$ receptor (Bard *et al.*, 1993; Plassat *et al.*, 1993), has been placed in the 'orphan' category. The 5-HT$_{1A}$ receptor has a high and selective agonist affinity for flesinoxan, 8-OH-DPAT and dipropyl-5-carboxamidotryptamine, the 5-HT$_{1B}$ receptor has a high selective agonist affinity for CP 93,129, while both 5-HT$_{1D}$ and 5-HT$_1$-like receptors have a relatively high affinity for sumatriptan. Selective antagonists have only recently been described for 5-HT$_{1A}$ (WAY 100135; Fletcher *et al.*, 1993) and 5-HT$_{1D}$ (GR 127935; Skingle *et al.*, 1993; Clitherow *et al.*, 1994) receptors, and undoubtedly, these will help in further characterization. With regard to the 5-HT$_1$-like receptors, it is to be noted that their structure has not been elucidated yet (Table 3) and that these may be heterogeneous (see Saxena and Villalón, 1990a; Hoyer *et al.*, 1994). The operational characteristics of 5-HT$_1$-like receptors resemble those of 5-ht$_{1D\alpha}$ and 5-ht$_{1D\beta}$ receptors, and it is possible that some 5-HT$_1$-like receptors may turn out to be identical to these or other recombinant receptors.

Table 3. *Classification of Serotonin Receptors based on Operational and Transductional Criteria (Hoyer* et al., *1994)*

Receptor subtype	Operational: Agonists	pEC_{50}	Operational: Antagonists	pK_B/pA_2	Structural: Ligands	Structural: Gene code	Structural: nAA	Structural: nTM	Transductional: Effector pathway	Location	Comments
5-HT$_1$											
5-HT$_{1A}$	DP-5-CT	8.7	SDZ 216525	10.0	[^{3}H]8-OH-DPAT	X13556	421	7	cAMP ↓	Neuronal,	Well-characterized, but
	5-CT	8.6	NAN 190	8.9	[^{3}H]5-HT				K^+ channel ↑	mainly CNS	potent silent, and
	8-OH-DPAT	8.2	Cyanopindolol	8.1	[^{3}H]Ipsapirone						selective antagonists only
	RU 24696	7.8	Methiothepin	7.7	[^{3}H]WB4101						recently available
	Flesinoxan	7.7	WAY 100135	~7.5	[^{125}I]PAPP						
5-HT$_{1B}$	RU 24969	8.4	Cyanopindolol	8.2	[^{125}I]Pindolol	M89954	386	7	cAMP ↓	CNS and	Appears to be rodent
	5-CT	7.9	Methiothepin	8.1	[^{3}H]5-HT					peripheral	equivalent of 5-HT$_{1D\beta}$
	CP 93,129	7.8	Isamoltane	7.3	[^{3}H]CP 93,129					nerves	receptor
5-HT$_{1D}$	L 694247	9.4	GR 127935	9.9	[^{3}H]5-HT	M81589	377	7	cAMP ↓	Mainly CNS	Two 5-HT$_{1D}$ types cloned
	5-CT	8.1	Methiothepin	7.7	[^{125}I]GTI	(5-ht$_{1D\alpha}$)					(5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$)
	NAN 190	7.6	Mianserin	6.5	[^{3}H]5-CT	M81590	390	7			
	Methysergide	7.0			[^{3}H]L 694247	(5-HT$_{1D\beta}$)					
	Sumatriptan	7.0									
5-ht$_{1E}$[1]	Ergotamine	6.2	Methiothepin	6.7	[^{3}H]5-HT	M91467	365	7	cAMP ↓	Only CNS	Functions yet unknown
	5-CT	5.2	Methysergide	6.5							5-CT: weak agonist
	Sumatriptan	5.6	Metergoline	5.6							Methiothepin: weak antagonist
5-ht$_{1F}$[2]	Sumatriptan	7.6	Methysergide	7.5	[^{3}H]5-HT	L04962	366	7	cAMP ↓	Mainly CNS	Functions yet unknown
	Ergotamine	6.8	Yohimbine	7.0							5-CT: weak agonist
	α-Methyl-5-HT	6.7	Metergoline	6.5							Methiothepin: weak antagonist
	5-CT	6.1	Methiothepin	6.2							
5-HT$_1$-like	5-CT	8.1	Methiothepin	8.5	None yet				cAMP ↓	Cephalic and	Not yet fully
	5-HT	7.6	Metergoline	6.8						some other	characterized, but some
	Sumatriptan	6.6								vasculature	may be 5-HT$_{1D}$, 5-ht$_{1F}$
	Methysergide	6.5[3]									or other recombinent receptor
											Previous name: 5-HT$_{1X}$

Continued

Table 3. *Continued*

Receptor subtype	Operational: Agonists	pEC_{50}	Operational: Antagonists	pK_B/pA_2	Structural: Ligands	Structural: Gene code	Structural: nAA	Structural: nTM	Transductional: Effector pathway	Location	Comments
5-HT$_2$											
5-HT$_{2A}$	DOI	7.6	Pirenperone	9.4	[^{3}H]Ketanserin	X57830	471	7	IP_3/DAG	Vascular smooth muscle	Classical 5-HT$_2$ receptor
	α-Methyl-5-HT	7.3	Ketanserin	9.3	[^{3}H]Spiperone						Previous names: 'D', 5-HT$_2$
	RU 24969	6.1	Methiothepin	9.0	[^{3}H]Mianserin						
			Mianserin	8.0	[^{125}I]DOI						
5-HT$_{2B}$[4]	5-MeO-t	8.15	Pizotifen	7.4	[^{3}H]5-HT	X66842	479	7	IP_3/DAG	Rat stomach fundus	Previous name: 5-HT$_{1Fundus}$
	Tryptamine	6.7	Rauwolscine	7.2							
	2-Methyl-5-HT	6.5	Methysergide	7.1							
5-HT$_{2C}$	α-Methyl-5-HT	7.3	Metergoline	10.6	[^{3}H]Mesulergine	M81778	458	7	IP_3/DAG	CNS, high concentrations in choroid plexus	Previous name: 5-HT$_{1C}$
	DOI	7.0	Mesulergine	9.1	[^{3}H]5-HT						
	mCPP	6.9	Methysergide	8.9	[^{125}I]DOI						
	RU 24969	6.2	LY 53857	8.5							
5-HT$_3$	2-Methyl-5-HT	7.7	Tropisetron	10.6	[^{3}H]GR 65630	M74425	487		Cation channel	Peripheral and central neurons	Previous name: 'M'
	Phenylbiguanide	6.8	Zacopride	10.1	[^{3}H]Granisetron	Ion channel unit					
			Granisetron	10.1	[^{3}H]Zacopride						
			Ondansetron	7.5	[^{3}H]Tropisetron						
			Renzapride	8.6							
5-HT$_4$	5-MeO-t	7.0	SB 204070	10.4	[^{3}H]GR 113808		387[5]	7	cAMP ↑	Human heart, GI-tract, urinary bladder	Seems to be absent on the heart ventricle
	Renzapride	6.9	GR 113808	9.7	[^{125}I]SB 207710		407[5]	7			
	Zacopride	6.0	SDZ 205557	7.4							
			SC-53606	7.9							
5-ht$_{5A}$[6]	Ergotamine	8.4	Methysergide	7.2	[^{125}I]Lysergide	Z18278	371	7	?	CNS	Functions unknown Sumatriptan insensitive
	5-CT	7.8	Methiothepin	7.0							
	RU 24969	6.5	Yohimbine	6.0							
5-ht$_{5B}$[6]	Ergotamine	8.5	Methiothepin	7.8	[^{125}I]Lysergide	X69867	357	7	?	CNS	Functions unknown Sumatriptan insensitive
	5-CT	7.4	Methysergide	6.9							
	RU 24969	6.4	Yohimbine	6.0							
5-ht$_6$[7]	DHE	7.9	Methiothepin	8.7		L03202	437	7	cAMP ↑	CNS	Functions unknown
	5-MeO-t	7.4	Metergoline	7.5							
	5-CT	6.1	Ritanserin	7.4							
5-ht$_7$[8]	5-CT	9.0	Methiothepin	8.4		L21195	445	7	cAMP ↑	CNS	Functions unknown
	5-MeO-t	8.3	Metergoline	8.2							
	Sumatriptan	6.0	Ketanserin	5.9							

'Orphan'					
?	5-CT	Methiothepin	cAMP ↑	Vascular smooth muscle	Arterial relaxation. Previous names: 5-HT_1-like, 5-HT_{1Y}
?	723C86	Cyproheptadine		Vascular endothelium	Relaxes the rabbit jugular vein
?				Rat motoneuron	Causes depolarization
?				Pig coronaries	Inhibits noradrenaline release
?				GI-tract neurons	Causes depolarization

[1]Levy *et al.* (1992b); [2]Adham *et al.* (1993); [3]partial agonist; [4]Foguet *et al.* (1992); [5]Two splice varients: short (5-HT_{4S}) and long (5-HT_{4L}) forms, Gerald *et al.* (1994); [6]Matthes *et al.* (1993); [7]Monsma *et al.* (1993); [8]Bard *et al.* (1993).

Abbreviations—DAG, Diacylglycerol; GI-tract, gastrointestinal tract; IP_3, inositol (1,4,5) triphosphate; nAA, number of amino acids in the receptor from one of the species (for more details, see Table 1); nTM, number of transmembrane domains.

Compounds—CP 93,129, 5-hydroxy-3(4-1,2,5,6-tetrahydropyridyl)-4-azaindole (Koe *et al.*, 1992); 5-CT, 5-carboxamidotryptamine; DHE, dihydroergotamine; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-amino propane; DP-5-CT, dipropyl-5-carboxyamidotryptamine; GR 113808, [1-[2-(methylsulphonyl)aminoethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate (Grossman *et al.*, 1993); GR 127935, *N*-[methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl) [1,1,-biphenyl]-4-carboxamide (Skingle *et al.*, 1993; Clitherow *et al.*, 1994); GR 65630, 3-(5-methyl-1H-imidazol-4-yl)-1-(1-methyl-1H-indol-3-yl)-1-propranone; GTI, 5-*O*-carboxyamidomethylglycyl[^{125}I]tyrosinamide-tryptamine; L 694247, 2-[5-[3-(4-methylsulphonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1H-indole-3-yl]ethylamine (Beer *et al.*, 1993); LY 53857, 4-isopropyl-7-methyl-9-(2-hydroxy-1-methylpropoxy carbonyl)-4,6,6A,7,8,9,10,10A-octahydroindolo[4,3FG]quinolone; 8-OH-DPAT, 8-hydroxy-2-(di)-*n*-propylamino-tetralin; mCPP, 1-(3-chlorophenyl)piperazine; 5-MeO-t, 5-methoxytryptamine; NAN 190, 1-(2-methoxyphenyl)-4-[4-(2-pthalimmido)butyl]piperazine hydrobromide (Glennon *et al.*, 1988); PAPP, 1-(2-[4-aminophynyl]ethyl)-4-(3-trifluoromethylphenyl)piperazine (LY 165163); RU 24696, 5-methoxy-3(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole; SB 204070, (1-butyl-4-piperidinylmethyl)-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate (Wardle *et al.*, 1993); SB 207710, (1-butyl-4-piperidinyl)methyl-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate (Gaster *et al.*, 1993); SC-53606, (1-S,8-S)-*N*-[(hexahydro-1H-pyrrolizin-1-yl)methyl]-6-chloroimidazol[1,2-a]pyridine-8-carboxamide hydrochloride; SDZ 205557, 2-methoxy-4-amino-5-chlorobenzoic acid 2-(diethylamino)ethyl ester; SDZ 216525, methyl-4-(4-[4-1,1,3-trioxo (2H-1,2-benzoiothiazol-2-yl)-butyl]-1-piperazinyl)1H-indole-2-carboxylate (Hoyer *et al.*, 1991); WAY 100135, *N*-tert-butyl-3-(4-[2-methoxyphenyl]piperazin-1-yl)-2-phenyl-propanamide dihydrochloride (Fletcher *et al.*, 1993; Mundey *et al.*, 1994); WB4101, 2-(2,6-dimethoxyphenoxyethyl) aminomethyl-1,4-benzodioxane; 723C86, (±)1-[5-(2-thenyloxy-1H-indol-3-yl)propan]-2-amine hydrochloride (Martin *et al.*, 1993).

The operational characteristics of 5-HT_2 receptor subtypes are similar, but not identical; ketanserin seems to be much more potent at the 5-HT_{2A} receptor than at the two other subtypes. In the case of the 5-HT_3 and 5-HT_4 receptors, potent and selective antagonists are now available.

4. RESPONSES MEDIATED BY SEROTONIN RECEPTORS

The functional responses associated with the different 5-HT_1 receptor subtypes are listed in Table 4. The 5-HT_{1A} receptor stimulation is associated with behavioural changes and a centrally mediated hypotensive response. The 5-HT_{1B} receptor is present in the rodent CNS and seems primarily associated with decrease in transmitter release. The same appears to be the case with 5-HT_{1D} receptors in other mammals. In addition, it is suggested, though not definitely established yet, that stimulation of 5-$ht_{1D\alpha}$ receptor decreases plasma extravasation following trigeminal nerve stimulation (Buzzi *et al.*, 1991; Matsubara *et al.*, 1991), while 5-$ht_{1D\beta}$ receptors mediate contraction of cerebral arteries (Hamel *et al.*, 1993). The contraction of cephalic arteries and arteriovenous anastomoses and inhibition of noradrenaline release from sympathetic nerve endings are mediated by 5-HT_1-like receptors, but some 5-HT_1-like receptors may be identical to the 5-HT_{1D} receptors (Hoyer *et al.*, 1994).

Table 5 present examples of functional responses mediated by 5-HT_2, 5-HT_3 and 5-HT_4 receptors. The 5-HT_{2A} receptor is ubiquitous and mediates mainly contraction of vascular and nonvascular smooth muscles, platelet aggregation and neuroexcitation. The 5-HT_{2B} receptor has been located primarily in the rat and mouse stomach fundus and mediates contraction. The 5-HT_{2C} receptor may regulate the amount and composition of the cerebrospinal fluid, as well as decrease locomotion and appetite. Undoubtedly, the 5-HT_3 receptor is involved in vomiting resulting from radiation and anticancer drugs. In addition, stimulation of the 5-HT_3 receptor, which is a part of a cation channel, results in depolarization of peripheral and central neurons. Stimulation of the 5-HT_4 receptor leads to decreases in K^+ conductance in colliculi neurons and increases in EEG energy. Peripherally, 5-HT_4 receptors affect motility of the gastrointestinal tract and mediate increases in the porcine and human atrial rate and contractility (Table 5). Interestingly, 5-HT_4 receptors seem to be absent on porcine (Saxena *et al.*, 1992; Schoemaker *et al.*, 1992), as well as human (Jahnel *et al.*, 1992; Schoemaker *et al.*, 1993) ventricles.

The structure of the recombinant 5-ht_{5A}, 5-ht_{5B}, 5-ht_6 and 5-ht_7 receptors is well-established, and these have been localized mainly in certain areas of the CNS, but the functions mediated are yet to be understood (Table 6). On the other hand, a number of serotonin receptors have been placed in a temporary 'orphan' category, since no structural data and only limited transductional and operational data are available yet (Table 6).

5. THERAPEUTIC USES OF SEROTONIN RECEPTOR LIGANDS

There are currently more than 70 pharmaceutical companies with interest in serotonergic drugs, and the leaders, in the rank order of the number of patents filed (and not the revenue earned), are shown in Fig. 4. This patent activity indicates that these companies expect to convert the new chemical entities into marketable products for therapeutic uses. The established, as well as some potential, therapeutic uses of serotonin receptor agonists and antagonists are listed in Table 7.

5.1. Anxiety States

The role of serotonin uptake inhibitors, as well as serotonin receptor ligands, in the treatment of anxiety states has been explored extensively (see Charney *et al.*, 1990; Murphy *et al.*, 1993). It appears that 5-HT_{1A} receptor partial agonists such as buspirone are clinically effective in generalized anxiety disorders and in anxiety associated with depression, but not in panic disorders. The effectiveness of these drugs in obsessive anxiety disorders has been investigated so far in only one controlled trial (see Murphy *et al.*, 1993). Animal experiments suggest that 5-HT_{1A} receptors located in the hippocampus, thalamus, amygdala and raphé nuclei are involved in the therapeutic effects of 5-HT_{1A} receptor partial agonists in anxiety (Charney *et al.*, 1990). Clinical results with the recently developed

Table 4. *Examples of Functional Responses Thought to be Mediated by 5-HT$_1$ Receptors Subtypes*[1]

Species	Tissues	Responses	References
5-HT$_{1A}$			
Several	Amygdala/raphé	Emotional changes	Hoyer *et al.*, 1986; Pazos *et al.*, 1987; Radja *et al.*, 1991
Rat	CNS	'Behaviour syndrome'	Tricklebank, 1985; Lucki, 1992
Cat	CNS	↓ BP, ↓ HR	Göthert and Kolassa, 1990
5-HT$_{1B}$			
Rat	Cerebral cortex	↓ 5-HT release	Middlemiss, 1986; Limberger *et al.*, 1991
Rat	Basal ganglia and other CNS areas	Changes in Ach and glutamate release	Middlemiss, 1986; Engel *et al.*, 1986; Limberger *et al.*, 1991
Rat	Vena cava	↓ NA release	Göthert *et al.*, 1986
Rat	Dura mater	Plasma extravasation	Saito *et al.*, 1988; Matsubara *et al.*, 1991
Rat	Caudal artery	Contraction	Craig and Martin, 1993
5-HT$_{1D}$			
Guinea-pig	Cerebral cortex	↓ 5-HT release	Middlemiss, 1986
Guinea-pig	Hippocampus	↓ ACh release	Harpel-Dupas *et al.*, 1991
Guinea-pig	Dura mater	Plasma extravasation	Buzzi *et al.*, 1991[2]
Pig	Coronary endothelium	EDRF-release	Schoeffter and Hoyer, 1990
Human	Cerebral arteries	Contraction	Hamel *et al.*, 1993[3]
5-ht$_{1E}$			
Human	Frontal cortex	Unknown	Leonhardt *et al.*, 1989
Several	CNS areas	Unknown	Beer *et al.*, 1992; Miller and Teitler, 1992
5-ht$_{1F}$			
Mouse/rat	CNS, mesentery, uterus	Unknown	Adham *et al.*, 1993; Lovenberg *et al.*, 1993b[4]
Mouse	Hippocampus	Unknown	Amlaiky *et al.*, 1992[4]
5-ht$_1$-like			
Human	Saphenous vein	Contraction	Bax *et al.*, 1992; Glusa and Müller-Schweinitzer, 1993
Dog	Saphenous vein	Contraction	Sumner and Humphrey, 1990; Müller-Schweinitzer, 1990; Sumner *et al.*, 1992
Rabbit	Saphenous vein	Contraction	Martin and MacLennan, 1990; Van Heuven-Nolsen *et al.*, 1990
Human	Pial arteries	Contraction	Hamel and Bouchard, 1991
Human	Basilar artery	Contraction	Parsons *et al.*, 1989
Monkey	Basilar artery	Contraction	Connor *et al.*, 1989b
Pig	Basilar artery	Contraction	Van Charldorp *et al.*, 1990
Dog	Basilar artery	Contraction	Connor *et al.*, 1989b
Guinea-pig	Basilar artery	Contraction	Chang and Owman, 1989
Pig	Carotid AVAs	Constriction	Saxena *et al.*, 1986, 1989
Human	Coronary artery	Contraction	Connor *et al.*, 1989a; Chester *et al.*, 1990; Bax *et al.*, 1993
Rabbit	Renal artery	Contraction	Tadipatri *et al.*, 1991, 1992
Guinea-pig	Iliac artery	Contraction	Sahin-Erdemli *et al.*, 1991; Schoeffter and Sahin-Erdemli, 1992
Human	Saphenous vein	↓ NA release	Moldering *et al.*, 1990
Dog	Saphenous vein	↓ NA release	Fenuik *et al.*, 1979; Watts *et al.*, 1981

[1]Based on Saxena and Villalón (1990a) and Hoyer *et al.* (1994); [2]claimed to resemble 5-HT$_{1D\alpha}$ subtype; [3]claimed to resemble 5-HT$_{1D\beta}$ subtype; [4]mentioned as 5-HT$_{1E\beta}$ or 5-HT$_{1E}$-like.

Abbreviations—Ach, acetylcholine; AVAs, arteriovenous anastomoses; BP, arterial blood pressure; EDRF, endothelium-derived relaxant factor (probably nitric oxide); HR, heart rate; NA, noradrenaline.

'silent' 5-HT$_{1A}$ receptor antagonists, such as WAY 100135 (Fletcher *et al.*, 1993), are awaited with interest to settle the question whether an agonist or antagonist activity is important in the anti-anxiety effect.

Some preliminary clinical trials suggest that 5-HT$_2$ and 5-HT$_3$ receptor antagonists may have a beneficial effect in generalized anxiety disorder patients (Murphy *et al.*, 1993; Greenshaw, 1993).

Table 5. *Examples of Functional Responses Thought to be Mediated by 5-HT$_2$, 5-HT$_3$ and 5-HT$_4$ Receptors*[1]

Species	Tissues	Responses	References
5-HT$_2$			
5-HT$_{2A}$			
Rat	Raphé cell bodies	Neuroexcitation	North and Uchimura, 1989
Monkey	Pituitary	Prolactin release	Heninger *et al.*, 1987
Dog	Adrenal medulla	Catecholamine release	Humphrey and Feniuk, 1987
Several	Many blood vessels	Contraction	Bradley *et al.*, 1986; Saxena and Villalón, 1990a
Several	Bronchial smooth muscle	Contraction	Bradley *et al.*, 1986
Several	Uterine smooth muscle	Contraction	Bradley *et al.*, 1986
Guinea-pig	Ileal smooth muscle	Contraction	Gaddum and Picarelli, 1957; Bradley *et al.*, 1986
Several	Blood platelets	Aggregation	Bradley *et al.*, 1986
5-HT$_{2B}$			
Mouse/rat	Stomach fundus	Contraction	Foguet *et al.*, 1992; Kursar *et al.*, 1992
Rat	Gut, heart, lung	Unknown	Foguet *et al.*, 1992
5-HT$_{2C}$			
Several	Choroid plexus	CSF composition?	Pazos *et al.*, 1984; Yagalof and Hartig, 1985
Rat	CNS areas	↓ Motion, feeding	Curzon and Kennett, 1990
5-HT$_3$			
Several	CNS areas	Not well understood, radiation vomiting, changes in cognition psychosis, drug craving	Kilpatrick *et al.*, 1987, 1990; Weber *et al.*, 1989; Hamon *et al.*, 1989; Laporte *et al.*, 1992
Several	Baro/chemoreceptors	Bezold-Jarisch reflex, radiation vomiting	Fozard, 1990; Saxena and Villalón, 1990a
Several	Peripheral neurons	Depolarization transmitter release	Fozard, 1990; Saxena and Villalón, 1990a
Cat	Parasympathetic neurons	Urinary bladder/gut contraction	Fozard, 1990; Saxena and Villalón, 1990a
Human	Skin neurons	Pain and flare	Orwin and Fozard, 1986
5-HT$_4$			
Mouse	Colliculi neurons	↓ K^+ conductance	Demuis *et al.*, 1988; Fagni *et al.*, 1992
Rat	CNS	↑ EEG-energy	Boddeke and Kalkman, 1990
Guinea-pig	Myenteric neurons	↑ Fast EPSP	Tonini *et al.*, 1989
Guinea-pig	Ileum	Contraction/peristalsis	Craig *et al.*, 1990; Buchheit and Buhl, 1991
Guinea-pig	Colon	Contraction	Elswood *et al.*, 1991; Wardle and Sanger, 1993
Rat	Ileum	Relaxation	Tuladhar *et al.*, 1991, 1992
Rat	Oesophagus	Relaxation	Baxter *et al.*, 1991a; Reeves *et al.*, 1991; Ford *et al.*, 1992
Human	Colon circular muscle	Contraction	Baxter *et al.*, 1991b; Tam *et al.*, 1992; McLean *et al.*, 1993
Human	Ileal musosa	↑ Short-circuit current	Burleigh and Brown, 1993
Monkey	Urinary bladder	Relaxation	Waiker *et al.*, 1994
Human	Urinary bladder	Contraction	Corsi *et al.*, 1991
Human	Adrenal cortex	Aldosterone release	Lefebvre *et al.*, 1993
Piglet	Atria	↑ Rate and force	Kaumann, 1990[2]
Pig	Heart	↑ Heart rate	Saxena, 1986; Villalón *et al.*, 1990, 1991[2]
Human	Atrial appendage	↑ Force	Kaumann *et al.*, 1990, 1991[3]

[1]Based on Hoyer *et al.* (1994); [2]porcine ventricles lack 5-HT$_4$ receptors (Saxena *et al.*, 1992; Schoemaker *et al.*, 1992); [3]human left ventricles lack 5-HT$_4$ receptors (Jahnel *et al.*, 1992; Schoemaker *et al.*, 1993).

Abbreviations—CSF, cerebrospinal fluid; EPSP, excitatory postsynaptic potential.

Table 6. *Examples of Functional Responses Thought to be Mediated by other Serotonin Receptors*

Species	Tissues	Responses	References
5-HT$_{5A/B}$			
Mouse/rat	CNS areas	Unknown	Plassat *et al.*, 1992; Matthes *et al.*, 1993; Erlander *et al.*, 1993
5-ht$_6$			
Rat	Striatum	Unknown	Monsma *et al.*, 1993; Ruat *et al.*, 1993a
5-ht$_7$			
Rat	Hypothalamus/thalamus	Unknown	Lovenberg *et al.*, 1993a
Rat	Cerebellum, heart, gut	Unknown	Plassat *et al.*, 1993
'Orphan' receptors			
'Orphan' (Vascular smooth muscle)			
Several	Vascular smooth muscle	Relaxation	Bradley *et al.*, 1986; Saxena and Villalón, 1990a
Pig	Vena cava	Relaxation	Trevethick *et al.*, 1986; Sumner, 1991
Cat	Saphenous vein	Relaxation	Humphrey and Fenuik, 1987
Rabbit	Jugular vein	Relaxation	Martin *et al.*, 1987
Pig	Carotid arterioles	Relaxation	Saxena *et al.*, 1986, 1989
Cat	Heart	↑ Heart rate	Saxena *et al.*, 1985; Connor *et al.*, 1986
'Orphan' (Vascular endothelium)			
Several	Vascular endothelium	EDRF release	Saxena and Villalón, 1990a
Rabbit	Jugular vein	Relaxation	Leff *et al.*, 1987; Martin *et al.*, 1987
Pig	Vena cava	Relaxation	Sumner, 1991
Pig	Pulmonary artery	Relaxation	Glusa, 1992
Chick	Jugular vein	Relaxation	Imaizumi *et al.*, 1984
'Orphan' (Rat motoneuron)			
Rat	Spinal motoneuron	Depolarization	Connell and Wallis, 1989
'Orphan' (Sympathetic neurons)			
Pig	Coronary artery	↓ NA release	Molderings *et al.*, 1989
'Orphan' (5-HT$_{1P}$)			
Several	Enteric neurons	Slow depolarization, ↓ Ach release	Gershon *et al.*, 1991; Frieling *et al.*, 1991

Abbreviations—Ach, acetylcholine; EDRF, endothelium-derived relaxant factor (probably nitric oxide); NA, noradrenaline.

Based on Saxena and Villalón (1990a) and Hoyer *et al.* (1994).

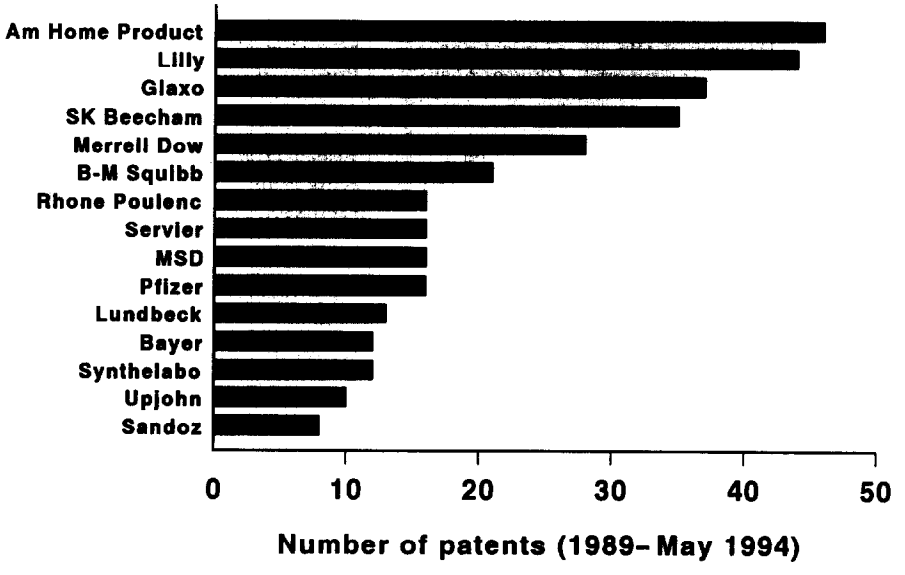

Fig. 4. Pharmaceutical companies with highest number of patents in the serotonin field (Anonymous, 1994).

Table 7. *Some Therapeutic uses of Drugs Acting at Serotonin Receptors*

Drug	Disease	Status	References
5-HT$_{1A}$ receptor (partial) agonists			
Buspirone	Anxiety	Marketed	Goldberg and Finnerty, 1979; Goa and Ward, 1986
Ipsapirone	Anxiety	Clinical phase 3	Glasser, 1988
Gepirone	Anxiety	Clinical phase 3	Costello *et al.*, 1991; Pecknold *et al.*, 1993
Urapidil[1]	Hypertension	Marketed	Ramage, 1986; Kolassa *et al.*, 1993; Saxena and Villalón, 1990b
5-HT$_{1A}$ receptor antagonists			
WAY 100135	Anxiety	Preclinical	Fletcher *et al.*, 1993
5-HT$_1$-like/5-HT$_{1D}$ receptor antagonists			
Sumatriptan	Migraine	Marketed	Ferrari and Saxena, 1993; Saxena and Tfelt-Hansen, 1993; Welch, 1993
Naratriptan	Migraine	Clinical phase 3	Connor *et al.*, 1993; Perren *et al.*, 1993
BW311C	Migraine	Clinical phase 2	Robertson *et al.*, 1991
MK-462	Migraine	Clinical phase 2	Beer *et al.*, 1994; Shepheard *et al.*, 1994
5-HT$_{1D}$ receptor antagonists			
GR127935	Depression	Preclinical	Skingle *et al.*, 1993
5-HT$_{2A}$ receptor antagonists			
Ketanserin[1]	Hypertension	Marketed	McGourty *et al.*, 1985; Saxena and Wouters, 1990
Ritanserin and Risperidone	Anxiety, psychosis, Sleep disorders	Clinical phase 3	Westernberg and Dan Boer, 1989; Castelao *et al.*, 1989
Methysergide[2]	Migraine	Marketed	Saxena and Den Boer, 1991
Pizotifen[2]	Migraine	Marketed	Saxena and Den Boer, 1991
5-HT$_{2C}$ receptor antagonists			
SB 200646	Feeding disorders	Preclinical	Kennett, 1993
SB 200646	Migraine	Preclinical	Fozard and Gray, 1989; Kennett, 1993
5-HT$_3$ receptor antagonists			
Ondansetron	Radiation vomiting	Marketed	Grunberg *et al.*, 1990; Marty *et al.*, 1990
Granisetron	Radiation vomiting	Marketed	Chevallier *et al.*, 1990
Tropisetron	Radiation vomiting	Marketed	Dogliotti *et al.*, 1990
Ondansetron	Psychosis	Clinical phase 2	Costall *et al.*, 1993
Tropisetron	Migraine	Ineffective	Ferrari, 1991; Ferrari *et al.*, 1991
Alosetron	Drug craving	Preclinical	Hagan *et al.*, 1993
Alosetron	Schizophrenia, IBS	Clinical phase 2	Hagan *et al.*, 1993
Alosetron	Memory impairment	Clinical phase 2	Preston *et al.*, 1992
5-HT$_4$ receptor agonists			
Cisapride[3]	Gastric motility	Marketed	Briejer *et al.*, 1993
Renzapride	Gastric motility	Clinical phase 3	King *et al.*, 1993b
SC 49518	Gastric motility	Preclinical	Gullikson *et al.*, 1993
5-HT$_4$ receptor antagonists			
GR 125487	IBS	Preclinical	Oxford, 1993
SB 207710	Cardiac arrhythmias	Preclinical	Kaumann and Sanders, 1994

[1]α-Adrenoceptor antagonist activity is apparently more important; [2]other actions are involved; [3]other properties probably are also involved.

Abbreviations—IBS, irritable bowel syndrome.

Compounds—BW311C, *N*,*N*-dimethyl-2-[5-(2-oxo-1,3-oxazolidin-4-yl-methyl)-1H-indol-3-yl]-ethylamine; GR 125487, [1-[2-[(methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl-5-fluoro-2-methoxy-1H-indole-3-carboxylate hydrochloride; GR 127935, *N*-[methoxy-3-(4-methyl-1-piperazinyl)-phenyl]-2′-methyl-4′-(5 methyl 1,2,4-oxadiazol-3-yl) [1,1,-biphenyl]-4-carboxamide; MK-462, *N*,*N*,-dimethyl-2-[5-(1,2,4-triazol-1-yl-methyl)-1H-indol 3-yl]ethylamine; SB 200646, *N*-(1-methyl-5-indoyl)-*N*-(3-pyridol urea hydrochloride) (Forbes *et al.*, 1993); SB 207710, [(1-butyl-4-piperidinylmethyl)-8-amino-7-iodo-1,4-benzodioxan-5-carboxylate]; SC 49518, *N*-[exo-(hexahydro-1H-pyrrolizine-1-yl]-2-methoxy-4-amino-5-chlorobenzamide hydrochloride; WAY 100135, *N*-tert-butyl-3-(4-[2-methoxyphenyl]piperazin-1-yl)-2-phenylpropanamide dihydrochloride.

However, the evidence so far is far from compelling, and the results of larger placebo-controlled clinical trials are awaited.

5.2. Other Central Nervous System Diseases

Drugs acting on serotonin receptors can have potential use in several other CNS diseases, like depression, schizophrenia, memory impairment, sleep disorders and substance abuse (see Table 7). Since 5-HT_{1D} receptors have been located at serotonergic nerves and can inhibit the transmitter release, antagonists at these autoreceptors may increase serotonin release and, thus, have antidepressant activity. The 5-HT_2 receptor antagonists, ritanserin and risperidone, which also blocks dopamine receptors, are being explored for use in psychosis and sleep disorders (Castelao *et al.*, 1989; Westenberg and Den Boer, 1989; Min *et al.*, 1993). Lastly, clinical investigations with 5-HT_3 receptor antagonists are being performed in schizophrenia, substance abuse and memory impairment (see Preston *et al.*, 1992; Costall *et al.*, 1993; Greenshaw, 1993; Hagan *et al.*, 1993). Results of more extensive and controlled clinical trials are awaited with great interest.

5.3. Migraine

A large number of studies has shown conclusively that sumatriptan, an agonist at 5-HT_1-like receptors, is effective in aborting migraine attacks (see Ferrari and Saxena, 1993; Saxena and Tfelt-Hansen, 1993; Welch, 1993). The success of this drug, both in a clinical and economic sense, has prompted a large number of pharmaceutical companies—Bristol–Myers Squibb (Smith *et al.*, 1992), Glaxo (Connor *et al.*, 1993; Johnson and North 1993; Perren *et al.*, 1993), Merck Sharp and Dohme (Baker *et al.*, 1994), Merrel Dow (McDonald *et al.*, 1992), Wellcome Foundation (King *et al.*, 1993a) and others—to try to develop novel 5-HT_1-like receptor agonists. In particular, the efforts are directed to make more lipid-soluble and selective compounds to improve oral bioavailability and avoid coronary artery vasoconstriction. High lipid solubility can turn out to be a double-edged weapon, since such molecules, unlike sumatriptan (Dallas *et al.*, 1989), would be expected to readily cross the blood–brain barrier and may then be associated with a higher incidence of unwanted effects. For example, in the case of compounds with a similar receptor profile as sumatriptan, the 5-HT_{1A} receptor agonism may lead to hypotension and bradycardia (see Saxena and Villalón, 1990a,b).

It is argued sometimes that sumatriptan owes its therapeutic activity solely to a presynaptic action, which inhibits neuropeptide releases and, therefore, 'neurogenic' inflammation (Moskowitz, 1993). Though this view is not shared universally (see Saxena and Ferrari, 1989; Humphrey and Feniuk, 1991; Ferrari and Saxena, 1993; Saxena and Tfelt-Hansen, 1993), it is of interest to note that NK_1 receptor antagonists, such as RP 67580 (Shepheard *et al.*, 1993), have been found far more potent than 5-$HT_{1B/D}$ receptor agonists (CP 93,129 and sumatriptan) in blocking neurogenic plasma extravasation following trigeminal ganglion stimulation. Should such compounds prove effective as antimigraine agents, the involvement of 'neurogenic' inflammation in migraine will have a stronger footing, though it will not be regarded as an argument against the involvement of vascular mechanisms (Saxena and Ferrari, 1989; Humphrey and Feniuk, 1991; Ferrari and Saxena, 1993; Saxena and Tfelt-Hansen, 1993).

Some antimigraine drugs are potent antagonists at 5-HT_{2A} receptors (methysergide, pizotifen, ergotamine, dihydroergotamine), but many other such agents (ketanserin, ritanserin, cyproheptadine, mianserin, methiothepin, metergoline, sergolexole, ICI 169,369) have not been found of much use in migraine therapy (Winther, 1985; Davies and Steiner, 1990; Tfelt-Hansen and Pedersen, 1992; Tfelt-Hansen and Saxena, 1993). It seems, therefore, that additional properties of these antimigraine drugs, for example, the vasoconstriction in the extracerebral cephalic circulation with methysergide, ergotamine and dihydroergotamine (partly via 5-HT_1-like receptors) and the antidepressant action with pizotifen, may be involved in their therapeutic action (Saxena and Den Boer, 1991). Based mainly on the ability of a 5-HT_{2C} receptor agonist, *m*-chloro-phenyl piperazine, to elicit migraine-like headaches in some patients and the ability of drugs such as mianserin to block this receptor, it has been advocated that 5-HT_{2C} receptor antagonism is important for antimigraine action (Fozard and Gray, 1989; Fozard, 1992; Kennett, 1993). It should be noted, however, that

m-chloro-phenyl-piperazine is not a selective agent and drugs that block the 5-HT_{2C} receptor (e.g. mianserin, sergolexole) are not particularly effective against migrainous headaches. Moreover, rather than being antagonists, the antimigraine drugs ergotamine and dihydroergotamine behave as potent agonists at the 5-HT_{2C} receptor (Brown *et al.*, 1991).

Despite the fact that many 5-HT_3 receptor antagonists are known for several years and three of them (ondansetron, granisetron and tropisetron) are in clinical use for the treatment of vomiting induced by anticancer drugs, only two such drugs (MDL 72222 and granisetron) have been reported to be effective in migraine (Loisy *et al.*, 1985; Couturier *et al.*, 1991). Though MDL 72222 was studied in a double-blind, placebo-controlled manner (Loisy *et al.*, 1985), this study has been flawed on several grounds (Ferrari, 1991; Ferrari *et al.*, 1991). Granisetron was evaluated in an open study on six patients (Couturier *et al.*, 1991) and, despite encouraging results, this study was discontinued, according to the investigators "for extraneous reasons". On the other hand, carefully designed and extensive investigations with tropisetron, both as acute and prophylactic migraine therapy, were largely negative (Ferrari, 1991; Ferrari *et al.*, 1991). Since no other positive results are known with any of the 5-HT_3 receptor antagonists, it must be concluded that this receptor does not play a major role in migraine.

The above analysis strongly suggests that within the bounds of serotonergic mechanisms, the antimigraine action mainly depends upon an agonist action at the 5-HT_1-like receptor subtype that mediates cephalovascular constriction (Saxena *et al.*, 1993).

5.4. Vomiting

Nausea and vomiting are extremely unpleasant side effects of anticancer drugs, and the dopamine D_2 receptor antagonists are not very effective as antiemetic agents. Following the report that high doses of metoclopramide, which also blocks 5-HT_3 receptors (Bradley *et al.*, 1986; Fozard, 1990), can prevent cisplatin-induced vomiting in cancer patients (Gralla *et al.*, 1981), it was realized that 5-HT_3 receptor blockade may play an important role in vomiting (Miner and Sanger, 1986). Indeed, ondansetron (Grunberg *et al.*, 1990; Marty *et al.*, 1990), granisetron (Chevallier *et al.*, 1990) and tropisetron (Dogliotti *et al.*, 1990) have all been shown to successfully suppress the acute phase of vomiting caused by cisplatin; unfortunately, the delayed phase is not much affected (see Wells *et al.*, 1993). The 5-HT_3 receptor antagonists are selectively effective against vomiting following cancer chemotherapy, radiation exposure or general anaesthesia; these drugs do not prevent vomiting due to other causes, such as motion sickness.

The mechanism of antiemetic action of 5-HT_3 receptor antagonists appears to be at the level of sensory vagal nerve terminals in the gastrointestinal mucosa, with a possible additional effect at the chemoreceptor trigger zone, where 5-HT_3 receptors have also been localized (Kilpatrick *et al.*, 1987; Wells *et al.*, 1993). Microdialysis measurements have clearly shown that cisplatin increases serotonin levels in the ileum, as well as the blood, and such increases are accompanied by vomiting episodes (Fukui *et al.*, 1993).

5.5. Hypertension

Both urapidil (5-HT_{1A} receptor agonist) and ketanserin (5-HT_{2A} receptor antagonist) have been approved for the treatment of hypertension. Indeed, it is claimed that these drugs decrease blood pressure by stimulating 5-HT_{1A} receptors located centrally in the nucleus tractus solitarus (urapidil) or by blocking 5-HT_{2A} receptors mediating peripheral vasoconstriction (ketanserin). However, as discussed in detail elsewhere (Saxena and Wouters, 1990), it does not appear that such effects are involved to a significant degree in the clinical effects of these drugs; both urapidil and ketanserin have a potent α_1-adrenoceptor antagonist activity, which can adequately explain the antihypertensive effect (see Saxena and Villalón, 1990b).

5.6. Gastric Motility Disorders

It is well known that high concentrations of serotonin are present in the gastrointestinal tract, where it appears to play an important physiological role in the peristaltic movements (see Gershon

et al., 1991). Although some progress has been made towards delineation of the nature and function of serotonin receptors in the gastrointestinal tract of several animal species (Dhasmana *et al.*, 1993), the knowledge with regard to the human gut is still scant (Talley, 1992; Tam *et al.*, 1992; McLean *et al.*, 1993). However, 5-HT_3 and 5-HT_4 receptor antagonists are being explored for therapeutic use in irritable bowel syndrome (Prior and Reed, 1993), since these drugs slow colonic transit in healthy volunteers (Gore *et al.*, 1990; Talley *et al.*, 1990).

The 5-HT_4 receptor agonists seem to have a prokinetic effect (Briejer *et al.*, 1993; Gullikson *et al.*, 1993; King *et al.*, 1993b; Stacher *et al.*, 1993), and their use in reflux oesophagitis (Geldof *et al.*, 1993) and idiopathic (Corinaldesi, 1993) and diabetic (Kawagishi *et al.*, 1993) gastroparesis is being advocated.

5.7. Pain

Recent preclinical studies suggest that 5-HT is involved in the mediation of pain, but it has multiple and opposing effects, which depend upon the location and the type of receptor involved (Greenshaw, 1993).

Within the superficial dorsal horn of the spinal cord, a dense band of 5-HT_3 receptors has been located on capsaicin-sensitive primary afferent nerve terminals. These 5-HT_3 receptors mediate an antinociceptive effect against intrathecal application of substance P and *N*-methyl-D-aspartate, possibly via γ-aminobutyric acid release (Alhaider *et al.*, 1991). In contrast, peripheral 5-HT_3 receptors mediate an algesic response following topical application of serotonin on blister base in humans (Richardson *et al.*, 1985; Fozard, 1990).

The nociceptive response to i.v. serotonin may be mediated by both 5-HT_2 and 5-HT_3 receptors located on capsaicin-sensitive vagal nerve afferents and, therefore, a combined use of 5-HT_2 and 5-HT_3 receptor antagonists has been suggested for the relief of pain in angina pectoris and other peripheral vascular disorders (Mellor *et al.*, 1992). Interestingly, both 5-HT_1 and 5-HT_2 receptors mediate human coronary artery constriction induced by 5-HT (Connor *et al.*, 1989a; Chester *et al.*, 1990; Bax *et al.*, 1993), as well as platelets, even after cyclooxygenase inhibition with aspirin (Bax *et al.*, 1994). Thus, it is advocated that a combined use of 5-HT_1 and 5-HT_2 receptor antagonists may have some role in the treatment of angina pectoris (Bax *et al.*, 1994).

5.8. Cardiac Disorders

Increases in the rate and contractility in the human atrium are mediated by 5-HT_4 receptors (see Table 5). Serotonin can induce arrhythmias in the human isolated atrium and, therefore, 5-HT_4 receptor antagonists could be useful in the treatment of cardiac arrhythmias (Kaumann and Sanders, 1994). However, it is not established yet if serotonin plays any role in the pathogenesis of cardiac arrhythmias.

The increase in atrial contractility by 5-HT_4 receptor agonists indicated that such drugs may have application in the therapy of heart failure. Any such hope has now been dashed, as recent investigations indicate that 5-HT_4 receptors are not present on human ventricles (Jahnel *et al.*, 1992; Schoemaker *et al.*, 1993).

6. CLOSING REMARKS

During the last decade, research in the field of serotonin has been boosted by the availability of potent and selective drug tools. These drug tools and increasing understanding of the transduction mechanisms, as well as the structure of the receptor protein, have enabled the characterization and nomenclature of serotonin receptors in a more meaningful way. Thus, four main classes with several subtypes (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4), as well as some recombinant (e.g. 5-ht_{5A}, 5-ht_{5B}, 5-ht_6, 5-ht_7; note the use of lower case alphabets) and 'orphan' serotonin receptors, have been recognized. The suggestions made by the Nomenclature Committee of the Serotonin Club and the criteria used in classifying serotonin receptors undoubtedly will be helpful to other groups involved in the classification of pharmacological receptors.

The molecular cloning and expression of a growing number of serotonin receptors in host cells now offers the possibility to screen new molecules relatively easily in order to recognize more selective ligands. However, this development poses new challenges. Obviously, one of the challenges involves the understanding of the precise function of the recombinant receptors at the various anatomical locations. Secondly, it may be asked why should there be so many serotonin receptor subtypes in the body. Is it that each receptor subtype mediates a specific function, or is it that more than one receptor subtype mediates the same function, perhaps under different circumstances, thus providing 'receptor backup'? The answers will dictate the strategy with regard to the degree of selectivity in developing therapeutically relevant molecules.

The responses mediated via many serotonin receptors are now well understood, and this, in turn, has resulted in the development and use of serotonergic drugs in the therapy of several diseases, including anxiety and migraine. Given the pace with which new knowledge is emerging, therapeutic potentials of serotonin-based drugs will undoubtedly be exploited further. The availability of newer and more selective serotonin ligands will help us better define the role of serotonin and its receptors in physiological processes and pathophysiological mechanisms. This knowledge, in turn, will provide access to better drugs for treatment of human ailments more efficiently. Thus, the future of serotonin research looks as bright as ever.

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