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VII. International Union of Pharmacology Classification of Receptors for 5-Hydroxytryptamine (Serotonin)

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I. Introduction

This classification of receptors for 5-HT is an attempted synthesis of current knowledge on 5-HT receptors into a robust and structured order. It is intended that such an exercise will not only lead ultimately to the provision of a simple unambiguous system of nomenclature but, more important, also provide insight into the phylogeny of 5-HT receptors and a wider understanding of their physiological and ontological significance (Green and Maayani, 1987). Clearly, lessons, which can be learned from our knowledge of 5-HT receptors, can be of benefit in advancing our understanding of other mediator-response-transducing receptor systems and will, therefore, be of interest to those classifying other cell membrane receptors.

A. Historical Background

Protein receptors that mediate the actions of 5-HT have existed in the membranes of a variety of animal cell types for millions of years, their ancestry being as old or older than that for the adrenoceptors and receptors for some peptide mediators (see Venter et al., 1988; Hen, 1992). It would seem likely that during such a long period of time, there has been ample opportunity for mutation and consequent evolutionary acceptance of multiple variants of receptors for all of these older neurotransmitters and hormones. This undoubtedly seems the case for 5-HT as well as for noradrenaline. Early skepticism about the almost "unbelievable" number of 5-HT receptor types is no longer tenable, as more and more 5-HT receptor genes are cloned, the amino acids of the corre-

sponding receptor proteins deduced, and the chromosome location of their genes identified (fig. 1). Although each 5-HT receptor can be potently activated by 5-HT itself, the differences in protein structure, and consequent affinities for different synthetic chemicals, provide a basis for identifying selective ligands, either agonist or antagonist, for each receptor variant. It also creates much opportunity for drug discovery and the medicinal chemist (Humphrey, 1992). It is the role of the biologist to define the receptors of interest and to define the type of ligand required for a particular therapeutic utility. It is for this reason that the authors of this review have spent more than a combined total of 100 years working on 5-HT receptors, to characterise them and to define their function and distribution. The classification of 5-HT receptors described here stems from that work, and that of others, and is intended to provide a timely update of the classification put forward by us in 1986, following informal ad hoc deliberations (Bradley et al., 1986a). Although the original scheme has been considered by many as a useful working framework, which focused attention on the need for rigour and discipline in characterising and naming receptors (Humphrey and Richardson, 1989), an enormous amount of new information is now available. Nevertheless, it undoubtedly helped to encourage thinking toward a uniform approach to receptor classification which in itself aids insight and understanding. The original proposal that there are three main groups of 5-HT receptor still appears valid, even with the knowledge gained from the cloning and structure determination of receptor types from each of the groups. However, the recent discovery of the now well-documented 5-HT_4 receptor raises the question of whether other groups exist; undoubtedly the definitive answer will come from receptor-cloning studies. Interestingly, 5-HT receptor gene-cloning work has identified yet other receptors tentatively called 5-ht_5, 5-ht_6, and 5-ht_7 (see below). Thus, it would seem that there is a need to review the conceptual thinking behind the Bradley classification of 5-HT receptors, which at least is in need of expansion. The classification of 5-HT receptors described here reflects an international view sanctioned by the Serotonin Club Receptor Nomenclature Committee which reports directly to the main IUPHAR Committee for Receptor Nomenclature. Some preliminary considerations have already been published in brief (Humphrey et al., 1993).

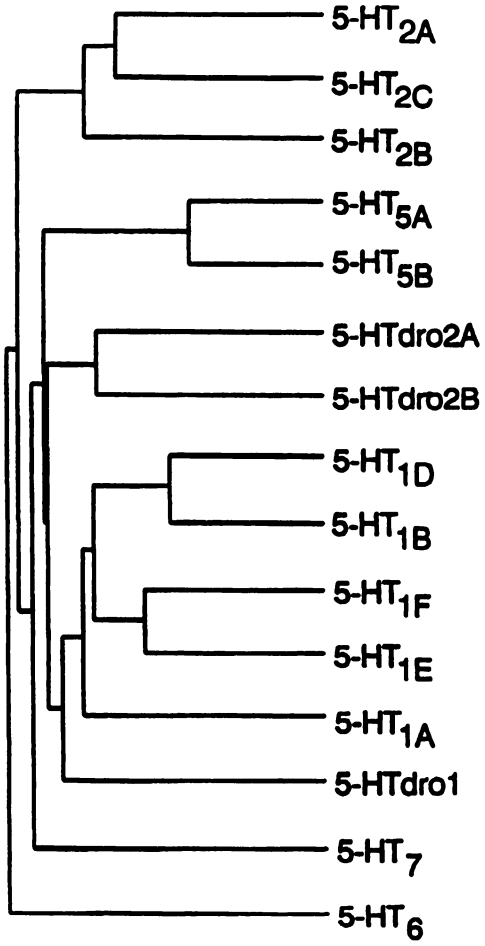

FIG. 1. Dendogram analysis of 5-HT receptors of the G-protein-coupled family. The dendogram shows how 5-HT receptors cluster into subgroups according to amino acid sequence similarity. The length of the horizontal bars is inversely proportional to sequence or group similarity. The *Drosophila* receptors 5-HT-dro1, dro2a, and dro2B (Hen, 1992), although not specifically discussed in this paper, are included to show sequence relationship. Amino acid sequence data were compiled and analysed using the Genetics Computer Group sequence software Lineup and Pileup (Madison, WI) (Devereux et al., 1984). The dendogram was kindly provided by Drs. J. G. Sutcliffe, T. W. Lovenberg, and M. G. Erlander, The Scripps Research Institute, La Jolla, CA.

B. Receptor Classification Approach

Ever since the work of Ahlquist (1948), who provided evidence for the subclassification of adrenoceptors into α- and β-types, there has been a growing interest in the classification of receptors that mediate the actions of neurotransmitters and hormones. Much of the impetus for this derives from a desire to produce more selective drugs. This is no better exemplified than by the studies that led to the development of the selective β_2-adrenoceptor agonist, salbutamol, and later the H_2 histamine receptor antagonists, emanating from the work on burimamide (Brittain et al., 1970; Black et al., 1972). However, there has been an underlying debate about the significance of data for synthetic drugs in relation to the nature of the receptor activated by the endogenous hormone or neurotransmitter itself (Black, 1987). Could the "drug-hunter" unwittingly be classifying drug receptors that, theoretically, given the relative size of chemical messenger and the receptor protein, might be almost infinite (Humphrey and Richardson, 1989). Frustratingly, to those interested specifically in the nature of the receptor protein for the endogenous mediator per se, the basic question of whether the agonist activation site for a natural ligand varies for each of its receptor types remains largely unanswered. Nevertheless, with the rapid

recent progress made in molecular biology techniques, many receptor genes have been cloned, and it is evident that there really are multiple subtypes of receptor protein for many or all neurotransmitters or chemical mediators (Lefkowitz et al., 1989; Hen, 1992). The key question now focuses on the relevance of receptor structure to function, a question that cannot be fully answered at present. It follows that the major challenge for those interested in receptor classification today is the reconciliation of operational data with structural data into a useful integrated classification scheme. Fortunately, it is apparent that biologists of all disciplines have a common interest in this aim. The definitive criteria have yet to be formally accepted, but there is general agreement about the "fingerprint" criteria required to characterise a given receptor (table 1). The three main criteria are operational (i.e., drug-related characteristics), transductional (receptor-effect coupling events), and structural (gene and receptor structural sequences for their nucleotide and amino acid components, respectively) (Humphrey et al., 1993). In providing the relevant data for characterisation of each receptor, rigour is essential, because poor data only lead to confusion, thereby hindering the process of understanding. The eminent biologist and taxonomist, Charles Darwin, noted more than a century ago, "I must begin with a good body of facts and not from a principle (in which I always suspect some fallacy) and then as much deduction as you please" (Strauss, 1968). There have been many pleas for care and rigour in conducting experiments relating to receptor characterisation (Furchgott, 1972; Humphrey, 1984; Leff and Martin, 1986, 1989). These have recently been reiterated in relation to the criteria considered essential by the IUPHAR receptor nomenclature committee (Kenakin et al., 1992) and are described and extended in table 1.

Thus, before one can be confident of proper characterisation of a given receptor type, one must have operational data with selective agonists and antagonists describing their functional activity in quantitative terms, with relative potencies of agonists as equi-effective molar concentration ratios and measures of affinity (usually dissociation constants) for antagonists. Binding studies with a suitable radiolabelled ligand allow the reliable measurement of affinity for agonists (difficult to obtain from functional studies) as well as for antagonists, and obviously such data should correlate with data from the corresponding studies on function.

Undeniably, the amino acid sequence, which is generally deduced from the cDNA, is the definitive mark of identity, but it does not necessarily reflect a receptor's operational characteristics or indicate whether it will behave in a manner different from that of a closely homologous receptor type. It seems likely that all of the information will have to be gathered before a receptor is fully characterised and can be assigned a proper appel-

TABLE 1
*Criteria for receptor characterisation**

Criteria	Definition
Operational	
a. Selective agonists	Agonists with unique or high selectivity for the receptor compared with their potencies at other receptors need to be identified. Their relative equieffective molar concentration ratios should be determined and a rank order of agonist potencies for the receptor established.
b. Selective antagonists	Receptor-blocking drugs (antagonists) are needed that can antagonise the actions of agonists by blocking the receptor. It should be determined whether these antagonists are selective for the one type or subtype of receptor or not and what their respective equilibrium dissociation constants (affinity measures) are for their interaction at the receptor.
c. Ligand-binding affinities	Dissociation constants for ligands (selective agonists and antagonists) in binding studies should correlate with corresponding data from functional studies. The additional data concerning agonist affinities are difficult to obtain from functional studies. Autoradiography also aids receptor distribution studies.
Structural	
d. Molecular structure	The amino acid sequence of the receptor protein provides definitive evidence of receptor identity. However, receptors that are structurally different may not necessarily be different in operational terms and vice versa. Relative homologies of receptor proteins can also provide useful data for classification purposes, enabling definition of families and subfamily groups (Hartig et al., 1992; fig. 1).
Transductional	
e. Intracellular transduction mechanisms	Important information that further defines the receptor superfamily (i.e., ligand-gated ion channel or G-protein linked). It also involves definition of the nature of the G-protein linkage, if any, that may be indicative of the nature of the intracellular protein structure of the receptor itself.

* The essential data (a to e) for classification provide a "fingerprint" basis on which to identify distinct receptors. Definitive characterisation of a receptor, in relation to drug action, demands proper definition of each criterion (operational, structural, and transductional) in terms of a rigorous quantitative analytical approach. The scheme is modified from Coleman and Humphrey, 1993, and Humphrey et al., 1993.

lation in a definitive scheme of classification. To distinguish recombinant receptors from native receptors identified in whole tissues, lower case letters will be used to identify recombinant receptors, a convention recently proposed by the IUPHAR receptor nomenclature committee (Kenakin et al., 1992). In keeping with this convention, we suggest that upper case lettering can be used later when analogous 5-HT receptors are identified in whole tissues.

It is evident that an understanding of the transduction system to which the receptor under investigation is linked is important. Thus, information about whether the receptor is G-protein linked or integral to an ion channel immediately indicates to what superfamily the receptor belongs and some of its functional characteristics. It is also clear that a thorough understanding of receptor-G-protein interaction is essential to interpretation of operational data from transfected recombinant receptors in cell lines (Kenakin, 1993). Furthermore, when we can explain the fundamental transduction mechanisms involved in receptor activation-response coupling, we will finally understand the pharmacological mystery of the nature of agonist efficacy.

Because all the necessary criteria for receptor characterisation cannot yet be defined for most of the receptors described in this review, it will be some time before a fully rational scheme of nomenclature can be applied. Nevertheless, there is undoubtedly much greater knowledge today about 5-HT receptors and the effects that they mediate, compared to that when we first attempted an overall scheme of 5-HT receptor classification some years ago, making this review most timely (Bradley et al., 1986a).

C. 5-Hydroxytryptamine Receptor Classification Synopsis

It is apparent that 5-HT receptors can be classified into at least three, possibly up to seven, classes (or groups) of receptor (Bradley et al., 1986a; Zifa and Fillion, 1992; Peroutka, 1993). They comprise the 5-HT_1, 5-HT_2, and 5-HT_3 classes, as well as the "uncloned" 5-HT_4 receptor (table 2). The 5-ht_5, 5-ht_6, and 5-ht_7 receptor genes have been cloned recently, but the receptors have yet to be fully characterised operationally and transductionally in intact tissues, and as such their appellations must be considered provisional.

However, there is now an inordinate volume of good evidence that several 5-HT_1 receptors, first identified as ligand-binding sites (e.g., 5-HT_{1A}), are functionally important and adequately characterised. Hence, the previously named "5-HT_1-like" receptor class is now simply referred to as the 5-HT_1 receptor class, although the 5-HT_1-like appellation itself may still be useful for some 5-HT_1 receptor subtypes, prior to full characterisation (Bradley et al., 1986b; Connor et al., 1991; see section II.G). It remains to be seen whether any of the new recombinant 5-HT receptors correlate with these. All 5-HT_1 receptors fully characterised so far are seven transmembrane domain receptors, which are negatively coupled to adenylyl cyclase via regulatory G-proteins. The one exception is the 5-HT_{1C} receptor which mediates activation of protein kinase C via increased phosphoinositide metabolism; this is entirely consistent with the operational and structural data, which shows it to be much more closely related to the 5-HT_2 rather than the 5-HT_1 receptor class (see section III.D).

Selective receptor agonists are available for 5-HT_{1A} and 5-HT_{1D} receptors, which have been important for their characterisation using operational techniques (Humphrey, 1992). In contrast no ideal potent, selective, and silent antagonists were available until recently, but the advent of (±)WAY 100135 and GR 127935, respectively, should prove invaluable for the purpose of further receptor characterisation (Fletcher et al., 1993; Skingle et al., 1993). The 5-HT_{1A}, 5-HT_{1B}, and two types of human 5-HT_{1D} receptor genes have been cloned and their operational and transductional characteristics well defined (see sections II.B, II.C, and II.D). More recently, 5-ht_{1E} and 5-ht_{1F} receptor cDNAs have been cloned and the recombinant proteins classified as 5-HT_1 receptor subtypes on the basis of their amino acid homology and their negative coupling to adenylyl cyclase in cell lines (Amlaiky et al., 1992; McAllister et al., 1992; Adham et al., 1993b; Lovenberg et al., 1993b). However, these receptors are operationally different from the other 5-HT_1 receptors because 5-CT has little or no affinity or agonist activity at these sites. Similarly, methiothepin displays low affinity and, where tested, low antagonist potency at both receptors (see sections II.E and II.F).

Until recently, there was no compelling evidence to subdivide 5-HT_2 receptors which are widespread and mediate many of the actions of 5-HT throughout the body (Leysen et al., 1983; Mylecharane, 1990). However, the close structural homology of the 5-HT_{1C} receptor with the 5-HT_2 receptor, together with a shared second-messenger transduction system and very similar operational characteristics, does clearly indicate that the 5-HT_{1C} receptor should now be considered as a 5-HT_2 subtype (Hoyer, 1988a; Hartig, 1989). With this in mind, we have recommended that it should now be called the 5-HT_{2C} receptor (see section III). This makes it possible to call the "classical" 5-HT_2 receptor 5-HT_{2A} and the newly sequenced rat stomach fundus 5-HT receptor the 5-HT_{2B} receptor (Foguet et al., 1992a,b), instead of the term 5-HT_{2F} (Kursar et al., 1992).

Much is known about the function of 5-HT_3 receptors because of the recent development of a number of highly potent selective antagonists (Fozard 1989; Tyers, 1990). 5-HT_3 receptors mediate the neuronal depolarising actions of 5-HT in both the periphery and the brain, being structurally intrinsic to a cationic channel, analogous to the nicotinic receptor for acetylcholine (Derkach et al.,

TABLE 2
Operational characteristics of 5-HT receptors

Receptor type	Subtype	Location	Response	Agonist	Antagonist	Comment
5-HT_1	5-HT_{1A}	Neuronal, mainly in CNS	Neuronal hyperpolarisation, hypotension	8-OH-DPAT, buspirone, 5-CT	WAY 100135 [methiothepin (nonselective)]	Well characterised but potent, silent, and selective antagonists only recently available
	5-HT_{1B}	CNS and some peripheral nerves	Inhibition of neurotransmitter release	CP 93,129, 5-CT	SDZ 21009 [methiothepin (nonselective)]	Appears to be the rodent equivalent of 5-$HT_{1D\beta}$ receptor subtype
	5-HT_{1D}	Mainly CNS	Inhibition of neurotransmitter release	Sumatriptan, L 694247, 5-CT	GR 127935 [metergoline, methiothepin (nonselective)]	Two-5-HT_{1D} gene types cloned (5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$)
	5-ht_{1E}	Only CNS	Inhibition of adenylyl cyclase	5-HT	None [methiothepin weak]	Functions mediated in intact tissues not known
	5-ht_{1F}	Mainly CNS	Inhibition of adenylyl cyclase	5-HT	None [methiothepin weak]	Functions mediated in intact tissues not known
	5-HT_1-like	Intracranial vasculature	Smooth muscle contraction	Sumatriptan, 5-CT	None [methiothepin (nonselective)]	Yet to be definitively characterised but may be 5-HT_{1D}, 5-ht_{1F}, or other recombinant receptor
5-HT_2	5-HT_{2A} (previously 5-HT_2)	Vascular smooth muscle, platelets lung, CNS, gastrointestinal tract	Vasoconstriction, platelet aggregation, bronchoconstriction	α-methyl-5-HT, DOI	Ketanserin, cinanserin, pirenperone	The classical 5-HT_2 receptor that increases phosphoinositide metabolism (Bradley et al., 1986a)
	5-HT_{2B} (previously 5-HT_{2F})	Mainly peripheral?	Rat stomach fundic muscle contraction	α-methyl-5-HT, DOI	SB 200646 (also 5-HT_{2C} antagonist)	Like 5-HT_{2A} receptors linked to increased phosphoinositide metabolism
	5-HT_{2C} (previously 5-HT_{1C})	CNS (high density in choroid plexus)	↑Phosphoinositide turnover	α-methyl-5-HT, DOI	Mesulergine (also 5-HT_{2A} antagonist)	Like 5-HT_{2A} receptors linked to increased phosphoinositide metabolism
5-HT_3		Peripheral and central neurones	Depolarization	2-methyl-5-HT, *m*-chlorophenylbiguanide	Ondansetron, tropisetron	Mediates many of the neuronal reflex effects of 5-HT in the periphery
5-HT_4		Gastrointestinal tract, CNS, heart, urinary bladder	Activation of acetylcholine release in gut, tachycardia, ↑ cAMP in CNS neurones	Metoclopramide, renzapride (usually partial agonists) relative to 5-HT	GR 113808, SB 204070, tropisetron (weak)	Pharmacologically distinct, but like certain other 5-HT receptors (orphan in smooth muscle, 5-ht_6, 5-ht_7), the 5-HT_4 receptor is positively linked to adenylyl cyclase
5-ht_{5A} and 5-ht_{5B}		CNS	Not known	5-HT	Methiothepin	Functions mediated in intact tissues not known (5-ht_{5A} and 5-ht_{5B} subtypes apparent). Transductional characteristics unknown

TABLE 2—*Continued*

Receptor type	Subtype	Location	Response	Agonist	Antagonist	Comment
5-ht$_6$		CNS	Activation of adenylyl cyclase (HEK 293 cells)	5-HT	Methiothepin	Functions mediated in intact tissues not known. Positively coupled to adenylyl cyclase
5-ht$_7$		CNS	Activation of adenylyl cyclase (HeLa cells and COS cells)	5-HT	Methiothepin	Functions mediated in intact tissues not known. Positively coupled to adenylyl cyclase

1989). There is good evidence for species variants of the 5-HT$_3$ receptor but not for intraspecies subtypes as yet (see section IV.B).

The 5-HT$_4$ receptor has now been identified in a variety of tissues, including the brain (Bockaert et al., 1992). Despite being operationally distinct from 5-HT$_1$ receptors, the 5-HT$_4$ receptor appears to be positively linked to adenylyl cyclase and may, therefore, be more closely related structurally to the 5-HT$_1$, and particularly to the recently cloned 5-ht$_6$ and 5-ht$_7$ receptors (also linked positively to adenylyl cyclase), than to the 5-HT$_2$ or 5-HT$_3$ receptors. The benzamides, such as metoclopramide, renzapride, and cisapride, are selective partial agonists for the 5-HT$_4$ receptor, and potent and selective receptor antagonists, such as GR 113808 and SB 207710, are now becoming available. However, definitive characterisation will await the cloning of the receptor gene, at which time it will be apparent whether its appellation is appropriate (see section V.A).

Two mouse and rat 5-ht$_5$ receptor genes have recently been cloned, but insufficient data are available to allow their classification with confidence. Nevertheless, their structural features suggest that they are quite distinct from other known mammalian 5-HT receptor types (Plassat et al., 1992; Matthes et al., 1993; Erlander et al., 1993). Indeed, they are only 26 to 34% homologous with other recombinant 5-HT receptors. Clearly, more information is required, as with any newly cloned receptor. The more recent cloning of the so-called 5-ht$_6$ and 5-ht$_7$ receptor genes (Monsma et al., 1993; Plassat et al., 1993; Lovenberg et al., 1993a) highlights the need for an integrated approach to receptor characterisation and classification that demands all aspects of receptor function to be defined before a receptor can be named with confidence (see section V).

II. 5-HT$_1$ Receptors

A. 5-HT$_1$ Receptor Heterogeneity

5-HT$_1$ receptors were first identified as a high-affinity site for 5-HT in radioligand-binding studies on brain homogenates using [^{3}H]5-HT (Peroutka and Snyder, 1979). Later, the subtypes 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$, and 5-HT$_{1D}$ were identified, which can be selectively labelled in the brain under appropriate conditions with [^{3}H]8-OH-DPAT, [^{125}I]cyanopindolol, [^{3}H]mesulergine, and [^{125}I]GTI, respectively (Gozlan et al., 1983; Hoyer et al., 1985a,b; Pazos et al., 1984; Bruinvels et al., 1991; Boulenguez et al., 1992). The genes for all of these receptors have now been cloned and the receptors shown to be distinct single-protein structures varying in size from 374 to 421 amino acids (see below). They have also been shown to be operationally relevant in terms of various brain functions, although the pharmacology of 5-HT$_{1D}$ receptors appears enigmatic, partly, it might be argued, as a consequence of having drug tools of only limited selectivity. However, molecular biology studies have demonstrated that there are two human 5-HT$_{1D}$ receptors, 5-HT$_{1D\alpha}$ and 5-HT$_{1D\beta}$, the latter having very close homology to the 5-HT$_{1B}$ receptor found in rodents (Hartig et al., 1992). Furthermore, a similar receptor in cerebral vascular smooth muscle is still referred to as 5-HT$_1$-like because its pharmacology is similar but apparently not identical with that of other 5-HT$_{1D}$ receptor(s) described to date (Humphrey and Feniuk, 1991; Perren et al., 1991; Hamel and Bouchard, 1991). The precise characterisation and classification of these receptors and other 5-HT$_1$ receptors remains to be determined. It would now seem that the 5-HT$_{1R}$ site identified in rabbit caudate is a species homologue of the 5-HT$_{1D}$ receptor in brain homogenates of higher species (Xiong and Nelson, 1989; Hoyer et al., 1992). The 5-ht$_{1E}$ receptor has consistently been identified as an additional site in brain preparations, from a variety of species, containing 5-HT$_{1D}$ receptors, but no functional correlate has yet been described (Sumner and Humphrey, 1989; Leonhardt et al., 1989; Beer et al., 1992). However, human 5-ht$_{1E}$ and also 5-ht$_{1F}$ receptor cDNAs have recently been cloned, and the recombinant receptors have been shown to negatively couple to adenylyl cyclase, which justifies their classification in the 5-HT$_1$ receptor group (McAllister et al., 1992; Adham et al., 1993b).

In addition to these various recombinant 5-HT receptors, there are a number of receptors that have been characterised solely using operational studies and have long been referred to as 5-HT$_1$-like. Thus, in addition to the 5-HT$_1$-like receptor referred to above, which has close

similarities with the 5-HT_{1D} receptor, there is also a receptor, hitherto referred to as 5-HT_1-like, that activates rather than inhibits adenylyl cyclase in vascular smooth muscle (Feniuk et al., 1983; Trevethick et al., 1986; see section V.E). Various other receptors have been referred to as 5-HT_1-like (see section II.G), although sometimes inappropriately. Thus, all receptors described as 5-HT_1 or 5-HT_1-like, on the basis of the Bradley classification, should be potently activated by 5-CT, where qualitatively 5-CT is at least of similar potency to 5-HT itself (Bradley et al., 1986a). However, because 5-CT has low affinity relative to 5-HT at both the 5-ht_{1E} and 5-ht_{1F} receptor (700 and 70 times less, respectively), this characteristic seems no longer appropriate for all 5-HT_1 receptors. This would be analogous to the situation with propranolol, at one time thought to be diagnostic for β-adrenoceptors, which poorly antagonises effects mediated via β_3-adrenoceptors (Hieble, 1991). The low affinity of 5-CT for the human 5-ht_{1E} receptor correlates with a corresponding low potency, relative to 5-HT, for inhibition of adenylyl cyclase (McAllister et al., 1992). However, the relative agonist potency of 5-CT at the 5-ht_{1F} receptor remains to be determined (Amlaiky et al., 1992; Adham et al., 1993b). At both receptors, methiothepin has low affinity.

It is abundantly evident that 5-HT_1 receptors make up an enigmatically heterogeneous class but to what extent remains to be determined, and many receptor identities have yet to be definitively resolved. Nevertheless, the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-ht_{1E}, and 5-ht_{1F} receptors have all been cloned and shown to share a high degree of homology (>60% in the transmembrane domains) and to have intronless genes in the coding sequence region (see below). They also have high affinity for 5-HT and share a common transduction system in being negatively coupled to adenylyl cyclase, presumably via a common or similar G-protein link. The 5-HT_{1C} receptor is not included because it is clearly a 5-HT_2, rather than a 5-HT_1 subtype, on the basis of all three important characterisation criteria (operational, transductional, and structural). For this reason, it has been renamed the 5-HT_{2C} receptor (Humphrey et al., 1993). It is recommended that the appellation 5-HT_{1C} be abandoned to avoid confusion.

B. 5-HT_{1A} Receptors

1. Distribution and function. The hippocampus contains a high density of 5-HT_1 sites, most of which belong to the 5-HT_{1A} subtype. Other brain areas are enriched in 5-HT_{1A} sites, including the septum, some of the amygdaloid, and raphé nuclei, particularly the dorsal raphé (Marcinkiewicz et al., 1984; Radja et al., 1991). Many of these regions are components of the pathways involved in the modulation of emotion, the limbic system. This distribution is common to several mammals, including humans (Hoyer et al., 1986a; Pazos et al., 1987a). The predominance of 5-HT_{1A} receptors in this system suggests that the reported effects of 5-HT and 5-HT receptor ligands in emotional mechanisms could be mediated by 5-HT_{1A} receptors (Iversen, 1984). Furthermore, the presence of high densities of 5-HT_{1A} receptors in the raphé nuclei indicates that 5-HT can modulate the activity of serotoninergic neurones. 5-HT_{1A} receptors are also present in the neocortex, the hypothalamus, and the substantia gelatinosa of the spinal cord. The localisation of 5-HT_{1A} receptors in these areas suggests that 5-HT_{1A} mechanisms could also be involved in the functions of the hypothalamus, in the regulation of propioception, and in integrative functions of the neocortex.

Activation of somatodendritic autoreceptors causes a reduction in 5-HT synthesis, release, and electrical activity (de Montigny and Blier, 1992). Destruction of serotoninergic neuronal cell bodies by lesions have shown that the cell bodies carry 5-HT_{1A} receptor sites (Vergé et al., 1986). Interestingly, no alterations in 5-HT_{1A} receptor-binding sites were seen after such lesions were created in forebrain areas, including the neocortex and the hippocampus. A possible explanation is that the density of presynaptic 5-HT_{1A} receptors in forebrain regions is low. Furthermore, destruction of areas such as the hippocampus, using kainic acid, causes a selective degeneration of pyramidal cells and interneurones, accompanied by the loss of 5-HT_{1A}-binding sites (Hall et al., 1985). This suggests that hippocampal 5-HT_{1A} receptors are essentially postsynaptic. The density of 5-HT_{1A} receptors in the hippocampus of patients with Alzheimer's disease is decreased in parallel with the loss of pyramidal cells. Thus, 5-HT_{1A} receptors in the hippocampus are probably postsynaptic to serotoninergic afferents as suggested from the lesion experiments (Cross et al., 1984, 1988).

The activation of central 5-HT_{1A} receptors induces a behavioural syndrome, which is characterised by flat body posture, reciprocal forepaw treading, and head weaving (Tricklebank, 1985). Typically, the administration of low doses of 8-OH-DPAT induces these behaviours which can be antagonised by compounds such as spiperone, BMY 7378, NAN 190, SDZ 216525, and β-adrenoceptor antagonists such as pindolol, propranolol, or alprenolol (Lucki, 1992). 5-HT_{1A} receptor agonists such as 8-OH-DPAT, gepirone, buspirone, and ipsapirone also cause hyperphagia which can be effectively antagonised with spiperone or pindolol. A variety of 5-HT_{1A} receptor agonists, especially those considered to be partial agonists, such as buspirone, gepirone, ipsapirone, or tandospirone, have anxiolytic effects in animal models of anxiety (Traber and Glaser, 1987). Such compounds are being, or have already been, developed as anxiolytics, although clinical data with such drugs suggest an additional antidepressant activity; this is not unexpected because some of these compounds are active in animal models for depression, such as the forced swimming test (Cervo et al., 1988; Wieland and Lucki, 1990). Finally, a

variety of agonists such as 8-OH-DPAT, flesinoxan, urapidil, and 5-methyl-urapidil produce a decrease in blood pressure and heart rate by activation of central 5-HT_{1A} receptors (Doods et al., 1988; Dreteler et al., 1990, 1991).

2. Agonists and antagonists. Several agonists show selectivity for 5-HT_{1A} receptors, e.g., 8-OH-DPAT, DP-5-CT, buspirone, ipsapirone, gepirone, 5-methyl-urapidil, flesinoxan, and MDL 72832 (Richardson and Hoyer, 1990). The number of selective antagonists is more limited, the most significant ones being NAN 190 (Glennon et al., 1988), MDL 73005 (Hibert and Moser, 1990), 5-F-8-OH-DPAT (Hillver et al., 1990), BMY 7378 (Yocca et al., 1987), SDZ 216525 (Hoyer et al., 1991; Schoeffter et al., 1993), and most recent, (±)WAY 100135 (Fletcher et al., 1993). However, some of these ligands may behave as partial agonists, depending on the system investigated (Hoyer et al., 1991; Cornfield et al., 1989; Hjorth and Sharp, 1990; Sharp et al., 1990; Yocca et al., 1987; Boddeke et al., 1992). The recently identified (±)WAY 100135 has been described as a selective antagonist that is devoid of any partial agonist activity (Bill et al., 1993; Fletcher et al., 1993; Starkey and Skingle, 1993). The potency estimates of the commonly used agonists and antagonists are summarised in table 3.

3. Radioligand binding. The classical radioligand-binding assays for 5-HT_{1A} receptors use [^{3}H]8-OH-DPAT (Gozlan et al., 1983) and homogenised preparations of cortex or hippocampus from rat, pig, or other species. Other radioligands have been described for 5-HT_{1A} sites, but none has surpassed [^{3}H]8-OH-DPAT in its overall usefulness (table 4).

4. Receptor structure and transduction. Lefkowitz's group, screening a human library with probes for the β_2-adrenoceptor, isolated the so-called clone G21 (Kobilka et al., 1987), which was subsequently shown to be the gene coding for the human 5-HT_{1A} receptor (Fargin et al., 1988). G21 is intronless, and the corresponding protein has a predicted 421 amino acids. The rat 5-HT_{1A} receptor gene has also been cloned (Albert et al., 1990) and the receptor has 99% sequence homology with the human equivalent in the putative TMRs.

De Vivo and Maayani (1985, 1986) first described 5-HT_{1A} receptor-mediated inhibition of forskolin-stimulated adenylyl cyclase in rat and guinea pig hippocampus. Similar findings with forskolin- and vasointestinal polypeptide-stimulated adenylyl cyclase were reported in mouse and guinea pig hippocampal cells or membranes (Weiss et al., 1986; Bockaert et al., 1987). In calf hippocampus, the rank order of potency of a large number of agonists and antagonists to inhibit forskolin-stimulated adenylyl cyclase correlated highly significantly with 5-HT_{1A} binding (Schoeffter and Hoyer, 1988). The G-protein coupling appears somewhat paradoxical, because in the hippocampus, 5-HT_{1A} receptors appear to mediate both stimulation and inhibition of adenylyl cyclase activity (Shenker et al., 1983, 1985, 1987). It would seem that either 5-HT_{1A} receptors are able to couple to at least two different G-proteins (G_s and G_i) in the same tissue (although not necessarily in the same cell) or, alternatively, inhibition and stimulation of adenylyl cyclase are mediated by two closely related but different receptors, which are difficult to distinguish pharmacologically. Hypothetically, the situation could be analogous to that with 5-HT_{2C} and 5-HT_{2A} receptors, which are very similar, both in terms of structure and pharmacology, and many of the available ligands do not distinguish between the two receptors (see sections III.B and III.D).

Transduction systems other than adenylyl cyclase have been described for the 5-HT_{1A} receptor. Andrade et al. (1986) reported the presence of a pertussis toxin-sensitive G-protein that couples 5-HT_{1A} receptors in hippocampal pyramidal cells to a K^+ channel. Activation of the receptor leads to channel opening and hyperpolarisation. 5-HT_{1A} receptor-mediated inhibition of carbachol-stimulated accumulation of inositol phosphates has been reported in neonatal, but not adult, rat hippocampus (Claustre et al., 1989). Fargin et al. (1989) reported that 5-HT_{1A} receptor clones transfected into HeLa cells stimulate inositol phosphate production and protein kinase C activity; however, significantly higher EC_{50} values were reported for agonists in this test, compared to those involving inhibition of adenylyl cyclase.

In these same HeLa cells, Fargin, Raymond, and collaborators (Fargin et al., 1989; Raymond et al., 1989, 1991; Middleton et al., 1990) reported that 5-HT_{1A} receptors mediate sodium-dependent potassium transport and Na^+/K^+ ATPase activity. Thus, in terms of second messengers, the 5-HT_{1A} receptor has been the most widely studied, and it is anticipated that other 5-HT receptors will similarly show that they can link to multiple transducing systems. However, such promiscuity of coupling may relate only to transfected receptor systems and not to the endogenous physiological receptor which appears to preferentially couple negatively to adenylyl cyclase (Kenakin, 1989; Richards, 1991).

There has been some debate about 5-HT_{1A} receptors being able to couple positively to adenylyl cyclase (Shenker et al., 1983). At present it appears that this receptor, like the other members of the 5-HT_1 family, negatively couples preferentially to adenylyl cyclase via α_i; in addition, it has been shown that recombinant 5-HT_{1A} receptors do not readily associate with α_s (Bertin et al., 1992). However, there is evidence that some isoforms of cyclase (types II and IV) which are present in the brain can be activated by β/γ-subunits (Tang and Gilman, 1991). This possibility has been elegantly demonstrated by Uezono et al. (1993), using *Xenopus* oocytes injected with mRNAs for the 5-HT_{1A} receptor in combination with adenylyl cyclase type II and the cystic fibrosis transmembrane conductance regulator gene. Activa-

TABLE 3
Potency of selected ligands at various 5-HT receptors

Receptor	Localisation within CNS	Rank order of potency*	
		Agonists	Antagonists
5-HT_{1A}	Dorsal raphé, hippocampus, cortex	DP-5-CT (8.7) 5-CT (8.6) 5-Methyl-urapidil (8.5) 8-OH-DPAT (8.2) RU 24969 (7.8) Spiroxatrine (7.8) LY 165163 (7.7) Flesinoxan (7.7) Metergoline (7.6) Ipsapirone (7.5) Buspirone (7.3) MDL 73005 (7.3) Isamoltane (6.8) TFMPP (6.7) Methysergide (6.4) CGS 12066 (6.4) mCPP (5.9) Sumatriptan (5.6)	SDZ 216525 (10.0) NAN 190 (8.9) SDZ 21009 (8.3) Cyanopindolol (8.1) Pindolol (7.9) Methiothepin (7.7) WAY 100135 (7.2–7.7) Spiperone (7.2) Propranolol (6.6) Quipazine (5.2)
5-HT_{1B}	Substantia nigra, basal ganglia, subiculum (rodent specific)	RU 24969 (8.4) 5-CT (7.9) CP 93,129 (7.8) CGS 12066 (7.6) Metergoline (7.2) TFMPP (6.9) Methysergide (6.7) mCPP (6.5) Sumatriptan (6.0) DP-5-CT (5.8) 8-OH-DPAT (4.9)	Cyanopindolol (8.2) Methiothepin (8.1) SDZ 21009 (8.0) Isamoltane (7.3) Propranolol (6.9) Pindolol (6.8) Quipazine (6.2) Yohimbine (6.1) Rauwolscine (6.0) Mianserin (6.0) Spiperone (4.4)
5-HT_{1D}	Substantia nigra, basal ganglia, superior colliculus (guinea pig, pig, calf, monkey, human)	L 694247 (9.4) 5-CT (8.1) LY 165163 (7.6) Metergoline (7.5) CGS 12066 (7.1) Methysergide (7.0) Sumatriptan (7.0) Rauwolscine (6.9) Yohimbine (6.8) Cyanopindolol (6.8) RU 24969 (6.8) DP-5-CT (6.6) SDZ 21009 (5.9) 8-OH-DPAT (5.8) TFMPP (5.8)	GR 127935 (9.9) Methiothepin (7.7) Mianserin (6.5) Quipazine (5.7) mCPP (5.1) Spiperone (4.8) Isamoltane (4.4) Buspirone (4.2)
5-HT_{2A}	Claustrum, olfactory tubercle, cortex	DOI (7.6) α-Methyl-5-HT (7.3) RU 24969 (6.1) 8-OH-DPAT (5.5) 5-CT (3.5)	Pirenperone (9.4) Ketanserin (9.3) Ritanserin (9.3) Cinanserin (9.2) Methiothepin (9.0) Spiperone (9.1) Mesulergine (9.1) Pizotifen (8.9) Metergoline (8.5) Mianserin (8.0) Propranolol (6.4) Pindolol (5.5)

* Agonists: pEC_{50} values; antagonists: pK_B or pA_2 values (all determined in second-messenger tests except for 5-HT_3 receptors). Models: 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptor-mediated inhibition of forskolin-stimulated adenylyl cyclase activity in calf hippocampus, rat substantia nigra, and calf substantia nigra, respectively. 5-HT_{2C} receptor-mediated stimulation of phospholipase C activity in pig choroid plexus. 5-HT_{2A} receptor-mediated stimulation of calcium mobilisation of A7r5 smooth muscle cells. 5-HT_3 receptor-mediated depolarisation of rat vagus nerve. 5-HT_4 receptor-mediated stimulation of adenylyl cyclase activity in colliculus and oesophagus. 5-HT_{2B} receptors have not been included because fewer data are available. See text for references.

TABLE 3—*Continued*

Receptor	Localisation within CNS	Rank order of potency*	
		Agonists	Antagonists
5-HT_{2C}	Choroid plexus, globus pallidus, substantia nigra	α-Methyl-5-HT (7.3) DOI (7.0) mCPP (6.9) TFMPP (6.8) Bufotenin (6.6) RU 24969 (6.2) Quipazine (6.2) 5-CT (5.7) Sumatriptan (4.3) CGS 12066 (4.1) 8-OH-DPAT (<4)	Metergoline (10.6) Mesulergine (9.1) Methysergide (8.9) Ritanserin (8.7) LY 53857 (8.5) Methiothepin (8.2) Cyproheptadine (7.9) Pirenperone (7.0) SB 200646 (6.9) Ketanserin (6.5) Cinanserin (6.2)
5-HT_3	Dorsal vagal nerve, solitary tract nerve, trigeminal nerve, area postrema, spinal cord, limbic system	2-Methyl-5-HT (7.7) Phenylbiguanide (6.8) 8-OH-DPAT (inactive) RU 24969 (inactive) 5-CT (inactive 5-MeOT (inactive)	Tropisetron (10.6) Zacopride (10.1) Granisetron (10.1) MDL 72222 (8.9) Ondansetron (8.6) Renzapride (8.6) Quipazine (8.0) Metoclopramide (6.4)
5-HT_4	Colliculus, hippocampus	Cisapride (7.1) 5-MeOT (7.0) Renzapride (6.9) Zacopride (6.0) BRL 20627 (5.5) 5-CT (5.5) Metoclopramide (5.3) 2-Methyl-5-HT (≪4)	SB 204070 (10.4) GR 113808 (9.7) SDZ 205557 (7.4) DAU 6285 (7.3) Tropisetron (6.2) MDL 72222 (≪5.3) Granisetron (≪5) Ondansetron (≪5) Ketanserin (inactive) Mesulergine (inactive) Methiothepin (inactive) Spiperone (inactive)

TABLE 4

*Major radioligands for 5-HT receptors**

5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{2A}	5-HT_{2C}	5-HT_3	5-HT_4
[^{3}H]8-OH-DPAT	[^{125}I]Iodocyanopindolol	[^{3}H]5-HT	[^{3}H]Ketanserin	[^{3}H]Mesulergine	[^{3}H]GR 65630	[^{3}H]GR 113808
[^{3}H]5-HT	[^{3}H]5-HT	[^{125}I]GTI	[^{3}H]Spiperone	[^{3}H]5-HT	[^{3}H]Granisetron	[^{125}I]SB 207710
[^{3}H]Ipsapirone	[^{3}H]DHE	[^{3}H]5-CT	[^{3}H]LSD	[^{3}H]LSD	[^{3}H]LY 278584	
[^{3}H]WB 4101	[^{125}I]GTI	[^{3}H]L 694247	[^{125}I]LSD	[^{125}I]LSD	[^{3}H]Zacopride	
[^{3}H]PAPP	[^{3}H]CP 93,129		[^{125}I]SCH 23982	[^{125}I]SCH 23982	[^{125}I]Zacopride	
[^{3}H]Spiroxatrine	[^{3}H]CP 96,501		[^{3}H]Mesulergine	[^{125}I]DOI	[^{3}H]GR 67330	
[^{3}H]Lisuride			[^{3}H]SCH 23390		[^{3}H]Tropisetron	
[^{125}I]PAPP			[^{3}H]Mianserin			
			[^{3}H]DOB			
			[^{125}I]DOI			

* [^{3}H]5-HT labels all 5-HT_1 sites and thus can only be used in combination with adequate masking ligands, e.g., 5-HT_{1D} binding is performed in the presence of 100 nM 8-OH-DPAT and mesulergine, or in tissue enriched in a particular receptor subtype, e.g., 5-HT_{2C} sites in the choroid plexus. For references see text. In transfected cells, 5-ht_{1E}, 5-ht_{1F}, 5-ht_{5A}, 5-ht_{5B}, 5-ht_6 and 5-ht_7 receptors have been labelled using either [^{3}H]5-HT and/or [^{125}I]LSD. Similarly, 5-HT_{2B} receptors have been labelled using [^{3}H]5-HT and [^{125}I]DOI.

tion of 5-HT_{1A} receptors led to cAMP* production which, via protein kinase A, stimulated the cystic fibrosis transmembrane conductance regulator, leading to chloride channel activation. However, although this represents a possible mechanism to explain 5-HT_{1A} receptor-stimulated activation of adenylyl cyclase in hippocampus, another possibility might be that the effects were mediated by 5-ht_7 receptors (see section V.D)

* Abbreviations: cAMP, cyclic AMP; cGMP, cyclic GMP; SRL, serotonin receptor-like; TMR, transmembrane-spanning region; CNS, central nervous system.

C. 5-HT_{1B} Receptors

1. Distribution and function. The basal ganglia (Pazos and Palacios, 1985), especially the globus pallidus, and the pars reticulata of the substantia nigra show high densities of 5-HT_1 sites. In the rat brain these sites are of the 5-HT_{1B} subtype, as assessed by their pharmaco-

logical profile (Pazos and Palacios, 1985). In contrast to the situation in rats and mice, [^{3}H]5-HT binding in the basal ganglia of other mammals displays a pharmacological profile characteristic of 5-HT_{1D} sites. Furthermore, there is no evidence from binding studies for the presence of 5-HT_{1B} sites in guinea pig, pig, calf, rabbit, dog, monkey, human, and even pigeon brain. In autoradiographic studies, sumatriptan displaced [^{3}H]5-HT binding from 5-HT_{1B} sites in rat brain and 5-HT_{1D} sites in monkey and human brain (Waeber et al., 1989c). It has been shown, using the recently introduced 5-HT_{1B}/5-HT_{1D} ligand, [^{125}I]GTI, that the distribution of 5-HT_{1B} sites in rat brain is similar to that of 5-HT_{1D} sites in guinea pig and human brain, with the highest concentration in substantia nigra, globus pallidus, dorsal subiculum, and superior colliculi (Segu et al., 1991; Boulenguez et al., 1992; Palacios et al., 1992). 5-HT_{1B} (5-$HT_{1D\beta}$) receptor mRNA has been reported in raphé nuclei, striatum, cerebellum (Purkinje cell layer), hippocampus (pyramidal cell layer of CA1), entorhinal and cingulate cortex (layer IV), subthalamic nucleus, and nucleus accumbens but not in the substantia nigra (Voigt et al., 1991; Maroteaux et al., 1992; Jin et al., 1992).

Many studies have established that terminal autoreceptors of the rat cortex are of the 5-HT_{1B} subtype and that there is a highly significant correlation between the potencies of drugs for the rat autoreceptors and their affinities at 5-HT_{1B}-binding sites (Middlemiss, 1984, 1985, 1986; Engel et al., 1986; Limberger et al., 1991). In contrast, it is evident that 5-HT autoreceptors from non-rodent species are of the 5-HT_{1D}, not the 5-HT_{1B}, type (Schipper et al., 1987; Galzin et al., 1988; Galzin and Langer, 1991; Middlemiss et al., 1988; Schipper and Tulp, 1988). This highlights the similar distribution and roles subserved by the two receptor types in different species (Hoyer and Middlemiss, 1989).

In the rat, lesion experiments have shown that 5-HT_{1B} receptors could be presynaptically localised on the terminals of the striatal intrinsic neurones that innervate the substantia nigra pars reticulata, because destruction of caudate neurones results in a dramatic decrease of binding in the substantia nigra pars reticulata (Hamon et al., 1990b). On the other hand, the lesion of dopaminergic neurones in the substantia nigra pars compacta does not induce a decrease of 5-HT_{1B}-binding sites. Thus, it appears that 5-HT_{1B} receptors are localised on cells controlling the activity of the basal ganglia, but that they are not linked to the dopaminergic innervation. Nevertheless, there is ample evidence that 5-HT_{1B} receptors not only function as autoreceptors on serotoninergic receptors but also function as terminal heteroreceptors to control the release of other neurotransmitters such as acetylcholine and glutamate (Engel et al., 1986; Middlemiss, 1986; Limberger et al., 1991; Maura and Raiteri, 1986; Raiteri et al., 1986). Indeed, presynaptic heteroreceptors may predominate, because lesions of serotoninergic neurones do not result in significant losses of 5-HT_1 binding in most areas examined.

Other functional correlates for 5-HT_{1B} receptors have been described in vascular tissues. Inhibition of noradrenaline release appears to be mediated by 5-HT_{1B} receptors in rat vena cava (Göthert et al., 1986b), but by 5-HT_{1D} receptors in human saphenous vein (Molderings et al., 1987, 1990). There is evidence that inhibition of plasma extravasation produced by stimulation of the trigeminal ganglion is mediated by 5-HT_{1B} receptors in rats and by 5-HT_{1D} receptors in guinea pig (Saito et al., 1988; Buzzi and Moskowitz, 1990; Buzzi et al., 1991a, 1991b). Indeed, these effects are produced by the 5-HT_{1B}/5-HT_{1D} receptor agonists (5-CT, sumatriptan, ergotamine, DHE, 5-benzyloxytryptamine) in both species, but the very selective 5-HT_{1B} receptor agonist, CP 93,129, is active in rat and inactive in guinea pig. Recently, Craig and Martin (1993) reported that 5-HT contracts the rat caudal artery via 5-HT_{1B} receptor activation.

5-HT_{1B} receptors have also been implicated in DNA synthesis in hamster fibroblast (Seuwen et al., 1988) and described in mouse and opossum kidney cells (Ciaranello et al., 1990; Murphy and Bylund, 1989).

There are few central behavioural effects that have been shown unequivocally to be mediated by 5-HT_{1B} receptors. The major difficulty comes from the paucity of selective antagonists and the poor brain penetration of the few selective ligands available. The 5-HT_{1B} receptor agonist, RU 24969, has clear effects on locomotion; despite its poor selectivity, the hyperlocomotor activity produced by RU 24969 can be antagonised by propranolol (Lucki, 1992). Penile erection in rat appears to involve, at least in part, 5-HT_{1B} receptors (Berendsen and Broekkamp, 1987); similarly, hypophagia may be due at least in part to activation of 5-HT_{1B} receptors (Kennett and Curzon, 1988a), although in both cases a 5-HT_{2C} receptor-mediated component may be involved.

2. Agonists and antagonists. Few selective ligands are available, although the recently described agonist, CP 93,129, does appear to be 5-HT_{1B} selective (Macor et al., 1990). Claims that RU 24969, TFMPP, and mCPP are 5-HT_{1B} receptor-selective agonists have not been confirmed (Hamon et al., 1986; Feniuk and Humphrey, 1989; Schoeffter and Hoyer, 1989b). However, the agonist CGS 12066 appears to have some 5-HT_{1B} receptor selectivity (Schoeffter and Hoyer, 1989b).

No good selective antagonists are available. Some indole β-adrenoceptor antagonists are potent 5-HT_{1B} receptor antagonists (e.g., SDZ 21009, cyanopindolol); however, their potency at 5-HT_{1A} receptors is similar.

The potency estimates of the most commonly used agonists and antagonists are summarised in table 3.

3. Radioligand binding. 5-HT_{1B} receptor binding can be performed with [^{3}H]5-HT in the presence of blocking concentrations of 5-HT_{1A} and 5-HT_{1C} (now 5-HT_{2C}) receptor ligands (Peroutka, 1988) or with [^{125}I]iodocya-

nopindolol in the presence of 30 μM isoprenaline to avoid β-adrenoceptor binding (Hoyer et al., 1985a,b). The binding can be performed in rat or mouse brain, usually striatum or cortex. Other radioligands used (table 4) include [^{3}H]DHE (Hamblin et al., 1987) and the more selective ligands [^{125}I]GTI (Segu et al., 1991; Boulenguez et al., 1992) or [^{3}H]CP 93,129/CP 96,501 (Koe et al., 1992a,b). It should be mentioned that [^{125}I]GTI also labels a second population of sites in the rat brain, which exhibits a 5-HT_{1D} profile, presumably representing 5-$HT_{1D\alpha}$ receptors (Bruinvels et al., 1993a, 1993b).

4. Receptor structure and transduction. Voigt et al. (1991) and Adham et al. (1992) identified the 5-HT_{1B} receptor using a probe derived from the human 5-$HT_{1D\beta}$ receptor clone. The rat receptor gene is intronless, encoding for a 386-amino acid protein, and has 96% homology in the TMR with the equivalent human clone, but the rat receptor exhibits the typical 5-HT_{1B} operational profile. Similarly, a mouse 5-HT_{1B} receptor has been cloned (Maroteaux et al., 1992); these receptors (human 5-$HT_{1D\beta}$ and rat/mouse 5-HT_{1B}) represent species homologues, as suggested earlier on the basis of their distribution in brain from a variety of species (Hoyer and Middlemiss, 1989). Thus, it appears that 5-HT_{1B} receptors that have been described in only a few species (rat, mouse, hamster, and opossum) are the equivalent of the 5-$HT_{1D\beta}$ receptor, found in most other mammals studied and birds (Hartig et al., 1992).

5-HT_{1B} receptors have been shown to be negatively coupled to adenylyl cyclase in homogenates of rat substantia nigra, which predominantly possess a high density of 5-HT_{1B} sites (Bouhelal et al., 1988). In this preparation, the rank order of potency of both agonists and antagonists correlates well with affinity values for 5-HT_{1B}-binding sites (Bouhelal et al., 1988; Schoeffter and Hoyer, 1989a). Similar findings have been reported in a hamster lung cell line (Seuwen et al., 1988), in which the mitogenic effects of 5-HT could be related to inhibition of adenylyl cyclase activity. Cells transfected with rat or mouse 5-HT_{1B} receptors have been shown to be linked to inhibition of adenylyl cyclase activity and to display an operational profile typical of the 5-HT_{1B} receptor (Adham et al., 1992; Maroteaux et al., 1992).

D. 5-HT_{1D} Receptors

1. Distribution and function. 5-HT_{1D} receptors have been found to exist in the brain of a range of non-rodent mammalian species including guinea pig, rabbit, dog, pig, calf, and human (Heuring and Peroutka, 1987; Waeber et al., 1988a; Hoyer and Schoeffter, 1988; Herrick-Davies and Titeler, 1988; Beer et al., 1992; Maura et al., 1993). 5-HT_{1B} sites appear to be absent in these species, and the 5-HT_{1D} receptor reflects the distribution and function of the 5-HT_{1B} receptor found in the rodent (see above). Nevertheless, there is evidence that 5-HT_{1D} receptors do exist in the rat, although radioligand-binding studies would suggest that their concentration is very low (Herrick-Davis and Titeler, 1988; Bruinvels et al., 1993b).

The regional distribution of 5-HT_{1D} receptors in non-rodent species appears similar to that of the 5-HT_{1B} receptor in rodents, with the highest density in the substantia nigra, basal ganglia, and nigrostriatal pathway and a lower density in the hippocampus, raphé, and cortex (Waeber et al., 1990). However, it should be appreciated that radioligand-binding techniques do not currently allow the differentiation of 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors. Nevertheless, Beer and Middlemiss (1993) reported that [^{125}I]GTI largely labels 5-$HT_{1D\beta}$ receptors in human cerebral cortex. This is in keeping with data from Bruinvels and colleagues (1993b) showing that in rat brain [^{125}I]GTI predominantly labels 5-HT_{1B} receptors.

The distribution of 5-HT_{1B} and 5-$HT_{1D\beta}$ receptor mRNA in the brain is similar across species (Voigt et al., 1991; Jin et al., 1992). However, it is apparent that the density of 5-$HT_{1D\alpha}$ receptor is much lower, although the mRNAs for these receptors (5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ or 5-HT_{1B}) appear to codistribute; thus, 5-$HT_{1D\alpha}$ receptor mRNA has been found in raphé nuclei, striatum, nucleus accumbens, hippocampus, and olfactory tubercle but not in globus pallidus and substantia nigra (Hamblin et al., 1992; Bach et al., 1993).

Similar functional correlates and distributions have been seen for 5-HT_{1B} and 5-HT_{1D} sites. Thus, the 5-HT_{1D} receptor was first identified as mediating inhibition of 5-HT release from cortical nerve terminals of the guinea pig brain (Middlemiss et al., 1988). Subsequently, it was shown that the potencies of a variety of agonists and antagonists at the 5-HT_{1D} receptor mediating inhibition of adenylyl cyclase correlated very significantly with their effects on [^{3}H]5-HT release in pig cortex slices (Schlicker et al., 1989). Similar findings have been reported in guinea pig and rabbit brain (Limberger et al., 1991). These studies strongly suggest that the terminal 5-HT autoreceptor is of the 5-HT_{1D} type in pig, guinea pig, human, and rabbit brain.

As is the case for 5-HT_{1B} receptors, 5-HT_{1D} receptors also appear to function as heteroreceptors, as judged by studies of nonserotoninergic nerves where 5-HT appears to inhibit release of glutamate from rat cerebellar synaptosomes and acetylcholine from guinea pig hippocampal synaptosomes (Raiteri et al., 1986; Harel-Dupas et al., 1991).

Other functional correlates have been proposed for 5-HT_{1D} receptors. Thus, endothelium-dependent relaxation in the pig coronary artery has been claimed to be mediated by 5-HT_{1D} receptors, based on the rank order of potencies of a variety of agonists and antagonists (Schoeffter and Hoyer, 1990). Hamel and collaborators (Hamel and Bouchard, 1991; Hamel et al., 1993a,b) have presented evidence for the presence of 5-HT_{1D} receptors in bovine and human cerebral arteries. In these prepa-

rations, the pharmacological profile of the 5-HT_1 receptor mediating contraction resembles more that of a 5-$HT_{1D\beta}$ receptor than that of a 5-$HT_{1D\alpha}$ receptor-mediated effect. In addition, these authors, using Northern blot analysis, were able to demonstrate the presence of 5-$HT_{1D\beta}$ receptor mRNA in cerebral artery preparations, whereas 5-$HT_{1D\alpha}$ receptor mRNA could not be detected. It has also been suggested that inhibition of plasma extravasation produced by stimulation of the trigeminal ganglion, is mediated by 5-HT_{1D} receptors in guinea pig (Buzzi et al., 1991a, 1991b; Matsubara et al., 1991).

2. Agonists and antagonists. Few if any ligands show selectivity for 5-HT_{1D} receptors. Sumatriptan possesses limited 5-HT_{1D} selectivity (Peroutka and McCarthy, 1989; Schoeffter and Hoyer, 1989c), whereas 5-benzyloxy-tryptamine is equally effective at 5-HT_{1D} and 5-HT_{1B} receptors (Peroutka et al., 1991). L 694247 has been identified as a very potent 5-HT_{1D} receptor agonist ($pK_D = 10.2$) (Beer et al., 1993). Unfortunately, no selective antagonist for 5-HT_{1D} receptors has been available until recently and receptor characterisation relied on the use of nonselective antagonists such as metergoline and methiothepin which block most 5-HT_1 and 5-HT_2 receptors. However, GR 127935 has now been identified as a very potent and selective 5-HT_{1D} receptor antagonist ($pK_D = 9.9$) (Skingle et al., 1993).

The affinity estimates of the most useful agonists and antagonists are summarised in table 3.

3. Radioligand binding. 5-HT_{1D} binding was initially reported in calf caudate (Heuring and Peroutka, 1987) and human caudate (Hoyer et al., 1988), using [^{3}H]5-HT in the presence of 100 nM 8-OH-DPAT and mesulergine to block 5-HT_{1A}/5-HT_{1C} binding. However, under these conditions binding is not homogeneous and includes the 5-ht_{1E} site (Sumner and Humphrey, 1989; Leonhardt et al., 1989; Beer et al., 1992). [^{125}I]GTI has apparent advantages (Bruinvels et al., 1991; Segu et al., 1991; Boulenguez et al., 1992) because this ligand labels what appear to be homogeneous 5-HT_{1D} sites in a variety of species (table 4).

4. Receptor structure and transduction. Primers derived from the putative canine RDC4 receptor (377 amino acids) which has limited homology (55%) with the human 5-HT_{1A} receptor (Libert et al., 1989) were used in the polymerase chain reaction to find the human equivalent that has 93% homology in the TMR. This human receptor exhibits typical 5-HT_{1D} receptor operational characteristics (Hamblin and Metcalf, 1991; Branchek et al., 1991; Weinshank et al., 1992) and is a single protein of 377 amino acids. When transfected into mammalian cells, the RDC4 gene also exhibited a 5-HT_{1D}-type pharmacology (Maenhaut et al., 1991, Zgombick et al., 1991). A rat equivalent gene, encoding for a 374-amino acid protein (95% homology in the TMRs), has been cloned (Hamblin et al., 1992; Bach et al., 1993); this receptor has 5-HT_{1D}-like characteristics, except that drugs such as ritanserin and ketanserin are reported to have high affinity for this site. In addition, Maroteaux et al. (1992) indicate that they have cloned the mouse equivalent to RDC4. These clones (derived from RDC4) were named 5-$HT_{1D\alpha}$ by Hartig et al. (1992), and it is important to note that, so far, none of these cloned receptors exhibits a 5-HT_{1B} pharmacology. It would seem that the RDC4-related gene products are expressed at very low levels (Libert et al., 1989; Weinshank et al., 1992) or at least that the mRNA levels are very low (Jin et al., 1992; Bruinvels et al., 1993a, b).

In humans, a second receptor relatively similar in terms of sequence (77% in the TMR) has been cloned. The human gene product which has 390 predicted amino acids (named 5-$HT_{1D\beta}$) is the species homologue of the rodent 5-HT_{1B} receptor (97% homology). However, the 5-$HT_{1D\beta}$ receptor exhibits a 5-HT_{1D} pharmacology that is indistinguishable from that of the 5-$HT_{1D\alpha}$ clone with the ligands used to date (Weinshank et al., 1992; Levy et al., 1992b; Jin et al., 1992). The obvious question is which of the two receptors (5-$HT_{1D\alpha}$ or 5-$HT_{1D\beta}$) is relevant to the various pharmacological effects of 5-HT_{1D} receptor activation described extensively in the literature? The parallel between 5-HT_{1B} and 5-HT_{1D} receptors (similar functions and distributions across species) and the much lower density of 5-$HT_{1D\alpha}$ receptor mRNA and protein would suggest that the 5-$HT_{1D\beta}$ receptor is the counterpart of what has been described in functional and biochemical studies as 5-HT_{1D} receptors. Evidence has been presented that this may indeed be so in human arteries because the operational characteristics of arterial 5-HT_1 receptors are closer to those of 5-$HT_{1D\beta}$ than to those of 5-$HT_{1D\alpha}$ receptors (Hamel et al., 1993a,b; Kaumann et al., 1993). This may also be the case for other "5-HT_{1D}" models (e.g., inhibition of cAMP production in calf substantia nigra, inhibition of 5-HT release in non-rodents, or porcine coronary artery contraction) where compounds such as ketanserin (or ritanserin) when tested are devoid of activity (it seems that these two antagonists have significant affinity for 5-$HT_{1D\alpha}$ receptors).

Activation of 5-HT_{1D} receptors leads to inhibition of forskolin-stimulated adenylyl cyclase activity in calf and guinea pig substantia nigra (Hoyer and Schoeffter, 1988; Schoeffter et al., 1988; Waeber et al., 1989d), which contain a high proportion of 5-HT_{1D} sites (Waeber et al., 1988c, 1989a). Most studies performed with cells transfected with 5-HT_{1D} receptors (both 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ types) show that these receptors are indeed negatively coupled to adenylyl cyclase. However, the canine RDC4 clone, depending on the type of cell system used, can be linked positively (Maenhaut et al., 1991) or negatively to adenylyl cyclase (Zgombick et al., 1991). It appears that, depending on the cell line used for the expression of 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors, promiscuous coupling can be observed, e.g., inhibition of adenylyl cyclase and stimulation of calcium mobilisation (Zgombick et al., 1993).

E. 5-ht$_{1E}$ Receptors

1. Distribution and function. The 5-ht$_{1E}$ receptor was first identified from binding studies with tritiated 5-HT (in the presence of excess 5-CT to block 5-HT$_{1A}$ and 5-HT$_{1D}$ binding) in homogenates of human frontal cortex (Leonhardt et al., 1989). However, in the absence of specific radioligands for autoradiography, it is not possible to readily determine the overall distribution of the 5-ht$_{1E}$ receptor in relation to other 5-HT$_1$ receptors, at which 5-HT also has high affinity. However, homogenate-binding studies indicate that the receptor is generally present in brain regions similar to those of the 5-HT$_{1D}$ receptor in varying relative proportions (Miller and Teitler, 1992; Lowther et al., 1992; Beer et al., 1992). Now that the receptor gene has been cloned it will be possible soon to determine the overall distribution of the mRNA encoding this receptor in tissues, using in situ hybridisation techniques (McAllister et al., 1992).

The function of the 5-ht$_{1E}$ receptor is not known, although it appears to be coupled negatively to adenylyl cyclase, Thus, in 5-ht$_{1E}$ receptor-transfected HEK293 cells, 5-HT potently inhibited forskolin-stimulated adenylyl cyclase activity (McAllister et al., 1992). However, the degree of inhibition was only about 20%, which might be explained by the artificiality of the system because Levy and colleagues (1992a) reported significantly higher intrinsic activity in their transfected cells.

2. Agonists and antagonists. No selective agonists or antagonists are known. 5-HT has high affinity and potency in inhibiting adenylyl cyclase activity in 5-ht$_{1E}$ receptor-transfected cells, but 5-CT was found to be 500 times weaker (McAllister et al., 1992).

3. Radioligand binding. The only radioligand used to date is [^{3}H]5-HT in the presence of suitable antagonists. 5-HT has high affinity with a K_D of approximately 5 to 10 nM (Leonhardt et al., 1989; McAllister et al., 1992). Certain high-affinity ligands for other 5-HT$_1$ receptors display very low affinity for the 5-ht$_{1E}$ receptor, including 5-CT and methiothepin, which is a weak antagonist (McAllister et al., 1992; Guderman et al., 1993).

4. Receptor structure and transduction. The intronless gene referred to as AC1 or S31 encodes the 5-ht$_{1E}$ receptor, whose amino acid sequence has been published (Levy et al., 1992a; McAllister et al., 1992). It consists of a single protein of 365 amino acids and appears typical of G-protein-linked seven transmembrane domain receptors. Radioligand-binding studies (Leonhardt et al., 1989) indicate that the receptor is linked operationally to a G-protein, although this could not be demonstrated in transfected cells, possibly because of a paucity of the appropriate G-protein. Nevertheless, the transfected receptor has been shown to mediate the inhibition of forskolin-stimulated adenylyl cyclase activity which justifies the inclusion of this receptor in the 5-HT$_1$ group (McAllister et al., 1992; Levy et al., 1992a; Guderman et al., 1993).

F. 5-ht$_{1F}$ Receptors

1. Distribution and function. As a newly identified receptor whose cDNA has been cloned, little is known about its distribution and function. However, from in situ hybridisation studies, the mRNA for the human receptor protein has been identified in the brain, mesentery, and uterus but not in kidney, liver, spleen, heart, pancreas, or testes. In the brain, the mRNA has been shown to be concentrated in the dorsal raphé, hippocampus, and cortex (Adham et al., 1993b). In the mouse, the 5-ht$_{1F}$ receptor (called 5-ht$_{1E\beta}$ by the authors) appears to be densely located in the hippocampus (Amlaiky et al., 1992). However, higher concentrations have been found in cortex and striatum with lower levels in thalamus and hypothalamus (Lovenberg et al., 1993b). No mRNA has been detected in liver, kidney, or heart.

In NIH3T3 cells, the transfected 5-ht$_{1F}$ receptor clones have both been shown to couple negatively to adenylyl cyclase like other 5-HT$_1$ receptors (Amlaiky et al., 1992; Adham et al., 1993b). Nothing is known about the role of these receptors in whole animals, although it has been suggested that the distribution of the 5-ht$_{1F}$ receptor indicates a role as another 5-HT autoreceptor type (Adham et al., 1993b).

2. Agonists and antagonists. No selective agonists or antagonists are available. However, 5-HT potently inhibited adenylyl cyclase activity via the transfected mouse and human 5-ht$_{1F}$ receptor in the nanomolar range (Amlaiky et al., 1992; Adham et al., 1993b; Lovenberg et al., 1993b). This effect was antagonised by methiothepin in an apparently competitive manner, consistent with a pK_D of 6.4 (Adham et al., 1993b).

3. Radioligand binding. Sumatriptan, methylergonovine, and methysergide have been shown, using [^{3}H]5-HT and [^{125}I]LSD as radioligands, to have high (nanomolar) affinity at the transfected human 5-ht$_{1F}$ receptor. It has been suggested, from this profile, that the 5-ht$_{1F}$ receptor may be involved in the mechanism of action of antimigraine drugs (Adham et al., 1993b). As at its closest genetic relative identified to date, the 5-ht$_{1E}$ receptor, the affinity of 5-CT for the 5-ht$_{1F}$ receptor is very low (Amlaiky et al., 1992). In keeping with other G-protein-linked receptors, the binding of 5-HT was concentration-dependently inhibited by guanylyl imidodiphosphate (Adham et al., 1993b).

4. Receptor structure and transduction. The intronless gene for the 5-ht$_{1F}$ receptor has a long open reading frame encoding a protein 366 (human and rat) or 367 (mouse) amino acids in length (Amlaiky et al., 1992; Adham et al., 1993b; Lovenberg et al., 1993a). The human receptor's homology with other related receptors has been described as 5-HT$_{1A}$ (53%), 5-HT$_{1D\alpha}$ (63%), 5-HT$_{1D\beta}$ (60%), and 5-ht$_{1E}$ (70%), when comparing the TMRs (Adham et al., 1993b). The transfected 5-ht$_{1F}$ receptor clones mediate the inhibition of forskolin-stimulated adenylyl cyclase activity by 5-HT with no evidence

for an effect on inositol phospholipid turnover (Amlaiky et al., 1992; Adham et al., 1993b). However, as with other 5-HT_1 receptors, promiscuous coupling has also been observed with 5-ht_{1F} receptors. Thus, whereas in NIH3T3 cells, 5-ht_{1F} receptors have only been reported to inhibit adenylyl cyclase activity, 5-ht_{1F} receptors transfected into LM (tk^-) fibroblasts mediate phospholipase C activation and Ca^{2+} mobilisation (Adham et al., 1993a).

G. 5-HT_1-like Receptors

5-HT_1-like receptors are a group of related receptors that have not yet been positively equated with any of the 5-HT_1-binding site subtypes, identified in the CNS. Although 5-HT_1-like receptors can be clearly distinguished from 5-HT_{1A}-, 5-HT_{1B}-, and 5-HT_{2C}-binding sites, it is sometimes not easy to distinguish them from 5-HT_{1D}-binding sites, which are themselves of at least two types (see section II.D). One of the main difficulties continues to be the lack of availability of selective agonists and antagonists for these sites. Moreover, whereas radioligand-binding assays are adequate for the CNS, they are usually not suitable for peripheral tissues (e.g., blood vessels), where many 5-HT_1-like receptors are located. Consequently, these receptors are still characterised solely operationally as discussed below.

1. Distribution and function. 5-HT_1-like receptors appear to mediate a number of functional responses which include smooth muscle contraction, a decrease in noradrenaline release from sympathetic nerves, and certain central effects (table 5).

The contractile responses to 5-HT in intracranial arteries and carotid arteriovenous anastomotic vessels are mediated predominantly by 5-HT_1-like receptors, although in some cerebral vessels (e.g., in the dog and monkey basilar artery) a variable proportion of 5-HT_2 receptors may also be found (reviewed by Saxena and Villalón, 1990). Some peripheral blood vessels may also contain 5-HT_1-like receptors, either almost exclusively (e.g., dog and rabbit saphenous vein, guinea pig iliac artery, and rabbit renal artery; Humphrey et al., 1988; Martin and MacLennan, 1990; Sahin-Erdemli et al., 1991a; Tadipatri et al., 1991, 1992) or in addition to a functionally more significant population of 5-HT_2 receptors, as in human coronary artery (Connor et al., 1989a). The 5-HT_1-like receptor mediating smooth muscle contraction has similarities to the 5-HT_{1D} receptor but nevertheless seems different, on the basis of metergoline's weak blocking activity (Perren et al., 1991; Den Boer et al., 1992). In human pial vessels, metergoline is slightly more potent than in canine cerebral vessels in antagonising the contractile action of 5-HT, and thus, it has been argued that human cerebral vessels contain 5-HT_{1D}, not 5-HT_1-like, receptors (Hamel and Bouchard, 1991). However, metergoline was at least 1 order of magnitude weaker than would have been expected for a 5-HT_{1D} site. Recently, it was shown using in situ hybridisation that mRNA for the 5-$HT_{1D\beta}$ receptor, but not the 5-$HT_{1D\alpha}$ receptor, was present in human and bovine cerebral arteries (Hamel et al., 1993a). It would seem that better antagonists, and further molecular biology studies, will be needed to definitively characterise the receptor type(s) involved in mediating contraction.

2. Agonists and antagonists. At present there are no completely selective agonists or antagonists for peripheral 5-HT_1-like receptors. However, the compounds used for characterisation of 5-HT_{1D} receptors are also used for characterisation of 5-HT_1-like receptors, using the following main criteria: (*a*) agonist rank order 5-CT $\geq$ 5-HT > sumatriptan > 8-OH-DPAT, (*b*) potent antagonism by methiothepin ($pA_2 > 7$), and (*c*) ineffectiveness of compounds acting as antagonists at other receptors, such as pindolol (5-HT_{1A} and 5-HT_{1B}), yohimbine or rauwolscine (5-HT_{1D}), ketanserin (5-HT_2), and ondansetron (5-HT_3) or GR 113808 (5-HT_4). It has often been found that metergoline, which has high affinity in ligand-binding assays for 5-HT_{1A} (pK_i 8.2), 5-HT_{1B} (pK_i 7.6), 5-HT_{2C} (pK_i 9.3), and 5-HT_{1D} (pK_i 8.4) sites (Hoyer, 1988b), has little ($pK_B < 7$) or no antagonist effects at 5-HT_1-like receptors; invariably, metergoline is also devoid of significant agonist action (Humphrey and Feniuk, 1989; Saxena and Villalón, 1990; Perren et al., 1991). Furthermore, ketanserin may have a weak antagonist action ($pK_B < 7$) at some 5-HT_1-like receptors (Martin and MacLennan, 1990; Tadipatri et al., 1991).

3. Radioligand binding. No radioligand-binding assay is available for 5-HT_1-like receptors. However, with the recent availability of [^{125}I]GTI as a new radioligand for 5-HT_1 receptors (table 4), one might expect to see binding experiments in peripheral tissues in the future. It may then become clear whether any of the 5-HT_1-like receptors can be equated with 5-HT_{1D}-binding sites.

4. Receptor structure and transduction. No cDNA clone can as yet be assigned to the 5-HT_1-like receptors, although it is possible that the two clones derived from RDC4, named 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ (Hartig et al., 1992), may be related to 5-HT_1-like receptors. Given the operational profile of 5-ht_{1E}/5-ht_{1F} receptors on the one hand, and 5-ht_5, 5-ht_6 and 5-ht_7 receptors on the other, one could suggest that these receptors and especially the latter group (which have intermediate to high affinity for 5-CT, methiothepin, and some ergolines), may represent candidates for some of the less well characterised "5-HT_1-like" receptors.

Relatively more information is available regarding the transduction mechanisms involved. The 5-HT_1-like receptor which mediates contraction of the dog isolated saphenous vein is negatively coupled to adenylyl cyclase; thus, 5-HT, 5-CT, and sumatriptan reduce prostaglandin E_2-stimulated cAMP accumulation and this response to sumatriptan is antagonised by methiothepin but not by metergoline, spiperone, or ondansetron (Sumner et al.,

TABLE 5

Functional responses thought to be mediated by 5-HT$_1$-like receptors

Response and species	Tissue	References
Contraction/constriction		
Human	Saphenous vein	Borton et al., 1990; Bax et al., 1992
Dog	Saphenous vein	Apperley et al., 1980; Feniuk et al., 1985; Humphrey et al., 1988; Sumner and Humphrey, 1990; Perren et al., 1991; Cohen et al., 1992; Sumner et al., 1992
Rabbit	Saphenous vein	Martin and MacLennan, 1990; Martin et al., 1991; van Heuven-Nolsen et al., 1990
Human	Dural vessels	Humphrey et al., 1991
Human	Pial arteries	Hamel and Bouchard, 1991
Sheep	Pial arteries	Gaw et al., 1990
Cat	Pial arteries	Connor et al., 1992
Human	Basilar artery	Parsons et al., 1989
Monkey	Basilar artery	Connor et al., 1989b
Pig	Basilar artery	van Charldorp et al., 1990
Dog	Basilar artery	Connor et al., 1989b
Sheep	Basilar artery	Gaw et al., 1990
Guinea pig	Basilar artery	Chang and Owman, 1989
Rabbit	Basilar artery	Bradley et al., 1986b; Parsons and Whalley, 1989
Sheep	Middle cerebral artery	Gaw et al., 1990
Pig	Carotid arteriovenous anastomotic vessels (in vivo)	Saxena et al., 1986, 1989; Bom et al., 1989; Villalón et al., 1990, den Boer et al., 1991
Dog	Carotid vascular bed (in vivo)	Saxena et al., 1983; Feniuk et al., 1989
Cat	Carotid arteriovenous anastomotic vessels (in vivo)	Perren et al., 1989
Human	Coronary artery	Connor et al., 1989a; Borton et al., 1990; Chester et al., 1990; Bax et al., 1993
Human	Umbilical artery	MacLennan et al., 1989
Dog	Renal artery (in vivo)	Cambridge et al., 1991
Rabbit	Renal artery	Tadipatri et al., 1991, 1992
Guinea pig	Iliac artery	Sahin-Erdemli et al., 1991a; Schoeffter and Sahin-Erdemli, 1992
Sheep	Tracheal smooth muscle	Webber et al., 1990
Dog	Terminal ileum	Boeckxstaens et al., 1990
Decreased transmitter release from sympathetic nerves		
Human	Saphenous vein	Göthert et al., 1986a; Molderings et al., 1990
Dog	Saphenous vein	Feniuk et al., 1979; Watts et al., 1981
Rat	Renal vessels	Charlton et al., 1986; Clarke et al., 1989a
Rat	Vas deferens	Docherty and Warnock, 1986
Guinea pig	Heart atrium	Adler-Graschinsky et al., 1989
Attenuation of the reflex pressor response to static muscle contraction (in vivo)		
Cat	Lumbosacral spinal cord	Hill and Kaufman, 1991
Inhibition of 5-HT release		
Pig	Cortical 5-HT neurones	Fink et al., 1988
Inhibition of glutamate release		
Rat	Cerebellum	Raiteri et al., 1986
Neuronal actions		
Rat	Spinal cord and raphé obscurus	Roberts et al., 1988
Rat	Brain stem	Davies et al., 1988

1992). However, evidence has been provided that 5-HT_1-like receptor activation in the dog saphenous vein also leads to the influx of extracellular calcium by an independent mechanism (Sumner et al., 1992).

5. Heterogeneity of 5-HT_1-like receptors. The relative potencies of some agonists in producing various responses, in different isolated preparations believed to be mediated by 5-HT_1-like receptors, is shown in table 6. It is evident that the 5-HT_1-like receptor mediating vasocontraction, which was first characterised in the dog saphenous vein, has distinct characteristics and it is commonly found in cerebral blood vessels. At this receptor 5-CT is characteristically of similar potency to 5-HT (usually slightly more potent) and sumatriptan is some 4- to 5-fold weaker. Methiothepin is a relatively potent antagonist (pA_2 approximately 8), although metergoline tends to be much weaker than at other 5-HT_1 receptors. Without good drug tools it is difficult to decide whether there are differences within this group of 5-HT_1-like receptors mediating contraction and to what extent, if any, they differ from 5-HT_{1D} receptors. Certainly 5-HT_1-like receptors in the dog vasculature appear somewhat different from brain 5-HT_{1D} receptors from various species (Perren et al., 1991) and endothelial 5-HT_{1D} receptors from pig and guinea pig (Schoeffter and Hoyer, 1990; Gupta, 1992). However, definitive classification requires the identification of good selective antagonists and, ultimately, receptor cloning studies in various species. It is worth pointing out that several authors have suggested that the 5-HT receptor mediating contraction of cerebral vessels is of the 5-HT_{1A} type (Peroutka et al., 1986; Taylor et al., 1986), but this overlooks the fact that 8-OH-DPAT has reasonable agonist activity at the 5-HT_1-like receptor in dog vasculature. Because this receptor is clearly not a 5-HT_{1A} receptor it would seem that 8-OH-DPAT is not as selective as was once thought (Humphrey et al., 1988; Perren et al., 1991). The 5-HT_1-like receptor mediating contraction of the rabbit saphenous vein and renal artery appears even more sensitive to the agonist effects of 8-OH-DPAT (table 6), and this is also the case for the "5-HT_{1D}-like" heteroreceptor inhibiting release of glutamate in rat cerebellum (Raiteri et al., 1986). The 5-HT_1-like receptor in rabbit vessels also appears to be somewhat more potently stimulated by α-methyl-5-HT than might be expected. In addition, ketanserin is an antagonist of both 5-HT and sumatriptan, albeit its blocking potency is less than at 5-HT_{2A} receptors. This latter observation may reflect a species-specific characteristic of rabbit 5-HT_1-like receptors that mediate contraction (Martin and MacLennan, 1990; Humphrey et al., 1988).

III. 5-HT_2 Receptors

A. 5-HT_2 Receptor Heterogeneity

For many years, it has been appreciated that 5-HT_2 receptors are ubiquitous and mediate many of the undesirable actions of 5-HT such as platelet aggregation and bronchoconstriction. However, until recently, little credence was given to the view that these receptors are heterogeneous, despite evidence to the contrary (Feniuk

TABLE 6

*Potencies of some agonists and antagonists for a number of functional responses mediated by 5-HT_1-like receptors in various isolated preparations**

Compounds	Dog saphenous vein (contraction)[a-d]	Dog saphenous vein neuronal (inhibition)[b,c,e]	Human saphenous vein (contraction)[f]	Human pial artery (contraction)[g,h]	Rabbit saphenous vein (contraction)[i,j]	Rabbit renal artery (contraction)[k,l]
Agonists						
5-HT	1 (7.4)	1 (8.0)	1 (6.8)	1 (7.6)	1 (6.9, 7.7)	1 (7.1)
5-CT	0.4	0.3	0.5	0.3	0.3	0.2
Sumatriptan	4.5	4.2	5.0	10	13	0.8
AH 25086	4	5.9				
8-OH-DPAT	50		>167	?	5, 79	1.6
Methysergide	7.7	Weak	3.1	13	10	
α-Methyl-5-HT	13	25	6.3	500	5, 63	0.8
2-Methyl-5-HT	250		100	13	380	7.7
Antagonists						
Methiothepin	7.8		7.2	8.5	8.2, 9.5	8.5
Methysergide	Partial agonist	Partial agonist			Partial agonist	
Metergoline	<7.0		6.9	6.8	6.5, 7.8	<7.0
Ketanserin	Inactive		Inactive	Inactive	7.0†	
Cyproheptadine		Inactive				
Cyanopindolol	Inactive	Inactive	6.4		5.7	
Spiperone	Inactive		5.3		5.5	

* Potencies of agonists are shown as equieffective molar ratios (5-HT = 1; pEC_{50} values in parentheses) such that values >1 indicate weaker agonists and values <1 indicate more potent agonists. Antagonist potencies are shown as pA_2 values or equivalent log values of estimated dissociation constants. In some cases more than one value is shown. References: a, Apperley et al., 1980; b, Humphrey et al., 1988; c, Humphrey and Feniuk, 1989; d, Perren et al., 1991; e, Feniuk et al., 1979; f, Bax et al., 1992; g, Hamel and Bouchard, 1991; h, Edvinsson et al., 1992; i, Martin et al., 1991; j, Van Heuven-Nolsen et al., 1990; k, Tadipatri et al., 1991; l, Tadipatri et al., 1992.

† Ketanserin displays surmountable, uncompetitive antagonism.

and Humphrey, 1989; Mylecharane, 1990). It is now clear that several subtypes do exist, which in many respects are quite similar, based on all of the criteria necessary for receptor characterisation. Three 5-HT_2 receptor subtypes are currently recognised (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}), and each has been cloned and shown to be a G-protein-linked single protein molecule of similar size and close homology (458 to 471 amino acids). All three subtypes mediate their effects through activation of phosphoinositide metabolism. In keeping with these similarities the operational characteristics are also similar, although there are differences in estimates of affinity for the various antagonists, which distinguish the various subtypes.

The 5-HT_{2A} receptor is a new appellation recently introduced to describe the historical 5-HT_2 receptor about which much is known. In the rest of this review, the term "5-HT_{2A}" will be used instead of "5-HT_2." The second 5-HT_2 subtype fully characterised was the 5-HT_{1C} receptor which we have recommended now to be called the 5-HT_{2C} (Humphrey et al., 1993). This receptor has long been appreciated as a close relative of the 5-HT_{2A} receptor and now definitively confirmed as such by its cloning and sequencing (see below). We recommend that the term 5-HT_{1C} receptor be no longer used, and henceforth we will refer to the old 5-HT_{1C} as the 5-HT_{2C} receptor. The 5-HT_{2B} receptor subtype is the recently cloned receptor, called SRL (Foguet et al., 1992b) or 5-HT_{2F} (Kursar et al., 1992) receptor by its discoverers. The 5-HT_{2B} appellation would seem more appropriate with regard to the overall classification of 5-HT receptors and will now be used in this review. The cloned 5-HT_{2B} receptor appears to be the receptor that mediates the contractile action of 5-HT in the rat isolated fundus (Kursar et al., 1992). The rat fundus receptor was first classified as a 5-HT_1-like receptor and later as an orphan 5-HT receptor (Bradley et al., 1986a) but now seems better characterised and more appropriately named. Apart from these three well-defined 5-HT_2 receptor subtypes, other subtypes may well occur, such as the 5-HT receptor types found in various endothelial locations (see section V.E).

B. 5-HT_{2A} Receptors

1. Distribution and function. 5-HT_{2A} receptors are widely distributed in peripheral tissues (Bradley et al., 1986a). The effects mediated by these receptors include contractile responses in many vascular smooth muscle preparations (e.g., rabbit aorta, rat caudal artery, dog gastrosplenic vein), contractile response in bronchial, uterine, and urinary smooth muscle, and part of the contractile effect of 5-HT in guinea pig ileum. In addition, platelet aggregation and increased capillary permeability can be included as 5-HT_{2A} receptor-mediated actions. The only central actions classified by Bradley and colleagues as 5-HT_2 receptor mediated were some behavioural effects in rodents (head twitch, wet-dog shake) and neuronal depolarisation (rat facial motoneurones, rat spinal motoneurones, cat preganglionic sympathetic neurones).

Nevertheless, 5-HT_{2A} receptors are enriched in many areas of the cortex (Pazos et al., 1985, 1987b; Hoyer et al., 1986b). In the neocortex, these sites are mainly concentrated in laminae I and IV (rat) and III and V (human). 5-HT_{2A} sites are also found in the claustrum, a region that is connected to the visual cortex, some components of the limbic system, particularly the olfactory nuclei, and parts of the basal ganglia. Attempts to determine the location of the cells expressing 5-HT_{2A} receptors in the neocortex, using lesion experiments, have suggested that these receptors are localised on the processes of intrinsic cells, because deafferentation and many other types of lesions do not result in changes in 5-HT_{2A} receptor densities (Leysen et al., 1983). On the other hand, cortical [^{3}H]ketanserin-binding sites have been reported to be decreased in senile dementia of the Alzheimer type, paralleling the loss of somatostatin immunoreactivity (Cross et al., 1984, 1988). This suggests that 5-HT_{2A} receptors could be located on intrinsic somatostatin-containing neurones in the cortex.

In terms of functions now characterised as being mediated by 5-HT_{2A} receptors, there has been considerable expansion, almost all being related to the CNS and neuroendocrine actions. 5-HT_{2A} receptors mediate neuroexcitation in guinea pig cortical pyramidal neurones (Davies et al., 1987), rat raphé cell bodies (Roberts and Davies, 1989), and rat nucleus accumbens neurones (North and Uchimura, 1989). The discriminative stimuli and learning behaviour properties of 5-HT and hallucinogens such as LSD and DOM seem to be mediated by 5-HT_{2A} receptors, although the lack of effect of ritanserin (a 5-HT_{2A} receptor antagonist with relatively less α_1-adrenoceptor but more dopamine receptor affinity than ketanserin) raises the possibility of involvement of α_1-adrenergic mechanisms (Tricklebank, 1985, 1987). Both 5-HT_1-like and 5-HT_{2A} receptors contribute to the inhibition of glutamate release from rat cerebellum; the 4-iodophenyl congener of DOM (DOI) can selectively identify the 5-HT_{2A} receptor-mediated component (Maura et al., 1988). Some neuroendocrine functions, such as release of β-endorphin, corticosterone, and luteinizing hormone in rats and prolactin release in rhesus monkeys, appear to be mediated by 5-HT_{2A} receptors (Koenig et al., 1987; Lenahan et al., 1987; Heninger et al., 1987). The 5-HT-induced release of adrenaline from the adrenal medulla in dogs also appears to be a 5-HT_{2A} receptor-mediated action (Humphrey and Feniuk, 1987).

2. Agonists and antagonists. The ready availability of a number of antagonists with potent blocking activity at functional 5-HT_{2A} receptors (table 3) has greatly aided the characterisation and mapping of the distribution of functional 5-HT_{2A} receptors in the brain and periphery.

In some instances, selective agonists have proved to be useful for identifying some 5-HT_{2A} receptors, such as the role of DOI in inhibition of glutamate release and the discriminative stimuli and learning properties of DOM.

However, there is still no ideal antagonist with the appropriate degree of selectivity. The most selective agents in terms of 5-HT_{2A} receptor affinities are ketanserin and pirenperone. Spiperone is also reasonably selective, because its 5-HT_{1A} affinity is approximately 80-fold less than its 5-HT_{2A} affinity. However, in functional studies, spiperone is also a potent antagonist at the 5-HT_1-like receptor mediating direct vasorelaxation (see section V.E). Pirenperone, cyproheptadine, and cinanserin are relatively selective, in that their affinities for 5-HT_{2C}-binding sites are 4- to 10-fold lower than for 5-HT_{2A} sites, but 5-HT_{2C} receptor-blocking effects are likely to be in evidence at the concentrations normally used. The other 5-HT_{2A} receptor antagonists have activity at one or more of the various 5-HT_1-binding site subtypes or other functional 5-HT_1-like receptor subtypes (table 3, section II.G). 5-HT_{2A} receptor antagonists also have potent actions at one or more non-5-HT receptors such as α-adrenoceptors, histamine, dopamine, and muscarinic receptors (Leysen et al., 1981; Mylecharane, 1990).

There is relatively little information concerning the 5-HT_2 receptor agonists (α-methyl-5-HT, DOM, DOI, DOB), and more information is needed. However, there are practical difficulties associated with the general use of DOM, DOI, and DOB, because of their hallucinogenic potential and, hence, limited availability.

Leff et al. (1986) evaluated several tryptamine analogues as 5-HT_{2A} receptor agonists in rabbit aorta and rat jugular vein following benextramine treatment to rule out any possible interference via α_1-adrenoceptor activation. N-Benzyl-5-MeOT was slightly more potent than 5-HT, and N,N-dimethyltryptamine was slightly less potent, but both had relatively low efficacies. Such agents may give a lead to the development of better selective 5-HT_2 receptor agonists and antagonists. The potency estimates of the most commonly used agonists and antagonists are summarised in table 3.

3. Radioligand binding. Peroutka and Snyder (1979) in their seminal work showed that 5-HT_2 sites could be labeled with [^{3}H]LSD and [^{3}H]spiperone but not [^{3}H]5-HT; this led to the proposed existence of 5-HT_1 and 5-HT_2 sites. It was clear that [^{3}H]LSD labelled both sites. Leysen et al. (1982) then described [^{3}H]ketanserin as the first selective 5-HT_{2A} radioligand. Other ligands have been described (table 4), but none is really selective, because they can all label 5-HT_{2C} sites as well (except spiperone and ketanserin). Two subtypes of 5-HT_{2A} receptors have been proposed (Peroutka et al., 1988) and labelled by [^{3}H]DOB and [^{3}H]ketanserin, but it appears that the agonist radioligands bind to a subpopulation of 5-HT_{2A} receptors in a high-affinity state (Teitler et al., 1990; Branchek et al., 1990).

4. Receptor structure and transduction. Pritchett et al. (1988) isolated the first cloned cDNA sequence encoding the complete 5-HT_{2A} receptor from a rat brain cDNA library. The similarities between 5-HT_{2A} and 5-HT_{2C} receptors in terms of second messengers and pharmacology guided the cloning strategy adopted by Pritchett et al. (1988); two oligonucleotides directed against two separate amino acid residue sequences in the cloned 5-HT_{2C} receptor gene that had been characterised by Julius et al. (1988) were used to probe the rat brain cDNA library. The predicted 5-HT_{2A} receptor polypeptide contains seven TMRs and the amino acid sequence within the transmembrane regions is 80% identical with that of the 5-HT_{2C} receptor. The cDNA was transiently expressed in a mammalian cell line; binding studies in membrane preparations from these cells confirmed the identity of the expressed 5-HT_{2A} receptors. Functional studies, measuring phosphatidylinositol hydrolysis and elevation of Ca^{2+} levels, in a transfected mammalian cell line were consistent with the pharmacology of a 5-HT_{2A} receptor. Julius (1991) and Hartig et al. (1992) have compared various 5-HT receptor clones; 5-HT_{2A} and 5-HT_{2C} receptors show greater homology with one another than with the other cloned 5-HT receptor genes (5-HT_{1A}, 5-HT_{1B}, 5-$HT_{1D\alpha}$, 5-$HT_{1D\beta}$).

It is well established that 5-HT_{2A} receptors are linked to phosphatidylinositol turnover. This has been demonstrated in rat cortex, aortic smooth muscle, and human platelets (Conn and Sanders-Bush, 1984, 1985; Roth et al., 1984; De Chaffoy et al., 1985; Doyle et al., 1986). The receptors are coupled to phospholipase C, and inositol phospholipid hydrolysis and Ca^{2+} mobilisation are involved in the postreceptor events. It follows that the measurement of phosphatidylinositol turnover (e.g., accumulation of inositol 1-phosphate) can serve as a useful means of monitoring functional effects of 5-HT_{2A} receptor activation in a variety of locations.

C. 5-HT_{2B} Receptors

1. Distribution and function. The rat stomach fundic strip has been known for a long time to be exquisitively sensitive to 5-HT (Vane, 1959). However, this receptor, whose activation leads to fundic smooth muscle contraction, has not been easy to characterise pharmacologically. It was originally classified as "5-HT_1-like," despite the relatively low potency of 5-CT (Bradley et al., 1986a). Although the fundus receptor shared some characteristics with the classical 5-HT_2 receptor, it was clear that it was not a 5-HT_{2A} receptor (Clineschmidt et al., 1985; Cohen and Wittenauer, 1987). Based on the rank order of potency of a variety of agonists, the fundus receptor was shown to bear resemblance to the 5-HT_{2C} receptor (formerly 5-HT_{1C}) (Buchheit et al., 1986); however, more thorough investigations showed that the fundus receptor

was not a 5-HT_{2C} receptor (Cohen, 1989; Kalkman and Fozard, 1991a). Furthermore, it could be demonstrated that 5-HT_{2C} mRNA is not to be found in rat fundus preparations (Baez et al., 1990; Foguet et al., 1992b). Eventually, the situation was clarified by the cloning of the rat and mouse "fundic" receptor (Foguet et al., 1992a,b; Kursar et al., 1992). Kursar et al. (1992) named this receptor 5-HT_{2F} (fundus). For reasons delineated above, we have recommended naming the fundus receptor 5-HT_{2B}, because the classical 5-HT_2 receptor and the 5-HT_{1C} receptors are now termed 5-HT_{2A} and 5-HT_{2C}, respectively (Humphrey et al., 1993).

Little is known about the distribution of the receptor in rat. For instance, Northern blot analysis did not reveal the presence of the 5-HT_{2B} receptor in rat brain (Kursar et al., 1992). On the other hand, Foguet et al. (1992b) by a quantitative polymerase chain reaction procedure were able to detect 5-HT_{2B} mRNA in a variety of tissues, including the fundus, gut, heart, kidney, and lung, and to some extent in brain. Loric et al. (1992) also cloned the mouse homologue of the rat receptor which appears to be expressed in mouse intestine and heart and to a lesser extent in brain and kidney.

Functionally, little is known about 5-HT_{2B} receptors, except in the rat stomach fundic strip where the main effect appears to be contraction. However, it has been known for some time that some 5-HT_2-like receptors mediating relaxation exist (see section V.E), and a recent report suggests that such a receptor with a pharmacological profile similar to that of 5-HT_{2B} is present in the pig pulmonary artery (Glusa and Richter, 1993).

2. Agonists and antagonists. The rat stomach fundic strip has been used by many investigators (Clineschmidt et al., 1985; Cohen and Wittenauer, 1987; Cohen, 1989; Kalkman and Fozard, 1991a). For agonists, the following rank order of potency has been reported: 5-HT = α-methyl-5-HT > 5-MeOT > TFMPP > 5-CT > quipazine > 2-methyl-5-HT > sumatriptan > 8-OH-DPAT.

The relative potencies of antagonists are in the order: 1-NP = ORG GC 94 = rauwolscine = yohimbine > pizotifen > propranolol > mianserin > pirenperone = cinanserin = spiperone. The recently described 5-HT_{2C} receptor antagonist, SB 200646, has even higher affinity for 5-HT_{2B} receptors (Forbes et al., 1993).

3. Radioligand binding. When functionally expressed in COS and other cells, the 5-HT_{2B} receptor displays high affinity for [^{3}H]5-HT and [^{125}I]DOI. Binding data obtained with the recombinant receptor correlated highly significantly with functional data obtained from rat fundic strips (Foguet et al., 1992a; Wainscott et al., 1993). There might be species differences in the pharmacological profile of the 5-HT_{2B} receptor, because the affinity values reported for the cloned mouse 5-HT_{2B} receptor (Loric et al., 1992) do not exactly equate with those reported for the cloned rat 5-HT_{2B} receptor (Foguet et al., 1992a; Kursar et al., 1992; Wainscott et al., 1993). However, in general the 5-HT_{2B} and 5-HT_{2C} receptors display very similar affinity values for the agonists tested; by contrast, the 5-HT_{2B} receptor has low affinity for compounds like spiperone, cinanserin and ketanserin; whereas 5-HT_{2B} receptors show high affinity for ergolines (e.g., methysergide, metergoline, LY 53857) and, when compared with 5-HT_{2A} and 5-HT_{2C} receptors, high affinity for yohimbine, rauwolscine, and RU 24969.

4. Receptor structure and transduction. Foguet et al. (1992b) screened a mouse genomic library and described a partial sequence of a G-protein-coupled receptor that was very similar to both 5-HT_{1C} and 5-HT_2 receptors (62 and 65%) with the same intron-exon boundaries. This receptor was called SRL and has a predicted size of 460 amino acids. By quantitative polymerase chain reaction, Foguet et al. (1992a) were then able to detect its presence in rat fundus mRNA and to clone the corresponding cDNA from a rat fundus cDNA library, the species equivalent to the mouse SRL. A similar approach was taken by Kursar et al. (1992) who cloned the same receptor from a rat fundus cDNA library. Both groups reported a predicted amino acid sequence of 479 amino acids for the rat receptor, whereas Loric et al. (1992) reported that there are 504 amino acids in the mouse receptor. Expression of SRL in *Xenopus* oocytes leads to activation of chloride channels, as described previously with 5-HT_{2C} receptors, an effect that is probably mediated by the activation of phospholipase C (Foguet et al., 1992a). Indeed, it has been shown that the recombinant fundus receptor is able to promote stimulation of phospholipase C activity (Kursar et al., 1992; Wainscott et al., 1993), but this has yet to be shown for the endogenous receptor (Cohen and Wittenauer, 1987; Secrest et al., 1991). Interestingly, Wang and colleagues (1993) found that the fundus 5-HT receptor appears to couple to a pertussis toxin-sensitive Gαz-like protein and in this regard may differ from other 5-HT_2 "receptor subtypes." Further studies with the natively expressed 5-HT_{2B} receptor are clearly desirable to determine whether or not this represents another example of cell-specific receptor coupling or a real difference in the transducer characteristics of members of the 5-HT_2 receptor group.

The human 5-HT_{2B} receptor gene has also been cloned (Schmuck and Lübbert et al., to be published). The human receptor protein is 80% homologous to the rat receptor, and the intron/exon distribution in the gene is conserved in both species. The human receptor also couples to phospholipase C.

D. 5-HT_{2C} Receptors

1. Distribution and function. The presence of high densities of binding sites in the choroid plexus was observed in early autoradiographic studies performed with 5-HT_1 receptor ligands such as [^{3}H]LSD and [^{3}H] 5-HT but not 5-HT_2 receptor ligands except [^{3}H] mesulergine (Meibach et al., 1980; Pazos et al., 1984). Thus,

it was assumed that these receptors belonged to the 5-HT_1 class and were named 5-HT_{1C} (Pazos et al., 1984; now renamed 5-HT_{2C} by us). These sites have been visualised in the choroid plexus of all of the mammalian species investigated thus far. The properties of these receptors are very similar regardless of the species studied. 5-HT_{2C} sites are enriched on the epithelial cells of the choroid plexus (Yagaloff and Hartig, 1985). Serotoninergic nerve terminals are present on the walls of the cerebral ventricles, and it has been suggested that 5-HT_{2C} receptors could regulate the composition and volume of the cerebrospinal fluid (Pazos et al., 1984). 5-HT_{2C} receptors are also present, although at lower densities than in the choroid plexus, in the limbic system and regions associated with motor behaviour (Pazos and Palacios, 1985). Interestingly, 5-HT_{2C} sites appear to be more abundant in the basal ganglia of humans, particularly the globus pallidus and in the substantia nigra (Pazos et al., 1987a). Using in situ hybridisation, Julius et al. (1988) observed high densities of 5-HT_{2C} receptor mRNA in the rat choroid plexus. 5-HT_{2C} transcripts were also found at significant densities in the olfactory nucleus, cingulate cortex, lateral habenula, and subthalamic nucleus (Mengod et al., 1990a).

The lack of truly selective 5-HT_{2C} receptor agonists and antagonists has severely limited our knowledge about the functional role of 5-HT_{2C} receptors (see table 3). With the very close structural and thus pharmacological similarities between 5-HT_{2C} and 5-HT_{2A} receptors, it would not be surprising to discover that some of the functional effects attributed to 5-HT_{2A} receptor activation may indeed be mediated by 5-HT_{2C} receptors. 5-HT_{2C} receptors have been suggested to play a role in a variety of processes such as locomotion, feeding and anorexia nervosa, cerebrospinal fluid production, adrenocorticotrophic hormone release, migraine, obsessive compulsive disorders, and anxiety (Kennett and Curzon; 1988b, Kennett et al., 1989; Brewerton et al., 1988; Fozard and Gray, 1989; Curzon and Kennett, 1990; Lucki 1992). However, these suggestions are based on findings obtained in animal models and/or human volunteers with compounds such as mCPP, TFMPP, and MK 212. Although none of these agonists is truly selective for 5-HT_{2C} receptors, the antagonism of their effects by a variety of antagonists known to interact (although not selectively) with 5-HT_{2C} receptors provides circumstantial support for the possible involvement of 5-HT_{2C} receptors.

Probably the best characterised 5-HT_{2C} receptor-mediated effects are hypolocomotion and hypophagia, induced by drugs such as mCPP, MK 212, and TFMPP (Curzon and Kennett, 1990). Usually, but not generally, these effects can be antagonised with low doses of mianserin, mesulergine, metergoline, methysergide, and ritanserin (Curzon and Kennett, 1990). In general, antagonists such as spiperone, ketanserin, or pipamperone require significantly higher doses to produce antagonism (if any). Other proposed 5-HT_{2C} receptor-mediated effects include penile erection, decreased social interaction, suppression of hypertonic saline consumption, and suppression of periaqueductal grey-induced aversion (for recent reviews, see Kalkman and Fozard, 1991b; Koek et al., 1992). However, because in many cases only a limited number of drugs have been tested and some discrepancies have been observed (e.g., ritanserin, a potent 5-HT_{2C} receptor antagonist, appears not to be generally effective); the possibility remains that some of these behaviours may be mediated by receptors closely related but not identical with the 5-HT_{2C} receptor (Koek et al., 1992; Lucki, 1992).

2. Agonists and antagonists. In general, compounds claimed to be 5-HT_{2A} receptor selective show similar affinity for 5-HT_{2C} receptors (Hoyer, 1988a). This is not surprising, given the very close structural similarity of these two receptors (Hartig, 1989). Thus, α-methyl-5-HT and DOI, reported as selective 5-HT_{2A} receptor agonists, show equal potency at 5-HT_{2C} receptors (Hoyer et al., 1989b). In contrast, the agonists, TFMPP and mCPP, have some limited 5-HT_{2C} receptor selectivity (Schoeffter and Hoyer, 1989b). Similarly, most of the reputed 5-HT_{2A} receptor antagonists, such as ritanserin, ICI 169369, cyproheptadine, LY 53857, mianserin, and mesulergine, are equally potent at 5-HT_{2C} receptors (Hoyer et al., 1989b; Sahin-Erdemli et al., 1991b). Nevertheless, ketanserin, cinanserin, and pirenperone display some 5-HT_{2A} receptor selectivity. SB 200646 has been recently described (Forbes et al., 1993) as an antagonist with selectively for 5-HT_{2C} over 5-HT_{2A} receptors (pK_i 6.9 and 5.2, respectively), but it is more potent at 5-HT_{2B} receptors (pA_2 7.5). The affinity estimates of the most useful agonists and antagonists are summarised in table 3.

3. Radioligand binding. The first evidence for the existence of 5-HT_{2C} sites came from autoradiographic studies (Cortés et al., 1984). It was realised that [^{3}H]LSD, [^{3}H]mesulergine, and [^{3}H]5-HT, but not [^{3}H]ketanserin, labeled a high density of sites in the choroid plexus of a variety of species (Pazos et al., 1984). Classically, 5-HT_{2C} binding is performed in pig choroid plexus with [^{3}H] mesulergine, but a variety of other radioligands can be used (table 4).

4. Receptor structure and transduction. Lübbert and colleagues (1987a,b) identified the receptor gene by expression cloning, and the sequence of the receptor in the rat was first described by Julius et al. (1988). In contrast to 5-HT_1 receptors, but similarly to 5-HT_{2A} and 5-HT_{2B} receptors, the gene for the 5-HT_{2C} receptor (predicted protein product of 460 amino acids) has introns, and it is possible that different gene products can occur due to alternate splicing. The mouse and human homologues have been cloned and show 98% homology in the TMRs (Yu et al., 1991; Saltzmann et al., 1991; Hoffman

and Mezey, 1989). 5-HT_{2C} receptor activation in rat, mouse, and pig choroid plexus leads to the stimulation of phospholipase C activity and accumulation of inositol phosphates (Conn et al., 1986; Conn and Sanders-Bush, 1986; Hoyer, 1988b; Hoyer et al., 1989b). Interestingly, these studies confirmed what was indicated by radioligand-binding studies, i.e., a variety of so-called 5-HT_{2A} ligands acted as potent agonists or antagonists at 5-HT_{2C} receptors (Sahin-Erdemli et al., 1991b). In developing rat hippocampus, 5-HT_{2C} receptors mediate stimulation of phospholipase C activity (Claustre et al., 1990). In oocytes injected with 5-HT_{2C} receptor mRNA, 5-HT activates a Cl^- channel (Lübbert et al., 1987b). In general, cells transfected with 5-HT_{2C} receptors have consistently been reported to show activation of phospholipase C activity in response to 5-HT (Julius et al., 1988).

IV. 5-HT_3 Receptors

A. 5-HT_3 Receptors

1. Distribution and function. 5-HT_3 receptors are found exclusively associated with neurones of both central (Yakel et al., 1988; Waeber et al., 1989b) and peripheral (Fozard, 1984a; Wallis, 1989) origin and in a variety of neuronally derived cell lines such as NIE-115, NCB-20, NG 108–15, and NI8 cells (Peters and Lambert, 1989; Yang, 1990; Peters et al., 1991). In the brain, the highest densities of 5-HT_3 receptors are found in discrete nuclei of the lower brain stem (e.g., dorsal vagal complex and spinal trigeminal nucleus), the area postrema and the nucleus tractus solitarius and the substantia gelatinosa at all levels of the spinal cord (Hamon et al., 1989; Pratt et al., 1990). Lower but significant densities of 5-HT_3-binding sites are also found in the cortex and areas of the limbic region such as the hippocampal formation, amygdala, and medial nucleus of the habenula (Kilpatrick et al., 1987; Waeber et al., 1988b, 1989b; Kilpatrick et al., 1990b; Pratt et al., 1990; Palacios et al., 1991; Laporte et al., 1992). In the periphery, 5-HT_3 receptors are located on pre- and postganglionic autonomic neurones and on neurones of the sensory and enteric nervous systems (Fozard, 1984a; Hoyer et al., 1989a; McQueen and Mir, 1989; Wallis, 1989; Peters et al., 1991; Wallis and Elliott, 1991).

5-HT_3 receptor activation triggers a rapid depolarisation because of a transient inward current response contingent on the opening of cation-selective channels (Peters et al., 1991; Reiser, 1991; Wallis and Elliott, 1991). The response desensitises and resensitises rapidly (Yakel et al., 1991). The channel opened by 5-HT permits the passage of Na^+ and K^+ with the reported permeability ratios of K^+ to Na^+ varying between 0.42 and 1.09 in different cells (Peters et al., 1991). The major consequence of cellular depolarisation is a rapid increase in the cytosolic Ca^{2+} concentration because of an influx of Ca^{2+} from the extracellular environment. Subsequent events triggered by the increase in cytosolic Ca^{2+} include neurotransmitter release from both peripheral (Fozard, 1984a; Wallis, 1989; Saria et al., 1990) and central (Blandina et al., 1989; Galzin and Langer, 1991; Paudice and Raiteri, 1991) neurones and, in NG 108–15 cells, an increase in cGMP because of activation of nitric oxide formation from L-arginine (Tohda and Nomura, 1990; Reiser, 1991; Tohda et al., 1991).

Functional in vitro preparations that contain 5-HT_3 receptors and that can be used in the evaluation of different ligands are guinea pig ileum (Craig et al., 1990), rabbit heart (Fozard, 1984b), and a variety of neuronal tissues such as rat and rabbit vagus nerve and several types of ganglia and cell lines (Wallis, 1989; Peters et al., 1991; Wallis and Elliott, 1991).

In intact animals, activation of 5-HT_3 receptors profoundly influences the principal body systems. Major effects on the cardiovascular system are seen on the heart, which may be inhibited or stimulated by a combination of local and reflex effects (Saxena and Villalón, 1991), and on blood vessels, where reflex activation results in vasodilation (Blauw et al., 1988; Orwin and Fozard, 1986). With respect to respiration, disturbances arise from activation of pulmonary and carotid body chemoreflexes (McQueen and Mir, 1989). At the level of the gastrointestinal tract, 5-HT_3 receptors mediate diverse effects in the control of intestinal tone (Costall and Naylor, 1990) and secretion (Furman and Waton, 1989). With respect to the sensory nervous system, activation of 5-HT_3 receptors induces pain and sensitisation of nociceptive neurones (Richardson et al., 1985; Hamon et al., 1990a; Fozard, 1993) and underlies the nausea and vomiting associated with cancer chemotherapy and radiotherapy (Andrews et al., 1988; Andrews and Bhandari, 1993). 5-HT_3 receptors also mediate the fast initial tonic contraction of the cat urinary bladder (Saxena et al., 1985a). In the CNS, 5-HT_3 receptor antagonists profoundly influence animal behaviour, implicating a role for 5-HT_3 receptors in psychosis, anxiety, cognition, the rewarding and withdrawal effects from drugs of abuse, and eating disorders (Costall et al., 1989; Barnes et al., 1992a).

A useful technique in vivo to quantify 5-HT_3 receptor activation is the Bezold-Jarisch reflex (Fozard, 1984b). In humans, pain in response to 5-HT applied to a blister base (Richardson et al., 1985) or the cutaneous flare response to intradermal injection of 5-HT (Orwin and Fozard, 1986) reflects 5-HT_3 receptor activation and is readily quantified.

2. Agonists and antagonists. With respect to agonists, 2-methyl-5-HT, phenylbiguanide, and *m*-chlorophenylbiguanide are the preferred, although by no means ideal, ligands with which to selectively activate 5-HT_3 receptors. *m*-Chlorophenylbiguanide is appreciably more potent than either phenylbiguanide or 2-methyl-5-HT and unlike the latter has no significant effects at other 5-HT receptor sites (Fozard, 1990; Kilpatrick et al., 1990a;

Tadipatri et al., 1992). However, all of these agents have the potential disadvantage of being partial agonists at the 5-HT_3 receptor (Ireland and Tyers, 1987; Fozard, 1990; Kilpatrick et al., 1990a; Sepulveda et al., 1991). Moreover, phenylbiguanide, and presumably *m*-chlorophenylbiguanide, is essentially inactive at the 5-HT_3 receptor present in guinea pig tissues (see section IV.B). The rank order of potency obtained from several functional 5-HT_3 receptor assays is *m*-chlorophenylbiguanide > 5-HT > 2-methyl-5-HT ≥ phenylbiguanide (Ireland and Tyers, 1987; Fozard, 1990; Hoyer, 1990; Peters et al., 1991; Sepulveda et al., 1991). Data from radioligand-binding studies are in broad agreement with this order of potency (see below).

A final point in the context of 5-HT_3 receptor agonists concerns 5-MeOT. This close analogue of 5-HT is devoid of activity at 5-HT_3 receptors and yet has potency close to that of 5-HT at all other 5-HT receptor subtypes (Craig et al., 1990; Fozard, 1990). Therefore, it offers a clear-cut indication, albeit by a negative criterion, as to whether a receptor that is responsive to 5-HT might be a 5-HT_3 receptor.

With respect to antagonists, there are now many compounds available that show high potency and selectivity for 5-HT_3 receptors (Glennon and Dukat, 1992). MDL 72222 (Fozard, 1984b), tropisetron (Richardson et al., 1985), ondansetron (Butler et al., 1988), and granisetron (Sanger and Nelson, 1989) have been the most thoroughly studied. However, one caveat about their use for definitive receptor characterisation is that, despite nanomolar concentrations of these antagonists being effective, the concentration-response curves to 5-HT_3 receptor agonists are often displaced dextrally in a nonparallel fashion, and there is significant depression of the maximum responses (Fozard, 1984b; Azami et al., 1985; Ireland and Tyers, 1987; Butler et al., 1988; Sanger and Nelson, 1989). However, very low concentrations of the antagonists generally cause parallel shifts in 5-HT concentration-response curves (Fozard, 1984b; Azami et al., 1985), and in 5-HT_3 receptor-binding assays the same antagonists invariably display competitive kinetics (Kilpatrick et al., 1987; Hoyer and Neijt, 1988). Noncompetitive kinetics in functional tests may, therefore, be more a reflection of the tissue and/or experimental conditions (and particularly the fact that agonist responses desensitise readily) than an intrinsic property of the particular antagonist (for further discussion of this point, see Fozard, 1990; Peters et al., 1991). With respect to tropisetron, it should be borne in mind that, unlike MDL 72222, granisetron and ondansetron, this compound exhibits surmountable blocking activity at 5-HT_4 receptors in the micromolar range (Bockaert et al., 1992).

The potency estimates for key selective agonists and antagonists useful for 5-HT_3 receptor characterisation are shown in table 7 (see also table 3).

3. Radioligand binding. The availability of potent and selective antagonists for 5-HT_3 receptors provided the means to develop radioligands for use in binding assays (table 4). Those used most frequently include [^{3}H]tropisetron, [^{3}H]quaternary tropisetron, [^{3}H]granisetron, [^{3}H]GR 65630, [^{3}H]GR 67330, [^{3}H]zacopride, [^{125}I]zacopride, and [^{3}H]LY 278584 (Fozard, 1990; Hoyer, 1990; Laporte et al., 1992). All bind with high (≤nM) affinity to a single class of saturable binding sites, and binding can be inhibited by low concentrations of drugs that show activity at 5-HT_3 receptors in functional tests (Hoyer, 1990; Fozard, 1990). Such radioligands have also been used extensively in autoradiography studies (Laporte et al., 1992).

A representative selection of data obtained with these ligands and the prototype 5-HT_3 receptor agonist and antagonist ligands are shown in table 8. With respect to the antagonists, although there are differences in the absolute values under different experimental conditions, the relative activities are similar and in good general agreement with affinity measures generated in functional tests (table 7). With respect to agonists, whereas 5-HT and 2-methyl-5-HT show broadly similar absolute and relative activities in each binding assay, the arylbiguanides are clearly less active in certain tissues (cat vagus nerve, rabbit ileum) than others (mouse NIE-115 cells, rat vagus nerve, rat brain) (table 8). Such differences form part of the evidence for the existence of 5-HT_3 receptor subtypes discussed below.

4. Receptor structure and transduction. The 5-HT_3 receptor is unique, not just among 5-HT receptors but also among mono- and diamine neurotransmitter receptors, in forming a ligand-gated ion channel (Derkach et al., 1989) analogous to nicotinic acetylcholine, γ-aminobutyric $acid_A$, and glycine receptors (Strange, 1988). Consistent with this, the molecular mass of the 5-HT_3 receptor-channel complex solubilised from NCB-20 cells has been estimated to be 249 kDa (McKernan et al., 1990). Recently, Maricq et al. (1991) isolated a cDNA clone encoding a single subunit of the 5-HT_3 receptor from NCB-20 cells. The predicted protein is 487 amino acids long and has a molecular weight of 55,966. It shows many of the features of the other members of the ligand-gated ion channel family and, when expressed in *Xenopus* oocytes, exhibits pharmacological and electrophysiological properties broadly similar to those of the native receptor.

Several observations refute the involvement of G-proteins and/or second messengers in channel activation following stimulation of 5-HT_3 receptors. First, the time course of the electrophysiological change is extremely rapid; such fast kinetics essentially preclude a role for second messengers or G-proteins. Second, responses to 5-HT can be recorded for many hours from buffer-irrigated membrane patches (Derkach et al., 1989). Third, neither 5-HT_3 receptor-evoked currents nor the binding characteristics of radioligands are affected by

TABLE 7
*Properties of antagonist ligands useful for discriminating 5-HT$_3$ receptors**

	Rabbit			Rat	Guinea pig			Mouse
	Vagus (pA_2)	Heart (pA_2)	Nodose ganglion (pIC_{50})	Vagus (pK_a)	Vagus (pK_B)	Ileum (pK_B)	Colon (pK_B)	NIE-115 (pIC_{50})
MDL 72222	7.9	9.3	9.4	7.9	6.4	6.7	6.7	8.7
Tropisetron	10.2	10.6	10.3	11.0	7.8	8.0	8.0	9.7
Granisetron	9.9	10.7	n.d.	9.8	7.9	8.1	8.1	n.d.
Ondansetron	9.4	10.1	10.1	8.6	7.0	7.3	7.1	9.6

* For data sources see Butler et al., 1990; Fozard, 1990; Peters et al., 1991. n.d., no data.

TABLE 8
*Effects of 5-HT$_3$ receptor ligands in a selection of radioligand binding assays**

Radioligand species/tissue	[^{3}H]Tropisetron (mouse: NIE-115 cells)	[^{3}H]Tropisetron (cat: vagus nerve)	[^{3}H]Granisetron (rat: cortex)	[^{3}H]GR 65630 (rat: vagus nerve)	[^{3}H]GR 67330 (rat: entorhinal cortex)	[^{3}H]Zacopride (human: hippocampus)	[^{3}H]GR 67330 (rabbit: ileum)
Agonists							
5-HT	6.4	6.7	6.8	7.0	6.9	n.d.	5.9
2-methyl-5-HT	5.9	7.0	6.2	n.d.	6.7	5.8	5.7
Phenylbiguanide	6.1	5.0	n.d.	6.5	6.9	5.9	5.0
m-Chlorophenylbiguanide	8.7	n.d.	n.d.	n.d.	8.8	n.d.	6.3
Antagonists							
MDL 72222	7.3	7.5	8.3	7.5	7.4	n.d.	7.3
Tropisetron	8.5	8.9	9.4	8.7	8.5	8.4	8.2
Granisetron	9.2	8.5	9.6	8.6	8.4	8.6	8.0
Ondansetron	8.5	n.d.	9.1	8.9	8.8	8.1	n.d.

* Values are pK_D or pIC_{50}. For data sources, see Fozard, 1990; Hoyer, 1990; Kilpatrick et al., 1990b, 1991. n.d., no data.

exposure to G-protein activators or inhibitors (Derkach et al., 1989; Kilpatrick et al., 1987). Of course, a plethora of second-messenger changes may follow a primary event such as an increase in $[Ca^{2+}]_i$ as a consequence of membrane depolarisation (Reiser, 1991; Edwards et al., 1991; section IV.A.1); such changes clearly do not reflect direct coupling of the 5-HT$_3$ receptor to a particular G-protein or second-messenger system.

B. 5-HT$_3$ Receptor Subtypes

Evidence is accumulating for the existence of 5-HT$_3$ receptor subtypes and the idea that species differences provide the basis of such heterogeneity. The evidence is pharmacological and based on the activities of structurally diverse agonist and antagonist ligands; details of the structure(s) of the putative receptor subtypes from molecular biology studies are not yet available. The evidence can be summarised as follows. (*a*) The blocking potency of selective 5-HT$_3$ receptor antagonists on guinea pig tissues (ileum, colon, vagus nerve, superior cervical ganglion, nodose ganglion) is consistently and substantially (≥1 to 2 log units) less than that on rabbit (heart, vagus nerve, nodose ganglion), rat (vagus nerve, superior cervical ganglion), or mouse (NIE-115 cells) tissues (table 7; Peters et al., 1991; Fozard, 1992; Kilpatrick and Tyers, 1991). Consistent with this, neither [^{3}H]GR 65630 nor [^{3}H]GR 67330 was able to label 5-HT$_3$ receptors in guinea pig brain or heart membranes from rat or rabbit (Kilpatrick et al., 1991). (*b*) Phenylbiguanide (and/or *m*-chlorophenylbiguanide) interact highly selectively as agonists with the 5-HT$_3$ receptors present on rabbit and rat autonomic and afferent neurones (Fozard, 1990) and mouse NIE-115 cells (Sepulveda et al., 1991) and displace tritiated radioligands from membranes prepared from mouse, rat, and human tissues (table 8). However, neither compound shows affinity for the 5-HT$_3$ receptors in a variety of guinea pig tissues (Butler et al., 1990; Newberry et al., 1991). (*c*) (+)-Tubocurarine has low nanomolar affinity for, and is appreciably (≥100-fold) more potent as an antagonist of, 5-HT$_3$ receptors in mouse tissues (superior cervical ganglion, nodose ganglion, NG 108–15 and NIE-115 cells, hippocampal cells in culture, cloned site from NCB-20 cells) than those from rabbit (nodose ganglion) and rat (superior cervical ganglion, nodose ganglion) (Yakel and Jackson, 1988; Newberry et al., 1991; Maricq et al., 1991; Peters et al., 1991). Conversely, cocaine appears to be substantially more potent as an antagonist at the 5-HT$_3$ receptors in rabbit than in mouse tissues (Fozard et al., 1979; Malone et al., 1991). (+)-Tubocurarine has only very weak activity at the 5-HT$_3$ receptors in a variety of guinea pig tissues (Newberry et al., 1991; Malone et al., 1991; Peters et al., 1991). (*d*) A comparison of the affinities of a large number of 5-HT$_3$ receptor ligands to inhibit the binding of [^{3}H]GR 67330 to membranes prepared from rat brain and ileum and rabbit ileum showed the two rat tissues to have similar pharmacology that differed in several important respects from that seen in the rabbit tissue; the exceptions included both agonists (e.g., phenylbiguanide and *m*-chlorophenylbiguanide) and antagonists (e.g., SDZ 206830 and quipazine) (Kilpatrick et al., 1991). (*e*)

Marked differences exist in the 5-HT_3 receptor single-channel conductance values in different tissues. For instance, the values from several cells derived from murine cell lines are substantially lower (0.3 to 4 pS) than those recorded from either guinea pig submucous plexus neurones (9 to 15 pS) or rabbit nodose ganglion (17 pS) (Yakel et al., 1990; Yang, 1990; Peters et al., 1991; Yakel, 1992).

No strong evidence is yet available for the existence of different 5-HT_3 receptors within the same species. However, a recent report showed differences between affinities of ligands for 5-HT_3 recognition sites in membranes from two mouse tissues, cortex and ileum, suggesting the possible existence of 5-HT_3 receptor subtypes within a single species (Bonhaus et al., 1993).

At this stage, the existence of 5-HT_3 receptor subtypes within a single species is predicted. However, their definition remains imprecise, and their formal recognition in any classification scheme must await the advent of more discriminatory ligands and, in particular, details of the structure of the receptor proteins.

V. Other 5-Hydroxytryptamine Receptors

A. 5-HT_4 Receptors

The 5-HT_4 receptor was first described by Bockaert and coworkers in mouse and guinea pig brain (Dumuis et al., 1988), followed by its definition in guinea pig ileum (Craig and Clarke, 1989, 1990), human heart (Kaumann et al., 1989, 1990), and porcine heart (Bom et al., 1988; Kaumann, 1990; Villalón et al., 1990, 1991). An overall account of early findings on the 5-HT_4 receptor was published by Clarke and colleagues (1989b) and reviewed more recently (Turconi et al., 1991; Bockaert et al., 1992; Clarke and Bockaert, 1993; Ford and Clarke, 1993).

1. Distribution and function. Currently, the 5-HT_4 receptor has been identified in a wide variety of tissues and species (table 9).

In the CNS (embryonic colliculi of mouse), the receptor appears to be located on nerve cells where they mediate inhibition of voltage-activated potassium channels via stimulation of a cAMP-dependent protein kinase (Fagni et al., 1992). In rat hippocampal pyramidal cells, 5-HT_4 receptor activation decreases a calcium-evoked potassium conductance (which produces after-hyperpolarisation) and induces a small voltage-dependent, slow depolarisation (Chaput et al., 1990; Andrade and Chaput, 1991a). Such an event would increase neuronal excitability. Indeed, it has been proposed that the electrophysiological findings described above may promote neurotransmitter release and thereby enhance synaptic transmission (Fagni et al., 1992; Bockaert et al., 1992); however, the neurotransmitter or neurotransmitters involved have not been identified. Speculation for a role of acetylcholine may be drawn from studies by Boddeke and Kalkman (1990) who reported that total hippocampal encephalogram energy was increased by 5-HT_4 receptor stimulation, an effect blocked, in part, by scopolamine. The encephalogram , however, is activated indiscriminately by both (*R*)- and (*S*)-zacopride (Boddeke and Kalkman, 1992), whereas these isomers differentially activate the 5-HT_4 receptor in vitro (Eglen et al., 1990; Baxter et al., 1991a).

Recently, it has become possible to label the 5-HT_4 receptor in rat and guinea pig brain utilising the selective, high-affinity ligands, [^{3}H]GR 113808 (Grossman et al., 1993b) and [^{125}I]SB 207710 (Brown et al., 1993). Areas of highest density include several limbic areas, such as olfactory tubercles and nucleus accumbens, corpus striatum, globus pallidus, and substantia nigra. This distribution, along with the presence of the receptor in the hippocampus and colliculus, suggests a possible involvement in affective disorders, psychoses, motor coordination, arousal, and visual perception, in addition to learning and memory. In this regard, it is important to note that the 5-HT_4 receptor has been identified recently in the cerebral cortex of humans (Monferini et al., 1993).

In the alimentary tract, the 5-HT_4 receptor is located on neurones (e.g., the myenteric plexus of guinea pig ileum; Craig and Clarke, 1990), smooth muscle cells (e.g., the tunica muscularis mucosae of rat oesophagus; Bieger and Triggle, 1985; Baxter et al., 1991a), and secretory cells (e.g., mucosa of rat colon; Bunce et al., 1991). Electrophysiological studies suggest that the 5-HT_4 receptor enhances nicotinic (fast) neurotransmission at enteric ganglia (Tonini et al., 1989) via the release of acetylcholine (Kilbinger and Wolf, 1992) from presynaptic nerve endings (Tonini et al., 1989). Additional acetylcholine release may occur from postsynaptic motor neurones innervating smooth muscle (Tonini et al., 1991), because contractile responses to 5-HT_4 receptor stimulation in guinea pig ileum and colon are blocked by atropine (Craig and Clarke, 1990; Eglen et al., 1990; Elswood et al., 1991). The identity of the 5-HT receptor involved in the initiation of slow depolarisations in enteric neurones (similar to those seen in rat hippocampus) is not resolved (for discussion, see Tonini et al., 1991). Evidence exists that the 5-HT_4 receptor functions in the alimentary tract to evoke secretions (Bunce et al., 1991) and the peristaltic reflex (Craig and Clarke, 1991; Buchheit and Buhl, 1991), the latter by modulating neuronal input to circular smooth muscle (Tonini et al., 1992). In this context, the 5-HT_4 receptor has been shown to contract the circular muscle of human colon (Tam et al., 1992), despite earlier negative findings in the small intestine of humans (Baxter et al., 1991b). Facilitation of the peristaltic reflex may explain the prokinetic action of metoclopramide and other gastrokinetic agents that act as agonists at the 5-HT_4 receptor (Craig and Clarke, 1991; Turconi et al., 1991). Recently, the 5-HT_4 receptor has been implicated in vomiting induced by zacopride and copper sulphate, possibly via activation of abdominal vagal afferents (Bhandari and Andrews, 1991). Electro-

TABLE 9
5-HT$_4$ receptor: distribution and functional responses

Species	Tissue	Mechanism	Transduction effect	References
Human	Cortex	↑ cAMP		Monferini et al. (1993)
Guinea pig	Hippocampus	↑ cAMP		Dumuis et al. (1988), Bockaert et al. (1990)
Rat	Hippocampus		↓ K^+ conductance, slow depolarization	Chaput et al. (1990), Andrade and Chaput (1991a)
Mouse	Colliculi neurones	↑ cAMP	↓ K^+ conductance	Dumuis et al. (1988), Fagni et al. (1992)
Rat	CNS		↑ Electroencephalogram energy	Boddeke and Kalkman (1990, 1992)
Rat	Vagus nerve		Depolarization	Rhodes et al. (1992)
Guinea pig	Myenteric neurones		↑ Fast excitatory postsynaptic potentials	Tonini et al. (1989)
Guinea pig	Ileum		Contraction, peristalsis	Craig and Clarke (1990, 1991), Craig et al. (1990), Eglen et al. (1990), Buchheit and Buhl (1991)
Guinea pig	Colon		Contraction	Elswood et al. (1991), Wardle and Sanger (1992)
Rat	Colon		↑ Short circuit current	Bunce et al. (1991)
Rat	Ileum		Relaxation	Tuladhar et al. (1991)
Rat	Oesophagus	↑ cAMP	Relaxation	Baxter et al. (1991a), Reeves et al. (1991), Ford et al. (1992)
Human	Colon		Circular muscle contraction	Tam et al. (1992)
Guinea pig	Atria		↑ Rate	Eglen et al. (1991), Kaumann (1991b)
Piglet	Atria	↑ cAMP	↑ Rate and force	Kaumann (1990), Kaumann et al. (1991a)
Pig	Heart		↑ Rate (in vivo)	Villalón et al. (1990, 1991)
Monkey	Heart		↑ Rate (in vivo)	Wood et al. (1991)
Human	Atrial appendage	↑ cAMP	↑ Force	Kaumann et al. (1990, 1991b), Turconi et al. (1991), Quadid et al. (1992)
Sheep	Pulmonary vein		Relaxation	Cocks and Arnold (1992)
Human*	Urinary bladder		↑ Contraction	Corsi et al. (1991)
Monkey	Urinary bladder		↓ Contraction	Waikar et al. (1992, 1994)
Frog	Adrenal	↑ cAMP	Steroid release	Idres et al. (1991)
Human	Adrenal	↑ cAMP	Steroid release	Lefebvre et al. (1992)

* Putative 5-HT$_4$; awaits full characterisation.

physiological evidence for 5-HT$_4$ receptors on vagal fibres has been advanced (Rhodes et al., 1992).

In the heart, 5-HT$_4$ receptor activation evokes tachycardia in isolated, spontaneously beating right atria of piglet (Kaumann, 1990) and a positive inotropic effect in isolated left atria (Kaumann et al., 1991a). These results complement findings of a tachycardiac response to 5-HT$_4$ receptor activation in vivo in anaesthetised pigs (Villalón et al., 1990, 1991) and monkeys (Wood et al., 1991). Similarly, isolated atrial appendages of humans respond with increased contractile force to 5-HT$_4$ receptor activation (Kaumann et al., 1990, 1991b). Hyperresponsiveness of human right atrial tissue to 5-HT has been reported following chronic β-adrenoceptor blockade (Kaumann, 1991a) and may be of pathophysiological significance. It should be noted, however, that, in contrast to atria, 5-HT$_4$ receptors seem to be absent on both porcine and human ventricular muscle (Schoemaker et al., 1992, 1993).

Evidence for a 5-HT$_4$ receptor in the urinary bladder of monkey (Waikar et al., 1992, 1994) and human (Corsi et al., 1991) is emerging. Activation of the receptor inhibits (monkey) or enhances (human) smooth muscle contraction. Another putative 5-HT$_4$ receptor mediates steroid secretion from adrenocortical cells of frog (Idres et al., 1991) and human (Lefebvre et al., 1992). Physiological activation of the receptor is postulated to result from the local (intraadrenal) release of 5-HT from mast cells (Lefebvre et al., 1992).

2. Agonists and antagonists. Agonists and antagonists at the 5-HT$_4$ receptor fall into three major, structurally distinct, classes: 5-HT and related indoles, substituted (4-amino-5-chloro-2-methoxy) benzamides, and azabicycloalkyl benzimidazolones (table 3).

5-HT is the most potent indole agonist at the 5-HT$_4$ receptor. 5-MeOT and α-methyl-5-HT are also potent agonists relative to 5-HT, whereas 5-CT is less potent,

and 2-methyl-5-HT is weak or inactive (Bockaert et al., 1992; Ford and Clarke, 1993). It should be noted, however, that absolute potency is markedly tissue dependent and 5-HT_4 receptor responsiveness may vary along the course of the intestine (Tuladhar et al., 1992; Wardle and Sanger, 1992). Reports of a low potency for 5-MeOT, relative to 5-HT, may be due to the less polar nature of 5-MeOT and, as a consequence, its greater access to intracellular deamination by monoamine oxidases (Reeves et al., 1989, 1991; Hill et al., 1990; Tuladhar et al., 1991). Although 5-MeOT is not a particularly selective agonist for 5-HT_4 receptors, it is useful because it is virtually devoid of activity at 5-HT_3 receptors which are known to coexist with 5-HT_4 receptors in the gut (Craig et al., 1990).

Substituted benzamides, such as cisapride, (*S*)- and (*R*)-zacopride, renzapride, zacopride, and metoclopramide exhibit agonist activity, with the recently developed benzamide, SC 53116, being the most potent in the rat oesophagus assay (Flynn et al., 1992). The relative potency of cisapride, and to a lesser extent renzapride, appears to exhibit a tissue dependence (for discussion, see Craig and Clarke, 1990; Baxter et al., 1991a; Kaumann et al., 1991b; Turconi et al., 1991). It is not known whether this difference (and others) is indicative of subtypes of the 5-HT_4 receptor, as has been discussed (Kaumann, 1990, 1991b; Kaumann et al., 1991b; Bockaert et al., 1992; Ford and Clarke, 1993; Medhurst and Kaumann, 1993), or whether other pharmacological properties of cisapride, in addition to 5-HT_4 agonism, serve to confound results.

The benzimidazolone agonists, exemplified by BIMU 1 and BIMU 8, are potent 5-HT_4 receptor agonists and are approximately equally effective (BIMU 8) or up to 10-fold less active (BIMU 1) than 5-HT, depending on the test system (Turconi et al., 1991; Bockaert et al., 1992). In several peripheral tissues, however, the benzimidazolones (particularly BIMU 1) and substituted benzamides (cisapride, renzapride, and zacopride) act as partial agonists relative to 5-HT, even in tissues such as rat oesophagus, where the receptor-response coupling efficacy is high. Thus, caution is required when using these agents as tools for 5-HT_4 receptor characterisation. In contrast, in embryonic mouse colliculi neurones, cisapride, renzapride, zacopride, and BIMU 8 exhibit higher intrinsic activity relative to 5-HT (Dumuis et al., 1989, 1991; Turconi et al., 1991). This may simply reflect drug differences in the rate of desensitisation of the 5-HT_4 receptor (see below) when accumulation of cAMP is measured over several minutes. In this regard, it would be interesting to compare initial rates of cAMP formation.

In addition to affinity for the 5-HT_4 receptor, both benzimidazolones and substituted benzamides, at high concentrations, exhibit muscarinic receptor-blocking activity which may confound results where cholinergic responses are integral to the overt expression of 5-HT_4 receptor agonism (e.g., ileum and ascending colon of guinea pig). In addition, both classes of compounds exhibit affinity for a "benzamide-binding site" (Bockaert et al., 1991) which may be distinct from or associated with the 5-HT_4 receptor (Waikar et al., 1993). The functional role of this site, if any, is not known. Similarly, (*R*)-zacopride, but not (*S*)-zacopride or 5-HT, binds to a novel site in the CNS (Kidd et al., 1992), and a functional correlate (reduction in extracellular levels of 5-HT in frontal cortex of rat) has been identified (Barnes et al., 1992b; Cheng et al., 1992). Finally, it is well established that all of the benzimidazolones and the substituted benzamides that interact with the 5-HT_4 receptor also exhibit affinity for 5-HT_3 receptors, although SC 53116 and cisapride are relatively weak in this regard. Indeed, SC 53116 has been reported to be the first selective 5-HT_4 receptor agonist (Flynn et al., 1992), but as yet, its affinity for muscarinic receptors has not been reported. Although most benzimidazolone and benzamide agonists act as antagonists at 5-HT_3 receptors, (*S*)-zacopride has been reported to exhibit agonist activity in some situations (for discussion, see Bhandari and Andrews, 1991).

Exposure of the 5-HT_4 receptor to agonists results in desensitisation (Dumuis et al., 1989; Craig et al., 1990) which, in tissues of the alimentary tract, is readily reversible when the agonist is removed (Craig et al., 1990). Desensitisation has been used as a tool to identify and characterise the receptor in tissues (Craig et al., 1990). In this regard, it should be borne in mind that no selective indole agonist exists for the 5-HT_4 receptor. More selective results may possibly be obtained using the substituted benzamides or benzimidazolones as desensitising agents.

A recent mechanistic study (Ansanay et al., 1992) indicates that desensitisation of the 5-HT_4 receptor resembles, in part, that seen with β-adrenoceptors. The process is agonist dependent but cAMP independent and is likely to involve both phosphorylation by β-adrenoceptor kinase or another specific agonist-dependent receptor kinase, as well as receptor sequestration.

Until recently, tropisetron was the only known antagonist at the 5-HT_4 receptor. However, its lack of selectivity for the 5-HT_4 receptor and its nonspecific actions, at or close to concentrations required for 5-HT_4 receptor antagonism (pA_2 = 6.5), limit usefulness (for further discussion, see Kaumann, 1990, 1991b; Kaumann et al., 1991b; Bockaert et al., 1992). Nevertheless, tropisetron has served as an invaluable initial probe for the 5-HT_4 receptor both in vitro (Clarke et al., 1989b; Turconi et al., 1991; Bockaert et al., 1992) and in vivo (Villalón et al., 1990, 1991; Wood et al., 1991).

Several other antagonists are now available, including SDZ 205557, DAU 6285, and RS-23597-190, but GR 113808 and SB 204070 are the most potent and selective

described to date (Ford and Clarke, 1993). SDZ 205557 exhibits a pA_2 value of 7.4 versus 5-HT at the 5-HT_4 receptor in guinea pig ileum but failed to obey competitive kinetics toward renzapride (Buchheit et al., 1991). Furthermore, lower pA_2 estimates were obtained versus (*RS*)-zacopride (pA_2 = 6.4 to 6.8) and metoclopramide (pA_2 = 5.4 to 5.8; Buchheit et al., 1992). No such differences were seen, however, in the rat oesophagus (Eglen et al., 1992a), where single-point pA_2 estimates ranging from 6.8 to 7.3 were obtained with SDZ 205557 versus 5-HT, (*S*)-zacopride, (*R*)-zacopride, renzapride, BIMU 1, and BIMU 8. Studies show that DAU 6285 acts as a silent, competitive antagonist versus 5-HT, renzapride, and BIMU 8 in tests measuring cAMP formation in cultures of mouse colliculi neurones (Dumuis et al., 1992) and in other functional assays in rat oesophagus, guinea pig ileum and colon, monkey bladder, and human atria (Baxter et al., 1991a; Schiavone et al., 1992; Turconi et al., 1991; Waikar et al., 1992, 1993, 1994). pA_2 values of 6.8 to 7.2 have been determined.

When affinity estimates are made at the 5-HT_3 receptor in guinea pig ileum, both SDZ 205557 and DAU 6285 appear selective for the 5-HT_4 receptor over the 5-HT_3 receptor (Buchheit et al., 1991, 1992; Turconi et al., 1991). However, the guinea pig expresses a 5-HT_3 receptor at which antagonists exhibit low potency (Butler et al., 1990). In other test preparations, neither antagonist displays marked selectivity. Thus, SDZ 205557 has a pK_i of 6.9 at 5-HT_3-binding sites in NG108–15 cells (Eglen et al., 1992a), and DAU 6285 has pK_i values of 6.1 to 6.5 at 5-HT_3-binding sites in rat cortical membranes (Turconi et al., 1991; Dumuis et al., 1992; Schiavone et al., 1992).

RS-23597–190 (Eglen et al., 1992b; Waikar et al., 1994) exhibits a pA_2 value at the 5-HT_4 receptor of 7.8 in oesophagus of rat and 7.3 in the urinary bladder of rhesus monkey. The compound is about 100-fold selective for 5-HT_4 receptors over 5-HT_3 receptors with little or no affinity for muscarinic cholinoceptors (Eglen et al., 1992b).

GR 113808 has recently been described as a very potent and selective 5-HT_4 receptor antagonist and as such should provide a valuable tool for better understanding the 5-HT_4 receptor. It behaves as a competitive antagonist with pA_2 values against 5-HT in guinea pig proximal colon and rat lower oesophagus of 9.2 and 9.5, respectively (Grossman et al., 1993a). It lacks antagonist affinity at other 5-HT receptor types, with the exception that it has weak affinity for the 5-HT_3 receptor (pK_i 6.0), being >1000-fold more selective for the 5-HT_4 receptor. GR 113808 does not have significant activity in blocking a wide range of non-5-HT receptor types even at concentrations 10,000-fold higher than are necessary to block 5-HT_4 receptors (Gale et al., 1994). On the basis of its high affinity, GR 113808 has also been synthesised as tritiated GR 113808 for use as a radioligand for 5-HT_4 receptor-binding studies (Grossman et al., 1993a, 1993b).

3. Radioligand binding. The synthesis of tritiated GR 113808 has now provided a much needed radioligand for the 5-HT_4 receptor (Grossman et al., 1993b). Characterisation of specific [^{3}H]GR 113808 binding in homogenates of guinea pig striatum and hippocampus has revealed a single high-affinity site in both brain areas (pK_D 9.7 and 9.9, respectively). Specific [^{3}H]GR 113808 binding has been shown to be stereoselectively inhibited by agonists and antagonists known to interact with 5-HT_4 receptors. Autoradiographic studies with the radioligand have shown a discrete localisation in both guinea pig and rat brain with high densities of binding sites in areas such as the striatum, globus pallidus, substantia nigra, and olfactory tubercle (Grossman et al., 1993b). More recently, [^{125}I]SB 207710 binding was reported in piglet hippocampus and caudate (Brown et al., 1993). SB 207710 is the iodinated derivative of SB 204070 which has a pA_2 value at the 5-HT_4 receptor of approximately 11 (Wardle et al., 1993).

4. Receptor structure and transduction. No cDNA clone has been described as yet for the 5-HT_4 receptor, but there are data describing the transduction mechanism involved. Thus, stimulation of adenylyl cyclase and elevation of cAMP appears to mediate the cellular responses following 5-HT_4 receptor activation (table 9). Such an event is consistent with observations of increased neurotransmitter release, such as acetylcholine release in intestine (Kilbinger and Wolf, 1992), positive inotropism in cardiac atria (Kaumann et al., 1990), smooth muscle relaxation in the tunica muscularis mucosa of rat oesophagus (Ford et al., 1992), and steroid release from adrenal cortical cells (Idres et al., 1991). 5-HT_4 receptor-induced closure of potassium channels in mouse colliculi neurones is mediated via a cAMP-dependent protein kinase (Fagni et al., 1992), as are increases in cardiac calcium current, via voltage-sensitive calcium channels (Kaumann et al., 1990; Quadid et al., 1992). Finally, direct G-protein-mediated coupling to close potassium channels is also a likely possibility and has been discussed (Ford and Clarke, 1993).

B. 5-ht$_5$ Receptors

The groups of Hen and Sutcliffe have reported the cloning of two putative mouse and rat receptor genes and called the recombinant receptors 5-ht_{5A} and 5-ht_{5B} (Plassat et al., 1992; Matthes et al., 1993; Erlander et al., 1993). There is at present no functional correlate for these receptors, and their transductional characteristics are unknown. As such they cannot be fully characterised and, hence, can only be provisionally classified.

Although both receptors display a pharmacological profile that is reminiscent of that of 5-HT_1 receptors, i.e., they show relatively high affinity for 5-CT, methiothepin, and a variety of ergolines such as LSD, er-

gotamine, and methysergide, there are several reasons to believe that 5-ht$_5$ receptors do not belong to the 5-HT$_1$ class. (*a*) Their structural characteristics are different from those of other 5-HT$_1$ receptors (5-HT$_{1A}$ to 5-ht$_{1F}$) in that the overall amino acid sequence homology is very limited (≤ 37%). (*b*) Both 5-ht$_{5A}$ and 5-ht$_{5B}$ receptor genes have an intron that is localised between the putative transmembrane segments 5 and 6. This is in contrast with 5-HT$_1$ receptor genes which, at least in their coding region, are intronless. (*c*) Although distinct from other 5-HT$_1$, 5-HT$_2$, and 5-HT$_3$ receptors (and presumably 5-HT$_4$, because 5-HT$_4$ receptor ligands show very low affinity at 5-ht$_5$ receptors), the two 5-ht$_5$ receptors appear to represent another receptor type based on their similar operational profile (table 10), gene intron/exon splicing, and overall structural similarity (88%).

TABLE 10

*Dissociation constants (pK$_D$) of various ligands for recombinant 5-ht$_5$, 5-ht$_6$, and 5-ht$_7$ receptors expressed in transfected cells**

Drug	5-ht$_{5A}$	5-ht$_{5B}$	5-ht$_6$	5-ht$_7$
5-HT	8.1†	6.6	7.25†	8.74
5-CT	9.5†	7.4	6.6†	9.48
5-MeOT			7.41	8.75
Sumatriptan	6.8†	5.1		6.24
8-OH-DPAT	7.0†	6.4	<5	7.45
mCPP			5.64	6.45
TFMPP	5.6	5.4	6.32	6.27
NAN 190			<5	6.84
Buspirone				6.16
RU24969	6.5	6.4		6.9
Yohimbine	6.0	6.0		
LSD	9.55	9.47	8.9	8.3
Lisuride			8.09	9.28
Ergotamine	8.4	8.5		7.49
DHE			7.88	6.82
Methiothepin	7.0	7.8	8.74	8.99
Metergoline	<6.0	<6.0	7.52	8.69
Mesulergine	<6.0	<6.0	5.76	8.15
Methysergide	7.2	6.9	6.43	7.9
Clozapine			7.89	7.87
Ritanserin			7.36	7.66
Cyproheptadine			6.87	7.32
Mianserin			7.34	6.95
Ketanserin	4.8	5.8	<5.0	6.69
Spiperone	5.6			7.7
DOI	<6.0	<6.0		4.6
Pindolol	4.7		<5.0	<6.0
Cyanopindolol				<5.0
Haloperidol				6.30
Chlorpromazine				7.15
Zacopride	<6.0	<6.0	<5.0	<6.0
MDL72222			<5.0	<6.0
Tropisetron			<5.0	<4.52
Metoclopramide			<5.0	<4.52
Renzapride			<5.0	<6.0

* The data for 5-ht$_6$ receptors determined using [^{125}I]LSD are from Plassat et al. (1992), Matthes et al. (1993), and Erlander et al. (1993) for mouse or rat receptors. The data for 5-ht$_6$ receptors are from Monsma et al. (1993) for rat receptors, determined using [^{125}I]LSD. The data for 5-ht$_7$ receptors are from Shen et al. (1993), Lovenberg et al. (1993a), Ruat et al. (1993b), and Plassat et al. (1993) for rat or mouse receptors, using [^{3}H]LSD, [^{125}I]LSD, or [^{3}H]5-HT.

† Values for high-affinity binding when competition curves were biphasic and analysed according to a two-site model.

Little is known about the localisation of 5-ht$_5$ receptors. However, in situ hybridisation studies indicate that 5-ht$_{5A}$ receptor mRNA is present in cerebral cortex, hippocampus, habenula, olfactory bulb, and the granular layer of the cerebellum (Plassat et al., 1992). The distribution of 5-ht$_{5B}$ receptor mRNA is much more limited because in situ hybridisation revealed hybridisation signals only in the habenula and CA1 field of the hippocampus. Although the functional significance of 5-ht$_5$ receptors remains to be established, it could be that the [^{3}H]5-CT-binding sites that show low affinity for sumatriptan may represent, at least in part, 5-ht$_5$ receptor binding (Mahle et al., 1991).

C. 5-ht$_6$ Receptors

Monsma et al. (1993) and Ruat et al. (1993a) recently reported the cloning of a new 5-HT receptor gene, which encodes for a receptor protein that positively links to adenylyl cyclase, that they have tentatively called 5-ht$_6$. They cloned, from rat striatal mRNA, a cDNA that encodes for a protein of the G-protein-coupled receptor family, with 436 amino acids and 41 to 36% homology in the putative TMR with that of various 5-HT$_1$ and 5-HT$_2$ receptors. The 5-ht$_6$ receptor gene reported by Monsma and colleagues has one intron located in the region encoding between TMR$_6$ and TMR$_7$ of the receptor protein. However, Ruat and colleagues reported the presence of an intron located in the region encoding between TMR$_5$ and TMR$_6$ of the receptor protein. It may be that the 5-ht$_6$ receptor gene has at least two introns in the coding region.

When expressed in COS cells, 5-ht$_6$ receptors show high affinity for [^{125}I]LSD and [^{3}H]5-HT. The pharmacological profile of the 5-ht$_6$ receptor is unique: the compound with highest affinity is methiothepin; the receptor also has high affinity for a variety of ergolines (e.g., LSD, DHE, lisuride, 2-Br-LSD, pergolide, metergoline). The receptor has only submicromolar affinity for 5-CT. One striking feature of the 5-ht$_6$ receptor is the high affinity for various antipsychotics and antidepressants (e.g., clozapine, amoxapine, amitriptyline, clomipramine, loxepine, mianserin, and ritanserin) which all have K_D values <100 nM. When expressed in COS cells, 5-ht$_6$ receptors do not couple to adenylyl cyclase, but 5-HT stimulates adenylyl cyclase activity when 5-ht$_6$ receptors are expressed in HEK 293 cells. The antidepressants and antipsychotics, where tested, display antagonism.

The distribution of the 5-ht$_6$ receptor protein is at present not known; however, in Northern blots, 5-ht$_6$ receptor mRNA appears to be exclusively present in the brain: striatum ≫ olfactory tubercle > cerebral cortex > hippocampus. There is no evidence for its presence in peripheral tissues.

The 5-ht$_6$ receptor appears to be different from other receptors cloned to date on the basis that (*a*) its sequence homology with other receptors is rather limited, and the presence of two introns in the coding region of the gene, one between transmembrane regions 5 and 6 and the other between transmembrane regions 6 and 7 of the protein, is unique; (*b*) the 5-ht$_6$ receptor (with the 5-ht$_7$ receptor) was the first recombinant 5-HT receptor shown to be positively linked to adenylyl cyclase stimulation; this is also a feature of the 5-HT$_4$ receptor whose gene has not yet been cloned; (*c*) the operational profile of the 5-ht$_6$ receptor is unique (table 10), although closest to that of some 5-HT$_1$-like receptors (Monsma et al., 1993). One could argue that 5-ht$_6$ and 5-HT$_4$ receptors might be members of the same family. Although this cannot be ruled out at present, this seems unlikely, because many of the ligands showing high affinity for 5-ht$_6$ receptors are poor ligands at 5-HT$_4$ receptors (e.g., methiothepin, ergolines, tricyclics) and the 5-HT$_4$ ligands show little or no affinity for 5-ht$_6$ receptors (e.g., tropisetron, DAU 6285).

At present the appellation 5-ht$_6$ can only be tentative, because the whole cell function of the receptors has not been described and 5-HT$_4$ receptors have not yet been cloned. Interestingly, the pharmacological profile of the 5-ht$_6$ receptor is similar to that of a receptor reported by Conner and Mansour (1990) in neuroblastoma NCB 20 cells which is also positively linked to adenylyl cyclase.

D. 5-ht$_7$ Receptors

The putative rat, mouse, and human 5-ht$_7$ receptor genes (Bard et al., 1993; Lovenberg et al., 1993a; Plassat et al., 1993; Ruat et al., 1993b; Meyerhof et al., 1993; Shen et al., 1993) have been cloned by polymerase chain reaction strategies similar to those used previously for the cloning of other 5-HT receptor genes (Libert et al., 1989).

From Northern blot analysis, the rat 5-ht$_7$ receptor appears to be predominantly expressed in rat hypothalamus and thalamus and to a lesser extent in other forebrain regions (Lovenberg et al., 1993a). No positive signals were found in cerebellum, striatum, heart, liver, kidney, adrenals, testes, or ovaries. In contrast, Plassat et al. (1993) reported the mRNA in mouse cerebellum, heart, and intestine. By in situ hybridisation, mRNA was apparently present in thalamic nuclei and the CA3 field of the hippocampus. Positive signals were also found in superficial layers of neo-, piriform, and retrosplenial cortex and in hypothalamus. The presence of mRNA in the suprachiasmatic nucleus led Lovenberg et al. (1993a) to suggest that the 5-ht$_7$ receptor may be involved in the regulation of circadian rhythms, which had been assigned to a 5-HT$_{1A}$-like receptor.

At present, no selective 5-ht$_7$ receptor agonists or antagonists are known. However, 5-HT and other drugs stimulate adenylyl cyclase activity at receptors expressed either in HeLa cells (Lovenberg et al., 1993a) or COS cells (Plassat et al., 1993). The rank order of potency of agonists was 5-CT = 5-HT = 5-MeOT > RU 24969 = bufotenine > 8-OH-DPAT; sumatriptan, DOI, and cisapride were inactive at 10 μM. The rank order of potency of antagonists was methiothepin = methysergide = mesulergine = metergoline = butaclamol = clozapine = ergotamine > spiperone; pindolol and propranolol were inactive at 10 μM (Plassat et al., 1993).

Radioligand binding was performed in transfected cells using [^{125}I]LSD (rat receptor, Lovenberg et al., 1993a) or [^{3}H]5-HT (mouse receptor, Plassat et al., 1993). 5-CT, 5-HT, and methiothepin have nanomolar affinities (table 10). The rank order of affinities was similar to that observed in adenylyl cyclase stimulation experiments.

The rat 5-ht$_7$ receptor gene encodes for 448 amino acids (Ruat et al., 1993b), although Shen et al. (1993) and Lovenberg et al. (1993a) reported 404 and 435, respectively. Such differences are explained by the presence of introns in the coding region and the difficulty in determining precisely the in-frame stop codon that establishes the NH_2 terminus of the protein. Shen et al. (1993) reported the presence of an intron in the region encoding the putative second loop, whereas Ruat et al. (1993b) found a second intron in the carboxy terminus region of the protein, which explains the extra 13 amino acids when compared with the sequence reported by Lovenberg et al. (1993a). Such differences are inherent to the methodology used, and it should be noted that the pharmacological profile and transductional mechanisms reported by all groups are very comparable. Thus, the 5-ht$_7$, like 5-ht$_5$ and 5-ht$_6$, receptors have introns in their gene-coding region which may lead to alternative splicing.

Although, the 5-ht$_7$ receptor has little structural characteristics to share with other 5-HT receptors, it is like the 5-ht$_6$ receptor positively linked to adenylyl cyclase. However, based on the absence of homology, it cannot be envisaged that the 5-ht$_7$ and 5-ht$_6$ receptors could be grouped together. By the same token, given the distinct operational characteristics of the 5-ht$_7$ receptor, one would not be inclined to link it to the 5-HT$_4$ group.

It remains to be seen whether 5-ht$_7$ receptors can actually be detected in situ using either biochemical or more functional experiments. Given the very high affinity of the 5-ht$_7$ receptor for 5-HT, 5-CT, methiothepin, and some ergolines, 5-ht$_7$ receptors (and for that matter 5-ht$_5$ and 5-ht$_6$ receptors) have operational features that are reminiscent of those of some less well-defined 5-HT$_1$-like receptors (table 10). Furthermore, it is clear that, because of the operational features of 5-ht$_7$ receptors, the lack of selectivity of some tryptamines and ergolines has become even more obvious. In addition, given the facts that the 5-ht$_7$ receptors are expressed in the limbic system, especially in the hippocampus and that this receptor is positively coupled to adenylyl cyclase and

given its pharmacological features (5-HT_1-like profile with significant affinity for 8-OH-DPAT), one might speculate that reports, in which 5-HT_{1A}-like receptors were identified in the hippocampus positively coupled to cyclase, reflect 5-ht_7 receptor-mediated effects (Shenker et al., 1987).

E. Putative Orphan 5-Hydroxytryptamine Receptors

A number of functional receptors for 5-HT have been described that do not truly fulfill the criteria for admission into any of the receptor types described above and in this context are "orphans" of the present classification scheme.

1. 5-Hydroxytryptamine receptor mediating smooth muscle relaxation. The vasorelaxant effect of 5-HT is mediated via receptors located at three different morphological sites, namely, sympathetic nerve terminals, vascular endothelium, and smooth muscle cells. In many instances these receptors have been shown, or claimed, to be of the 5-HT_1-like type (Bradley et al., 1986a; Saxena and Villalón, 1990). Of these, the 5-HT_1-like receptor mediating smooth muscle relaxation directly has been best characterised (Feniuk et al., 1983; Trevethick et al., 1984, 1986; Connor et al., 1986; Martin et al., 1987) and seems to be distributed widely throughout the vasculature and in parts of the gut. Thus, this receptor has been demonstrated, among other locations, in the cat saphenous vein (Feniuk et al., 1983; Humphrey and Feniuk, 1989), the pig vena cava (Trevethick et al., 1984, 1986; Sumner et al., 1989; Sumner, 1991), the carotid arterioles (Saxena et al., 1986, 1989), the rabbit jugular vein (Martin et al., 1987), the sheep tracheal arterioles (Webber et al., 1990), and the guinea pig ileum (Feniuk et al., 1983). In addition, this receptor may also mediate the 5-HT-induced tachycardia in the cat (Saxena et al., 1985b; Connor et al., 1986) and hypotension in both the cat (Connor et al., 1986) and rat (Kalkman et al., 1983; Saxena and Lawang, 1985).

At present, there are no selective agonists or antagonists for this 5-HT receptor, but the 5-HT_1-like receptor ligands, 5-CT and methiothepin, act as very potent agonist and antagonist, respectively (Feniuk et al., 1983; Trevethick et al., 1984, 1986; Connor et al., 1986). However, in contrast to the 5-HT_1-like receptor mediating vascular contraction (see section II.G), the 5-HT receptor mediating smooth muscle relaxation is insensitive to agonists such as sumatriptan or 8-OH-DPAT and is positively linked to adenylyl cyclase. Thus, 5-HT and 5-CT, but not sumatriptan, relax porcine vena cava and elevate cAMP, whereas methiothepin, methysergide, and spiperone, but not cyanopindolol, ketanserin, or ondansetron, block these responses (Trevethick et al., 1984; Sumner et al., 1989). In view of the *positive* linkage to adenylyl cyclase, we recommend that this 5-HT receptor should no longer be referred as 5-HT_1-like or classified within the 5-HT_1 group of receptors which are all *negatively* coupled to adenylyl cyclase (see section II). It remains to be established whether or not this receptor corresponds to one of the more recently identified recombinant receptors, in particular the 5-ht_7 receptor with which it appears to share very similar operational and transductional characteristics.

2. 5-Hydroxytryptamine receptor on vascular endothelium. The ability of 5-HT to elicit vascular relaxation indirectly, by stimulating the release of an endothelium-derived relaxing factor, has been demonstrated in isolated arteries and veins from a variety of species. First recognised by Cocks and Angus (1983) in ring segments of dog and pig coronary artery (see also Houston and Vanhoutte, 1988; Molderings et al., 1989a; Schoeffter and Hoyer, 1990), this property has now been described in the jugular vein of chick (Imaizumi et al., 1984), rabbit (Leff et al., 1987; Martin et al., 1987), rat (Bodelsson et al., 1993), and guinea pig (Gupta, 1992), as well as pig vena cava (Sumner and Humphrey, 1988; Sumner, 1991) and pig pulmonary artery (Glusa, 1992). In all of these studies, relaxations were obtained in tonically contracted vessel segments consistent with a receptor-mediated release of endothelium-derived relaxing factor. However, in only a few of the tissues (e.g., rabbit jugular vein, pig vena cava, and pig pulmonary artery) were relaxations shown to be inhibited by analogues of L-arginine, suggesting that the liberated mediator was nitric oxide.

Unfortunately, an attempt was not made in any of the above studies to classify the endothelial 5-HT receptor in terms of the presently accepted criteria. Nevertheless, there is evidence to suggest that two distinct 5-HT receptor types are involved. Whereas in pig coronary artery and guinea pig jugular vein the receptor profile fulfills the criteria for a 5-HT_1 receptor classification and shares many similarities with the 5-HT_{1D} receptor (see section II), this is patently not the case for the receptor type described in rabbit jugular vein, pig vena cava, and pig pulmonary artery. In these tissues 5-HT is an exceptionally potent agonist, its estimated affinity in rabbit jugular vein ($pK_A = 8.4$) being higher than at any other functional 5-HT receptor yet described (Leff et al., 1987). Moreover, responses are unaffected by archetypal 5-HT_{2A} receptor antagonists (ketanserin and spiperone) and selective 5-HT_3 receptor antagonists (MDL 72222 or tropisetron) but are inhibited by nanomolar concentrations of methysergide, methiothepin, and cyproheptadine (with this respective order of potency). Although these results with antagonists are not inconsistent with interactions at a 5-HT_1-like receptor, the actions of agonists rule out this possibility. In all three tissues the rank order of agonist potencies is essentially the same (rabbit jugular vein pEC_{50} values): 5-HT (8.5) = (±)α-methyl-5-HT (8.4) > 5-MeOT (8.1) > 5-CT (7.9) > tryptamine (7.0) > RU 24969 (6.6) ≫ 8-OH-DPAT (<5.0) ≃ sumatriptan (<4.5) (Leff et al., 1987; Martin, unpublished). Most important, the potency of 5-HT is

matched by α-methyl-5-HT at this receptor, whereas 5-CT is considerably less potent than 5-HT. This contrasts with the agonist potency order for classification in the 5-HT_1-like class which is 5-CT > 5-HT ≫ α-methyl-5-HT (Bradley et al., 1986a).

One exception to the potency order of the above agonists on endothelial orphan receptors deserves mention. In rabbit jugular vein and pig pulmonary artery, 5-CT is 7- and 20-fold less potent than 5-HT, respectively, but in pig vena cava it is devoid of activity. This discrepancy might be accounted for, in part, by the orphan receptor directly mediating vasorelaxation which is present in both pig vena cava and rabbit jugular vein (Sumner et al., 1989; Martin et al., 1987); the potent effects of 5-CT at this receptor were effectively eliminated with mesulergine in studies in pig vena cava but not in rabbit jugular vein. Consequently, the activity of 5-CT in the latter case may have been overestimated. However, there is no evidence for endothelium-independent relaxations to 5-HT in pig pulmonary artery (Glusa, 1992); hence, the reason for the difference in this tissue remains obscure. In all other respects the pharmacological identity among the receptors in these three tissues appears excellent, implying involvement of the same endothelial 5-HT receptor. Based on the high potency of 5-HT in chick jugular vein and the susceptibility of responses to cyproheptadine, this tissue may also possess this receptor type (Imaizumi et al., 1984).

Although clearly an orphan of the present classification scheme, the endothelial 5-HT receptor nevertheless shares pharmacological features with the 5-HT_2 receptor class. Not only is it sensitive to many of the recognised 5-HT_2 receptor antagonists, in the rabbit jugular vein a number of agonists considered selective for 5-HT_2 receptors are also effective. Hence, in addition to (±)α-methyl-5-HT, DOI (pEC_{50}=7.7), and the arylpiperazines, mCPP (pEC_{50}=6.8) and TFMPP (pEC_{50}=6.9) are potent agonists (Martin et al., 1993). Nevertheless, antagonist and tryptamine agonist affinities distinguish between endothelial and 5-HT_{2A} receptors (Leff et al., 1987), and it remains to be established whether or not the receptor is a 5-HT_{2B} or 5-HT_{2C} subtype (Martin et al., 1993; Glusa and Richter, 1993). Other 5-HT_2 receptor ligands demonstrating affinity at the endothelial receptor include (pA_2) metergoline (7.2), cinanserin (6.5), quipazine (7.2), 1-naphthylpiperazine (7.9), and N-benzyl-5-methoxytryptamine (7.3). Methysergide, methiothepin, cyproheptadine, and BW 501C67 are potent nonsurmountable antagonists. Those reported as inactive include ketanserin, spiperone, mesulergine. and trazodone (Leff et al., 1987; Martin et al., 1987; Sumner, 1991; Martin, unpublished observations).

3. 5-Hydroxytryptamine receptor mediating depolarisation of rat motoneurones. In a variety of central and peripheral neuronal systems, 5-HT_1 and 5-HT_1-like receptors appear to elicit predominantly neuronal inhibition, whereas 5-HT_2, 5-HT_3, and 5-HT_4 receptors tend to be associated with excitatory responses to 5-HT (Humphrey and Feniuk, 1987; Andrade and Chaput, 1991b; Bockaert et al., 1992). However, studies using rat spinal and facial motoneurone systems suggest that an orphan receptor may be at least partly responsible for 5-HT-evoked depolarisations of these neurones (Connell and Wallis, 1989; Larkman and Kelly, 1991; Wallis et al., 1991). In both cases, involvement of 5-HT_3 receptors can be excluded by the inactivity of MDL 72222 and tropisetron as well as the inability of 2-methyl-5-HT and quipazine to mimic 5-HT effects. The high concentration of tropisetron (10 μM) used in the facial motoneurone study (Larkman and Kelly, 1991) also makes unlikely any role for 5-HT_4 receptors. Whether or not 5-HT_{2A} receptors participate is less clear. In spinal motoneurones, 5-HT-induced depolarisations recorded extracellularly are surmountably antagonised by (pA_2) cyproheptadine (8.9), metergoline (7.2), mesulergine (8.8), and spiperone (8.2); whereas methysergide (10 nM) is a potent nonsurmountable antagonist. Methiothepin, on the other hand, is inactive (Connell and Wallis, 1988, 1989). The effectiveness of other, possibly more slowly dissociating antagonists such as ketanserin and ritanserin appears to vary according to the experimental conditions and recording technique used. When extracellular recordings are made, ketanserin produces equivocal antagonism, whereas ICI 169369 and ritanserin appear ineffective. However, a more recent study using intracellular recording methods and longer antagonist incubation times showed that ketanserin, ritanserin, and LY 53857 are effective antagonists of 5-HT-induced depolarisations (Elliot and Wallis, 1992). A broadly similar picture is obtained in facial motoneurones with the intriguing exception that in this tissue spiperone is inactive (Larkman and Kelly, 1991). Conceivably, these results reflect the coexistence of a small, variable population of 5-HT_{2A} receptors, a possibility reinforced in the facial motoneurone by the demonstration of a high density of mRNA encoding the 5-HT_{2A} receptor in the cell bodies and proximal dendrites of these neurones (Mengod et al., 1990b).

The inability of methiothepin to block 5-HT-evoked depolarisations coupled with the inactivity of some subtype selective agonists (8-OH-DPAT, RU 24969, mCPP, TFMPP) indicates that a 5-HT_1-like receptor does not contribute to the response (Connell and Wallis, 1989; Elliot and Wallis, 1992). Although this is further supported by the low potency of 5-CT relative to 5-HT in the spinal motoneurone, the two agonists appear equally effective in the facial motoneurone. However, this discrepancy may result from inappropriate experimental conditions in the latter tissue, because Connell and Wallis (1988) have demonstrated the presence of a citalopram-sensitive saturable uptake of 5-HT in spinal motoneurones. When uptake is eliminated in this tissue,

indolamine agonist potencies follow the rank order (equally effective molar ratios): 5-HT (1.0) ≥ (+)α-methyl-5-HT (2.7) > 5-CT (16.9).

Although definitive studies remain to be performed, the available evidence suggests that 5-HT-induced depolarisation of rat spinal and facial motoneurones is mediated by the same orphan receptor type. However, although the low potency of 5-CT relative to 5-HT and the activity of some 5-HT_2 receptor antagonists are reminiscent of the receptor types in rat stomach fundus and on vascular endothelium, resistance of the motoneurone receptor to block by methiothepin and the inactivity of mCPP and TFMPP strongly imply that the orphan receptors involved in these responses are different.

4. 5-Hydroxytryptamine receptor mediating inhibition of [^{3}H]noradrenaline release in pig coronary artery. Presynaptic inhibitory 5-HT receptors have been described on a variety of peripheral neurones and, although heterogeneous in nature, generally conform to a 5-HT_1 or a 5-HT_1-like receptor classification (Clarke et al., 1989a). The inhibitory 5-HT heteroreceptor on sympathetic terminals in pig coronary artery appears to be an exception (Molderings et al., 1989b). 5-HT potently inhibits the electrically evoked release of [^{3}H]noradrenaline in this tissue, but the effect is not blocked by methiothepin, ketanserin, or tropisetron at concentrations expected to selectively exclude actions at 5-HT_1, 5-HT_2, and 5-HT_3 receptors. Mesulergine, (±)propranolol, and yohimbine are likewise ineffective as antagonists. On the other hand, the effects of 5-HT are mimicked by bufotenine, 5-aminotryptamine, RU 24969, and tryptamine (with this respective rank order of potency), but 5-CT, (±)α-methyl-5-HT, 5-MeOT, and 8-OH-DPAT are all devoid of activity. The inactivity of 5-MeOT is particularly striking because this contrasts with its potent agonist properties at receptors in the 5-HT_1 and 5-HT_2 classes and, additionally, suggests that the receptor does not belong to the 5-HT_4 class (Bockaert et al., 1992). In summary, the pharmacological profile obtained for this inhibitory 5-HT receptor appears to be unique and incompatible with any of the currently recognised 5-HT receptor subtypes, including the orphan receptor types described above.

5. 5-HT_{1P} receptor. The existence of an atypical 5-HT receptor on enteric neurones was first suggested by Gershon and colleagues (1990) based on the results of electrophysiological and radioligand-binding sites. Using [^{3}H]5-HT, Branchek et al. (1984) demonstrated high affinity (K_D approximately 3 nM), saturable binding to enteric membranes, and autoradiography established that binding was localised to neuronal elements of the gut. Subsequent studies provided evidence that this high-affinity binding of [^{3}H]5-HT reflected binding to a receptor evoking slow depolarisation of myenteric type II/AH neurones by decreasing Ca^{2+}-activated K^+ conductance (Takaki et al., 1985; Gershon et al., 1991). The term 5-$HT_{1P(eripheral)}$ was coined to distinguish this receptor from the high-affinity 5-HT_1 receptors in the CNS and from a second, lower affinity receptor type (5-HT_{2P}) eliciting fast depolarisation of the same myenteric II/AH neurones. This latter receptor is now recognised to be a 5-HT_3 receptor.

5-HT_{1P} receptors mediating slow depolarisation of myenteric neurones are selectively blocked by the tryptophan dipeptides N-hexanoyl- and N-acetyl-5-HTP-DP, whereas 5- and 6-OHIP mimic the actions of 5-HT (Takaki et al., 1985; Branchek et al., 1988). Postjunctional 5-HT_{1P} receptors have been found using the above-cited ligands as probes on submucous as well as myenteric neurones in the small and large bowel (Surprenant and Crist, 1988; Frieling et al., 1991). Inhibitory prejunctional 5-HT_{1P} receptors also appear to inhibit the release of acetylcholine at ganglionic nicotinic synapses (Takaki et al., 1985). Importantly, 5-HTP-DP blocks slow excitatory postsynaptic potentials in these tissues, implying a physiolocal role for the receptor (Takaki et al., 1985).

Data from electrophysiological studies of the 5-HT_{1P} receptor presently provide only a limited basis for comparison with other functional 5-HT receptors, in part because microiontophoretic application of drugs precludes determination of agonist and antagonist relative potencies. Nevertheless, a discrete pharmacological profile is beginning to emerge. Hence, in addition to the hydroxylated indalpines, 2-methyl-5-HT, mCPP, and (*S*)-zacopride also elicit slow depolarisation of type II/AH neurones, and in each case the response is blocked by either 5-HTP-DP or renzapride at a concentration approximately 10-fold lower than is required to block the 5-HT_3 receptor (Surprenant and Crist, 1988; Mawe et al., 1986, 1989; Frieling et al., 1991; Wade et al., 1991). Methysergide (10 μM) also suppresses 5-HT depolarisations (Frieling et al., 1991). On the other hand, ketanserin, tropisetron, DOI, and 5-MeOT are devoid of either agonist or antagonist activity. On a cautionary note, renzapride is reported to behave as an agonist at the inhibitory prejunctional 5-HT_{1P} receptor (Mawe et al., 1989), conceivably because of a higher density and/or greater coupling efficiency of the receptors on these neurones.

In addition to these functional studies, the pharmacology and distribution of 5-HT_{1P} receptors have been explored using [^{3}H]5-HT, [^{3}H]5-OHIP, and polyclonal anti-idiotypic antibodies to label the receptor on enteric membranes (Gershon et al., 1990, 1991). Good agreement between the results obtained from functional and radioligand displacement experiments provides confidence that binding is specific for 5-HT_{1P} receptors. Moreover [^{3}H]5-HT binding is sensitive to GTPγS, consistent with the labelling of a G-protein-coupled receptor (Gershon et al., 1991; Kirchgessner et al., 1992). In accordance with the functional experiments, these studies show that 5-HT_{1P} receptors are distributed throughout the gut on

submucous as well as myenteric ganglia and on a subepithelial plexus of neurones. Moreover, selective labelling of sites in the pancreas, cardiac tissue, and skin implies that the receptor occurs outside the enteric nervous system (Branchek et al., 1988; Kirchgessner et al., 1992). If we accept that this binding is specific for the 5-HT_{1P} receptor, affinity estimates determined from displacement studies emphasise the conclusion from functional experiments that the receptor has a unique pharmacological profile. Hence, the affinities of known agonists decrease in the order (pK_i): 5-HT (8.7) = 5-OHIP (8.7) > 6-OHIP (8.0) > bufotenine (7.6) ≥ 2-methyl-5-HT (7.5). α-Methyl-5-HT (10 μM) also displaces [^{3}H]5-HT, implying a modest affinity at the receptor, but tryptamine, 5-MeOT, 5-CT, and 5-aminotryptamine are all inactive ($pK_i < 6.0$), consistent with results obtained in functional assays (Branchek et al., 1984, 1988; Kirchgessner et al., 1992). Furthermore, ligands traditionally used to identify 5-HT_1 (8-OH-DPAT, methiothepin, spiperone, and methysergide), 5-HT_2 (ketanserin), 5-HT_3 (tropisetron, MDL 72222, quipazine), or 5-HT_4 (tropisetron, 5-MeOT) receptors also fail to affect [^{3}H]5-HT binding (Kirchgessner et al., 1992). An anomaly worthy of mention at this point is the failure of zacopride and renzapride to displace [^{3}H]5-HT, in spite of their ability to interact with 5-HT_{1P} receptors in functional systems (Branchek et al., 1988). Conversely, 5-HTP-DP only poorly inhibits the binding of [^{3}H]zacopride to enteric membranes, whereas renzapride is highly effective (Wade et al., 1991). The implication is that substituted benzamides do not interact syntopically with 5-HT-related ligands at the 5-HT_{1P} receptor but may act allosterically or on postreceptor events via a specific benzamide recognition site. Notwithstanding this complexity, the available functional and radioligand-binding studies confirm the orphan status of the 5-HT_{1P} receptor and emphasise the need to establish a rigorous basis for its positive identification.

On a final note, an elegant study using rat pinealocytes in culture indicates that 5-HT_{1P} receptors may be functionally represented in the CNS (Sugden, 1990). Addition of 5-HT to these cells amplifies (by 3- to 4-fold) isoprenaline-induced stimulation of N-acetyltransferase, the enzyme responsible for the formation of melatonin from 5-HT. This amplifying property of 5-HT is mimicked by 5-OHIP, 6-OHIP, bufotenine, 2-methyl-5-HT, α-methyl-5-HT, and 5-CT, although relative potencies were not determined. In contrast, DOI, 8-OH-DPAT, indalpine, 5-MeOT, and tryptamine are inactive. Moreover, the effect is not antagonised by ketanserin or selective antagonists at 5-HT_3 receptors (tropisetron, ondansetron) but is weakly inhibited by 10 μM methysergide. Although 5-HTP-DP was not tested as an antagonist in this study, the profile described is otherwise that expected for the 5-HT_{1P} receptor.

VI. Summary

It is evident that in the last decade or so, a vast amount of new information has become available concerning the various 5-HT receptor types and their characteristics. This derives from two main research approaches, operational pharmacology, using selective ligands (both agonists and antagonists), and, more recently, molecular biology. Although the scientific community continues to deliberate about the hierarchy of criteria for neurotransmitter receptor characterisation, there seems good agreement between the two approaches regarding 5-HT receptor classification. In addition, the information regarding transduction mechanisms and second messengers is also entirely consistent. Thus, on the basis of these essential criteria for receptor characterisation and classification, there are at least three main groups or classes of 5-HT receptor: 5-HT_1, 5-HT_2, and 5-HT_3. Each group is not only operationally but also structurally distinct, with each receptor group having its own distinct transducing system. The more recently identified 5-HT_4 receptor almost undoubtedly represents a fourth 5-HT receptor class on the basis of operational and transductional data, but this will only be definitively shown when the cDNA for the receptor has been cloned and the amino acid sequence of the protein is known.

Although those 5-HT receptors that have been fully characterised and classified to date (and, hence, named with confidence) would seem to mediate the majority of the actions of 5-HT throughout the mammalian body, not all receptors for 5-HT are fully encompassed within our scheme of classification. These apparent anomalies must be recognised and need further study. They may or may not represent new groups of 5-HT receptor or subtypes of already known groups of 5-HT receptor.

Even though the cDNAs for the 5-ht_{1E}, 5-ht_{1F}, 5-ht_5, 5-ht_6, and 5-ht_7 receptors have been cloned and their amino acid sequence defined, more data are necessary concerning their operational and transductional characteristics before one can be confident of the suitability of their appellations. Therefore, it is important to rationalise in concert all of the available data from studies involving both operational approaches of the classical pharmacological type and those from molecular and cellular biology. It remains to be determined whether 5-HT, as a hormone and neurotransmitter which occurred early in the evolutionary process, has a greater number of receptor types through which it mediates its effects than do other chemical messenger molecules. In this respect, it would be interesting to address the nature of invertebrate 5-HT receptors which are obviously different from mammalian 5-HT receptors and have not been considered in this review, except with regard to the receptor similarity data illustrated in figure 1 (Greenberg, 1960; Gerschenfeld and Paupardin-Tritsch, 1974; Cadogan and Humphrey, 1991).

Notwithstanding such considerations, the present

classification of 5-HT receptors greatly aids understanding of the pharmacology of 5-HT and its many related drugs. It reflects the consolidation and extension of our earlier classification, which as we had hoped has provided a suitable framework for such an endeavour. Nevertheless, it is important that we continue to rigorously examine the basis for the classification and attempt to understand any anomalies, with a view to gaining greater insight into the significance of the remarkable phenomenon of receptor subtype evolution and its relevance to modern therapeutics.

VII. Glossary of Drug Names

1-NP	1-(1-Naphthyl)piperazine
5-CT	5-Carboxamidotryptamine
5-HT	5-Hydroxytryptamine (serotonin)
5-HTP-DP	5-Hydroxytryptophyl-5-hydroxytryptophan amide
5-MeOT	5-Methoxytryptamine
5-OHIP	5-Hydroxyindalpine
6-OHIP	6-Hydroxyindalpine
8-OH-DPAT	8-Hydroxy-2-(di-*n*-propylamino)tetralin
AH 25086	3-(2-aminoethyl)-N-methyl-1H-indole-5-acetamide
BIMU 1	Endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-ethyl-2-oxo-1H-benzimidazole-1-carboxamide
BIMU 8	Endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-(1-methyl)ethyl-2-oxo-1H-benzimidazole-1-carboxamide
BMY 7378	8-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspiro[4.5]-decane-7,9-dione
BRL 20627	(2α, 6β, 9aα)-(±)-4-Amino-5-chloro-2-methoxy-N-(octahydro-6-methyl-2H-quinolizin-2-yl)benzamide
BW501C67	2-Anilino-N-(2-(3-chlorophenoxy)propyl acetamidine
CGS 12066	7-Trifluoromethyl-4-(4-methyl-1-piperazinyl)-pyrrolo[1,2-*a*]quinoxaline
CP 93,129	3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo[3,2-*b*]pyrid-5-one
CP 96,501	3-(1,2,5,6-Tetrahydropyrid-4-yl)5-n-propoxyindole
DAU 6285	Endo-6-methoxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl-2,3-dihydro-2-oxo-1H-benzimidazole-1-carboxylate
DHE	Dihydroergotamine
DOB	1-(2,5-Dimethoxy-4-bromophenyl)-2-aminopropane
DOI	1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane
DOM	1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane
DP-5-CT	Dipropyl-5-carboxamidotryptamine
GR 65630	3-(5-Methyl-1H-imidazol-4-yl)-1-(1-methyl-1H-indol-3-yl)-1-propranone
GR 67330	(±)-1,2,3,9-Tetrahydro-9-methyl-3-[(5-methyl-1H-imidazol-4-yl)methyl]-4H-carbazol-4-one
GR 113808	[1-[2-(Methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl 1-methyl-1H-indole-3-carboxylate
GR 127935	N-[4-Methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1-biphenyl]-4-carboxamide
GTI	5-O-Carboxamidomethylglycyl[^{125}I] tyrosinamide-tryptamine
ICI 169369	2-(2-Dimethylaminoethylthio)-3-phenylquinoline
L 694247	2-[5-[3-(4-Methylsulphonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1H-indole-3-yl]ethylamine
LSD	(+)-Lysergic acid diethylamide
LY 165163	1-(2-(4-aminophenyl)ethyl)-4-(3-trifluoromethylphenyl)piperazine (PAPP)
LY 278584	1-Methyl-N-(8-methyl-8-azabicyclo-[3.2.1]oct-3-yl)-1H-indazole-3-carboxamide
LY 53857	4-Isopropyl-7-methyl-9-(2-hydroxy-1-methylpropoxycarbonyl)-4,6,6A,7,8,9,10,10A-octahydroindolo[4,3-FG]quinolone
mCPP	1-(3-Chlorophenyl)piperazine
MDL 72222	1αH, 3α, 5αH-Tropan-3-yl-3,5-dichlorobenzoate
MDL 72832	8-(4-[1,4-Benzodioxan-2-ylmethylamino]butyl)-8-azaspiro[4,5]decane-7,9-dione
MDL 73005	8-(2-[2,3-Dihydro-1,4,benzodioxin-2-ylmethylamino]ethyl)-8-azaspiro[4,5]decane-7,9-dione
MK 212	6-Chloro-2-(1-piperazinyl)pyrazine
NAN 190	1-(2-Methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine
ORG GC 94	1,3,4,14b-Tetrahydro-2,7-dimethyl-2H-dibenzo[b,f]pyrazino[1,2-d][1,4]oxazepine
PAPP	1-(2-[4-Aminophenyl]ethyl)-4-(3-trifluoromethylphenyl)piperazine (LY 165163)
RS 23597-190	3-(Piperidin-1-yl)propyl 2-methoxy-4-amino-5-chlorobenzoate

RU 24969	5-Methoxy-3(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole
SB 200646	N-(1-Methyl-5-indolyl)-N-(3-pyridyl) urea
SB 204070	(1-Butyl-4-piperidinylmethyl)-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate
SB 207710	(1-Butyl-4-piperidinylmethyl)-8-amino-7-iodo-1,4-benzodioxan-5-carboxylate
SC 53116	Exo-(1S,8S)-2-methoxy-4-amino-5-chloro-N-[(hexhydro-1H-pyrrolizin-1-yl)methyl]benzamide
SCH 23390	*R*-(+)-7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro(1H)-3-benzazepine
SCH 23982	*R*-(+)-7-Hydroxy-8-[^{125}I]-3-methyl-1-phenyl-2,3,4,5-tetrahydro(1H)-3-benzazepine
SDZ 205557	2-Methoxy-4-amino-5-chlorobenzoic acid 2-(diethylamino)ethyl ester
SDZ 206830	(3α-Homotropanyl)-1-methyl-5-fluoro-indole-3-carboxylic acid ester
SDZ 21009	4(3-Terbutylamino-2-hydroxypropoxy)indol-2-carbonic acid-isopropylester
SDZ 216525	Methyl-4(4-[4-(1,1,3-trioxo-2H-1,2-benziosothiazol-2-yl)butyl]-1-piperazinyl)1H-indole-2-carboxylate
TFMPP	N-(3-Trifluoromethyl-phenyl)piperazine
WAY 100135	N-tert-butyl-3-(4-[2-methoxyphenyl] piperazin-1-yl)-2-phenylpropanamide
WB 4101	2-(2,6-Dimethoxyphenoxy-ethyl)aminomethyl-1,4-benzodioxane

Some other drugs have been generally known by their code names until recently. The names of these drugs, as used in this review, and their previous code names are: granisetron (BRL 43694); ondansetron (GR 38032F); renzapride (BRL 24924); sumatriptan (GR 43175); tropisetron (ICS 205930).

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