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Molecular, pharmacological and functional diversity of 5-HT receptors

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Abstract

Serotonin (5-hydroxytryptamine, 5-HT) is probably unique among the monoamines in that its effects are subserved by as many as 13 distinct heptahelical, G-protein-coupled receptors (GPCRs) and one (presumably a family of) ligand-gated ion channel(s). These receptors are divided into seven distinct classes (5-HT_1 to 5-HT_7) largely on the basis of their structural and operational characteristics. Whilst this degree of physical diversity clearly underscores the physiological importance of serotonin, evidence for an even greater degree of operational diversity continues to emerge. The challenge for modern 5-HT research has therefore been to define more precisely the properties of the systems that make this incredible diversity possible. Much progress in this regard has been made during the last decade with the realisation that serotonin is possibly the least conservative monoamine transmitter and the cloning of its many receptors. Coupled with the actions of an extremely avid and efficient reuptake system, this array of receptor subtypes provides almost limitless signalling capabilities to the extent that one might even question the need for other transmitter systems. However, the complexity of the system appears endless, since posttranslational modifications, such as alternate splicing and RNA editing, increase the number of proteins, oligomerisation and heteromerisation increase the number of complexes, and multiple G-protein suggest receptor trafficking, allowing phenotypic switching and crosstalk within and possibly between receptor families. Whether all these possibilities are used in vivo under physiological or pathological conditions remains to be firmly established, but in essence, such variety will keep the 5-HT community busy for quite some time. Those who may have predicted that molecular biology would largely simplify the life of pharmacologists have missed the point for 5-HT research in particular and, most probably, for many other transmitters. This chapter is an attempt to summarise very briefly 5-HT receptor diversity. The reward for unravelling this complex array of serotonin receptor–effector systems may be substantial, the ultimate prize being the development of important new drugs in a range of disease areas. © 2002 Published by Elsevier Science Inc.

Keywords: Serotonin; 5-HT; 5-Hydroxytryptamine; Receptor families and subtypes

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) produces its effects through a variety of membrane-bound receptors. 5-HT and its receptors are found both in the central and peripheral nervous system (CNS/PNS), as well as in a number of nonneuronal tissues in the gut, cardiovascular system and blood. In evolutionary terms, 5-HT is one of the oldest neurotransmitters and has been implicated in the aetiology of numerous disease states, including depression, anxiety, social phobia, schizophrenia, and obsessive–compulsive and panic disorders; in addition to migraine, hypertension, pulmonary hypertension, eating disorders, vomiting and, more recently, irritable bowel syndrome (IBS).

With the exception of the 5-HT_3 receptor, which is a ligand-gated ion channel, 5-HT receptors belong to the G-protein-coupled receptor (GPCR) superfamily and, with at least 14 distinct members, represent one of the most complex families of neurotransmitter receptors. However, for a number of years, there has been no new addition to the 14 known receptors, with the exception of a second (5-ht_{3B}) and possibly a third (5-ht_{3C}) subunit for the 5-HT_3 receptor. Nevertheless, multiple splice variants (5-HT_4, 5-HT_7) or RNA edited isoforms (5-HT_{2C}) have been described, whilst there is evidence that amongst the heptahelical 5-HT receptors, homo- and heterodimerisation (5-$HT_{1B/1D}$) can occur, as reported for other GPCRs. Furthermore, peptide or lipid

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receptor modulators have been reported, such as 5-HT moduline (Leu–Ser–Ala–Leu (LSAL), a putative product of a chromogranin), which demonstrates selectivity for the 5-HT_{1B} and 5-HT_{1D} receptors, or oleamide, which acts on several 5-HT receptors (including 5-$HT_{2A/2C}$ and 5-HT_7).

Not surprisingly, the 5-HT receptor family has been a long-standing target of intense research, in both the academia and the pharmaceutical industry, even before the complexity of the system was unravelled by molecular cloning. Current efforts pursue in the identification of more potent and selective ligands for the different receptor subtypes. It is anticipated that such selective receptor probes will provide the tools to advance definition of functional effects in situ, be it in vitro or in vivo, and, in addition, lead to enhanced drug treatments with fewer side effects for a variety of disorders. Moreover, molecular genetic approaches offer a complementary strategy for studying distinct 5-HT receptor subtypes via the generation of gene-targeted and transgenic lines of mice with altered expression of 5-HT receptor genes. 5-HT is also a substrate for the 5-HT transporter, itself an important target in the treatment of depression and social phobia; however, the transporter will not be addressed here. Suffice, it is the target for selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine and citalopram, which is one of the most important classes of drugs to have emerged during the 20th century.

2. Current criteria for classifying 5-HT receptors

The classification of 5-HT receptors began in 1957, when it was demonstrated that functional responses of the guinea pig ileum could be partially blocked by morphine (M), whilst the remainder of the response was inhibited by dibenzyline (D). This led Gaddum and Picarelli (1957) to propose a subdivision of these novel receptors naming them M and D receptors, respectively. However, this classification was scrutinised due to the nonspecific effects of these discriminatory ligands on other neurotransmitter systems (Lewis, 1960; Day and Vane, 1963). Consequently, in 1976, utilising radioligand-binding techniques, with rat cortical membranes, the presence of putative 5-HT receptors was postulated (Bennett and Snyder, 1976). Regardless, there was no attempt to correlate these sites with any functional response, an essential requirement for receptor classification (see below). In 1979, Peroutka and Snyder demonstrated the presence of two distinct 5-HT receptor binding sites, utilising the radioligands [^{3}H]-5-HT, [^{3}H]-spiperone and [^{3}H]-LSD. 5-HT was the only neurotransmitter capable of displacing these radioligands; thus, the sites were named 5-HT_1 and 5-HT_2.

The M receptor was found to be distinct from the 5-HT_1 and 5-HT_2 receptors in both function and distribution, whilst the D receptor corresponded pharmacologically to the 5-HT_2 binding site. In 1986, Bradley et al. elaborated on this classification scheme for 5-HT receptors. They proposed to consider three main groups of 5-HT receptors, namely 5-HT_1-like, 5-HT_2 and 5-HT_3, the latter corresponding to the M receptor. The scheme, based primarily on functional criteria, proved to be a robust and useful framework for the classification of these receptor subtypes. With the widespread use of radioligands and second messenger readout systems, subtypes of 5-HT_1 receptor binding sites were described (see Hoyer et al., 1985a,b), but it became obvious that the 5-HT_{1C} receptor would be better classified within the 5-HT_2 receptor group (Hoyer, 1988). Second, a novel 5-HT receptor was identified in the gastrointestinal (GI) tract and brain, termed 5-HT_4. Third, shortly after the Bradley et al. paper, the molecular biology era started in earnest; initially, the β_2 adrenoceptor was cloned, followed swiftly by G21 or alternatively, as it is now known, the 5-HT_{1A} receptor (Fargin et al., 1988). From this point onwards, most known or suspected 5-HT receptors were cloned in rapid succession. The majority of this aforementioned work took place between 1987 and 1992 and led to the identification of a number of 'new' receptors, without obvious physiological counterparts. Tentatively termed 5-ht_{1E}, 5-ht_{1F}, 5-ht_{5A}, 5-ht_{5B}, 5-ht_6, 5-HT_7 and others, these also required integration into the classification system (note that the use of lower case designates a receptor that has not been definitively demonstrated to 'function' in native systems).

In addition, as efforts have progressed to sequence the human genome, it has become clear that receptors for hormones and neurotransmitters are likely to represent up to 2% of the genome, or as many as several hundreds of distinct gene products. Furthermore, posttranslational modifications are likely to yield many more operationally distinct protein entities. To date, hundreds of receptors have been identified, either functionally and/or by cloning; hitherto there are approximately 150 cloned orphan GPCRs (Lee et al., 2001). Presently, it is unclear how many will be attributed to the 5-HT receptor family. Thus, the Serotonin Club Receptor Nomenclature Committee proposed a new classification system based on operational, structural and transductional information (Humphrey et al., 1993). It was agreed at the time that no single criterion should be exclusive or predominant. This implies that the term receptor should only be applied to an entity for which all three classes of information are available, and that providing reasonable evidence for a functional role can be documented.

These principles have subsequently been adapted to additional receptor families by the receptor Nomenclature Committee of the International Union of Pharmacology (NC-IUPHAR). The current classification (Hoyer et al., 1994) has been progressively adapted to accommodate new information, obtained with both recombinant and native receptors and favours an alignment of nomenclature with the human genome to avoid species differences (see Hartig et al., 1996; Hoyer and Martin, 1997). Currently,

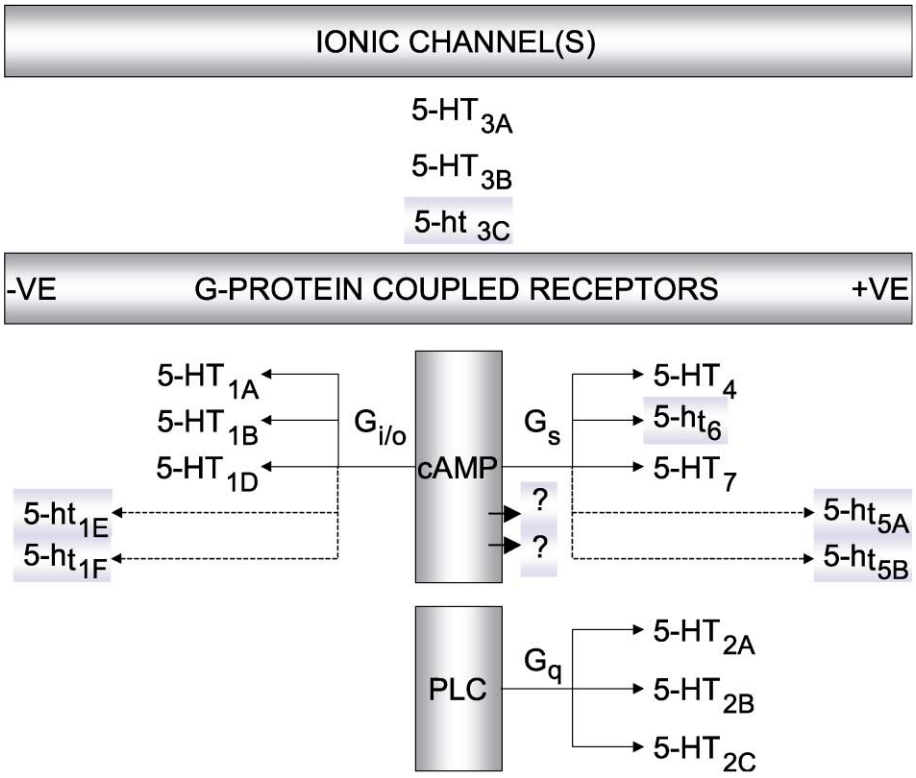

Fig. 1. Graphical representation of the current classification of 5-HT receptors. Receptor subtypes represented by coloured boxes and lower case designate receptors that have not been demonstrated to definitively function in native systems. Abbreviations: 3′-5′ cyclic adenosine monophosphate (cAMP); phospholipase C (PLC); negative (−ve); positive (+ve).

seven families of 5-HT receptors have been recognised (Fig. 1).

3. The 5-HT$_1$ receptor class

The 5-HT$_1$ receptor class is comprised of five receptor subtypes (5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-ht$_{1E}$ and 5-ht$_{1F}$), which, in humans, share 40–63% overall sequence identity and couple preferentially, although not exclusively, to G$_{i/o}$ to inhibit cAMP formation (see Tables 1 and 2). The 5-ht$_{1E}$ and 5-ht$_{1F}$ receptors are given a lower case appellation to denote that endogenous receptors with a physiological role have not yet been found. In contrast, 5-HT$_{1A}$, 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors have been demonstrated functionally in a variety of tissues from various species. The 5-HT$_{1C}$ designation is now vacant, since this receptor was reclassified to 5-HT$_{2C}$ due to structural, operational and transductional similarities with the 5-HT$_2$ receptor subclass (Hoyer et al., 1994).

3.1. 5-HT$_{1A}$ receptors

5-HT$_{1A}$ receptors are largely distributed throughout the CNS. In the raphé nuclei, they are somatodendritic and act as autoreceptors to inhibit cell firing; postsynaptic 5-HT$_{1A}$ receptors are present in a number of limbic structures, particularly the hippocampus. Activation of 5-HT$_{1A}$ receptors causes neuronal hyperpolarisation, an effect mediated through G-protein-coupled K^+ channels (see Aghajanian, 1995). Furthermore, in the GI tract, 5-HT$_{1A}$ receptors were identified on the guinea pig myenteric plexus where they function as inhibitory modulators of fast excitatory postsynaptic potentials. The human 5-HT$_{1A}$ receptor is located on chromosome 5q11.2–q13 (see Hoyer et al., 1994).

The involvement of 5-HT$_{1A}$ receptors in a number of physiological and behavioural effects has been established. 5-HT$_{1A}$ receptors have been implicated in the neuroendocrine regulation of adrenocorticotrophic hormone (ACTH), but not prolactin secretion (Jorgensen et al., 2001). However, whether certain responses are mediated via pre- or postsynaptic mechanisms remains equivocal. Yet, it has been established that activation of postsynaptic 5-HT$_{1A}$ receptors induces a behavioural syndrome, characterised by flat body posture, reciprocal forepaw treading and head weaving. Moreover, the spontaneous tail-flick response has also been attributed to postsynaptic 5-HT$_{1A}$ receptor activation (Tricklebank, 1985; Lucki, 1992; Bervoets et al., 1993); whereas evidence for a presynaptic 5-HT$_{1A}$ (auto)receptor in the hyperphagia response appears convincing (Simansky, 1998). Conversely, a species-dependent mechanism appears to be in operation with respect to the hypothermic response to 5-HT$_{1A}$ agonists; in the rat, both pre- and postsynaptic mechanisms appear to mediate this response, whilst in the mouse, a presynaptic mechanism has been proposed (Lars-

Table 1
Serotonin receptor homology

Subtype	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-ht$_{1E}$	5-ht$_{1F}$	5-HT$_{2A}$	5-HT$_{2B}$	5-HT$_{2C}$	*5-HT$_3$	5-HT$_4$	5-ht$_{5A}$	*r5-ht$_{5B}$*	5-ht$_6$	5-HT$_7$
5-HT$_{1A}$	100	53	52	49	53	42	42	45	14	36	48	*49*	43	49
5-HT$_{1B}$	43	100	71	56	60	43	39	38	27	39	43	*42*	39	46
5-HT$_{1D}$	43	63	100	58	57	41	40	42	44	40	45	*43*	41	46
5-ht$_{1E}$	40	48	48	100	66	45	40	43	30	41	46	*47*	40	48
5-ht$_{1F}$	42	49	48	57	100	46	42	44	29	44	48	*46*	42	48
5-HT$_{2A}$	30	30	29	34	32	100	52	57	0	36	36	*35*	36	38
5-HT$_{2B}$	34	27	27	30	29	45	100	53	29	37	37	*37*	36	37
5-HT$_{2C}$	32	28	30	32	32	51	42	100	18	39	40	*36*	37	37
*5-HT$_3$	14	22	22	10	14	0	18	16	100	21	32	*22*	29	0
5-HT$_4$	29	32	31	32	34	28	29	28	21	100	42	*38*	35	42
5-ht$_{5A}$	36	35	34	35	37	27	26	31	22	32	100	*75*	38	42
r5-ht$_{5B}$	*39*	*34*	*33*	*35*	*36*	*27*	*29*	*29*	*22*	*30*	*70*	100	*38*	*44*
5-ht$_6$	34	31	32	32	32	27	27	27	24	27	30	*31*	100	40
5-HT$_7$	38	37	38	39	38	28	28	28	0	32	33	*34*	33	100

Values in the upper right portion represent overall percentage amino acid similarity (i.e. the two sequences have either an identical or, alternatively, a similar amino acid); whilst those in the shaded lower left portion demonstrate overall percentage amino acid sequence identity. Data refer to human receptors; except the 5-ht$_{5B}$ receptor, which was derived from the rat.

* The actual overall homology of the 5-HT$_3$ versus other 5-HT receptors was very low (< 10%); the numbers indicated in the table represent similarity within certain segments of the 5-HT$_3$ receptor. Furthermore, the 5-HT$_{2C\text{-}LONG}$, 5-HT$_{4\text{-}LONG}$ and 5-HT$_{7A}$ sequences were used to represent these receptor subtypes. The results were generated using the GAP algorithm (Wisconsin Sequence Analysis Package; Accelrys), with gap and length weights of 14 and 3, respectively. Darker shading indicates clusters of receptors with higher similarity.

son et al., 1990; Bill et al., 1991; Millan et al., 1993). In addition, a decrease in blood pressure and heart rate and increased locomotor responses can be induced by central 5-HT$_{1A}$ receptor activation, whilst fluoxetine-induced penile erections can be markedly potentiated by combined 5-HT$_{1A/1B}$ receptor blockade (Wilkinson and Dourish, 1991; Dreteler et al., 1991; Kalkman, 1995; Millan et al., 1997).

The proposed role of 5-HT$_{1A}$ receptors in modulating anxiety-related behaviours is supported by recent studies utilising 5-HT$_{1A}$ receptor knockout (KO) mice. These animals demonstrated increased anxiety in a number of experimental paradigms. The KO animals spent less time in the open arms of the elevated plus maze, the elevated zero maze and the centre of an open field, and less time exploring a novel object. Moreover, these animals demonstrated decreased baseline immobility in the forced swimming and tail suspension tests (Heisler et al., 1998; Parks et al., 1998).

5-HT$_{1A}$ receptor agonists, such as buspirone or gepirone, are being used or developed for the treatment of anxiety and depression (Tunnicliff, 1991; Den Boer et al., 2000). Furthermore, the 5HT$_{1A}$ receptor antagonist and beta adrenoceptor blocker, pindolol, was reported to enhance the therapeutic efficacy and shorten the onset of action of SSRIs when coadministered in depressed patients. However, both positive and negative findings have been reported, as is common in depression trials (for review, see Artigas et al., 2001). Flesinoxan, another 5-HT$_{1A}$ receptor agonist, was initially developed as an antihypertensive agent, however, its effects in patients were disappointing, and this approach has now been abandoned.

Several agonists show selectivity for the 5-HT$_{1A}$ receptor, particularly 8-hydroxy-di-*n*-propylamino tetralin (8-OH-DPAT), which acts as a full agonist in most systems, whilst the anxiolytics, buspirone and gepirone, and other ligands, such as MDL 72832, are partial agonists. The synthesis of selective and silent antagonists at this receptor has proven more difficult. To date, the only selective high-affinity silent antagonist at this receptor is WAY 100635 (Forster et al.,

1995; Fletcher et al., 1996; Table 2). Nevertheless, additional noteworthy ligands include the agonists U-92016A and (+)UH 301, and the antagonists (−)UH 301 and NAD 299 (McCall et al., 1994; Newman-Tancredi et al., 1998; Martin et al., 1999; Ross et al., 1999).

3.2. 5-HT$_{1B}$ receptors

The 5-HT$_{1B}$ receptor and its counterpart the 5-HT$_{1D}$ receptor, have experienced a complex and debated history. The 5-HT$_{1B}$ receptor was originally defined according

Table 2

5-HT$_1$ receptor nomenclature proposed by the NC-IUPHAR subcommittee on 5-HT receptors

Nomenclature	5-HT$_{1A}$	5-HT$_{1B}$[a,b]	5-HT$_{1D}$[a]	5-ht$_{1E}$	5-ht$_{1F}$
Previous names	–	5-HT$_{1D\beta}$	5-HT$_{1D\alpha}$	–	5-ht$_{1E\beta}$, 5-HT$_6$
Selective agonists	8-OH-DPAT	Sumatriptan L 694247	Sumatriptan PNU 109291	–	LY 334370
Selective antagonists (pK_B)	(±)WAY 100635 (8.7)	GR 55562 (7.4) SB 224289 (8.5) SB 236057 (8.9)	BRL 15572 (7.9)	–	–
Radioligands	[^{3}H]WAY100635 [^{3}H]8-OH-DPAT	[^{125}I]GTI [^{125}I]CYP (rodent) [^{3}H]Sumatriptan [^{3}H]GR 125743	[^{125}I]GTI [^{3}H]Sumatriptan [^{3}H]GR 125743	[^{3}H]5-HT	[^{125}I]LSD [^{3}H]LY 334370
13)G-protein effector	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$	G$_{i/o}$
Gene/chromosomal localisation	*HTR1A*/5q11.2–q13	*HTR1B*/6q13	*HTR1D*/1p34.3–36.3	*HTR1E*/6q14–15	*HTR1F*/3p11–p14.1
Structural information	h421 P8908 m421 Q64264 r422 P19327	h390 P28222 m386 P28334 r386 P28564	h377 P28221 m374 Q61224 r374 P28565	h365 P28566	h366 P30939 m366 Q02284 r366 P30940

5-HT$_{2,3,4}$ receptor nomenclature proposed by the NC-IUPHAR subcommittee on 5-HT receptors

Nomenclature	5-HT$_{2A}$	5-HT$_{2B}$	5-HT$_{2C}$[c]	5-HT$_3$	5-HT$_4$
Previous names	D/5-HT$_2$	5-HT$_{2F}$	5-HT$_{1C}$	M	–
Selective agonists	DOI[d]	BW 723C86	Ro 600175	SR 57227 *m*-chlorophenyl-biguanide	BIMU 8 RS 67506 ML 10302
Selective antagonists (pK_B)	Ketanserin (8.5–9.5) MDL 100907 (9.4)	SB 200646 (7.5)[e] SB 204741 (7.8)	Mesulergine (9.1) SB 242084 (9.0) RS 102221 (8.4)	granisetron (10) ondansetron (8–10) tropisetron (10–11)	GR 113808 (9–9.5) SB 204070 (10.8) RS 100235 (11.2)
Radioligands	[^{125}I]DOI [^{3}H]Ketanserin [^{3}H]MDL 100907	[^{3}H]5-HT	[^{125}I]LSD [^{3}H]Mesulergine	[^{3}H]*(S)*-zacopride [^{3}H]tropisetron [^{3}H]granisetron [^{3}H]GR 65630 [^{3}H]LY 278584[f]	[^{125}I]SB 207710 [^{3}H]GR 113808 [^{3}H]RS 57639
G-protein effector	G$_{q/11}$	G$_{q/11}$	G$_{q/11}$		G$_s$
Gene/chromosomal localisation	*HTR2A*/13q14–q21	*HTR2B*/2q36.3–q37.1	*HTR2C*/Xq24	*HTR3*/11q23.1–q23.2	*HTR4*/5q31–33
Structural information	h471 P28223 m471 P35362 r471 P14842	h481 P41595 m504 Q02152 r479 P30994	h458 P28335 m459 P34968 r460 P08909	Multisubunit[g] 5-HT$_{3A}$, 5-HT$_{3B}$, 5-ht$_{3C}$	h387 Y09756[AS] m387 Y09587[AS] r387 U20906[AS]

5-HT$_{5,6,7}$ receptor nomenclature proposed by the NC-IUPHAR subcommittee on 5-HT receptors

Nomenclature	5-ht$_{5A}$	5-ht$_{5B}$	5-ht$_6$	5-HT$_7$
Previous names	5-HT$_{5\alpha}$	–	–	5-HT$_X$ 5-HT$_1$-like
Selective agonists	–	–	–	–
Selective antagonists (pK_B)	–	–	Ro 630563 (7.9) SB 271046 (7.8) SB 357134 (8.5)	SB 258719 (7.9) SB 269970 (9.0)
Radioligands	[^{125}I]LSD [^{3}H]5-CT	[^{125}I]LSD [^{3}H]5-CT	[^{125}I]SB 258585 [^{125}I]LSD [^{3}H]5-HT	[^{125}I]LSD [^{3}H]SB 269970 [^{3}H]5-CT [^{3}H]5-HT
G-protein effector	G$_{i/o}$	None identified	G$_s$	G$_s$
Gene/chromosomal localisation	*HTR5A*/7q36.1	*htr5b*/2q11–q13	*HTR6*/1p35–36	*HTR7*/10q23.3–24.3
Structural information	h357 P47898 m357 P30966 r357 P35364	m370 P31387 r370 P35365	h440 P50406 m440 NP_067333 r438 P31388	h445 P34969[AS] m448 P32304 r448 P32305[AS]

to operational criteria and was thought to be a rodent-specific receptor. However, similarities in transductional features, function and brain distribution led to the opinion that the rodent '5-HT_{1B}' and nonrodent '5-HT_{1D}' receptors were species homologues (Hoyer and Middlemiss, 1989), which was demonstrated unequivocally when the receptors were cloned (Hartig et al., 1992). The pharmacologically defined human 5-HT_{1D} receptor was, in fact, a composite of two subtypes, encoded by distinct genes, which were called 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$. This notation reflected the fact that the operational profiles of these two receptors, utilising the ligands available at that time, were almost indistinguishable. It was subsequently shown, in spite of overt differences in their pharmacological profiles, that 5-HT_{1B} and 5-$HT_{1D\beta}$ receptors are respectively rodent and nonrodent species homologues with 97% overall sequence homology.

Indeed, the differences in the pharmacology of these two homologues are now attributable to the mutation of a single amino acid in the transmembrane spanning region Asp^{123} to Arg^{123}. Identification of the 5-$HT_{1D\alpha}$ gene in rats confirmed that 5-$HT_{1B/1D}$ receptors represent only two different classes, prompting the need to revise the receptor notation according to the classification principles. Accordingly, the 5-$HT_{1D\beta}$ receptor is now known as 5-HT_{1B}, consistent with the fact that it is the human homologue of the original rodent 5-HT_{1B} receptor. The human 5-HT_{1B} receptor is located on chromosome 6q13. However, it is important to remember that, because the human receptor now assumes preeminence, the operational characteristics of the 5-HT_{1B} class are those defined for the human receptor.

5-HT_{1B} receptors are expressed in the CNS, concentrated in the basal ganglia, striatum and frontal cortex and are thought to serve as terminal autoreceptors. In addition, the receptor may also act as a terminal heteroreceptor controlling the release of other neurotransmitters, such as acetylcholine, glutamate, dopamine, noradrenaline and γ-aminobutyric acid (see Pauwels, 1997). The receptors are also found on cerebral arteries and other vascular tissues. Peripheral effects have been described, such as inhibition of noradrenaline release in vena cava and inhibition of plasma extravasation produced by trigeminal ganglion stimulation in guinea pigs and rats. 5-HT_{1B} receptors mediate contraction of rat caudal arteries. In nonrodents, they exhibit the 5-HT_{1D} 'pharmacology.'

Interest in 5-HT_{1B} receptor agonists has been enhanced by the antimigraine properties of sumatriptan, a nonselective 5-$HT_{1D/1B}$ receptor agonist; thus, agonists have been developed for this indication (dihydroergotamine (DHE), zolmitriptan, naratriptan, rizatriptan, elitriptan, almotriptan, donitriptan and others; see Leysen et al., 1996). The putative $5HT_{1B}$ receptor agonist, anpirtoline, has analgesic and antidepressant-like properties in rodents and, interestingly, 5-HT_{1B} receptor KO mice were reported to be both highly aggressive and have an increased preference for alcohol (Saudou et al., 1994; Ramboz et al., 1995; Crabbe et al., 1996). However, recent findings have diminished the perceived utility of 5-HT_{1B} receptor KO mice as a model of alcoholism as attempts to replicate such abnormalities in ethanol consumption were unsuccessful (Crabbe et al., 1999; Risinger et al., 1999). Furthermore, as opposed to the 5-HT_{1A} receptor KO mouse, the 5-HT_{1B} receptor KO animals demonstrates a somewhat different and, in most cases, contrary behavioural profile, displaying decreases in measures of anxiety in the elevated plus maze, open field and tail suspension test, in addition to an increase in aggression in the resident intruder paradigm (Saudou et al., 1994; Zhuang et al., 1999; Mayorga et al., 2001). An attempt was made to develop 5-HT_{1B} agonist 'serenics,' such as eltoprazine; however, the expected antiaggressive effects were not observed in patients (De Koning et al., 1994).

RU 24969 was the first reported full agonist at the 5-HT_{1B} receptor, and earlier studies utilised the strong locomotor response to this ligand, as a model of postsynaptic receptor function. However, the response demonstrates species differences; in the mouse, evidence for the involvement of 5-HT_{1B} receptors is persuasive; whereas the same response in the rat can be attributed to 5-HT_{1A} receptor activation (Cheetham and Heal, 1993; Kalkman, 1995). Additional effects tentatively attributed to central 5-HT_{1B} receptor activation, in rats, include hypophagia, hypothermia and penile erection (Middlemiss and Hutson, 1990; Millan and Perrin-Monneyron, 1997).

Other selective 5-HT_{1B} agonists characterised include MK 462 (rizatriptan), BW 311C90 (zolmitriptan), SKF 99101H, GR 46611, L 694247 and CP 93129 (in rodents). In addition, some of these agents, e.g. sumatriptan and,

Notes to Table 2:

[a] The 5-HT_{1B} and 5-HT_{1D} receptor nomenclature has been revised (Hartig et al., 1996), only the nonrodent form of the receptor was previously called 5-$HT_{1D\beta}$.

[b] Displays a different pharmacology to the rodent form of the receptor.

[c] Multiple isoforms of the 5-HT_{2C} receptor are produced by RNA editing.

[d] Also activates the 5-HT_{2C} receptor.

[e] Nonselective blockade.

[f] The 5-HT_3 receptor is a transmitter-gated cation channel that exists as a pentamer of 4TM subunits.

[g] Human, rat, mouse, guinea pig and ferret homologues of the 5-HT_{3A} receptor have been cloned, which exhibit interspecies variation in pharmacology. A second 5-HT_3 receptor subunit, 5-HT_{3B}, imparts distinctive biophysical properties upon heterooligomeric (5-HT_{3A}/5-HT_{3B}) versus homooligomeric (5-HT_{3A}) recombinant receptors.

more recently, LY 334370 (Johnson et al., 1997), have significant affinity to 5-ht$_{1F}$ receptors (see below). Clearly, some of these molecules will recognise 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors almost equally, e.g. L 694247. However, SB 216641 (h5-HT$_{1B}$) and BRL 15572 (h5-HT$_{1D}$) have permitted discrimination of the effects mediated by one or the other of these receptors, in appropriate species, at the level of presynaptic auto- and heteroreceptors (see Price et al., 1997; Schlicker et al., 1997; Hopwood and Stamford, 2001; Roberts and Price, 2001). With respect to antagonists, there are few with selectivity for the 5-HT$_{1B}$ receptor. The most commonly used (in rodents), pindolol, cyanopindolol and SDZ 21009, are equipotent at the 5-HT$_{1A}$ receptor, where they have antagonist or partial agonist properties and are more potent as beta-adrenoceptor antagonists. SB 216641, SB 272183 and GR 55562 demonstrate a certain degree of 5-HT$_{1B}$ selectivity, whilst others demonstrate inverse agonism (e.g. SB 224289 and SB 236057), thus allowing the characterisation of 5-HT$_{1B}$ receptor tone. Moreover, the use of these new compounds, displaying different levels of intrinsic activity at these receptors, demonstrates that terminal 5-HT autoreceptors are those of the 5-HT$_{1B}$ type (see Price et al., 1997; Roberts and Price, 2001; Roberts et al., 1997, 2000; Schlicker et al., 1997; Gaster et al., 1998; Selkirk et al., 1998; Middlemiss et al., 1999; Hopwood and Stamford, 2001; Watson et al., 2001). Useful radiolabelled ligands include [^{3}H]-GR 125743, a 5-HT$_{1D/1B}$ receptor antagonist (Domenech et al., 1997) that can be used, similarly to [^{125}I]5-hydroxytryptamine-5-*O*-carboxymethylglycyltyrosinamide (GTI) (Bruinvels et al., 1991) or [^{3}H]alniditan (Leysen et al., 1996). In rodents, [^{125}I]cyanopindolol is capable of labelling 5-HT$_{1B}$ sites under appropriate conditions (Hoyer et al., 1985a,b; Ase et al., 2001).

3.3. 5-HT$_{1D}$ receptors

The 5-HT$_{1D}$ receptor (formerly 5HT$_{1D\alpha}$) is located on chromosome 1p34.3–p36.3 and possesses 63% overall structural homology with the 5-HT$_{1B}$ receptor (formerly 5-HT$_{1D\beta}$). Its level of expression is very low compared with 5-HT$_{1B}$ receptors, and it has thus been difficult to assign a functional role to 5-HT$_{1D}$ receptors. The characteristics of the 5-HT$_{1B}$ and 5-HT$_{1D}$ subtypes are now particularly well established. Moreover, the use of new 5-HT$_{1B}$ receptor compounds (see above) has suggested the presence of a 5-HT$_{1D}$ autoreceptor in the dorsal raphé nuclei (see Roberts and Price, 2001; Roberts et al., 1997; Buhlen et al., 1996; Pineyro et al., 1996; Hopwood and Stamford, 2001). Moreover, 5-HT$_{1D}$ receptors have been found in the human heart, where they modulate 5-HT release.

The currently available antimigraine drugs do not distinguish between 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors. It has been proposed that neurogenic inflammation and nociceptive activity within trigeminovascular afferents may be 5-HT$_{1D}$ receptor mediated due to the presence of 5-HT$_{1D}$, but not 5-HT$_{1B}$, receptor mRNA in the trigeminal ganglia, but this has not been confirmed. However, the selective 5-HT$_{1D}$ receptor agonist, PNU 109291, has been shown to play a significant role in the suppression of meningeal neurogenic inflammation and trigeminal nociception in guinea pig models, suggesting that the 5-HT$_{1D}$ receptor subtype may represent a useful therapeutic target for migraine and related headaches (Cutrer et al., 1999). Furthermore, immunocytochemical analysis has also demonstrated both 5-HT$_{1B}$ and 5-HT$_{1D}$ receptor immunoreactivity, in human trigeminal ganglia, where these receptors appear to colocalise with calcitonin gene-related peptide, substance P and nitric oxide synthase (Hou et al., 2001).

3.4. 5-ht$_{1E}$ Receptors

The putative 5-ht$_{1E}$ receptor was first identified in binding studies in homogenates of human frontal cortex, but it was not possible to readily determine its overall distribution and pharmacology. It is a 365-amino acid protein negatively linked to adenylyl cyclase in recombinant cell systems. The receptor was mapped to human chromosome 6q14–q15; however, its function is presently unknown, and selective ligands are largely unavailable. Although 5-ht$_{1E}$ receptor mRNA (Bruinvels et al., 1994) and recognition sites exhibiting the pharmacological characteristics of the receptor have been mapped in the rodent and human brain (Miller and Teitler, 1992; Barone et al., 1993, 1994), confirmation of a true physiological role for 5-ht$_{1E}$ receptors is still lacking; hence, they retain their lower case appellation. A thorough characterisation of the 5-ht$_{1E}$ receptor in combination with the development of selective ligands is anticipated.

3.5. 5-ht$_{1F}$ Receptors

The 5-ht$_{1F}$ receptor consists of a 366-amino acid protein, negatively linked to adenylyl cyclase in recombinant cell systems. The 5-ht$_{1F}$ receptor is most closely related to the 5-ht$_{1E}$ receptor with $>70\%$ sequence homology across the seven TM domains and is located on chromosome 3p11. Little is known about the distribution and function of the 5-ht$_{1F}$ receptor; mRNA for the human receptor protein has been identified in the brain (concentrated in the dorsal raphé, hippocampus, cortex, striatum, thalamus and hypothalamus), mesentery and uterus, but not in kidney, liver, spleen, heart, pancreas or testis. Its distribution suggests that it may possess a role as a 5-HT autoreceptor.

Interestingly, the antimigraine 5-HT$_{1B/1D}$ agonist sumatriptan labels 5-ht$_{1F}$ sites with high affinity. Moreover, naratriptan also has affinity for 5-ht$_{1F}$ receptors. Indeed, hampered by the lack of selective radioligand probes, Waeber and Moskowitz (1995) have used [^{3}H]sumatriptan (in the presence of selective ligands to mask non-5-ht$_{1F}$ sites) to identify a distinct distribution of putative 5-ht$_{1F}$ receptors in guinea pig brain. The binding site distribution obtained was very similar to that for 5-ht$_{1F}$ mRNA, encour-

aging the opinion that the radioligand binding was to 5-ht_{1F} sites. In support of this, Beer et al. (1993) had described 5-CT-insensitive 5-HT_1 binding sites in the same regions of rat brain. However, the extent to which these radioligand-binding studies specifically labelled 5-ht_{1F} recognition sites is questionable. Nevertheless, it has been hypothesised that the 5-ht_{1F} receptor might be a target for drugs with anti-migraine properties and 5-ht_{1F} receptor mRNA has been detected in the trigeminal ganglia, stimulation of which leads to plasma extravasation in the dura, a component of neurogenic inflammation thought to be a possible cause of migraine (Hamon and Bourgoin, 2000).

LY 334370, a selective 5-ht_{1F} receptor agonist, inhibits trigeminal stimulation-induced early activated gene (Fos protein) expression in nociceptive neurones in the rat brainstem (Johnson et al., 1997). LY 334370 has also been used as a radioligand and demonstrated a reasonable correlation between the receptor protein and mRNA distribution, with prominent binding in the cortical areas, striatum, hippocampus and olfactory bulb. Further selective ligands are currently in development, i.e. LY 344864 and BRL 54443, however, these also have affinity for 5-ht_{1E} receptors (see Phebus et al., 1997; McKune and Watts, 2001).

4. The 5-HT_2 receptor class

This class comprises the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors, which exhibit 46–50% overall sequence identity and couple preferentially to $G_{q/11}$ to increase the hydrolysis of inositol phosphates and elevate cytosolic [Ca^{++}] (see Tables 1 and 2). The 5-HT_{2A} receptor refers to the classical D receptor initially described by Gaddum and Picarelli (1957), which was later defined as the 5-HT_2 receptor by Peroutka and Snyder (1979). The 5-HT_{2B} receptor mediates the contractile action of 5-HT in the isolated rat fundus. However, it is yet to be confirmed that this receptor is coupled to the hydrolysis of inositol phosphates in native tissues. Indeed, in human pulmonary artery endothelial cells, 5-HT_{2B} receptor stimulation causes intracellular calcium release via an independent mechanism (Ullmer et al., 1996), similar to that seen in the rat stomach fundus (Cox and Cohen, 1996). In neither tissue was the 5-HT_{2B} receptor coupled to phosphatidylinositol hydrolysis. The third 5-HT_2 subtype corresponds to the previously known 5-HT_{1C} receptor, which as mentioned previously was reclassified as the 5-HT_{2C} receptor (Hoyer et al., 1994).

4.1. 5-HT_{2A} receptors

The 5-HT_{2A} receptor has been located on human chromosome 13q14–q21 and comprises of 471 amino acids in rats, mice and humans (Table 2). It is widely distributed in peripheral and central tissues; this entity corresponds to the former 5-HT_2 or D receptor (Bradley et al., 1986). 5-HT_{2A} receptors mediate contractile responses in many vascular smooth muscle preparations, e.g. bronchial, uterine and urinary smooth muscle, and part of the contractile effects of 5-HT in the guinea pig ileum. In addition, platelet aggregation and increased capillary permeability following exposure to 5-HT have been attributed to 5-HT_{2A} receptor-mediated functions.

Centrally, these receptors are principally located in the cortex, claustrum and basal ganglia. 5-HT_{2A} receptor activation stimulates hormone secretion, e.g. ACTH, corticosterone, oxytocin, renin and prolactin (Van de Kar et al., 2001). Moreover, 5-HT_2 receptor agonists, in addition to precursors of 5-HT and 5-HT releasing agents, mediate certain behavioural syndromes in vivo. Head twitching in mice, and wet-dog shakes and back muscle contractions in rats, can be inhibited with 5-HT_2 receptor antagonists with a potency correlating with their affinity for 5-HT_{2A} receptor binding sites. In confirmation, such head twitching has been demonstrated to be inhibited with the selective 5-HT_{2A} receptor antagonist MDL 100907 (Green and Heal, 1985; Fone et al., 1989; Schreiber et al., 1995). Moreover, the production of drug discriminative stimulus properties to 5-HT_2 receptor agonists, e.g. (−)2,5,-dimethoxy-4-methamphetamine (DOM) can be blocked by 5-HT_2 receptor antagonists, such as ketanserin, suggesting that the discriminative cue is 5-HT_{2A} receptor mediated (Fiorella et al., 1995a,b).

The most selective agents, in terms of 5-HT_{2A} receptor affinity, are ketanserin and MDL 100907. The former agent was developed for the treatment of hypertension, but it remains to be established whether 5-HT_{2A} receptor antagonism is a valid antihypertensive principle, since ketanserin is also an α_1 adrenoceptor antagonist. 5-HT_{2A} receptor antagonists, such as risperidone, ritanserin, seroquel, olanzapine or MDL 100907, demonstrate divergent selectivity and have been indicated/developed for the treatment of schizophrenia. However, development of MDL 100907 for acute schizophrenia was terminated, apparently for insufficient efficacy; although other similar molecules are still in the pipeline.

It appears that the combination of dopamine D_2 and 5-HT_{2A} receptor antagonism may best explain the antipsychotic activity of drugs such as clozapine, olanzapine, seroquel and others. Moreover, it has been proposed for some time that LSD and other hallucinogens produce their effects via 5-HT_{2A} receptors. This is the best possible explanation (see Vollenweider et al., 1998; Aghajanian and Marek, 1999), although their selectivity vis-a-vis 5-HT_{2B} and 5-HT_{2C} receptors is rather limited. Truly selective agonists have not been described as αMe-5-HT, DOI and DOB also recognise other receptors of the 5-HT_2 receptor class.

4.2. 5-HT_{2B} receptors

The latest introduction to the 5-HT_2 receptor class is the 5-HT_{2B} receptor. Activation of this receptor subtype leads to fundic smooth muscle contraction. However, it has proven

difficult to pharmacologically characterise due to operational characteristics similar to those of other members of the 5-HT_2 family (Humphrey et al., 1993). Thus, confusion as to the pharmacological nature of the fundus receptor led to its original classification as a member of the 5-HT_1 subclass of 5-HT receptors despite the relative low potency of 5-CT with respect to 5-HT in this preparation (Buchheit et al., 1986). The receptor also defied classification in terms of the recognised subtypes of the high-affinity [^{3}H]-5-HT binding sites. The phenylpiperazines, such as mCPP, antagonised 5-HT-induced contractions of the fundus; however, their antagonist potencies did not correlate with affinities with either the 5-HT_{1A} or the 5-HT_{1B} binding sites (Cohen and Wittenauer, 1986). The fact that 5-CT was approximately 10-fold less active than 5-HT was more consistent with the receptor in the fundus being a 5-HT_{1C} receptor. Moreover, a highly significant correlation was observed between pK_D values for 5-HT_{2C} (at the time designated as 5-HT_{1C} binding sites) and pD_2 values for the contractile responses of some 25 agonists tested (Buchheit et al., 1986). However, the involvement of 5-HT_{2C} receptors was excluded on the basis of antagonist studies; compounds such as mianserin, ketanserin and pirenperone were inactive at concentrations which should have theoretically occupied 5-HT_{2C} receptors. Thus, although the fundus receptor shared some characteristics with the classical 5-HT_2 receptor, it was clear, however, that it was not a 5-HT_{2A} receptor (Clineschmidt et al., 1985). Furthermore, additional investigations showed that the fundus receptor was not a 5-HT_{2C} receptor, as 5-HT_{2C} mRNA could not be found in the rat fundus preparation.

Eventually, the situation was clarified with the cloning of the rat, mouse and human 'fundic' receptors; also known as 5-HT_{2F} for a short time (Kursar et al., 1992; Table 2). In humans, it is located on chromosome 2q36.3–2q37.1. 5-HT_{2B} receptor mRNA is found in the rat fundus, gut, heart, kidney, lung and brain. The mouse homologue is expressed in the intestine, heart, kidney and brain. Selective agonists (BW 723C86; see Kennett et al., 1997a) and antagonists (RS 127445; see Bonhaus et al., 1999) will undoubtedly facilitate in the classification of 5-HT_{2B} receptor-mediated effects.

Centrally, 5-HT_{2B} receptor-like immunoreactivity has been reported restricted to a few brain regions particularly cerebellum, lateral septum, hypothalamus and medial amygdala (Duxon et al., 1997a). Interestingly, direct injection of BW 723C86 into the medial amygdala was reported to have anxiolytic properties in the rat social interaction test (Duxon et al., 1997b). Moreover, 5-HT_{2B} receptor activation has been implicated in mediating hyperphagia and bringing about a reduction in grooming frequency (Kennett et al., 1997a).

The 5-HT_{2B} receptor is present in endothelial cells of pig pulmonary arteries where it mediates vasorelaxation (via NO release) upon activation. This observation is further supported by the presence of 5-HT_{2B}, and not 5-HT_{2C}, receptor mRNA in a number of blood vessels (Ullmer et al., 1995). Moreover, 5-HT_{2B} receptors mediate endothelium-dependent relaxation in isolated rat jugular vein and contraction of longitudinal muscle in human small intestine, and when stably expressed in a mouse fibroblast cell line, they have been reported to cause mitogenesis, via MAP kinase activation, linked to tumour-transforming activity. SB 200646 and SB 206553 have been reported as selective 5-$HT_{2C/2B}$ receptor antagonists, with low affinity for 5-HT_{2A} and other sites (Kennett et al., 1994, 1996). SB 204741 has been reported as the first selective 5-HT_{2B} receptor antagonist, whilst LY 53857 has high affinity at recombinant human 5-HT_{2B} receptors. Agonists with some selectivity are α-Me-5-HT and 5-methoxytryptamine, which act as a full agonist with high affinity for the 5-HT_{2B} site (Jerman et al., 2001). BW 723C86 has been reported to have selectivity at the rat 5-HT_{2B} receptor, although such selectivity was less pronounced at human recombinant receptors.

5-HT_{2B} receptor antagonists, such as SB 200646, are relatively new and may be indicated for the treatment of migraine prophylaxis, given the vasodilatatory role of this receptor subtype and also that a number of 'older' drugs impart such activity. Moreover, it appears that the 5-HT_{2B} receptor, expressed in cardiac valves, is responsible for the valvulopathies reported from dex-fenfluramine containing preparations utilised as appetite suppressant agents (see Fitzgerald et al., 2000; Rothman et al., 2000).

4.3. 5-HT_{2C} receptors

The 5-HT_{2C} receptor was one of the first of this family to be cloned, although full-length sequences were difficult to obtain due to a complex exon–intron structure. The receptor was mapped to human chromosome Xq24. Given its similar pharmacological and transductional features with the 5-HT_{2A} receptor (Hoyer, 1988), it did not take long to establish the sequence of the latter, based on homology cloning. However, due to the lack of truly selective 5-HT_{2C} receptor ligands, our current knowledge concerning a functional role of this receptor is rather limited. Thus far, its distribution has been limited to the CNS and choroid plexus, the latter being where this receptor was originally identified. Although it has been demonstrated that 5-HT_{2C} receptors in the choroid plexus couple to PLC activity, additional functional correlates remain to be established. Hitherto, at least 14 functional isoforms (and potentially many more) of the 5-HT_{2C} receptor have been identified; they were produced by adenine deaminase editing of the receptor mRNA (Burns et al., 1997; Fitzgerald et al., 1999; see also Section 7).

MK 212 and Ro 600175 represent moderately selective agonists, whilst amongst the antagonists, LY 53857, ZM 170809, ritanserin, mianserin and mesulergine have been utilised, but they are essentially nonselective (see Hoyer et al., 1994). Moreover, it has been suggested that the anxiogenic component of mCPP is mediated by 5-HT_{2C} receptor

activation, and selective 5-HT_{2C} receptor antagonists, such as SB 242084, display anxiolytic properties in various animal models (Kennett et al., 1997b). However, additional studies utilising selective agonists are required (e.g. Ro 600175, Dekeyne et al., 1999). Following treatment with agents such as mCPP and Ro 600175 additional characteristic behavioural responses, attributed to central 5-HT_{2C} receptor activation, include hypoactivity, hypophagia, increased penile grooming/erections and oral dyskinesia (see Kennett et al., 1994; Millan et al., 1997; Martin et al., 1998; Mehta et al., 2001; Vickers et al., 2001). 5-HT_{2C} receptor activation has been shown to exert a tonic, inhibitory influence upon frontocortical dopaminergic and adrenergic, but not serotonergic, transmission and, in part, to play a role in the neuroendocrine function (Millan et al., 1998; Jorgensen et al., 1999; see also Raap and Van de Kar, 1999). Consistent with its action as a 5-HT_{2C} receptor antagonist, RS 102221 increased food intake and weight gain in rats, yet, it failed to reverse the hypolocomotion induced by mCPP, possibly due to restricted brain penetration (Bonhaus et al., 1997). Moreover, the 5-HT_{2C} receptor KO mouse suffers from spontaneous convulsions, cognitive impairment, increased food intake and obesity, but similar effects are not reproduced by selective antagonists, suggesting that these changes may result from neuroadaptation. Nevertheless, the 5-HT_{2C} receptor is an attractive target for the discovery of novel treatment for feeding disorders (see Bickerdike et al., 1999).

5. The 5-HT_3 receptor class: an intrinsic ligand-gated channel

5-HT_3 receptors (M receptors of Gaddum and Picarelli, 1957) have been, based on their overall electrophysiological features and sequence, placed within the ligand-gated ion channel receptor superfamily, similar to the nicotinic acetylcholine or $GABA_A$ receptors (Boess and Martin, 1994). The receptors are found on neurones, of both central and peripheral origin, where they trigger rapid depolarisation due to a transient inward current, subsequent to the opening of nonselective cation channels (Na^+, Ca^{++} influx, K^+ efflux). The response desensitises and resensitises rapidly. The human homologue of the receptor was mapped to chromosome 11q23.1–q23.2 (see Weiss et al., 1995). However, the role of the 5-HT_3 receptor acting as a presynaptic modulator of neurotransmitter release, in the CNS, has recently been questioned (Van Hooft and Vijverberg, 2000).

5-HT_3 receptors are present in several brain regions, including the CA1 pyramidal cell layer in the hippocampus, the dorsal motor nucleus of the solitary tract and the area postrema (Laporte et al., 1992). In the periphery, they are located on pre- and postganglionic autonomic neurones and on neurones of the sensory nervous system. In addition to its pronounced effect on the cardiovascular system, 5-HT induces diverse effects, via 5-HT_3 receptor activation, throughout the GI tract regulating both motility and intestinal secretion (De Ponti and Tonini, 2001).

A cDNA clone encoding a single subunit of the 5-HT_{3A} receptor was isolated from a neuronally derived cell line (Maricq et al., 1991). Two splice variants were subsequently described in neuroblastoma–glioma cells (NCB-20, NG 108-15) and rat native tissues. These variants appear to possess similar distribution, pharmacological profiles and electrophysiological characteristics when expressed as homomers (see, for example, Hope et al., 1993; Miquel et al., 1995). The native receptor, as revealed by electron microscopy performed with neuroblastoma–glioma cells, is indeed a pentamer (Boess et al., 1995). 5-HT_3 receptor subtypes may exist, yet, it appears that species differences provide the basis of the pharmacological heterogeneity reported thus far. However, after extensive investigation, a second subunit, 5-HT_{3B}, has been cloned (Davies et al., 1999). It appears that the heteromeric combination of 5-HT_{3A} and 5-HT_{3B} subunits is necessary to provide the full functional features of the 5-HT_3 receptor; since either subunit alone results in receptors with very low conductance and response amplitude, as determined in electrophysiological experiments (Dubin et al., 1999; Hanna et al., 2000). Moreover, the 5-HT_3 receptor appears to be directly modulated by a divergent range of compounds, including alcohols, certain anaesthetic agents and divalent cations (however, the latter may represent receptor channel blockade). Nevertheless, this receptor, like other members of the ligand-gated ion channel receptor superfamily, possesses additional, pharmacologically distinct, recognition sites, whereby the function of the receptor can be allosterically modulated. The structural diversity of these agents suggests the presence of multiple modulatory sites on the 5-HT_3 receptor complex (Parker et al., 1996). Moreover, patent literature has recently reported the cloning of a third subunit, 5-ht_{3C}, but no additional details are presently available (Dubin et al., 2001).

5-HT_3 receptors are involved in chemotherapy- and radiotherapy-induced nausea and vomiting, which are treated with ondansetron, granisetron and tropisetron. Since 5-HT_3 receptor activation in the brain leads to dopamine release and 5-HT_3 receptor antagonists produce central effects comparable to those of antipsychotics and anxiolytics, schizophrenia and anxiety were considered, at that time, as potential indications. 5-HT_3 receptor antagonists have also been reported to induce cognition enhancing effects in rats, suggesting utility as memory-enhancing agents. However, to date, there are no clinical data to substantiate such activities. Similarly, the hypothesis that 5-HT_3 antagonists may prove useful in the treatment of migraine did not materialise in clinical studies, suggesting that in these cases, animal models have their limitations. More recently, alosetron was developed for the treatment of women suffering from IBS with diarrhoea, but it had to be withdrawn (for the time being) due to safety reasons (De Ponti and Tonini, 2001).

6. Receptors positively coupled to adenylate cyclase: 5-$HT_{4,6,7}$ receptors

Although the 5-HT_4, 5-ht_6 and 5-HT_7 receptors all couple preferentially to G_s and promote cAMP formation, they are classified as distinct receptor classes because of their limited (<35%) overall sequence identities (Table 1). This subdivision is recognised as arbitrary and may be subject to future modification. However, the sequence dissimilarity justifies classification into different groups. Although the common approach has been to perform analogy cloning, based on known sequences (e.g. 5-ht_6 and 5-HT_7 receptors, which also couple positively to cAMP production, were known for some time), this approach was unsuccessful for the cloning of the 5-HT_4 receptor, which explains the additional time taken for its structural characterisation.

6.1. 5-HT_4 receptors

Prior to the cloning of the 5-HT_4 receptor (Gerald et al., 1995), the existence of the endogenous receptor had been widely recognised in both central and peripheral tissues, although there has been, on occasion, confusion between 5-HT_3 and 5-HT_4 receptors (Hoyer, 1990). 5-HT_4 receptors were initially characterised in the late eighties by Bockaert and colleagues (1992) using mouse and guinea pig brain, although its existence was speculated in rat neonatal colliculi 20 years ago (see Clarke et al., 1989). Thus, substituted benzamide derivatives like cisapride, renzapride or zacopride, acted as agonists at the 'atypical' 5-HT receptor in mouse colliculi. Interestingly, the potent 5-HT_3 receptor antagonist tropisetron (ICS 205–930) was described as the first competitive 5-HT_4 receptor antagonist. The human 5-HT_4 receptor was mapped to chromosome 5q31–33 (Claeysen et al., 1997). Hitherto, multiple human 5-HT_4 receptor isoforms have been described. Seven C-terminal splice variants of the receptor have been identified (5-HT_{4A-H}; Blondel et al., 1997, 1998; Claeysen et al., 1997, 1999; Van den Wyngaert et al., 1997; Mialet et al., 2000a,b). Moreover, a novel splice variant, 5-HT_{4HB}, with a 14-amino acid insertion in the second extracellular loop has recently been published (Bender et al., 2000); additional splice variants are anticipated.

These receptor variants couple positively to adenylate cyclase, and available data show that the pharmacology of the variants is similar. However, one important feature of the receptor is the level of constitutive activity, which is expressed at rather low receptor levels. This feature may well explain differences that have been observed with respect to variable intrinsic activity of a number of ligands, depending on tissue and/or species. Tissue distribution studies demonstrate specificity in the pattern of expression of the human 5-HT_4 receptor isoforms. Moreover, the h5-HT_{4D} receptor isoform appears to be unique, because in contrast to the other isoforms, it has not been described in any other species yet (Mialet et al., 2000b). Its expression appears to be restricted to the gut (Blondel et al., 1998), whereas the other isoforms are expressed in cardiac atria and brain (Blondel et al., 1998; Mialet et al., 2000a). In addition to adenylate cyclase stimulation, direct coupling to potassium channels and voltage-sensitive calcium channel have been proposed as postreceptor events.

The receptor can be labelled with [^{3}H]GR 113808, [^{3}H]RS 57639 and [^{125}I]SB 207710. In the brain, the distribution of receptor mRNA is similar to the distribution of radioligand-binding sites. RT–PCR studies have also demonstrated that 5-HT_4 receptor mRNA is present in vascular smooth muscle (Ullmer et al., 1995), as already indicated by functional studies (see Martin and Humphrey, 1994). 5-HT_4 receptor activation triggers acetylcholine release in the guinea pig ileum and contracts the oesophagus and colon. In addition to its modulator function on GI motility, the 5-HT_4 receptor is also involved in mediating secretory responses to 5-HT in intestinal mucosa. Electrogenic ion transport is stimulated through 5-HT_4 receptors in the small intestine, whilst in the piglet heart, the receptors mediate tachycardia (right atria) and positive inotropic effects (left atria). Similarly, isolated human atrial appendages respond with increased contractile force to 5-HT_4 receptor agonists. 5-HT_4 receptors in the CNS appear to modulate neurotransmitter (acetylcholine, dopamine, serotonin and GABA) release and enhance synaptic transmission, and they may also play a role in memory enhancement; however, positive clinical studies are still eagerly awaited (Barnes and Barnes, 1998). Exposure of the receptor to agonists results in desensitisation in many experimental in vitro models, which, in tissue preparations of the alimentary tract, is readily reversible upon agonist removal.

Several potent and selective 5-HT_4 receptor ligands are now available, such as the agonists BIMU 8, RS 67506 and ML 10302 (Eglen, 1997) and the antagonists GR 113808, SB 204070, SB 203186, RS 23597-190 and RS 39604 (Bonhaus et al., 1994; Clark, 1998), which should allow definition of the (patho)physiological role of this receptor. Selective 5-HT_4 receptor ligands have been proposed to possess putative therapeutic utility in a number of disorders, including cardiac arrhythmia (Kaumann and Sanders, 1994; Rahme et al., 1999), neuro-degenerative diseases (Reynolds et al., 1995; Wong et al., 1996) and urinary incontinence (Boyd and Rohan, 1994; Hegde and Eglen, 1996). Cisapride, a gastroprokinetic agent, acts as an agonist at the 5-HT_4 receptor, whilst a new generation 5-HT_4 receptor partial agonist, tegaserod (HTF-919), is currently prescribed for constipation predominant IBS (Buchheit et al., 1995; Norman, 2000). Furthermore, its therapeutic activity in functional motility disorders of the upper GI tract is currently under clinical investigation (Camilleri, 2001).

6.2. 5-ht_6 Receptors

The 5-ht_6 receptor has been cloned from rat cDNA based on its homology to previously cloned GPCRs. The rat

receptor has 438 amino acids and is positively coupled to adenylyl cyclase via G_s. The human gene has been cloned, demonstrating 89% sequence homology with its rat equivalent, and mapped to human chromosome region 1p35–p36 (Kohen et al., 1996). Circumstantial evidence suggests the putative 5-ht_6 receptor to be expressed endogenously in neuronal tissue. The rat and human 5-ht_6 receptor mRNA is located in the striatum, amygdala, nucleus accumbens, hippocampus, cortex and olfactory tubercle, but it has not been found in peripheral organs.

The recombinant receptor promotes intracellular accumulation of cAMP, and a receptor with similar operational characteristics is found in mouse neuroblastoma N18TG2 cells, as determined in cAMP formation and binding studies using [^{125}I]LSD. In addition, NCB 20 cells (Conner and Mansour, 1990) and rat striatal neurones in culture (Sebben et al., 1994) express a receptor that couples positively to adenylyl cyclase and displays an operational profile consistent with the recombinant 5-ht_6 receptor. Perhaps more relevant to a potential physiological role, evidence for the putative 5-ht_6 receptor has been obtained in homogenates of the pig caudate nucleus. Whereby, cAMP accumulation was stimulated by agonists with a rank order of potency compatible with a 5-ht_6 receptor profile. The effects were adequately antagonised by clozapine and methiothepin. [^{3}H]Clozapine binds with nanomolar affinity to two distinct sites in the rat brain; one site displays the operational profile of the recombinant 5-ht_6 receptor.

Selective ligands are now becoming available for the 5-ht_6 receptor. The site can be labelled with [^{125}I]SB 258585 (Hirst et al., 2000). Moreover, Bromidge et al., (1999) reported SB 271046 as a potent, selective and bioavailable 5-ht_6 receptor antagonist (see also Routledge et al., 2000; Bos et al., 2001; Bromidge et al., 2001 (SB 357134)), whilst Glennon et al. (2000) have recently described the identification of EMDT, a selective 5-ht_6 receptor agonist.

5-ht_6 Receptor antisense oligonucleotides have been used to determine possible physiological functions in the rat (Bourson et al., 1995). Repeated intracerebroventricular injections gave rise to a specific behavioural syndrome of yawning, stretching and chewing and caused a 30% reduction in the number of [^{3}H]LSD binding sites (measured in the presence of 300 nM spiperone). Interestingly, the antisense-induced behavioural syndrome can be dose-dependently antagonised by atropine, implying a modulatory role for 5-ht_6 receptors on cholinergic neurones. Similarly, the selective 5-ht_6 receptor antagonist, Ro 04-6790, produces a behavioural syndrome involving an increase in acetylcholine neurotransmission (Bourson et al., 1995; Sleight et al., 1998). Moreover, enhanced retention of spatial learning following both antisense oligonucleotides and Ro 04-6790 has been reported (Woolley et al., 2001; Meneses, 2001). These studies indicate a potential role for the 5-ht_6 receptor in the control of central cholinergic function, and thus a putative target for the treatment of cholinergic defects in cognitive dysfunction such as Alzheimer's Disease. In addition, antisense oligonucleotide treatment reduced both food consumption and body weight; the later effect was also seen following Ro 04-6790, suggesting a putative role for the 5-ht_6 receptor in the regulation of feeding.

In pharmacological studies, several antipsychotic agents (notably clozapine, olanzapine, fluperlapine and seroquel) and antidepressants (clomipramine, amitryptyline, doxepin and nortryptyline) have high affinity and act as antagonists at 5-ht_6 receptors. This attribute tempted speculation of a potential involvement of the 5-ht_6 receptor in the pathogenesis of psychiatric disorders. Furthermore, polymorphisms in the 5′-upstream region of the human 5-ht_6 receptor gene have been identified. However, case-control association studies could not demonstrate any difference in genotype, or allele frequency, between controls and schizophrenic patients. The results suggest that 5-ht_6 receptor gene polymorphism does not confer increased susceptibility to schizophrenia (Ohmori et al., 2001). However, chlorpromazine-resistant patients, presenting the aforementioned polymorphism, demonstrated significantly improved responses to clozapine, suggesting that the 5-ht_6 genotype may help predict patient responses. The role of 5-ht_6 receptors has been recently reviewed by Branchek and Blackburn (2000).

6.3. 5-HT$_7$ receptors

The 5-HT_7 receptor has been cloned from the rat, mouse, guinea pig and human cDNA and is located on human chromosome 10q23.3–q24.4. Despite demonstrating high interspecies homology (>90%; To et al., 1995), the receptor shares a low homology with other members of the 5-HT receptor family (<50%). The human receptor has 445 amino acids and was shown to positively modulate cAMP formation via G_s (Bard et al., 1993; Lovenberg et al., 1993; Adham et al., 1998), most likely acting via calmodulin-stimulated adenylate cyclase (Baker et al., 1998). The receptor also activates the mitogen-activated protein kinase, ERK, in primary neuronal cultures (Errico et al., 2001). The cDNA encoding the receptor contains two introns; one located in the second intracellular loop (Bard et al., 1993; Shen et al., 1993) and the second in the predicted intracellular carboxyl terminal (Ruat et al., 1993). Alternate splicing of this latter intron has been reported to generate four 5-HT_7 receptor isoforms (5-HT_{7A-D}), which differ in their C-termini (Heidmann et al., 1997). However, these isoforms, to date, have not been shown to differ in their respective pharmacology, signal transduction or tissue distribution (Jasper et al., 1997; Heidmann et al., 1998). Conversely, the pharmacological profile of the receptor is characterised by a high affinity for the prototypical 5-HT_1 agonists 5-CT, 5-MeOT and 8-OH-DPAT, the $5HT_2$ receptor ligand LSD and the antagonists, ritanserin, metergoline, methysergide and mesulergine. Indeed, operational

studies have confirmed that the 5-HT_7 receptor has an extensive vascular distribution and is responsible for the prominent, persistent vasodilator response to 5-HT in anaesthetised animals (see Martin and Humphrey, 1994). Moreover, the receptors are expressed in nonvascular smooth muscle (Ullmer et al., 1995; Carter et al., 1995) and the CNS.

Thus, To et al. (1995) used [^{3}H]-5-CT, in the presence of (−)-cyanopindolol and sumatriptan to demonstrate the presence of 5-HT_7 recognition sites in guinea pig cerebral cortex membranes. Subsequent autoradiographic analysis revealed a discrete localisation of binding sites in the medial thalamic nuclei and related limbic and cortical regions of the guinea pig brain, with more moderate binding densities in the sensory relay nuclei, substantia nigra, hypothalamus, central grey and dorsal raphe nuclei. This distribution corresponds to that observed for 5-HT_7 receptor mRNA. Essentially, similar results have been obtained from studies using rat brain (Gustafson et al., 1996). Further, evidence for a central functional role of 5-HT_7 receptors has been obtained. Using whole-cell voltage clamping, in postnatal rat suprachiasmatic (SCN) neurones, Kawahara et al. (1994) have shown that a γ-aminobutyric acid activated current (I_{GABA}) is reversibly inhibited by 5-HT. Operational data obtained by the authors' point towards an involvement of the 5-HT_7 receptor, consistent with the predicted presence of these receptors in the SCN from the early studies of Lovenberg et al. (1993). Moreover, the cellular localisation of rat hypothalamic 5-HT_7 receptors was suggested to be postsynaptic, with respect to serotonergic neurones, and regulated by altered synaptic levels of endogenous neurotransmitter (Clemett et al., 1999). However, evidence to establish a 5-HT autoreceptor role for 5-HT_7 receptors were not forthcoming (Roberts et al., 2001). Additional investigation with selective 5-HT_7 receptor agonists is required to confirm these data.

The distribution of 5-HT_7 binding sites in the limbic system and thalamocortical regions suggests a possible role in the pathophysiology of affective disorders. Further, support of this hypothesis stems from the observation that atypical antipsychotics, e.g. clozapine, risperidone and antidepressants, have high affinity for the 5-HT_7 receptor (Roth et al., 1994). Furthermore, a down-regulation of 5-HT_7 receptors occurs after chronic antidepressant treatment (Sleight et al., 1995; Mullins et al., 1999), whilst acute, but not chronic, stress has been demonstrated to regulate 5-HT_7 receptor mRNA expression (Yau et al., 2001).

Currently, a number of ligands have been reported, which will allow further characterisation of these receptors in native tissues and in vivo, particularly, the antagonists SB 258719 and SB 269970 (Thomas et al., 1998a; Hagan et al., 2000). Indeed, a role for the 5-HT_7 receptor has been proposed in the regulation of 5-CT-induced hypothermia in guinea pigs as the response was blocked by both SB 269970 and the nonselective 5-HT_7 receptor antagonist, metergoline. Moreover, when administered at the start of the sleep period, SB 269970 significantly reduced time spent in paradoxical sleep during the first 3 h of EEG recording in conscious rats (Hagan et al., 2000). Furthermore, [^{3}H]SB 269970 can be used as a selective radioligand for 5-HT_7 receptors (Lovell et al., 2000; Thomas et al., 2000). Finally, it is now clear that this receptor is the orphan receptor originally described as the '5-HT_1-like' receptor mediating relaxation of the guinea pig isolated ileum and cat saphenous vein (Feniuk et al., 1983); subsequently, it was shown to mediate elevation of cAMP and relaxation in neonatal porcine vena cava (Trevethick et al., 1986).

7. Orphan receptors: the putative 5-ht_5 receptors

To date, no evidence has been obtained to confirm that the recombinant 5-ht_5 receptor is expressed in an endogenous setting. Two subtypes of the 5-ht_5 receptor (5-ht_{5A} and 5-ht_{5B}), sharing 70% overall sequence identity, have been found in rodents, whereas the 5-ht_{5A} subtype has been found in humans and mapped to chromosome 7q36.1 (Erlander et al., 1993; Matthes et al., 1993; Schanen et al., 1996; Grailhe et al., 2001). The 5-ht_{5B} receptor gene has been mapped to human chromosome 2q11–q13; however, it has been shown that the gene failed to encode a functional protein due to the presence of stop codons in its coding sequence (Matthes et al., 1993; Grailhe et al., 2001). There have been no published reports concerning a physiological functional response, and specific binding to a 5-ht_5 recognition site has not been described. However, the receptor transduction mechanism has been suggested by Carson et al. (1996). The authors reported that in the rat, the recombinant 5-ht_{5A} receptor may be negatively coupled to adenylate cyclase activity and predominantly expressed in astrocytes, as suggested by the use of receptor-specific antisera. In confirmation, when transfected into C6 glioma cells, HEK 293 and Sf9 cells, human recombinant 5-ht_{5A} receptor activation produced an inhibition of forskolin-stimulated cAMP production, indicating negative coupling to cAMP via G_i and G_o (Francken et al., 1998, 2000); however, the receptor may also couple positively to cAMP. Moreover, when expressed in *Xenopus* oocytes, the human 5-ht_{5A} receptor was demonstrated to couple to the inwardly rectifying K^+ channel, $GIRK_1$ (Grailhe et al., 2001).

Labelled structures included hypothalamus, hippocampus, corpus callosum, fimbria, cerebral ventricles and glia. The morphology and distribution of the cells labelled with antiserum were consistent with those of astrocytes (codistribution with GFAP was prominent), except in the olfactory bulb and cortex where low levels were associated with neurones. These observations are supported by RT–PCR performed with cortical glial cells in culture, which suggests marked expression of 5-ht_{5A} receptor cDNA. It was also noticed that receptor levels might be increased in

reactive gliosis. Moreover, a putative role for 5-ht_{5A} receptors in the acquisition of adapted behaviour under stressful situations has been postulated (see Branchek and Zgombick, 1997).

8. Other putative orphan 5-HT receptors

A number of endogenous 5-HT receptors have been identified and defined in terms of recognitory and/or transductional characteristics, but a corresponding gene product encoding the receptor has yet to be identified. In the absence of structural information enabling unequivocal classification, these receptors are regarded as orphans of the present classification scheme. One of these, the so-called '5-HT_1-like' receptor mediating direct vasorelaxation has been shown to correspond to the 5-HT_7 receptor (see above). However, the situation with the remaining orphan receptors (see Hoyer et al., 1994) has not evolved further and, thus, the status quo ante remains. In particular, no progress has been made with the 5-HT_{1P} receptor, which is present in the gut and whose pharmacology is reminiscent of the 5-HT_4 receptors, with the restriction that some of the ligands described, like the 5-HT dipeptides, do not affect 5-HT_4 receptors (Gershon, 1999). In addition, a high-affinity binding site for [^{3}H]-5-HT with novel '5-HT_1-like' pharmacology has been reported in the mammalian brain (Castro et al., 1997), but it has yet to be sufficiently characterised for inclusion in the 5-HT_1 receptor family.

9. Modulation of 5-HT receptor function by endogenous ligands, dimerisation and expression by RNA editing

9.1. 5-HT_{2C} receptor RNA editing

The 5-HT_{2C} receptor is the only GPCR reported so far to be subjected to RNA editing (Burns et al., 1997; Fitzgerald et al., 1999). Deamination of one or more adenine bases present at five specific sites in the receptor pre-mRNA, results in conversion of the edited bases to inosine. Upon translation of the mature mRNA, these inosine bases are read as guanine, resulting in an alteration of the amino acids present in the second intracellular loop and the formation of distinct receptor isoforms. RNA editing may alter coupling energetics within the ternary complex, thereby altering agonist-binding affinities, G-protein coupling and functional responses. Moreover, editing results in a systematic reduction in coupling efficiency to the PLC signalling cascade and a loss of constitutive activity (Herrick-Davis et al., 1999). Recombinant human 5-HT_{2C} receptor isoforms display differential binding affinities for agonists, depending on whether the ligands prefer to bind to either the coupled or uncoupled form of the receptor; whereas antagonists appear unaffected (Niswender et al., 1999). Tissue (choroid plexus versus other brain regions)- and species-specific differences in 5-HT_{2C} mRNA editing have been documented, and it is conceivable that this process represents a novel mechanism for achieving phenotypic specificity of signalling for 5-HT_{2C} receptor-mediated events. It has been proposed that editing alterations of the 5-HT_{2C} receptor may play a role in the incidence of suicide (Niswender et al., 2001).

9.2. Modulation of receptors by endogenous lipids: oleamide

Oleamide, an unsaturated fatty acid amide that accumulates in the CSF of animals during sleep deprivation, induces EEG measured sleep; however, the mechanism of this hypnotic action is unclear. Such activity may derive from enhancements of GABA or 5-HT receptor function, or alternatively from changes in the catabolism or uptake of related fatty acid amides (see Boger et al., 2000; Nicholson et al., 2001). Opposing effects of oleamide on 5-$HT_{2A/2C}$ and 5-HT_7 receptor function have been reported (see Thomas et al., 1997; Hedlund et al., 1999). The compound acts as an endogenous allosteric modulator, which promotes IP_3 production, via 5-HT_2 receptors, whereas cAMP production, via 5-HT_7 receptors, is negatively modulated (Thomas et al., 1998b). Moreover, it has been shown that oleamide can elicit dramatic increases in c-*fos* mRNA and Fos protein in distinct brain regions. Thomas et al. (1999) demonstrated that in the thalamus and hypothalamus, the majority of neurones induced for c-*fos* expression also expressed the 5-HT_7 receptor, suggesting that alterations in transcription may account for its physiological effects. Furthermore, additional endogenous candidates of lipidic nature have been found, which may affect the 5-HT receptor function.

9.3. Effects of 5-HT moduline on 5-HT_{1B} and 5-HT_{1D} receptors

5-HT moduline is an endogenous tetrapeptide (LSAL) that may be produced from a chromogranin, which selectively and allosterically interacts to reduce both 5-HT_{1B} and 5-HT_{1D} receptor activity (Massot et al., 1996). 5-HT-moduline binds at a site distinct from that bound by 5-HT. Moreover, since 5-HT_{1B} receptors are important in mediating presynaptic autoinhibition of 5-HT, the role of 5-HT moduline was anticipated to be augmentation of 5-HT release, which has recently been demonstrated in the rat prefrontal cortex (Ohashi et al., 2001). Similar effects are seen on immunocompetent cells in which the proliferative effects of 5-HT_{1B} receptor activation are inhibited, suggesting an immunomodulatory role for 5-HT moduline (Sibella-Arguelles, 2001). Moreover, 5-HT moduline release is increased following acute restraint stress in rats, whilst deactivation of 5-HT moduline, by specific antibodies in mice, significantly modified their behaviour in both the

open field and elevated plus maze, consistent with an anxiolytic effect of the antibody and suggesting a potential physiological role in the control of anxiety (Bonnin et al., 1999; Grimaldi et al., 1999).

Thus, the fact that 5-HT-moduline increases 5-HT release suggests that synthetic agents capable of recognising the 5-HT-moduline binding site and mimicking the effect of the peptide may represent novel antidepressant or anxiolytic agents (Fillion, 2000; Bourin and Hascoet, 2001). Furthermore, it is interesting that the peptide interacts with two of the few 5-HT receptors, which, so far, have been shown to be subjected to homo- and heterodimerisation (see also Fillion et al., 1996; Massot et al., 1996; Cloez-Tayarani et al., 1997, 1998; Grimaldi et al., 1997; Bentue-Ferrer et al., 1998).

9.4. Receptor dimerisation: 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors

That an endogenous modulator is produced, which negatively regulates a heptahelical receptor, may be surprising; however, the recent discovery that both 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors are capable of forming homodimers when expressed alone, and heterodimers when expressed together, like an increasing number of other GPCRs, intuitively seems to make sense (Xie et al., 1999). These findings are interesting, since it has proven difficult to identify a 5-HT$_{1D}$ receptor-mediated effect, whereas most effects have been attributed to 5-HT$_{1B}$ receptors. This is more apparent in rodents where the two receptors show differences in pharmacological profile, in contrast to what is seen in higher species, i.e. an almost indistinguishable pharmacology, using the majority of commercially available ligands, with the exception of very recent new additions, which have obviously not yet been utilised extensively. If one considers that 5-HT$_{1D}$ receptors do, in most cases, cosegregate with 5-HT$_{1B}$ receptors, does heterodimerisation result in 5-HT$_{1B}$ pharmacology? Such a scenario has been reported for GABA$_{B1}$ and GABA$_{B2}$ receptors; whereby when these two GPCRs heterodimerise, they express exquisite GABA$_{B1}$ pharmacology, otherwise, they are not functional. Moreover, similar data have been reported for opiate receptors (see George et al., 2000). Therefore, one may not expect to find many functional responses that have 5-HT$_{1D}$ receptor pharmacology, since there are only very few tissues where this receptor may be expressed in the absence of the 5-HT$_{1B}$ receptor. Still more surprising may be the finding that 5-HT and dopamine receptors may heterodimerise (Lee et al., 2000).

10. Conclusion

The challenge for the next decade of 5-HT research is to define to what extent the almost incredible diversity in receptors and transporters fulfils specific physiological and/or pathophysiological roles. Since the molecular tools are now in place, it may soon be possible to determine which form of a given receptor is expressed in a given tissue of interest, leading to a better understanding of its effects in situ, rather than relying on measurements made with recombinant receptors. This may therefore assist in designing drugs with an adequate profile at the target organ, assuming that this is known, and could consequently be confirmed in human tissues. However, the diversity in receptors described herein suggests that under both physiological and, presumably even more so, under pathological conditions, the status of the receptors may vary dramatically from one subject to another. This may even be the basis for differences in responder rates to a given treatment. Obviously, such a phenomenon may not be restricted to 5-HT receptors. It is clear that receptor crosstalk, which is rather common amongst 5-HT and other receptors, will considerably affect the responsiveness of one patient versus another. For example, vascular reactivity towards triptans may vary significantly between patients, depending on the manner by which 5-HT$_{1B}$ receptors may have been 'primed' by other receptors. Similarly, depending on the nature of the receptor isoforms (5-HT$_4$, 5-HT$_7$ or 5-HT$_{2C}$) expressed in the GI tract/vessel/brain, it could be anticipated that certain patients may demonstrate enhanced responsivity to particular treatments, i.e. titration may represent a rule rather than an exception. Finally, since the human genome has been cloned, one may anticipate knowing whether there are more receptors for the 5-HT receptor family, assuming that we know how to deal with orphan receptors. However, given the interactions with accessory proteins, in addition to homo- and heterodimerisation, one can easily envisage that the situation will not prove any simpler 10 years from now.

Chemical names

5-CT: 5-carboxamidotryptamine
8-OH-DPAT: 8-hydroxy-2-(di-*n*-propylamino)tetralin
BIMU 8: (endo-*N*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-isopropyl-2-oxo-1*H*-benzimidazol-1-carboxamide hydrochloride
BRL 15572: 3-[4-(3-chlorophenyl) piperazin-1-yl]-1,1,-diphenyl-2-propanol
BRL 54443: 3-(1-methylpiperidin-4-yl)1*H*-indol-5-ol
BW 311C90: (*S*)-4-[[3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-2-oxazolidinone
BW 723C86: 1-[5(2-thienylmethoxy)-1*H*-3-indolyl]propan-2-amine hydrochloride
CP 93129: 5*H*-Pyrrolo[3,2-*b*]pyridin-5-one, 1,4-dihydro-3-(1,2,3,6-tetrahydro-4-pyridinyl)
DOB: 2,5-dimethoxy-4-bromoamphetamine
DOI: 2,5-dimethoxy-4-iodoamphetamine
EMDT: 2-ethyl-5-methoxy-*N*,*N*-dimethyltryptamine
GR 113808: [1-2[(methylsuphonyl)amino]ethyl]-4-piperidinyl]methyl-1-methyl-1*H*-indole-3-carboxylate

GR 125743: *n*-[4-methoxy-3-(4-methyl-1-piperizinyl)phenyl]-3-methyl-4-(4-pyrindinyl)benzamide
GR 46611: 2-Propenamide, 3-[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]-*N*-[(4-methoxyphenyl)methyl]
GR 55562: 3-[3-(dimethylamino)propyl]-4-hydroxy-*N*-[4-(4-pyridinyl)phenyl]benzamide
GR 65630: 3-(5-methyl-1*H*-imidazol-4-yl)-1-(1-methyl-1*H*-indol-3-yl)-1-propanone
GTI: 5-hydroxytryptamine-5-*O*-carboxymethylglycyltyrosinamide
HTF 919: Hydrazinecarboximidamide, 2-[(5-methoxy-1*H*-indol-3-yl)methylene]-*N*-pentyl-, (*Z*)-2-butenedioate
L 694247: 2-[5-[3-(4-methylsulphonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1*H*-indol-3yl] ethanamine
LY 278584: 1-methyl-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-indazole-3-carboxamide
LY 334370: 5-(4-flurobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1*H*-indole fumarate
LY 344864: *N*-[(3*R*)-3-(dimethylamino)-2,3,4,9-tetrahydro-1*H*-carbazol-6-yl]-4-fluoro-benzamide
LY 53857: Ergoline-8-carboxylic acid, 6-methyl-1-(1-methylethyl)-, 2-hydroxy-1-methylpropyl ester, (8*b*)-, (2*Z*)-2-butenedioate
mCPP: 2-(2-methyl-4-chlorophenoxy)propanoic acid
MDL 100907: (±)2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol]
MDL 72832: 8-[4-[[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino]butyl]
MK 212: 4-(6-chloro-2-pyrazinyl)piperazine
MK 462: 1*H*-Indole-3-ethanamine, *N*,*N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)
ML 10302: 2-(1-piperidinyl)ethyl-4-amino-5-chloro-2-methoxybenzoate
NAD 299: 2*H*-1-benzopyran-5-carboxamide
PNU 109291: (*S*)-3,4-dihydro-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-methyl-1*H*-2-benzopyran-6-carboximide
Ro 04-6790: 4-amino-*N*-[2,6-bis(methylamino)-4-pyrimidinyl]-benzenesulfonamide
Ro 600175: (*S*)-2-(6-chloro-5-fluroindol-1-yl)-1-methyethylamine
Ro 630563: 4-amino-*N*-[2,6-bis(methylamino)pyridin-4-yl]-benzenesulphonamide
RS 100235: 1-(8-amino-7-chloro-1,4-benzodioxan-5-yl)-5-((3-(3,4-dimethoxyphenyl)prop-1-yl)piperidin-4-yl)-propan-1-one
RS 102221: 8-[5-(5-amino 2,4-dimethoxyphenyl) 5-oxopentyl]-1,3,8-triazaspiro[4,5]decane-2,4-dione
RS 127445: 2-Amino-4-(4-fluoronaphth-1-yl)-6-isopropylpyrimidine
RS 23597-190: Benzoic acid, 4-amino-5-chloro-2-methoxy-, 3-(1-piperidinyl)propyl ester, monohydrochloride
RS 39604: Methanesulfonamide, *N*-[2-[4-[3-[4-amino-5-chloro-2-[(3,5-dimethoxyphenyl)methoxy]phenyl]-3-oxopropyl]-1-piperidinyl]ethyl]-, monohydrochloride
RS 57639: 4-amino-5-chloro-2-methoxy benzoic acid 1-(3-[2,3-dihydrobenzo[1,4]dioxin-6yl)-propyl]-piperidin-4yl methyl ester
RS 67506: 1-(4-amino-5-chloro-2-methoxyphenyl)-3-(1-*n*-butyl-4-piperidinyl)-1-propanone
RU 24969: 1*H*-Indole, 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-butanedioate
SB 200646: *N*-(1-methyl-5-indonyl)-*N*′-(3-pyridyl) urea hydrochloride
SB 203186: 1*H*-Indole-3-carboxylic acid, 2-(1-piperidinyl)ethyl ester
SB 204070: 1-butyl-4-piperidinylmethyl-8-amino-7-chloro-1-4-benzoioxan-5-carboxylate
SB 204741: *N*-(1-methyl-5-indoylyl)-*N*′-(3-methyl-5-isothiazolyl)urea
SB 206553: (5-methyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole)
SB 207710: 1-butyl-4-piperidinylmethyl-8-amino-7-iodo-1,4-benzodioxan-5-carboxylate
SB 216641: [1,1′-Biphenyl]-4-carboxamide, *N*-[3-[2-(dimethylamino)ethoxy]-4-methoxyphenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)
SB 224289: 1′-methyl-5[[2′-methyl-4′-)5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]carbonyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4′-piperidine]oxalate
SB 236057: 1′-ethyl-5-(2′-methyl-4′-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indol3-3,4′-piperidine
SB 242084: 6-chloro-5-methyl-1-[2-(2-methylpyridyl-3-oxy)-pyrid-5-yl carbamoyl] indoline
SB 258585: 4-iodo-*N*-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-benzenesulphonamide
SB 258719: (*R*)-3,*N*-dimethyl-*N*-[1-methyl-3-(4-methylpiperidin-1-yl)propyl]benzene sulphonamide
SB 269970: (*R*)-3-(2-(2-(4-methylpiperidin-1-yl)ethyl)pyrrolidine-1-sulphonyl)phenol
SB 271046: 5-chloro-*N*-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulphonamide
SB 272183: 1*H*-Indole-1-carboxamide, 5-chloro-2,3-dihydro-6-(4-methyl-1-piperazinyl)-*N*-[4-(4-pyridinyl)-1-naphthalenyl]
SB 357134: *N*-(2,5-dibromo-3-flurophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulphonamide
SDZ 21009: 1*H*-Indole-2-carboxylic acid, 4-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-, 1-methylethyl ester
SKF 99101H: 1*H*-Indole-3-ethanamine, 4-chloro-*N*,*N*-dimethyl-5-propoxy-, (*E*)-2-butenedioate
SR 57227: 4-amino-(6-chloro-2-pyridyl)-1-piperidine hydrochloride
U 92016A: 3*H*-benz[*e*]indole-2-carbonitrile, 8-(dipropylamino)-6,7,8,9-tetrahydro-, monohydrochloride
UH 301: 1-naphthalenol, 7-(dipropylamino)-4-fluoro-5,6,7,8-tetrahydro-, hydrobromide
WAY 100635: *N*-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-*N*-(2-pyridyl)-cyclohexanecarboxamide trichloride

ZM 170809: 2-Propanamine, *N*,*N*,2-trimethyl-1-[(3-phenyl-2-quinolinyl)thio]-monohydrochloride

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