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Serotonin receptors and systems: endless diversity?

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ABSTRACT Serotonin 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 a ligand-gated ion channel family (5-HT_3). These receptors are divided into seven distinct classes (5-HT_1 to 5-HT_7) largely on the basis of their structural, transductional and operational characteristics. While this degree of physical diversity clearly underscores the physiological importance of serotonin, evidence for an even greater degree of operational diversity continues to emerge. Here, we will review this diversity and its physiological and possibly pathophysiological consequences. Indeed, 5-HT research which is about 50 years old, has resulted in numerous therapeutic agents, some of which have a major impact on disease management. Thus, selective 5-HT reuptake inhibitors (SSRIs) are among the most widely used drugs in depression and other disorders such as anxiety, social phobia, panic disorders, or obsessive compulsive disorders (OCDs) to name a few. The discovery of 5-$HT_{1B/1D}$ receptor agonists (the triptans) for treating migraine, 5-HT_3 receptor antagonists for chemotherapy and radiation-induced emesis, and finally the emergence of 5-HT_3/ 5-HT_4 ligands to treat irritable bowel syndrome (IBS), all represent major advances in the field. Finally, the role of 5-HT in the mechanism of action of antipsychotic agents still is a topic of intense research, which promises better treatments for schizophrenia.
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Serotonin (5-hydroxytryptamine; 5-HT) produces its effects through a variety of membrane-bound receptors both in the central and peripheral nervous system (CNS/PNS) as well as in a number of non-neuronal tissues (e.g. gut, cardiovascular system and blood). The main source of 5-HT is in the gut, more precisely enterochromaffin cells, where it is synthesised from tryptophan. It can be released into the gut lumen e.g. as a reaction to pressure and act on receptors located on the smooth muscle, or into the portal blood circulation, by a variety of nervous or alimentary stimuli. 5-HT is also found in enteric neurones. In the blood, the vast majority of 5-HT is not free, but to be found in the platelets, which are endowed with a very active uptake system (they do probably not synthesise 5-HT) and 5-HT is stored in storage granules. Large amounts of 5-HT are released during platelet aggregation, and it can act locally on endothelial cells and vascular smooth muscle. 5-HT is also found in mast cells. In the central and peripheral nervous system, 5-HT acts as a neurotransmitter on a large variety of receptors, which may be located pre or post synaptically. 5-HT is also found in the pineal gland, where it is believed to serve essentially as a precursor for the synthesis of melatonin by 5-HT-N-acetyltransferase and hydroxyindole-O-methyltransferase, under the control of the clock in the suprachiasmatic nucleus which during the circadian rhythm modulates enzyme activity levels up to 50 fold.

The serotoninergic system is one of the oldest neurotransmitter/hormone systems in evolution, which may explain why 5-HT interacts with such a diversity of receptors of the G protein coupled family and the ligand gated family, similarly to acetylcholine, GABA or glutamate. 5-HT was discovered in the gut in the 1930s and called enteramine, then rediscovered in the 1940s in the blood and called serotonin, as it had vasoconstrictor features. 5-HT is synthesised from L-tryptophan, the tryptophan hydroxylase forming 5-hydroxytrytophan (5-HTP), which by the L amino acid decarboxylase leads to 5-HT; serotonin can be conjugated with glucuronide or sulfate or in nerves metabolised via monoamine oxydase to 5-hydroxyindolacetaldehyde and finally to 5-hydroxyindolacetic acid (via aldehydedehydrogenase). It can also lead to 5-hydroxytryptophol by an aldehyde-reductase in some peripheral nerves. Thus, 5-HT acts both as a neurotransmitter with all the features, such as intracellular storage, activity dependent release, the existence of both pre- and postsynaptic receptors, an active uptake system, via the serotonin transporter and metabolising/inactivating enzymes and a hormone, released into the blood or gut to work more distantly.

With the exception of 5-HT_3 receptors (ligand-gated ion channels), 5-HT receptors belong to the G protein-coupled receptor (GPCR) superfamily and, with at least fourteen distinct members, represents one of the most complex

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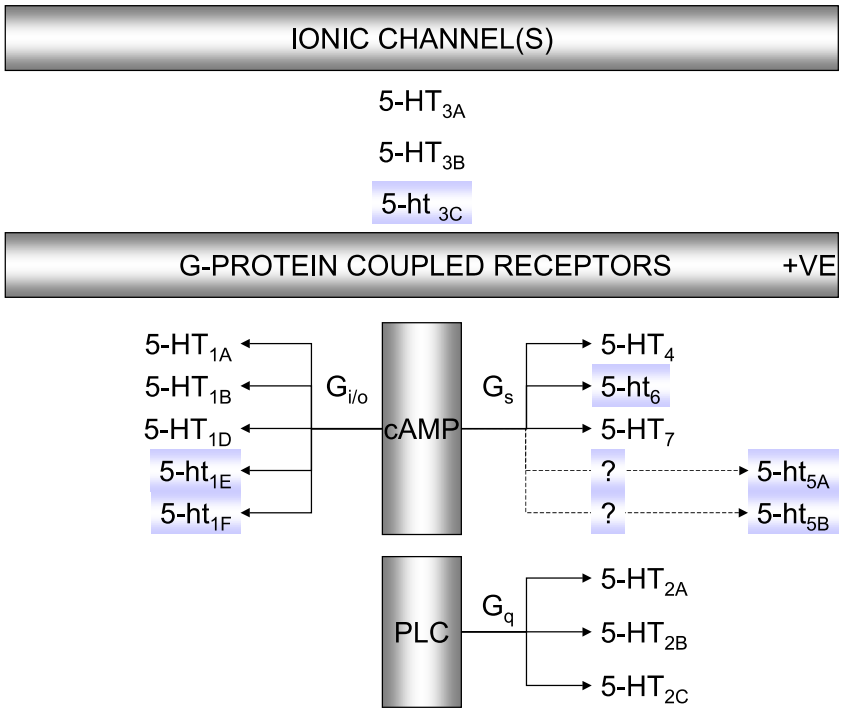

Receptor subtypes represented by shaded boxes and lower case designate receptors that have not been demonstrated to definitively function in native systems. Abbreviations: 3'-5' cyclic adenosine monophosphate (cAMP); phospholipase C (PLC); negative (-ve); positive (+ve).

Figure 1. Graphical representation of the current classification of 5-hydroxytryptamine (5-HT) receptors.

families of neurotransmitter receptors. Multiple splice variants (5-HT_4, 5-HT_7) or RNA edited isoforms (5-HT_{2C}) have been described; there is also evidence that homo- and heterodimerisation (5-$HT_{1B/1D}$) can occur. Furthermore, peptide or lipid modulators of 5-HT receptors have been described such as 5-HT moduline (Leu-Ser-Ala-Leu (LSAL), a putative product of a chromogranin), which has selectivity for the 5-HT_{1B} and 5-HT_{1D} receptors, or oleamide, which acts on several receptors (e.g. 5-$HT_{2A/2C}$ and 5-HT_7).

The 5-HT receptor family has been a target of intense research, in both academia and the pharmaceutical industry, with the identification of more potent and selective ligands for the different receptor subtypes as a major goal. Such selective receptor probes should help to better define the function(s) of these receptors, and lead to drug treatments with fewer side effects. Molecular genetics offer another approach 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 or transporter genes. 5-HT is also a substrate for the 5-HT transporter, itself an important target in the treatment of depression and social phobia. It is the target for selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine and citalopram. Thus, 5-HT has been implicated in the aetiology of numerous disease states, including depression, anxiety, social phobia, schizophrenia, obsessive-compulsive, panic-disorders, migraine, hypertension, pulmonary hypertension, eating disorders, vomiting and irritable bowel syndrome (IBS).

Current criteria for classifying 5-HT receptors

The classification of 5-HT receptors began in 1957, when it was found that 5-HT effects in the guinea pig ileum could be blocked in part by morphine (M), and in part by dibenzyline (D). Gaddum and Picarelli proposed a subdivision into 5-HT M and 5-HT D receptors (Gaddum and Picarelli 1957). However, neither morphine nor dibenzyline are selective. In 1976 utilising radioligand-binding, the presence of 5-HT receptors was postulated in brain. Then in 1979, Peroutka and Snyder demonstrated the presence of two distinct 5-HT receptor binding sites, using [^{3}H]5-HT, [^{3}H]spiperone, and [^{3}H]LSD. These sites were named 5-HT_1 and 5-HT_2. The M receptor was distinct from the 5-HT_1 and 5-HT_2 receptors in both function and distribution, whereas the D receptor corresponded pharmacologically to the 5-HT_2 binding site. As a result, Bradley and colleagues (1986) proposed the existence of three groups of 5-HT receptors, named 5-HT_1-like, 5-HT_2 and 5-HT_3, the latter corresponding to the M

Table 1. 5-HT_1 receptor nomenclature proposed by the NC-IUPHAR Subcommittee on 5-HT receptors.

Nomenclature	5-HT_{1A}	†$ 5-HT_{1B}	†5-HT_{1D}	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
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_{1B} and 5-HT_{1D} receptor nomenclature has been revised (Hartig et al. 1996); only the non-rodent form of the receptor was previously called 5-$HT_{1D\beta}$. $Displays a different pharmacology to the rodent form of the receptor.

receptor. The scheme, based primarily on functional criteria, represented a useful classification framework, but with the widespread use of radioligands and second messenger systems in the mid 1980's, subtypes of 5-HT_1 receptor binding sites were described; and it became rapidly obvious that the 5-HT_{1C} receptor would be better classified within the 5-HT_2 family, suggesting 5-HT_2 subtypes also. A novel 5-HT receptor was identified in the gastrointestinal (G. I.) tract and brain, termed 5-HT_4. In 1988 then, the molecular biology era started with the cloning of the 5-HT_{1A} receptor. Soon, most known or suspected 5-HT receptors were cloned in close succession. This work 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, they required integration into the classification. Thus, the Serotonin Club Receptor Nomenclature Committee proposed a new classification system based on operational, structural and transductional information (Humphrey et al. 1993). These principles were subsequently applied to additional receptor families by the receptor Nomenclature Committee of the International Union of Pharmacology (NC-IUPHAR). The current classification (Hoyer et al. 1994) is progressively adapted to incorporate 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, seven families of 5-HT receptors have been recognised. A graphical representation of the current classification of 5-HT receptors is given in Figure 1.

5-HT_1 receptors

The 5-HT_1 receptor class comprises five receptors (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 somewhat preferentially 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. The 5-HT_{1C} designation is vacant, as the receptor was renamed 5-$HT_{2C,}$ due to structural, operational and transductional similarities with the 5-HT_2 receptor subclass (Hoyer et al., 1994).

5-HT_{1A} receptors

The human 5-HT_{1A} receptor is located on chromosome 5q11.2-q13. 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 limbic structures, particularly the hippocampus. 5-HT_{1A} receptors mediate neuronal hyperpolarisation, via G-protein coupled K^+ channels. In the G.I. tract, 5-HT_{1A} receptors on the guinea pig myenteric plexus act as inhibitory modulators of fast excitatory postsynaptic potentials.

5-HT_{1A} receptors have been implicated in the neuroendocrine regulation of adrenocorticotrophic hormone (ACTH) secretion. Activation of postsynaptic 5-HT_{1A} receptors induces a behavioural syndrome: flat body posture, reciprocal forepaw treading and head weaving. The sponta-

neous tail-flick response has also been attributed to postsynaptic 5-HT_{1A} receptor activation, whereas evidence for a presynaptic 5-HT_{1A} (auto)receptor in the hyperphagic response appears convincing. The hypothermic response to 5-HT_{1A} agonists in the rat implies both pre- and postsynaptic mechanisms. A decrease in blood pressure and heart rate, and increased locomotor responses can be induced by central 5-HT_{1A} receptor activation. The proposed role of 5-HT_{1A} receptors in modulating anxiety-related behaviours is supported by recent studies utilising 5-HT_{1A} receptor knock-out (KO) mice. They display increased anxiety in a number of tests (e.g. elevated plus maze, elevated zero maze, open field). Moreover, they show decreased baseline immobility in the forced swim and tail suspension tests.

5-HT_{1A} receptor agonists, such as buspirone or gepirone, are being used/developed for the treatment of anxiety and depression. Furthermore, the $5HT_{1A}$ receptor and beta adrenoceptor antagonist, pindolol, was reported to enhance the therapeutic efficacy, and shorten the onset of action of SSRIs, upon co-administration in severely depressed patients. However, both positive and negative findings have been reported, as is common in depression trials. Flesinoxan, a 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), a full agonist in most systems, whilst the anxiolytics, buspirone and gepirone, and other ligands such as MDL 72832 are partial agonists. To date, the only selective high affinity silent antagonist at this receptor is WAY 100635. The agonists U-92016A and (+)UH 301 and the antagonists, (-) UH 301 and NAD 299 are other tools of interest.

5-HT_{1B} receptors

The 5-HT_{1B} and 5-HT_{1D} receptors have experienced a complex and debated history. The 5-HT_{1B} receptor was originally defined according to operational criteria (high affinity for some indole blockers) and was thought to be a rodent specific receptor, whereas the 5-HT_{1D} receptor was found in other species (similar distribution and function, but different "pharmacology"). It turned out that in all species investigated, two related receptors could be cloned (5-HT_{1B} and 5-HT_{1D}). The differences in the pharmacology of the 5-HT_{1B} receptor across species are attributable to the mutation of a single amino acid Asp^{123} to Arg^{123}. The human 5-HT_{1B} receptor is located on chromosome 6q13.

5-HT_{1B} receptors are expressed in the CNS, in the basal ganglia, striatum and frontal cortex and are thought to serve as terminal autoreceptors. 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. Additional effects tentatively attributed in rats to central 5-HT_{1B} receptor activation, include hyperlocomotion, hypophagia, hypothermia and penile erection. The receptors are also found on cerebral arteries and other vascular tissues. 5-HT_{1B} receptors mediate contraction of rat caudal arteries. Other 5-HT_{1B} effects include inhibition of noradrenaline release in vena cava and inhibition of plasma extravasation produced by trigeminal ganglion stimulation in guinea pigs and rats.

Interest in 5-HT_{1B} receptor agonists has been triggered by the anti-migraine properties of sumatriptan, a non-selective 5-$HT_{1D/1B}$ receptor agonist; various agonists have been developed for this indication (dihydroergotamine (DHE), zolmitriptan, naratriptan, rizatriptan, elitriptan, almotriptan, donitriptan and others). 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 highly aggressive and show an increased preference for alcohol. In contrast to the 5-HT_{1A} receptor KO mouse, the 5-HT_{1B} receptor KO has a different, and in most cases opposite behavioural profile, displaying decreases in measures of anxiety in the elevated plus maze, open field and tail suspension tests, in addition to an increase in aggression in the resident intruder paradigm. However, the development of 5-HT_{1B} agonist 'serenics' such as eltoprazine was not successful; the expected anti-aggressive effects were not observed in patients.

Selective 5-HT_{1B} agonists include MK 462 (rizatriptan), BW 311C90 (zolmitriptan), SKF 99101H, GR 46611, L 694247, and CP 93129 (in rodents). However, some of them, e.g. sumatriptan or LY 334370 have significant affinity to 5-ht_{1F} receptors. 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. Of 5-HT_{1B} receptor antagonists, 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 potent beta-adrenoceptor antagonists). SB 216641, SB 272183 and GR 55562 demonstrate a certain degree of 5-HT_{1B} selectivity. SB 224289 and SB 236057 are inverse agonists, allowing the characterisation of 5-HT_{1B} receptor tone. These new compounds confirm that terminal 5-HT autoreceptors are of the 5-HT_{1B} type.

Radiolabelled ligands include [^{3}H]-GR 125743, a 5-$HT_{1D/1B}$ receptor antagonist, [^{125}I]5-hydroxytryptamine-5-*O*-carboxymethylglycyltyrosinamide (GTI) or [^{3}H]alniditan. Finally, in rodents, [^{125}I]cyanopindolol under appropriate conditions labels 5-HT_{1B} sites.

5-HT$_{1D}$ receptors

The 5-HT$_{1D}$ receptor is located on chromosome 1p34.3-p36.3 and possesses 63 % overall structural homology with the 5-HT$_{1B}$ receptor. Its level of expression is very low compared with 5-HT$_{1B}$ receptors and it has been difficult to assign a functional role. The characteristics of the 5-HT$_{1B}$ and 5-HT$_{1D}$ subtypes are now well established, and the use of the new 5-HT$_{1B/1D}$ selective ligands, SB 216641 (h5-HT$_{1B}$) and BRL 15572 (h5-HT$_{1D}$), suggests the presence of a 5-HT$_{1D}$ autoreceptor in the dorsal raphé nuclei. 5-HT$_{1D}$ receptors in human heart modulate 5-HT release. The currently available anti-migraine drugs do not distinguish between 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors. 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, suggesting the 5-HT$_{1D}$ receptor related headaches, but such drugs are devoid of vascular activity confirming that it is the 5-HT$_{1B}$ receptor that mediates the vasoconstrictor effects produced by sumatriptan and analogues. Both 5-HT$_{1B}$ and 5-HT$_{1D}$ receptor immunoreactivity is found in human trigeminal ganglia, where the receptors colocalise with calcitonin gene-related peptide, substance P and nitric oxide synthase.

5-ht$_{1E}$ receptors

The putative 5-ht$_{1E}$ receptor was identified in binding studies in human frontal cortex, but its overall distribution is still to be described due to the absence of adequate tools. It is a 365 amino acid protein negatively linked to adenylyl cyclase in recombinant cell systems, present on human chromosome 6q14-q15. 5-ht$_{1E}$ receptor mRNA and recognition sites exhibiting the pharmacological characteristics of the receptor have been mapped in rodent and human brain. However, 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 awaits the development of selective ligands.

5-ht$_{1F}$ receptors

The 5-ht$_{1F}$ receptor located on chromosome 3p11, has 366 amino acids, is negatively linked to adenylyl cyclase in recombinant cell systems, and most closely related to the 5-ht$_{1E}$ receptor with > 70 % sequence homology across the seven transmembrane domains. 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 (dorsal raphé, hippocampus, cortex, striatum, thalamus and hypothalamus), mesentery and uterus. The anti-migraine 5-HT$_{1B/1D}$ agonist sumatriptan labels 5-ht$_{1F}$ sites with high affinity. The binding site distribution obtained was very similar to that for 5-ht$_{1F}$ mRNA. Naratriptan also has affinity for 5-ht$_{1F}$ receptors and it has been hypothesised that they might be a target for anti-migraine drugs. 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. LY 334370, a selective 5-ht$_{1F}$ receptor agonist, inhibits trigeminal stimulation-induced early activated gene expression in nociceptive neurones in the rat brainstem. LY 334370, as a radioligand, shows prominent binding in the cortical areas, striatum, hippocampus and olfactory bulb compatible with 5-ht$_{1F}$ mRNA distribution.

5-ht$_{1F}$ selective ligands i.e. LY 344864 and BRL 54443, are currently in development (migraine), however they also have affinity for 5-ht$_{1E}$ receptors.

5-HT$_2$ receptors

5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors exhibit 46-50 % overall sequence identity and couple preferentially to G$_{q/11}$ to increase inositol phosphates and cytosolic [Ca^{++}] (see Tables 1 and 3). The 5-HT$_{2A}$ receptor refers to the classical D receptor initially described by Gaddum and Picarelli (1957), and later defined as the 5-HT$_2$ receptor by Peroutka and Snyder (1979). 5-HT$_{2B}$ receptors mediate the contractile action of 5-HT in the rat fundus. In human pulmonary artery endothelial cells, 5-HT$_{2B}$ receptor stimulation causes intracellular calcium release. The third 5-HT$_2$ subtype corresponds to the previously known 5-HT$_{1C}$ receptor, which was reclassified as 5-HT$_{2C}$ (Hoyer et al. 1994).

5-HT$_{2A}$ receptors

The 5-HT$_{2A}$ receptor located on human chromosome 13q14-q21, has 471 amino acids in rat, mouse and humans. It is widely distributed in peripheral and central tissues. 5-HT$_{2A}$ receptors mediate contractile responses in many vascular and non-vascular smooth muscle preparations, e.g. bronchial, uterine, ileal and urinary smooth muscle. 5-HT$_{2A}$ receptors mediate platelet aggregation and increased capillary. 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. 5-HT$_2$ receptor agonists, in addition to precursors of 5-HT and 5-HT releasing agents, produce head twitching in mice, and wet-dog shakes and back muscle contractions in rats. Truly selective agonists have not been described, since aMe-5-HT, DOI, DOM and DOB all recognise other receptors of the 5-HT$_2$ receptor class. 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. LSD and other hallucinogens most probably produce hallucinations via 5-HT$_{2A}$ receptors. Although their selectivity *vis a vis* 5-HT$_{2B}$ and 5-HT$_{2C}$ receptors is rather limited, this represents currently the best possible explanation.

Table 2. 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}*	5-HT_3	5-HT_4
Previous names	D / 5-HT_2	5-HT_{2F}	5-HT_{1C}	M	-
Selective agonists	DOI†	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)†† 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	[^{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	Multi-subunit¥ 5-HT_{3A}, 5-HT_{3B}, 5-ht_{3C}	h387 Y09756[AS] m387 Y09587[AS] r387 U20906[AS]

†Also activates the 5-HT_{2C} receptor. ††Nonselective blockade. *Multiple isoforms of the 5-HT_{2C} receptor are produced by RNA editting. §The 5-HT_3 receptor is a transmitter-gated cation channel that exists as a pentamer of 4TM subunits. ¥Human, rat, mouse, guinea-pig and ferret homologues of the 5-HT_{3A} receptor have been cloned that exhibit interspecies variation in pahrmacology. A second 5-HT_3 receptor subunit, 5-HT_{3B}, imparts distinctive biophysical properties upon hetero-oligomeric (5-HT_{3A}/5-HT_{3B}) versus homo-oligomeric (5-HT_{3A}) recombinant receptors.

Ketanserin and MDL 100907 are selective antagonists. Ketanserin was developed for the treatment of hypertension, but 5-HT_{2A} receptor antagonism as a valid anti-hypertensive principle is not questioned, since ketanserin is a potent α_1 adrenoceptor antagonist. 5-HT_{2A} receptor antagonists such as risperidone, ritanserin, seroquel, olanzapine or MDL 100907 have been indicated/developed for the treatment of schizophrenia. However, development of MDL 100907 for acute schizophrenia was stopped. The combination of dopamine D_2 and 5-HT_{2A} receptor antagonism may still explain the antipsychotic activity of drugs such as clozapine, olanzapine, seroquel and others.

5-HT_{2B} receptors

The 5-HT_{2B} receptor mediates fundic smooth muscle contraction. It was difficult to characterise pharmacologically, due to operational features similar to those of other members of the 5-HT_2 family (Humphrey et al. 1993). Eventually, the cloning of the rat, mouse and human 'fundic' receptors (also known as 5-HT_{2F}) clarified the issue. It is located on human chromosome 2q36.3-2q37.1. 5-HT_{2B} receptor mRNA is found in rat fundus, gut, heart, kidney, lung and brain. Centrally, 5-HT_{2B} receptor-like immunoreactivity is restricted to cerebellum, lateral septum, hypothalamus and medial amygdala. Application of BW 723C86 into the medial amygdala produces anxiolytic properties in rat social interactions. 5-HT_{2B} receptor activation has been implicated in mediating hyperphagia. 5-HT_{2B}, but not 5-HT_{2C}, receptor mRNA is found in a number of blood vessels. 5-HT_{2B} receptors on endothelial cells of pig pulmonary arteries and in rat jugular vein mediate vasorelaxation via NO release. 5-HT_{2B} receptors contract longitudinal muscle in human small intestine and when expressed in mouse fibroblast cells, cause mitogenesis linked to tumour transforming activity, via MAP kinase activation.

SB 204741 was the first selective 5-HT_{2B} receptor antagonist. 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. BW 723C86 has agonist selectivity at the rat 5-HT_{2B} receptor, although less marked at human receptors. 5-HT_{2B} receptor antagonists such as SB 200646 may be indicated for the treatment of migraine prophylaxis, given the vasodilatatory role of this receptor and that a number of 'older' antimigraine drugs share 5-HT_{2B} receptor antagonism. Activation of the 5-HT_{2B} receptor is most probably responsible for the valvulopathies reported for appetite suppressant preparations containing dex-fenfluramine.

5-HT_{2C} receptors

The 5-HT_{2C} receptor was mapped to human chromosome Xq24. Given its similar pharmacological and transductional features with the 5-HT_{2A} receptor, the sequence of the latter was established by homology cloning based on the 5-HT_{2C} sequence. However, due to the lack of truly selective 5-HT_{2C} receptor ligands, our current knowledge concerning a func-

tional role of this receptor is still rather limited. Thus far, its distribution has been limited to the CNS and choroid plexus, where the receptor was originally identified. 5-HT_{2C} receptors in the choroid plexus couple to PLC activity, but additional functional correlates remain largely to be found. At least fourteen functional 5-HT_{2C} receptor isoforms are produced by adenine deaminase editing of the receptor mRNA.

MK 212 and Ro 600175 are moderately selective 5-HT_{2C} agonists; amongst the antagonists, LY 53857, ZM 170809, ritanserin, mianserin and mesulergine have been utilised, but are essentially non-selective. The anxiogenic component of mCPP may be 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. However, additional studies utilising selective agonists are required (e.g. Ro 600175). mCPP or Ro 600175 cause additional behavioural responses attributed to central 5-HT_{2C} receptor activation, e.g. hypoactivity, hypophagia, increased penile grooming/erections and oral dyskinesia. 5-HT_{2C} receptor activation produces a tonic, inhibitory influence upon frontocortical dopaminergic and adrenergic, but not serotonergic transmission and, in part, to play a role in neuroendocrine function. RS 102221 increased food-intake and weight gain in rats, but failed to reverse the mCPP induced hypolocomotion, possibly due to restricted brain penetration. 5-HT_{2C} receptor KO mice have spontaneous convulsions, cognitive impairment, increased food intake and obesity, but similar effects are not reproduced by selective antagonists, suggesting that these changes may result in part from neuroadaptation. Nevertheless, the 5-HT_{2C} receptor is an attractive target for the discovery of novel treatment for feeding disorders.

5-HT_3 receptors

5-HT_3 receptors (M receptors of Gaddum and Picarelli 1957) belong to the ligand-gated ion channel receptor superfamily, similar to the nicotinic acetylcholine or $GABA_A$ receptors and share electrophysiological and structural patterns. The receptors are found on central and peripheral neurones, where they trigger rapid depolarisation due to the opening of non-selective cation channels (Na^+, Ca^{++} influx, K^+ efflux). The response desensitises and resensitises rapidly. The native 5-HT_3 receptor, as revealed by electron microscopy in neuroblastoma-glioma cells, is a pentamer.

A cDNA encoding a single subunit of the 5-HT_{3A} receptor was isolated from a neuronally derived cell line. The human homologue maps to chromosome 11q23.1-q23.2. Two splice variants were reported in neuroblastoma-glioma cells (NCB-20, NG 108-15) and rat native tissue, with similar distribution, pharmacological profiles and electrophysiological characteristics when expressed as homomers. 5-HT_3 receptors are present in the CA1 pyramidal cell layer in the hippocampus, the dorsal motor nucleus of the solitary tract and the area postrema. In the periphery, they are located on pre- and postganglionic autonomic neurones and on neurones of the sensory nervous system. 5-HT_3 receptor activation has pronounced effects on the cardiovascular system and regulates both motility and intestinal secretion throughout the entire G.I. tract. Species differences provide the basis of the pharmacological heterogeneity reported thus far. But, after extensive investigation, a second subunit, 5-HT_{3B}, was cloned. The heteromeric combination of 5-HT_{3A} and 5-HT_{3B} subunits provides the full functional features of the 5-HT_3 receptor; since the 5-HT_{3A} subunit alone results in receptors with very low conductance and response amplitude, whereas 5-HT_{3B} homomers have no activity. The patent literature has recently reported the cloning of a third subunit, 5-ht_{3C}, but no details are presently available on its features. The 5-HT_3 receptor, like other members of the ligand-gated ion channel receptor superfamily, possesses additional, pharmacologically distinct, recognition sites, subject to allosterical modulation.

5-HT_3 antagonists ondansetron, granisetron and tropisetron are used clinically in chemotherapy- and radiotherapy-induced nausea and vomiting. 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 anti-psychotics and anxiolytics; schizophrenia and anxiety were considered as potential indications. 5-HT_3 receptor antagonists have been reported to induce cognition enhancing effects. However, there are not enough clinical data to substantiate such activities. Similarly, that 5-HT_3 antagonists should prove useful in the treatment of migraine did not materialise in clinical studies. More recently, alosetron was developed for the treatment of women suffering from IBS with diarrhoea, had to be withdrawn due to safety reasons, but has been accepted again by the FDA with some label restrictions.

5-HT_4 receptors

5-HT_4, 5-ht_6 and 5-HT_7 receptors all couple preferentially to G_s and promote cAMP formation, yet they are classified as distinct receptor classes because of their limited (< 35 %) overall sequence identities. This subdivision is arbitrary and may be subject to future modification.

The 5-HT_4 receptor had been well described in both central and peripheral tissues long before cloning, although confusion between 5-HT_3 and 5-HT_4 receptors occurred at times. Their existence was reported in rat neonatal colliculi over 20 years ago, but they were not properly identified at the time: the 5-HT4 receptor was really charaterised by Bockaert and colleagues using substituted benzamide derivatives like cisapride, renzapride or zacopride, acted as agonists at the 'atypical' 5-HT receptor in mouse colliculi stimulation cAMP. Interestingly, the potent 5-HT_3 receptor antagonist tropisetron

Table 3. 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}

(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. At least seven C-terminal splice variants of the receptor have been identified (5-HT_{4a}-5-HT_{4h}), in addition to a novel splice variant, 5-HT_{4hb}, with a 14 amino acid insertion in the second extracellular loop.

The 5-HT_4 receptor variants couple positively to adenylyl cyclase and share pharmacological profiles. One important feature of the receptor is the level of constitutive activity, which is expressed at rather low receptor levels, which may well explain differences observed with respect to variable intrinsic activity of a number of ligands, depending on tissue and/or species. The pattern of expression of the human 5-HT_4 receptor isoforms is tissue specific. The h5-HT_{4d} receptor isoform has not yet been described in other species. It is limited to the gut, whereas the other isoforms are more widely expressed. In addition to adenylate cyclase stimulation, direct coupling to potassium channels and voltage-sensitive calcium channel have been proposed.

The receptor is labelled with [^{3}H]GR 113808, [^{3}H]RS 57639 and [^{125}I]SB 207710. In the brain, the distribution of radioligand binding sites and mRNA is similar. RT-PCR studies have also demonstrated 5-HT_4 receptor mRNA is present in vascular smooth muscle, confirming functional studies. 5-HT_4 receptor activation triggers acetylcholine release in the guinea-pig ileum and contracts the oesophagus and colon. The 5-HT_4 receptor stimulates secretory responses to 5-HT in intestinal mucosa. Electrogenic ion transport is stimulated through 5-HT_4 receptors in the small intestine; whilst in 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, enhance synaptic transmission and may play a role in memory enhancement; confirmation by clinical studies is lacking though. Desensitisation is seen in many experimental in vitro models, though readily reversible upon agonist removal in G.I. tract preparations.

Potent and selective 5-HT_4 receptor ligands are available, e.g. the agonists BIMU 8, RS 67506 and ML 10302, and the antagonists GR 113808, SB 204070, SB 203186, RS 23597-190 and RS 39604; which should allow definition of the (patho)physiological role of this receptor. Selective 5-HT_4 receptor ligands may have therapeutic utility in a number of disorders, including cardiac arrhythmia, neurodegenerative diseases and urinary incontinence. Cisapride, a gastroprokinetic agent, acts as an agonist at the 5-HT_4 receptor. Tegaserod (HTF-919, Zelmac/Zelnorm), a new generation 5-HT_4 receptor partial agonist, is used to treat constipation predominant IBS, and its therapeutic activity in functional motility disorders of the upper G.I. tract is currently under clinical investigation.

5-ht_5 receptors

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 found in humans, was mapped to chromosome 7q36.1. The human 5-ht_{5B} receptor gene does not encode a functional protein, due to the presence of stop codons in its coding sequence. Human recombinant 5-ht_{5A} receptors inhibit forskolin stimulated cAMP production, although the receptor may also couple positively to cAMP. In *Xenopus* oocytes, the human 5-ht_{5A} receptor couples to the inwardly rectifying K^+ channel, $GIRK_1$.

5-ht$_5$ mRNA is present in hypothalamus, hippocampus, corpus callosum, fimbria, cerebral ventricles and glia, and a role has been sugested in reatcive gliosis. A physiological functional response or specific 5-ht$_5$ binding are still missing.

5-ht$_6$ receptors

The rat 5-ht$_6$ receptor has 438 amino acids and is positively coupled to adenylyl cyclase via G_s. The human gene has 89 % sequence homology with its rat equivalent, and maps chromosome region 1p35-p36. Rat and human 5-ht$_6$ receptor mRNA is located in the striatum, amygdala, nucleus accumbens, hippocampus, cortex and olfactory tubercle, but has not been found in peripheral organs. Circumstantial evidence suggests the 5-ht$_6$ receptor to be expressed endogenously in neuronal tissue.

The 5-ht$_6$ receptor promotes accumulation of cAMP. NCB 20 and N18TG2 cells and rat striatal neuronal cultures express a receptor which couples positively to adenylyl cyclase and displays an operational profile consistent with the recombinant 5-ht$_6$ receptor. Similar evidence for the putative 5-ht$_6$ receptor has been obtained in homogenates of pig caudate nucleus: cAMP accumulation had a 5-ht$_6$ receptor profile and was antagonised by clozapine and methiothepin. [^{3}H]clozapine binds with nanomolar affinity to two distinct sites in rat brain; one site displays the operational 5-ht$_6$ receptor profile.

SB 271046 is a potent, selective, and bioavailable 5-ht$_6$ receptor antagonist; EMDT is a selective 5-ht$_6$ receptor agonist. The 5-ht$_6$ receptor is labelled with [^{125}I]SB 258585. Intracerebroventricular injections of 5-ht$_6$ receptor antisense oligonucleotides 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). The antisense-induced behavioural syndrome can be dose-dependently antagonised by atropine, implying a modulatory role for 5-ht$_6$ receptors on cholinergic neurones. The selective 5-ht$_6$ receptor antagonist, Ro 04-6790, produces a behavioural syndrome involving an increase in acetylcholine neurotransmis-sion. Enhanced retention of spatial learning following both antisense oligonucleotides and Ro 04-6790 have been reported. A role for the 5-ht$_6$ receptor in the control of central cholinergic function, and thus a putative target for cognitive dysfunction such as Alzheimer's disease is thus suggested. In addition, antisense oligonucleotide treatment reduced both food consumption and body weight; the later effect was also seen following Ro 04-6790 suggesting potential in feeding disorders.

Antipsychotics (clozapine, olanzapine, fluperlapine and seroquel) and antidepressants (clomipramine, amitryptyline, doxepin and nortryptyline) are 5-ht$_6$ receptor antagonists, in addition to multiple other affinities. This attribute tempted speculation of an involvement of the 5-ht$_6$ receptor in psychiatric disorders.

5-HT$_7$ receptors

The 5-HT$_7$ receptor gene is located on human chromosome 10q23.3-q24.4. It has 445 amino acids and positively modulates cAMP formation via G_S. The receptor shares a low homology with other members of the 5-HT receptor family (< 50 %). The receptor also activates the mitogen-activated protein kinase, ERK, in primary neuronal cultures. The cDNA encoding the receptor contains two introns; one located in the second intracellular loop, the other in the predicted intracellular carboxyl terminal. Alternate splicing of this latter intron has been reported to generate four 5-HT$_7$ receptor isoforms (5-HT$_{7a}$-5-HT$_{7d}$), which differ in their C-termini. The various isoforms have similar pharmacology, signal transduction and to a lesser extent tissue distribution. The 5-HT$_7$ receptor has 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. It has an extensive vascular distribution, and is responsible for the prominent, persistent vasodilator response to 5-HT in anaesthetised animals, and is also expressed in non-vascular smooth muscle and the CNS.

[^{3}H]5-CT, in the presence of (-)-cyanopindolol and sumatriptan, labels 5-HT$_7$ recognition sites in guinea pig cerebral cortex membranes. Autoradiographic analysis revealed binding sites in the medial thalamic nuclei and related limbic and cortical regions of the guinea pig brain, with lower densities in the sensory relay nuclei, substantia nigra, hypothalamus, central grey and dorsal raphé nuclei, in agreement with 5-HT$_7$ receptor mRNA. In rat suprachiasmatic (SCN) neurones, a gamma-aminobutyric acid activated current (I_{GABA}) is inhibited by 5-HT, consistent with the presence of 5-HT$_7$ receptors in the SCN. 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.

The presence of 5-HT$_7$ sites in the limbic system and thalamocortical regions, suggest a role in the affective disorders; indeed, atypical antipsychotics, e.g. clozapine, risperidone and antidepressants have high affinity for the 5-HT$_7$ receptor. 5-HT$_7$ receptor down-regulation occurs after chronic antidepressant treatment, and acute, but not chronic, stress regulates 5-HT$_7$ receptor mRNA expression.

The antagonists SB 258719 and SB 269970 are selective. A role for the 5-HT$_7$ receptor has been proposed in the 5-CT-induced hypothermia in guinea pigs which is blocked by both SB 269970 and the non-selective 5-HT$_7$ receptor antagonist, metergoline. SB 269970 significantly reduced time spent in paradoxical sleep in rats. [^{3}H]SB 269970 is a selective radioligand for 5-HT$_7$ receptors. The 5-HT$_7$ receptor is the orphan known as the '5-HT$_1$-like' receptor mediating relaxation of the guinea pig isolated ileum and cat saphenous vein

and subsequently shown to mediate elevation of cAMP and relaxation in neonatal porcine vena cava.

Putative orphan 5-HT receptors

Several endogenous 5-HT receptors have been defined phamacologically, although a corresponding gene product encoding the receptor has yet to be identified. As long as their structure is unknown, these receptors are regarded as orphans in the current nomenclature. One of these however, the so-called '5-HT_1-like' receptor mediating direct vasorelaxation corresponds to the 5-HT_7 receptor (see above). On the other hand, 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. Also, a high affinity binding site for [^{3}H]5-HT with novel '5-HT_1-like' pharmacology has been reported in mammalian brain, but has yet to be sufficiently characterised for inclusion in the 5-HT_1 receptor family.

Conclusion

Whether the almost endless diversity in 5-HT receptors and transporters fulfils specific physiological and/or pathophysiological roles is an open question. However, it may soon be possible to determine which form of a given receptor is expressed in a given tissue. This will then assist in designing drugs with an adequate profile at the target organ, assuming it is known. The diversity in receptors described here suggests that under physiological and more so under pathological conditions, the status of the receptors may vary dramatically from one subject to another, explaining differences in responder rates to a given treatment. It is clear that receptor cross-talk will considerably affect the responsiveness of one patient versus another. Indeed, vascular reactivity towards triptans varies significantly between patients possibly because of such possibilities. Depending on the nature of the receptor isoforms (5-HT_4, 5-HT_7 or 5-HT_{2C}) expressed in the G.I. 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. The human genome being almost completely sequenced, we will know soon whether there are more 5-HT receptors. However, given the interactions with accessory proteins, in addition to homo- and heterodimerisation, one can predict that the situation will not prove simpler in the short term.

Drugs

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]-1H-indol-5-yl]methyl]-2-oxazolidinone

BW 723C86: 1-[5(2-thienylmethoxy)-1*H*-3-indolyl]propan-2-amine hydrochloride

CP 93129: 5H-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]-1H-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-1H-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-[(3R)-3-(dimethylamino)-2,3,4,9-tetrahydro-1H-carbazol-6-yl]-4-fluoro-benzamide

LY 53857: Ergoline-8-carboxylic acid, 6-methyl-1-(1-methylethyl)-, 2-hydroxy-1-methylpropyl ester, (8b)-, (2Z)-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: 1H-Indole-3-ethanamine, N,N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)

ML 10302: 2-(1-piperidinyl)ethyl-4-amino-5-chloro-2-methoxybenzoate

NAD 299: 2H-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 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
RS 67506: 1-(4-amino-5-chloro-2-methoxyphenyl)-3-(1-*n*-butyl-4-piperidinyl)-1-propanone
RU 24969: 1H-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: 1H-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: 1H-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: 1H-Indole-2-carboxylic acid, 4-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-, 1-methylethyl ester
SKF 99101H: 1H-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: 3H-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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