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Perspective

Central Serotonin Receptors as Targets for Drug Research

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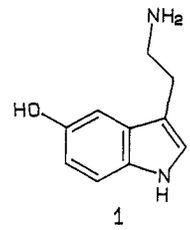
Appetite, memory, thermoregulation, sleep, sexual behavior, anxiety, depression, and hallucinogenic behavior are some of the the processes that have been linked with the neurotransmitter serotonin. Whether serotonin plays a primary role or a modulatory role has yet to be determined; nevertheless, it does seem to be involved in numerous actions that would be difficult to explain on the basis of the interaction of a single neurotransmitter with a single type of receptor. However, with the recent discovery of multiple populations of central serotonin binding (receptor?) sites has come a renewed interest in this neurotransmitter, particularly in light of the possibility that its interaction with different types of central sites might explain its various actions. There has been a spillover effect in that there is also increased interest in peripheral serotonergic systems. The entire issue of central serotonin binding sites is relatively new, fraught with controversy, and still in the developmental stage. New binding sites are being reported, multiple-state binding and regulatory processes are being examined, and the functional significance of these sites is being explored. This is probably the most exciting period that serotonin has enjoyed since the pioneering days of serotonin research in the late 1950s and early 1960s. One of the most significant problems facing serotonin research today is a lack of site-selective agonists and antagonists; a continued lack of such tools will surely retard further advances in this field. Investigations of functional correlates of central binding, for example, are highly dependent upon the availability of these tools. Following a brief description of the recent advances in the field of serotonin binding sites will be a discussion of the agents that interact with these sites. Hopefully, this will stimulate a search for new site-selective agents. The final section of this Perspective will describe some of the pharmacological effects that these agents produce and the types of functional roles that are currently being considered for these sites.

Serotonin Binding Sites

Serotonin was isolated from blood in 1948 and was shortly thereafter identified as 5-hydroxytryptamine (5-HT; 1). Subsequent studies revealed that this agent was



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also present in the central nervous system (CNS) of a variety of animal species and, ultimately, it was suggested that 5-HT was a neurotransmitter substance. For detailed discussions of early work on 5-HT, see Woolley[1] and Erspamer.[2] During the 1950s, efforts were devoted to the formulation of structure–activity relationship (SAR) for serotonergic activity and to the development of novel 5-HT agonists and antagonists, using peripheral 5-HT receptor preparations. But, as early as 1957 it was recognized that multiple types of 5-HT receptors might exist within the same tissue; Gaddum and Picarelli, for example, suggested that guinea pig ileum possesses two distinct types of 5-HT receptors: D receptors—present on smooth muscle cells, and M receptors—located on the enteric cholinergic neurons.[3] A 5-HT_x system of nomenclature has recently been proposed for the classification of peripheral 5-HT receptors.[4] "5-HT_1-like" receptors are those associated with, for example, prejunctional inhibition of neuronal transmitter release, smooth muscle relaxation, and contraction of some cardiac and vascular smooth muscle; peripheral 5-HT_1-like receptors may consist of several subtypes and these are the object of current studies. 5-HT_2 receptors are those serotonin receptors responsible for gastrointestinal and vascular smooth muscle contraction and platelet aggregation and appear to be similar to the D receptors proposed by Gaddum and Picarelli. The classical M receptors (5-HT_M receptors) are now termed 5-HT_3 receptors, and here also, there is evidence of multiple subpopulations of sites. Criteria for the classification, distribution, and function of peripheral 5-HT receptors have been reviewed.[4-6]

The 1970s ushered in the use of radioligand-binding techniques. [^{3}H]Lysergic acid diethylamide (LSD) was initially used to label central 5-HT binding sites; however, with the subsequent availability of [^{3}H]-5-HT, it was soon shown that the binding characteristics of these two ligands were not identical.[7,8] In 1978, it was reported that the

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tritiated neuroleptic agent spiperone (spiroperidol; **24**), though possessing a high affinity for dopamine binding sites in caudate, also labels a certain population of 5-HT sites.[9,10] The following year, Peroutka and Snyder[11] proposed the existence of two major populations of central serotonin binding sites: 5-HT_1 sites—those labeled with high affinity by [^{3}H]-5-HT, and 5-HT_2 sites—those labeled (in rat frontal cortex) by [^{3}H]spiperone. LSD possesses a similar affinity for, and [^{3}H]LSD labels, both types of 5-HT binding sites.[11] A variety of tritiated ligands were explored as potentially selective labels [e.g., metergoline, mianserin (**29**), methiothepin (**30**), quipazine (**10**); see Hamon et al.[12] for a review] until the quinazolinedione derivative ketanserin (**26**) was introduced in 1981.[13] Tritiated ketanserin[14] is now the most commonly employed radioligand for labeling 5-HT_2 sites. Several reviews describing various aspects of these binding sites, and agents that interact therewith, are now available.[12,15-21]

5-HT_1 Binding Sites. Serotonin displays a high affinity (K_i = 1–10 nM) for 5-HT_1 sites. The highest density of 5-HT_1 binding sites in rat brain is found in the hippocampus, striatum, and cerebral cortex as determined by the binding of [^{3}H]-5-HT.[7] There is some evidence that 5-HT_1 sites may be similar to 5-HT_1-like receptors; however, this remains to be determined.[4] As with 5-HT_1-like receptors, 5-HT_1 binding sites also appear to be heterogeneous; [^{3}H]-5-HT labels more than one population of sites and two distinct subpopulations can be differentiated by spiperone and, to a lesser extent by (+)-butaclamol.[22] 5-HT_{1A} sites represent spiperone-sensitive 5-HT_1 sites whereas 5-HT_{1B} sites display a 100- to 3000-fold lower affinity for spiperone.[22,23] More recently, 5-HT_{1C} sites have been described. Species and tissue distribution of 5-HT binding sites have been investigated.[24,25]

5-HT_{1A} Sites. Whereas the 5-, 6-, and 7-monohydroxy analogues of 2-(di-*n*-propylamino)tetralin display dopaminergic character, the 8-hydroxy derivative (i.e., 8-OH-DPAT, **2**) behaves as a serotonin agonist.[26] Furthermore, 8-OH-DPAT is not only selective for 5-HT_1 vs. 5-HT_2 sites, but it also displays a high affinity (K_i = 2–10 nM) and 500-fold selectivity for 5-HT_{1A} vs. 5-HT_{1B} sites.[27] As such, this agent might be considered a prototypic 5-HT_{1A} agonist. Subsequently, [^{3}H]-8-OH-DPAT has been used as a label for 5-HT_{1A} sites.[28] Tritiated 8-OH-DPAT binds with high affinity to 5-HT sites in the rat hippocampus and represents the first useful radioligand for labeling 5-HT_{1A} sites ([^{3}H]-8-OH-DPAT also labels sites in the striatum; these will be discussed below). 8-Methoxy-2-[*N*-(2-chloropropyl)-*N*-propylamino]tetralin (**4**) irreversibly alkylates, presumably via aziridinium ion formation, 5-HT_{1A} sites in the hippocampus (and the sites in the striatum); 5-HT_{1B} sites are also alkylated by this agent.[29] Other tritiated ligands that label 5-HT_{1A} sites include PAPP[30] (**13**), i.e., 1-[3-(trifluoromethyl)phenyl]-4-[2-(4-aminophenyl)ethyl]piperazine, and the α_1-adrenergic label WB4101.[31]

5-HT_{1B} Sites. Radioligand binding and autoradiographic studies support the concept of multiple populations, or subpopulations, of 5-HT_1 binding sites (e.g., see ref 32–35). Recently, [^{125}I]iodocyanopindolol ([^{125}I]CYP) (in the presence of isoproterenol to suppress binding to β-adrenoceptors) has been introduced as a specific label for 5-HT_{1B} sites in rat cortical membranes.[36] Binding at these sites is stereoselective, and the 5-HT_{1A} agonist 8-OH-DPAT displays a low affinity (K_i = ca. 63 000 nM) for these sites.[36]

5-HT_{1C} Sites. In 1984, autoradiographic evidence was provided for the existence of 5-HT_{1C} binding sites.[33] Subsequently, [^{3}H]mesulergine (**20**), an agent introduced earlier as a ligand for 5-HT_2 sites,[37] was shown to label these 5-HT_{1C} sites in porcine choroid plexus and, to a lesser extent, in porcine frontal cortex.[34,38] Further support for these sites is derived from studies with the β-adrenoceptor antagonist (−)-isopropyl 4-[3-(*tert*-butylamino)-2-hydroxypropoxy]indol-2-yl carbonate, which produces triphasic competition curves for [^{3}H]-5-HT binding in rat cortex (and rat hippocampus). Affinities for the high, intermediate, and low affinity sites were approximately 0.15 (0.5 for hippocampus), 15 (10), and 24 000 (5000) nM, respectively; comparable affinities were obtained for this agent at [^{3}H]-8-OH-DPAT-labeled (pig cortex) 5-HT_{1A} sites (0.4 nM), [^{125}I]CYP-labeled (rat cortex) 5-HT_{1B} sites

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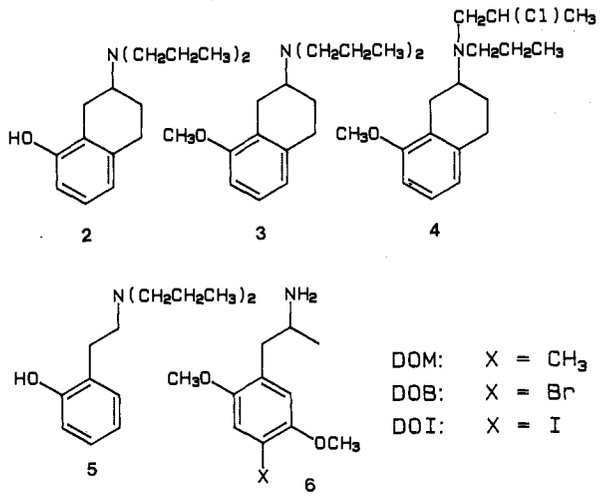
(12 nM), and [^{3}H]mesulergine-labeled (pig choroid plexus) 5-HT_{1C} sites (5370 nM).[39] [^{125}I]-2-Iodo-LSD ([^{125}I]-LSD)(**18**, R = ^{125}I)[40] and its N_1-methyl derivative [^{125}I]-MIL,[41,42] initially introduced as radioligands for 5-HT_2 sites, also label porcine choroid plexus 5-HT_{1C} sites. These sites have recently been solubilized with use of a zwitterionic detergent.[42]

5-HT_2 Binding Sites. 5-HT_2 binding sites, originally identified in rat frontal cortex homogenates with use of [^{3}H]spiperone,[11] have been further characterized by using the more selective agent [^{3}H]ketanserin ([^{3}H]KET).[14] There is evidence that these binding sites might constitute the CNS counterpart of peripheral 5-HT_2 (i.e., "D") receptors.[4] The highest density of 5-HT_2 sites is found in the frontal parts of the cortex, and 5-HT_2 sites have been identified in brain tissue from a variety of mammalian species including humans (e.g., see ref 43–47). There have been several reports of the solubilization of 5-HT_2 binding sites.[48–50] Other radioligands that have been used to label 5-HT_2 sites include [^{3}H]mesulergine,[37] [^{125}I]LSD,[40] and [^{125}I]MIL.[41] Ketanserin (**26**), a 5-HT antagonist, possesses a high affinity (K_i < 1 nM) for 5-HT_2 sites; in general, agents that display a high affinity for 5-HT_2 sites are those that are usually considered as being serotonin antagonists. Classical 5-HT agonists, on the other hand, commonly display a relatively low affinity for 5-HT_2 sites. 5-HT is a good example of such an agent; the affinity (K_i) of 5-HT for [^{3}H]KET-labeled 5-HT_2 sites is in the 400–1000 nM range. However, several phenylisopropylamine derivatives have now been identified as potential 5-HT_2 agonists; these agents include 1-(2,5-dimethoxy-4-substituted-phenyl)-2-aminopropanes, where, for example, X = methyl (DOM) and bromo (DOB) (i.e., **6**).[51–53] Subsequent SAR studies revealed that the intact DOB molecule displays optimal affinity/selectivity for 5-HT_2 sites,[54] and [^{3}H]DOB was ultimately prepared and evaluated as a label for these sites.[55] [^{3}H]DOB appears to label the high-affinity state

Chart I. Aminotetralins and Phenalkylamines



of 5-HT_2 sites (i.e., 5-HT_{2H} sites), whereas [^{3}H]KET in the presence of guanine nucleotides apparently labels the low-affinity state (i.e., 5-HT_{2L} sites).[55] Serotonin antagonists such as spiperone (**24**) and ketanserin (**26**) possess affinities for [^{3}H]DOB-labeled 5-HT_2 sites that are not significantly different from those for [^{3}H]KET-labeled sites; however, serotonin agonists such as 5-HT and (*R*-(−)-DOB display a higher affinity (by 1–2 orders of magnitude) for [^{3}H]DOB-labeled sites than for [^{3}H]KET-labeled sites.[54] For example, at [^{3}H]DOB-labeled sites, the affinity (K_i) for 5-HT is 6 nM (Table I). Another example is quipazine (**10**). Quipazine binds to [^{3}H]-5-HT-labeled 5-HT_1 sites and [^{3}H]KET-labeled 5-HT_2 sites with what appears to be an identical affinity (K_i = 230 nM in both cases); competition studies using [^{3}H]DOB as the radioligand reveal that quipazine binds to 5-HT_2 sites with a K_i value of 17 nM (Table I).

5-HT_3 Binding Sites. Several different groups of investigators have applied the term "5-HT_3 sites" to recently described 5-HT binding sites. To date, however, there is no reason to believe that any of these purported 5-HT_3 sites is related to the above-mentioned peripheral 5-HT_3 receptors. Although [^{3}H]-8-OH-DPAT labels 5-HT_{1A} sites in hippocampal homogenates, it labels a different (i.e., 5-HT_3) population of sites in striatal homogenates.[57] Competition studies (using [^{3}H]-8-OH-DPAT) with various 5-HT agonists and antagonists reveal distinct differences in the binding characteristics of these two sites, and suggestions have been made that the striatal sites might constitute presynaptic 5-HT sites. Other investigators have also used this term to describe some novel 5-HT sites;[58,59] however, very little is known about these sites at this time.

Serotonergic Agents

At one time, the general statement was made that 5-HT agonists display a high affinity for 5-HT_1 sites and 5-HT antagonists display a high affinity for 5-HT_2 sites. In fact,

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Table I. Binding Characteristics of Selected Serotonergic Agents

	K_i values,[a] nM						
site: ligand:	5-HT_1[b] [^{3}H]-5-HT	5-HT_{1A}[c] [^{3}H]-8-OH DPAT	5-HT_{1B}[c] [^{125}I]ICYP	5-HT_{1C}[c,d] [^{3}H]MES	5-HT_2[c] [^{3}H]KET	5-HT_2[e] [^{3}H]KET	5-HT_2[f] [^{3}H]DOB
5-HT	2	3	25	35	2950	560	6
O-Me-5-HT	2		400			690	14
8-OH-DPAT	160	2	63000	7250	7100	5500	700
TFMPP	20	1950[g]	30[g]			160	
mCPP		2400[g]	75[g]				
RU 24969	2	5	4	400	1000	780	
(−)-DOB	4200					24	0.4
(−)-DOI	2300					10	
5-OMe-DMT	50[h]	20[h]	90[h]		1200[h]	390	
ICYP		4	0.3	9800			
(−)-pindolol	100[i]	20	80	54000	29500	200000[i,j]	
(−)-propranolol	300[i]	115	50	1400	3500	5900[i,j]	
quipazine	230	3300	320	200	645	230	17
ketanserin	[k]	1900	1900	100	1	0.4[l]	1
pirenperone	[k]	1700	6600	60	1	0.3[l]	
metergoline	20[m]	6	25	0.5	1	0.3[l]	
mianserin	1100[m]		4700	10	10	1.4[l]	
spiperone	160[m]	40	4800	1150	2	0.5[l]	1
mesulergine		300	13000	1.5	4	2[n]	
cinanserin	3500[m]		10000	200	4	4	4

[a] Binding data are approximate and assays employed rat cortex unless otherwise noted. [b] References 52–54, 67. [c] Reference 39. [d] Pig choroid plexus. [e] References 52, 56, 67. [f] Reference 55 and Titeler et al., unpublished data. [g] Reference 177. [h] Reference 23. [i] Reference 87. [j] [^{3}H]Spiperone was used as the radioligand. [k] Inactive at 10 000 nM. [l] Reference 14. [m] Reference 13. [n] Reference 37.

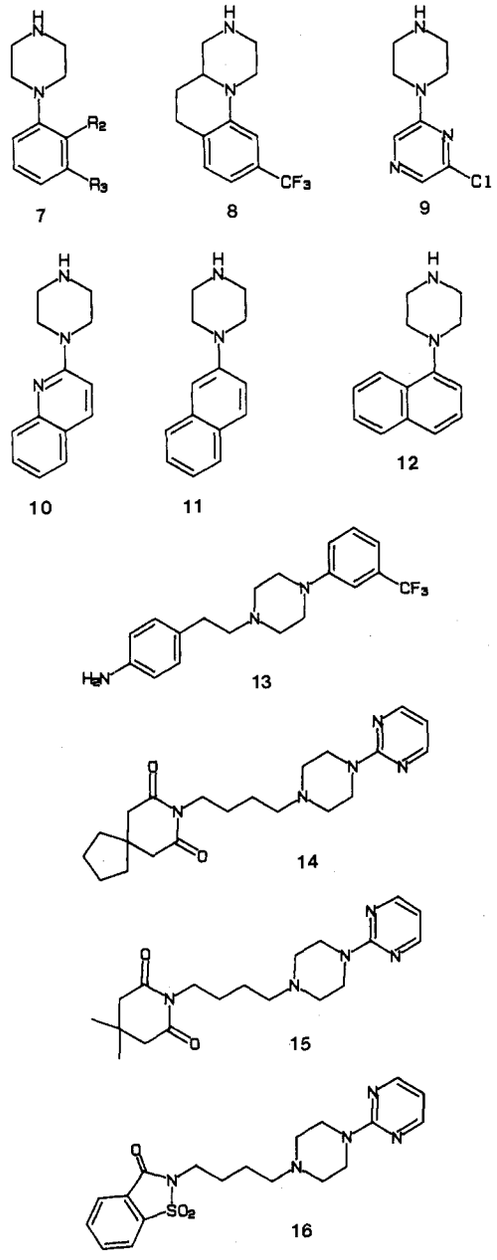
it was thought that the former might represent agonist binding sites, and the latter, antagonist binding sites. There is increasing evidence suggesting that this is not the case. Nevertheless, there still exists a paucity of site-selective agonists and antagonists. Until very recently (i.e., before the introduction of some of the newer radioligands), binding data were reported only in terms of overall 5-HT_1 or 5-HT_2 affinities, thus making it difficult (if not impossible, in the case of 5-HT_1 sites) to formulate valid and comprehensive SAR and to draw conclusions with regard to selectivity. Nevertheless, a brief discussion of the available data may provide some insight regarding trends between structure and selectivity. With the availability of radioligands that selectively label subpopulations of 5-HT_1 binding sites comes the possibility to make more reliable statements regarding SAR; unfortunately, because these ligands have only recently been introduced, very little data are currently available. For example, it might be noted that agonists that display high affinity/selectivity for 5-HT_{1A} sites are tertiary amines whereas those with a higher affinity/selectivity for 5-HT_{1B} sites are usually secondary amines. This might be a feature worth exploiting in the future design of site-selective agents. Some of the structural classes currently being explored as central 5-HT agonists and antagonists are described below.

1. Aminotetralins. As described above, 8-OH-DPAT (**2**; Chart I) is a prototypic 5-HT_{1A} agonist (Table I). The structural requirements for serotonergic activity within a series of related aminotetralins appears to be quite strict. Examining the effect of aminotetralins on 5-hydroxytryptophan accumulation, Arvidsson et al.[60] found that the two *n*-propyl groups of 8-OH-DPAT appear to impart optimal activity, with the corresponding dimethyl and diethyl derivatives being somewhat less potent and di-*n*-butyl derivative being significantly (i.e., more than 100-fold) less potent. Secondary amine analogues, such as the monomethyl, monoethyl, and mono-*n*-propyl derivatives of 8-OH DPAT, are several-fold less potent than the corresponding tertiary amine derivatives. The *O*-methyl ether of 8-OH-DPAT (i.e., 8-OMe-DPAT; **3**) is approximately one-fifth as potent as the parent compound.[60] Surprisingly few 8-OH-DPAT analogues have been examined in radioligand-binding studies. 8-OMe-DPAT (**3**) binds to [^{3}H]-8-OH-DPAT-labeled 5-HT_{1A} sites with an affinity comparable to that of 8-OH-DPAT itself.[61] Removal of the two *n*-propyl groups of 8-OH-DPAT decreases its affinity for (pig cortex) 5-HT_{1A} sites by more than 60-fold.[39] 2-Hydroxy-*N*,*N*-di-*n*-propylphenethylamine (**5**), a ring-opened analogue of 8-OH-DPAT, is 2 orders of magnitude less potent than 8-OH-DPAT at 5-HT_{1A} sites.[62] The results of some preliminary ^{1}H and ^{13}C NMR studies suggest that the ring-opened analogue may undergo internal hydrogen bonding between the hydroxyl group and the terminal amine to alter the conformation of the site chain.[62] 8-OH-DPAT represents one of the most site-selective 5-HT agonists yet discovered; it is rather disappointing that more work has not been done with related 2-aminotetralin derivatives.

2. Arylpiperazines. 1-(3-Chlorophenyl)piperazine (mCPP; **7**, R_2 = H, R_3 = Cl; Chart II) was postulated to be a metabolite of the antidepressant agent trazodone;[63] subsequent studies showed this to be the case.[64,65] Early studies (e.g., Maj et al.[63]) revealed the 5-HT agonist character of mCPP. mCPP possesses a significant affinity for 5-HT_1 binding sites; the corresponding trifluoromethyl derivative (TFMPP; **7**, R_2 = H, R_3 = CF_3) is somewhat more potent than mCPP.[67] TFMPP is a fairly selective 5-HT_{1B} vs. 5-HT_{1A} agonist (Table I), although it possesses only a 3- to 18-fold selectivity for 5-HT_1 vs. 5-HT_2 sites. 1-(2-Methoxyphenyl)piperazine (2-MPP; **7**, R_2 = OCH_3,

(60) Arvidsson, L.-E.; Hacksell, U.; Johansson, A. M.; Nilsson, J. L. G.; Lindberg, P.; Sanchez, D.; Wilström, H.; Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1984**, *27*, 45.
(61) Middlemiss, D. N., personal communication.
(62) Glennon, R. A.; Hauck, A. E.; Pierson, M. E.; Westkaemper, R.; Middlemiss, D. N., unpublished data.
(63) Maj, J.; Palider, W.; Rawlow, A. *J. Neural Trans.* **1979**, *44*, 237.
(64) Caccia, S.; Ballabio, M.; Samanin, R.; Zanini, M. G.; Garattini, S. *J. Pharm. Pharmacol.* **1981**, *33*, 477.
(65) Caccia, S.; Fong, M. H.; Garattini, S.; Notarnicola, A. *Biochem. Pharmacol.* **1985**, *34*, 393.
(66) Fuller, R. W.; Mason, N. R.; Molloy, B. B. *Biochem. Pharmacol.* **1980**, *29*, 833.
(67) Lyon, R. A.; Titeler, M.; McKenney, J. D.; Glennon, R. A. *J. Med. Chem.*, in press.

Chart II. Arylpiperazines



R_3 = H) possesses a 100-fold selectivity for 5-HT_1 vs. 5-HT_2 sites and an affinity for 5-HT_1 sites comparable to that of TFMPP.[67] The binding of 2-MPP to 5-HT_1 subpopulations has not yet been investigated. A conformationally restricted analogue of TFMPP (i.e., the pyrazino[1,2-*a*]-quinoline derivative **8**) is about twice as potent as, but is no more selective than, TFMPP at 5-HT_1 sites.[68] 1-Piperazinyl-6-chloropyrazine (MK-212, **9**) is a structurally related serotonin agonist;[67,70] however, this agent does not seem to possess a significant affinity for either 5-HT_1 or 5-HT_2 sites.[68] Interestingly, in studies using a peripheral receptor preparation, MK-212, unlike certain other arylpiperazines, displays a low affinity but a high efficacy at 5-HT receptors;[71] this might explain some of the inconsistencies that have been previously reported between binding and in vivo activity. It has also been suggested that MK-212 may interact with an as yet uncharacterized subset of 5-HT receptors.[70]

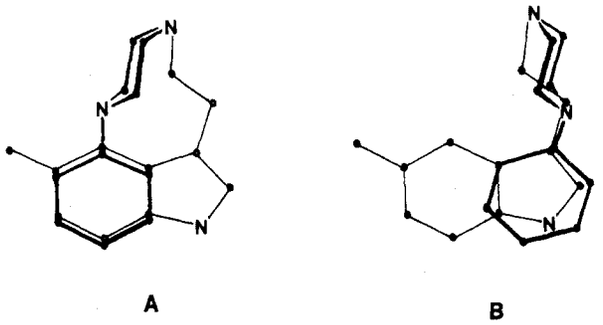


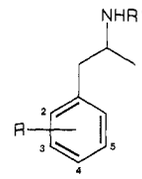
Figure 1. Two representations for the possible overlap of an arylpiperazine (heavy lines) and serotonin at 5-HT binding sites. At the binding site, the aromatic portion of the arylpiperazine may mimic the benzene ring (as shown by A) and/or (?) the pyrrole portion (as shown by B) of 5-HT. (From ref 56.)

One of the older non-indolic serotonergic agents is quipazine (**10**).[72] Although it, too, is structurally similar to TFMPP, it seems to produce pharmacological effects more closely resembling 5-HT_2 agonism than 5-HT_1 agonism; furthermore, its affinity for 5-HT_2 sites seems to be comparable to its affinity for 5-HT_1 sites (Table I). However, in competition experiments using the new radioligand [^{3}H]DOB to label 5-HT_2 sites, quipazine (**10**) displays selectivity for 5-HT_2 vs. 5-HT_1 sites (Table I). Removal of the quinoline nitrogen atom of quipazine, to afford deazaquipazine (2-naphthylpiperazine; 2-NP, **11**), has no effect on its affinity for 5-HT_1 sites and only slightly enhances its affinity (by about 3-fold) for 5-HT_2 sites.[56] Removal of the fused ring of 2-NP, to afford 1-phenylpiperazine (**7**, R_2 = R_3 = H), results in a compound with an affinity (K_i = 135 nM) for 5-HT_1 sites comparable to that of 2-NP (K_i = 265 nM), but with an affinity for 5-HT_2 sites 30-fold less than that of 2-NP (**11**). Thus, the fused ring may contribute to the affinity and selectivity of 2-NP (and of quipazine) for 5-HT_2 sites. [Likewise, benz fusion at the *c* face of 1-phenyl-2-aminopropane (K_i = >40 000 nM) enhances its affinity for 5-HT_2 sites by more than 2 orders of magnitude (unpublished data).] 2-NP (**11**) results from benz fusion at the *c* face of 1-phenylpiperazine; benz fusion at the *b* face affords 1-naphthylpiperazine (1-NP, **12**). 1-NP possesses a 25-fold higher affinity for 5-HT_1 sites (i.e., K_i = 5 nM) and a 100-fold higher affinity for 5-HT_2 sites (i.e., K_i = 18 nM) than does 1-phenylpiperazine.[56] In further studies with these agents, quipazine and 2-NP behave pharmacologically as 5-HT_2 agonists whereas 1-NP acts as a 5-HT_2 antagonist; 1-NP also acts as a central 5-HT_1 agonist with properties similar to those of TFMPP.[56] 1-NP (**12**) is also a peripheral 5-HT antagonist.[73] Figure 1 shows how the structures of these agents may be related to that of 5-HT.

The arylpiperazines are not a simple class of agents; we have already seen examples of such compounds acting as a 5-HT_{1B} agonist, 5-HT_2 agonist, and 5-HT_2 antagonist. Recently, Shih and co-workers[74] demonstrated that the arylpiperazine PAPP (**13**; i.e., LY 165163) is a 5-HT_{1A} agonist and that [^{3}H]PAPP selectively labels 5-HT_{1A} sites.

(68) Huff, J. R.; King, S. W.; Saari, W. S.; Springer, J. P.; Martin, G. E.; Williams, M. *J. Med. Chem.* **1985**, *28*, 945.
(69) Clineschmidt, B. V. *Gen. Pharmacol.* **1979**, *10*, 287.
(70) Yarbrough, G. G.; Singh, D. K.; Pettibone, D. J. *Neuropharmacology* **1984**, *23*, 1271.
(71) Clineschmidt, B. V.; Reiss, D. R.; Pettibone, D. J.; Robinson, J. L. *J. Pharmacol. Exp. Ther.* **1985**, *235*, 696.
(72) Hong, E.; Sancillio, L. F.; Vargas, R. *Eur. J. Pharmacol.* **1969**, *6*, 274.
(73) Cohen, M. L.; Wittenauer, L. A. *J. Pharmacol. Exp. Ther.* **1985**, *233*, 75.
(74) Asarch, K. B.; Ransom, R. W.; Shih, J. C. *Life Sci.* **1985**, *36*, 1265.

Table II. Affinities of Selected Phenalkylamines for 5-HT_1 and 5-HT_2 Binding Sites



	R_2	R_3	R_4	R_5	R'	K_i values,[a] nM 5-HT_1	5-HT_2
PIA	H	H	H	H	H	7660	43000
OMA	OMe	H	H	H	H	3500	8130
MMA	H	OMe	H	H	H	2660	7850
PMA	H	H	OMe	H	H	79400	33600
3,4-DMA	H	OMe	OMe	H	H	64600	43300
2,5-DMA	OMe	H	H	OMe	H	1020	5200
2,4,5-TMA	OMe	H	OMe	OMe	H	46400	1650
(*R*)-(−)-MDA	H	H	OCH_2O		H	13000	3420
DOF	OMe	H	F	OMe	H	3370	1110
DON	OMe	H	NO_2	OMe	H	14100	300
(*R*)-(−)-DON	OMe	H	NO_2	OMe	H	13200	210
DOM	OMe	H	Me	OMe	H	2890	100
(*R*)-(−)-DOM	OMe	H	Me	OMe	H	3550	60
N-Me-DOM	OMe	H	Me	OMe	Me	3870	415
(*R*)-(−)-N-Me DOM	OMe	H	Me	OMe	Me	4300	260
DOET	OMe	H	Et	OMe	H	4570	100
DOPR	OMe	H	*n*-Pr	OMe	H	3170	69
DOB	OMe	H	Br	OMe	H	3340	41
(*R*)-(−)-DOB	OMe	H	Br	OMe	H	4200	24
(*S*)-(+)-DOB	OMe	H	Br	OMe	H	5000	145
N-*n*-Pr-DOB	OMe	H	Br	OMe	*n*-Pr	1320	1930
(*R*)-(−)-DOI	OMe	H	I	OMe	H	2290	10
(*S*)-(+)-DOI	OMe	H	I	OMe	H	920	35

[a] Data from ref 52–54 and from Glennon, Titeler, Seggel, and Lyon (submitted). [^{3}H]KET was used for 5-HT_2 studies.

Agents such as buspirone (**14**), gepirone (**15**), and ipsapirone (**16**; formerly isapirone or TVX Q 7821) may also produce some of their pharmacological effects via a 5-HT_1 mechanism. Buspirone and ipsapirone display a high affinity for 5-HT_{1A} sites; both compounds are essentially inactive at 5-HT_{1B} sites (IC_{50} = 26 000 nM for both) and at 5-HT_2 sites (IC_{50} = 2100 and 10 000 nM, respectively).[75] Ipsapirone is about twice as potent (IC_{50} = 9.5 nM) as buspirone at 5-HT_{1A} sites.[28,75] Similar results have been reported by Engel et al.[76] for ipsapirone; pK_D values are as follows: 5-HT_{1A} = 7.73, 5-HT_{1B} = 3.87, 5-HT_{1C} = 4.53, 5-HT_2 = 5.07.

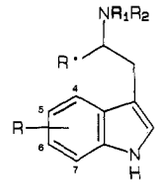
As a chemical class, the arylpiperazines cannot be termed site selective. On the other hand, when the appropriate substituents are appended, arylpiperazines can be made to be site selective. Furthermore, as serotonergic agents, the arylpiperazines appear to constitute one of the more versatile structural templates available at this time.

3. Phenalkylamines. Phenalkylamines generally display a low affinity for 5-HT binding sites; however, certain 2,5-dimethoxy derivatives not only possess a significant affinity but are fairly selective for 5-HT_2 vs. 5-HT_1 sites.[52–54] 2,5-DMA [1-(2,5-dimethoxyphenyl)-2-aminopropane; **6**, X = H] is not particularly potent at, or selective for, 5-HT_2 sites; as shown in Table II, the introduction of small alkyl or halo groups at the 4-position results in a dramatic increase in affinity and selectivity. Binding appears to be stereoselective; the *R*-(−) isomers constitute the eutomeric series but the enantiomeric potency ratio is small (i.e., 2 to 6).[54] Apparently the stereochemical requirements in this vicinity of the binding site are not very strict with respect to substituents the size of a methyl group. A recent SAR study conducted with the 4-bromo derivative DOB (**6**, X = Br) reveals that the intact structure results in optimal affinity/selectivity for 5-HT_2 sites.[54] [^{3}H]DOB is an effective radioligand for labeling 5-HT_2 sites,[55] and preliminary data suggest that it labels the high-affinity state of 5-HT_2 binding sites. Unlike other agents (e.g., tritiated ketanserin, spiperone) that label 5-HT_2 sites, DOB is not a 5-HT_2 antagonist but appears to behave as a 5-HT_2 agonist.[54,77]

4. Indolylalkylamines. It might have been thought, 5-HT being an indolylalkylamine, that this structural class would have been well-studied with respect to its binding characteristics. Unfortunately, relatively little has been done, and this has been reported only relatively recently. Some selected binding data are shown in Table III. N-Monomethylation and N,N-dimethylation of 5-HT decrease its affinity for 5-HT_1 binding sites. Relocation of the hydroxyl group to the 4- or 6-position (i.e., 4-hydroxytryptamine and 6-hydroxytryptamine, respectively) also decreases affinity (except that the affinity of 4-hydroxytryptamine is not very different from that of 5-HT for 5-HT_{1C} sites). Removal of the 5-hydroxyl group of serotonin decreases affinity at 5-HT_{1A} sites by about 50-fold and at 5-HT_{1B} sites by 500-fold, but has little effect at 5-HT_{1C} sites (Table III). Few indolylalkylamines are as potent as serotonin at 5-HT_1 binding sites; two such agents notable for their high affinity are RU 24969 (**17**; Chart III) and 5-(aminocarbonyl)tryptamine. RU 24969 is one member of a series of tetrahydropyridoindole derivatives initially synthesized by Hunt and Oberlander;[78]

(75) Peroutka, S. J. *Biol. Psychiat.* **1985**, *20*, 971.
(76) Engel, G.; Gothert, M.; Hoyer, D.; Schlicker, E.; Hillenbrand, K. *Naunyn-Schmeideberg's Arch. Pharmacol.* **1986**, *332*, 1.
(77) Glennon, R. A.; Young, R.; Benington, F.; Morin, R. *J. Med. Chem.* **1982**, *25*, 1163.
(78) Hunt, P.; Oberlander, C. In *Serotonin: Current Aspects of Neurochemistry and Function*; Haber, B., Gabay, S., Issidorides, M. R., Alivisatos, S. G. A., Eds.; Plenum: New York, 1979; p 457.

Table III. Binding Properties of Some Indolylalkylamines



agent	R_1	R_2	R_4	R_5	R_6	R'	affinity,[a] nM 5-HT_{1A}	5-HT_{1B}	5-HT_{1C}	5-HT_2 [^{3}H]KET	5-HT_2 [^{3}H]DOB
tryptamine	H	H	H	H	H	H	170	10200	50	2895[b]	50
4-hydroxytryptamine	H	H	OH	H	H	H	95	1050	40	725	
5-hydroxytryptamine (5-HT)	H	H	H	OH	H	H	3	23	33	2950 560[b]	6
6-hydroxytryptamine	H	H	H	H	OH	H	1590	5890	5500	11500	
α-Me-5-HT	H	H	H	OH	H	Me	85	1000	60	125	
N-Me-5-HT	H	Me	H	OH	H	H	5	45	280	180	
bufotenine	Me	Me	H	OH	H	H	25	910	70	380 480[b]	
5-OMe-tryptamine	H	H	H	OMe	H	H	9	400	45	2570	14
5-(aminocarbonyl)tryptamine	H	H	H	$CONH_2$	H	H	0.2	5	620		
RU 24969 (17)							5	4	400	1000 690[b]	

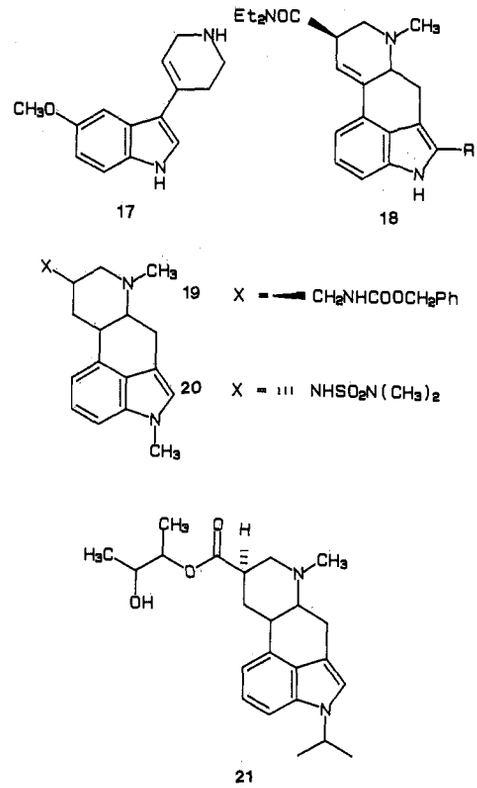
[a] Data are from Engel et al.[76] and Hoyer et al.[39] except for [^{3}H]DOB binding results; also see footnote *b*. Values are approximate and are derived from pK_D values as reported by Engel et al.[76] Results of competition studies using [^{3}H]DOB are reported as K_i (nM) values; Titeler et al.[55] and unpublished data. [b] Data (K_i values, nM) are from Battaglia et al.[178]

competition studies using [^{3}H]-5-HT reveal that this agent is nearly as potent as 5-methoxytryptamine and is more potent than 5-methoxy-*N*,*N*-dimethyltryptamine. RU 24969 is now considered to be a 5-HT_{1B} agonist and has been reported to possess from a 2- to 70-fold selectivity for 5-HT_{1B} vs. 5-HT_{1A} sites.[23,79] 5-(Aminocarbonyl)tryptamine possesses a 5- to 10-fold higher affinity for 5-HT_{1A} and 5-HT_{1B} sites than does 5-HT (Table III); as a consequence, this agent is currently undergoing a variety of pharmacological evaluations.[80-82]

In general, indolylalkylamines display a lower affinity for 5-HT_2 sites than for 5-HT_1 sites. The binding of serotonin to 5-HT_2 sites also seems to be somewhat insensitive to certain types of structural modification when [^{3}H]KET is used as the radioligand (e.g., O-methylation; see Table III). The affinity of indolylalkylamines for 5-HT_2 sites is significantly higher (by 1–2 orders of magnitude) when [^{3}H]DOB is used to label these sites (e.g., see Table III); however, too little data are currently available with this radioligand to allow any conclusions to be drawn at this time.

5. Ergolines. Ergolines played a role in the initial binding studies involving 5-HT sites (i.e., as discussed above, [^{3}H]LSD was used as a radioligand to label such sites). The ergolines seem to possess an inherent advantage and disadvantage over many other agents: many ergolines display a very high affinity, but a rather low selectivity, for 5-HT binding sites. LSD is a case in point. The affinity of (+)-LSD (18, R = H) for 5-HT_1 and 5-HT_2 sites is nearly identical;[11] the affinity of this agent for 5-HT subpopulations is as follows: 5-HT_{1A}, 2.6 nM; 5-HT_{1B}, 150 nM; 5-HT_{1C}, 12 nM; and 5-HT_2, 2.4 nM.[76] In addition to their high affinity for serotonin sites, many ergolines display a high affinity for dopaminergic and adrenergic

Chart III. Indolylalkylamines and Ergolines

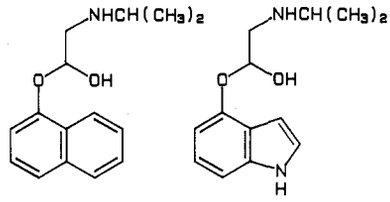


binding sites. The binding profiles of various ergolines have been reported.[83,84]

Tritiated LSD and [^{125}I]iodo-LSD (18, R = ^{125}I) have been used as radioligands. Tritiated mesulergine (19) has also been employed to label 5-HT_{1C} and 5-HT_2 sites. Other ergolines, such as metergoline (20) and methysergide are

(79) Middlemiss, D. N. *J. Pharm. Pharmacol.* **1985**, *37*, 434.
(80) Feniuk, W.; Humphrey, P. P. A.; Watts, A. D. *Br. J. Pharmacol.* **1984**, *82*, 209P.
(81) Shenker, A.; Maayani, S.; Weinstein, H.; Green, J. P. *Eur. J. Pharmacol.* **1985**, *109*, 427.
(82) Saxena, P. R.; Verdouw, P. D. *Br. J. Pharmacol.* **1985**, *84*, 533.
(83) Closse, A.; Frick, W.; Dravid, A.; Bolliger, G.; Hauser, D.; Sauter, A.; Tobler, H.-J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1984**, *327*, 95.
(84) Beart, P. M.; McDonald, D.; Cincotta, M.; De Vries, D. J.; Gundlach, A. L. *Gen. Pharmacol.* **1986**, *17*, 57.

Chart IV. (Aryloxy)propanolamines

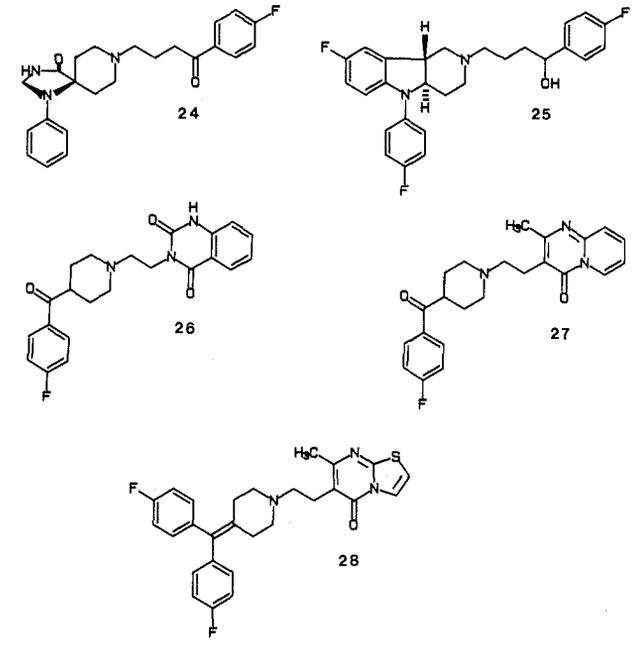


22 23

5-HT antagonists; with respect to binding, both of these agents are 50- to 100-fold more potent at 5-HT_2 sites than at [^{3}H]-5-HT-labeled 5-HT_1 sites. A more detailed examination of the binding of metergoline to 5-HT_1 subpopulations reveals that this agent also possesses a high affinity for 5-HT_{1C} sites (0.6 nM) relative to 5-HT_{1A} (8 nM), 5-HT_{1B} (40 nM), and 5-HT_2 (0.9 nM) sites.[76] Various ergopeptines act as mixed serotonin agonists/antagonists;[83] the high affinity of ergopeptines, such as bromocriptine and dihydroergocryptine, at 5-HT binding sites suggests that there exists a region of bulk tolerance to accommodate the large 8-position substituent.[83,84] Because of the unusually high affinity of ergolines for serotonin binding sites, it would seem that structural modification of these agents (in order to achieve a greater selectivity) would be a worthwhile goal. LY 53857 (**21**), for example, is an ergoline derivative that acts as a 5-HT_2 antagonist but that possesses minimal affinity for adrenergic receptors.[85]

6. (Aryloxy)propanamines. In 1977, Middlemiss and co-workers[86] demonstrated that certain β-adrenergic blocking agents could bind in a stereoselective manner to 5-HT_1 binding sites. Propanolol (**22**; Chart IV) and pindolol (**23**) also bind selectively to 5-HT_1 vs. 5-HT_2 sites;[87] binding is stereoselective with the S-(−) isomers being more potent than their *R*-(+) enantiomers.[87] Interestingly, whereas both of these agents possess a rather low affinity for 5-HT_{1C} sites, (−)-propanolol is somewhat selective for 5-HT_{1B} sites and (−)-pindolol somewhat selective for 5-HT_{1A} sites (Table I).[39] Racemic cyanopindolol is more potent than either pindolol or propanolol and binds equally well to 5-HT_{1A} and 5-HT_{1B} sites,[76] but iodocyanopindolol seems to be somewhat selective for 5-HT_{1B} sites and [^{125}I]iodocyanopindolol has been used as a radioligand to label these sites.[36] From a pharmacological standpoint, it is unclear as to what type of activity these agents possess. Evidence suggests that they may act as 5-HT_1 antagonists,[88-94] and if this is the case, then they constitute one of the first examples of 5-HT_1-selective antagonists. However, being β-adrenergic antagonists, these agents are obviously not selective for 5-HT; there is also some evidence that their antagonism of some 5-HT-mediated behavior may involve their action at 5-HT_2 sites.[95]

Chart V. Alkylpiperidines



7. Alkylpiperidines. Although "alkylpiperidines" is probably not the most descriptive term that might be used to classify this group of agents, the alkylpiperidine moiety appears to be one of the few structural features that these agents have in common. All of the agents to be discussed act as 5-HT antagonists and, for the most part, as 5-HT_2 antagonists. Several butyrophenone neuroleptics, most notably spiperone (**24**; Chart V), possess a high affinity for 5-HT_2 binding sites.[11,14] Spiperone also possesses a high affinity for 5-HT_{1A} sites (Table I) and dopamine binding sites. As mentioned above, [^{3}H]spiperone has been used to label 5-HT_2 sites and played an instrumental role in the original definition of 5-HT_2 (and 5-HT_{1A}) sites.[11,22] Another agent that played a pivotal role in 5-HT research is ketanserin (**26**). This agent was developed as part of a program on histamine antagonists and the discovery of its antiserotonin properties, coupled with the fact that it was a new structural prototype, generated considerable interest. Unlike spiperone, ketanserin (**26**) has a low affinity for 5-HT_1[13] and 5-HT_{1A}[28,39] binding sites (Table I). However, ketanserin does display an appreciable affinity for dopaminergic, histaminergic, and adrenergic binding sites.[13] Ketanserin also displays an appreciable affinity for 5-HT_{1C} sites,[39] though its affinity for these sites is still at least 50 times less than that at 5-HT_2 sites. Pirenperone (**26**) is a structurally related agent with a binding profile similar to that of ketanserin.[96] The newest relative of ketanserin is ritanserin (**27**). Ritanserin has no affinity for 5-HT_1 sites (at concentrations of up to 10000 nM) and is more selective than ketanserin in in vitro binding to various other neurotransmitter binding sites.[97] Preliminary results suggest that ritanserin is a potent and selective 5-HT_2 antagonist.[97-99]

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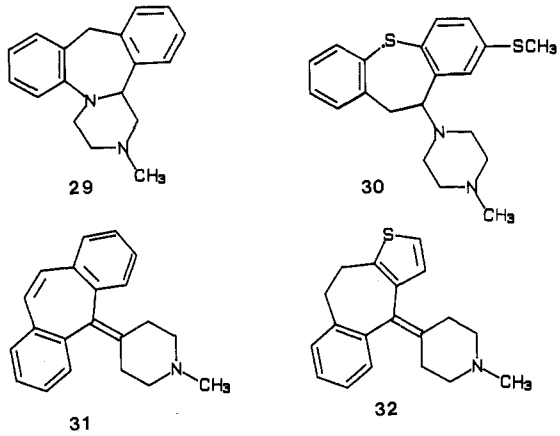
Chart VI. Miscellaneous Structures



Another agent that falls into this category is dihydroflutroline (CP 52, 215) (**28**), which, like flutroline, possesses a high affinity for 5-HT and dopamine binding sites[100] and acts as a 5-HT_2 antagonist.[99]

Detailed SAR studies on this class of 5-HT_2 antagonists have not yet been published. However, casual inspection of the structures of these agents reveals several similarities. These agents all possess a piperidine ring attached to an aromatic ring via a four-atom spacer (the third atom of which possesses either a carbonyl oxygen or a hydroxyl group). In several instances [e.g., ketanserin (**26**), piperperone (**27**), ritanserin (**28**)], the spacer is incorporated into a cyclic structure. Also, in each case, the 4-position of the piperidine ring is attached to an sp^2-hybridized carbon atom or a heteroatom. As with the ergolines, these agents possess a high affinity, but in many cases a low selectivity, for 5-HT (vs. other neurotransmitter) binding sites; structural modification of these compounds might result in agents with greater selectivity for 5-HT sites.

8. Miscellaneous Structures. Before concluding this section, there are several other agents worthy of mention. Agents such as mianserin (**29**; Chart VI), methiothepin (**30**), cyproheptadine (**31**), and pizotyline (pizotifen, BC-105) (**32**) have all been shown to (amongst other things) behave as serotonin antagonists; see Arvidsson et al.[20] for a review. Each of these agents binds, with varying degrees of selectivity, to 5-HT_2 sites.[15] [^{3}H]Methiothepin and [^{3}H]mianserin have seen limited application for the labeling of 5-HT sites,[12] and [^{3}H]mianserin is still used on occassion for this purpose.[84] Mianserin and cyproheptadine share a similar binding profile[74] (shown for mianserin in Table I); it might be noted that these agents display a significant affinity for 5-HT_{1C} sites. Methiothepin is somewhat less selective amongst subpopulations of 5-HT_1 binding sites.[39]

Functional Significance of Serotonin Sites

It should be noted from the very outset that, while extensive efforts are being made to determine the functional significance of serotonin binding sites, very few conclusions can be drawn at this time.

1. Serotonin-Related Events. The 5-HT_{1A} agonist 8-OH-DPAT facilities male rat sexual behavior,[101,102] but a role for 5-HT_{1A} binding sites is still in question.[103] 8-OH-DPAT also produces a pronounced hypotensive effect in animals; this effect may be 5-HT_{1A}-mediated.[104] In general, 5-HT_{1A} agonists produce a hypothermic response in rodents,[20] whereas 5-HT_2 agonists produce hyperthermia in animals; in fact, this hyperthermia test was once used as a model for hallucinogenic activity.[20] The hypothermic effect of 8-OH-DPAT (**2**) may be due to its agonist action at presynaptic 5-HT receptors[106] and is not antagonized by 5-HT_2 antagonists;[105] indeed, certain 5-HT_2 antagonists can produce hypothermia.[105,106]

Serotonin agonists are capable of producing an effect in animals (most characteristically in rodents, but also observed in other animals) that has been termed the "serotonin syndrome". This syndrome consists of, for example, hindlimb abduction, forepaw treading, and Straub tail. Other symptoms occasionally observed are head twitch and "wet dog shake". Apparently, certain aspects of the serotonin syndrome are produced by 5-HT_{1A} and 5-HT_{1B} agonists, whereas head twitch/wet dog shake are produced by 5-HT_2 agonists (e.g., see Green and Heal,[94] Peroutka et al.,[107] and Lucki et al.[108]).

8-OH-DPAT also serves as a training drug in tests of discriminative stimulus control of behavior in rats. By use of an operant procedure, animals can be trained to recognize or discriminate a centrally acting agent (i.e., a "training drug") from saline vehicle. Administration of "challenge drugs" to these animals can result in "stimulus generalization" if the animals perceive the challenge drug as producing stimulus effects similar to those of the training drug. The 8-OH-DPAT stimulus generalizes to 8-OMe-DPAT (**3**) but not to the 5-HT_2 agonist DOM (**6**, X = CH_3) or the 5-HT_{1B} agonist TFMPP (**7**, R_2 = H, R_3 = CF_3),[109] suggesting that 8-OMe-DPAT, but not DOM or TFMPP, produces effects similar to those of 8-OH-DPAT.

Several groups of investigators have argued that serotonin autoreceptors may be related to 5-HT_1 binding sites.[110,111] There has been some disagreement as to which subpopulation of 5-HT_1 sites may be most closely related to autoreceptors; current evidence favors the 5-HT_{1B} sites,[76,91,112] although the 5-HT autoreceptors located on the serotonergic cell body in the dorsal raphe may be of the 5-HT_{1A} type.[113] Because various 5-HT uptake inhibitors reduce the potency of 5-HT autoreceptor agonists,[114,115] there may be a functional relationship between autoreceptors and uptake sites.

The general pharmacology of TFMPP, mCPP, and related arylpiperazines has been reviewed.[116,117] Recent

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reports suggest the involvement of a 5-HT_{1B} mechanism in the modulation of aggression in rodents.[118,119] TFMPP serves as a training drug in drug discrimination studies; the TFMPP stimulus generalizes with mCPP, RU 24969, and 2-MPP, but not with the 5-HT_{1A} agonist 8-OH-DPAT or the 5-HT_2 agonists DOM and DOB.[120,121] Recently, clinical trials have been conducted with mCPP;[122,123] however, there has not yet been a demonstration of the existence of 5-HT_{1B} sites in human brain.

5-HT_{1C} sites represent the newest 5-HT_1 subpopulation of sites; relatively little information is available about these sites. Mammalian choroid plexus is rich in 5-HT_{1C} sites; Pazos et al.[38] reason that because the main physiological role of the choroid plexus is the control of the volume and composition of cerebrospinal fluid (CSF), 5-HT_{1C} sites may play a role in the regulation of CSF production and in cerebral circulation. As a consequence, they speculate that there might be some involvement of these sites in migraine and stroke. Because of the influence of CSF on CNS activity, it was further speculated (although the authors emphasized that no data are yet available) that 5-HT_{1C} sites might also be involved in the regulation of analgesia, sleep, and cardiovascular function.

A 5-HT_2 mechanism may be involved in certain behavioral effects produced by serotonin agonists[124,125] (also see above discussion of head twitch/wet dog shake behavior). The 5-HT_2 agonists DOM and DOI serve as training drugs in drug discrimination studies; stimulus generalization occurs with other 5-HT_2 agonists, but not with the 5-HT_{1A} agonist 8-OH-DPAT or the 5-HT_{1B} agonists TFMPP, mCPP, or RU 24969.[51,99]

There are other facets of central and noncentral serotonin sites that need to be further explored. For example, postmortem studies reveal a decrease in the density of 5-HT_2 binding sites in patients suffering from Huntingtons disease[126] and Alzheimers type senile dementia.[127] Serotonin may play a role in memory and learning. Alaproclate and zimelidine facilitate memory retrieval in mice; these effects are antagonized by quipazine, but not by cyproheptadine.[128] Direct- and indirect-acting 5-HT agonists increase serum corticosterone, growth hormone, and prolactin levels in rodents[117,129] and can reduce food intake in animals.[117] With respect to this latter activity, postsynaptic 5-HT agonists generally decrease feeding; 8-OH-DPAT elicits feeding in satiated rats and it has been proposed that this is due to direct stimulation of 5-HT_{1A} autoreceptors.[130] Buspirone and ipsapirone also increase food intake, whereas mCPP, RU 24969, and quipazine cause anorexia in rats.[131]

2. Drugs with Serotonergic Properties. Neuroleptic Agents. Neuroleptic agents are commonly thought to act via a dopaminergic mechanism; however, many neuroleptics bind with high affinity to 5-HT_2 sites, and some (e.g., clozapine) possess a higher affinity for these sites than they do for dopamine receptor sites.[14,45,132] Bennett et al.[133] have reported changes in serotonin receptors in postmortem brain tissue of schizophrenics, but these findings are still controversial.[145] Although it is not known whether 5-HT_2 sites play a role in the mechanism of action of neuroleptic agents, it is clear that various neuroleptics possess activity as 5-HT_2 antagonists.[132,134]

Antidepressants. Various antidepressants, like the neuroleptics, possess a high affinity for serotonin (and, in particular, for 5-HT_2) binding sites.[14,135,136] There does not appear to be a direct correlation between binding affinities and antidepressant potencies for a series of structurally unrelated antidepressants.[136] However, chronic antidepressant treatment results in adaptive changes in postsynaptic 5-HT mechanisms that appear to result in 5-HT sub- or supersensitivity development depending on the particular 5-HT system being analyzed.[137] Chronic antidepressant treatment leads to a decrease in the number of 5-HT_2 sites in cortical tissue from animals[138,139] and from suicide victims.[46] However, the relevance of reduced numbers of 5-HT_2 sites to antidepressant activity is not clear. Chronic and acute treatment of animals with 5-HT_2 antagonists also results in a decrease in 5-HT_2 binding sites, leading to the suggestion that 5-HT_2 antagonists might be effective antidepressants. But, this effect may be more related to 5-HT_2 antagonism than to antidepressant activity in that certain of the agents that produce this effect lack activity as antidepressants.[140] Nevertheless, some agents with activity as 5-HT_2 antagonists (e.g., trazodone, mianserin, pizotyline) do possess antidepressant activity.[20] The new 5-HT_2 antagonist ritanserin also shows beneficial clinical effects in the treatment of neurotic depression.[141] A recent hypothesis for the efficacy of 5-HT_2 antagonists in the treatment of

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mood disorders is acute blockade of 5-HT_2 sites followed by down regulation of these sites.[142]

Hallucinogenic Agents. Hallucinogenic agents have long been postulated to act via a serotonergic mechanism. Many of the early studies focused on the mechanism of action of LSD (18, R = H), an agent now known to interact both at 5-HT_1 and 5-HT_2 sites as well as at other neurotransmitter sites. Ketanserin antagonizes mescaline-induced head twitch in rats,[14] and pirenperone was initially introduced as an LSD antagonist.[143] Glennon and coworkers[51] demonstrated that both of these 5-HT_2 antagonists can attenuate the stimulus effects of the hallucinogen DOM and that pirenperone prevents DOM-stimulus generalization to, for example, LSD and mescaline. Speculation that hallucinogenic agents might be acting as 5-HT_2 agonists were supported by recent studies that demonstrate a significant correlation between the affinities of a series of agents for 5-HT_2 sites and their human hallucinogenic potencies.[53] Colpaert and Janssen[144] have suggested that the discriminative stimulus properties of LSD might also involve a 5-HT_1 component. It remains to be determined if the same is true of the stimulus or hallucinogenic actions of other hallucinogenic agents; 5-HT_1 agonists such as MK-212 and mCPP are not hallucinogenic in humans.[70,122] Quipazine is the one example of a 5-HT_2 agonist that has not been reported to be hallucinogenic.[145] This situation remains to be resolved, but may be related to a possible lack of selectivity of quipazine for 5-HT_2 vs. some other neurotransmitter binding site. Clinical studies involving the administration of 5-HT_2 antagonists in combination with hallucinogenic agents have not been reported.

Antianxiety Agents. Serotonin has long been recognized as being involved, in one way or another, in the action of anxiolytic agents.[146-148] The exact nature of this relationship is unclear with respect to the benzodiazepine anxiolytics, and indeed, these agents bind at 5-HT_1 and 5-HT_2 sites with a rather low affinity.[149] However, some of the "second generation" anxiolytic agents (e.g., buspirone, gepirone, ipsapirone) bind with high affinity to 5-HT_1, and in particular to 5-HT_{1A}, sites.[75,76,150,151] Because these agents possess a low affinity for benzodiazepine binding sites, it has been speculated that their action might be an expression of a 5-HT_{1A}-site interaction. Anxiolytic agents that bind at the benzodiazepine/GABA supramolecular complex produce muscle relaxation, sedation, ataxia, and anticonvulsant activity in addition to their antianxiety effect. With the second generation anxiolytics, these "side effects" are apparently lacking, or are at least minimized, in various animal models.[150,152] These serotonergic anxiolytics, then, offer the prospect of an entirely new mechanistic class of anxiolytic and, in fact, anxioselective agents. Clinical trials with some structurally related agents have also shown anxiolytic activity with a lack of sedative and muscle relaxant effects,[153] and buspirone apparently produces less memory impairment than diazepam.[154]

At this time, there is evidence that these serotonergic anxiolytic agents can produce both agonist and antagonist effects; whether they act as mixed agonist–antagonists or whether they act as agonists at one site and as antagonists at another site is unknown. For example, 8-OH-DPAT is active in a particular (i.e., licking conflict) animal model for anxiolytic activity, but reverses a similar effect produced by *p*-chlorophenylalanine in the same procedure.[95] There has also been a claim that certain 5-HT agonists, including 8-OH-DPAT, produce an anxiogenic effect in animals.[155] With use of rats trained to discriminate the 5-HT_{1A} agonist 8-OH-DPAT from saline, stimulus generalization results upon administration of buspirone, gepirone, and/or ipsapirone,[156,157] suggesting that these agents may be acting as 5-HT_{1A} agonists. Likewise, animals trained to discriminate ipsapirone from saline generalized to 8-OH-DPAT and buspirone (but not to TFMPP, RU 24969, quipazine, diazepam, or pentobarbital).[158] However, 8-OH-DPAT evokes the "serotonin syndrome" in rodents whereas buspirone[159] and ipsapirone[158,159] do not. Ipsapirone produces a dose-dependent inhibition of 8-OH-DPAT-induced hypothermia in mice, suggesting that it may be an antagonist of presynaptic (possibly somatodendritic) 5-HT_{1A} sites;[160] on the other hand, 8-OH-DPAT-induced hypothermia is only partially antagonized by ipsapirone in rats.[160] Although ipsapirone has no effect on RU 24969-induced locomotor activity and 5-HTP-induced head twitch behavior in mice and rats, it enhances 5-OMe-DMT-induced head twitch in mice.[160] Both buspirone and ipsapirone can antagonize 5-OMe-DMT- and 8-OH-DPAT-induced serotonin syndrome,[159] and buspirone, ipsapirone, and gepirone antagonize quipazine-induced head shake behavior in rats,[159,161] but ipsapirone fails to antagonize the stimulus effects of 8-OH-DPAT.[162] Buspirone possesses a considerable dopaminergic component of action,[163] but it is unlikely that this is related to its anxiolytic effects in that gepirone and several other structurally related agents lack this dopaminergic activity.[164,165] Gardner has reviewed other effects of these and related agents on various animal models of anxiety.[152]

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There is also some evidence of a relationship between antianxiety activity and 5-HT_2 antagonism. The antidepressant trazodone is claimed to produce an antianxiety profile in animals and anxiolytic activity in humans.[166] Ritanserin is active in some animal models of anxiolytic activity (e.g., emergence), but not in others (e.g., conflict).[97,98] Nevertheless, ritanserin is a clinically effective, nonsedating anxiolytic agent,[167] and its anxiolytic properties appear to be qualitatively different from those of the benzodiazepines.[168,169] Pirenperone and several other 5-HT_2 antagonists produce an anxiolytic profile (though not necessarily as pronounced or robust as that of ritanserin) in animal models.[98,170,171]

Cardiovascular Agents. A motivating factor that led Page and co-workers to the discovery of serotonin was a search for endogenous substances responsible for hypertension. Today, over 35 years later, it is realized that 5-HT and 5-HT agonists exert a complex action on cardiovascular function, and the exact role of 5-HT in the pathogenesis of hypertension remains controversial. Janssen has commented that antagonism of the vasoconstrictor effects of 5-HT is a general property of 5-HT_2 antagonists;[170] ketanserin in particular is being investigated in several cardiovascular areas, including hypertension (essential hypertension, acute hypertensive episodes), peripheral vascular disease (intermittent claudication, scleroderma, Raynaud syndrome, acute peripheral vasoconstriction), thrombic or embolic episodes (acute peripheral thrombophlebitis, acute hemorrhoidal thrombosis, pulmonary embolism), and cardiopulmonary emergencies (heart failure, respiratory failure, ischemic heart disease, acute anuria).[96,170] Much of the work in these areas has been summarized at a meeting of the International Society for Hypertension[172] and in a recent monograph by Vanhoutte.[173] Ketanserin produces a hypotensive effect in animals and, after acute administration in humans, lowers blood pressure in normal subjects and in hypertensive patients.[172] It appears to act by reducing systemic vascular resistance, but it is unclear whether this effect is a result of 5-HT_2 antagonism, α_1-adrenergic antagonism, or a combination of both. Although evidence is mounting for the latter, the finding that ketanserin lowers blood pressure in patients with autonomic dysfunction suggests that the effects of ketanserin (at least in these patients) is not α_1-mediated.[174] Amery and co-workers[175] have reviewed some of the current evidence that implicates a role for serotonin in the acute hypotensive effects of ketanserin; these include inhibition of 5-HT-induced platelet aggregation, inhibition of (direct) 5-HT-induced vasoconstriction of vascular smooth muscle, and reduction in plasma aldosterone levels. Although the hypotensive/antihypertensive effects of 5-HT_2 antagonists seem to be peripherally mediated, there is evidence that in some species (e.g., dogs) these effects may involve centrally mediated 5-HT_2 antagonism.[176]

Epilogue

It is clear that serotonin has received a considerable amount of attention over the past 5 years. (And it might be added that this Perspective is not a comprehensive review of the serotonin literature; for example, scant mention was made of peripheral serotonin receptors, and no mention was made of important issues such as the regulatory processes involved in binding.) However, with the possible exception that a novel class of anxiolytic agents may act via a serotonergic mechanism, no new claims have been made for serotonin. That is, serotonin has not been implicated in any activity for which there had not already been prior evidence of serotonergic involvement. On the other hand, the discovery of multiple populations of 5-HT binding sites provides an opportunity to study the actions of serotonin in finer detail and to develop agents that, if selective for a particular site, might be selective in their actions. The most exciting example of this is, again, the serotonergic anxiolytic agents.

In addition to the treatment of anxiety, selective modulation of serotonergic systems may ultimately find therapeutic application in the treatment of various other mood disorders, mental disorders, cardiovascular diseases, and obesity. But, as a cautionary note, much more work is necessary in order to avoid some of the confusion that was encountered in the dopamine field when attempts were made to extrapolate binding data to receptor sites or therapeutic targets.

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