Pharmacology Biochemistry & Behavior, Vol. 40, pp. 1009–1017. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Serotonin Receptors and Their Ligands: A Lack of Selective Agents

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GLENNON, R. A. AND M. DUKAT. *Serotonin receptors and their ligands: A lack of selective agents.* PHARMACOL BIOCHEM BEHAV **40**(4) 1009–1017, 1991.—Four major families of serotonin (5-hydroxytryptamine; 5-HT) receptors have been identified: 5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_4. At this time, there is a general consensus that the 5-HT_1 family can be further subdivided into 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, and 5-HT_{1P} subpopulations. In addition, there are several other populations of less well-defined 5-HT receptors. The purpose of this presentation is to discuss 5-HT receptor nomenclature and the agents that are commonly used to investigate each receptor population in as much as it will serve to provide background for the remainder of the symposium. There is presently available an abundance of serotonergic agents; however, these agents are only semiselective, and none can be considered truly selective for a particular population of 5-HT receptors. As useful as these agents have been for the identification and characterization of 5-HT receptors, there remains a need for the development of new, more selective ligands.

Serotonin receptors 5-HT_1 5-HT_2 5-HT_3 5-HT_4 Ligands Binding

THE present overview is not meant to supplant other, more extensive reviews. Rather, its goal is 1) to provide a brief survey of the most common (and some newer) agents employed in serotonin (5-HT) receptor research and 2) to serve as a general introduction for the subsequent presentations of this symposium. Indeed, very little detail will be provided and reference will be made, as much as possible, to review articles rather than to the primary literature. Another goal of this paper is to emphasize the nonselective nature and shortcomings of the presently available agents and to reinforce the idea that there exists a need for the development of newer, more selective serotonergic ligands.

Serotonin Receptor Nomenclature

Serotonin receptor/binding sites can be divided into several different families: 5-HT_1, 5-HT_2, 5-HT_3, and 5-HT_4 (Fig. 1). 5-HT_{pre} sites have also been described (26). The 5-HT_1 family is further divided into subpopulations. The first 5-HT_1 subpopulations to be described were 5-HT_{1A} and 5-HT_{1B} (44). 5-HT_{1A} receptors are the most widely investigated of the 5-HT_1 subpopulations, and have attracted considerable interest for their potential clinical significance (11, 20, 56). 5-HT_{1B} receptors, on the other hand, have been much less investigated; 5-HT_{1B} receptors are found in certain species of animals (e.g., rat, mouse), but are believed to be absent in the human brain. Indeed, 5-HT_{1D} receptors are present in those regions of human brain where 5-HT_{1B} receptors are expected to be found (32). This has led to speculation that 5-HT_{1D} receptors are evolutionary counterparts of 5-HT_{1B} receptors in higher animals. There is also some evidence for multiple populations of 5-HT_{1D} receptors (42). More recently described 5-HT_1 subpopulations include 5-HT_{1E}, 5-HT_{1P} and 5-HT_{1R} sites. 5-HT_{1E} sites (37), originally thought to be homogeneous, may actually consist of a heterogeneous population of 5-HT_1 sites that are labeled by [^{3}H]5-HT once all other populations of 5-HT_1 sites have been masked; these sites deserve additional investigation. 5-HT_{1P} receptors [see Gershon et al. (18) and Sanger and Wardle (51) for reviews] are a 5-HT_1 subpopulation found in the gastrointestinal tract, and appear to be different from other, previously described 5-HT_1 receptors. Two populations of "P" receptors were originally described: 5-HT_{1P} and 5-HT_{2P}; it is now thought that the 5-HT_{2P} and 5-HT_3 receptors are synonymous [see Gershon et al. (17) for further discussion]. 5-HT_{1R} receptors (43), found in rabbit brain, may be heterogeneous and may constitute a rabbit counterpart of 5-HT_{1B} or 5-HT_{1D} receptors. 5-HT_{1A} (14), 5-HT_{1C} (34), and, more recently, 5-HT_{1D} (5) receptors have been cloned; the amino acid sequence for 5-HT_{1A} and 5-HT_{1C}, but not 5-HT_{1D}, have been published.

5-HT_2 receptors were originally described in 1979 (46); these receptors have also been referred to, on occasion, as S_2 receptors. The amino acid sequence of the 5-HT_2 and 5-HT_{1C} receptors shows an 80% homology in the transmembrane region and are 51% homologous overall (28). Both types of receptors are coupled to a phosphoinositol second messenger system, and agents that bind at one receptor typically bind at the other. It has been suggested that the 5-HT_2 and 5-HT_{1C} receptors be termed 5-HT2A and 5-HT2B (47) or 5-$HT_{2\alpha}$ and 5-$HT_{2\beta}$ receptors (27), respectively. It has been further suggested that 5-HT_2 receptors exist in two states: a G-protein-coupled high-affinity state (5-HT_{2H}) and a uncoupled low-affinity state (5-HT_{2L}) (57). It has been alternatively argued (45) that these two states represent two distinct receptors: 5-HT_{2A} and 5-HT_{2B} receptors (not to be confused with the above mentioned 5-HT2A and 5-HT2B receptors). Using cells transfected with cloned 5-HT_2 receptor genes (rat and human), recent radioligand binding studies have concluded that only a single receptor type is expressed (4,57).

ALPHABETICAL LISTING OF STRUCTURES

1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane (DOI)	10B
1-(3-Trifluoromethylphenyl)piperazine (TFMPP)	8A
1-(4-Bromo-2,5-dimethoxyphenyl)-2-aminopropane (DOB)	10A
2-Methyl 5-HT	11A
5-Carboxamidotryptamine (5-CAT; 5-CT)	2B
5-Fluoro 8-OH DPAT	7E
5-HTQ	11C
5-Methoxy-N,N-dimethyltryptamine (5-OMe DMT)	2A
8,11-Dimethoxyaporphine	7F
8-OH DPAT [8-Hydroxy-2-(di-n-propylamino)tetralin]	5A
10-Methyl-11-hydroxyaporphine (MHA)	5B
BMY 7378	7A
Buspirone	5C
CC-263	9B
CP-93,129	8C
Cyanopindolol	8E
DOB	10A
DOI	10B
Gepirone	5D
GR 38032	12A
GR 65630	12B
ICS 205-930	12F
Ipsapirone	5E
Ketanserin	10C
LY 278585	12G
Lysergic acid diethylamide	2C
mCPBG	11B
MDL 72222	12C
MEP-177	7G
meta-Chlorophenylbiguanide	11B
Methiothepin	2E
Methysergide	2F
MHA	5B
NAN-190	7B
Ondansetron	12A
Pindolol	6C
Pirenperone	10E
Propranolol	6B
Quipazine	2D
Renzapride	12E
Ritanserin	10D
RK-153	7H
RK-167	7I
RU 24969	8B
Serotonin O-glycyltyrosinamide	9C
SM-3997 (Tandospirone)	7C
Spiperone	6A
Sumatriptan	9A
Tandospirone (SM-3997)	7C
TFMPP	8A
Wy-47,846	7D
Zacopride	12D

Although it seems likely that 5-HT_2 (i.e., 5-$HT_{2\alpha}$) receptors are homogeneous, and although they and 5-HT_{1C} receptors may belong to the same family, only the terms 5-HT_2 and 5-HT_{1C} will be used in this review in order to avoid needless confusion.

5-HT_3 receptors have been found in the brain and in the periphery and belong to a ligand-gated ion channel super family. Although there is some evidence for heterogeneity (i.e., 5-HT_{3A}, 5-HT_{3B}, 5-HT_{3C}) [e.g., see Richardson et al. (49) and Wallis (60)] from studies with peripheral tissue, only a single type of 5-HT_3 receptor has been detected in brain tissue [for reviews, see: (9, 16, 22, 23, 35)]. Most of what follows deals almost exclusively with 5-HT_1, 5-HT_2 and 5-HT_3 receptors. For additional information on these and the other 5-HT receptors, see reviews by Glennon et al. (22), Glennon and Raghupathi (23) and Peroutka (45).

Commonly Used Agents

The purpose of this section is to describe those agents that are generally considered to be fairly selective for a particular population of 5-HT receptors and/or agents that are routinely used as standard agonists and antagonists. Comments will be made about the selectivity and/or advantages and disadvantages of each agent. This is not meant to be a comprehensive listing, and the interested reader is referred to several reviews for greater detail (22,23). Several newer (and consequently less well-investigated) agents will also be mentioned; here too, there is no intent to be comprehensive [the reader is referred to (22) and (62) for discussions of newer serotonergic agents]. At the very outset, it should be realized that there are no site-specific serotonergic agents, i.e., agents that bind exclusively at a single population of 5-HT receptors. There are available, however, a number of semiselective agents (21), i.e., agents that bind predominantly at one or two types of receptors with significantly lower affinity for other populations of 5-HT receptors. These agents have been the mainstay of 5-HT pharmacology and account for most of what is currently known about 5-HT receptors.

Nonselective agents. Several agents were once thought to be site-selective but, with the discovery of additional populations of 5-HT receptors, it is now realized that these agents are quite nonselective. Other agents have been historically used as 5-HT agonists or antagonists and are also nonselective. Nevertheless, these agents are still in use today and constitute important ligands for investigating 5-HT receptors (see Fig. 2 for some representative examples). Most tryptamine analogs are nonselective; 5-methoxytryptamine, i.e., the O-methyl derivative of 5-HT, and 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT) are 5-HT_1/5-HT_2/5-HT_4 agonists. The presence of the O-methyl group reduces the agonist potency of these agents at 5-HT_3 receptors. Bufotenine (5-OH DMT) binds at all (including 5-HT_3) populations of 5-HT receptors. 5-Carboxamidotryptamine (5-CAT) is considered a universal 5-HT_1 agonist; however, its affinity and potency at the various subpopulations of 5-HT_1 receptors vary considerably [e.g., see (31,33)].

Some agents are nonselective and act as agonists at certain populations of receptors and as antagonists at others; for example, the arylpiperazine quipazine is a 5-HT_{1B}/5-HT_2 agonist (22) and a 5-HT_{1A}/5-HT_3 antagonist (60). There are a number of nonselective 5-HT antagonists; agents such as mianserin, metergoline, methysergide are mixed 5-HT_1/5-HT_2 antagonists. Most, although not all, 5-HT_1/5-HT_2 antagonists are either inactive or are only weakly active as 5-HT_3 antagonists. The ergolines represent an interesting series of compounds; ergolines do not bind at 5-HT_3 receptors and, typically, display little selectivity for the various other populations of 5-HT sites. They can behave, depending upon their substituents, as agonists, partial agonists, or antagonists. Indeed, certain ergolines, such as (+)LSD, bind at most populations of 5-HT receptors with very high affinity ($Ki<10$ nM). Because the ergolines constitute conformationally restricted and stereochemically defined entities, and because many ergolines bind in a nonselective manner, it seems logical that they represent a conformation by which 5-HT interacts at these receptors (i.e., "common template hypothesis" or "com-

MAJOR FAMILIES OF 5-HT RECEPTORS

Family:	5-HT$_1$-Like	5-HT$_2$	5-HT$_3$	5-HT$_4$
Subpopulations:	5-HT$_{1A}$	5-HT$_2$	5-HT$_{3A}$ (?)	5-HT$_4$
	5-HT$_{1B}$		5-HT$_{3B}$ (?)	
	---------->	5-HT$_{1C}$	5-HT$_{3C}$ (?)	
	5-HT$_{1D}$			
Transduction mechanism:	Cyclase-coupled	PI-coupled	Ligand-gated ion channel	Cyclase-coupled

FIG. 1. Major families of 5-HT receptor/binding sites. See text for further discussion of these and other sites.

mon conformation hypothesis") (23). Conversely, because ergolines do not bind with appreciable affinity at 5-HT$_3$ receptors, either they represent a conformation that is not suitable for binding at these receptors, or the 5-HT$_3$ receptors cannot tolerate the added bulk of the ergoline structure relative to that of 5-HT. We have utilized this structural relationship to investigate the different populations of 5-HT receptors. For example, 1-phenylpiperazine binds with relatively low affinity (K_i = 500–10,000 nM) at most populations of 5-HT receptors. In its preferred chair conformation, it can mimic either the benzene ring or the pyrrole ring of the ergolines (Fig. 3). Regardless of its mode of binding, benz-fusion to 1-naphthylpiperazine (1-NP) should complement its ability to bind and result in significantly enhanced affinity; indeed, 1-NP binds with high affinity at, for example, 5-HT$_{1A}$ (K_i = 11 nM), 5-HT$_{1D}$ (K_i = 14), and 5-HT$_2$ (K_i = 18 nM) receptors (23). The 5-methoxy group of tryptamine analogs contributes to their binding and removal of this substituent consistently decreases affinity by about 5 to 10 fold; consequently, incorporation of the appropriate methoxy substituent into the structure of 1-NP should result in enhanced affinity. This is found to be the case; 7-methoxy 1-NP (7-OMe 1-NP) binds at 5-HT$_{1A}$ (K_i = 3.3 nM), 5-HT$_{1D}$ (K_i = 2.0 nM), and 5-HT$_2$ (K_i = 1.8 nM) receptors with 3- to 10-fold higher affinity than 1-NP. Furthermore, 2-methoxy 1-NP (2-OMe 1-NP) binds with a 3- to 10-fold lower affinity (K_i = 34, 545, and 250 nM, respectively) than 1-NP, suggesting that the phenylpiperazine portion of the methoxynaphthylpiperazines most likely mimics the pyrrole portion of the ergolines in each case. It should be realized however that an exact atom-by-atom fit is not required and that other modes of orientation may be possible. Although the naphthylpiperazines, like many of the ergolines, are nonselective high-affinity agents, the structures of agents with much greater selectivity can also be related to that of the ergolines (see Fig. 4). For additional discussion of the common template hypothesis, see (23) and the subsequent article in this series by Westkaemper and Glennon (61).

5-HT$_{1A}$ agents. The most widely used 5-HT$_{1A}$ agonist is 8-hydroxy-2-(di-n-propylamino)tetralin or 8-OH DPAT (11). Although this agent binds at 5-HT$_{pre}$ sites (26), it is the most selective agent currently available in the armamentarium of

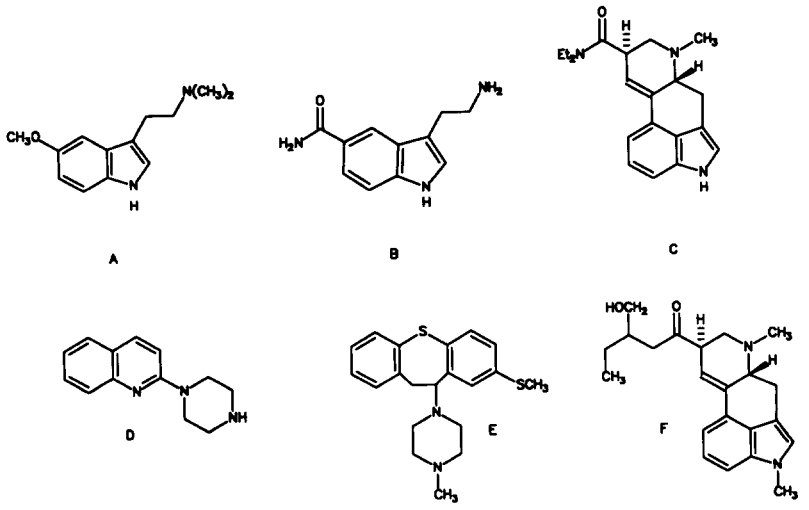

FIG. 2. Examples of some nonselective serotonergic agents: 5-methoxy-N,N-dimethyltryptamine (A), 5-carboxamidotryptamine (5-CAT; B), quipazine (D), methiothepin (E), and the ergolines (+)lysergic acid diethylamide (LSD; C) and methysergide (F).

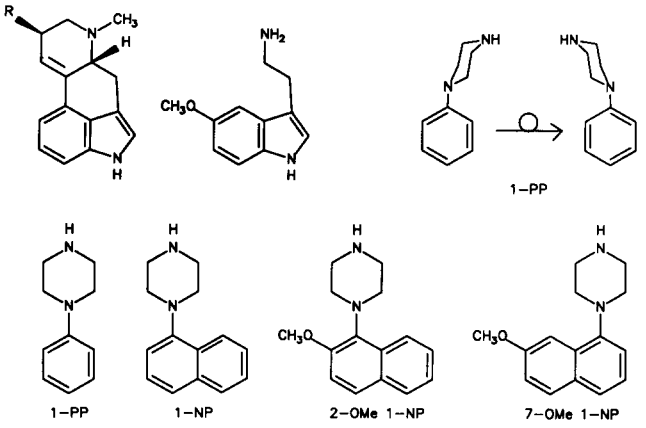

FIG. 3. Structural relationships between an ergoline, 5-methoxytryptamine, and 1-phenylpiperazine (two different rotamers are shown for the latter agent), and (bottom row) 1-phenylpiperazine (1-PP), 1-naphthylpiperazine (1-NP), 2-OMe 1-NP, and 7-OMe 1-NP.

serotonergic agents. Several different radioligands have been used to label 5-HT_{1A} receptors; however, [^{3}H]8-OH DPAT is the radioligand of choice. The di-n-propyl groups of 8-OH DPAT may contribute to its affinity and selectivity (23) and the di-n-propyl analogs of 5-CAT and 5-HT, although still nonselective, are more selective for 5-HT_{1A} receptors than are their primary amine counterparts 5-CAT and 5-HT, respectively (23,32). Another high-affinity agonist is R(−)-10-methyl-11-hydroxyaporphine (7). This agent has been referred to as being selective, but a complete binding profile has yet to be published. Various arylpiperazines are reported to be 5-HT_{1A} agonists or partial agonists; the most popular and widely published of these are buspirone, gepirone and ipsapirone (see Fig. 5 for structures).

The most widely used 5-HT_{1A} antagonists are spiperone, propranolol and pindolol (Fig. 6). Spiperone binds at 5-HT_2 and dopamine receptors with high affinity, and propranolol and pindolol are β-adrenergic antagonists that bind with higher affinity at β-adrenergic receptors than they display for 5-HT_{1A} receptors. (−)Propranolol and (−)pindolol bind at 5-HT_{1B} receptors and may be partial agonists. There is also evidence that these two agents are 5-HT_{1D} agonists (54). Thus none of these agents can be considered to be selective. Some newer agents that are beginning to attract attention include BMY 7378, NAN-190, SM-3997, and WY-47,846 (Fig. 7). Although these agents bind with high affinity at 5-HT_{1A} receptors, they possess varying degrees of efficacy and/or selectivity. One problem inherent to many of these arylpiperazines is their high affinity for α1-adrenergic receptors; NAN-190, for example, binds equally well at 5-HT_{1A} and α1-adrenergic receptors (48). RK-153 and RK-167 are two NAN-190 analogs that bind at 5-HT_{1A} receptors with a 160- and 75-fold selectivity, respectively (48). S(−)5-Fluoro 8-OH DPAT is a new 5-HT_{1A} antagonist that binds at 5-HT_{1A} receptors with modest affinity; however, it displays only an 8-fold selectivity for 5-HT_{1A} versus dopamine D2 receptors (29). MEP-177 is an analog of propranolol that lacks significant affinity for 5-HT_{1B} and β-adrenergic receptors (23). Although relatively little has been published, R(−)8,11-dimethoxyaporphine seems to represent a novel class of 5-HT_{1A} antagonists (6). 5-HT_{1A} antagonists are further discussed in a subsequent paper by Nelson. To date, an ideal 5-HT_{1A}-selective antagonist has not yet been identified.

5-HT_{1B} agents. In the past, 1-(3-trifluoromethylphenyl)piperazine (TFMPP) and its chloro counterpart mCPP (Fig. 8) were considered 5-HT_{1B} selective agonists. These agents are now realized to lack selectivity; in fact, they bind at nearly all populations of 5-HT receptors (19, 32, 52). Nevertheless, they are still widely, and incorrectly, used as "5-HT_{1B}-selective agonists." A somewhat more selective and more potent 5-HT_{1B} agonist is RU-24969; however, this commonly used agent binds at 5-HT_{1A} receptors with an affinity only slightly less than its affinity for 5-HT_{1B} receptors (32), is a weak, low-efficacy 5-HT_{1C} agonist (33), is a weak 5-HT_{1D} agonist (54) and, at high concentrations, is also a 5-HT_2 agonist (15). In fact, in animals lacking 5-HT_{1B} receptors (i.e., pigeon), it has been demonstrated that RU-24969 behaves primarily as a 5-HT_{1A} agonist (30). CP-93,129, an analog of RU-24969 (Fig. 8), is probably the most 5-HT_{1B}-selective agent currently available (40); however, this agent is of limited utility because of its apparent inability to penetrate the blood-brain barrier (40). Isamoltane has also been described as a 5-HT_{1B} antagonist; recent studies show that although it binds with a 1000-fold selectivity at 5-HT_{1B} versus 5-HT_{1D} receptors, it is not discriminated in terms of efficacy, and is a pure antagonist at both receptors (54). Isamoltane is also a 5-HT_{1A} partial agonist with about a 50% efficacy (52). Propranolol, pindolol, and related derivatives have been used as 5-HT_{1B} antagonists; as discussed earlier, these agents are not selective and, in addition, may be partial agonists. For a recent review of 5-HT_{1B} re-

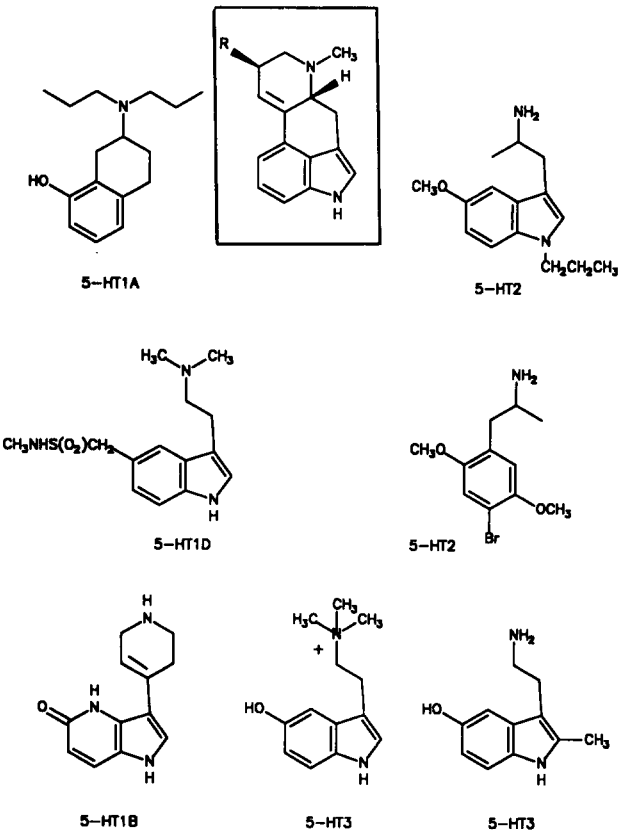

FIG. 4. Structural resemblance of the ergoline framework (boxed structure) to various serotonergic agents; the heading beneath each structure is the population of 5-HT receptors for which the agent possesses the greatest selectivity. The agents are (in a clockwise fashion from the upper right corner) 5-methoxy-N-n-propyl-α-methyltryptamine, DOB, 2-methyl 5-HT, 5-HTQ, CP-93,129, sumatriptan, and 8-OH DPAT.

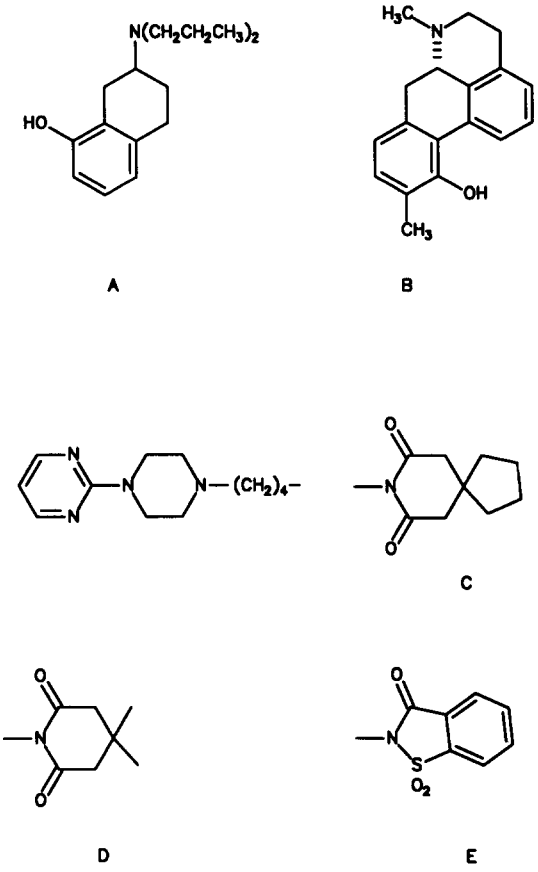

FIG. 5. Structures of several agents used as 5-HT_{1A} agonists: 8-OH DPAT (A), R(−)-10-methyl-11-hydroxyaporphine (B), buspirone (C), gepirone (D), and ipsapirone (E).

ceptor pharmacology, see Middlemiss and Hutson (41).

5-HT_{1C} agents. Nearly all agents that bind at 5-HT_{1C} receptors also bind at 5-HT_2 receptors. Thus most agents generally described as 5-HT_2 agonists or antagonists are more accurately referred to as 5-HT_{1C}/5-HT_2 agents (usually with a somewhat lower affinity for 5-HT_{1C} than for 5-HT_2 receptors). The prototypical 5-HT_2 agonists DOB and DOI, for example, bind at 5-HT_{1C} receptors (58) and are most likely 5-HT_{1C} agonists (50), or at least partial agonists (33,50). TFMPP and mCPP are interesting agents; they seem to be 5-HT_{1C} agonists, but may be only partial agonists, or even antagonists, at 5-HT_2 receptors (8,19). It should be noted, however, that TFMPP and mCPP are also partial agonists at 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors (52). The ergolines [^{3}H]mesulergine and [^{125}I]2-iodo LSD are used to label 5-HT_{1C} receptors in radioligand binding studies; however, these agents also bind at 5-HT_2 receptors and were, in fact, originally introduced as 5-HT_2 ligands. These ergolines, as well as ketanserin-related agents, seem to be 5-HT_{1C} antagonists. Mianserin, though nonselective, is a 5-HT_{1C} antagonist with somewhat higher affinity for 5-HT_{1C} versus 5-HT_2 receptors. Spiperone, on the other hand, seems to display greater selectivity for 5-HT_2 receptors (33). Thus, although several agents are available to study 5-HT_{1C} receptors, no 5-HT_{1C} selective agents have been reported.

5-HT_{1D} agents. The only agent reported to be a useful

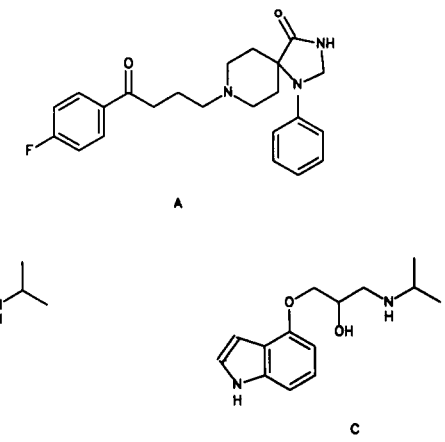

FIG. 6. Standard nonselective 5-HT_{1A} antagonists: spiperone (A), propranolol (B), and pindolol (C).

5-HT_{1D} agonist is sumatriptan (GR 43175) (Fig. 9). In addition to its modest selectivity for 5-HT_{1D} relative to 5-HT_{1B} and 5-HT_{1A} receptors, sumatriptan does not readily penetrate the blood-brain barrier (52,59). 5-(4-Chlorobenzyloxy)tryptamine binds

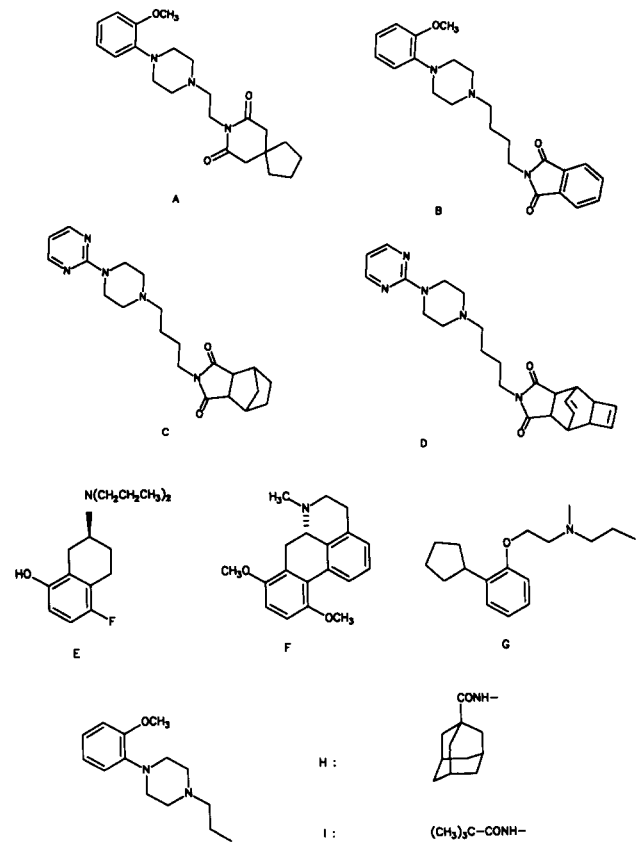

FIG. 7. Structures of some newer 5-HT_{1A} antagonists: BMY 7378 (A), NAN-190 (B), SM-3997 (C), WY-47,846 (D), S(−)5-fluoro 8-OH DPAT (E), R(−)8,11-dimethoxyaporphine (F), MEP-177 (G), RK-153 (H), and RK-167 (I).

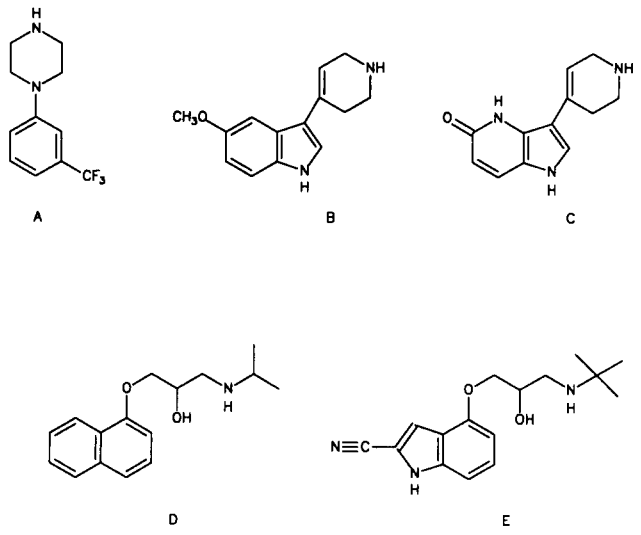

FIG. 8. Agents used as 5-HT_{1B} agonists and antagonists. Agonists: TFMPP (A), RU-24969 (B), CP-93,129 (C); antagonists: propranolol (D) and cyanopindolol (E). With the possible exception of CP-93,129, none of these agents is selective for 5-HT_{1B} receptors.

at 5-HT_{1D} sites with about a 15-fold higher affinity, but with a somewhat lower selectivity, than sumatriptan (25). It has been recently reported that serotonin O-glycyltyrosinamide (Fig. 9) is a selective 5-HT_{1D} ligand, and a radioiodinated version of this agent has been used in radioligand binding studies (3). It is not known if this agent is a 5-HT_{1D} agonist or antagonist. See Waeber et al. (59) and Hoyer et al. (32) for recent reviews of 5-HT_{1D} receptors and Glennon et al. (25) for a discussion of structure-affinity relationships.

5-HT_2 agents. The prototypic 5-HT_2 agonists are the bromo compound DOB and its iodinated counterpart DOI (Fig. 10). Both [^{3}H]DOB and [^{125}I]DOI are available for radioligand binding studies. Under the appropriate conditions, [^{125}I]DOI can label 5-HT_{1C} receptors (e.g., in choroid plexus) (1). Because these agents also bind, though with somewhat lower affinity, at 5-HT_{1C} receptors, they cannot be considered selective. Typical 5-HT_2 antagonists include ketanserin and spiperone (Fig. 10); tritiated analogs of both are used in radioligand binding studies. Although [^{3}H]spiperone is the older of the two agents, its use for labeling 5-HT_2 receptors has, for the most part, been replaced by [^{3}H]ketanserin. Some of the problems with spiperone were discussed above. Ketanserin, though quite selective for 5-HT_2 versus most other 5-HT receptors, binds with high affinity at histamine and adrenergic receptors (38), and also labels what may be a tetrabenazine-sensitive transporter site (39). Certain ketanserin-related analogs, such as pirenperone and ritanserin (Fig. 10), may be somewhat more selective than ketanserin; however, they still bind at 5-HT_{1C} receptors. Numerous useful 5-HT_2 antagonists have now been reported [e.g., (22, 23, 56, 62)], and ketanserin remains the prototypic 5-HT_2 antagonist. Nevertheless (although in some instances complete binding profiles are unavailable), few, if any, of these agents can be termed site-selective.

5-HT_3 agents. The most widely used 5-HT_3 agonist is 2-methyl 5-HT (Fig. 11). This agent, although it binds with somewhat lower affinity than 5-HT and is slightly less potent than 5-HT as an agonist, binds in a rather selective fashion at 5-HT_3 receptors [for reviews, see: (9, 35, 56, 59, 62)]. Phenylbiguanide

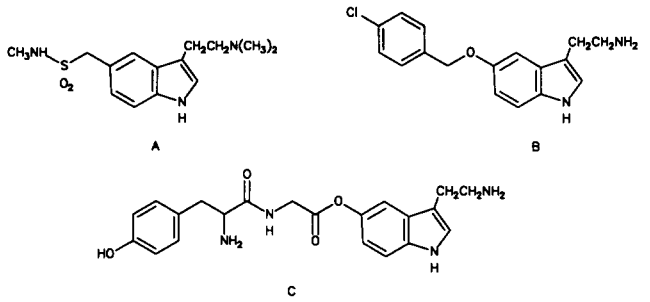

FIG. 9. 5-HT_{1D} ligands: sumatriptan (A), 5-(4-chlorobenzyloxy)tryptamine (CC- 263; B), serotonin O-glycyltyrosinamide (C).

is a 5-HT_3 agonist or partial agonist that binds at 5-HT_3 receptors with about one-fifth the affinity of 5-HT. The 3-chloro derivative of phenylbiguanide, meta-chlorophenylbiguanide (mCPBG; Fig. 11), was recently reported to bind with about 1000 times the affinity of the parent compound (36). Another 5-HT_3 agonist is the N,N,N-trimethyl derivative of 5-HT (i.e., 5-HTQ; Fig. 11) (24,49); this agent binds at 5-HT_3 receptors with about a 10-fold higher affinity, and with significantly greater selectivity, than 5-HT (24). Because 5-HTQ is a quaternary amine, it would not be expected to readily penetrate the blood-brain barrier in in vivo studies, making it useful as a peripherally selective 5-HT_3 agent.

There are numerous 5-HT_3 antagonists (Fig. 12) (9, 16, 23, 35, 56, 59, 62); among the most widely used agents are granisetron (BRL 43694), ICS 205-930, ondansetron (GR 38032), renzapride (BRL 24924), and zacopride. These agents were once considered quite selective for 5-HT_3 receptors. However, recent studies reveal that ICS 205-930 is a weak 5-HT_4 antagonist (and essentially the only 5-HT_4 antagonist currently available), renzapride and zacopride may be both 5-HT_{1P} and 5-HT_4 agonists [(2,12); see also (22) for specific literature citations and further discussion]. Certain other 5-HT_3 antagonists remain to be evaluated at 5-HT_{1P} and 5-HT_4 receptors; thus the selectivity of these agents remains to be determined.

5-HT_4 agents. To date, there are no 5-HT_4-selective agents. The nonselective 5-HT agonists 5-methoxytryptamine, α-methyl 5-HT, and 5-CAT are about one-half, one-twentieth, and one one-hundredth as potent, respectively, as 5-HT as 5-HT_4 agonists (2). Cisapride appears to be about one-tenth as potent as 5-HT as a 5-HT_4 agonist (2), but also binds at 5-HT_2 and 5-HT_3 receptors. The only agent with 5-HT_4 antagonist activity is the 5-HT_3 antagonist ICS 205-930 (2,13).

Conclusion

Most of the standard (and some newer) serotonergic agents have been described. As is evident from the foregoing discussion, few, if any, of these agents can be considered selective, and none can be truly termed site-specific. Certain of the agents also suffer from other shortcomings, such as their inability to penetrate the blood-brain barrier, or that they are mixed agonist/antagonists (i.e., agonists at one population of receptors and antagonists at others). Many agents considered as agonists are only partial agonists. Consequently, depending upon the particular functional assay being used, agents may be reported by one group of investigators as being an agonist, and by another group as an antagonist. Recent studies also suggest functional interactions between 5-HT receptor populations, such that an agonist at one population may seemingly behave as an antagonist at another population at which it does not bind (21). Additionally,

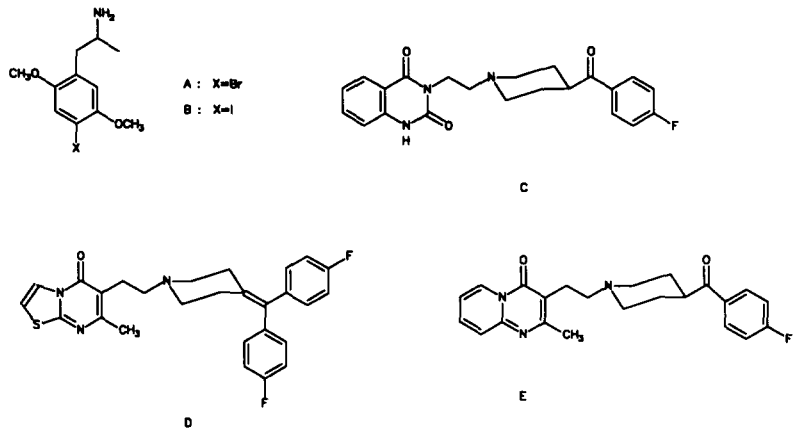

FIG. 10. Structures of some representative 5-HT_2 agonists: DOB (A), DOI (B) and antagonists: ketanserin (C), ritanserin (D), and pirenperone (E).

little has been reported regarding the indirect effect of these agents (i.e., their ability to release or block the uptake of 5-HT). Further confounding 5-HT research is the very rapid progress being made in this field. Due to normal delays in publication, results of a study may be outdated nearly as quickly as they appear in the literature. Nevertheless, these semiselective agents have been, and remain, quite useful. For example, in radioligand binding studies, selection of tissue rich in 5-HT_{1C} sites (e.g., choroid plexus) reduces the need for a 5-HT_{1C}-selective agent. However, attempts to implicate 5-HT_{1C} involvement for a particular in vivo effect can be much more difficult. For example, if the 5-HT_{1B}/5-HT_{1C} (actually, nonselective partial) agonist TFMPP and the 5-HT_{1C}/5-HT_2 agonist DOB produce a common effect that is not produced by the 5-HT_{1A} agonist 8-OH DPAT, and that is antagonized more potently by spiperone than ketanserin, and that is not antagonized by the 5-HT_3/5-HT_4 antagonist ICS 205-930, this may be taken as evidence for involvement of a 5-HT_{1C} mechanism. In the absence of selective agents, implication of a specific mechanism can be tedious and time consuming.

A great deal of progress has been made in serotonin research during the past decade—a period referred to by Sjoerdsma and Palfreyman (55) as the "new wave" of 5-HT research. This wave, however, has yet to crest. There are no agents with any significant degree of selectivity for 5-HT_{1C} or 5-HT_4 receptors, no 5-HT_{1A}-, 5-HT_{1B}-, or 5-HT_{1D}-selective antagonists, and no agonists that can discriminate 5-HT_{1C} from 5-HT_2 receptors. Tools for the investigation of 5-HT_{1D} receptors are currently limited to the agonist sumatriptan, an agent with modest selectivity; the issue is further clouded by a recent report of two different populations of 5-HT_{1D} receptors (42). 5-HT_{1E} receptors, as originally described by Titler and coworkers (37), have received very little attention; indeed, the term 5-HT_{1E} has been recently applied to yet another population of receptors detected on human blood platelets (10). Agents once thought to be selective for 5-HT_3 receptors are now being demonstrated to interact at 5-HT_{1P} and/or 5-HT_4 receptors. Even the 5-HT_2 receptors, the best studied population of all the different members of the 5-HT family, still lack what may be considered a truly selective agonist or antagonist. Again, it should be emphasized that there are a number of semiselective agents that are useful for the investigation of 5-HT pharmacology; nevertheless, there still exists a need for agents with even greater selectivity.

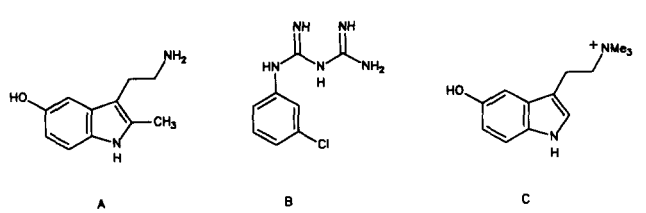

FIG. 11. Structures of 5-HT_3 agonists: 2-methyl 5-HT (A), meta-chlorophenylbiguanide (mCPBG; B), and 5-HTQ (C).

ACKNOWLEDGEMENT

Work from the authors' laboratory was supported in part by U.S. PHS grant NS 23520.

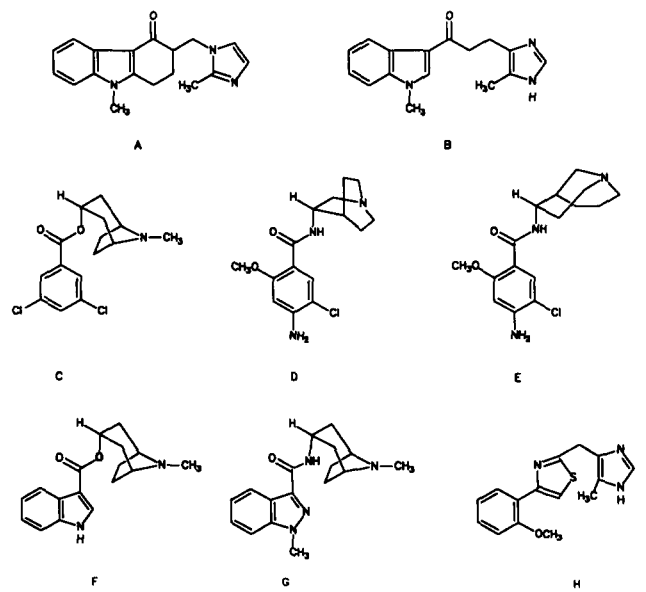

FIG. 12. Structures of some representative 5-HT_3 antagonists: ondansetron (GR 38032; A), GR 65630 (B), MDL 72222 (C), zacopride (D), renzapride (E), ICS 205-930 (F), LY 278585 (G), and a new thiazole derivative (H).

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