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5-Hydroxytryptamine Receptors

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I. Introduction

THE first experimental evidence suggesting the existence of an endogenous vasoconstrictor substance was presented by Stevens and Lee (1884) and by Brodie (1900), who showed that the serum obtained after blood clotting increased vascular tonus. Vialli and Erspamer (1933) observed the presence of "enteramine" in the gut, and Rapport et al. (1947) reported the existence of a vasotonic substance in the serum, which was, therefore, called "serotonin." The latter substance was identified as 5-HT* (Rapport et al., 1948; Rapport, 1949) and was rapidly shown to be identical with enteramine. Hamlin and Fisher (1951) were able to synthesize it. Twarog and Page (1953) demonstrated its presence in mammalian brain, and Amin et al. (1954) showed that its distribution

* Abbreviations: 5-HT, 5-hydroxytryptamine; 5-BT, 5-benzyloxytryptamine; 5-CT, 5-carboxamidotryptamine; 5-MeO-T, 5-methoxytryptamine; LSD, lysergic diethylamide acid; TFMPP, 1-(3-trifluoromethylphenyl)piperazine; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino)tetraline; cAMP, cyclic adenosine monophosphate; GMP, guanosine monophosphate; 5,7-DHT, 5,7-dihydroxytryptamine; IP_3, inositol triphosphate; G_s, stimulatory G protein; G_i, inhibitory G protein; GABA, γ-aminobutyric acid; GTP, guanosine-5-triphosphate; GTP γ-S, guanosine-5-O-thiotriphosphate; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; TCA, tricyclic antidepressant; ACh, acetylcholine; mCPP, 1-(3-chlorophenyl) piperazine; pCPA, *p*-chlorophenylalanine; REM, rapid eye movement (sleep); CNS, central nervous system; DOB, 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane; cDNA, complementary DNA; mRNA, messenger RNA; DOM, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane; BIMU 1, (endo-N-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-ethyl-2-oxo-^{1}H-benzimidazol-1-carboxamide hydrochloride; BIMU 8, (endo-N-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-iso-propyl-2-oxo-^{1}H-benzimidazol-1-carboxamide hydrochloride; BMY 7378, 8-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl-8- azapirol[4.5]-decane-7.9-dione dihydrochloride; BRL 20627, (2-α,6β,9aα)-(±)-4-amino-5-chloro-2-methoxy-N-(octahydro-6-methyl-2-H-quinolizin)-benzamide; BRL 24924, endo-2-methoxy-4-amino-5-chloro-N-(1-azabicyclo-[3.3.1]-non-4-yl) benzamide mono-hydrochloride; BRL 43694, (granisetron), endo-*N*-(9-methyl-9-azabicyclo [3,3,1]non-3-yl)-1-methyl-imidazole-3-carboxamide; BRL 47204, 1-methyl-*N*-(endo-9-methyl-9-azabicyclo-[3,2,1]non-3-yl)indol-3-yl carsboxylic acid amide; CGS 12066B, 7-trifluoromethyl-4(4-methyl-1-piperazinyl)-pyrolo-(1,2-a) quinoxaline 1:2 maleate salt; cisapride, *cis*-4-amino-5-chloro-N-{1-[3-(4-fluoro-phenoxy) propyl]-3-methoxy-4-piperidinyl}-2-methoxybenzamide; compound No. 1, N,N′-bis[3-(4-indolyloxy)-2-hydroxy-propyl]-(Z)-1.8-diamino-*p*-methane; compound No. 2, N^8-[3-(4-indolyloxy)-2-hydroxypropyl]-N^1-(propidoyl)-(z)-1.8-diamino-*p*-methane-granisetron,endo-N-(methyl-9-azabicyclo-[3.3.1]-non-3-yl)-1-methyl-indazol-3-carboxamide(or BRL43694); CP-93,129, 3-(1,2,5,6-tetrahydro-4-pyridyl)pyrrolo[2,3-b]-pyril-5-one; CP-96,501, 3-(1,2,5,6-tetrahydro-4-pyridyl)5-*n*-propoxyindol; GR 65630, 3-(5-methyl-^{1}H-imidazol-4-yl)-1-(1-methyl-^{1}H-indol-3-yl)-1-propanone; GR 67330, 1,2,3,9-tetrahydro-9 methyl-3-[(5-methyl-^{1}H-imidazol-4-yl)-methyl]-^{4}H-carba-zol-4one; GR 38032, (±)-1,2,3,9-tetrahydro-9-methyl-3[(2-methyl-^{1}H-imidazol-1-yl)methyl]-^{4}H-carbazol-4-one; ICI 169–369, 2-(2-dimethylaminoethylthio)-3-phenylquinoline; ICS 205–930, (3-α-tropanyl)^{1}H-indole-3-carboxylic acid ester; ICYP, iodocyanopindolol; IMAO, inhibitors of monoaminoxidases; LY 165–163, *p*-aminophenyl ethyl-*m*-trifluoromethyl phenyl piperazine (or PAPP); LY 211–000, (8-methyl-8-azabicyclo[3.2.1]ocl-3-yl)-*1*H-indazole-3-carboxylic acid ester; LY 258–458, N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-^{1}H-indazole-3-carboxamide; LY 278–584, 1-methyl-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-^{1}H-indazole-3-carboxamide; MDL 72222, 1-αH-3α-5αH-tropan-3-yl-3,5-dichlorobenzoate; MDL 72832, 8-[4-[(1,4-benzodioxan-2-ylmethyl)amino]butyl azapiro [4.5] decane-7,9-dione; MDL 73005EF, 8-[2-(2,3-dihydro-1.4-benzodioxin-2-yl)Me-thylamino]-8-azaspiro [4.5]decan-7,9-dione methyl sulfonate; MK 212, 6-chloro-2-(1-piperazinyl)pyrazine; NAN-190, (1-(2-methoxyphenyl)-4-(4 (2phtalimido) butyl)piperazine; ondansetron, (1,2,3,9-tetrahydro-9-methyl-3[(2-methyl-^{1}H-imidazol-1-yl)-methyl]-4-one (or GR 38032); PAPP, 1[2-(4-aminophenyl)ethyl]-4-(3trifluoro methylphenyl) piperazine (or LY 165–163); PKC, protein kinase C; PLC, phospholipase C; QICS 205–930, quaternized-(3-α-tropanyl)-^{1}H-indole-3-carboxylic acid ester; quipazine, 2-(1-piperazinyl)quinoline; [^{3}H]rauwolscine, (2-methoxy-1.4-[6.7^{3}H]benzodioxan-2-yl)-2-imidazolin (or RX821002); RP 62203, 2-(3-[4-fluorophenyl)piperazinyl]-propyl) naphto-[1,8-c,d]-isothiazole-1,1-dioxide; RS 30199–193, 5-chloro-2-methyl-1,2,3,4,8,9,10,10a-octahydronaphth-[1.8-cd]-azepine; RU 24969, 5-methoxy-3(1,2,3,6-tetrahydro-4-pyridinyl)^{1}H indole succinate; SCH 23390, 7-chloro-8-hydroxy-1-phenyl-2,3,4,5-tetrahydro-^{1}H-3-benzazapine; SCH 23982, (+)-8-iodo-2,3,4,5-tetrahydro-3-methyl-5-phenyl-^{1}H-3-benzazepine-7-old; S-CM-GT NH_2, serotonin-O-carboxymethyl-glycyl-tyrosinamide; S-14063, N-[1-(benzothiazol-2-yl)]-N-[4-[(methoxy-2-ethoxy)-2-phenyl]methylamino]piperidine; S-14671, 4-[(thenoyl-2)aminoethyl]-1-(7-methoxynophtyl piperazine); SDZ 205–557, 2-methoxy-4-amino-5-chloro-benzoic acid 2-(diethylamino)ethyl ester; SDZ 206–792, (N-desmethyl-3-α-homotropanyl)-^{1}H-indole-3-carboxylic acid ester; SDZ 206–830, (3α-homotropanyl)-1-methyl-5-fluoro-indole-3-carboxylic acid ester; SDZ(−)21009, 4[3-terbutyl-amino-2-hydroxypropoxyl-indol-2-carbonic acid-isopropylester SDZ 210–204, (−)-(1*R*,2*R*,4*S*)-^{1}H-indole-3-carboxylic acid-7-methyl-7-azabicyclo-[2.2.1]hept-2-yl-ester; SDZ 216–525, 4-[4-[4-(1-1,3-trioxo-2H-1,2-benziosothiazol-2-yl)butyl]-1-piperazinyl]1H-indole-Z-carboxylate; (S)-UH-301, (*S*)-5-fluoro-8-hydroxy-2-(di-*n*-propylamino) tetra-

was heterogeneous in dog brain. This led to the suggestion that 5-HT might act as a neurotransmitter in the CNS (Bogdanski et al., 1956; Brodie and Shore, 1957).

Indeed, serotonin is involved in numerous physiological events. At the peripheral level, it affects smooth muscle fibers, causing constriction or relaxation, and thus exerts a major effect on the vascular bed and the digestive tract (Vanhoutte, 1985; Frohlich and Van Zwieten, 1987; Breckenridge et al., 1988; Hollenberg, 1988; Saxena et al., 1989; Saxena and Villalon, 1991; Parsons, 1991). Serotonin to some extent affects various functions of the CNS: sleep (Jouvet, 1962, 1967; Koella, 1988), thermoregulation (Feldberg and Myers, 1964; Jacob and Girault, 1979; Myers, 1981), learning and memory (Altman and Normile, 1986, 1988; McEntee and Crook, 1991), pain (Tenen, 1967; LeBars, 1988; Richardson, 1990), behavior such as aggressive (Sheard, 1969; Di Chiara et al., 1971), sex (Hoyland et al., 1970; Meyerson and Malmnas, 1978; Fernandez-Guasti et al., 1987; Gorzalka et al., 1990), and feeding (Blundell, 1977, 1984; Marazziti et al., 1988; Curzon, 1990), neuroendocrine regulations (Schneider and McCann, 1970; Charli et al., 1978; Tuomisto and Mannisto, 1985; Fuller, 1990; Van de Kar, 1991; Cowen et al., 1990), motor activity (Gershon and Baldessarini, 1980; Sternbach, 1991), and biological rhythms (Wesemann and Weiner, 1990).

Serotonin is thought to play a role in various types of pathological conditions: psychiatric disorders such as anxiety (Iversen, 1984; Gardner, 1985, 1986; Johnsson and File, 1986; Kahn et al., 1988; Nutt and George, 1990), depression (Schildkraut, 1965; Meltzer and Lowy, 1987; Cowen, 1988, 1990; Curzon, 1988; Kalus et al., 1989; Plaznik et al., 1989; Meltzer, 1990; Van Praag et al., 1990), aggressivness (Pucilowski and Kostowski, 1983; Miczek and Donat, 1989; Olivier et al., 1989; Coccaro, 1989; Wetzler et al., 1991), panic (Eriksson, 1987; Sheeham et al., 1988), obsessive-compulsive disorders (Zohar and Insel, 1987; Zak et al., 1988; Charney et al., 1988; Insel et al., 1990), schizophrenia (Csernansky et al., 1992), suicidal behavior (Roy and Linnoila, 1988; Coccaro and Astill, 1990; Mann et al., 1990), and autism (Cook, 1990; Anderson et al., 1990); neurodegenerative disorders, such as Alzheimer's disease, Parkinsonism, and Huntington's chorea (Morgan et al., 1987; Cross, 1988, 1990; Cross et al., 1988), migraine (Fozard, 1990; Anthony, 1986; Humphrey et al., 1990), emesis (Fozard, 1987; Bunce et al., 1991), and alcoholism (Tollefson, 1989; Sellers et al., 1992).

Specific receptors mediate the physiopathological events triggered.

line; sumatriptan, 3-(2-dimethylamino)ethyl-N-methyl-^{1}H-indole-5-methane sulfonamide (or GR 43175); tandospirone, (3aα,4β,7β,7aα)-hexahydro-2-(4-(4-(2-pyrimidinyl)-1-piperazinyl)-butyl)-4,7-methano-^{1}H-isoindole-1,3-(^{2}H)-dione dihydrogen citrate(or SM-3997); WB 4101, 2-(2,6-dimethoxyphenoxyethyl)aminomethyl-1,4-benzodioxane; zacopride, 4-amino-N-(1-aza-bicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide.

II. Classification of Serotonin Receptors

Evidence for the existence of serotonergic receptors was first presented by Gaddum and Picarelli (1957), who experimented with the isolated guinea pig ileum. They described two types of receptors controlling muscle contraction: D receptors, for those blocked by dibenzyline, and M receptors, for those blocked by morphine. Receptor sites were tentatively observed by Marchbanks (1966, 1967), using [^{3}H]5-HT, and by Farrow and van Vunakis (1972, 1973), who showed that [^{3}H]LSD binding could be displaced by 5-HT. The earliest evidence for a selective high-affinity and saturable binding of [^{3}H]5-HT was presented by Bennett and Snyder (1975, 1976) and Fillion et al. (1976). That [^{3}H]spiroperidol could also label a serotonergic receptor (Leysen et al., 1978) led Peroutka and Snyder (1979) to propose the existence of two classes of serotonergic receptors, 5-HT$_1$ (labeled with high affinity by [^{3}H]5-HT) and 5-HT$_2$ (labeled by [^{3}H]spiperone). In their report, Peroutka and Snyder provided the initial evidence that the 5-HT$_1$ receptors might be heterogeneous, because the inhibition of [^{3}H]5-HT binding, caused by spiroperidol, was biphasic. Pedigo et al. (1981) confirmed these results and proposed the existence of two sites labeled by [^{3}H]5-HT: 5-HT$_{1A}$ (exhibiting a high affinity for spiroperidol) and 5-HT$_{1B}$ (a low affinity for spiroperidol). A third [^{3}H]5-HT-binding site, designated 5-HT$_{1C}$, was proposed on the basis of the high-affinity displacement of [^{3}H]5-HT by mesulergine (Pazos et al., 1985b). Functional studies attempted to attribute a physiological role to these binding sites (Fozard and Kilbinger, 1985; Engel et al., 1985).

It became necessary to reconcile the different nomenclatures and classify the serotonergic receptors by establishing criteria that also respected receptor definition (e.g., binding sites having physiological properties). A group of scientists (Bradley et al., 1986) proposed three major serotonergic receptor classes: "5-HT$_1$-like," 5-HT$_2$, and 5-HT$_3$.

The term "5-HT$_1$-like" was proposed for the heterogeneous group of receptors having a high affinity for 5-HT and 5-CT, was antagonized by methiothepin and methysergide, and was not fully characterized as functional entities.

The term "5-HT$_2$" was proposed for the D receptors that had been described much earlier by Gaddum and Picarelli (1957). These receptors mediate a variety of peripheral actions of 5-HT and correspond to the cortical 5-HT$_2$-binding sites described by Peroutka and Snyder (1979) having a low affinity for 5-HT and a high affinity for particular serotonergic antagonists, such as ketanserin, methysergide, mianserin, and metergoline.

The 5-HT$_3$ receptors corresponded to the M receptors (Gaddum and Picarelli, 1957) present in peripheral neurons which mediate the depolarizing actions of 5-HT. They were characterized by their high affinity for cocaine derivatives (ICS 205–930 and MDL 72222). However,

the presence of specific binding sites in brain was not demonstrated at that time.

This classification was later slightly modified by Peroutka (1990) who incorporated new data, such as the existence of a novel 5-HT_1 subtype, called 5-HT_{1D} (Heuring and Peroutka, 1987) (fig. 1), the pharmacological and molecular similarities between 5-HT_{1C} and 5-HT_2 receptors (Hoyer, 1988; Hartig, 1989a), and the clear confirmation of the functional role of the 5-HT_1-like receptors. Peroutka proposed three main classes of receptors: 5-HT_1 (including 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} subtypes), 5-HT_2 (including 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{1C} subtypes), and 5-HT_3. Peroutka proposed that the latter class was homogenous; the pharmacological differentiation of 5-HT_3 receptor subtypes previously presented by Richardson and Engel (1986) was interpreted as species and tissues differences.

Although useful, this classification, which was based on agonist and antagonist drug specificity, did not account for receptors such as 5-$HT_{1nonA,nonB,nonC}$ which have a high affinity for 5-HT and a low affinity for 5-CT (Fayolle et al., 1988) or for 5-HT_{1P} receptors which have a high affinity for 5-HT and a pharmacological profile different from that of the other 5-HT_1 receptors (Mawe et al., 1986; Branchek et al., 1988). Moreover, this classification cannot distinguish receptors such as 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ which have similar pharmacological properties but are encoded by two different genes (Hartig et al., 1992). In contrast, the classification distinguishes between the 5-HT_{1B} and the 5-$HT_{1D\beta}$ receptors based of their pharmacological properties, whereas the genes encoding these receptors are proposed as species homologues (Hartig et al., 1992).

Moreover, several potential receptors, characterized either by their binding or by their functional properties, have a specific pharmacological profile that does not allow one to classify them in any of the proposed categories. This is the case for the following binding sites: 5-HT_{1E} sites (high affinity for 5-HT and low affinity for 5-CT) (Leonhardt et al., 1989), 5-HT_{1S} sites (high affinity for 5-HT and not antagonized by methysergide) (Zelman et al., 1990; Zelman and Schwab, 1991), and 5-HT_{1R} sites (Xiong and Nelson, 1989). On the other hand, potential receptors that mediate 5-HT activities have a pharmacological profile different from that of the following known 5-HT receptors: 5-HT_4 receptors stimulating the adenylyl cyclase activity (Dumuis et al., 1988b; see Bockaert et al., 1992), the novel 5-HT receptors depolarizing neonatal rat motoneurons (Connell and Wallis, 1989), receptors enhancing a hyperpolarization-activated cationic current (I_h) (Pape and McCormick, 1989; Bobker and Williams, 1989), receptors inhibiting the release of endogenous aspartate (Maura et al., 1991), receptors coupled to cyclic GMP production in NG108–15 cells (Tohda et al., 1991a,b), and receptors mediating slow excitatory responses in neurons of the CA1 region of the hippocampus (Chaput et al., 1990).

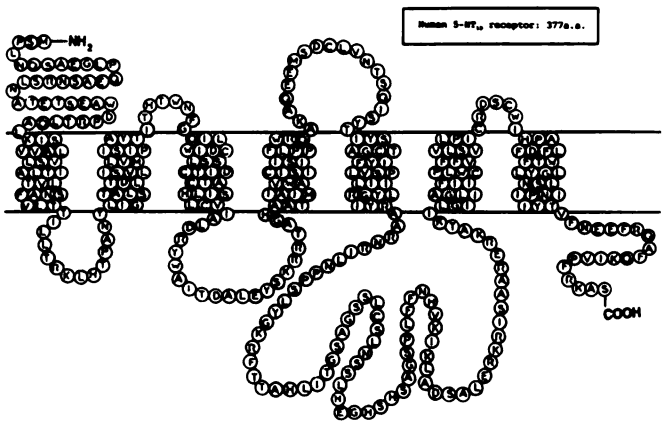

FIG. 1. Topographical model of the 5-HT_{1D} receptor. The amino acid sequence is deduced from the nucleotide sequence of the human gene (Hamblin and Metcalf, 1991). The horizontal lines correspond to the membrane separating extracellular (top) and intracellular (bottom) spaces. The receptor is a monomeric protein possessing seven transmembranal hydrophobic domains linked by three extracellular and three intracellular loops. The NH_2 terminal is extracellular, and the COOH terminal is intracellular.

Thus, since the initial observations of Gaddum and Picarelli (1957), great progress has been made, thanks to the successive discoveries of new ligands which have provided a better understanding of specific 5-HT receptors. However, because of the lack of specific ligands, several potential receptors are still awaiting appropriate classification. Results of molecular biological studies have provided new important perspectives concerning the existence of receptor subtypes. These data will contribute to complete and precise classification of the serotonergic receptors.

Hartig (1989a) proposed simply to classify the 5-HT receptors on the basis of their structural homology, which had been established by molecular biology, and their predominant transduction system. He distinguished serotonergic receptors, the activity of which are coupled to a G protein, from those directly linked to an ionic channel. Of the former, the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_4 receptors were associated with adenylyl cyclase, whereas the 5-HT_{1C} and 5-HT_2 receptors were associated with PLC.

Three receptors had been cloned by the time Hartig proposed this classification scheme (5-HT_{1A}, 5-HT_{1C}, and 5-HT_2); these were found to belong to the multigenic family of the G protein-related receptors having a monomeric structure (420 to 460 amino acids) with seven highly conserved transmembrane domains of 20 to 28 amino acids each; the recognition sites for the agonistic ligands are presumably included in these domains (Strader et al., 1989; Curtis et al., 1989). These structures have an extracellular amino-terminal domain containing glycosylation sites, an intracellular carboxy-terminal part which often possesses phosphorylation sites, and three extracellular and three intracellular loops. The

extramembranal domains (intra- and extracellular), are not highly conserved and thus appear to be more specific for each receptor than the intramembranal domain. The third intracellular loop is thought to involve a coupling with the G protein (Strader et al., 1989; Lechleiter et al., 1990) and may have phosphorylation sites. The COOH-terminal domain, particularly the part that is close to the membrane, also might be involved in coupling with the G protein (Strader et al., 1989; O'Dowd et al., 1989).

The recent findings from 5-HT receptor research have progressed so rapidly, especially in molecular biology, that the primary molecular structures of a number of receptors have been described, allowing one to propose a more precise classification (table 1). A definite classification of the receptors based on molecular biology and pharmacology likely will be rapidly established.

Finally, a classification analogous to that used for enzymes was proposed by Frazer et al. (1990). Thus, receptors can be classified by four numbers, the first referring to the activating ligand (e.g., 5-HT), the second to the superfamily (e.g., G protein linked), the third to the predominant second-messenger system (e.g., adenylyl cyclase), and the fourth to the primary amino acid sequence in chronological order of their publication. The merit of this classification is the ability to identify precisely the profile of the receptor following a simple examination of its "enzyme-like code" and then clearly underlining similarities and differences between receptors. However, the pharmacological specificity is not shown, and the fourth code number is not an intrinsic characteristic of the receptor.

The aim of this review is to present the main characteristics of the serotonergic receptors with regard to their molecular biological, pharmacological, and functional properties at the cellular as well as the integrated level in vivo. It should be pointed out that excellent exhaustive reviews of 5-HT receptors were recently published (Sanders-Bush, 1988a; Osborne and Hamon, 1988).

III. 5-HT_1 Receptors

These receptors are characterized by a high affinity (<10 nM) for 5-HT and 5-CT, a medium affinity (10 to 1000 nM) for methiothepin, methysergide, quipazine, and TFMPP, and a low affinity (>1000 nM) for ICS 205–930, MDL 72222, and ketanserin.

The artifactual nature of these receptors has often been proposed, because it was thought that high-affinity binding could not be a characteristic of a functional receptor (Fozard, 1983; Leysen, 1984a,b; Bradley et al., 1986). However, it is now clear that 5-HT_1 receptors belong to a large family of functional receptors and are likely to be involved in slow neuromodulatory phenomena.

In this review, three subclasses of 5-HT_1 receptors are considered: 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D}; 5-HT_{1C}, according to the suggestion of Hartig (1989a), will be presented as a member of the 5-HT_2 class.

A. 5-HT_{1A} Receptor Subtype

Pedigo et al. (1981) showed that spiperone can be used to discriminate between two different subclasses of 5-HT_1 sites: one having a high affinity for spiperone (5-HT_{1A}) and the other one a low affinity (5-HT_{1B}). The ratio of these two sites in the hippocampus differs from that in the cortex.

1. Selective radioligands and pharmacological properties. The investigation of 5-HT_{1A} receptors became possible when Hjorth et al. (1982) discovered a tetraline derivative, 8-OH-DPAT, and Gozlan et al. (1983) demonstrated that this drug, labeled with tritium ([^{3}H]8-OH-DPAT), bound selectively to the 5-HT_{1A} site. The following ligands have since been used for studies of receptor binding: [^{3}H]ipsapirone ([^{3}H]TVXQ 7821) (Dompert et al., 1985; Glaser and Traber, 1985), [^{3}H]WB 4101 (Norman et al., 1985), [^{3}H]PAPP (Ramson et al., 1986), [^{3}H] 5-MeO-DPAT (Cossery et al., 1987), [^{3}H]spiroxatrine (Herrick-Davis and Titeler, 1988a), ^{125}I-BH-8-MeON-

TABLE 1
Serotoninergic receptor classification

Receptor type	Receptor family	Transduction system (predominant)	Characterized receptors	Potential receptors
G protein-related receptors		Adenylyl cyclase	5-HT_{1A}	5-HT_{1A} subtypes ?
	5-HT_1	(cAMP production)		
			5-HT_{1D}	5-HT_{1R}
7 transmembrane domains				5-HT_{1E}
			5-HT_{1B}	5-$HT_{1nonA, nonB, nonC}$
				5-HT_4
			5-HT_2	
	5-HT_2	Phospholipase C		
		(IP_3/DAG production)	5-HT_{1C}	
				5-HT_3-LIKE
Ionic channel receptors				5-HT_{3A}
	5-HT_3	Monovalent cations flux	5-HT_3	5-HT_{3B}
				5-HT_{3C}

PAT (Gozlan et al., 1988), [^{3}H]buspirone (Brüning et al., 1989), [^{3}H]NAN-190 (Rydelek-Fitzgerald et al., 1990), and [^{3}H]tandospirone (Tanaka et al., 1991). Recently, [^{3}H]rauwolscine ([^{3}H]RX821002), a marker for α_2-adrenoceptors, was presented as a potential 5-HT$_{1A}$ marker in the human frontal cortex (De Vos et al., 1991).

The highly selective prototypical 5-HT$_{1A}$ agonist, 8-OH-DPAT (an aminotetralin), remains unique in its combination of both high efficacy and striking potency in vivo. Numerous 5-HT$_{1A}$ agonists are presently available and exhibit potential therapeutic value, notably for the treatment of anxiety and depression; however, most of these drugs are partial agonists which also have antagonistic properties: pyrimidinylpiperazines (buspirone, ipsapirone, gepirone, tandospirone), napthylpiperazines (S-14671), benzodioxanes (MDL 72832, spiroxatrine, MDL 73005EF, WB 4101), heterobicyclic arylpiperazines (flesinoxan), and phenylpiperazines (BMY 7378, NAN-190). Other agonistic drugs that interact potently with the 5-HT$_{1A}$ receptor, but are nonselective for 5-HT receptor subtypes, are ergot derivatives (*d*-LSD, metergoline) and various indoles (5-HT, 5-CT, N,N-dipropyl-5-CT, and RU 24969).

The 5-HT$_{1A}$ receptor antagonists currently used are not selective; spiperone and spiroxatrine also bind with a high affinity to 5-HT$_2$ and dopamine sites, propranolol and pindolol bind to 5-HT$_{1B}$ and β-adrenoceptor sites, and methiothepin is nonselective with respect to different 5-HT receptors and binds with a high affinity to histaminergic and dopaminergic sites. In addition, MDL 73005EF (Hibert et al., 1988) and the phenylpiperazine derivatives BMY 7378 and NAN-190, which first appeared to be 5-HT$_{1A}$ antagonists (Chaput and de Montigny, 1988a; Glennon et al., 1988, 1989), have been shown to be mixed partial agonists/antagonists (Yocca et al., 1987). Presently, Four drugs are proposed to be selective and potent 5-HT$_{1A}$ antagonists: N^1-(bromoacetyl)-[N^8)-(3-(4-indolyloxy)-2-hydroxypropyl]-(Z)-1,8-diamino-*p*-methane, a pindolol derivative quite selective of 5-HT$_{1A}$ receptors (an order of magnitude less potent at the β-adrenoceptors) (Liau et al., 1991); S-14063, devoid of β-adrenoceptor-blocking properties (Dabiré et al., 1991), SDZ 216–525, proposed as a potent, selective, and silent 5-HT$_{1A}$ receptor antagonist, both in vitro and in vivo (Hoyer et al., 1992); and a novel 8-OH-DPAT analog, (*S*)-UH-301, able to antagonize completely several (*R*)-8-OH-DPAT-induced effects (Johansson et al., 1991; Björk et al., 1991). The confirmation of the antagonistic nature of these drugs and the development of new 5-HT$_{1A}$-specific antagonists are urgently needed to really understand the physiological and functional role(s) of 5-HT$_{1A}$ receptors.

The differences in intrinsic activity and potency of the compounds acting at 5-HT$_{1A}$ receptors depend on the brain region and on the functional model used. 8-OH-DPAT, ipsapirone, gepirone, buspirone, MDL 73005EF, BMY 7378, and NAN-190, in electrophysiological and behavioral studies, act as full agonists at raphe 5-HT$_{1A}$ receptors and as antagonists at hippocampal receptors (Smith and Peroutka, 1986; Martin and Mason, 1987; Sprouse and Aghajanian, 1988; Moser et al., 1990; Gartside et al., 1990; Yocca, 1990; Van den Hooff and Galvan, 1991) (table 2). 8-OH-DPAT, buspirone, and ipsapirone act as full agonists in inhibiting the cAMP production in hippocampus, whereas they are either partial agonists (8-OH-DPAT) or competitive antagonists (buspirone, ipsapirone) in cortex (Dumuis et al., 1988c). Moreover, in the hippocampus, 8-OH-DPAT produces a greater reduction in amplitude of population spikes in the CA1 area than in the dentate gyrus (Klancnik et al., 1991). Intrinsic activity values of 5-HT$_{1A}$ agonists also depend on the test model; in the hippocampus, 8-OH-DPAT, ipsapirone, and gepirone are full agonists in inhibiting adenylyl cyclase activity (De Vivo and Maayani, 1986), whereas they are partial agonists or even antagonists on the hyperpolarizing response to 5-HT (Segal et al., 1989); NAN-190 antagonizes the 8-OH-DPAT-induced syndrome, whereas it was shown to be an agonist inhibiting the release of 5-HT in microdialysis studies (Hjorth and Sharp, 1990).

Surprisingly, the pharmacological properties of the 5-HT$_{1A}$ recognition sites in raphe, hippocampus, and cortex are similar. Several mechanisms were proposed to explain the variations of the intrinsic activities of 5-HT$_{1A}$ ligands. One hypothesis is that there are regional differences in 5-HT$_{1A}$ spare receptor number. Indeed, a large receptor reserve exists in the raphe nucleus (Meller et al., 1990) but not in the hippocampus (Yocca et al., 1990a). Then, it would be expected that partial agonists elicit a full agonistic response in the raphe, whereas in the hippocampus, the partial agonist activity of the compound is insufficient to evoke an agonistic response and will result in an antagonist effect (Van den Hooff and Galvan, 1991). However, the fact that partial agonists such as buspirone or ipsapirone are full agonists in the hippocampus, which is devoid of spare receptors (De Vivo and Maayani, 1986), suggests that the mechanism might be more complex. Indeed, the intrinsic activity of agonists is dependent not only on ligand binding to 5-HT$_{1A}$ receptor but also depends on the formation of the ligand-receptor-G protein ternary complex. The fact that compounds acting at receptors with similar recognition domains may have different efficacies suggests the existence of differences in postreceptor signal transduction processes (different G$_i$ proteins, different coupling, or stoichiometry between receptor and G$_i$ proteins) (Yocca and Maayani, 1990). Finally, another hypothesis proposes the existence of several types of 5-HT$_{1A}$ receptors (Dumuis et al., 1988c; Sprouse et al., 1990).

Several recent findings have supplied additional information concerning the mechanism of action of agonist/antagonist 5-HT$_{1A}$ drugs. Boddeke et al. (1992), compar-

TABLE 2

Affinity values of drugs for 5-HT$_{1A}$ recognition sites in mammalian brain membranes

Drug	Affinity	Reference
Very high affinity (K_i < 10 nM)		
5-CT	0.21	Hoyer et al., 1985b
	0.31	Harrington et al., 1991
	0.316	Hoyer and Schoeffter, 1991
	2.13	Engel et al., 1986
DP-5-CT	0.28	Van Wijngaarden et al., 1990
	0.316	Hoyer and Schoeffter, 1991
MDL 72832	0.79	Van Wijngaarden et al., 1990; Hoyer and Schoeffter, 1991
8-OH-DPAT	0.4	Dompert et al., 1985
	1	Peroutka, 1986; Harrington et al., 1991
	1.86	Engel et al., 1986; Hoyer and Schoeffter, 1991
	2.45	Van Wijngaarden et al., 1990
	3	Gozlan et al., 1983
DHE	1.2	Hoyer and Schoeffter, 1991
Compound No. 1	1	Liau et al., 1991; Harrington et al., 1991
No. 2	2.2	Liau et al., 1991; Harrington et al., 1991
Flesinoxan	1.5	Van Wijngaarden et al., 1990
d-LSD	0.31	Dompert et al., 1985
	2.2	Harrington et al., 1991
	2.57	Hoyer and Schoeffter, 1991
	3.0	Hall et al., 1985
	3.9	Peroutka, 1986
Lisuride	0.2	Norman et al., 1985
	0.79	Hoyer and Schoeffter, 1991
	1.8	Harrington et al., 1991
	3.8	Hall et al., 1985
NAN-190	1.3	Van Wijngaarden et al., 1990
5-HT	1.9	Harrington et al., 1991
	2.2	Peroutka, 1986
	3.1	Engel et al., 1986; Hoyer and Schoeffter, 1991
	3.3	Schlicker et al., 1989
	4.3	Dompert et al., 1985
	6.7	Norman et al., 1985
	6.8	Gozlan et al., 1983
Ipsapirone	2.2	Dompert et al., 1985
(TVXQ 7821)	2.9	Peroutka, 1986
	5.9	Van Wijngaarden et al., 1990
	7.9	Harrington et al., 1991
	19	Hoyer and Schoeffter, 1991
WB 4101	2.0	Peroutka, 1986
	3.8	Norman et al., 1985
	5.6	Harrington et al., 1991
	12.5	Hoyer and Schoeffter, 1991
RU 24969	2.5	Peroutka, 1986
	4.3	Harrington et al., 1991
	5.1	Hoyer et al., 1985b
	7.9	Hoyer and Schoeffter, 1991
	9.8	Gozlan et al., 1983
(±)CYP	2.29	Engel et al., 1986
	5.37	Hoyer and Schoeffter, 1991
	4.8	Harrington et al., 1991
BMY 7378	2.39	Van Wijngaarden et al., 1990
	2.4	Yocca et al., 1987
5-MeO-DMT	2.5	Peroutka, 1986
	9.12	Schlicker et al., 1989
(±)ICYP	3.4	Harrington et al., 1991
	4.1	Hoyer et al., 1985b
Ergotamine	3.9	Hoyer and Schoeffter, 1991
α-Dihydroergocryptine	3.98	Hoyer and Schoeffter, 1991
Bufotenine	5.0	Peroutka, 1986
	7.7	Harrington et al., 1991
	21.4	Gozlan et al., 1983
PAPP	6.16	Schoeffter and Hoyer, 1989a
SDZ(−)21009	5.1	Harrington et al., 1991
	7.4	Hoyer et al., 1985b
	10	Hoyer and Schoeffter, 1991
Spiroxatrine	7.94	Hoyer and Schoeffter, 1991
Metergoline	6	Hoyer et al., 1985b
	7.9	Hoyer and Schoeffter, 1991
	13	Peroutka, 1986
	34	Gozlan et al., 1983
High affinity (K_i = 10–100 nM)		
Buspirone	14	Dompert et al., 1985
	14.8	Van Wijngaarden et al., 1990
	15	Peroutka, 1986
	25	Hoyer and Schoeffter, 1991
	29.5	Gozlan et al., 1983
(−)Pindolol	19	Hoyer and Schoeffter, 1991
	23.4	Hoyer et al., 1985b
Methysergide	25	Peroutka, 1986; Hoyer and Schoeffter, 1991
	40	Dompert et al., 1985
	70.8	Gozlan et al., 1983
Spiperone	23	Dompert et al., 1985
	41.7	Hoyer et al., 1985b
	48	Hall et al., 1985
	63	Hoyer and Schoeffter, 1991
	74	Norman et al., 1985
	320	Wander et al., 1987
Bromocriptine	25.1	Hoyer and Schoeffter, 1991
l-LSD	38	Peroutka, 1986
Eltoprazine	42–50	Sijbema et al., 1990
(+)CYP	53	Engel et al., 1986
CGS 12066B	64.5	Schoeffter and Hoyer, 1989a
Urapidil	63.0	Hoyer and Schoeffter, 1991
	117	Schlicker et al., 1989
RP 62203	68.5	Doble, 1990
Gepirone	79.4	Hoyer and Schoeffter, 1991
Methiothepin	72	Hoyer et al., 1985b
	79	Hoyer and Schoeffter, 1991
	89.1	Gozlan et al., 1983
Low affinity (K_i = 100–1,000 nM)		
Isamoltane	125	Schoeffter and Hoyer, 1989a
Yohimbine	125	Hoyer and Schoeffter, 1991
	138	Schlicker et al., 1989
8-OH-AT	132	Hoyer et al., 1985b
α-Me-5HT	158	Gozlan et al., 1983
5-BT	160	Peroutka, 1991b
Mesulergine	177	Van Wijngaarden et al., 1990
	588	Schlicker et al., 1989
3,6-DHT	260	Peroutka, 1986
mCPP	245	Schoeffter and Hoyer, 1989a
	316	Hoyer and Schoeffter, 1991
TFMPP	194	Van Wijngaarden et al., 1990
	288	Schoeffter and Hoyer, 1989a
	501	Hoyer and Schoeffter, 1991
Cyproheptadine	110	Peroutka, 1986
	316	Hoyer and Schoeffter, 1991
	977	Gozlan et al., 1983
Sumatriptan	239	Van Wijngaarden et al., 1990
LY 53857	398	Hoyer and Schoeffter, 1991
Pitozifen	630	Hoyer and Schoeffter, 1991
Cinanserin	740	Peroutka, 1986
	1,100	Gozlan et al., 1983
	1,170	Hoyer et al., 1985b

TABLE 2—*Continued*

Drug	Affinity	Reference	Drug	Affinity	Reference
GR 43175	794	Hoyer and Schoeffter, 1991	Quipazine	780	Peroutka, 1986
d-Butaclamol	800	Wander et al., 1987		3,231	Schoeffter and Hoyer, 1989a
Mianserin	800	Peroutka, 1986		3,310	Hoyer et al., 1985b
	933	Schlicker et al., 1989		3,390	Gozlan et al., 1983
	1,000	Hoyer and Schoeffter, 1991	Ketanserin	1,170	Dompert et al., 1985
	1,150	Hoyer et al., 1985b		1,258	Hoyer and Schoeffter, 1991
Amitriptyline	960	Peroutka, 1986		1,290	Norman et al., 1985
Very low affinity (K_i > 1,000 nM)				1,910	Hoyer et al., 1985b
Piremperone	1,258	Hoyer and Schoeffter, 1991		4,170	Gozlan et al., 1983
	1,700	Hoyer et al., 1985b	Haloperidol	2,800	Wander et al., 1987
	2,500	Peroutka, 1986	Chlorpromazine	3,200	Wander et al., 1987
2-Me-5-HT	1,698	Van Wijngaarden et al., 1990	Ritanserin	831	Van Wijngaarden et al., 1990
				6,309	Hoyer and Schoeffter, 1991
Clozapine	1,800	Wander et al., 1987	DOI	6,938	Van Wijngaarden et al., 1990
Tryptamine	3,720	Gozlan et al., 1983	Imipramine	21,000	Gozlan et al., 1983

ing the effects of a variety of 5-HT_{1A}-selective drugs on the PLC/calcium cascade in H7 and H6 cells (H6 cells express five to six times more 5-HT_{1A} receptors than H7 cells), demonstrated that the intrinsic activity of a ligand can vary widely, depending on tissue variables such as receptor density or presence of second-messenger systems. They concluded that the differences are probably related to both the degree of receptor reserve and the receptor-effector coupling. Moreover, Radja et al. (1992) provided experimental evidence suggesting the existence of different 5-HT_{1A} receptor subtypes in the CA1 area and in the dentate gyrus of rat brain.

Another parameter that affects the intrinsic activity of the 5-HT_{1A} drugs involves their stereoisomeric properties. The partial agonist properties of several racemic mixtures of 5-HT_{1A} drugs presumably reside in the fact that the two enantiomers have different intrinsic activities (i.e., the *R*-enantiomer of 8-OH-DPAT acts as a full agonist in inhibiting the cAMP production, whereas the *S*-enantiomer acts as a partial agonist) (Cornfield et al., 1991). Screening the 5-HT_{1A} activity of the enantiomers of 8-OH-DPAT analogs can ultimately be used to differentiate full agonists from partial agonists or antagonists, thereby establishing the importance of the orientation of the aminotetralin nucleus relative to the substitution in determining intrinsic activity. The three-dimensional model described recently by Mellin et al. (1991) proposed a flexible pharmacophore based on the relative position of the aromatic nucleus and a nitrogen-dummy atom vector of various DPAT derivatives; this was independent of the orientation of the N-alkyl group. These studies will favor the design of new 5-HT_{1A} agonists.

2. Regional distribution within the brain. The distribution of 5-HT_{1A} receptors within the brain has been studied in many animals species, including rat (Marcinkiewicz et al., 1984; Pazos and Palacios, 1985), mouse, guinea pig, calf, cat (Waeber et al., 1989a), pig (Hoyer et al., 1985b), monkey (Köhler et al., 1986), and humans (Hoyer et al., 1986a; Pazos et al., 1987a). A similar receptor distribution was reported in all of these species. Thus, the highest density was observed in the limbic system: hippocampus (dentate gyrus and CA1), septum, amygdala, and the cortical limbic area (entorhinal cortex). The preferential distribution of 5-HT_{1A} receptors in limbic areas is consistent with their involvement in the control of mood and anxiety. These receptors are generally sparce in brain areas rich in other 5-HT_1 subtypes (5-$HT_{1B/1D}$).

Interestingly, 5-HT_{1A} receptors are highly localized in raphe dorsal and median nuclei that contain serotonergic cell bodies. In this area, the 5-HT_{1A} receptors act as somatodendritic autoreceptors regulating the firing of serotonergic neurons. These autoreceptors are involved in neural mechanisms of spontaneous locomotor activity (median raphe) and in the mediation of thermoregulation (dorsal raphe), hyperphagia (dorsal raphe), and male rat sexual behavior (dorsal and median raphe) (see Hillegaart, 1991).

3. Cellular localization. The 5-HT_{1A} receptors located in raphe nuclei are presynaptic and correspond to somatodendritic sites present on serotonergic neurons (autoreceptors). This pattern was shown by Weissman-Nanopoulos et al. (1985) and Vergé et al. (1985, 1986) who observed a marked decrease of the receptor density after provoking selective serotonergic lesions by using 5,7-DHT. However, the decrease was only 50% which strongly suggests that some of the receptors are not located on serotonergic neurons.

5-HT_{1A} receptors also are localized postsynaptically to the 5-HT nerve terminals (e.g., hippocampal pyramidal cells). This was shown by Hall et al. (1985) and Vergé et al. (1986) who observed no decrease in these sites after treatment with 5,7-DHT but reported a 50% decrease after kainic acid lesions were produced in this area. The latter observation suggests that, in the hippocampus, the 5-HT_{1A} receptors are somatodendritic and also are located at terminals of nonserotonergic neurons or on glial cells.

4. Molecular structure. The cloning of the 5-HT_{1A} receptor made it possible to determine precisely the

molecular structure of the receptor protein. Kobilka et al. (1987), studying human β-adrenoceptors, isolated a cloned gene (G21) located on chromosome 5 which was later identified by Fargin et al. (1988) as that encoding the 5-HT_{1A} receptor. The efficiency of β-adrenergic antagonists at 5-HT_{1A} receptors (i.e., propranolol, pindolol) can be explained by the close homology of the two receptors. Albert et al. (1990) and Fujiwara et al. (1990) cloned the 5-HT_{1A} receptor in the rat; it was found to have an 88% homology with the human receptor. Surprisingly, there is greater similarity between the 5-HT_{1A} and β-adrenoceptor than between 5-HT_{1A} and the serotonergic receptors 5-HT_{1C} (18 and 40% identity for total structure and transmembranal domains, respectively) and 5-HT_2 (19 and 41% identity, respectively) (Hartig et al., 1990a; Harrisson et al., 1991). Genes coding for proteins resembling 5-HT_{1A} receptors have been cloned from *Drosophila* (Witz et al., 1990) and dog (RDC4 gene) (Libert et al., 1989, 1991). However, a partial sequence of RDC4 was recently used to isolate the human gene coding for a different receptor subtype (5-HT_{1D}) (Hamblin and Metcalf, 1991).

The 5-HT_{1A} gene has been shown to be located on chromosome 5 in humans, at bands 5q11.2 to q13, on the proximal side of D5S76 (Kobilka et al., 1987; Melmer et al., 1991), and on chromosome 13 in mouse (Oakey et al., 1991); a conserved linkage has been described for these chromosomes in the two species (Maurer et al., 1985).

The 5-HT_{1A} protein receptor consists of a monomeric chain (422 amino acids in rat, 421 amino acids in human) characterized by a short carboxy-terminal domain (16 amino acids) and a long third intracellular loop (128 amino acids); in contrast, the β_2-adrenoceptor contains a long carboxy-terminal chain and a short third intracellular loop (Strader et al., 1989). The third intracellular loop is one of the most specific domains of G protein-coupled receptors; thus, El Mestikawy et al. (1990) raised antibodies against a 26-amino acid portion of this loop that were specific for 5-HT_{1A} receptors. The third 5-HT_{1A} intracellular loop has no target either for protein kinase A (cAMP-dependent kinase), as does the β-adrenoceptor (Benovic et al., 1988), or for protein kinase II (calcium/calmodulin II-dependent kinase), which is abundant in the hippocampus. However, this loop possesses two threonine residues, targets for PKC phosphorylation.

The close link between phosphorylation and desensitization of the human 5-HT_{1A} receptor was demonstrated by Raymond (1991a), who found that the efficacy of the coupling to adenylyl cyclase decreased upon PKC activation in Chinese hamster ovary cells transfected with the 5-HT_{1A} receptor gene. Moreover, acute (2 min) pretreatment with 12-O-tetradecanoyl phorbol-13-acetate, a phorbol ester activator of protein kinase C, preferentially blocks some functions related to 5-HT_{1A} activation (IP_3 production and increase in $[Ca^{2+}]_i$ in LZD-7 cells and inhibition of cAMP basal production in CH_4ZD_{10} cells) but not others (inhibition of forskolin-stimulated cAMP production in both LZD-7 and CH_4ZD_{10} cells) (Liu and Albert, 1991). The action of protein kinase C was potentiated by activation of protein kinase A, indicating that second messengers may modulate the expression of the pathways related to the 5-HT_{1A} receptor (Liu and Albert, 1991). The reduction of 5-HT_{1A} receptor function controlled by 5-HT_2 receptors, known to be coupled to phosphatidylinosides turnover and PKC activation (Kidd et al., 1990, 1991; Backus et al., 1990), may be of functional significance in this mechanism shown only in transfected cells.

Another particular feature of the 5-HT_{1A} structure is the presence of a "leucine zipper" in transmembrane domain III (Hartig et al., 1990a). This zipper exists in a series of DNA-binding proteins and oncogenes, where it is thought to facilitate dimer formation and, thus, interaction with other proteins (Landschulz et al., 1988; Struhl, 1989). This property is shared by 5-HT_2 receptors but not by other G protein-coupled receptors (Hartig et al., 1990a). Thus, although not demonstrated, it is not excluded that the functional interactions observed between 5-HT_2 and 5-HT_{1A} receptors may involve such protein-protein interactions.

As shown by mutagenesis experiments (Strader et al., 1989), the recognition site for agonistic ligands in the β-adrenoceptor included the Asp-113 residue. This residue is also present in 5-HT_{1A} transmembrane domain III, where it is thought to play a similar role (Hartig et al., 1990b). Hibert et al. (1991), using computerized modeling of receptors related to the G protein, suggested that this aspartate residue forms an ion pair with the amino group of 5-HT; this binding is stabilized by surrounding aromatic groups (one tryptophan and two phenylalanines). The indole moiety is also stabilized by a corresponding aromatic group, and, finally, the hydroxyl group of 5-HT is located in front of a serine residue. Weinstein and Osman (1990) proposed that the positively charged side chain (imidazolium) of the His-162 residue is involved in the binding of agonistic ligands and that such binding induces a proton transfer which, in turn, activates the receptor.

5. Transduction systems. The predominant transducing system linked to 5-HT_{1A} receptors is that of adenylyl cyclase. 5-HT_{1A} receptor was demonstrated to exert a negative control of adenylyl cyclase activity in numerous experiments, in which the activity of the enzyme was first strongly stimulated by forskolin in rat (De Vivo and Maayani, 1986; Oksenberg and Peroutka, 1988), guinea pig (De Vivo and Maayani, 1986, 1990), and calf hippocampus (Schoeffter and Hoyer, 1988), by vasoactive intestinal polypeptide in mice neuronal cultures from striatum, hippocampus, and cortex (Weiss et al., 1986; Bockaert et al., 1987; Dumuis et al., 1988c) or by calcium in rat hippocampus (Mörk and Geisler, 1990). The phar-

macological correlation of this activity with the 5-HT_{1A}-binding site is well established (Bockaert et al., 1987; Schoeffter and Hoyer, 1988).

The negative coupling of 5-HT_{1A} receptor with adenylyl cyclase was confirmed by Harrington et al. (1988) and Okada et al. (1989), who showed that pertussis toxin, a specific inhibitor of G_i protein, attenuated the observed effect. Moreover, Fargin et al. (1989) and Albert et al. (1990), using cultured transfected cells (COS-7, HeLa, and GH_4ZD_{10}) expressing 5-HT_{1A} receptors, demonstrated that 5-HT (in the nanomolar range) inhibited forskolin-stimulated adenylyl cyclase activity. Electrophysiological experiments (Andrade et al., 1986; Clarke et al., 1987) with pertussis toxin also indicated that 5-HT_{1A} receptor is coupled to a G_i protein.

Although, the negative coupling of 5-HT_{1A} receptors with adenylyl cyclase activity is well established and involves G_i protein, several experimental observations indicate that there may also be a positive coupling. Initially, serotonergic agonists were found to activate this enzyme in vitro in the rat hippocampus (Barbaccia et al., 1983a; Markstein et al., 1986), guinea pig hippocampus (Shenker et al., 1983, 1985, 1987), and rat brain cortex (Fayolle et al., 1988, Mörk and Geisler, 1990). Recently, an increase in cAMP production induced by 8-OH-DPAT and antagonized by *d*-propranolol was observed in vivo by using a microdialysis technique (Sijbesma et al., 1991). The activation of adenylyl cyclase correlates pharmacologically to 5-HT_{1A}-binding sites, suggesting that the receptors are coupled to a G_s protein.

However, other authors did not observe any 5-HT_{1A}-related activation in the cortex (Weiss et al., 1986; De Vivo and Maayani, 1990) or in the hippocampus (Oksenberg and Peroutka, 1988). Maayani's group, who initially reported the activation of adenylyl cyclase by 5-HT_{1A} in guinea pig hippocampus (Shenker et al., 1985, 1987), did not find the same pharmacological profile of the 5-HT-induced activation after modifying the experimental procedure (De Vivo and Maayani, 1990).

Thus, the adenylyl cyclase activation related to 5-HT_{1A} receptors might be attributed to experimental artifacts, because preparation of the tissue may result in the coupling of receptors to G_s-proteins, which are not normally present in the same cellular compartment. However, it is difficult to conceive that membrane proteins (G_s) may be released into the medium and relocated in other membranes close to 5-HT_{1A} receptors as functional entities. Moreover, these activations have been demonstrated in vivo by a microdialysis technique (Sijbesma et al., 1991).

The stimulation of the enzyme by 5-HT_{1A} agonists raises the question of whether the 5-HT_{1A} receptors related to the activation and/or the inhibition of the adenylyl cyclase activity correspond to two different receptors (not distinguished by the existing ligands) linked to G_s and G_i, respectively, or to a single type coupled either to G_i or to G_s protein. Experimental evidence showed, on the one hand, that reconstituted receptors coupled to a G_s protein (D_1 or β_2-adrenoceptors) are also able to couple to inhibitory G proteins (i.e., G_i) in the presence of G_s (Sidhu et al., 1991; Rubenstein et al., 1991). The alternative coupling of the receptor may depend on the phosphorylation of the third loop by a protein kinase A. The β_2-adrenoceptor-G_s protein coupling was drastically reduced (resulting in a total loss of adenylyl cyclase stimulatory activity) after phosphorylation of a serine residue located in the third intracellular loop of the receptor; at the same time, the coupling with G_i protein was potentiated (Okamoto et al., 1991). On the other hand, G_i-coupled inhibitory receptors (α_2, D2, A1) expressed in cultured cells could also stimulate cAMP synthesis through the activation of a particular type of adenylyl cyclase (type II) by β subunits of a G_i protein (Federman et al., 1992).

In conclusion, the fact that 5-HT_{1A} receptors have been found to inhibit or to stimulate the adenylyl cyclase activity may be due either to the existence of different 5-HT_{1A} receptors specifically linked to G_i or to G_s or to the same receptor linked alternatively to G_i or G_s, depending on its phosphorylation state, or even an inhibitory G protein can mediate the stimulation of certain types of adenylyl cyclase through $\beta\gamma$ subunits.

The 5-HT_{1A} receptors are also directly linked to the PLC activity. This signal transduction pathway of the 5-HT_{1A} receptor depends on the cell type in which it is expressed. 5-HT_{1A} receptors stimulate PLC in HeLa and LZD-7 cells but not in GH_4ZD_{10} pituitary and COS-7 kidney cells (Fargin et al., 1989; Raymond et al., 1989b; Liu and Albert, 1991). In HeLa cells, the EC_{50} of 5-HT for phosphatidylinositides turnover was 10-fold higher than it was for inhibition of adenylyl cyclase; however, the EC_{50} values for these two actions were similar in LZD-7 cells.

The increase of the IP_3 production is sensitive to pertussis toxin and independent of cAMP (Fargin et al., 1989). It is accompanied by the mobilization of calcium (Middleton et al., 1990), by an increase of the sodium-dependent phosphate uptake via protein kinase C activation (Raymond et al., 1989b, 1991), and by an activation of Na^+/K^+-ATPase (Middleton et al., 1990).

That PLC activation is observed in transfected cells expressing an unusually high density of 5-HT_{1A} receptors may raise the question of the relevance of the mechanism under physiological conditions. However, the level of expression of 5-HT_{1A} receptors in LZD-7 cells (1.9 pmol/mg protein) is comparable to that of their expression in CH_4ZD_{10} cells (1.1 pmol/mg protein), in which no changes in phosphatidylinositides hydrolysis is observed. This indicates that the high density of expressed receptors in transfected cells is not the sole factor responsible for the activation of the PLC. Moreover, the IP_3 production was shown to be induced by 5-HT_1 receptors in the

hippocampus (Janowsky et al., 1984); a more complete understanding of the pharmacology is needed to attribute this effect to 5-HT_{1A} receptor function.

On the other hand, Claustre et al. (1988a) showed that 8-OH-DPAT (10 nM) reduces the IP_3 production induced by muscarinic receptor activation; this effect is independent of cAMP, K^+ channels, and pertussis toxin and is probably related to phospholipase A_2 interacting with carbachol- stimulated PLC (Claustre et al., 1991).

In addition to the coupling of 5-HT_{1A} receptors with membrane-bound enzymes (adenylyl cyclase, phospholipase), these receptors also control G protein-coupled K^+ channels, notably in the hippocampus (Andrade et al., 1986), in the dorsal raphe nucleus (Innis et al., 1988), and in the ventromedial hypothalamus (Newberry, 1992). This system is sensitive to pertussis toxin (Andrade et al., 1986; Clarke et al., 1987) and to 4-aminopyridine (Haj-Dahmane et al., 1991) and clearly does not require second messengers such as cAMP, diacylglycerol, and IP_3. Activation of the 5-HT_{1A} receptor leads to the hyperpolarization of the cell membrane through increased K^+ conductance, resulting in decreased neuronal firing. In the hippocampus, the opening of the potassium channels by 5-HT_{1A}, $GABA_B$ (Andrade et al., 1986; Colino and Hallivell, 1987; Innis and Aghajanian, 1987), and A_1 receptors (Zgombick et al., 1989) involves a pertussis toxin-sensitive G protein, which may directly couple these receptors to the same K^+ channel, because their responses are nonadditive.

It is not surprising that 5-HT_{1A} receptors take part in different transduction systems, because a similar situation prevails for other neurotransmitter receptors, namely, m_1 (Stein et al., 1988), m_2 (Ashkenazi et al., 1987; Lai et al., 1991), m_4 muscarinic receptors (Peralta et al., 1988), and D_1 dopaminergic (Sidhu et al., 1991). The existence of these multifunctional receptors raises certain questions. Data indicate that various receptors may interact with more than one of the G proteins present in the membrane (see review by Birnbaumer et al., 1990, and above, this section). Although the molecular mechanism by which a single receptor couples to multiple G proteins is poorly understood, the phosphorylation of the receptor seems to be an important mechanism in defining the specificity of the coupling with a given G protein (Okamoto et al., 1991; Liu and Albert, 1991). Another question is whether the different electrophysiological and biochemical responses occur in the same cell or in different neuronal populations. This question is still unresolved, although it was addressed by Andrade (1990). In addition, further investigations are needed to explain the relative importance of the receptors coupled to several transduction systems, in the function of a single cell or in that of different cell populations.

6. Possible heterogeneity of the 5-HT_{1A} receptor subtype. Several experimental observations suggest the existence of different 5-HT_{1A} receptor subtypes. In the raphe, the 5-HT_{1A} receptors are not linked to the inhibition of adenylyl cyclase activity as they are in the hippocampus (Yocca and Maayani, 1990). Moreover, as demonstrated by electrophysiological, biochemical and behavioral studies, several 5-HT_{1A} agonists have different efficacies, depending on the brain region (raphe, hippocampus, cortex, or even different areas of hippocampus such as CA1 or dentate gyrus). Brown et al. (1990), who compared the efficacy of RS 30199–193 in rat brain and ileum, also suggested the existence of several 5-HT_{1A} receptor subtypes.

Studies of the adaptive regulatory mechanisms of 5-HT_{1A} receptors in response to chronic treatment with various drugs also revealed differences between the pre- and postsynaptic receptors. For example, chronic treatment with IMAO (Blier and de Montigny, 1985), SRI (Blier and de Montigny, 1983; Chaput et al., 1986), or the 5-HT_{1A} agonists, gepirone (Blier and de Montigny, 1987b, 1990) and ipsapirone (Schechter et al., 1990), provokes a desensitization of the somatodendritic 5-HT_{1A} autoreceptors (raphe), without any change of hippocampal postsynaptic 5-HT_{1A} receptors.

The possibility that regional differences exist for 5-HT_{1A} receptors in the CNS was recently investigated by Radja et al. (1992) using quantitative autoradiography. Although pronounced regional differences in the pharmacological properties were not observed, physicochemical properties of the receptors revealed a heterogeneity more related to the CA1 area versus dentate gyrus than to the pre- or postsynaptic location of these receptors. Therefore, the functional and regulatory differences that depend on the stimulation of pre- or postsynaptic receptors could not be due to the intrinsic properties of binding sites but, rather, might be related to the intracellular pathways of transduction.

These data suggest that all 5-HT_{1A} receptors are not identical throughout the brain. In agreement with these findings, a northern blot analysis by Albert et al. (1990) of 5-HT_{1A} mRNAs in rat brain showed that the detected mRNA sequences had sizes of 3.9, 3.6, 3.3, and 2.2 kb in some brain areas. This suggests that there are either different transcriptional start sites or different polyadenylation sites. Similar results were obtained in our laboratory with a more specific probe (unpublished results). Further experiments are needed to explain the functional relevance of these bands.

7. Regulation. In vitro, 5-HT_{1A} receptors, like G protein-related receptors, interact with the guanine nucleotides. GTP modulates receptor affinity allosterically in a reversible manner; it decreases the receptor affinity without any change in the apparent B_{max} of the [^{3}H]8-OH-DPAT-binding sites. However, its nonhydrolysable analogs (5-guanylyl imidodiphosphate, GTP γ-S) induce a persistent decrease in both the affinity and the apparent density of 5-HT_{1A} sites (Hall et al., 1985; Schlegel and Peroutka, 1986; Harrington and Peroutka, 1990a).

According to the model proposed by Harrington and Peroutka (1990a), the receptor-G protein complex can exist in different interconverting states and only few of them would bind the agonist. The K_d and the B_{max} values depend on the equilibrium that exists among the different states. The addition of GTP moves the equilibrium toward "nonbinding" states, resulting in a lower affinity of the agonist. The significant decrease of the B_{max} by the nonhydrolysable nucleotides could be explained by the persistent nature of their binding to G proteins, resulting in a disruption of the interconvertibility of the receptor states.

A GTP-insensitive component of the 5-HT_{1A}-solubilized binding sites was described (Emerit et al., 1991; Elliott and Phipps, 1992). It was proposed that the different states of oxidation of SH-groups of the receptor may influence the coupling with the G protein and induce the occurrence of the GTP-insensitive component.

During brain development, 5-HT_{1A} receptors are highly regulated. Thus, Daval et al. (1987) showed that the number of 5-HT_{1A} receptors in the rat cortex, hippocampus, and septum increases markedly during the first 3 weeks after birth and is stable up to an advanced age (Gozlan et al., 1990). In contrast, in the human brain, an age-related decrease of 5-HT_{1A} binding is observed that is specific to cortical, hippocampal, and raphe nuclei (Dillon et al., 1991). A different regulation mechanism exists in the cerebellum where a high number of functional receptors are already present at birth but disappear by adulthood (Daval et al., 1987; Hamon et al., 1990b). This presence of 5-HT receptors at an early stage of the cerebellum development might reflect a trophic role of the serotonergic system in this area.

In general, long-term variations of receptor stimulation regulate the receptor number. However, lesions of the serotonergic neurons that project to the hippocampus, when provoked by repetitive administration of 5,7-DHT, modify neither the number of 5-HT_{1A} receptors (Vergé et al., 1986) nor their activity (Hamon et al., 1990b). Several studies have shown that a single administration of a 5-HT_{1A} agonist causes a rapid, marked, and prolonged decrease of the 5-HT_{1A}-mediated functions (hypothermia, hyperalgesia) (Larsson et al., 1990; Kennett et al., 1987c; Beer et al., 1990); these decreases are accompanied by a 25% rapid downregulation of the number of 5-HT_{1A}-binding sites in the raphe but not in the hippocampus (Beer et al., 1990). Hjorth (1991), however, did not observe any alteration of the inhibitory effect of 8-OH-DPAT on 5-HT release under similar conditions; these discrepancies could be resolved if it turns out that a large pool of autoreceptors is held in reserve (Meller et al., 1990). That hypothermia and hyperphagia are desensitized, whereas 5-HT release is not affected under the same conditions, suggests that different 5-HT_{1A} receptor populations are involved in these phenomena. The validity of this hypothesis remains to be established.

Functional interactions occur between 5-HT_2 and 5-HT_{1A} receptors; in particular, the former seem to control the activity of the latter. Weiss et al. (1986) showed that, in vitro, in cortical neurons, ketanserin, at low concentration, significantly increases the negative effect of 5-HT on the adenylyl cyclase activity. This interaction also takes place in vivo because long-term treatment with a 5-HT_2 antagonist (ketanserin) or agonist (DOI), which both desensitize the 5-HT_2 receptors, decreased the 5-HT_{1A} autoreceptor effect on 5-HT release (Kidd et al., 1990, 1991). Moreover, acute administration of ritanserin or ketanserin, which desensitizes 5-HT_2 receptors, increased the 5-HT_{1A} syndrome (Backus et al., 1990). In addition, activation of 5-HT_2 receptors on pyramidal cells of layer V of the medial prefrontal cortex reduces the ability of 5-HT_{1A} receptors to hyperpolarize these cells (Araneda and Andrade, 1991). Thus, it is likely that 5-HT_2 activity inhibits the function of 5-HT_{1A} receptors.

However, Arnt and Hyttel (1989), measuring forepaw treading in the rat, reported that DOI facilitated 5-HT_{1A} function. Moreover, Garratt et al. (1991) recently showed that the inhibitory effects of DOI on the firing of 5-HT neurons and the decrease of the extracellular 5-HT concentration in the frontal cortex were not mediated by 5-HT_2 because they were not antagonized by ketanserin, ritanserin, or pindolol. Recent findings demonstrating the membrane-stabilizing properties of DOI (Martin et al., 1991b) may explain these contradictory results. In addition, the 5-HT_{1A}-5-HT_2 interactions, as shown by Pranzatelli and Pluchino (1991), are limited to a few behavior patterns involving serotonergic receptors, i.e., forepaw myoclonus, shaking behavior, and thermoregulation, but are not involved in skin jerks, flat body posture, or head weaving. On the other hand, Yocca et al. (1990b) proposed that 5-HT_{1A} receptors may control the 5-HT_2 head shake response in rats, suggesting the reciprocal interaction of 5-HT_{1A} on the 5-HT_2-induced activity.

Many experimental studies have been devoted to the interaction of antidepressant drugs with 5-HT_{1A} receptors. However, at the present time, the mechanism of this interaction is not fully understood. Two interpretations of data concerning what occurs after long-term antidepressant treatment have been presented: one favors a desensitization of the postsynaptic 5-HT_{1A} receptors; the other suggests the hypersensitization of these receptors that may be related to a desensitization of the presynaptic autoreceptors in raphe. Indeed, long-term treatment with various antidepressants (IMAO, TCA, 5-HT_{1A} agonists, electroconvulsive shock) or with lithium have been shown to downregulate the postsynaptic 5-HT_{1A} receptors located in the cortex or in the hippocampus (Mizuta and Segawa, 1988, 1989; Odakaki et al., 1990; Pandey et al., 1991), or to induce a desensitization of their effect on adenylyl cyclase activity (Sleight et al., 1988; Newman and Leler, 1988a; Varrault et al., 1991;

Newman et al., 1991, 1992), or their effect on the serotonergic syndrome (Lucki and Frazer, 1982; Goodwin, 1989).

On the other hand, it was also shown that long-term treatment with antidepressants led to the hypersensitivity of the postsynaptic 5-HT_{1A} receptors or to the desensitization of the autoreceptors in the raphe, resulting in both cases in a facilitation of the serotonergic transmission. Indeed, chronic treatment with TCAs (amitriptyline, imipramine, desimipramine), or electroconvulsive shock increased the number of 5-HT_{1A} receptors in the cortex and the hippocampus and the responsiveness of hippocampal pyramidal neurons to 5-HT without modifying 5-HT_{1A} receptors in the raphe (Blier et al., 1988; Welner et al., 1989; Nowak and Dulinski, 1991). TCA, IMAO, 5-HT uptake inhibitors (zimelidine or citalopram), 5-HT_{1A} agonists (buspirone, gepirone, ipsapirone), or lithium exerted the following effects: in the raphe, they desensitized the 5-HT_{1A} receptors and reduced their number (Welner et al., 1989; Gobbi et al., 1991); they weakened their inhibitory effect on serotonergic neuronal firing (Blier and de Montigny, 1983, 1985, 1987a,b; Chaput et al., 1986, 1988; Schechter et al., 1990); they enhanced the release of 5-HT from serotonergic neurons (Sharp et al., 1991), and they attenuated their hypothermic response both in mice (Goodwin et al., 1985a; De Souza et al., 1986; Goodwin, 1989) and in humans (Lesh et al., 1990) without changing the postsynaptic activity of the 5-HT_{1A} receptors located in the hippocampus. These effects resulting in a facilitation of the serotonergic transmission are in agreement with the decrease of hippocampal 5-HT_{1A} sites observed in suicidal/depressed individuals (Cheetham et al., 1989, 1990).

In addition to these contradictory results, several experiments in which chronic treatment with different antidepressants was used failed to show any modification in [^{3}H]8-OH-DPAT-binding sites in the hippocampus and in the raphe regions (Frazer and Hensler, 1990; Schechter et al., 1990; Newman et al., 1990, 1991; Hensler et al., 1991; Pandey et al., 1991), in the serotonergic syndrome (Lucki and Frazer, 1982), in the response of cortical or hippocampal pyramidal neurons to iontophoretically applied 5-HT (Olpe and Schellenberg, 1981; Olpe et al., 1984), or in the inhibition of the forskolin-stimulated adenylyl cyclase induced by 5-HT in hippocampus (Frazer and Hensler, 1990; Schechter et al., 1990).

It is difficult to reconcile these results and explain the discrepancies. Differences exist in the effects of different antidepressants in similar experiments, or even in the effects of a single antidepressant in the same model, depending on the investigators, not only between electrophysiological and biochemical data but also between the regulatory properties of pre- and postsynaptic 5-HT_{1A} receptors. Thus, we can make no conclusions from the adaptive changes of 5-HT_{1A} receptors in response to the antidepressant treatments. That the heterogeneity of 5-HT_{1A} receptors is likely at various levels (genes, physicochemical properties, transduction systems, regional distribution, and regulation mechanisms) might explain some of the results reported in the literature. A better understanding of the identity and functions related to these receptors, as well as their interactions with other receptors, will certainly allow a clarification of the role of 5-HT_{1A} receptors in the mechanism of action of the antidepressants.

The 5-HT_{1A} receptors appear to be regulated by hormonal levels. The 8-OH-DPAT-induced corticosterone release was attenuated by ovariectomy in female rats, and, in contrast, this effect was enhanced by castration in male mice (Matsuda et al., 1991). These findings suggest that the adrenocortical effect of 8-OH-DPAT is altered by gonadal hormones. Indeed, estrogen treatment (3 to 5 days) in ovariectomized female rats or in castrated mice increases 5-HT_{1A}-related adenylyl cyclase activity (Clarke and Maayani, 1990), electrophysiological activity (Beck et al., 1989; Clarke and Goldfard, 1989), and corticosterone release (Matsuda et al., 1991). However, the mechanism for estrogen's enhancement of 5-HT_{1A} responsiveness is unknown.

The existence of a bidirectional intramembrane interaction between 5-HT_{1A} and galanin receptors was demonstrated by Fuxe et al. (1988; Hedlund and Fuxe, 1991). Thus, galanin (10 nM), in vitro, selectively reduces the affinity of the 5-HT_{1A} receptors within the rat ventral limbic cortex, without altering the binding of 5-HT_{1B} or 5-HT_2 receptors. In contrast, the 5-HT_{1A} receptor agonist, 8-OH-DPAT (10 nM), increases the affinity of the galanin receptors by approximately 55% in various telencephalic and diencephalic areas (Hedlund et al., 1991a). The increased affinity of galanin-binding sites by 8-OH-DPAT seems to reflect a G protein-independent intramembrane receptor-receptor interaction between 5-HT_{1A} and galanin receptors. This interaction, observed in vitro, is of biological relevance, because the receptors interact synergistically in the control of central cardiovascular regulation (Hedlund et al., 1991b).

Several opioid narcotics (sufentanil, fentanyl) at high concentrations inhibit the binding of [^{3}H]8-OH-DPAT to rat membranes; this inhibition appears to be competitive, because these drugs increase the K_d without altering the number of 5-HT_{1A} sites. However, no changes in the sensitivity of 5-HT_{1A} receptors to guanine nucleotides are observed. These findings suggest that these narcotics disrupt neurotransmission at 5-HT_{1A} receptors during clinical anesthesia (Martin et al., 1991a).

It is known that alcohol consumption modifies serotonin levels (Carlsson et al., 1980; Gorelick, 1989), serotonin turnover (Morinan, 1987), and the serotonin transport system (Gross-Isseroff and Biegon, 1988) in rat and human brain. Recently, it was demonstrated that alcohol consumption coincides with the alteration of binding to

5-HT_{1A} receptors; cortical [^{3}H]-8-OH-DPAT binding was decreased in subjects in whom alcohol was detected at autopsy (Dillon et al., 1991).

Deficits of the serotonergic system have been established in Alzheimer disease (see review by Cross, 1990) and include a reduction in the number of 5-HT_{1A}-binding sites in the frontal, temporal, and parietal cortices (Middlemiss et al., 1986). However, the modulation of [^{3}H]8-OH-DPAT binding by guanine nucleotides did not vary significantly in these regions in control patients and those with Alzheimer's disease, suggesting that the functional capacity of 5-HT_{1A} receptor is intact in the brain of persons with Alzheimer's disease (O'Neill et al., 1991).

8. Cellular functions. 5-HT_{1A} receptors are present in the raphe on 5-HT neurons as presynaptic autoreceptors that regulate 5-HT neuronal activity (Aghajanian, 1978; Van der Maelen et al., 1986; Sprouse and Aghajanian, 1987) and 5-HT synthesis and release (Hjorth and Magnusson, 1988; Hamon et al., 1988; Hjorth and Sharp, 1991). Meller et al. (1990) suggested the existence of a large reserve of these 5-HT_{1A} autoreceptors. Interestingly, Sinton and Fallon (1988) and Blier et al. (1990) reported that the serotonergic neurons in the dorsal raphe were less sensitive to 5-HT_{1A} agonists than were those in the median raphe, suggesting the existence of different mechanisms regulating the activity of the ascending 5-HT projections. However, Hjorth and Sharp (1991), using in vivo microdialysis, demonstrated that the inhibition of 5-HT release by 5-HT_{1A} was identical in several areas innervated by dorsal or median raphe, except in the globus pallidus.

5-HT_{1A} receptors are also located on nonserotonergic neurons, either as heterologous presynaptic receptors on terminals or as postsynaptic receptors on soma or dendrites. These receptors are thought to modulate the release of other neurotransmitters. For example, 8-OH-DPAT enhances ACh release in rat or guinea pig cortex (Siniscalchi et al., 1990a). 5-HT_{1A} receptors also reduce the glutamate-induced excitation of adrenergic neurons in the locus coeruleus (Charlety et al., 1991). Chaouloff and Jeanrenaud (1987) reported that 8-OH-DPAT is involved in the control of the adrenaline-induced hyperglycemia resulting from enhanced adrenaline release via 5-HT_{1A} receptor activation (Bagdy et al., 1989; Chaouloff et al., 1990). Hamon et al. (1988) reported that 5-HT_{1A} agonists (gepirone, buspirone, ipsapirone) increase the dopamine turnover, however, 8-OH-DPAT was inactive, suggesting that this effect was not mediated by 5-HT_{1A} autoreceptors. In contrast, Benloucif and Galloway (1991) using microdialysis showed that the dopamine-releasing effect occurs in the presence of TFMPP, mCPP, RU 24969, and also 8-OH-DPAT and proposed that 5-HT_{1A} receptors are involved in dopamine release.

The core of experimental results in this domain deals with the effect of 5-HT_{1A} receptors on the control of the hypothalamo-hypophysis axis. 8-OH-DPAT, buspirone, gepirone, and ipsapirone stimulate the release of adrenocorticotropine (Gilbert et al., 1987, 1988b; Sciullo et al., 1990), β- endorphin (Koening et al., 1987, 1988; Sciullo et al., 1990), corticosterone (Koening et al., 1987, 1988; Matheson et al., 1989; Haleem et al., 1989; Matsuda et al., 1991; Owens et al., 1990), and corticotropin-releasing factor (Owens et al., 1990). These effects, presumably, are not due to an interaction with the cholinergic system (Gilbert et al., 1988a) but more likely to an action on the observed secretions via a 5-HT_{1A} postsynaptic receptor (Gilbert et al., 1988a). This mechanism might be involved in the circadian regulation of these secretions (Halasz and Banky, 1986), their negative feedback (Beaulieu et al., 1986), or their involvement in stress mechanisms (Haleem et al., 1989).

9. 5-HT_{1A} receptors and behavior. Investigations of animal behavior have been considerably facilitated by the development of selective drugs for 5-HT_{1A} receptors. These receptors appear to be involved in many kinds of behavior (cf. reviews by Lucki and Wieland, 1990; Glennon, 1990b; Murphy, 1990; Glitz and Pohl, 1991; Wilkinson and Dourish, 1991; Lucki, 1992).

The main and most obvious effect of 5-HT_{1A} agonists in vertebrates is that they provoke the serotonergic syndrome, which consists in mice and rats of an overstimulated state leading to motor modifications (hyperlocomotion, head weaving, reciprocal forepaw treading, flat body posture) (Tricklebank, 1987; Yamada et al., 1988, 1989). In humans, this syndrome results in confusion, nervousness, hypereflexia, restlessness, hypomania, excitation, myoclony, and shivering (Sternbach, 1991). Postsynaptic 5-HT_{1A} receptors are thought to mediate these effects (Tricklebank, 1987). In the rat, the different components of the serotonergic syndrome manifest themselves at different phases during postnatal ontogenesis; hyperlocomotion and head weaving occur as early as the fifth day after birth, whereas hindlimb scratching and forepaw treading are observed only after the third postnatal week (Jackson and Kitchen, 1989).

Presynaptic autoreceptors in the median raphe are more likely to induce hypolocomotion, especially affecting the horizontal movements (Hillegaart et al., 1989; Hillegaart and Hjorth, 1989; Mittman and Geyer, 1989). Ahlenius et al. (1991) also observed an increase of the forward and peripheral locomotion under similar conditions.

Sexual behavior is controlled in part by 5-HT_{1A} activity; however, the mechanism by which it does so is not yet precisely known. In male rats, 5-HT_{1A} agonists (8-OH-DPAT, buspirone, ipsapirone, flesinoxan) facilitate sexual activity (Schnur et al., 1989; Ahlenius and Larsson, 1989; Berendsen and Broekkamp, 1990; Mos et al., 1990; Ahlenius et al., 1991), although 5-HT or its precursors have been reported to inhibit it (Ahlenius and Larsson, 1987). An explanation for this paradox might reside in the preferential presynaptic activity of 8-OH-

DPAT but also may result from a 5-HT_{1B} inhibition of male sexual behavior (Fernandez-Guasti et al., 1989).

The effect of 5-HT_{1A} on sexual behavior is sex dependent; in female rats, 8-OH-DPAT inhibits lordosis behavior (Mendelson and Gorzalka, 1986a), in contrast to its facilitatory effect in male rats. This effect is presumably due to the 5-HT_{1A} control of hypothalamic activity, because the lordosis behavior is suppressed by intrahypothalamic administration of 8-OH-DPAT (Uphouse et al., 1991a,b). The difference in the observed 5-HT_{1A} activity in the male and female might be expected, because functional and anatomical differences between males and females with respect to the 5-HT system are present (Uphouse et al., 1991b). Furthermore, this effect is species dependent. In male mice, 8-OH-DPAT inhibits sexual behavior (Svensson et al., 1987), whereas in male rats it is facilitatory. Effects are dose dependent, because whether ipsapirone and gepirone have facilitatory or inhibitory effects on lordosis behavior depends on the dose (Fernandez-Guasti et al., 1987).

5-HT_{1A} receptors participate in body temperature regulation. Agonists induce hypothermia in rats (Hjorth, 1985; Goodwin et al., 1987) and mice (Goodwin et al., 1985b). The mechanism of temperature regulation has not yet been fully clarified. In the mouse, there is good evidence that the 5-HT_{1A} receptor mediating 8-OH-DPAT-induced hypothermia are presynaptic, because 5,7-DHT administration for 2 weeks with pCPA abolished the hyperthermia induced by 8-OH-DPAT (Goodwin et al., 1985b; Bill et al., 1991). In the rat, there is some controversy as to whether thermoregulatory 5-HT_{1A} receptors are presynaptic (Goodwin et al., 1987) or postsynaptic (Hjorth, 1985; Hutson et al., 1987). The latter authors found that 5-HT depletion or 5,7-DHT lesions, rather than attenuating 8-OH-DPAT-induced hypothermia, tended to enhance the response. However, Goodwin et al. (1987) found that pCPA-induced 5-HT depletion prevented 8-OH-DPAT-induced hypothermia in the rat, concluding that the 5-HT_{1A} receptors mediating this response are presynaptic. In an attempt to resolve this controversy Bill et al. (1991), carried out two parallel series of experiments (5-HT depletion techniques by 5,7-DHT and pCPA and use of agents that facilitated the 5-HT release) in rat and mouse. They concluded that an important species difference exists, because the 8-OH-DPAT-induced hypothermia is mediated by presynaptic autoreceptors in the mouse and by postsynaptic 5-HT_{1A} receptors in the rat.

A sex difference in the hypothermic effect of 8-OH-DPAT has also been reported. This effect, more marked in female than in male rats (Carlsson and Eriksson, 1987), may reflect a differential clearance of the drug (Kato, 1974) or even a differential sensitivity of the pre- and postsynaptic 5-HT_{1A} receptors in male and female rats. Indeed, the 5-HT system is reported to be more active in females than in males; for example, females exhibit less evidence of a behavior that requires autoreceptor activation (e.g., hyperalgesia) and greater evidence of behaviors that require activation of the postsynaptic sites (e.g., hypothermia, 5-HT syndrome) (Uphouse et al., 1991a,b).

The 5-HT_{1A} receptors play an important role in feeding behavior. 5-HT_{1A} agonists (8-OH-DPAT, ipsapirone, buspirone, gepirone, LY 165–163) increase food intake in rats (Dourish et al., 1985; Gilbert and Dourish, 1987; Hutson et al., 1988), mice (Shepherd and Rodgers, 1990), and cats (Jacobs et al., 1989). This effect is opposite to that of 5-HT itself (Blundell, 1977). This difference might be explained by the activation of the 5-HT_{1A} presynaptic autoreceptors, which decreases the serotonergic activity. This hypothesis is supported by the fact that local injection of 8-OH-DPAT in the raphe increases food intake (Hutson et al., 1986; Bendotti and Samanin, 1987) and by the absence of 8-OH-DPAT- and LY 165–163-induced hyperphagia after depletion of 5-HT by pCPA (Bendotti and Samanin, 1986; Dourish et al., 1986a,b,c). Moreover, this effect of 5-HT_{1A} agonists on feeding behavior leads to rapid tolerance development, presumably due to desensitization of the autoreceptors (Kennett et al., 1987c; Goudie et al., 1989). Hyperphagia was most evident in diestrous females and least evident in proestrous and estrous rats; these findings are interpreted as the modulation of somatodendritic 5-HT_{1A} autoreceptors by the estrous cycle (Uphouse et al., 1991b).

A major reason for the interest in 5-HT_{1A} receptors is their implication in psychiatric disorders, such as anxiety and depression. Anxiolytic properties of 5-HT_{1A} agonists in humans have been reported for buspirone (Goldberg and Finnerty, 1979; Rickels et al., 1982; Feighner et al., 1982; Goa and Ward, 1986; Robinson et al., 1989; Böhm et al., 1990; Rakel, 1990), gepirone (Csanalosi et al., 1987; Cott et al., 1988; Harto et al., 1988; Robinson et al., 1989), ipsapirone (Glaser, 1988; Beneke et al., 1988; Kuemmel et al., 1988), and tandospirone (Hirose et al., 1986; Heym et al., 1987; Shimizu et al., 1987). The anxiolytic properties of the 5-HT_{1A} agonists are clearly different from those of the benzodiazepines. A delay of several days is required before 5-HT_{1A} agonists begin to have a therapeutic effect, whereas the effect is almost immediate with benzodiazepines. Furthermore, the 5-HT_{1A} agonists do not produce sedation, ataxia, or amnesia and are not associated with withdrawal reactions following abrupt discontinuation (Goa and Ward, 1986; Harto et al., 1988; Taylor and Moon, 1991). Thus, for treating anxiety, these substances have several advantages over benzodiazepines. However, that chronic treatment with buspirone increases (41%) the number of benzodiazepine receptors in the substantia nigra suggests that the two systems interact (Gobbi et al., 1991).

Drugs related to 5-HT_{1A} have also been found to be anxiolytic in various experimental animal models (cf.

reviews by Gardner, 1986; Dourish, 1987; Traber and Glaser, 1987, Traber et al., 1988; Young and Glennon, 1988), such as electric shock- or isolation-induced aggressiveness, ultrasonic vocalization in newborn rats (Benton and Nastiti, 1988; Hard and Engel, 1988; White et al., 1991), exploration in an aversive environment (Merlo-Pich and Samanin, 1986; Costall et al., 1988b), aggressiveness in wild rats (Blanchard et al., 1988), and the drinking conflict test (Chojnacka-Wojcik and Przegalinski, 1991). On the other hand, 8-OH-DPAT increases the isolation-induced social behavioral deficit that is reversed by 5-HT_{1B} agonists, benzodiazepines, or chronic treatment with antidepressants (Francès et al., 1990). However, it should be pointed out that the role of 5-HT_{1A} agonists in animal models of anxiety is controversial, because these drugs had variable or no effects in several conflict models of anxiety in primates or rodents (Geller and Hartmann, 1982; see reviews by Traber and Glaser, 1987; Wilkinson and Dourish, 1991); 5-HT_{1A} agonists are efficient apparently only in the pigeon conflict model. Moreover, these drugs were reported to have no effect in the social interaction test in the rat (File, 1985; Pellow et al., 1987). In addition, anxiogenic-like effects were reported after systemic injections (Critchley and Handley, 1987; Moser et al., 1990).

These contradictory observations might have several explanations, one of which is that the actual efficacy of some 5-HT_{1A} agonists is lacking; more likely, the animal models used to determine the anxiolytic effects of the drugs are not adapted to the 5-HT_{1A} mechanism of action, i.e., they may measure impulsivity rather than anxiety (Soubrié, 1986). Also, the experimental conditions used to determine this activity do not consider the fact that the anxiolytic effect in humans occurs after several days of treatment.

The anxiolytic properties of 5-HT_{1A} agonists are mediated by mechanisms that have not been fully clarified. An important question resides in determining the nature of the anxiolytic compounds as full or partial 5-HT_{1A} agonists at pre- and postsynaptic receptors. The anxiolytic effects of the 5-HT_{1A} agonists in the Vogel conflict test and social interactions paradigm possibly involve presynaptic autoreceptors, because these effects are observed after local injections of 8-OH-DPAT, ipsapirone, or buspirone in the dorsal raphe area (Higgins et al., 1988, 1989). Moreover, the anxiolytic effect of an injection of buspirone in the median raphe is blocked by a 5,7-DHT lesion (Carli et al., 1989). The same authors did not observe an anxiolytic action of buspirone after injection into the dorsal raphe area in the light/dark box model.

Several experimental arguments suggest that postsynaptic 5-HT_{1A} receptors are also involved, because anxiolytic effects of buspirone are still seen when there are lesions in the raphe (Davis et al., 1988). The main hypothesis presented to explain the mechanism of anxiolytic action of the 5-HT_{1A} agonists is based on their full activity at presynaptic autoreceptors in the raphe and their partial, or even antagonistic, properties at postsynaptic receptors. This is suggested by the numerous observations reported above on electrophysiological, biochemical, and behavioral grounds.

In summary, although the 5-HT_{1A} agonists appear to possess promising anxiolytic properties, their therapeutic effect is not yet fully characterized. It should be pointed out that anxiolytic properties of 5-HT_{1A} agonists are usually observed after a single administration in animal models, whereas this effect is obtained only after several days of treatment in humans. This raises the question of whether the therapeutic effect is observed after the increase of the serotonergic activity (acute effects) or its decrease (chronic treatment resulting in desensitization of the autoreceptors). A better understanding of the serotonergic mechanisms involved in anxiety presumably will lead to an enhancement of the therapeutic properties of these drugs.

5-HT_{1A} receptors appear to be involved also in depression and in the mechanism of action of antidepressants. The following 5-HT_{1A} agonists have been shown to have antidepressant properties in humans: buspirone (Schweizer et al., 1986; Robinson et al., 1989), gepirone (Amsterdam et al., 1987; Cott et al., 1988; Robinson et al., 1989; Jenkins et al., 1990; Raush et al., 1990), and ipsapirone (Glaser, 1988). They also exhibit these properties in the following animal models of depression (for review see Robinson et al., 1989): learned helplessness (Giral et al., 1988; Martin et al., 1990a,b, 1991c), forced swimming test (Cervo and Samanin, 1987; Cervo et al., 1988; Wieland and Lucki, 1990; Chojnacka-Wojcik et al., 1991), and open-field test (Kennett et al., 1987a).

These new antidepressants are of great therapeutic interest because they are characterized by a shorter delay of onset of action than that shown by the "classical" antidepressants and because they lack secondary effects. The mechanism of action of these drugs as antidepressants is still unknown. Cervo et al. (1988) proposed that presynaptic 5-HT_{1A} autoreceptors may play a role in the effects of antidepressants. Martin et al. (1990b, 1991c), using the learned helplessness as a paradigm, and local injections of 5-HT_{1A} agonist in the raphe or in the hippocampus, proposed that 5-HT_{1A} postsynaptic receptors were also involved.

As in the case of the anxiolytic properties, the antidepressant activity of these drugs appears to depend on pre- and postsynaptic receptors. The partial or full agonistic activity of the drugs at these receptors sites seems to play a key role in their therapeutic effect. Nevertheless, it seems that, according to the theory of a serotonergic deficit occurring in depression, the antidepressant activity of 5-HT_{1A} agonists would be related to an increase of the serotonergic activity after chronic treatment. New 5-HT_{1A} partial agonists or antagonists are

needed to determine the relative importance of the pre- and postsynaptic effects, that of particular receptor subtypes possibly located in distinct areas, and that of their regulation in the mechanism of their therapeutic activity.

The involvement of the 5-HT system in pain has been documented by several authors (LeBars, 1988). Although it does not seem that 5-HT_{1A} receptors play a major role in pain transmission, the 5-HT_{1A} agonists have been reported to have some analgesic effects (see review by Wilkinson and Dourish, 1991). The latter effect might be explained by the anxiolytic properties of the drugs. Nonetheless, Hamon's group reported the presence of 5-HT_{1A} receptors in the dorsal horns of the spinal cord and proposed that they play a role in pain transmission.

The serotonergic control of the sleep-waking cycle is well established (Jouvet, 1977; Koella, 1988). However, the 5-HT_{1A} receptors do not seem to be functionally important in this phenomenon, although 8-OH-DPAT has been reported to alter the REM sleep latency period (Kafi de St-Hilaire et al., 1987).

B. 5-HT_{1B} Receptor subtype

The 5-HT_{1B} receptor subtype was initially defined as being less sensitive to spiperone than the 5-HT_{1A} subtypes (Pedigo et al., 1981).

1. Selective radioligands and pharmacological properties. A marker specific for the 5-HT_{1B}-binding sites has not yet been found; however, these sites were specifically labeled by using [^{3}H]5-HT in the presence of drugs that mask 5-HT_{1A} and 5-HT_{1C} receptors (Peroutka, 1986). They were also labeled with [^{125}I]iodocyanopindolol used in combination with isoprenaline, which blocks the β-adrenergic sites (Hoyer et al., 1985a; Offord et al., 1988) and [^{3}H]dihydroergotamine in the presence of phentolamine and 8-OH-DPAT, which block the α-adrenergic and the 5-HT_{1A} sites, respectively (Hamblin et al., 1987). Recently, a small peptide, S-CM-GT NH_2, with a tyrosine residue susceptible to ^{125}I iodination was demonstrated to have preferential affinity for 5-HT_{1B} sites in the rat and for 5-HT_{1D} sites in the guinea pig (Boulenguez et al., 1991a,b). The radioactive iodinated form of this ligand was used to label 5-HT_{1B} receptors in the rat brain (Boulenguez et al., 1992). A novel tritiated analog of RU 24969, [^{3}H]CP-96,501, also binds with a high affinity (K_d = 0.21 nM) to 5-HT_{1B} sites in rat brain (Koe et al., 1992). The latter, which has greater affinity (30-fold) for 5-HT_{1B} than 5-HT_{1D} receptors, may be a useful tool to discriminate the two receptors.

Only a few drugs are able to bind to 5-HT_{1B} receptors with a nanomolar affinity. These are 5-HT, 5-CT, cyanopindolol, dihydroergotamine, ergotamine, RU 24969, and SDZ(−)21009; yet, none of these is specific to the 5-HT_{1B} site. Other drugs bind to this site with a lower affinity (10 to 1000 mM) (mCPP, quipazine, TFMPP) (table 3) but do not discriminate between it and other receptors; for example, some of them have been reported to recognize the 5-HT transporter with the same affinity with which they recognize 5-HT_{1B} (Wolf and Kuhn, 1991). CP-93,129, a new tetrahydropyridyl derivative structurally related to the mixed 5-HT_{1A}/5-HT_{1B} receptor ligand RU 24969, was recently reported to be a putative specific 5-HT_{1B} receptor agonist, with >150-fold higher affinity for 5-HT_{1B} versus other 5-HT_1 and 5-HT_2 sites, without interacting with the transporter (Hjorth and Tao, 1991). 5-BT was recently presented as a relatively selective 5-$HT_{1B/1D}$ agent (Peroutka et al., 1991). The final characterization of 5-HT_{1B} receptors awaits the development of selective and potent antagonists.

2. Regional distribution. 5-HT_{1B} receptor subtypes occur in rat and mouse brain (Pazos and Palacios, 1985; Hoyer et al., 1985a). These receptors are not observed in guinea pig, cat, pig, calf, pigeon, frog, or humans (Heuring et al., 1987; Hoyer et al., 1986a; Pazos et al., 1988, Martial et al., 1989; Waeber et al., 1989a). Their distribution within the rodent brain is heterogeneous. The highest density of 5-HT_{1B} receptors has been found in substantia nigra, globus pallidus, dorsal subiculum, and superior colliculi.

3. Cellular localization. Middlemiss (1984) and Engel et al. (1986) showed that the release of 5-HT from serotonergic terminals was controlled by autoreceptors characterized as 5-HT_{1B}, strongly suggesting that these were homologous presynaptic receptors. However, their postsynaptic location as heterologous presynaptic receptors is also documented by the lack of effect of serotonergic neuron lesions on the number of 5-HT_{1B} receptors (Vergé et al., 1986) and by the existence of a serotonergic inhibition of the ACh release in synaptosomes (Harel-Dupas et al., 1991b).

4. Molecular structure. The cloning of the 5-HT_{1B} gene was recently reported in rat by Voigt et al. (1991). The receptor consists of a monomeric chain (386 amino acids) having seven spanning domains and homology with the canine RDC4 receptor (5-HT_{1D}) (63%) and with the 5-HT_{1A} receptor (43%). A new 5-HT_{1D} subtype (5-$HT_{1D\beta}$) has been cloned in humans by Weinshank et al. (1992), and its sequence was reported by Adham et al. (1992). The sequence homology of this subtype is 93% with that of the 5-HT_{1B} gene in the rat, suggesting that these two genes are species homologues (Hartig et al., 1992). The pharmacological properties of 5-HT_{1B} and 5-$HT_{1D\beta}$ receptors expressed in COS-7 cells are quite different (namely, for iodocyanopindolol), although the sequences of the genes are very close (the differences being from 0 to 2 amino acids in each transmembrane region). This suggests that a mutation affecting only a few nucleotides (i.e., Asp-385) plays a very important role in the binding of pindolol derivatives.

In situ hybridization experiments revealed the expression of a high level of 5-HT_{1B} mRNA in raphe, in agreement with the nature of presynaptic autoreceptors. A high density was also observed in areas rich in 5-HT

TABLE 3

Affinity values of drugs for 5-HT$_{1B}$ recognition sites in mammalian brain membranes

Drug	Affinity	Reference
Very high affinity (K_i < 10 nM)		
(±)ICYP	0.32	Hoyer et al., 1985a
SDZ(−)21009	0.42	Hoyer et al., 1985a
DHE	0.79	Hoyer and Schoeffter, 1991
RU 24969	0.38	Peroutka, 1986
	3.8	Hoyer et al., 1985a
	5.8	Van Wijngaarden et al., 1990
	6.8	Hamblin et al., 1987
(−)CYP	1.8	Engel et al., 1986
SDZ(±)21009	2.95	Engel et al., 1986
(±)CYP	5	Hoyer and Schoeffter, 1991
	5.4	Schlicker et al., 1989
5-CT	5.12	Hoyer and Schoeffter, 1991
5-CONH$_2$-T	5.13	Engel et al., 1986
5-HT	2.45	Van Wijngaarden et al., 1990
	7.6	Peroutka, 1986
	11	Hamblin et al., 1987
	16.5	Schoeffter and Hoyer, 1989b
	24.5	Hoyer and Schoeffter, 1991
High affinity (K_i = 10–100 nM)		
Ergotamine	10.9	Hoyer and Schoeffter, 1991
5-MY	15	Peroutka, 1986
(−)Pindolol	15.8	Hoyer and Schoeffter, 1991
	77.6	Hoyer et al., 1985a
S-CM-GTNH$_2$	22.4	Boulenguez et al., 1991a
Metergoline	25.7	Hoyer et al., 1985a
	39.8	Hoyer and Schoeffter, 1991
	40.7	Engel et al., 1986
	52	Peroutka, 1986
Eltoprazine	25–38	Sijbesma et al., 1990
SDZ(+)21009	31.6	Hoyer and Schoeffter, 1991
5-BT	40	Peroutka, 1991a
W-N-CH$_3$-5HT	44.6	Hoyer et al., 1985a
(−)Propranol	46.8	Hoyer et al., 1985a
	50.1	Hoyer and Schoeffter, 1991
TFMPP	45	Peroutka, 1986
	48	Van Wijngaarden et al., 1990
	131	Schoeffter and Hoyer, 1989
	398	Hoyer and Schoeffter, 1991
Methiothepin	50	Hoyer and Schoeffter, 1991
Bufotenine	52	Peroutka, 1986
(+)CYP	56	Engel et al., 1986
(+)Propranolol	85.1	Engel et al., 1986
Low affinity (K_i = 100–1,000 nM)		
Isamoltane	112	Schoeffter and Hoyer, 1989b
CGS 12066B	114	Schoeffter and Hoyer, 1989b
Sumatriptan	154	Van Wijngaarden et al., 1990
d-LSD	151	Engel et al., 1986
	170	Peroutka, 1986
Methergine	199	Hoyer and Schoeffter, 1991
Lisuride	199	Hoyer and Schoeffter, 1991
mCPP	251	Hoyer and Schoeffter, 1991
	338	Schoeffter and Hoyer, 1989b
Quipazine	260	Peroutka, 1986
	316	Hoyer and Schoeffter, 1991
	309	Schoeffter and Hoyer, 1989
5-MeO-DMT	390	Peroutka, 1986
GR 43175	398	Hoyer and Schoeffter, 1991
5-MeO-T	398	Schlicker et al., 1989
Methysergide	520	Peroutka, 1986
	1,584	Hoyer and Schoeffter, 1991
NAN-190	616	Van Wijngaarden et al., 1990
MDL 72832	630	Hoyer and Schoeffter, 1991; Van Wijngaarden et al., 1990
5-NH$_2$-T	676	Hoyer et al., 1985a; Engel et al., 1986
2-Me-5HT	724	Van Winjgaarden et al., 1990
Flesinoxan	812	Van Wijngaarden et al., 1990
Cyproheptadine	840	Peroutka, 1986
Amitriptyline	840	Peroutka, 1986
Very low affinity (K_i > 1,000 nM)		
(±)ICI 118-551	1,230	Hoyer et al., 1985a
(±)ICI 89406	2,454	Hoyer et al., 1985a
Mesulergine	1,148	Van Wijngaarden et al., 1990
	12,589	Hoyer and Schoeffter, 1991
	13,200	Hoyer et al., 1985a
Ritanserin	1,737	Van Wijngaarden et al., 1990
Ketanserin	1,910	Hoyer and Schoeffter, 1991
WB 4101	1,995	Hoyer and Schoeffter, 1991
	4,400	Peroutka, 1986
DOI	2,041	Van Wijngaarden et al., 1990
LY 53857	3,162	Hoyer and Schoeffter, 1991
Yohimbine	3,162	Hoyer and Schoeffter, 1991
Phentolamine	4,270	Hoyer et al., 1985a
Mianserin	4,680	Hoyer et al., 1985a
	6,390	Hoyer and Schoeffter, 1991
	10,000	Peroutka, 1986
Spiperone	4,790	Hoyer et al., 1985a
	5,011	Hoyer and Schoeffter, 1991
	5,370	Engel et al., 1986
(+)Pindolol	5,128	Engel et al., 1986
Cinanserin	6,200	Peroutka, 1986
	6,309	Hoyer and Schoeffter, 1991
	10,000	Hoyer et al., 1985a
5,6-DHT	6,165	Engel et al., 1986
MK 212	9,332	Engel et al., 1986
DP-5-CT	12,581	Hoyer and Schoeffter, 1991
8-OH-DPAT	1,778	Van Wijngaarden et al., 1990
	24,000	Peroutka, 1986
	60,100	Hoyer and Schoeffter, 1991
Ipsapirone	3,548	Van Wijngaarden et al., 1990
	52,000	Peroutka, 1986
	125,892	Hoyer and Schoeffter, 1991
Buspirone	3,019	Van Wijngaarden et al., 1990
	68,000	Peroutka, 1986
	125,890	Hoyer and Schoeffter, 1991
Spiroxatrine	125,892	Hoyer and Schoeffter, 1991
Gepirone	125,893	Hoyer and Schoeffter, 1991

nerve terminals, such as hippocampus (CA1), cerebellum, caudate putamen, and layer IV of the cortex, in agreement with the nature of heterologous presynaptic receptors. However, this mRNA was not found in globus pallidus and substantia nigra, areas that contain the greatest density of 5-HT_{1B} receptors. This might be the result of the expression of the genes in the cell body of the neuron outside the globus pallidus and the migration of the receptor protein toward the terminals inside this region.

5. Transduction system. The 5-HT_{1B} receptors are negatively coupled to adenylyl cyclase. In rat substantia nigra, 5-HT_{1B} agonists inhibit forskolin-stimulated adenylyl cyclase activity (Bouhelal et al., 1988; Schoeffter and Hoyer, 1989a). In hamster cultured fibroblasts, such agonists inhibit the enzyme activity stimulated by cholera toxin (Seuwen et al., 1988). However, surprisingly, the autoreceptor present on serotonergic terminals in the hippocampus is not coupled to G_i, G_s, or G_o proteins as shown by the lack of interaction with pertussis toxin, cholera toxin, and *N*-ethyl-maleimide (Blier, 1991). These results suggest that 5-HT_{1B} receptor-coupling mechanisms are heterogeneous.

6. Regulation. As in the case of 5-HT_{1A} receptors, the 5-HT_{1B} sites are modulated by GTP and its nonhydrolysable analogs. In rat brain (Hamblin et al., 1987; Stratford et al., 1988; Ariani et al., 1989) and in mouse liver (Ciaranello et al., 1990), the presence of guanine nucleotides shifts the equilibrium to the nonbinding state of the site (see section III.A.7).

To our knowledge, the pre- or postnatal development of 5-HT_{1B} receptors has not been extensively studied. Voigt et al. (1991) examined the developmental expression of 5-HT_{1B} mRNA. They showed that no quantitative changes were observed during development in most brain areas; however, in caudate-putamen, thalamus, and cerebellum, the high density of the mRNA observed at P0, P6, and P12 strongly decreased at the adult age. A moderate decrease in 5-HT_{1B} receptor number has been observed in the caudate nucleus (−27%) and in the substantia nigra (−20%) between 3 and 22 months in rats (Gozlan et al., 1990).

The regulation that occurs following serotonergic neuronal degeneration induced by 5,7-DHT is not yet well understood; indeed, the number of 5-HT_{1B} sites is not modified in rat brain except in the pars reticulata in the substantia nigra, where it increases (Weissmann et al., 1986) or decreases (Vergé et al., 1986). When nigrostriatal fibers degenerate after intrastriatal injection of kainic acid, 5-HT_{1B} sites decrease in the substantia nigra; this result indicates that 5-HT_{1B} sites are located on the terminals of nonserotonergic fibers originating from the striatum (Palacios and Dietl, 1988; Hamon et al., 1990b). Accordingly, the related adenylyl cyclase inhibitory activity is also reduced (Hamon et al., 1990b).

Antidepressants interact with the 5-HT_{1B} receptor function. In the rat, lithium interferes with regulation of 5-HT release via the inactivation of the hippocampal 5-HT_{1B} receptors (Hide and Yamawaki, 1989). In rat hippocampal slices or synaptosomes, the inhibition of the K^+-evoked ACh release is mediated by 5-HT_{1B} receptors; antidepressants at low concentrations, in vitro, partially reverse this inhibitory effect (Bolanos and Fillion, 1989; Harel-Dupas et al., 1991a). Additionally, the effect of TFMPP on 5-HT_{1B} sites, which reduces the "isolation-induced social behavior deficit," is antagonized by chronic treatment with antidepressant (fluoxetine or phenalzine), suggesting the existence of a link between these antidepressants and the 5-HT_{1B} receptor function (Francès and Khidichian, 1990). Using an animal model of depression (learned helplessness), Edwards et al. (1991c) demonstrated that the number of 5-HT_{1B} receptors increased in the cortex, the hippocampus, and the septum but decreased in the hypothalamus. However, Martin and Puech (1991), using the same experimental model, did not obtain similar results. Furthermore, Montero et al. (1991) did not find any modification in the number of 5-HT_{1B}-binding sites after acute, chronic, or even prenatal treatment with antidepressants (chlorimipramine, tianeptine, iprindole).

These results do not clearly demonstrate the involvement of 5-HT_{1B} receptors in depression or in the mechanism of action of antidepressants. However, in the experimental model of depression, the number of 5-HT_{1B} sites is increased in serotonergic areas, in agreement with the observation that, in vitro, antidepressants antagonize the cellular functional effect of the receptors. Whether these receptors, or their equivalent in humans, are significantly involved in depression remains to be established.

7. Cellular functions. A major function of the 5-HT_{1B} receptors is the control of 5-HT release from the serotonergic neuron terminals (presynaptic homologous autoreceptors), as demonstrated by Middlemiss (1984), Engel et al. (1986), Göthert et al. (1987), and Chaput and de Montigny (1988b). These receptors are also located on nonserotonergic terminals (presynaptic heterologous receptors) where they inhibit the release of other neurotransmitters, i.e., ACh in rat hippocampus (Maura and Raiteri, 1986; Maura et al., 1989; Harel-Dupas et al., 1991b), noradrenaline in peripheral tissues (Molderings et al., 1987, 1990; Molderings and Göthert, 1990), and possibly dopamine, as shown in vivo by microdialysis (Benloucif and Galloway, 1991). They also stimulate the release of prolactin in the rat (Van de Kar et al., 1989a,b). Thus, it appears that the 5-HT_{1B} receptors may play an important role in the control of CNS function by modulating the release of other neurotransmitters at the level of the nerve terminal.

Serotonin stimulates the proliferation of vascular smooth muscle cells in synergy with platelet-derived growth factor and insulin (Nemecek et al., 1986). Its role

as a regulator of neuronal growth in fetal tissue has been proposed on the basis of several experimental studies (Lauder and Krebs, 1978; Haydon et al., 1984; Chubakov et al., 1986; Whitaker-Azmitia et al., 1987; see review of CNS by Hamon et al., 1989). Seuwen et al. (1988) showed that 5-HT_{1B} receptors were directly involved in the mitogenic effect that 5-HT has on hamster cultured fibroblasts (CCL39). This effect is sensitive to pertussis toxin and, therefore, depends on coupling with a G_i protein; however, it does not seem that the production of cAMP or IP_3 is modified (Seuwen and Pouysségur, 1990). Thus, the 5-HT_{1B} receptors that are involved in mitogenesis may have a transduction mechanism different from those involved in cAMP or IP_3 production. Although it is plausible that 5-HT_{1B} receptors play a role in cell proliferation, in the CNS or during synaptogenesis this remains to be demonstrated.

8. 5-HT_{1B} receptors and behavior. The absence of 5-HT_{1B} receptors in humans and many other species limits behavioral studies to mice and rats. Moreover, these investigations are hampered by the absence of selective ligands. Despite these restrictions, a number of results have been reported. TFMPP, mCPP, and RU 24969 decrease body temperature (Tricklebank et al., 1986) and food intake (Bendotti and Samanin, 1987; Kennett et al., 1987b). These effects probably involve receptors located on nonserotonergic neurons because the activity is still observed after pCPA administration which depletes the cells of 5-HT. It has also been proposed that fenfluramine, sertraline, and fluoxetine interact with feeding behavior through 5-HT_{1B} receptors, although this hypothesis is far from being proven (Wilkinson and Dourish, 1991).

The role of 5-HT_{1B} receptors in rat sexual behavior has been studied with various agonistic drugs which, unfortunately, lack specificity; an inhibitory effect is generally observed and may be exerted through the 5-HT_{1B} receptors; this effect is opposite to that of the 5-HT_{1A} presynaptic activity (Berendsen and Broekkamp, 1987; Fernandez-Guasti et al., 1989). How 5-HT_{1B} receptors participate in rat sexual behavior is not yet totally understood.

TFMPP, RU 24969, CGS 12066B, and mCPP reduce stress in the isolation-induced social deficit model (Francès, 1988a,b; Francès and Monier, 1991) and aggressiveness in a model of social interaction (Olivier et al., 1989). Therefore, these results suggest that 5-HT_{1B} receptors play a role in the behavior studied in these experimental paradigms. Moreover, in an animal model of depression (learned helplessness), these agonistic drugs inhibit the effect of serotonin reuptake inhibitors (Martin and Puech, 1991); in the forced swimming test, they reduce the duration of immobility and antagonize the effects of antidepressants (Cervo et al., 1989). In light of the recent finding that 5-HT_{1B} agonists interact at nanomolar concentrations with the 5-HT transport system, the observed effects would appear to be independent of the 5-HT_{1B} receptor function. More specific 5-HT_{1B} receptor agonists or antagonists are needed to further elaborate the participation of 5-HT_{1B} receptors in these experimental models.

C. 5-HT_{1D} Receptor Subtype

The existence of the 5-HT_{1D} receptor subtype was proposed by Heuring and Peroutka (1987) on the basis of binding studies performed with bovine brain using [^{3}H]5-HT labeling in the presence of drugs masking 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C} subtypes; the remaining binding was called 5-HT_{1D}.

1. Selective radioligands and pharmacological properties. The [^{3}H]5-HT binding observed under the experimental conditions generally used strictly represents 5-$HT_{1nonA,\ nonB,nonC}$ binding, because it is observed with drugs that selectively mask 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C} sites. This binding is limited mainly to 5-HT_{1D} sites but also may include other sites having the same high affinity for 5-HT and a different affinity for particular ligands. Until recently, no ligand specific for 5-HT_{1D} was available; Bruinvels et al. (1991) reported that serotonin-5-O-carboxymethylglycyl-^{125}I-tyrosinamide labeled a homogeneous population of 5-HT_{1D} sites in human substantia nigra. This radiolabeled-ligand has been used for a direct visualization of 5-HT_{1D} receptors in human brain (Palacios et al., 1992).

The 5-HT_{1D} subtype is characterized by its high affinity (<10 nM) for 5-HT, 5-CT, 5-MeO-T, metergoline, and ergometrine. It has some affinity (10 to 100 nM) for 5-BT, *d*-LSD, methiothepin, ergotamine, RU 24969, yohimbine, and methysergide (table 4). However, none of these drugs is specific for this receptor. GR 43175 (sumatriptan) has been presented as one of the best selective agonists for 5-HT_{1D} sites (K_d = 17 nM) (Waeber et al., 1989d; Schoeffter and Hoyer, 1989b; Peroutka and McCarthy, 1989; Peroutka, 1991a); this drug, however, recognizes 5-HT_{1B} sites with a similar affinity (K_d = 27 nM) and 5-HT_{1A} sites with a slightly lower affinity (K_i = 100 nM) (Peroutka and McCarthy, 1989). Other authors have reported lower affinities of 5-HT_{1D} for this drug: K_d = 68 nM (Van Wijngaarden et al., 1990) and 251 nM (Sumner and Humphrey, 1989).

Is the 5-HT_{1D} receptor the sole 5-$HT_{1nonA,\ nonB,\ nonC}$ subtype? The experimental conditions used to observe the so-called 5-HT_{1D}-binding site, in fact, revealed all binding sites other than 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C}, because [^{3}H]5-HT binding was measured in the presence of drugs masking 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C} receptors. Therefore, the remaining binding, whether homogeneous or heterogeneous, may represent not only 5-HT_{1D} receptors but also other binding subtypes that are not discriminated by 5-HT itself.

The first evidence for a 5-HT_{1D} heterogeneity was given by Waeber et al. (1988c), who examined [^{3}H]5-HT

TABLE 4

Affinity values (K_i) of drugs for different 5-$HT_{1nonA,nonB,nonC}$ recognition sites in mammalian brain membranes

Drugs	5-HT_{1D} nonmurides species				"5-HT_{1D}" rat cortex striatum	5-HT_{1E} human cortex	5-$HT_{1nonA,nonB,nonC}$ rat cortex	5-HT_{1R} rabbit caudate
	Heuring et al. (1987)	Hoyer and Schoeffter (1991)	Bruinvels et al. (1991)	Herrick-Davis (1989)	Herrick-Davis and Titeler (1988b)	Leonhardt et al. (1989)	Fayolle et al. (1988)	Xiong and Nelson (1989)
<10 nM								
5-HT	3.2	3.98	6.16	1.9–2.6	2.1–1.8	3.5	2.5	10.96
5-CT	0.75	2.5	0.6	0.8–2.9	48–33	910	122.5	
5-MeO-T	2.5	7.07		4.1–11	70–72		138	
Metergoline	4.2	0.79	7.76					57.54
Ergometrine		0.319		0.9				
Sumatriptan			4.67					
10–100 nM								
Ergotamine		15.8	7.41	0.9		155		
DHE		19.9	10.96				202.5	
d-LSD	24	6.3		0.7–3.3	10–7.7		44.5	
RU 24969	25	50					800	69
Methiothepine	36	50.1	70.8				2,150	169.8
Tryptamine	36	39.8						
Yohimbine	39	79	15.48					
DP-5-CT		63						
GR 43175		31						
Lisuride		36.6						
100–1,000 nM								
Cyanopindolol		125						
Methysergide	120	3.9		8.8–15	41–100	59	10,000	120
N-N-DMT	190							
TFMPP	280	630		250–450	520–220	570	2,680	69
Mianserine	480	398	338				1,260	
WB 4101	590	316						
8-OH-DPAT	700	1,258	28	200–520	820–870	826	1,010	562
Quipazine	800	1,258						
MDL 72832		398						
SDZ(−)21009		398						
CGS 12066 B		446	8.7					
<1,000 nM								
Cyproheptine	1,200							
mCPP	1,400	1,584						
Mesulergine	6,500	6,309		1,200–1,800	3,200–2,800		5,000	7,244
(−)pindolol	7,000	6,309	954		>10,000			
(−)propranolol	7,200	3,162						
Haloperidol	8,200							
Metoclopramide	9,000							
Spiroxatrine		7,943						
Ipsapirone	16,000	12,589	1,905	5,200–9,200	1,100–1,500		4,950	
Buspirone		31,622	19,054					
Ketanserine	53,000	1,000		3,200–6,200	>10,000	>10,000	8,500	
Ritanserine		1,584					727	
Spiperone	>100,000	5,011						2,754
MDL-72222	>100,000			>10.00	>10,000		>10,000	
(+)DOB				970–1,300	3,400–1,800	556		
CP 93129			954					
Isamoltane			1,174					

binding in the presence of 8-OH-DPAT (100 nM) and mesulergine (100 nM); the displacing curves presented for 5-CT in bovine, porcine, and human caudate membranes were clearly biphasic, which would correspond to two populations of receptors representing about 50% each. Sumner and Humphrey (1989), using newborn pig caudate, confirmed that 5-CT found two subpopulations of the 5-$HT_{1nonA\ nonB\ nonC}$ binding at about the same ratio and demonstrated that the high-affinity component for 5-CT was selectively displaced by sumatriptan (K_i = 251 nM). This particular property led Peroutka (1991a), using calf, guinea pig, pig, human cortex and caudate, to define the 5-HT_{1D} sites as those binding [^{3}H]5-HT in the presence of 8-OH-DPAT (100 nM) and mesulergine (100 nM) and displaced by 10^{-5} M sumatriptan. Moreover, Mahle et al. (1991), using [^{3}H]5-CT binding in the presence of 100 nM 8-OH-DPAT and mesulergine, demonstrated in the guinea pig brain that the high-affinity binding for 5-

CT was heterogeneous, indicating the existence of two compartments having high (K_i = 27 nM) and low affinity (K_i = 400 nM) for sumatriptan in the cortex; this heterogeneity was not observed in the striatum.

The heterogeneity of the 5-$HT_{1nonA\ nonB\ nonC}$ binding was also studied by Leonhardt et al. (1989) using pindolol (1000 nM) and mesulergine (100 nM); these authors confirmed and extended the findings previously obtained with human cortex, showing high- and low-affinity subpopulations for 5-CT (K_i = 4 and 155 nM, respectively). The 5-CT low-affinity component (50% of the binding) was called 5-HT_{1E}, and its pharmacological properties were examined; no drug was found to have a high affinity for this site, except 5-HT itself (K_d = 3.5 nM) and methysergide (K_i = 59 nM). Interestingly, this binding was GTP dependent, suggesting that it might be related to a G protein. The regional distribution of 5-HT_{1E} is heterogeneous within the brain and initially reported to parallel that of 5-HT_{1D} (Palacios et al., 1991). However, Lowther et al. (1991) showed, in postmortem human brain samples, that the 5-HT_{1D}/5-HT_{1E} ratio differed depending on the brain region; the proportion of 5-HT_{1D} was high in globus pallidus and that of 5-HT_{1E} was high in caudate-putamen. Moreover, different regional distributions were also demonstrated for the 5-HT_{1E} binding, indicating a high proportion of these sites in cortex versus striatum (Mahle et al., 1991). Whether the 5-HT_{1E} site is a true functional receptor remains to be established.

The existence of another receptor, 5-HT_{1R}, different from 5-HT_{1D} in the strictest sense, which is not 5-HT_{1A}, 5-HT_{1B} or 5-HT_{1C}, was reported by Xiong and Nelson (1989), who observed [^{3}H]5-HT binding in the presence of 8-OH-DPAT (100 nM) and mesulergine (100 nM) in the rabbit caudate nucleus. The affinities of 5-HT_{1R} for methiothepin, methysergide, and spiperone differ from those of 5-HT_{1D}. However, 5-CT and sumatriptan were not examined in these studies, so the differences or similarities between 5-HT_{1R} and 5-HT_{1E} are still not known.

On the other hand, in rat brain cortex, Fayolle et al. (1988), using spiperone (1000 nM) and propranolol (3000 nM), reported the existence of a 5-$HT_{1nonA\ nonB\ nonC}$ binding characterized by pharmacological properties different from those of 5-HT_{1D}. In particular, the site they found has a low affinity for 5-CT (IC_{50} = 245 nM). The functional nature of this site was indicated by the pharmacological correlation of its binding with a positive coupling to adenylyl cyclase activity. Moreover, the regulation of this receptor was studied during postnatal development in the rat brain cortex (Zifa et al., 1988). This receptor develops mainly during synaptogenesis (the second and third week after birth), and a significant activity is already present at birth. This receptor may be involved in the mechanism that functionally links the CNS and the immune system; rabies virus infection in rats induces a rapid and marked decrease in the density of the 5-$HT_{1nonA\ nonB\ nonC}$ receptors in rat brain cortex (Fillion et al., 1990).

A further indication of the heterogeneity of 5-HT_{1D} receptors, depending on the region or the species considered, is the variation in the abilities of different drugs to compete for 5-HT_{1D} binding in calf, pig, guinea pig, and human cortex and caudate (Peroutka, 1991a).

In conclusion, the 5-$HT_{1nonA\ nonB\ nonC}$ binding corresponds not only to 5-HT_{1D}, in the strictest sense, but also to other sites. Some of these sites may represent functional receptors belonging to a 5-HT_{1D} family.

2. Regional distribution. 5-HT_{1D} sites have been found in the brain of the following species (for reviews, see Waeber et al., 1990a): pigeon (Waeber et al., 1989a), hamster (Beer et al., 1992), guinea pig (Waeber et al., 1989a; Limberger et al., 1991), rabbit (Limberger et al., 1991), dog (Beer et al., 1992), pig (Waeber et al., 1988c; Sumner and Humphrey, 1989), calf (Waeber et al., 1988c; Heuring and Peroutka, 1987), monkey (Waeber et al., 1989c), and humans (Waeber et al., 1988a,c; Hoyer et al., 1988; Herrick-Davis and Titeler, 1988b; Palacios et al., 1992). In these species, 5-HT_{1B} sites are absent. It has been proposed that 5-HT_{1D} plays the same role in these species as does 5-HT_{1B} in rat, mouse, and opossum. This proposition is based not only on the structural homology between these two subtypes but also on the similarities between their pharmacological properties, regional distribution, transduction systems, and cellular functions as homologous or heterologous presynaptic receptors (Hoyer and Middlemiss, 1989). However, it is likely that 5-HT_{1D} sites also exist in the rat brain (Herrick-Davis and Titeler, 1988b; Limberger et al., 1991) or the rat periphery (Berendsen and Broekkamp, 1991a,b). Further studies are needed to clarify the situation.

The regional distribution of 5-HT_{1D} sites in the mammalian brain is heterogeneous. In the substantia nigra, basal ganglia, and striatonigral pathway (Waeber et al., 1990b), these sites are dense, accounting for 90% of the 5-HT_1 binding (Waeber and Palacios, 1990). A lower density is observed in the hippocampus, cortex, and raphe. 5-HT_{1D} receptors also have been identified in porcine coronary artery (Schoeffter and Hoyer, 1990) and in canine basilar artery (Connor et al., 1989). The presence of these receptors in the vascular bed may be responsible for some pharmacological properties of 5-HT_{1D} agonists (see section III.C.8).

3. Cellular localization. The localization of 5-HT_{1D} receptors has been shown to be mostly postsynaptic on nonserotonergic terminals. Indeed, quinolinic acid lesion of striatal cellular bodies induces a decrease of 5-HT_{1D} receptors in substantia nigra and in globus pallidus, indicating their localization on nonserotonergic terminals (presynaptic heterologous). However, the fact that their numbers decrease also in striatum under these experimental conditions suggests their possible location

either on cell bodies, or on dendrites, or on terminals of interneurons (Waeber et al., 1990b). Moreover, Waeber and Palacios (1990) demonstrated in guinea pig the presynaptic localization of 5-HT_{1D} receptors on nonserotonergic terminals in superior colliculi using unilateral enucleation. In humans, binding experiments on samples from brain tissue from patients with Huntington's chorea, where the striatal intrinsic neurons degenerate, demonstrated a decrease in 5-HT_{1D} receptor number in this area, whereas the [^{3}H]paroxetine binding, which labels the serotonergic terminals, was not affected (Waeber and Palacios, 1989; Gonzalez-Heydrich and Peroutka, 1991). The location of 5-HT_{1D}-binding sites on serotonergic terminals is likely, although it has not yet been demonstrated on the basis of lesion experiments; however, functional evidence indicates that some of these receptors are homologous presynaptic receptors.

4. Molecular structure. Hamblin and Metcalf (1991) recently cloned the human 5-HT_{1D} receptor (MA6A clone) by using a probe consisting of canine thyroid cDNA (RDC4), obtained by polymerase chain reaction (Libert et al., 1989). This clone carries an intronless gene encoding 377 amino acids; the seven hydrophobic domains of the protein are characteristic of G protein-linked receptors. The amino-terminal region contains three glycosylation sites, the second extracellular loop contains one, and the third intracellular loop (83 amino acids) possesses two cAMP-dependent protein kinase sites and other potential phosphorylation sites, such as serine and threonine residues. The COOH-terminal region is very short (19 residues) and lacks the cysteine residue present in many members of this family. The amino acid sequences for MA6A and RDC4 have the same length and are 88% identical. The most probable localization for the RDC4 gene is at the 1p34.3-1p36.3 region of the human genome (Libert et al., 1991).

Among the sequences that have been reported for members of the G protein-linked receptor family, the one most similar to that of the 5-HT_{1D} receptor is that of the 5-HT_{1A} receptor (43% deduced amino acid identity); the similarity between the human 5-HT_{1D} receptor and other serotonin receptors is less marked, i.e., 37% for the *Drosophila* 5-HT_{dro} receptor, 33% for the rat 5-HT_{1C}, and 31% for the rat 5-HT_2.

Expressed in COS-7 cells, the 5-HT_{1D} human gene induces the production of a protein that binds serotonergic drugs with the following order of potency: 5-CT > 5-MeOT = 5-HT > RU 24969 > yohimbine > TFMPP > 8-OH-DPAT > mesulergine = spiperone = ICS 205–930. That the affinities of dihydroergotamine and metergoline are higher for this cloned receptor than for those in human membranes, and the existence of other minor pharmacological differences, raises various questions, e.g., whether different 5-HT_{1D} subtypes exist (Hamblin and Metcalf, 1991). This hypothesis was confirmed because a second gene also expressing a 5-HT_{1D} receptor has been cloned (5-$HT_{1D\beta}$) (Weinshank et al., 1992). Its sequence, presented by Adham et al. (1992), is distinct from the 5-HT_{1D} gene presented by Hamblin and Metcalf (1991), termed 5-$HT_{1D\alpha}$, the sequence homology being only 77% in the membrane-spanning domains; surprisingly, the pharmacological properties are identical. The 5-$HT_{1D\beta}$ human gene closely resembles the rat 5-HT_{1B} gene (Adham et al., 1992), although they code for receptors having very different pharmacological properties (i.e., the pindolol derivatives have a high efficacy for the sole 5-HT_{1B} receptors).

Therefore, it appears, on the one hand, that two different genes code for receptors having very similar pharmacological properties (5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$) and represent intraspecies differences and, on the other hand, that two very similar genes code for receptors having different pharmacological properties (5-$HT_{1D\beta}$ and 5-HT_{1B}) and represent interspecies variations. Thus, the 5-HT_{1D} receptors appear as a multigenic family with different members in the same species, i.e., 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ in humans and 5-$HT_{1D\alpha}$ (Hartig et al., 1992) and 5-HT_{1B} in rodents. Two partial serotonin 5-HT_{1D} receptor sequences have been cloned in the mouse, suggesting the existence of two additional receptors of the 5-HT_{1D} type, i.e., different from those already discussed (Weydert et al., 1992). Because the 5-HT_{1B} receptor in rodents and the 5-HT_{1D} receptor in the other species have the same functional profile (Hoyer and Middlemis, 1989), their respective roles have to be defined more closely if they actually are present in the same species.

The existence of this large family of receptor subtypes present in a single species may correspond to specific function, particular regional or cellular distribution, and/or particular mechanisms of regulation of a given receptor. The fact that different receptors present similar or different pharmacological characteristics raises the problem of the validity of the pharmacological classification and that of the pharmacological screening models. One of the final goals of this research will be to determine the functional role of each of these subtypes.

5. Transduction system. The 5-HT_{1D} receptor appears to be negatively coupled to adenylyl cyclase activity in calf substantia nigra, as demonstrated by the inhibition of the forskolin-stimulated enzyme activity (Hoyer and Schoeffter, 1988; Schoeffter et al., 1988). In other brain areas, such as the striatum, negative coupling was not found (Waeber and Palacios, 1990). These authors explained the lack of activity as being due to either a "dilution" of the effect by the high basal adenylyl cyclase activity in this area or the coupling of the 5-HT_{1D} receptor to G proteins different from the G_i. It is also possible that 5-HT_{1D} receptors are heterogeneous in the brain.

The transduction system was also examined in transfected cells (Chinese hamster ovary-K1); it consisted of a pertussis toxin-dependent negative coupling with adenylyl cyclase (Hamblin and Metcalf, 1991).

6. Regulation. Like all receptors linked to G proteins, 5-HT_{1D} receptors are modulated by GTP in two binding states which are presumably related to their functional activity (Herrick-Davis and Titeler, 1989; Harrington and Peroutka, 1990b).

The density of 5-HT_{1D}-binding sites was studied by quantitative autoradiography in brain slices collected postmortem from patients with Parkinson disease and Huntington's chorea (Waeber and Palacios, 1989; Gonzalez-Heydrich and Peroutka, 1991); no change in the density of 5-HT_{1D} receptors was observed in brains from patients with Parkinson's disease, whereas a significant decrease occurred in the basal ganglia and substantia nigra of brains from patients with Huntington's chorea.

7. Cellular functions. The role of the 5-HT_{1D} receptor as an autoreceptor that is situated on 5-HT terminals and that inhibits the release of serotonin is well documented for guinea pig (Middlemiss et al., 1988; Schipper and Tulp, 1988), pig (Schlicker et al., 1989), and humans (Galzin et al., 1989). This receptor is also present on nonserotonergic terminals where it regulates the K^+-evoked release of ACh in the guinea pig hippocampus (Harel-Dupas et al., 1991a) and noradrenaline in the human saphenous vein (Molderings et al., 1990).

8. 5-HT_{1D} receptors and behavior. It is difficult to determine the role of 5-HT_{1D} receptors in behavior as long as there is no specific agonist or antagonist. Recently, a novel serotonergic agent, sumatriptan (formerly called GR 43175), was found to be a selective 5-HT_{1D} receptor agonist. This drug was reported to be extremely effective in the acute treatment of migraine and to have minimal side effects (Doenicke et al., 1988; Perrin et al., 1989; Tfelt-Hansen et al., 1989; Ferrari et al., 1989; Byer et al., 1989; Ferrari, 1991). 5-HT has an important role in the pathophysiology of the migraine believed to result from excessive dilation of cerebral blood vessels (Anthony, 1986). Sumatriptan, which does not penetrate the blood-brain barrier (Sleight et al., 1990; Deliganis and Peroutka, 1991), blocks this phenomenon through 5-HT_1-like receptors mediating the constriction of arteriovenous anastomosis (Humphrey et al., 1990; Peroutka, 1991b,c).

The 5-HT_1-like receptors are identified as 5-HT_{1D} receptors in vascular models, such as the relaxation of pig coronary arteries (Schoeffter and Hoyer, 1990) or the contraction of human saphenous vein (Bax et al., 1992). The 5-HT_1-like receptors controlling the porcine carotid circulation, however, does not seem to be identical with the 5-HT_{1D} subtype (Den Boer et al., 1992). If the 5-HT_1-like receptor is in fact the 5-HT_{1D} receptor, then this receptor may prove to be an important target in the acute treatment of the migraine.

The contralateral rotation induced by an intracerebral, unilateral local infusion of 5-HT into the guinea pig substantia nigra constitutes an experimental animal model that is claimed to selectively involve 5-HT_{1D} receptors (Higgins et al., 1991b). The locomotor changes observed in this model may be analogous to those observed in patients with Huntington's chorea, who exhibit a selective decrease in 5-HT_{1D} receptors in the caudate. The definitive classification of this behavioral response will require more specific agonists and antagonists to become available.

The "hindlimb scratching" induced by systemic injection of serotonergic compounds in rats is thought to involve peripheral 5-HT_{1D}-like receptors (Berendsen and Broekkamp, 1991a). This behavior decreases with age (Berendsen and Broekkamp, 1991b). Intracerebroventricular administration of sumatriptan induces hypothermia and hyperlocomotion in mice (Bill et al., 1989). Because sumatriptan also has a high affinity for 5-HT_{1B}, and 5-HT_{1A} receptors, further pharmacological characterization is needed to attribute these effects solely to the 5-HT_{1D} receptors. The role of 5-HT_{1D}-like receptors in rodents remains to be established.

9. Conclusion. The existence of 5-HT_{1D} receptors is now well established. The use of sumatriptan has allowed this receptor subtype to be more precisely characterized. The existence of other sites or receptors, resembling 5-HT_{1D} insofar as they are 5-$HT_{1nonA,\ nonB,\ nonC}$-binding sites, has been established. Specific ligands are needed to characterize the molecular, cellular, and functional properties of these receptors.

IV. 5-HT_2 Receptors

The 5-HT_2 receptor was initially identified as a site that could bind [^{3}H]spiroperidol and that had specific serotonergic pharmacological properties (Leysen et al., 1978). Two subtypes have been reported for the 5-HT_2 family. Recent pharmacological and molecular biological studies strongly suggest that the 5-HT_{1C} receptor subtype (originally classified as a 5-HT_1-like site) should be included in the 5-HT_2 receptor family. The members of the 5-HT_2 receptor family are characterized by their high affinity for serotonergic antagonists, such as cyproheptadine, mesulergine, methysergide, mianserin, metergoline, and pizotifen.

A. "Classical" 5-HT_2 Receptor

The functional correlates of 5-HT_2 binding were recognized early because of the availability of high-affinity antagonists. Numerous experimental works concerning this subject have been reviewed (Lyon and Titeler, 1988; Göthert, 1990; Leysen, 1990). Therefore, the present review will be limited to recent studies.

1. Selective radioligands and pharmacological properties. In initial studies, [^{3}H]spiperone was used to label the 5-HT_2-binding site (Leysen et al., 1978; List and Seeman, 1981). Other radioligands were demonstrated thereafter to recognize this site: [^{3}H]mianserin (Peroutka and Snyder, 1981), [^{3}H]metergoline (Hamon et al., 1981), [^{3}H]ketanserin (Leysen et al., 1982b), [^{3}H]mesulergine (Closse, 1983), ^{125}I-LSD (Hartig et al., 1983; Engel et al.,

1984; Nakada et al., 1984), ^{125}I-N^{1}-methyl-2-*l*-LSD (Hoffman et al., 1985, 1987), [^{3}H]N-methyl-spiperone (Lyon et al., 1986), [^{3}H]7-amino-ketanserin (Wouters et al., 1986a) and [^{125}I]7-amino-8-iodo-ketanserin (Wouters et al., 1986b; Schotte and Leysen, 1989). These radioligands were antagonists; only recently have agonistic ligands been developed: [^{3}H]DOB (Titeler et al., 1985, 1987), [^{77}Br]DOB (Wang et al., 1988; Peroutka et al., 1988) and [^{125}I]DOI (McKenna and Peroutka, 1989).

There is controversy regarding the nature of agonist binding to 5-HT$_2$ receptor. Various radioligand-binding studies were interpreted as demonstrating the existence of two distinct 5-HT$_2$ sites, a 5-HT$_{2A}$ receptor possessing a high affinity for agonists and antagonists and a 5-HT$_{2B}$ receptor possessing a low affinity for agonists and a high one for antagonists (Pierce and Peroutka, 1989); other investigators proposed the existence of two affinity states for the same 5-HT$_2$ receptor, corresponding to high and low affinities for the agonists (Lyon et al., 1987; Leonhardt and Titeler, 1989). For example, the antagonistic drugs recognize [^{3}H]ketanserin and [^{77}Br]DOB sites with the same affinity, whereas the agonists recognize [^{3}H] DOB sites with an affinity 200 times higher than that for [^{3}H]ketanserin sites (McKenna and Peroutka, 1989). Moreover, it was shown that only part of the [^{3}H]ketanserin-binding sites was labeled by 5-HT$_2$ agonists (19% in rat cortex) (Lyon et al., 1987; Peroutka et al., 1988) and that 5-HT displaced [^{3}H]ketanserin with a shallow curve (slope of the curve corresponding to a Hill coefficient = 0.67) in rat and human cortical membranes (Pierce and Peroutka, 1989; McKenna and Peroutka, 1989). These data suggest that [^{3}H]ketanserin labels more than one population of 5-HT$_2$ receptors. By contrast, 5-HT competition curves in bovine cortex present a Hill coefficient of 0.98, suggesting that [^{3}H]ketanserin labels a single site; this result is in agreement with the finding that [^{3}H]DOB cannot be detected in bovine membranes. However, to define distinct receptor subtypes on the basis of agonist-binding data in different species can be dangerous (Leysen, 1990; Strange and Peroutka, 1990).

To provide more evidence in favor of a two-state hypothesis or a two-receptor hypothesis, Hartig et al. (1990a) and Teitler et al. (1990) used the cloned human or rat 5-HT$_2$ receptor. They demonstrated, by transfecting mammalian fibroblasts (NIH 3T3) and green monkey kidney cells (COS-7), that a single 5-HT$_2$ gene expressed a protein that bound both agonists and antagonists. Interestingly, [^{3}H]DOB sites represented only approximately 30% of the density of [^{3}H]ketanserin labeled binding sites. These data suggest that the 5-HT$_2$ receptor gene product contains both the agonist- and the antagonist-binding sites, supporting the hypothesis of the existence of two distinct, but noninterconverting, states which differ in their binding characteristics. However, posttranslational receptor changes resulting in two slightly different forms of the 5-HT$_2$ receptors cannot be ruled out.

In addition to the high affinity for a series of serotonergic antagonists shared by the members of the 5-HT$_2$ family, the classical 5-HT$_2$ receptors (labeled by antagonistic radioligands) show a high affinity for chlorpromazine, cinanserin, ketanserin, ritanserin, and spiperone; moreover, they have a low affinity (K_d = 100 to 1000 nM) for 5-HT and its tryptamine derivatives (5-MeOT, 5-OH-DMT, 5-MeO-DMT) and no affinity for ligands selective for 5-HT$_1$ (8-OH-DPAT, RU 24969) or 5-HT$_3$ (2-methyl-5-HT, phenylbiguanide) (table 5).

2. Regional distribution in the brain. The distribution of 5-HT$_2$ receptors (see reviews by Palacios and Dietl, 1988; Pazos et al., 1988) has been studied in rat (Pazos et al., 1985a) and in human brain (Hoyer et al., 1986b; Biegon et al., 1986; Pazos et al., 1987b). It is heterogeneous in the brain, and some species differences have been reported. In the cortex (frontal, entorhinal, cingulate), these sites occur at high density, whereas in the rat brain, the layer IV is labeled more strongly than it is in the human brain, where layers III and V are the most heavily labeled. In the hippocampus, the subiculum is weakly labeled, whereas the CA1 and CA3 layers show a higher density of sites. In the basal ganglia, the caudate, putamen, and nucleus accumbens are labeled with an intermediate density, whereas the globus pallidus has a low density. Interestingly, the unspecific binding of [^{3}H] ketanserin in these areas is unusually high.

The nucleus basalis of Meynert is characterized by a low density of 5-HT$_2$ receptors. The thalamus shows a heterogeneous labeling (from intermediate to low density), whereas the hypothalamus, the corpus mamillare, and the cortex are the most enriched areas. The midbrain area ranges from low to very low density, and in the cerebellum these receptors are present at very low density.

3. Cellular localization. Lesion of the serotonergic system provoked by 5,7-DHT do not reduce the number of 5-HT$_2$ sites in rats (Fischette et al., 1987); therefore, the 5-HT$_2$ receptors are located on nonserotonergic neurons. The fact that cortical [^{3}H]ketanserin-binding sites decreased in Alzheimer dementia, paralleling the loss of somatostatin immunoreactivity and the decrease of GABA concentration in this region, suggests that 5-HT$_2$ receptors could be located on intrinsic GABA- or somatostatin-containing neurons in the cortex. In situ, hybridization studies have confirmed this assumption and demonstrated that cells intrinsic to the neocortex express mRNA coding for 5-HT$_2$ receptors (Mengod et al., 1990). Blue et al. (1988) observed a close spatial relationship between 5-HT$_2$ receptors and fine 5-HT axons. Because the cortex contains a high density of fine 5-HT axon terminals arising from the dorsal raphe nucleus, it appears likely that 5-HT$_2$ receptors may be selectively linked to this particular type of 5-HT axon terminal,

TABLE 5
*Affinity values of drugs for ^{3}H-antagonists or ^{3}H-agonists of 5-HT$_2$ recognition sites in mammalian brain**

Drugs	^{3}H-antagonists K_i (nM)	^{3}H-agonists K_i (nM)
Agonists		
(−)DOB	24[c]	0.39[c], 0.62[d]
(±)DOB	41[c]	0.79[c]
(±)DOI		1.3[c]
(+)DOB	146[c]	2.3[c], 18[d]
TFMPP	161[c], 251[e]	16[c]
mCPP	199[e]	22[d]
Quipazine	228[c]	17[c], 31[d]
5-OH-DMT	297[c]	6[c]
5-MeO-T	305[c]	5[c]
5-MeO-DMT	616[c]	15[c]
Spiroxatrine	630[e]	
Buspirone	794[e]	
RU 24969	777[c], 1,000[e]	42[c], 91[d]
5-HT	928[c], 3,162[e]	7.8[c], 3.5[d]
DMT	1,183[c]	64[c]
DP-5-CT	5,011[e]	48[c]
Tryptamine	2,005[c]	320[d]
8-OH-DPAT	5,350[c], 10,000[e]	>10,000[b]
5-CT	19,952[e]	633[c], 2,700[d]
WB 4101	1,258[a], >10,000[a]	
GR 43175	195,526[e]	
Antagonists		
Spiperone	0.4[c], 0.5–1.2[a], 1.6[e], 2[b]	0.8[c], 3.8[d]
Ketanserin	0.39–2.1[a], 1.2[c], 3.1[b]	1.3[c], 4.8[d]
Ritanserin	1.48[e]	
(+)Butaclamol	2.4[c]	13[c], 29[d]
Chlorpromazine	2.8[c], 3.3–20[a]	7[c], 70[d]
Cinanserin	2–41[a], 4.8[c], 19[e], 21[b]	3.8[c], 7.2[d]
Metergoline	0.28–0.8[a], 1[e]	2.7[d]
Mesulergine	3.98[e]	4.5[d]
Methiothepin	0.4–1.9[a], 1.58[e]	6.5[d]
Pitozifen	0.28–6.5[a], 4.4[b]	
d-LSD	2.5–8.2[a], 2.5[e]	4.8[d]
DHE	2.5[e]	
Cyproheptadine	3.16[c], 3.46[g]	
Mianserin	1.4–13[a], 5[b], 7.9[e]	
Methysergide	0.94–12[a], 2.5[e]	
Clozapine	2–16[a], 34[b]	
Piremperone	1.58[e]	
Amitriptyline	4.2–21[a]	
Lisuride	5.01[e]	
Chlorimipramine	9.8–82[a]	
Haloperidol	22–48[a]	
Trazodone	24[b]	
Imipramine	37–260[a]	
LY 53857	50[e]	
MDL 72832	158[e]	
NAN-190	218[f]	
BMY 7378	263[f]	
Nomifensine	372[a]	
(±)Propranolol	590–758[g]	
Yohimbine	660[e]	
(+)Propranolol	2,490[c]	1,301[c]
MDL 73005	3,162[f]	
(−)Butaclamol		10,000[d]
ICS 205-930		17,000[d]
Prazosin	>10,000[e]	>10,000[d]
Cyanopindolol	31,622[e]	
SDZ(−)21009	10,000[e]	
(−)Pindolol	29,512[g]–39,800[e]	
(±)CYP	29,512[g]	
(+)CYP	25,118[g]	
(−)CYP	26,302[g]	
(+)Pindolol	38,018[g]	

* References: [a] Leysen et al., 1982a; [b] Conn and Sanders-Bush, 1986a; [c] Lyon and Titeler, 1988; [d] Peroutka et al., 1988; [e] Hoyer and Schoeffter, 1991; [f] Van Wijngaarden et al., 1990; [g] Engel et al., 1986.

mediating the effects of dorsal, but not median raphe, projections.

4. Molecular structure. In 1988, Pritchett et al., by screening a rat brain library, isolated a cDNA clone carrying cDNA homologous to the 5-HT$_{1C}$ receptor. After transfection in embryonic human renal cells, this clone produced receptor sites having the characteristics of 5-HT$_2$ receptors, although 5-HT itself had a higher affinity for the cloned receptor than it did for receptors occurring naturally in membranes.

Julius et al. (1990) also cloned this gene from rat brain and corrected the published sequence of Pritchett et al. for one nucleotide. The sequence of the human 5-HT$_2$ receptor, cloned by Kao et al. (1989), corresponds closely to that corrected sequence and shows a high degree of identity with the rat sequence (90%). The entire receptor protein consists of 471 amino acids. The slight difference of three amino acids in the membrane-spanning domain and of two amino acids in the third intracellular loop might explain the difference in binding exhibited for mesulergine (K_i = 4 nM in rat and 150 nM in humans; Hoyer et al., 1986b). The receptor gene (HTR2) has been localized on human chromosome 13 (q14-q21) (Sparkes et al., 1991) and on mouse chromosome 14 (closely linked with the marker ES 10) (Liu et al., 1991).

The 5-HT$_2$ receptor is homologous to the 5-HT$_{1C}$ receptor (78% identity in transmembrane domains: 141 amino acids of 180 amino acids are identical), whereas it is only 41% identical for the 5-HT$_{1A}$ receptor (73 of 177 amino acids). This receptor is characterized by the presence of a leucine zipper in the first membrane-spanning domain in rat and human sequences (such a zipper is also present in the 5-HT$_{1A}$ receptor but not in the 5-HT$_{1C}$ receptor). This feature may favor dimerization of the receptor or its interaction with other membranal proteins.

Buck et al. (1991) studied the functional importance of NH_2 and COOH terminals using deletion mutants expressed in *Xenopus* oocytes. These authors observed an insignificant loss of electrophysiological activity when extracellular NH_2-terminal and intracellular COOH-terminal residues from 398 to 471 amino acids were deleted. However, when cysteine-397 was replaced by serine, the activity was totally lost. That deletion of amino acids 398 to 471 does not markedly reduce activity suggests that this part of the receptor does not play a major role in the regulatory processes.

Weinstein and Osman (1990), studying a theoretical model of interaction of 5-HT with this receptor, proposed that 5-HT was recognized by two aromatic residues separated by a hydrophilic residue and that these recognitions led to receptor activation through a structural rearrangement. This model, which is based on neutral interaction, differs from the one proposed by the same authors for the 5-HT$_{1A}$ receptor, which involved a proton transfer.

5. Transduction systems. The 5-HT_2 receptors appear to be directly coupled to the phosphoinositide turnover; this coupling increases IP_3 production in brain cortical tissue in vitro (Conn and Sanders-Bush, 1984, 1986a) and in vivo (Hide et al., 1989). However, the stimulating effect of serotonergic agonists has not been reported to be mediated by 5-HT_2 receptors in other areas of the brain (Janowsky et al., 1984; Conn and Sanders-Bush, 1985). 5-HT_2 receptors are also directly involved in phosphatidyl inositide metabolism in human (De Chaffoy de Courcelles et al., 1985) and rabbit blood platelets (Schachter et al., 1985), in aortic myocytes (Roth et al., 1986; Cory et al., 1986), in A_7r_5 cultured smooth muscle cells (Coughlin et al., 1984; Doyle et al., 1986), in WRK_1 cells originating from a rat mammary tumor (Cory et al., 1987), and in a pituitary cell line P11 cells (Ivins and Molinoff, 1990, 1991). In C6 glioma cells, Ananth et al. (1987) presented experimental evidence for the coupling of 5-HT_2 receptors with the IP_3 production; however, the pharmacological properties of this effect did not entirely correlate with that of 5-HT_2 receptors (Sanders-Bush, 1988b). In American Tissue Culture Collection human embryonic kidney 293 cells transfected with the 5-HT_2 receptor gene, 5-HT also induces phospholipid breakdown and increases of intracellular Ca^{++} (Pritchett et al., 1988).

It was also shown that serotonin, via a 5-HT_2 receptor, stimulates phospholipase A_2 and thus induces the release of arachidonic acid in hippocampal and cortical neurons (but not in glial cells); this mechanism is independent of inositol phospholipid hydrolysis (Felder et al., 1990).

5-HT_2 receptors play an electrophysiological role in facial motor neurons, initially examined by McCall and Aghajanian (1980), Van der Maelen and Aghajanian (1980), and, more recently, others (see review by Andrade and Chaput, 1991a), in nucleus accumbens (North and Uchimura, 1989) and brain cortical neurons (Davies et al., 1987; Araneda and Andrade, 1988). Pharmacological analysis revealed that the 5-HT-induced depolarization of the neuronal cells was 5-HT_2 dependent. Two distinct mechanisms were involved: a slow depolarization phase resulting from the closing of K^+ channels, which reduced K^+ conductance, and a posthyperpolarization phase controlled by a Ca^{++}- regulated potassium channel. These slow responses seem to involve the breakdown of membrane phosphatidylinositides; however, this mechanism has not yet been totally elucidated.

Pritchett et al. (1988) found that in *Xenopus laevis* oocytes transfected with the 5-HT_2 receptor gene, 5-HT was able to induce a rapid Cl^- influx through a Ca^{++}-dependent chloride channel. The physiological role of this mechanism remains to be demonstrated.

6. Regulation. The 5-HT_2 receptors were reported to be modulated by guanyl nucleotides, because these compounds significantly reduced the number of 5-HT_2 receptors (Kendall and Nahorski, 1983; Battaglia et al., 1984). However, this effect was not confirmed (Peroutka et al., 1979; Engel et al., 1984; Shearman and Strange, 1988). The 5-HT_2 receptors labeled with antagonist radioligands were not affected by GTP and its analogs, whereas the affinity state (or the site) labeled by the 5-HT_2 agonists was guanyl nucleotide sensitive (Lyon et al., 1987; Teitler et al., 1990).

The regulation of the 5-HT_2 receptors during ontogenesis has been studied in rat brain (Roth et al., 1991). Roth et al. showed that mRNA-expressing 5-HT_2 receptors appeared in parallel to the binding sites, i.e., both increased markedly (eight times for the sites, 13 for the mRNAs) from embryonic day 17 to postnatal days 10 to 13 and then were reduced by 50% after days 25 to 27. These receptors appeared to be functional in young immature rats (day 8) as Claustre et al. (1988b) demonstrated, by examining the 5-HT_2-induced phosphatidyl inositide breakdown; the stimulating effect of 5-HT was six times greater in immature than in adult rat cortex.

In aged rats, 5-HT_2 receptor sites continue to diminish in number (−20%), as reported by Battaglia et al. (1987) and Gozlan et al. (1990). A similar age-dependent reduction in 5-HT_2 receptors has been reported to occur in the human brain (Wong et al., 1984; Marcusson et al., 1984; Reynolds et al., 1984; Gross-Isseroff et al., 1990).

Serotonergic denervation by 5,7-DHT generally does not modify the binding properties of the 5-HT_2 receptors (Blackshear et al., 1981; Quik and Azmitia 1983; Leysen et al., 1983; Barbaccia et al., 1983b; Hall et al., 1984; Stockmeier and Kellar, 1986; Conn and Sanders-Bush, 1986a; Fischette et al., 1987; Butler et al., 1990), nor does it modify IP_3 production (Conn and Sanders-Bush, 1986a; Godfrey et al., 1988b). These results indicate, first, that 5-HT_2 receptors are postsynaptically located and, second, that they are regulated by a mechanism different from that controlling other postsynaptic neurotransmitter receptors; the latter receptors are usually "upregulated" after denervation, resulting in the induction of a hypersensitivity. However, the following variations have been reported after serotonergic denervation: a decrease (Leysen et al., 1982a) or an increase in the number of 5-HT_2 receptors (Barbaccia et al., 1983b; Heal et al., 1985), an enhancement of IP_3 production (Butler et al., 1990), and a facilitation of 5-HT-induced head twitches, reflecting 5-HT_2 activation (Heal et al., 1985; Godfrey et al., 1988b).

Given that agonist exposure elicits a desensitization of 5-HT_2 receptors, the generally observed lack of denervation-hypersensitivity for these receptors suggested that the receptors are not under the tonic control of the serotonergic system (for further discussion, see Sanders-Bush, 1990) or that 5-HT itself is not the natural full agonist for this receptor (Roth et al., 1984, 1985). These authors also proposed the existence of a corresponding peptidic endogenous ligand.

A nonclassical regulation of the 5-HT_2 receptors is

observed after antagonist administration. Rather than eliciting the classical supersensitivity and upregulation, chronic antagonist administration elicits a decrease in 5-HT_2 receptor density (Blackshear and Sanders-Bush, 1982; Blackshear et al., 1983; Gandolfi et al., 1985; May et al., 1986; Leysen et al., 1986; Roth et al., 1989; Roth and Ciaranello, 1991; Pranzatelli, 1991) and a subsensitive phosphoinositide response (Conn and Sanders-Bush, 1986a). Interestingly, Roth and Ciaranello (1991) showed that the decrease of 5-HT_2 binding observed after mianserin treatment is not paralleled by a decrease in mRNA production, suggesting a posttranscriptional regulation mechanism.

Similarly, chronic treatment with a partial agonist (LSD) or with full agonists (DOI, DOB, and DOM) also decreases the B_{max} for [^{3}H]ketanserin (Buckholtz et al., 1988; Leysen et al., 1989; McKenna et al., 1989; Pranzatelli, 1991), and [^{3}H]DOB (Pranzatelli, 1991) causes desensitization of the head shake behavior in rats (Leysen et al., 1989).

Thus, the action of 5-HT_2 agonists and antagonists on the regulation of the 5-HT_2 receptors is not totally elucidated. A possible explanation is that 5-HT_2 receptors receive a very low stimulation under physiological conditions. Because of the low stimulation, the receptors could exist in a supersensitive state, and then, their chronic blockade would not produce further supersensitivity. The significant desensitization and downregulation of the receptor could be a defense mechanism against excessive stimulation (Sanders-Bush, 1990). The elucidation of the mechanism of 5-HT_2 receptor downregulation by antagonists, and the question of whether it differs from the agonists-induced downregulation, requires additional studies. Isolated cells in culture represent a promising model for these studies (Ivins and Molinoff, 1991).

The regulation of 5-HT_2 receptors observed after long-term antidepressant treatment stimulated much interest in how 5-HT_2 receptors participate in depression and in the mechanism of action of antidepressant drugs. Chronic treatment with antidepressants usually causes a downregulation of the 5-HT_2-binding sites (Peroutka and Snyder, 1980; Kellar et al., 1981; Blackshear and Sanders-Bush, 1982; Barbaccia et al., 1983b; Goodwin et al., 1984; Kendall and Nahorski, 1985; Metz and Heal, 1986; Mizuta and Segawa, 1989). This decrease is also observed after treatment with lithium (Treiser and Kellar, 1980; Wajda et al., 1986; Mizuta and Segawa, 1989; Newman et al., 1990) and some antipsychotics (Wilmot and Szezpanik, 1989; Matsubara and Meltzer, 1989; O'Dell et al., 1990). This downregulation of the sites is also accompanied by a decrease of the 5-HT_2 receptor activity as evidenced by a decrease in IP_3 production (Kendall and Nahorski, 1984, 1985; Conn and Sanders-Bush, 1986a; Godfrey et al., 1988b; Newman and Lerer, 1988b; Newman et al., 1990) and head twitch response (Goodwin et al., 1984, 1986; Metz et al., 1985; Godfrey et al., 1988b). Roth and Ciaranello (1991) demonstrated that chronic treatment with mianserin fails to affect 5-HT_2 mRNA levels in rat brain, although it reduces (44 to 59%) the number of 5-HT_2 receptors.

Accordingly, the number of 5-HT_2 receptors is increased in depressed suicidal patients studied postmortem (Stanley and Mann, 1983; Mann et al., 1986; McKeith et al., 1987; Arora and Meltzer, 1989; Arango et al., 1990; Yates et al., 1990) and in blood platelets of depressed patients (Biegon et al., 1987, 1990). Yates et al. (1990) further showed that in still depressed patients treated with antidepressants, the 5-HT_2 binding is similar to the control; in depressed patients after euthymic recovery, however, the 5-HT_2 sites were markedly decreased. Other authors observed no modification in the brains of depressed patients examined postmortem (Crow et al., 1984; Cheetham et al., 1988). In an animal model of depression (learned helplessness), the number of 5-HT_2 receptors was either unchanged (Martin et al., 1990a) or increased (Barone et al., 1990).

On the other hand, electroconvulsive shock increases the number of 5-HT_2 receptors (Kellar et al., 1981; Vetulani et al., 1981; Green et al., 1983; Newman et al., 1987; Biegon and Israeli, 1987; Godfrey et al., 1988b); this effect may be sex dependent (Biegon and Israeli, 1987). The mechanisms responsible for 5-HT_2 receptor regulation by different antidepressive treatments remain to be defined.

5-HT_2 receptors may be involved in other psychiatric diseases because their number is reduced in persons suffering from schizophrenia (Mita et al., 1986), Parkinson's disease (Reisine et al., 1877; Maloteaux et al., 1988; Cheng et al., 1991), Alzheimer's disease (Cross et al., 1988, Cheng et al., 1991), and senile dementia of Lewe body type (Cheng et al., 1991).

The functional properties of 5-HT_2 receptors are modified by the $GABA_B$ agonist baclofen in vivo (Metz et al., 1985) and in vitro (Godfrey et al., 1988a), by noradrenergic denervation (Eison et al., 1988), and by the administration of β-adrenergic agonists (Handley and Singh, 1986). These results suggest that GABAergic and adrenergic systems participate in the control of 5-HT_2 receptor activity.

Interestingly, 5-HT_{1B} receptors can modulate 5-HT_2-mediated behaviors, such as the DOI-induced ear scratch stereotypy in mice. Similtaneous costimulation of 5-HT_{1B} receptors by both TFMPP and RU 24969 potently inhibits this behavior (Darmani et al., 1990a). 5-HT_{1A} receptor activation also seems to inhibit 5-HT_2 receptor function. Indeed, the 5-HT_2 receptor-mediated head shakes, evoked in rats by DOI, could be attenuated by 8-OH-DPAT (Berendsen and Broekkamp, 1990). In addition, the 5-HT_2 receptor-mediated quipazine-induced head shake response in rats could be blocked by the 5-HT_{1A} agonists 8-OH-DPAT, buspirone, gepirone, and

ipsapirone (Yocca et al., 1990a). Similarly, the 5-HT_2 receptor-mediated head twiches, evoked in mice and rats by DOI, was inhibited by 8-OH-DPAT (Arnt and Hyttel, 1989; Darmani et al., 1990b). Moreover, chronic buspirone administration also produces downregulation of 5-HT_2 receptors in rats (Taylor and Hyslop, 1991).

These results, together with the behavioral and biochemical data demonstrating a negative control of 5-HT_2 receptors on the 5-HT_{1A} receptor function (section III.A.7), strongly demonstrate an interaction between the two receptor systems. Although the mechanism of this interaction is unknown, it is possible that it involves a second-messenger production, because the dibutyryl-cAMP can enhance the density of the 5-HT_2-binding sites that regulate the expression of the 5-HT_2 receptor gene (Shigeri et al., 1992) and because the PKC activation can desensitize 5-HT_{1A} receptor function (Raymond, 1991; Liu and Albert, 1991). The 5-HT_{1A}-5-HT_2 interaction may be involved in the reciprocal modulations between 5-HT_1 and 5-HT_2 receptors proposed in the "5-HT receptor imbalance" hypothesis (Deakin, 1988, 1989). This hypothesis explains how a 5-HT_{1A} deficit may be involved in a depressive syndrome and how 5-HT_2/5-HT_{1C} excessive neurotransmission may be involved in anxiety.

The existence of an endogenous ligand interacting directly with the 5-HT_2 receptors has been proposed by Costa's group. A cerebral peptidic fraction (6000 daltons) was isolated that displaced [^{3}H]ketanserin in rat brain cortex (Roth et al., 1984, 1985; Barbaccia and Costa, 1986; Apud and Ito, 1991). Its function is not known.

7. Cellular functions. 5-HT_2 receptors are involved in the control of neurotransmitters other than 5-HT. K^+-evoked ACh release is selectively inhibited by 5-HT_2 agonists in the hippocampus (Muramatsu et al., 1988a) and rat brain cortex (Muramatsu et al., 1990), whereas the activation of 5-HT_2 receptors increases the basal release of ACh in the striatum (Bianchi et al., 1989). These effects are reduced by antidepressant drug treatment (Siniscalchi et al., 1990b; Muramatsu et al., 1990). 5-HT_2 receptors, and possibly 5-HT_{1C} receptors, have potent and direct excitatory actions on the GABAergic neurons of the thalamic reticular nucleus; this postsynaptic response appears to result from the suppression of a potassium current (McCormick and Wang, 1991). Experiments in which serotonin agonists and antagonists were applied intraventricularly suggest that the serotonergic negative control of noradrenergic release in the locus coeruleus is mediated through 5-HT_2 receptors (Gorea and Adrien, 1988). 5-HT_2 receptors also inhibit the K^+-evoked release of glutamate and aspartate in the cerebellum (Maura et al., 1988, 1991) and the release of dopamine in the striatum (Muramatsu et al., 1988b). In the spinal cord, their activation increases the K^+-evoked release of substance P (Iverfeldt et al., 1986).

DOI increases the secretion of renin by activating both peripheral and brain 5-HT_2 receptors (Rittenhouse et al., 1991). 5-HT_2 receptors also regulate the secretion of vasopressin (Rittenhouse et al., 1990) and play a secondary role in regulating the activity of the hypothalamo-hypophysis axis (Koening et al., 1987).

8. 5-HT_2 receptors and behavior. 5-HT_2 receptors are involved in motor behavior in rats and mice. The head twitch is induced in rodents by serotonergic agonists and antagonized by the following selective antagonists: metergoline, cinanserin, cyproheptadine, methysergide, 2-bromo-LSD, piramperone, and ketanserin (Malick et al., 1977; Friedman and Dallob, 1979; Matthews and Smith, 1980; Peroutka et al., 1981; Colpaert and Janssen, 1983a,b; Lucki et al., 1984; Heal et al., 1985; Ögren and Fuxe, 1989). The "wet dog shake" is also inhibited by 5-HT_2 antagonists (Bedard and Pycock, 1977; Matthews and Smith, 1980; Vetulani et al., 1980; Yap and Taylor, 1983; Fone et al., 1989). 5-HT_2 receptors may mediate the contraction of back muscles, but 5-HT_{1C} activation may also be required for this activity (Fone et al., 1989).

Gudelsky et al. (1986, 1987) reported that 5-HT_2 receptors are involved in temperature regulation. These authors showed that hyperthermia induced by MK 212 is antagonized by ketanserin; however, the involvement of 5-HT_{1C} and possibly 5-HT_{1A} receptors in this mechanism was not excluded. Similarly, the hypothermia induced by 5-MeO-DMT might be controlled via 5-HT_2 receptors and also 5-HT_{1C} and 5-HT_{1A} subtypes (Gudelsky et al., 1986).

It is not likely that 5-HT_2 receptors are directly involved in regulating food intake. However, Hewson et al. (1988), who studied the effects of quipazine, and Schechter and Simansky (1988), who studied the effects of DOI, have proposed that these receptors play a role in reducing food intake. Wilkinson and Dourish (1991) concluded that the anorectic effects of 5-HT_2 agonists, particularly DOI, might be mediated by 5-HT_{1C} receptors. Peripheral 5-HT_2 activity may also be responsible for these effects (Massi and Marini, 1987).

It is likely that 5-HT_2 receptors play a role in sexual behavior in female rats because selective 5-HT_2 antagonists inhibit lordosis behavior (Mendelson and Gorzalka, 1986b; Hunter et al., 1985) and 5-HT_2 agonists facilitate it (James et al., 1989). The dual effect of LSD suggests the involvment of several types of receptors (Sietnieks and Mayerson, 1983). Although 5-HT_2 antagonists reduce male sexual activity (Mendelson and Gorzalka, 1986b) and the 5-HT_2 agonist DOI stimulate global sexual activity in male rats (Foreman et al., 1989), the actual role of 5-HT_2 receptors is still unclear, because LSD and DOM do not alter male sexual behavior (Ahlenius and Larsson, 1987) and DOI has also been reported to inhibit the copulatory behavior in male rats; the latter effect is reversed by 5-HT_2 antagonists (Watson and Gorzalka, 1991).

In various experimental behavioral tests (Berge, 1982;

Post et al. 1986), analgesic effects of 5-HT_2 agonists were blocked by specific 5-HT_2 antagonists. These effects seem to involve other neurotransmission systems because the 5-HT_2 receptors exert negative effects on the firing of the dopaminergic and noradrenergic neurons located supraspinally which control nociception (Alhaider, 1991). Furthermore, it was recently reported that the nociceptive actions of intravenously administered 5-HT require dual activation of 5-HT_2 and 5-HT_3 receptors subtypes (Meller et al., 1991).

5-HT_2 receptors play an important role in regulating sleep. In rats, specific 5-HT_2 agonists (RP 62203, DOM, and DOI), (Dugovic and Wauquier, 1987; Dugovic et al., 1989; Stutzmann et al., 1990) decrease the light and REM sleep and increase the duration of slow-wave sleep. Certain 5-HT_2 antagonists (ritanserin) block the increase in slow-wave sleep but do not affect REM sleep, suggesting that 5-HT_2 receptors may not be involved to the same extent in the two cases. Other 5-HT_2 antagonists (2(2-dimethylamino-2-methylpropylthio)3-phenyl quinoline and ICI 169–369), however, alter REM sleep (Tortella et al., 1989). In humans, 5-HT_2 antagonists increase slow-wave sleep (Idzikowski et al., 1986; Sharpley et al., 1990b); interestingly, this effect did not occur in depressed patients (Sharpley et al., 1990a). 5-HT_2 receptors are regulated during circadian rhythm (Wesemann and Weiner, 1990), and they might also regulate the sleep-waking cycle. For example, ritanserin is able to counteract jet lag (Hoppenbrouwers et al., 1988).

Although anxiolytic properties of 5-HT_2 have been described in various experimental models, these properties are not yet fully established. 5-HT_2 antagonists (cyproheptadine, methysergide, metergoline, pizotifen, ritanserin) exhibit anxiolytic properties; these effects are limited and not consistently dose related, as shown in the conflict test (Meert and Colpaert, 1986) and the elevated X-maze test (Critchley and Handley, 1987). However, in the Vogel conflict test, as well as in the open-field test, ritanserin appears to act in a dose-dependent manner (Colpaert et al., 1985). RP 62203, a new 5-HT_2 antagonist, is anxiolytic in the elevated X-maze test, whereas ritanserin is not (Stutzmann et al., 1991).

5-HT_2 antagonists are not yet recognized as being anxiolytic in humans, although from preliminary clinical observations it would seem that ritanserin (Ceulemens et al., 1985; Reyntjens et al., 1986; Pangalia-Ratu Langi and Janssen, 1988; Meert and Janssen, 1989) and trazodone (Al-Yassiri et al., 1981) play an anxiolytic role. These effects might be due to the presence of 5-HT_2 receptors in the amygdala, an area that has been proposed to play an important role in this disorder (Deakin, 1989).

The number of 5-HT_2 receptors has been shown to decrease in schizophrenic patients (Mita et al., 1986). 5-HT_2 antagonists are being developed as neuroleptics on the basis of experimental results (Ortmann et al., 1982; Gelders et al., 1986; Wander et al., 1987; Lowe et al., 1988; Van der Heyden, 1989). However, the neuroleptic activity of the 5-HT_2 antagonists has not yet been clearly demonstrated.

5-HT_2 receptors may play an important role in the mechanism of action of hallucinogenic drugs (Glennon, 1985; Glennon et al., 1985; Sadzot et al., 1989). However, this mechanism is far from well understood. Initially, the 5-HT_2 antagonistic properties of *d*-LSD were thought to be responsible for its hallucinogenic properties (Pierce and Peroutka, 1988), but some authors think that, on the contrary, these properties are due to its agonistic activities (Glennon, 1990a). It has also been proposed that 5-HT_{1C} receptors are involved in these effects (Glennon, 1990a).

Serotonergic agonists favor electroconvulsions and pentylenetetrazol-induced seizures in mice. That this effect is antagonized by ketanserin suggests the participation of 5-HT_2 receptors in epilepsy (Löscher and Czuczwar, 1985).

The role of 5-HT_2 receptors in the periphery is important, particularly in cardiovascular physiology, but is beyond the scope of this review (Hollenberg, 1988; Saxena et al., 1989; Wiernsperger, 1990).

It is surprising that 5-HT_2 receptors, which are strongly regulated in many pathological circumstances, apparently do not play an important physiological role. It was proposed that they receive little stimulation under normal physiological conditions and function only in "emergency" or pathological conditions (Leysen, 1990).

B. 5-HT_{1C} Receptors

The 5-HT_{1C} receptors, considered initially as 5-HT_1-like receptors on the basis of their relatively high affinity for [^{3}H]5-HT, are present at high density in the choroid plexus (Pazos et al., 1985b). Their pharmacological characteristics are similar to those of the 5-HT_2 receptors. It was, therefore, suggested that they might be related to these receptors (Hoyer, 1988). This has now been definitely established; comparison of their nucleotide sequences showed 5-HT_{1C} and 5-HT_2 receptors to be homologous (see review by Hartig et al., 1990a,b).

1. Selective radioligands and pharmacological properties. The 5-HT_{1C} sites were initially identified by using [^{3}H]5-HT, [^{3}H]mesulergine, and [^{3}H]LSD (Pazos et al., 1985b) and later by using ^{125}I-LSD (Yagaloff and Hartig, 1985), ^{125}I-1-methyl-LSD (Yagaloff and Hartig, 1986), [^{3}H]mianserin (Sanders-Bush and Breeding, 1988), [^{3}H] SCH 23390 (Nicklaus et al., 1988), and [^{3}H]SCH 23982 (Hoyer and Karpf, 1988).

At present, no ligand has been found that specifically recognizes the 5-HT_{1C} receptor. This receptor has a medium affinity for 5-HT (K_d = 10 to 30 nM), whereas other 5-HT_1 subtypes exhibit a high affinity for 5-HT (K_d = 1 to 5 nM); 5-HT_2 and 5-HT_3 receptors exhibit a low affinity (K_d = 900 to 3000 and 600 to 900 nM,

respectively). The 5-HT_{1C} site also shows a low affinity for 5-CT (K_d = 630 nM). The serotonergic drugs that are antagonistic at the 5-HT_2 receptors generally are also recognized by 5-HT_{1C} sites with a high affinity (<10 nM). However, the 5-HT_{1C} site recognizes ketanserin and cinanserin with 10 to 30 times lower affinity than do 5-HT_2 sites; spiperone has a 1000-fold lower affinity. The latter drug, therefore, allows 5-HT_2 and 5-HT_{1C} receptor subtypes to be distinguished. The phenylalkylamine derivatives (DOM, DOB, DOI), considered to bind selectively at 5-HT_2 receptors, also recognize 5-HT_{1C} receptors with the same affinity (Glennon et al., 1992).

The 5-HT_2 receptor antagonists are potent and competitive displacers at the 5-HT_{1C} sites in pig choroid plexus (Sahin-Erdemli et al., 1991). Thus, the 5-HT_{1C} receptors apparently do not undergo allosteric modulation as described previously for 5-HT_2 receptors (Kaumann and Frenken, 1985). Interestingly, the 5-HT_{1A} agonist 8-MeO-2′-chloro-8-methoxy-2[N-propyl-N-propylamino]tetraline irreversibly blocks not only the 5-HT_{1A} receptors but also the 5-HT_{1C} receptors in the rat choroid plexus (Radja et al., 1989).

2. Regional distribution within the brain. Several laboratories have demonstrated the high concentration of 5-HT_{1C} receptors in the choroid plexus of different species: rat (Yagaloff and Hartig, 1985; Peroutka, 1986), pig (Pazos et al., 1985b; Yagaloff and Hartig, 1985), mouse (Mengod et al., 1990), and humans (Hoyer et al., 1986b). Transgenic mice spontaneously developing a choroid plexus tumor exhibit in this area the highest density of 5-HT_{1C} receptor found in any tissue (>6.000 fmol/mg protein) (Yagaloff et al., 1986).

Autoradiographic studies demonstrated that 5-HT_{1C} receptors are present at low levels in many other areas of the brain, including the substantia nigra, globus pallidus, cerebral cortex, and olfactory tubercules (Pazos et al., 1985b, 1988). Studies of the distribution of the mRNA encoding for 5-HT_{1C} receptors confirmed and extended these results (Molineaux et al., 1989; Hoffman and Mezey, 1989; Mengod et al., 1990) and suggested that the function of the 5-HT_{1C} receptors is not limited to that performed in the choroid plexus.

3. Cellular localization. The 5-HT_{1C} receptors have been studied more extensively in choroid plexus than in any other tissue. They appear to be located on epithelial cells where they regulate the production and composition of cerebrospinal fluid (Pazos and Palacios, 1985). Dopaminergic lesions do not affect 5-HT_{1C} binding in this area (Palacios and Dietl, 1988), suggesting that 5-HT_{1C} receptors are not located on dopaminergic neurons. Provoking specific lesions in the serotonergic neurons by using 5,7-DHT-hypersensitized 5-HT_{1C} receptors, as measured by the increase of IP_3 production (Conn et al., 1987), strongly suggested that these receptors are located on nonserotonergic neurons.

4. Molecular structure. Lübbert et al. (1987a,b) cloned the 5-HT_{1C} receptor by using a cloning strategy based on electrophysiological assays of *X. laevis* oocytes. These cells were injected with mRNA from a mouse choroid plexus tumor previously fractionated by gel electrophoresis. The 5-HT_{1C} mRNA expressed in the oocytes was detected by voltage-clamp measurements of currents induced by 5-HT. Then, a cDNA library was constructed using this mRNA, and a clone carrying a 5-HT_{1C} gene fragment of 1.9 kb was identified. Julius et al. (1988) used an mRNA fraction from the choroid plexus to construct a cDNA library transcribed in vitro with T7 RNA polymerase. The cDNA transcripts injected into oocytes or into NIH 3T3 fibroblasts were screened to select those producing a functional 5-HT_{1C} receptor. One cDNA clone containing the entire 5-HT_{1C}-coding region was isolated and characterized.

The 5-HT_{1C} receptor, cloned from rat brain, is a monomeric protein belonging to the large multigenic family characterized by seven membrane-spanning domains and linked to a G protein. It consists of 460 amino acids with a molecular weight of 51,899 daltons; the amino terminal (19 amino acids) possesses a glycosylation site. An aspartate residue located in the second transmembrane domain may play an important role in agonist recognition, as occurs in the β-adrenoceptor (Strader et al., 1989). The third intracellular loop (77 amino acids) and the carboxy terminal (29 amino acids) contain potential phosphorylation sites, i.e., four of the last 12 amino acids of the COOH terminal are serine. This receptor does not possess a leucine zipper. Its sequence is homologous to that of 5-HT_2 (78% identity in the transmembranal domains) but not to that of the 5-HT_{1A} receptor (40% identity in transmembranal domain).

Recently, Yu et al. (1991) cloned the mouse 5-HT_{1C} gene and proposed, on the basis of hydrophobicity analysis, that the corresponding encoded protein contains eight hydrophobic domains capable of forming membrane-spanning α-helices; this observation contrasts with the usual "seven-helix" paradigm described for other GTP-related receptors. The existence of this hydrophobic region, designated domain E, near the amino terminal of the receptor (Yu et al., 1991), raises the question of its functional significance. The 5-HT_{1C} receptor gene, designated Htr1c, has been assigned to the X chromosome, and thus, its chromosomal location differs from that of 5-HT_{1A} and 5-HT_2 genes mapped to autosomes.

5. Transduction system. 5-HT_{1C} receptors are coupled to the breakdown of phosphatidyl inositides as shown in rat (Conn and Sanders-Bush, 1986b) and pig (Hoyer et al., 1989); these receptors are not linked to adenylyl cyclase activity (Palacios et al., 1986). IP_3 production controls a Ca^{2+}-dependent chloride channel (Lübbert et al., 1987a,b) via a calcium-calmodulin dependant protein kinase (Tohda et al., 1991a,b) and a Ca^{2+}-independent potassium channel (Panicker et al., 1991) in *Xenopus* oocytes transfected with 5-HT_{1C} mRNA. However, the

control of these channels has not yet been confirmed in brain tissue.

Recently, Hartig et al. (1990b) reported that 5-HT_{1C} activity may be directly linked to the stimulation of cyclic GMP production.

6. Regulation. The postnatal development of 5-HT_{1C} receptors has been studied in rat brain choroid plexus. The number of binding sites increases markedly between days 3 and 20 after birth (Zilles et al., 1986), and the 5-HT_{1C} receptor develops earlier than do other 5-HT_1 subtypes. In parallel to the 2-fold increase in 5-HT_{1C} sites in rat brain, production of the corresponding mRNA increases 5-fold between days 17 and 27 (Roth et al., 1991). Roth et al. (1990) reported that in the raphe a "burst" expression for the receptor gene occurs at postnatal day 7; these authors suggested that a transcriptional process was involved.

The mechanisms responsible for regulating 5-HT_{1C} receptors by exogenous or endogenous compounds are not currently clear (see review by Roth et al., 1990). The modifications of mRNA production following treatment with various drugs (antidepressants, lithium) generally have not been studied in parallel with alterations of the binding sites. To our knowledge, only one study has been performed in which chronic treatment with mianserin was used. In this study, the production of mRNA increased, whereas the number of 5-HT_{1C}-binding sites decreased (Roth et al., 1989). These results suggest that mianserin regulates 5-HT_{1C} receptors through a post-transcriptional mechanism.

The alteration of 5-HT_{1C} binding by antidepressants in the choroid plexus was studied Mizuta and Segawa (1989). 5-HT_{1C} binding partially disappeared after chronic treatment with imipramine and lithium. In vitro studies with *Xenopus* oocytes showed that imipramine and desipramine, at nanomolar concentrations, block the chloride current induced by 5-HT_{1C} activation (Tohda et al., 1989; Tohda and Nomura, 1991). Thus, the mechanism of action of some antidepressants may involve 5-HT_{1C} receptors.

Recently, Walter et al. (1991) cloned the gene of a protein that controls the sensitivity of both the 5-HT_{1C} and the M_1 muscarinic receptors; the regulatory mechanism has not yet been explored, but it may represent an important phenomenon in serotonergic physiopathology.

7. Cellular functions. The main function attributed to the 5-HT_{1C} receptor is the control of the exchanges between the CNS and cerebrospinal fluid (Hartig, 1989b). In particular, Tsutsumi et al. (1989) and Tsutsumi and Sanders-Bush (1990) demonstrated that the production of transferrin by choroid plexus epithelial cells is regulated through 5-HT_{1C} receptors.

A potentially important role of the 5-HT_{1C} and 5-HT_2 receptor gene is that of protooncogenes (Julius et al., 1989, also see review by Julius, 1991). When the receptor gene is expressed in transfected fibroblasts NIH 3T3, and these cells are then exposed at length to 5-HT, foci form that can induce malignant tumors in athymic or nude mice. Nevertheless, 5-HT_{1C} activation in neuronal cells does not lead to cell proliferation under normal conditions. Therefore, whether the 5-HT_{1C} gene acts as a protooncogene apparently depends closely on its cellular environment.

8. 5-HT_{1C} receptors and behavior. A clear role of 5-HT_{1C} in behavior has not yet been established because of the lack of specific ligands known for this receptor. However, motor effects have been produced especially by piperazine agonists (TFMPP and mCPP) and unselective ligands, such as MK 212, which induce hyperlocomotion (Sills et al., 1984; Kennett and Curzon, 1988; Lucki et al., 1989; Klodzinska et al., 1989). The latter effect is blocked by metergoline, methysergide, and mianserin but not by ketanserin or α_1-, α_2-, or β-adrenergic antagonists, suggesting the specific involvement of 5-HT_{1C} receptors.

Dourish et al. (1989) proposed that postsynaptic 5-HT_{1C} receptors located in the ventromedial hypothalamus play an important role in regulating feeding, because mCPP and TFMPP also decrease food intake in rats (Kennett and Curzon, 1988, 1991; Curzon and Kennett, 1990).

mCPP and TFMPP, which induce dysphoria (Murphy et al., 1989) and panic in humans (Charney et al., 1987), are also anxiogenic in rats (Kennett et al., 1989; Whitton and Curzon, 1990). Their effect might be related to 5-HT_{1C} receptors, because these behaviors are blocked by mianserin, cyproheptadine, metergoline but not ketanserin and cyanopindolol. However, the observation that ritanserin, which has a high affinity for 5-HT_{1C} (K_d = 1.9 nM), is not active does not favor this hypothesis.

Finally, 5-HT_{1C} receptors may play a role in initiating migraine attacks (Fozard and Gray, 1989). Recent evidence favoring this proposal is that ergotamine and dihydroergotamine, effective antimigraine agents, are potent 5-HT_{1C} receptor antagonists in piglet choroid plexus (Brown et al., 1991).

V. 5-HT_3 Receptors

The first indications of the existence of another serotonergic receptor, called "M receptor" by Gaddum and Picarelli (1957), were obtained from pharmacological studies carried out on isolated guinea pig ileum. These receptors control muscle contraction via ACh release, and their effect is antagonized by morphine. Later, Fozard et al. (1979) found that cocaine inhibits the sympathomimetic-like effects induced by these receptors in isolated rabbit heart. This observation led to the development and use of several cocaine derivatives (MDL 72222, ICS 205–930, and BRL 24924) (see review by Richardson and Buccheit, 1988).

Richardson and Engel (1986) proposed that the 5-HT_3 peripheral receptors are heterogeneous and include the

5-HT_{3A} subtype present in the vagus nerve, superior cervical ganglion, and sensory nerves, the 5-HT_{3B} subtype present in sympathetic and parasympathetic nerves, and the 5-HT_{3C} subtype present in enteric nerves. However, because the experimental models used to define these hypothetical subtypes make use of different tissues and species, doubt remains concerning their existence (Hoyer, 1990). Rapid developments in molecular biology will soon make it possible to characterize potential subtypes.

Various reviews deal with 5-HT_3 receptors, including peripheral types (Fozard, 1984; Richardson and Engel, 1986; Richardson and Buccheit, 1988). The present review will be limited to those receptors found in the CNS.

A. Selective Radioligands and Pharmacological Properties

Specific 5-HT_3-binding sites in the CNS were initially demonstrated by Kilpatrick et al. (1987) using [^{3}H]GR 65630. Other specific radioligands have now been discovered and used to characterize these receptors, including [^{3}H]zacopride (Barnes et al., 1988a), [^{3}H]quipazine (Peroutka and Hamick, 1988, Milburn and Peroutka, 1989), [^{3}H]ICS 205–930 (Hoyer and Neijt, 1988), [^{3}H]BRL 43694 (granisetron) (Nelson and Thomas, 1989), [^{3}H] QICS 205–930 (Watling et al., 1988), [^{3}H]GR 67330 (Kilpatrick et al., 1990b), [^{3}H]LY 278–584 (Wong et al., 1989; Gehlert et al., 1991), and ^{125}I-zacopride (Hamon et al., 1990a).

To further characterize the 5-HT_3-binding sites, Miquel et al. (1991) pretreated membranes with various reagents known to chemically modify specific amino acid residues. Among all the reagents tested, N-bromosuccinimide, a specific tryptophan reagent, modified the binding characteristics of [^{3}H]zacopride (60% reduction of the B_{max}), suggesting that intact tryptophan residue(s) are required for the specific binding of [^{3}H]zacopride. Further studies are needed for a direct demonstration of this involvement.

Many serotonergic agonistic drugs are not highly selective and generally have only a moderate affinity for the receptor: 5-HT (100 to 800 nM), α-methyl-5-HT (200 nM), bufotenine (210 nM), phenylbiguanide (300 to 1000 nM), 2-methyl-5-HT (approximately 1000 nM) (table 6).

Recently, Kilpatrick et al. (1990b) discovered a high-affinity agonist, 1-(*m*-chlorophenyl)-biguanide (K_i = 0.3 nM). Interestingly, the same authors observed that [^{3}H] GR 67330 could label a heterogeneous population of binding sites in the entorhinal cortex, which might correspond either to different 5-HT_3 subtypes or to different conformations of the same receptor, in a manner similar to those described for the nicotinic receptor (Changeux, 1981). In fact, agonistic drugs displace 5-HT_3 radioligands with a Hill coefficient >1, suggesting the occurrence of complex interactions, possibly related to conformational changes induced by these agonists. These phenomena are not observed with antagonists.

Many antagonists are specific and have a very high affinity, e.g., quipazine, SDZ 206–830, LY 278–584, zacopride, GR 38032 (ondansetron), GR 67330, 1H-indole-3-carboxylic acid-*trans*-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-ester methane sulfonate, ICS 205–930 (tropisetron), BRL 43694 (granisetron), MDL 72222, BRL 24924, and BRL 47204. The 5-HT_1 and 5-HT_2 antagonists do not interact with a high affinity with 5-HT_3 receptors (table 7).

Computerized modeling has been used to study the pharmacophore structure and, in particular, to predict the affinities with which new drugs bind to 5-HT_3 receptors (Schmidt and Peroutka, 1989, 1990). The advantage of this approach is that agents active at the receptor can be analyzed and identified with minimal dependence on the use of animals and radioactive compounds.

B. Regional Distribution within the Brain

The distribution of the 5-HT_3 receptors in the peripheral tissues is mainly, if not totally, neuronal (enteric nerve system, parasympathetic, sympathetic, sensorial system) (Fozard, 1984; Richardson and Buccheit, 1988).

The regional distribution of these receptors in the CNS has been studied in various species: rat (Kilpatrick et al., 1987; Barnes et al., 1990a), mouse (Waeber et al., 1988b; Kilpatrick et al., 1989), ferret (Kilpatrick et al., 1989; Barnes et al., 1988b), rabbit (Kilpatrick et al., 1989), cynomolgus monkey (Kilpatrick et al., 1990a), and human brain (Waeber et al., 1989b; Barnes et al., 1989a). These studies demonstrated that the highest density of 5-HT_3-binding sites occurs in the area postrema; other areas of the brain also contain 5-HT_3 sites: entorhinal cortex > retrosplenic cortex > frontal cortex > amygdala > hippocampus > accumbens > septum > thalamus > hypothalamus; the cerebellum is almost totally devoid of specific sites. When compared with other serotonergic receptors, the 5-HT_3 receptors exhibit a particularly low density in the brain (approximately 10 times less in the richest areas).

The presence of the 5-HT_3 receptors in the area postrema is of particular interest because this area is involved in the emesis mechanism, and anti-5-HT_3 compounds are antiemetics when administered systemically or injected locally into this area. The 5-HT_3 receptors involved in this phenomenon have not yet been precisely localized, but it has been shown that 5-HT_3 receptors are present on dorso-vagal complex afferent fibers in the tractus solitarius, a region close to the area postrema (Reynolds et al., 1989a,b; Pratt and Bowery, 1989; Pratt et al., 1990).

Neuronal cell lines may provide a good source of 5-HT_3 because the murine neuroblastoma cell line NIE 115 (Hoyer and Neijt, 1988) and the neuroblastoma-glioma hybrid NG 108–15 (Hoyer and Neijt, 1987; Neijt

TABLE 6

Affinity values of drugs for 5-HT$_{1C}$ recognition sites in mammalian brain membranes

Drug	Affinity	Reference
Very high affinity (K_i < 10 nM)		
Metergoline	0.51	Hoyer et al., 1985b
	0.64	Engel et al., 1986; Hoyer and Schoeffter, 1991
Ritanserin	0.2	Sanders-Bush, 1988b
	0.54	Van Wijngaarden et al., 1990
	1.25	Hoyer and Schoeffter, 1991
Mesulergine	1.0	Sanders-Bush, 1988b
	1.6	Hoyer et al., 1985b; Hoyer and Schoeffter, 1991
	1.2–3.9	Pazos et al., 1985b
Methysergide	1.9–3.6	Pazos et al., 1985b
	2.5	Hoyer and Schoeffter, 1991
	62	Peroutka, 1986
Mianserin	1.9	Yagaloff and Hartig, 1985
	2.0	Sanders-Bush, 1988b
	6.3–12	Pazos et al., 1985b
	10	Hoyer and Schoeffter, 1991
Methiothepin	3.16–15	Pazos et al., 1985b
	27	Schlicker et al., 1989
	25	Hoyer and Schoeffter, 1991
d-LSD	4.4	Yagaloff and Hartig, 1985
1-NP	5.24	Schoeffter and Hoyer, 1989a
SCH 23390	5.49	Hoyer, 1988
LSD	5–7.9	Pazos et al., 1985b
	11.7	Engel et al., 1986
	12.5	Hoyer and Schoeffter, 1991
DOI	6.45	Van Wijngaarden et al., 1990
	18.6	Hoyer, 1988
Pitozifen	7.94	Hoyer and Schoeffter, 1991
LY 53857	7.94	Hoyer and Schoeffter, 1991
ICI 169-369	9.33	Sahin-Erdemli et al., 1991
High affinity (K_i = 10–100 nM)		
5-HT	11	Peroutka, 1986
	30.4	Yagaloff and Hartig, 1985
	31.6	Hoyer and Schoeffter, 1991
Cyproheptadine	8.3	Hoyer, 1988
	12.58	Hoyer and Schoeffter, 1991
	13.3	Engel et al., 1986
mCPP	19.9	Hoyer and Schoeffter, 1991
Lisuride	19.9	Hoyer and Schoeffter, 1991
5-MeO-T	23.4	Schlicker et al., 1989
	25	Peroutka, 1986
Methergine	24.5	Hoyer and Schoeffter, 1991
Ketanserin	28	Yagaloff and Hartig, 1985
	30	Sanders-Bush, 1988b
	50.1	Pazos et al., 1985b
	95	Van Wijngaarden et al., 1990
	97.7	Hoyer and Schoeffter, 1991
Piremperone	12.5–25	Pazos et al., 1985b
	50	Hoyer and Schoeffter, 1991
	61,000	Peroutka, 1986
Ergometrine	31.6	Hoyer and Schoeffter, 1991
Tryptamine	46.7	Engel et al., 1986
Ergotamine	50	Hoyer and Schoeffter, 1991
TFMPP	12	Van Wijngaarden et al., 1990
	50	Schoeffter and Hoyer, 1989a
	63	Hoyer and Schoeffter, 1991
	1,000	Peroutka, 1986
5-MeO-DMT	57	Peroutka, 1986
	87	Hoyer, 1988
5-NH_2-T	70	Engel et al., 1986
Imipramine	100	Sanders-Bush, 1988b
α-Dihydroergocriptine	100	Hoyer and Schoeffter, 1991
Low affinity (K_i = 100–1,000 nM)		
Cinanserin	74	Yagaloff and Hartig, 1985
	199	Hoyer and Schoeffter, 1991
	199–1,584	Pazos et al., 1985b
	5,600	Peroutka, 1986
(+)Butaclamol	158	Pazos et al., 1985b
RU 24969	47.8	Van Wijngaarden et al., 1990
	150	Peroutka, 1986
	158–199	Pazos et al., 1985b
	316	Hoyer and Schoeffter, 1991
Bufotenine	70	Hoyer, 1988
	110	Peroutka, 1986
(−)Propranolol	158	Hoyer et al., 1985b
	407	Hoyer and Schoeffter, 1991
Quipazine	186	Schoeffter and Hoyer, 1989
	9,900	Peroutka, 1986
Bromocriptine	199	Hoyer and Schoeffter, 1991
WB 4101	398	Hoyer and Schoeffter, 1991
	1,100	Peroutka, 1986
5-BT	370	Peroutka, 1991b
5,6-DHT	410	Peroutka, 1986
	707	Engel et al., 1986
2-Me-5HT	489	Van Wijngaarden et al., 1990
	1,445	Engel et al., 1986
5-CO-NH_2-T	588	Engel et al., 1986
MDL 72832	501	Van Wijngaarden et al., 1990

TABLE 6—*Continued*

Drug	Affinity	Reference	Drug	Affinity	Reference
MK 212	691	Engel et al., 1986	Amitriptyline	5,800	Peroutka, 1986
(±)Propranonol	588	Schlicker et al., 1989	Spiroxatrine	7,943	Hoyer and Schoeffter, 1991
	736	Yagaloff and Hartig, 1985	Buspirone	2,940	Sanders-Bush, 1988b
	1,200	Sanders-Bush, 1988b		7,940	Hoyer and Schoeffter, 1991
NAN-190	602	Van Wijngaarden et al., 1990		110,000	Peroutka, 1986
PAPP	602	Schoeffter and Hoyer, 1989b	Sumatriptan	8,128	Van Wijngaarden et al., 1990
5-CT	630	Hoyer and Schoeffter, 1991	(±)ICYP	9,770	Hoyer et al., 1985b
			Ipsapirone	9,000	Peroutka, 1986
Phentolamine	891	Hoyer and Schoeffter, 1991		31,622	Hoyer and Schoeffter, 1991
	1,250	Yagaloff and Hartig, 1985	SDZ(+)21009	8,912	Engel et al., 1986
				10,000	Hoyer and Schoeffter, 1991
Very low affinity (K_i > 1,000 nM)					
Spiperone	1,000–1,995	Pazos et al., 1985b	CGS 12066B	12,882	Schlicker et al., 1989
	1,150–1,258	Hoyer et al., 1985b; Hoyer and Schoeffter, 1991	Gepirone	25,118	Hoyer and Schoeffter, 1991
				26,200	Sanders-Bush, 1988b
	1,148	Engel et al., 1986	(+)Pindolol	39,810	Hoyer et al., 1985b
	4,800	Peroutka, 1986		65,600	Hoyer and Schoeffter, 1991
SDZ(−)21009	1,995	Pazos et al., 1985b			
	5,011	Hoyer and Schoeffter, 1991	Yohimbine	39,810	Hoyer and Schoeffter, 1991
Haloperidol	4,600	Sanders-Bush, 1988b		42,657	Schlicker, 1989
8-OH-DPAT	5,011	Pazos et al., 1985b	(±)CYP	>10,000	Schlicker et al., 1989
	7,200	Peroutka, 1986, Hoyer and Schoeffter, 1991	*l*-LSD	>5,000	Yagaloff and Hartig, 1985
				>10,000	Peroutka, 1986
	7,700	Yagaloff and Hartig, 1985	Urapidil	15,848	Hoyer and Schoeffter, 1991
	16,500	Sanders-Bush, 1988b			

et al., 1988a; Bolanos et al., 1990) possess these receptors at high density, i.e., about 50 times that found in brain tissues.

C. Molecular Structure

The 5-HT_3 receptor is a ligand-gated ion channel, which, when activated, causes fast, depolarizing responses, similar to those seen following nicotinic ACh receptor activation (Changeux et al., 1987). Recently, Maricq et al. (1991), using expression cloning, isolated a cDNA clone encoding a 5-HT_3 receptor from NCB-20 cells. They injected size-fractionated polyadenylated mRNA from NCB-20 cells into *Xenopus* oocytes and tested for the presence of serotonin-gated currents that could be blocked by selective 5-HT_3 antagonists. They then constructed a cDNA library from the positive mRNA fraction; the RNA transcripts were injected separately into *Xenopus* oocytes to select those producing the 5-HT_3 functional receptor.

The sequence analysis revealed that this receptor is a new member of the ligand-gated ion channel superfamily. The predicted protein corresponds to 487 amino acids and contains four hydrophobic transmembrane regions (M1 to M4), a large cytoplasmic loop connecting M3 to M4, and a large amino-terminal domain containing the Cys-Cys loop, a signature of this family, thought to participate in the formation of a disulfide bond.

The pharmacological and electrophysiological characteristics of the cloned receptor are largely consistent with the properties of native 5-HT_3 receptors. The mRNA encoding this receptor is identified in brain, spinal cord, and heart but not in cerebellum, liver, spleen, or intestine; the absence of signal in the intestine suggests that the intestinal 5-HT_3 receptor is a distinct subtype encoded by a separate gene.

The receptor protein was previously solubilized by Miquel et al. (1990) and McKernan et al. (1990).

D. Transduction System

The 5-HT_3 receptor appears to be directly linked to the opening and closing of an ionic channel that is not selective for monovalent cations (K^+ and Na^+) and which is independent of a G protein. Its activation induces a rapid depolarization. Derkach et al. (1989), using a preparation of peripheral nerves (submucous plexus), were the first to demonstrate this electrophysiological func-

TABLE 7

Affinity values of drugs for 5-HT$_3$ recognition sites in mammalian brain membrane or cellular cultures

Drug	Affinity	Reference
Very high affinity (K_i < 10 nM)		
GR 67330	0.038	Kilpatrick et al., 1989
SDZ 206-830	0.158	Hoyer and Neijt, 1988
	0.93	Kilpatrick et al., 1990b
QICS 205-930	0.45	Watling et al., 1988
BRL 24682	0.331	Nelson and Thomas, 1989
LY 278-584	0.575	Milburn and Peroutka, 1989
	0.71	Schmidt and Peroutka, 1990
LY 258-458	0.75	Milburn and Peroutka, 1989
	0.94	Schmidt and Peroutka, 1990
Zacopride	0.1	Nelson and Thomas, 1989
	0.27	Kilpatrick et al., 1989
	0.32	Hoyer and Neijt, 1988
	0.42	Milburn and Peroutka, 1989
	0.99	Kilpatrick et al., 1990b
	1.9	Barnes et al., 1989b
S(−)Zacopride	0.325	Bolanos et al., 1990
Tropisetron	0.38	Milburn and Peroutka, 1989
(ICS 205-930)	0.40	Nelson and Thomas, 1989
	0.812	Hoyer and Neijt, 1988
	0.89	Kilpatrick et al., 1989
	1.9	Barnes et al., 1988a
	3.09	Kilpatrick et al., 1987
	3.23	Kilpatrick et al., 1990b
Ondansetron	0.87	Nelson and Thomas, 1989
(GR 38032)	1.62	Kilpatrick et al., 1989
	2.88	Kilpatrick et al., 1987
	4.78	Barnes et al., 1988a
	6.02	Bolanos et al., 1990
	13.48	Hoyer and Neijt, 1988
RP 62203	0.26	Doble, 1990
SDZ 206-792	0.724	Hoyer and Neijt, 1988
Granisetron	0.26	Nelson and Thomas, 1989
(BRL 43694)	0.38	Milburn and Peroutka, 1989
	0.588	Kilpatrick et al., 1987
	1.17	Kilpatrick et al., 1989
	1.41	Hoyer and Neijt, 1988
	2.69	Barnes et al., 1988a
	4.17	Kilpatrick et al., 1990b
Quipazine	0.22	Kilpatrick et al., 1989
	0.501	Milburn and Peroutka, 1989
	1.23	Nelson and Thomas, 1989
	2.04	Hoyer and Neijt, 1988
GR 65630	1.34	Barnes et al., 1989b
	1.58	Kilpatrick et al., 1987
BRL 47204	1.07	Nelson and Thomas, 1989
R(+)Zacopride	2.29	Bolanos et al., 1990
BRL 24924	3.16	Hoyer and Neijt, 1988
	23.9	Kilpatrick et al., 1990b
SDZ 210-204	5.01	Hoyer and Neijt, 1988
	7.8	Neijt et al., 1988a
MDL 72222	5.3	Nelson and Thomas, 1989
	6.3	Hoyer and Neijt , 1988; Milburn, 1989
	37.15	Bolanos et al., 1990
	42.1	Kilpatrick et al., 1990b
	54.98	Kilpatrick et al., 1987
LY 211-000	1.9	Schmidt and Peroutka, 1990
	4.2	Milburn and Peroutka, 1989
High affinity (K_i = 10–100 nM)		
mCPP	10	Milburn and Peroutka, 1989
	40.2	Kilpatrick et al., 1990b
	48.9	Bolanos et al., 1990
	54.9	Kilpatrick et al., 1987
	102	Hoyer and Neijt, 1988
MK 212	12	Schmidt and Peroutka, 1990
Mianserin	5.8	Nelson and Thomas, 1989
	64.5	Hoyer and Neijt, 1988
	223	Bolanos et al., 1990
SDZ 210-205	33.1	Hoyer and Neijt, 1988
Bufotenine	33.8	Milburn and Peroutka, 1989
Pitozifen	42	Schmidt and Peroutka, 1990
Clozapine	49	Schmidt and Peroutka, 1990
	204	Bolanos et al., 1990
Low affinity (K_i = 100–1,000 nM)		
Metoclopramide	120	Milburn and Peroutka, 1989
	160	Nelson and Thomas, 1989
	223	Hoyer and Thomas, 1988
	323	Barnes et al., 1989b
	338	Bolanos et al., 1990
	363	Kilpatrick et al., 1987
	1,400	Kilpatrick et al., 1990b
Indalpine	120	Schmidt and Peroutka, 1990
	1,202	Bolanos et al., 1990
Cizapride	134	Nelson and Thomas, 1989
	512	Bolanos et al., 1990
Cyproheptadine	140	Schmidt and Peroutka, 1990
	263	Hoyer and Neijt, 1988
2-Methyl-5HT	87	Milburn and Peroutka, 1989
	210	Kilpatrick et al., 1990b
	426	Bolanos et al., 1990
	620	Nelson and Thomas, 1989
	954	Hoyer and Neijt, 1987
	977	Neijt et al., 1988a
	1,122	Barnes et al., 1988a
	1,445	Van Wijngaarden et al., 1990
Amitriptyline	260	Schmidt and Peroutka, 1990
LY 278-989	330	Schmidt and Peroutka, 1990
Imipramine	570	Schmidt and Peroutka, 1990
ICI 169-369	680	Schmidt and Peroutka, 1990
	990	Nelson and Thomas, 1989
5-HT	130	Kilpatrick et al., 1990b
	160	Nelson and Thomas, 1989
	363	Van Wijngaarden et al., 1990
	380	Bolanos et al., 1990
	645	Barnes et al., 1988a
	891	Hoyer and Neijt, 1987
Phenylbiguanide	34	Milburn and Peroutka, 1989
	130	Kilpatrick et al., 1990b
	446	Bolanos et al., 1990
	1,348	Hoyer and Neijt, 1987
	1,819	Neijt et al., 1988a
TFMPP	160	Schmidt and Peroutka, 1990
	2,089	Van Wijngaarden et al., 1990
5,7-DHT	190	Schmidt and Peroutka, 1990
Very low affinity (K_i > 1,000 nM)		
NAN-190	1,202	Van Wijngaarden et al., 1990
Cocaine	1,513	Milburn and Peroutka, 1989
	3,311	Barnes et al., 1989b
	3,630	Kilpatrick et al., 1987
	12,400	Kilpatrick et al., 1990b
α-Methyl-5-HT	1,600	Kilpatrick et al., 1990b
5-MeO-T	1,900	Schmidt and Peroutka, 1990
Mepyramine	2,400	Nelson and Thomas, 1989
Methiothepin	3,000	Nelson and Thomas, 1989
	9,700	Kilpatrick et al., 1990b
RU 24969	3,800	Van Wijngaarden et al., 1990
Ritanserin	5,300	Nelson and Thomas, 1989
	7,244	Van Wijngaarden et al., 1990
Metergoline	7,400	Nelson and Thomas, 1989
8-OH-DPAT	12,589	Bolanos et al., 1990
	17,200	Kilpatrick et al., 1990b
Methysergide	19,500	Kilpatrick et al., 1990b

tion. Numerous studies have since been performed on peripheral tissue preparations (see review by Andrade and Chaput, 1991a; Goldfarb, 1990) and neurons or cell cultures (Yakel and Jackson, 1988; Lambert et al., 1989; Neijt et al., 1988b; Peters and Lambert, 1989). The observed electrophysiological responses consist of a very rapid (100 to 300 ms) opening of the channel, leading to an increase in cationic conductance. This response, in contrast to 5-HT_1 or 5-HT_2 G protein-related responses, is rapidly desensitized; it is not sensitive to GTP or to pertussis toxin.

Interestingly, 5-HT_3 receptors are present on lymphocytes, where they regulate a voltage-gated conductance, accelerating the inactivation process of the cell (Choquet and Korn, 1988).

Recent experimental results indicate that a 5-HT_3-like receptor may be coupled to a G protein. In cingulate and entorhinal cortex, brain areas rich in 5-HT_3 receptors, the IP_3 production is stimulated by 5-HT_3 agonists and inhibited by 5-HT_3 antagonists (Ashby et al., 1990; Edwards et al., 1991a,b). Phenylbiguanide and 2-methyl-5-HT (Ashby et al., 1991) induce a current-dependent suppression of the firing rate in medial prefrontal cortical cells; this phenomenon may be related to this G protein-linked molecular mechanism. Additionally, cyclic GMP production in 108 CC15 cells is stimulated by 5-HT_3 agonists (Reiser and Hamprecht, 1989). These findings suggest that subtypes other than the 5-HT_3 receptor described before also may exist but are structurally different from it, although they possess pharmacological similarities.

E. Regulation

The mechanism controlling the function of the 5-HT_3 receptor is probably one of conformational changes leading to a rapid desensitization (Derkach et al., 1989; Yakel and Jackson, 1988), as is usually observed for receptors linked directly to an ionic channel. Because these receptors were discovered only recently, there have been few studies of the mechanisms by which they are regulated (Kilpatrick et al., 1987). Chronic treatment of rats with lithium led to a decrease of the binding affinity in the hippocampus but not of the maximal number of 5-HT_3 sites; imipramine treatment, in contrasts, did not alter these receptors (Mizuta and Segawa, 1988).

F. Cellular Functions

5-HT_3 receptors have been demonstrated to facilitate the electrically evoked release of [^{3}H]5-HT from guinea pig frontal cortex and rat hypothalamic slices (Galzin and Langer, 1991); this effect was mimicked by 2-CH_3-5-HT and antagonized by ondansetron (100 nM) and ICS 205–930 (10 nM). Thus, these results strongly suggest the existence of presynaptic facilitatory autoreceptors of a 5-HT_3 type.

However, the main function of the 5-HT_3 receptors is the modulation of the neuronal release of other neurotransmitters. Initially, Feuerstein and Hertting (1986) showed that 5-HT stimulated the release of noradrenaline from hippocampal slices; this effect was antagonized by ICS 205–930 and MDL 72222, but only at high concentrations (10 μM and 1 μM respectively). Therefore, the actual involvement of 5-HT_3 receptors in the release of noradrenaline is not firmly established. Blandina et al. (1991) obtained contradictory results. Using rat hypothalamic slices, they demonstrated that 5-HT_3 receptors inhibit noradrenaline release.

5-HT_3 receptors control dopamine release. In accumbens and amygdala, 5-HT_3 agonists stimulate the release of dopamine as shown in vivo (Costall et al., 1987b,c,d; Hagan et al., 1990) or by microdialysis (Imperato and Angelucci, 1989; Carboni et al., 1989a). A similar effect occurs in the striatum, as shown in experiments on superfused tissue slices (Blandina et al., 1988, 1989). Yi et al. (1991) proposed that the stimulatory effect of 5-HT on dopamine release in rat striatum synaptosomes does not result from the activation of 5-HT_3 but rather occurs via the transport of 5-HT into the dopaminergic terminals. In any case, the 5-HT_3 control of dopaminergic activity has been proposed to explain the antipsychotic activities of 5-HT_3 antagonists (see review by Costall et al., 1990), because an increase in dopaminergic activity is thought to favor psychosis (Costall et al., 1987d; Tricklebank, 1989; Hagan et al., 1990; Abbott, 1990).

Barnes et al. (1989b) showed that 5-HT_3 receptors also mediate inhibition of K^+-evoked ACh release from rat entorhinal cortex.

Finally, Alhaider et al. (1991) showed that the serotonin 5-HT_3 receptors appear to be involved in controlling the GABAergic system, i.e., they evoke the release of GABA in spinal cord. Furthermore, activation of the 5-HT_3 receptors increases the K^+-evoked GABA release in rat caudate-putamen; ICS 205–930 and MDL 72222 antagonize this effect (Meyer et al., 1991). Moreover, 5-HT_3 receptors mediate the serotonergic activation of the GABAergic interneurons inhibiting the hippocampal CA1 pyramidal cells (Ropert and Guy, 1991). However, in guinea pig hippocampal synaptosomes, 5-HT_3 agonists inhibit K^+-evoked GABA release, and this inhibition is blocked by 5-HT_3 antagonists (Cloez et al., 1990). These findings suggest that 5-HT_3 receptors can control GABA release through several different mechanisms.

G. 5-HT_3 Receptors and Behavior

Under normal conditions, 5-HT_3 antagonists appear to have very few effects; this would favor their therapeutic use. The main therapeutic interest of 5-HT_3 antagonists resides in their activity as antiemetics, an action especially useful in conjunction with cancer therapies involving cytotoxic drug treatments (cisplatin, doxorubicin, or cyclophosphamide) or radiation. The antiemetic effect has been demonstrated in several experimental

models: ferret (Miner and Sanger, 1986; Miner et al., 1986, 1987; Costall et al., 1986, 1987a; Gylys et al., 1988; Fukuda et al., 1991) and cat and dogs (Gylys et al., 1988; Smith et al., 1988). Clinical studies have also clearly established that 5-HT_3 antagonists are antiemetic in humans (Leibundgut and Lancranjan, 1987; Cunningham et al., 1987, 1989; Carmichael et al., 1988; Marty et al., 1989; Miln and Heel, 1991; Jones et al., 1991; Smith et al., 1991).

Recently, ondansetron also has been proposed as a safe and effective antiemetic for the treatment of postoperative nausea and vomiting after general anesthesia (Larijani et al., 1991). The 5-HT_3 antagonists (ICS 205–930, MDL 72222, zacopride, and ondansetron) are not active in apomorphine-induced emesis (Miner et al., 1987) and are inefficient in "motion-sickness" in cats (Lucot, 1989) or in humans (Stott et al., 1989); motion-sickness is prevented by 5-HT_{1A} agonists in the cat (Lucot and Crampton, 1989). These results suggest that emesis may be provoked by several distinct mechanisms.

The 5-HT_3-related emesis presumably originates from a central effect involving the area postrema (Higgins et al., 1989), but it may also partly involve a peripheral effect. Indeed, both cytotoxic drugs and radiation disrupt the gastrointestinal mucosa, inducing the release of 5-HT from the enterochromaffin cells; this 5-HT stimulates the 5-HT_3 receptors located on vagal fibers which, in turn, may initiate emesis through a mechanism involving the area postrema and the nucleus of the solitarius tract (see review by Andrews et al. 1988; Aapro, 1991).

The first indication that the 5-HT_3 receptors are involved in pain was proposed in a study of inflammatory-related nociception (Eschalier et al., 1989). Antinociceptive effects of intrathecal and intracerebroventricular administration of 5-HT or 2-methyl-5-HT, and antagonized by MDL 72222 or ICS 205–930, were reported for the rat (Glaum et al., 1988; Giordano, 1991; Alhaider et al., 1991). Similarly, 4-amino-5-chloro-N-[2-pyrrolidylmethyl]-2,3-dihydrobenzo[b]furan-7-carboxamide, a novel 5-HT_3 antagonist, produced significant analgesia in the formalin-induced inflammatory pain test in rats (Sufka and Giordano, 1991). These findings support the hypothesis that 5-HT_3 has a role in the spinal transmission of nociceptive impulses, probably by controlling GABA release (Alhaider et al., 1991).

5-HT_3 antagonists may also be useful in the treatment of migraine (Loisy et al., 1985), but this application has still to be established.

5-HT_3 receptors do not play an important a role in feeding behavior as do 5-HT_{1A} (Hutson et al., 1988) and 5-HT_{1C} receptors (Kennett and Curzon, 1988). Nevertheless, ICS 205–930 has been shown to increase gastric emptying in rats and guinea pigs (Buchheit et al., 1985), and BRL 24924 blocks the inhibitory effect of 5-HT on the gastric secretion of peptides (Johansen and Bech, 1991). In the dog, on the other hand, 5-HT_3 antagonists do not display these properties (Gullikson et al., 1991).

A great deal of interest is developing in the potential activities of the 5-HT_3 receptors in psychiatry. The 5-HT_3 receptors may play a role in tolerance-dependence mechanisms. 5-HT_3 antagonists decrease or inhibit the effects of withdrawal following the chronic use of nicotine, cocaine, ethanol, and benzodiazepines (Costall et al., 1988a, 1989a,b,c; Carboni et al., 1989b; Goudie and Leathley, 1990) and decrease ethanol consumption (Sellers et al., 1988; Oakley et al., 1988). However, effects on withdrawal symptoms have not been found consistently (Mos et al., 1989; Carboni et al., 1989a). Therefore, although the decrease in dopaminergic activity mediated by 5-HT_3 antagonists favors their use as antipsychotic drugs, additional studies are needed to assess whether they can be developed as therapeutic tools in that domain.

5-HT_3 receptors may play an interesting role in the neurochemical processes involved in anxiety. Indeed, low doses of ondansetron, granisetron, tropisetron, MDL 72222, and zacopride increase social interaction in rats under aversive conditions (Tyers et al., 1987; Tyers, 1989; Jones et al., 1988; Piper et al.., 1988; Costall et al., 1988a, 1989b; Young and Johnson, 1991). In primates, these drugs reduce aggressiveness directed against threatening stimuli (Tyers et al., 1987; Jones et al., 1988; Piper et al., 1988; Costall et al., 1988a). However, these anxiolytic properties are not evidenced in all experimental tests, e.g., Vogel conflict test (Jones et al., 1988; Tyers et al., 1987), conditioned suppression in pigeon (Ahlers and Barrett, 1988), punished exploratory behavior (Mos et al., 1989), and elevated X-maze (Johnsson and File, 1988). Moreover, ondansetron and granisetron at high doses exhibit anxiogenic properties (Costall et al., 1988a).

These results and the fact that 5-HT_3 antagonists have a delay of onset of action longer than that of the benzodiazepines indicate that these drugs operate by different modes of action. In an attempt to determine the neuroanatomical site of action for the disinhibitory, perhaps anxiolytic, properties of 5-HT_3 receptor antagonists, Higgins et al. (1991a) examined the effects of such compounds in the social interaction test following injection into amygdala or dorsal raphe nucleus of the rat. Their results suggest that the amygdala, rather than the dorsal raphe nucleus, is involved in the effects of the 5-HT_3 antagonists. The anxiolytic therapeutic properties of 5-HT_3 antagonists have still to be confirmed.

Finally, interesting properties have been revealed in experimental models of cognition. For example, ondansetron and granisetron, unlike the benzodiazepines, increase "learning" in rodents and primates (Barnes et al., 1990b; Chugh et al., 1991). These properties might be exploited for a particular therapeutic application, such as in the treatment of Alzheimer's disease.

VI. Other 5-HT Receptors

Several recent pharmacological studies have led to the proposal that, in addition to 5-HT_1, 5-HT_2, and 5-HT_3 receptors, a 5-HT_4 receptor may also exist. Although it was present in several tissues where it had different functions, the absence of labeling of its binding sites did not allow a final classification as a fully recognized receptor (see review by Bockaert et al., 1992).

Dumuis et al. (1988b) obtained results with neuronal primary cell cultures of mouse embryo colliculi suggesting the existence of a new type of receptor that is positively coupled to adenylyl cyclase activity (table 8). They showed that 5-HT (K_m = 109 nM) and 5-MeO-T increase cAMP production, whereas tryptamine, bufotenin, and 2-methyl-5-HT are partial agonists and 8-OH-DPAT and RU 24969 are inefficient. Among the serotonergic antagonists, only ICS 205–930 (tropisetron) competitively inhibits 5-HT-induced cAMP production. This effect was observed at high concentrations of ICS 205–930 (K_i = 710 nM; 100 times greater than that required to inhibit 5-HT_3 receptor activity), suggesting that the observed phenomenon is not related to 5-HT_3 receptor function (Dumuis et al., 1988a). Moreover, MDL 72222 is a very weak antagonist of this effect (K_i > 5000 nM), whereas it is a potent 5-HT_3 antagonist. In addition, 5-HT_1 and 5-HT_2 antagonists are inefficient in inhibiting cAMP production. Dumuis et al. (1988b) proposed that the receptor exerting this effect was the same as that previously identified in guinea pig hippocampus (R_L) that has a low affinity for 5-CT and that increases cAMP production (Shenker et al., 1987). They suggested calling the receptor 5-HT_4.

More recent findings established three families of compounds as 5-HT_4 agonists: indolamine derivatives (5-HT, 5-CT, 5-MeOT, bufotenin, 5-MeO-N-N-DMT), benzamides (metoclopramide, BRL 24924, BRL 20967, cisapride, and zacopride) (Dumuis et al., 1989a,b; Bockaert et al., 1990), and azabicycloalkyl benzimidazolone (BIMU 1, BIMU 8) (Dumuis et al., 1991). Recently, DAU 6285 (Dumuis et al., 1992) and SDZ 205–557 (Buchheit et al., 1991, 1992) were proposed as selective antagonists for 5-HT_4 receptors. These compounds, having a lower affinity for 5-HT_3 receptors, may represent a new interesting tool for investigating the pharmacological and physiological properties of 5-HT_4 receptors. So far, the recognition sites for these receptors have not been identified.

5-HT_4 receptors appear to mediate slow excitatory responses to 5-HT in the brain, because they elicit a slow membrane depolarization and a decrease in the calcium-activated afterhyperpolarization in rat hippocampal pyramidal neurons (Andrade and Chaput, 1991b). Inhibition of K^+ channels also was mediated by 5-HT_4 receptors; it was demonstrated using individual collicular patch-clamped neurons (see Bockaert et al., 1992). The mechanism by which these receptors inhibit K^+ channels seems to involve cAMP production and consequent activation of cAMP-dependent protein kinase A.

TABLE 8

Affinity of agonists at 5-HT_4 receptors positively coupled to adenylyl cyclase in mouse embryo colliculi neurons in primary culture and in adult guinea pig hippocampal membranes

Agonistic drugs	Colliculi neuron EC_{50} (nM)		Hippocampal membrane EC_{50} (nM)	
Cisapride	72.44	(Dumuis et al., 1989b)	210	(Bockaert et al., 1990)
BIMU 8	72	(Dumuis et al., 1991)		
5-HT	92	(Dumuis et al., 1989a)		
	106	(Dumuis et al., 1991)	263	(Dumuis et al., 1988b)
	109	(Dumuis et al., 1988b)		
5-MeO-T	100	(Dumuis et al., 1988b)		
BRL 24924	116	(Dumuis et al., 1989a)	33	(Bockaert et al., 1990)
	125	(Dumuis et al., 1989b)		
BIMU 1	360	(Dumuis et al., 1991)		
RU 28253	560	(Dumuis et al., 1988b)	3,500	(Dumuis et al., 1988b)
Zacopride	1,122	(Dumuis et al., 1989b)		
Bufotenine	1,580	(Dumuis et al., 1988b)	29,500	(Dumuis et al., 1988b)
5-CT	3,160	(Dumuis et al., 1988b)		
BRL 20627	3,235	(Dumuis et al., 1989b)		
Metoclopramide	4,570	(Dumuis et al., 1989a)		
5-MeO-N,N,DMT	17,780	(Dumuis et al., 1988b)		
Tryptamine	>10,000	(Dumuis et al., 1988b)		
d-LSD	>10,000	(Dumuis et al., 1988b)		
2-CH_3-5-HT	>10,000	(Dumuis et al., 1988b)	Inactive	(Dumuis et al., 1988b)
8-OH-DPAT	Inactive	(Dumuis et al., 1988b)	Inactive	(Dumuis et al., 1988b)
Ipsapirone	Inactive	(Dumuis et al., 1988b)		
Buspirone	Inactive	(Dumuis et al., 1988b)		
Metergoline	Inactive	(Dumuis et al., 1988b)		
Methysergide	Inactive	(Dumuis et al., 1988b)		
l-Phenylbiguanide	Inactive	(Dumuis et al., 1988b)		
RU 24969	Inactive	(Dumuis et al., 1988b)		

These receptors are also present at the periphery where they control the contraction of guinea pig ileum (Craig and Clarke, 1990) and ascending colon (Elswood et al., 1991) and relaxation of esophageal tunica muscularis mucosae in rat (Baxter et al., 1991) and humans (Kaumann, 1990; Kaumann et al., 1991). It is generally believed that the stimulation of the 5-HT_4 receptor in the ileum causes the release of ACh, because atropine attenuates the contraction elicited by 5-MeO-T (Fozard, 1990) and by low concentrations of 5-HT (Eglen et al., 1990). Stimulation of 5-HT_4 receptors by 5-MeO-T also causes an increase in the electrically evoked twitch contraction of the guinea pig ileum due to an increase in the evoked ACh release (Craig and Clarke, 1990; Kilbinger and Wolf, 1992). Moreover, this receptor is involved in the serotonin-induced cardiac effects in both porcine and human heart (Villalon et al., 1991, Ouadid et al., 1991).

5-HT_4 receptors might represent a functionally important family of serotonergic receptors; however, further experimentation is needed to determine whether this is so. Furthermore, additional work should be done to elucidate the biochemical, molecular, and cellular characteristics of this receptor.

VII. Conclusion

The explosive development of research in the serotonergic system led to the discovery that different 5-HT receptors are involved in numerous physiopathological functions mediated by serotonergic neurotransmission. Initially, the receptors were often suspected of being artifactual because the existence of multiple receptors for a single neurotransmitter was considered unrealistic. The results of recent studies using molecular biological techniques clearly confirm the reality of the existence of several types of serotonergic receptors. The characterization of their molecular structure has confirmed the initial classification of Bradley et al. (1986) and has demonstrated subclasses of receptors that are coupled to G proteins as well as those that function as an ionic channel. These observations now constitute a general framework in which new receptor subtypes can be inserted.

That multiple receptors exist for a single neurotransmitter constitutes an important adaptive advantage. Indeed, the multiplicity of the 5-HT receptors allows differential interactions of 5-HT with biological tissues. The variety of the effects produced depends on the presence and the number of a given receptor subtype in the considered tissue, their cellular localization, i.e., pre- or postsynaptic, their pharmacological specificity, the nature of their transduction system, and the expression of the gene coding for the particular receptor subtype.

The serotonergic cerebral system is both highly localized, the neuronal cell bodies being all contained in the raphe nuclei, and ubiquitous because the serotonergic fibers innervate all brain areas. These observations support the hypothesis that the serotonergic system may control aspects of CNS function through the modulation of other neurotransmitter activities. The multiplicity of the serotonergic receptors also constitutes an important factor in the selectivity of the serotonergic interactions with other neurotransmitter systems.

The mode of action of the serotonergic system generally involves two mechanisms: one corresponding to a synaptic transmission; the other corresponding to a nonsynaptic one, analogous to an endocrine-like neuromodulation. These two mechanisms have been described as "wiring transmission" and "volume transmission," respectively (Fuxe et al., 1989). They require the existence of receptor types having different affinities for the neurotransmitter, i.e., the nonsynaptic transmission can occur only via receptors having a high-affinity constant similar to that exhibited by 5-HT_1 receptors; however, the latter receptors can also be involved in the synaptic form of transmission.

Because multiple 5-HT receptors control various molecular and cellular activities, it is not surprising that the serotonergic system participates in a variety of quite different physiological events such as temperature regulation, food intake, and sexual behavior. Because dysfunctions in these activities will have important pathological consequences, it is important to know the fundamental mechanisms involved in the function of the serotonergic system and to define the pharmacological agents that interact with the activities linked to the stimulation or activation of the 5-HT receptors.

In the near future, it is expected that each of the serotonergic receptors will be defined on the basis of their molecular characteristics, thus providing access to a precise identification of the binding epitopes for both serotonin agonists and antagonists as well as to the molecular mechanisms involved in the activation of each receptor. A precise characterization of receptor properties will allow the development of potent, selective, and stereospecific ligands. Such studies should lead to the characterization of the molecular, cellular, and functional features of the receptors as well as the regulatory mechanisms that particularly affect their gene expression. It is hoped that new and more efficient treatments may result from such basic studies.

Addendum. During the editing of this manuscript, significant findings were reported; among the most important ones was the demonstration of the existence and cloning of 5-HT_{1E} receptors (McAllister et al., 1992) and of a new receptor subtype mediating inhibition of adenylyl cyclase (S31) (Levy et al., 1992).

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REFERENCES

AAPRO, M. S.: 5-HT_3 receptor antagonists. An overview of their present status and future potential in cancer therapy-induced emesis. Drugs 42: 551–568, 1991.

ABBOTT, A.: 5-HT_3 antagonists and ligands for dopamine D1 and autoreceptors offer new leads for antipsychotic drugs. Trends Pharmacol. Sci. 11: 49–51, 1990.

ADHAM, N., ROMANIENKO, HARTIG, P., WEINSHANK, R. L., AND BRANCHEK, T.:

The rat 5-hydroxytryptamine-1B receptor is the species homologue of the human 5-hydroxytryptamine-1Dβ receptor. Mol. Pharmacol. **41:** 1–7, 1992.

AGHAJANIAN, G. K.: Feedback of central monoaminergic neurons: evidence from single-cell recording studies. *In* Essays in Neurochemistry and Neuropharmacology, ed. by M. B. Youdim, Y. Lorenberg, D. F. Sharman, and J. R. Lagnado, pp. 1–32, Wiley Ltd., New York, 1978.

AHLENIUS, S., AND LARSSON, K.: Evidence for a unique pharmacological profile of 8-OH-DPAT by evaluation of its effects on male rat sexual behavior. *In* Brain 5-HT_{1A} Receptors: Behavioral and Neurochemical Pharmacology, ed. by C. T. Dourish, S. Ahlenius, and P. H. Hutson, pp. 185–198, Ellis Horwood Ltd., Chichester, United Kingdom, 1987.

AHLENIUS, S., AND LARSSON, K.: Antagonism by pindolol but not betaxolol, of 8-OH-DPAT-induced facilitation of male rat sexual behavior. J. Neural Transm. **77:** 163–170, 1989.

AHLENIUS, S., LARSSON, K., AND WIJKSTRÖM, A.: Behavioral and biochemical effects of the 5-HT_{1A} receptor agonists flesinoxan and 8-OH-DPAT in the rat. Eur. J. Pharmacol. **200:** 259–266, 1991.

AHLERS, S. T., AND BARRETT, J. E.: Examination of the effects of the $5HT_3$ receptor antagonist MDL 72222 on punished responding in pigeons. Soc. Neurosci. Abstr. **14:** 847, 1988.

AL-YASSIRI, M. M., ANKIER, S. I., AND BRIDGES, P. K.: Minireview: trazodone—a new antidepressant. Life Sci. **28:** 2449–2485, 1981.

ALBERT, P. R., ZHOU, Q.-Y., VAN TOL, H. H. M., BUNZOW, J. R., AND CIVELLI, O.: Cloning, functional expression and mRNA tissue distribution of the rat 5-HT_{1A} receptor gene. J. Biol. Chem. **265:** 5825–5832, 1990.

ALHAIDER, A. A.: Antinoceptive effect of ketanserin in mice: involvement of supraspinal $5HT_2$ receptors in nociceptive transmission. Brain Res. **543:** 335–340, 1991.

ALHAIDER, A. A., LEI, S. Z., AND WILCOX, G. L.: Spinal 5-HT_2 receptor-mediated antinociception: possible release of GABA. J. Neurosci. **11:** 1881–1888, 1991.

ALTMAN, H. J., AND NORMILE, H. J.: Serotonin, learning and memory: implications for the treatment of dementia. *In* Treatment Development Strategies For Alzheimer's Disease, ed. by T. Crook, R. Bartus, S. Ferris, and S. Gershon, pp. 361–381, Marc Powley Associates Inc., Madison, CT, 1986.

ALTMAN, H. J., AND NORMILE, H. J.: What is the nature of the role of the serotonergic nervous system in learning and memory: prospects for development of an affective treatment strategy for senile dementia. Neurobiol. Aging **9:** 627–638, 1988.

AMIN, A. H., CRAWFORD, T. B. B., AND GADDUM, J. H.: The distribution of substance P and 5-HT in the central nervous system of the dog. J. Physiol. **126:** 596–618, 1954.

AMSTERDAM, J. D., BERWISH, N., POTTER, L., AND RICKELS, K.: Open trial of gepirone in the treatment of major depressive disorder. Curr. Ther. Res. Clin. Exp. **41:** 185–193, 1987.

ANANTH, U. S., LELI, U., AND HAUSER, G.: Stimulation of phosphoinositide hydrolysis by serotonin in C6 glioma cells. J. Neurochem. **48:** 253–261, 1987.

ANDERSON, G. M., HORNE, W. C., CHATTERJEE, D., AND COHEN, D. J.: The hyperserotonemia of autism. Ann. N. Y. Acad. Sci. **600:** 331–340, 1990.

ANDRADE, R.: 5-HT_{1A} receptors regulate adenylyl cyclase mediated responses in the hippocampus. Soc. Neurosci. Abstr. **16:** 1196, 1990.

ANDRADE, R., AND CHAPUT, Y.: The electrophysiology of serotonin receptor subtypes. *In* Serotonin Receptor Subtypes Basic and Clinical Aspects, ed. by S. J. Peroutka, pp. 103–124, John Wiley Ltd, New York, 1991a.

ANDRADE, R., AND CHAPUT, Y.: 5-Hydroxytryptamine$_4$-like receptors mediate the slow excitatory response to serotonin in the rat hippocampus. J. Pharmacol. Exp. Ther. **257:** 930–937, 1991b.

ANDRADE, R., MALENKA, R. C., AND NICOLL, R. A.: A G protein couples serotonin and GABA-B receptors to the same channels in hippocampus. Science **234:** 1261–1265, 1986.

ANDREWS, P. L. R., RAPEPORT, W. G., AND SANGER, G. J.: Neuropharmacology of emesis induced by anti-cancer therapy. Trends Pharmacol. Sci. **9:** 334–341, 1988.

ANTHONY, M.: The biochemistry of migraine. *In* Handbook of Clinical Neurology: Headache, ed. by F. C. Rose, vol. 48, pp. 85–105, Elsevier, Amsterdam, 1986.

APUD, J. A., AND ITO, Y.: Semi-separative purification of an endogenous ligand for brain serotonin-2 receptors by coil planet centrifuge countercurrent chromatography. J. Chromatogr. **538:** 177–185, 1991.

ARANEDA, R., AND ANDRADE, R.: 5-Hydroxytryptamine-2 and 5-hydroxytryptamine-1A receptor mediate opposing responses on membrane excitability in rat association cortex. Neuroscience **40:** 399–412, 1991.

ARANEDA, R. C., AND ANDRADE, R.: 5-HT_2 receptors in rat prefrontal cortex. Soc. Neurosci. Abstr. **14:** 846, 1988.

ARANGO, V., ERNSBERGER, P., MARZUK, P. M., CHEN, J-S., TIERNEY, H., STANLEY, M., REIS, D. J., AND MANN, J. J.: Autoradiographic demonstration of increased serotonin 5-HT_2 and beta-adrenergic receptor binding sites in the brain of suicide victims. Arch. Gen. Psychiatry **47:** 1038–1047, 1990.

ARIANI, K., HAMBLIN, M. W., TAN, G. L., STRATFORD, C. A., AND CIARANELLO, R. D.: G protein dependent alterations in [^{125}I]-iodocyspindolol and (+)cyanopindolol binding at 5-HT_{1B} binding sites in rat brain membranes. Neurochem. Res. **14:** 835–843, 1989.

ARNT, J., AND HYTTEL, J.: Facilitation of 8-OH-DPAT-induced forepaw treading of rats by the 5-HT_2 agonist DOI. Eur. J. Pharmacol. **161:** 45–51, 1989.

ARORA, R. C., AND MELTZER, H. Y.: Serotonergic measures in the brains of suicide victims: 5-HT_2 binding sites in the frontal cortex of suicide victims and control subjects. Am. J. Psychiatry **146:** 730–736, 1989.

ASHBY, C. R., MINABE, Y., EDWARDS, E., AND WANG, R. Y.: 5-HT_3-like receptors in the rat medial prefrontal cortex: an electrophysiological study. Brain Res. **550:** 181–191, 1991.

ASHBY, C. R., JR., EDWARDS, E., MINABE, Y., AND WANG, R. Y.: Functional characterization of 5-HT_3-like receptors in the rat medial prefrontal cortex: biochemical and electrophysiological studies. Eur. J. Pharmacol. **183:** 1958–1959, 1990.

ASHKENAZI, A., WINSLOW, J. W., PERALTA, E. G., PETERSON, G. L., SCHIMERLICK, M. I., CAPON, D. J., AND RAMACHANDAM, J.: An M2 muscarinic receptor subtype coupled to both adenylate cyclase and phosphoinositide turnover. Science **238:** 672–675, 1987.

BACKUS, L. I., SHARP, T., AND GRAHAME-SMITH, D. G.: Behavioural evidence for a functional interaction between central 5-HT_2 and 5-HT_{1A} receptors. Br. J. Pharmacol. **100:** 793–799, 1990.

BAGDY, G., SZEMEREDI, K., AND MURPHY, D. L.: Marked increases in plasma catecholamine concentrations precede hypotension and bradycardia caused by 8-OH-DPAT in conscious rats. J. Pharm. Pharmacol. **41:** 270–272, 1989.

BARBACCIA, M. L., BRUNELLO, N., CHUANG, D. M., AND COSTA, E.: Serotonin-elicited amplification of adenylate cyclase activity in hippocampal membranes from adult rat. J. Neurochem. **40:** 1671–1679, 1983a.

BARBACCIA, M. L., AND COSTA, E.: Endogenous ligands for the [^{3}H]imipramine and [^{3}H]ketanserin recognition sites. Clin. Neuropharmacol. **9** (suppl. **4**)**:** 223–225, 1986.

BARBACCIA, M. L., GANDOLFI, O., CHUANG, D.-M., AND COSTA, E.: Differences in the regulatory adaptation of the 5-HT_2 recognition sites labelled by [^{3}H] mianserin or [^{3}H]ketanserin. Neuropharmacology **22:** 123–126, 1983b.

BARNES, J. M., BARNES, N. M., CHAMPANERIA, S., COSTALL, B., AND NAYLOR, R. J.: Characterization and autoradiographic localisation sites identified with [^{3}H]-(S)-zacopride in the forebrain of the rat. Neuropharmacology **29:** 1037–1045, 1990a.

BARNES, J. M., BARNES, N. M., COSTALL, B., IRONSIDE, J. W., AND NAYLOR, R. J.: Identification and characterization of 5-HT_3 recognition sites in human brain tissue. J. Neurochem. **53:** 1787–1793, 1989a.

BARNES, J. M., BARNES, N. M., COSTALL, B., NAYLOR, R. J., AND TYERS, M. B.: 5-HT_3 receptors mediate inhibition of acetylcholine release in cortical tissue. Nature **338:** 762–763, 1989b.

BARNES, J. M., COSTALL, B., COUGHLAN, J., DOMENEY, A. M., GERRARD, P. A., KELLY, M. E., NAYLOR, R. J., ONAIVI, E. S., TOMKINS, D. M., AND TYERS, M. B.: The effects of ondansetron, a 5-HT_3 receptor antagonist, on the cognition in rodents and primates. Pharmacol. Biochem. Behav. **35:** 955–962, 1990b.

BARNES, N. M., COSTALL, B., AND NAYLOR, R. J.: [^{3}H]Zacopride, ligand for the identification of 5-HT_3 recognition sites. J. Pharm. Pharmacol. **40:** 548–551, 1988a.

BARNES, N. M., COSTALL, B., NAYLOR, R. J., AND TATTERSALL, F. D.: Identification of 5-HT_3 recognition sites in the ferret area postrema. J. Pharm. Pharmacol. **40:** 586–588, 1988b.

BARONE, P., ATGER, F., MARTIN, P., PUESH, A., AND FILLION, G.: Increased number of 5-HT_2 receptors in the learned helplessness paradigm. Eur. J. Pharmacol. **183:** 1900, 1990.

BATTAGLIA, G., NORMAN, A. B., AND CREESE, I.: Differential serotonin-2 receptor recovery in mature and senescent rat brain after irreversible receptor modification: effect of chronic reserpine treatment. J. Pharmacol. Exp. Ther. **243:** 69–75, 1987.

BATTAGLIA, G., SHANNON, M., AND TITELER, M.: Guanyl nucleotide and divalent cation regulation of cortical S2 serotonin receptors. J. Neurochem. **43:** 1213–1219, 1984.

BAX, W. A., VAN HEUVEN-NOLSEN, D., BOS, E., SIMOONS, M. L., AND SAXENA, P. R.: 5-HT receptors and a receptor resembling the 5-HT_{1D} receptor subtype mediate contractions in human saphenous vein. Br. J. Pharmacol. **104:** 99P, 1992.

BAXTER, G. S., CRAIG, D. A., AND CLARKE, D. E.: 5-HT_4 receptors mediate relaxation of the rat oesophageal tunica muscularis mucosae. Naunyn Schmiedebergs Arch. Pharmacol. **343:** 439–446, 1991.

BEAULIEU, S., DI PAOLO, T., AND BARDEN, N.: Control of ACTH secretion by the central nucleus of the amygdala: implication of the serotonergic system and its relevance to the glycocorticoid delayed negative feedback mechanism. Neuroendocrinology **44:** 247–254, 1986.

BECK, S. G., CLARK, W. P., AND GOLDFARD, J.: Chronic estrogen effects on 5-HT mediated responses in hippocampal pyramidal cells of female rats. Neurosci. Lett. **106:** 181–187, 1989.

BEDARD, P., AND PYCOCK, C. J.: "Wet-dog" shake behavior in the rat: a possible quantitative model of central 5-hydroxytryptamine activity. Neuropharmacology **16:** 663–670, 1977.

BEER, M., KENNETT, G. A., AND CURZON, G.: A single dose of 8-OH-DPAT reduces raphe binding of [^{3}H]8-OH-DPAT and increases the effect of raphe stimulation of 5-HT metabolism. Eur. J. Pharmacol. **178:** 179, 1990.

BEER, M. S., STANTON, J. A., BEVAN, Y., CHAUHAN, N. S., AND MIDDLEMISS, D. N.: An investigation of the 5-HT_{1D} receptor binding affinity of 5-hydroxytryptamine, 5-carboxyamidotryptamine and sumatriptan in the central nervous system of seven species. Eur. J. Pharmacol. **213:** 193–197, 1992.

BENDOTTI, C., AND SAMANIN, R.: 8-OH-DPAT elicits feeding in free feeding rats by acting on central serotonin neurons. Eur. J. Pharmacol. **121:** 147–150, 1986.

BENDOTTI, C., AND SAMANIN, R.: The role of putative 5-HT_{1A} and 5-HT_{1B} receptors in the control of feeding in rats. Life Sci. **41:** 635–642, 1987.

BENEKE, M., KÜMMEL, B., AND SPECJTMEYER, H.: Treatment of anxiety neurosis with ipsapirone. Psychopharmacology **96** (suppl.): 353, 1988.

BENLOUCIF, S., AND GALLOWAY, M. P.: Facilitation of dopamine release in vivo by serotonin agonists: studies with microdialysis. Eur. J. Pharmacol. **200:** 1–8, 1991.

BENNETT, J. P., AND SNYDER, S. H.: Stereospecific binding of *d*-lysergic acid diethylamide (LSD) to brain membranes: relationship to serotonin receptors. Brain Res. **94:** 523–544, 1975.

BENNETT, J. P., AND SNYDER, S. H.: Serotonin and lysergic acid diethylamide binding in rat brain membrane. Relationship to postsynaptic serotonin receptors. Mol. Pharmacol. **12:** 373–389, 1976.

BENOVIC, J. R., BOUVIER, M., CARON, M. G., AND LEFKOWITZ, R. J.: Regulation of adenylyl cyclase-coupled beta-adrenergic receptors. Annu. Rev. Cell Biol. **4:** 405–428, 1988.

BENTON, D., AND NASTITI, K.: The influence of psychotropic drugs on the ultrasonic calling of mouse pups. Psychopharmacology **95:** 99–102, 1988.

BERENDSEN, H. H. G., AND BROEKKAMP, C. L. E.: Drug induced penile erections in rats: indications of serotonin-1B receptor mediation. Eur. J. Pharmacol. **135:** 279–287, 1987.

BERENDSEN, H. H. G., AND BROEKKAMP, C. L. E.: Behavioural evidence for functional interactions between 5-HT receptor subtypes in rats and mice. Br. J. Pharmacol. **101:** 667–673, 1990.

BERENDSEN, H. H. G., AND BROEKKAMP, C. L. E.: A peripheral 5-HT_{1D}-like receptor involved in serotonergic induced hindlimb scratching in rats. Eur. J. Pharmacol. **194:** 201–208, 1991a.

BERENDSEN, H. H. G., AND BROEKKAMP, C. L. E.: Age dependence of 5-methoxytryptamine-induced scratching in rats. Eur. J. Pharmacol. **199:** 107–109, 1991b.

BERGE, O. G.: Effects of 5-HT receptor agonists and antagonists on a reflex response to radiant heat in normal and spinally transected rats. Pain **13:** 253–266, 1982.

BIANCHI, C., SINISCALCHI, A., AND BEANI, L.: Effect of 5-HT on [^{3}H]-acetylcholine release from guinea pig striatal slices. Br. J. Pharmacol. **97:** 213–221, 1989.

BIEGON, A., GRINSPOON, A., BLUMENFELD, B., BLEICH, A., APTER, A., AND MESTER, R.: Increased serotonin 5-HT_2 receptor binding on blood platelets of suicidal men. Psychopharmacology **100:** 165–167, 1990.

BIEGON, A., AND ISRAELI, M.: Quantitative autoradiographic analysis of the effects of electroconvulsive shock on serotonin-2 receptors in male and female rats. J. Neurochem. **48:** 1386–1391, 1987.

BIEGON, A., KARGMAN, S., AND SNYDER, L.: Characterization and localization of serotonin receptors in human brain post-mortem. Brain Res. **363:** 91–98, 1986.

BIEGON, A., WEIZMAN, A., KARP, L., RAM, A., TIANO, S., AND WOLFF, M.: Serotonin 5-HT_2 receptor binding on blood platelets—a peripheral marker for depression. Life Sci. **41:** 2485–2492, 1987.

BILL, D. J., FORSTER, E. A., AND FLETCHER, A.: Behavioral effects of GR 43175 and other 5-HT_1 agonists following central administration in the mouse. Br. J. Pharmacol. **96:** 305P, 1989.

BILL, D. J., KNIGHT, M., FORSTER, E. A., AND FLETCHER, A.: Direct evidence for an important species difference in the mechanism of 8-OH-DPAT-induced hypothermia. Br. J. Pharmacol. **103:** 1857–1864, 1991.

BIRNBAUMER, L., ABRAMOWITZ, J., AND BROWN, A. M.: Receptor-effector coupling by G-proteins. Biochem. Biophys. Acta **1031:** 163–224, 1990.

BJÖRK, L., CORNFIELD, J., NELSON, D. L., HILLVER, S.-E., ANDÉN, N., LEWANDER, T., AND HACKSELL, U.: Pharmacology of the novel 5-hydroxytryptamine-1A receptor antagonist (S)-5-fluoro-8-hydroxy-2-(dipropylamino)tetralin: inhibition of (R)-8-hydroxy-2-(dipropylamino)tetralin-induced effects. J. Pharmacol. Exp. Ther. **258:** 58–65, 1991.

BLACKSHEAR, A., FRIEDMAN, R. L., AND SANDERS-BUSH, E.: Acute and chronic effects of serotonin (5HT) antagonists on serotonin binding sites. Naunyn Schmiedebergs Arch. Pharmacol. **324:** 125–129, 1983.

BLACKSHEAR, M. A., AND SANDERS-BUSH, E.: Serotonin receptor sensitivity after acute and chronic treatment with mianserin. J. Pharmacol. Exp. Ther. **221:** 303–308, 1982.

BLACKSHEAR, M. A., STERANKA, L. R., AND SANDERS-BUSH, E.: Multiple serotonin receptors: regional distribution and effect of raphe lesions. Eur. J. Pharmacol. **76:** 325–334, 1981.

BLANCHARD, D. C., RODGERS, R. J., HENDRIE, C. A., AND HORI, K.: "Taming" of wild rats (*rattus rattus*) by 5-HT_{1A} agonists buspirone and gepirone. Pharmacol. Biochem. Behav. **31:** 269–278, 1988.

BLANDINA, P., GOLDFARB, J., CRADDOCK-ROYAL, B., AND GREEN, J. P.: Release of endogenous dopamine by stimulation of 5-HT_3 receptors in rat striatum. J. Pharmacol. Exp. Ther. **251:** 803–809, 1989.

BLANDINA, P., GOLDFARB, J., AND GREEN, J. P.: Activation of a 5-HT_3 receptor releases dopamine from rat striatal slice. Eur. J. Pharmacol. **155:** 349–350, 1988.

BLANDINA, P., GOLDFARB, J., WALCOTT, J., AND GREEN, J. P.: Serotonergic modulation of the release of endogenous norepinephrine from rat hypothalamic slices. J. Pharmacol. Exp. Ther. **256:** 341–347, 1991.

BLIER, P.: Terminal serotonin autoreceptor function in the rat hippocampus is not modified by pertussis and cholera toxins. Naunyn Schmiedebergs Arch. Pharmacol. **344:** 160–166, 1991.

BLIER, P., AND DE MONTIGNY, C.: Electrophysiological investigations on the effect of repeated zimelidine administrations on serotonergic neurotransmission in the rat. J. Neurosci. **3:** 1270–1278, 1983.

BLIER, P., AND DE MONTIGNY, C.: Serotonergic but not noradrenergic neurons in rat central nervous system adapt to long-term treatment with monoamines oxidase inhibitors. Neuroscience **16:** 949–955, 1985.

BLIER, P., AND DE MONTIGNY, C.: Effect of chronic tricyclic antidepressant treatment on the serotonergic autoreceptor: a microiontophoretic study in the rat. Naunyn Schmiedebergs Arch. Pharmacol. **314:** 123, 1987a.

BLIER, P., AND DE MONTIGNY C.: Modification of 5-HT neuron properties by sustained administration of the 5-HT_{1A} agonist gepirone: electrophysiological studies in the rat brain. Synapse **1:** 470–480, 1987b.

BLIER, P., AND DE MONTIGNY, C.: Electrophysiological investigation of the adaptive response of the 5-HT system to the administration of 5-HT_{1A} receptor agonists. J. Cardiovasc. Pharmacol. **15** (suppl. 7): S42–S48, 1990.

BLIER, P., DE MONTIGNY, C., AND CHAPUT, Y.: Electrophysiological assessment of the effects of antidepressant treatments on the efficacy of 5-HT neurotransmission. Clin. Neuropharmacol. **11** (suppl. 2): S1–S10, 1988.

BLIER, P., SERRANO, A., AND SCATTON, B.: Differential responsiveness of the rat dorsal and median raphe 5-HT systems to 5-HT_1 receptor agonists and *p*-chloroamphetamine. Synapse **5:** 120–133, 1990.

BLUE, M. E., YAGALOFF, K. A., MAMOUNAS, L. A., HARTIG, P. R., AND MOLIVER, M. E.: Correspondence between 5-HT_2 receptors and serotonergic axons in rat neocortex. Brain Res. **3:** 315–328, 1988.

BLUNDELL, J. E.: Is there a role for 5-hydroxytryptamine in feeding? Int. J. Obesity **1:** 15–42, 1977.

BLUNDELL, J. E.: Serotonin and appetite. Neuropharmacology **23:** 1537–1551, 1984.

BOBKER, D. H., AND WILLIAMS, J. T.: Serotonin augments the cationic current Ih in central neurons. Neuron **2:** 1535–1540, 1989.

BOCKAERT, J., DUMUIS, A., BOUHELAL, R., SEBBEN, M., AND CORY, R. N.: Piperazine derivates including the putative anxiolytic drugs, buspirone and ipsapirone, are agonists at 5-HT_{1A} receptors negatively coupled with adenylate cyclase in hippocampal neurons. Naunyn Schmiedebergs Arch. Pharmacol. **335:** 588–592, 1987.

BOCKAERT, J., FOZARD, J. R., DUMUIS, A., AND CLARKE, D. E.: The 5-HT_4 receptor: a place in the sun. Trends Pharmacol. Sci. **13:** 141–145, 1992.

BOCKAERT, J., SEBBEN, M., AND DUMUIS, A.: Pharmacological characterization of 5-HT_4 (5-HT_4) receptors positively coupled to adenylate cyclase in adult guinea pig hippocampal membranes: effect of substituted benzamide derivatives. Mol. Pharmacol. **37:** 408–411, 1990.

BODDEKE, H. W. G. M., FARGIN, A., RAYMOND, J. R., SCHOEFFTER, P., AND HOYER, D.: Agonist/antagonist interactions with cloned human 5-HT_{1A} receptors: variations in intrinsic activity studied in transfected HeLa cells. Naunyn Schmiedebergs Arch. Pharmacol. **345:** 257–263, 1992.

BOGDANSKI, D. F., PLETSCHER, A., BRODIE, B. B., AND UDENFRIEND, S.: Identification and assay of serotonin in brain. J. Pharmacol. Exp. Ther. **117:** 88–98, 1956.

BÖHM, C., PLACCHI, M., STALLONE, F., GAMMANS, R. E., AND ALMS, D. R.: A double-blind comparison of buspirone, clobazam, and placebo in patients with anxiety. J. Clin. Psychopharmacol. **10** (suppl.): 38S–42S, 1990.

BOLANOS, F., AND FILLION, G.: Minaprine antagonises the serotonergic inhibitory effect of TFMPP on acetylcholine release. Eur. J. Pharmacol. **168:** 87–92, 1989.

BOLANOS, F. J., SCHECHTER, L. E., MIQUEL, M. C., EMERIT, M. B., RUMIGNY, J. F., AND HAMON, M., AND GOZLAN, H.: Common pharmacological and physicochemical properties of 5-HT_3 binding sites in the rat cerebral cortex and NG 108–15 clonal cells. Biochem. Pharmacol. **40:** 1541–1550, 1990.

BOUHELAL, R., SMOUNYA, L., AND BOCKAERT, J.: 5-HT_{1B} receptors are negatively coupled with adenylate cyclase in rat subtantia nigra. Eur. J. Pharmacol. **151:** 189–196, 1988.

BOULENGUEZ, P., CHAUVEAU, J., SEGU, L., MOREL, A., DELAAGE, M., AND LANOIR, J.: Pharmacological characterization of serotonin-*O*-carboxymethyl-glycyl-tyrosinamide, a new selective indolic ligand for 5-hydroxytryptamine 5-HT_{1B} and 5-HT_{1D} binding sites. J. Pharmacol. Exp. Ther. **259:** 1360–1365, 1991a.

BOULENGUEZ, P., CHAUVEAU, J., SEGU, L., MOREL, A., LANOIR, J., AND DELAAGE, M.: A new 5-hydroxy-indole derivative with preferential affinity for 5-HT_{1B} binding sites. Eur. J. Pharmacol. **194:** 91–98, 1991b.

BOULENGUEZ, P., SEGU, L., CHAUVEAU, J., MOREL, A., LANOIR, J., AND DELAAGE, M.: Biochemical and pharmacological characterization of serotonin-*O*-carboxymethylglycyl[^{125}I]iodotyrosinamide, a new radioiodinate probe for 5-HT_{1B} and 5-HT_{1D} binding sites. J. Neurochem. **58:** 951–959, 1992.

BRADLEY, P. B., ENGEL, G., FENIUK, W., FOZARD, J. R., HUMPHREY, P. P. A., MIDDLEMISS, D. N., MYLECHARANE, E. J., RICHARDSON, B. P., AND SAXENA, P. R.: Proposals for the classification and nomenclature of functional receptors for 5-hydroxytryptamine. Neuropharmacology **25:** 563–576, 1986.

BRANCHEK, T. A., MAWE, G. M., AND GERSHON, M. D.: Characterization and localization of a peripheral neural 5-hydroxytryptamine receptor subtype (5-HT_{1P}) with a selective agonist, [^{3}H]5-hydroxyindalpine. J. Neurosci. **8:** 2582–2595, 1988.

BRECKENRIDGE, A. M., HOLLENBERG, N. K., AND OMAE, T.: The role of serotonin in cardiovascular disease. Drugs **36** (suppl. 1): 1–151, 1988.

BRODIE, T. G.: The immediate action of an intravenous injection of blood serum. J. Physiol. **26:** 48–71, 1900.

BRODIE, T. G., AND SHORE, P. A.: A concept for a role of serotonin and norepinephrine as chemical mediators in the brain. Ann. N. Y. Acad. Sci. 1957.

BROWN, A. M., PATCH, T. L., AND KAUMANN, A. J.: The antimigraine drugs ergotamine and dihydroergotamine are potent 5-HT_{1C} receptor agonists in piglet choroid plexus. Br. J. Pharmacol. **104:** 45–48, 1991.

BROWN, C. M., SMALL, C., AND SPEDDING, M.: 5-HT_{1A} receptor subtypes. *In* The Second International Union of Pharmacology Satellite Meeting on Serotonin, Basel, Switzerland, pp. 49, 1990.

BRUINVELS, A. T., LANDWEHRMEYER, B., WAEBER, C., PALACIOS, J. M., AND HOYER, D.: Homogeneous 5-HT_{1D} recognition sites in the human subtantia nigra identified with a new iodinated radioligand. Eur. J. Pharmacol. **202:** 89–91, 1991.

BRÜNING, G., KAULEN, P., SCHNEIDER, U., AND BAUMGARTEN, H. G.: Quantitative autoradiographic distribution and pharmacological characterization of [^{3}H]buspirone binding to sections from rat bovine and marmoset brain. J. Neural Transm. **78:** 131–144, 1989.

BUCHHEIT, K. H., COSTAL, B., ENGEL, G., GUNNING, S. J., NAYLOR, R. J., AND RICHAR, T.: 5-HT receptor antagonism by metoclopramide and ICS 205–930 in the guinea pig leads to enhancement of contractions of stomach muscle strips induced by electrical field stimulation and facilitation of gastric emptying in vivo. J. Pharm. Pharmacol. **37:** 664–667, 1985.

BUCHHEIT, K. H., GAMSE, R., AND PFANNKUCHE, H-J.: SDZ 205–557, a selective antagonist at 5-HT_4 receptors in the isolated guinea pig ileum. Eur. J. Pharmacol. **200:** 373–374, 1991.

BUCHHEIT, K.-H., GAMSE, R., AND PFANNKUCHE, H.-J.: SDZ 205–557, a selective, surmountable antagonist for 5-HT_4 receptors in the isolated guinea pig ileum. Naunyn Schmiedebergs Arch. Pharmacol. **345:** 387–393, 1992.

BUCK, F., MEYERHOF, W., WERR, H., AND RICHTER, D.: Characterization of N- and C-terminal deletion mutants of the rat serotonin-2 receptor in *Xenopus laevis* oocytes. Biochem. Biophys. Res. Commun. **178:** 1421–1428, 1991.

BUCKHOLTZ, N. S., ZHOU, D., AND FREEDMAN, D. X.: Serotonin-2 agonist administration down-regulates rat brain serotonin-2 receptors. Life Sci. **42:** 2439–2445, 1988.

BUNCE, K., TYERS M., AND BERANEK, P.: Clinical evaluation of 5-HT_3 receptor antagonists as anti-emetics. Trends Pharmacol. Sci. **12:** 46–48, 1991.

BUTLER, P. D., PRANZATELLI, M. R., AND BARKAI, A. I.: Regional central serotonin$_2$ receptor binding and phosphoinositide turnover in rats with 5,7-DHT lesions. Brain Res. Bull. **24:** 125–129, 1990.

BYER, J., GUTTERMAN, D. L., PLACHETKA, J. R., BHATTACHARYYA, H.: Dose response study for subcutaneous GR43175 in teh treatment of acute migraine. Cephalalgia **9** (suppl. 10): 349–350, 1989.

CARBONI, E., ACQUAS, E., FRAU, R., AND DI CHIARA, G.: Differential inhibitory effects of a 5-HT_3 antagonist on drug-induced stimulation of dopamine release. Eur. J. Pharmacol. **164:** 515–519, 1989a.

CARBONI, E., ACQUAS, E., LEONE, P., AND DI CHIARA, G.: 5-HT_3 receptor antagonists block morphine- and nicotine- but not amphetamine-induced reward. Psychopharmacology **97:** 175–178, 1989b.

CARLI, M., PRONTERA, C., AND SAMANIN, R.: Evidence that central 5-hydroxytryptaminergic neurones are involved in the anxiolytic activity of buspirone. Br. J. Pharmacol. **96:** 829–836, 1989.

CARLSSON, A., ADOLFSSON, R., AQUILONIUS, S. M., FOHFRIES, C. G., ORELAND, L., SVENNERHOLM, L., AND WINBLAD, B.: Biogenic amines in human brain in normal aging, senile dementia and chronic alcoholism. *In* Advances in Biochemical Psychopharmacology, ed. by M. Goldstein, D. B. Calne, A. N. Lieberman,and M. O. Thorner, vol.23, pp. 295–304, Raven Press, New York, 1980.

CARLSSON, M. A., AND ERIKSSON, E.: Comparison between male and female rats with respect to behavioral, biochemical, hypothermic and prolactin-releasing effect of 8-OH-DPAT. *In* Brain 5-HT_{1A} Receptors: Behavioral and Neurochemical Pharmacology, ed. by C. T. Dourish, S. Ahlenius, and P. H. Hutson, pp. 177–184, Ellis Horwood Ltd., Chichester, United Kingdom, 1987.

CARMICHAEL, J., CANTWELL, B. M. J., EDWARDS, C. M., RAPEPORT, W. G., AND HARRIS, A. L.: The serotonin type 3 receptor antagonist BRL 43694 and nausea and vomiting induced by cisplatin. Br. Med. J. **297:** 110–111, 1988.

CERVO, L., GRIGNASCHI, G., AND SAMANIN, R.: 8-OH-DPAT, a selective serotonin-1A receptor agonist, reduces the immobility of rats in the forced swimming test by acting on the nucleus raphe dorsalis. Eur. J. Pharmacol. **158:** 53–59, 1988.

CERVO, L., GRIGNASCHI, G., NOWAKOWSKA, E., AND SAMANIN, R.: TFMPP in the ventral tegmental area reduces the effect of desipramine in the forced swimming test in rats: possible involvement of serotonin receptors. Eur. J. Pharmacol. **171:** 119–125, 1989.

CERVO, L., AND SAMANIN, R.: Potential antidepressant properties of 8-OH-DPAT, a selective serotonin1A receptor agonist. Eur. J. Pharmacol. **144:** 223–229, 1987.

CEULEMENS, D. L., HOPPENBROUWERS, M. L., GELDERS, Y. G., AND REYNTJENS, A. J.: The influence of ritanserin, a serotonin antagonist, in anxiety disorders: a double-blind placebo-controlled study versus lorazepam. Pharmacopsychiatry **18:** 303–305, 1985.

CHANGEUX, J. P.: The acetylcholine receptor an "allosteric" membrane protein. Harvey Lect. **75:** 85–254, 1981.

CHANGEUX, J. P., GIRAUDOT, J., AND DENNIS, M.: The nicotine acetylcholine receptor, molecular architecture a ligand-regulated ion channel. Trends Pharmacol. Sci. **8:** 465–472, 1987.

CHAOULOFF, F., BAUDRIE, V., AND LAUDE, D.: Evidence that 5-HT_{1A} receptors are involved in the adrenaline-releasing effects of 8-OH-DPAT in conscious rat. Naunyn Schmiedebergs Arch. Pharmacol. **341:** 381–384, 1990.

CHAOULOFF, F., AND JEANRENAUD, B.: 5-HT_{1A} and alpha$_2$-adrenergic receptors mediate the hyperglycemic and hypoinsulinemic effects of 8-OH-DPAT in the conscious rat. J. Pharmacol. Exp. Ther. **243:** 1159–1166, 1987.

CHAPUT, Y., ARANEDA, R. C., AND ANDRADE, R.: Pharmacological and functional analysis of a novel serotonin receptor in the rat hippocampe. Eur. J. Pharmacol. **182:** 441–456, 1990.

CHAPUT, Y., BLIER, P., AND DE MONTIGNY, C.: Acute and long term effects of antidepressant serotonin reuptake blockers on the efficacy of 5-HT neurotransmission: electrophysiological studies in the rat central nervous system. Adv. Biol. Psychiatry **17:** 1–17, 1988.

CHAPUT, Y., AND DE MONTIGNY, C.: Effects of the 5-hydroxytryptamine-1 receptor antagonist, BMY 7378, on 5-hydroxytryptamine neurotransmission: electrophysiological studies in the rat central nervous system. J. Pharmacol. Exp. Ther. **246:** 359–370, 1988a.

CHAPUT, Y., AND DE MONTIGNY, C.: Effects of the 5-HT_1 receptor antagonist, BMY 7378, on the 5-HT neurotransmission: electrophysiological studies in the rat central nervous systems. J. Pharmacol. Exp. Ther. **246:** 359–370, 1988b.

CHAPUT, Y., DE MONTIGNY, C., AND BLIER, P.: Effects of a selective 5-HT reuptake blocker, citalopram, on the sensitivity of 5-HT-autoreceptors: electrophysiological studies in the rat brain. Naunyn Schmiedebergs Arch. Pharmacol. **333:** 342–348, 1986.

CHARLETY, P. J., ASTON-JONES, G., AKAOKA, H., BUDA, M., AND CHOUVET, G.: Participation des récepteurs 5-HT_{1A} dans la diminution par la sérotonine de l'excitation des neurones du locus coeruleus évoquée par la glutamate. C. R. Acad. Sci. Paris **312:** 421–426, 1991.

CHARLI, J. L., ROTZSTEIN, W. H., PATTON, E., AND KORDON, C.: Effect of neurotransmitters on in vitro release of luteinizing-hormone-releasing hormone from the medio-basal hypothalamus of male rats. Neurosci. Lett. **10:** 159–163, 1978.

CHARNEY, D. S., GOODMAN, W. K., PRICE, L. H., WOODS, S. W., RASMUSSEN, S. A., AND HENINGER, G. R.: Serotonin function in obsessive-compulsive disorder. Arch. Gen. Psychiatry **45:** 177–185, 1988.

CHARNEY, D. S., WOODS, S. W., GOODMAN, W. K., AND HENINGER, G. R.: Serotonin function in anxiety. II. Effects of the serotonin agonist m-CPP in panic disorder patients and healthy subjects. Psychopharmacology **92:** 14–24, 1987.

CHEETHAM, S. C., CROMPTON, M. R., KATONA, C. L. E., AND HORTON, R. W.: Brain 5-HT_2 receptor binding sites in depressed suicide victims. Brain Res. **443:** 272–280, 1988.

CHEETHAM, S. C., CROMPTON, M. R., KATONA, C. L. E., AND HORTON, R. W.: 5-HT_1 and 5-HT_{1A} binding sites in depressed suicides. Br. J. Pharmacol. **96:** 1, 1989.

CHEETHAM, S. C., CROMPTON, M. R., KATONA, C. L. E., AND HORTON, R. W.: Brain 5-HT_1 binding sites in depressed suicides. Psychopharmacology **102:** 544–548, 1990.

CHENG, A. V. T., FERRIER, I. N., MORRIS, C. M., JABEEN, S., SAHGAL, A., MCKEITH, I. G., EDWARDSON, J. A., PERRY, R. H., AND PERRY, E. K.: Cortical serotonin-S2 receptor binding in Lewy body dementia, Alzheimer's and Parkinson's diseases. J. Neurol. Sci. **106:** 50–55, 1991.

CHOJNACKA-WOJCIK, E., AND PRZEGALINSKI, E.: Evidence for the involvement of 5-HT_{1A} receptors in the anticonflict effect of ipsapirone in rats. Neuropharmacology **30:** 703–709, 1991.

CHOJNACKA-WOJCIK, E., TATARCZYNSKA, E., GOLEMBIOWSKA, K., AND PRZEGALINSKI, E.: Involvement of 5-HT_{1A} receptors in the antidepressant-like activity of gepirone in the forced swimming test in rat. Neuropharmacology **30:** 711–717, 1991.

CHOQUET, D., AND KORN, H.: Dual effects of serotonin on a voltage-gated conductance in lymphocytes. Proc. Natl. Acad. Sci. USA **85:** 4557–4561, 1988.

CHUBAKOV, A. R., GROMOVA, E. A., KONOVALOV, G. V., SARKISOVA, E. F., AND CHUMASOV, E. I.: The effects of serotonin on the morpho-functional development of rat cerebral neocortex in tissue culture. Brain Res. **369:** 285–297, 1986.

CHUGH, Y., SAHA, N., SANKARANAYANAN, A., AND SHARMA, P. L.: Memory enhancing effects of granisetron (BRL 43694) in a passive avoidance task. Eur. J. Pharmacol. **203:** 121–123, 1991.

CIARANELLO, R. D., TAN, G. L., AND DEAN, R.: G protein-linked serotonin receptors in mouse kidney exhibit identical properties to 5-HT_{1B} receptors in brain. J. Pharmacol. Exp. Ther. **252:** 1347–1354, 1990.

CLARKE, W. P., DE VIVO, M., BECK, S. G., MAAYANI, S., AND GOLDFARD, J.: Serotonin decreases population spike amplitude in hippocampal cells through a pertussis toxin substrate. Brain Res. **410:** 357–361, 1987.

CLARKE, W. P., AND GOLDFARD, J.: Estrogen enhances a 5-HT_{1A} response in hippocampal slices from female rats. Eur. J. Pharmacol. **160:** 195–197, 1989.

CLARKE, W. P., AND MAAYANI, S.: Estrogen effects on 5-HT_{1A} receptors in hippocampal membranes from ovariectomized rats: functional and binding studies. Brain Res. **518:** 287–291, 1990.

CLAUSTRE, Y., BENAVIDES, J., AND SCATTON, B.: 5-HT_{1A} receptor agonists inhibit carbachol-induced stimulation of phosphoinositide turnover in the rat hippocampus. Eur. J. Pharmacol. **149:** 149–153, 1988a.

CLAUSTRE, Y., BENAVIDES, J., AND SCATTON, B.: Potential mechanisms involved in the negative coupling between serotonin 5-HT_{1A} receptors and carbachol-stimulated phosphoinositide turnover in the rat hippocampus. J. Neurochem. **56:** 1276–1285, 1991.

CLAUSTRE, Y., ROUQUIER, L., AND SCATTON, B.: Pharmacological characterization of serotonin-stimulated phosphoinositide turnover in brain regions of the immature rat. J. Pharmacol. Exp. Ther. **244:** 1051–1056, 1988b.

CLOEZ, I., HAREL-DUPAS, C., AND FILLION, G.: Serotonergic modulation of [^{3}H] GABA release from guinea-pig hippocampal synaptosomes. Fundam. Clin. Pharmacol. **4:** 566, 1990.

CLOSSE, A.: [^{3}H]-Mesulergine: a selective ligand for serotonin$_2$ receptors. Life Sci. **32:** 2485–2495, 1983.

COCCARO E. F.: Central serotonin and impulsive aggression. Br. J. Psychiatry **155** (suppl. 8)**:** 52–62, 1989.

COCCARO, E. F., AND ASTILL, J. L.: Central serotonergic function in parasuicide. Progr. Neuropsychopharmacol. Biol. Psychiatry **14:** 663–674, 1990.

COLINO, A., AND HALLIVELL, J. V.: Differential modulation of three separate K-conductances in hippocampal CA1 neurons by serotonin. Nature **328:** 73–76, 1987.

COLPAERT, F. C., AND JANSSEN, P. A. J.: A characterization of LSD-antagonist effects of pirenperone in the rat. Neuropharmacology **22:** 1001–1005, 1983a.

COLPAERT, F. C., AND JANSSEN, P. A. J.: The head-twich response to intraperitoneal injection of 5-hydroxytryptophan in the rat: antagonist effects of purported 5-hydroxytryptamine antagonists and of pirenperone, a LSD antagonist. Neuropharmacology **22:** 993–1000, 1983b.

COLPAERT, F. C., MEERT, T. F., NIEMEGEERS, C. J. E., AND JANSSEN, P. A. J.: Behavioral and 5-HT antagonist effects of ritanserin: a pure and selective antagonist of LSD discrimination in rat. Psychopharmacology **86:** 45–54, 1985.

CONN, P. J., JANOWSKY, A., AND SANDERS-BUSH, E.: Denervation supersensitivity of 5-HT$_{1C}$ receptors in rat choroid plexus. Brain Res. **400:** 396–398, 1987.

CONN, P. J., AND SANDERS-BUSH, E.: Selective 5-HT$_2$ antagonists inhibit serotonin stimulated phosphatidyl inositol metabolism in cerebral cortex. Neuropharmacology **23:** 993–996, 1984.

CONN, P. J., AND SANDERS-BUSH, E.: Serotonin-stimulated phosphoinositide turnover: mediation by the S2 binding site in rat cerebral cortex but not in subcortical regions. J. Pharmacol. Exp. Ther. **234:** 195–203, 1985.

CONN, P. J., AND SANDERS-BUSH, E.: Regulation of serotonin-stimulated phosphoinositide hydrolysis: relation to the serotonin 5-HT$_2$ binding site. J. Neurosci. **6:** 3669–3675, 1986a.

CONN, P. J., AND SANDERS-BUSH, E.: Agonist-induced phosphoinositide hydrolysis in choroid plexus. J. Neurochem. **47:** 1754–1760, 1986b.

CONNELL, L. A., AND WALLIS, D. I.: 5-Hydroxytryptamine depolarizes neonatal rat motor-neurones through a receptor unrelated to an identified binding site. Neuropharmacology **28:** 625–634, 1989.

CONNOR, H. E., FENIUK, W., AND HUMPHREY, P. P. A.: Characterization of 5-HT receptors mediating contraction of canine and primate basilar artery by use of GR 43175, a selective 5-HT$_1$-like receptor agonist. Br. J. Pharmacol. **96:** 379–387, 1989.

COOK, E. H.: Autism: review of neurochemical investigation. Synapse **6:** 292–308, 1990.

CORNFIELD, L. J., LAMBERT, G., ARVIDSSON, L.-E., MELLIN, C., VALLGARDA, J., HACKSELL, U., AND NELSON, D. L.: Intrinsic activity of enantiomers of 8-OH-DPAT and its analogs at 5-HT$_{1A}$ receptors that are negatively coupled to adenylate cyclase. Mol. Pharmacol. **39:** 780–787, 1991.

CORY, R. N., BERTA, P., HAIECH, J., AND BOCKAERT, J.: 5-HT$_2$ receptor-stimulated inositol phosphate formation in rat aorta myocytes. Eur. J. Pharmacol. **131:** 153–157, 1986.

CORY, R. N., ROUOT, B., GUILLION, G., SLADECZEK, F., BALESTRE, M. N., AND BOCKAERT, J.: The 5-HT$_2$ receptor stimulates inositol phosphate formation in intact and broken WRK1 cells: determination of occupancy-response relationships for 5-HT agonists. J. Pharmacol. Exp. Ther. **241:** 258–267, 1987.

COSSERY, J. M., GOZLAN, H., SPAMPINATO, U., PERDIKAKIS, C., GUILLAUMET, G., PICHAT, L., AND HAMON, M.: The selective labelling of central 5-HT$_{1A}$ receptor binding site by [^{3}H]5-methoxy-3-(di-n-propylamino)chroman. Eur. J. Pharmacol. **140:** 143–155, 1987.

COSTALL, B., DOMENEY, A. M., GERRARD, P. A., KELLY, M. E., NAYLOR, R. J., AND TYERS, M. B.: Inhibition by ondansetron of behavioural effects in the rat which follow withdrawal from treatment with drugs of abuse. Br. J. Pharmacol. **96:** 340P, 1989a.

COSTALL, B., DOMENEY, A. M., GERRARD, P. A., KELLY, M. E., AND NAYLOR, R. J.: Zacopride: anxiolytic profile in rodent and primate models of anxiety. J. Pharm. Pharmacol. **40:** 302–305, 1988a.

COSTALL, B., DOMENEY, A. M., GUNNING, S. J., NAYLOR, R. J., NORIA, V., OWERA-ATEPO, J. B., SIMPSON, K. M., TAN, C. C. W., AND TATTERSALL, F. D.: The action of zacopride to enhance gastric emptying and antagonise emesis. Neuropharmacology **26:** 669–677, 1987a.

COSTALL, B., DOMENEY, A. M., AND NAYLOR, R. J.: Behavioural and biochemical consequences of persistent over stimulation of meso-limbic dopamine system of the rat and marmoset brain. Br. J. Pharmacol. **92:** 881–894, 1987b.

COSTALL, B., DOMENEY, A. M., NAYLOR, R. J., AND TATTERSALL, F. D.: 5-hydroxytryptamine M-receptor antagonism to prevent cisplatin-induced emesis. Neuropharmacology **25:** 959–961, 1986.

COSTALL, B., DOMENEY, A. M., NAYLOR, R. J., AND TYERS, M. B.: Effects of the 5-HT$_3$ receptor antagonist GR 38032F, on raised dopaminergic activity in the mesolimbic system of the rat and marmoset brain. Br. J. Pharmacol. **92:** 881–894, 1987c.

COSTALL, B., DOMENEY, A. M., NAYLOR, R. J., AND TYERS, M. B.: Inhibition by 5-HT$_3$ antagonists of hyperactivity caused by dopamine infusion into the rat nucleus accumbens. Br. J. Pharmacol. **93:** 194P, 1987d.

COSTALL, B., JONES, B. J., KELLY, E. M., NAYLOR, R. J., OAKLEY, N. R., ONAIVI, E. S., AND TYERS, M. B.: The effects of ondansetron (GR 38032F) in rats and mice treated subchronically with diazepam. Pharmacol. Biochem. Behav. **34:** 769–778, 1989b.

COSTALL, B., KELLY, M. E., NAYLOR, R. J., AND ONAIVI, E. S.: Actions of buspirone in a putative model of anxiety in the mouse. J. Pharm. Pharmacol. **40:** 494–500, 1988b.

COSTALL, B., KELLY, M. E., NAYLOR, R. J., ONAIVI, E. S., AND TYERS, M. B.: Neuroanatomical sites of action of 5-HT$_3$ receptor agonist and antagonists for alteration of aversive behaviour in the mouse. Br. J. Pharmacol. **96:** 325, 1989c.

COSTALL, B., NAYLOR, R. J., AND TYERS, M. B.: The psychopharmacology of 5-HT$_3$ receptors. Pharmacol. Ther. **47:** 181–202, 1990.

COTT, J. M., KURTZ, N. M., ROBINSON, D. S., LANCASTER, S. P., AND COPP, J. E.: A 5-HT$_{1A}$ ligand with both antidepressant and anxiolytic properties. Psychopharmacol. Bull. **24:** 164–167, 1988.

COUGHLIN, S. R., MOSKOWITZ, M., AND LEVINE, L.: Identification of a serotonin type-2 receptor linked to prostacyclin synthesis in vascular smooth muscle cells. Biochem. Pharmacol. **33:** 692–695, 1984.

COWEN, P. J.: Recent views on the role of 5-HT in depression. Curr. Opinion Psychiatry **1:** 56–59, 1988.

COWEN, P. J.: A role for 5-HT in the action of antidepressant drugs. Pharmacol. Ther. **46:** 43–51, 1990.

COWEN, P. J., ANDERSON, I. M., AND GARTSIDE, S. E.: Endocrinological responses to 5-HT. Ann. N. Y. Acad. Sci. **600:** 250–259, 1990.

CRAIG, D. A., AND CLARKE, D. E.: Pharmacological characterization of a neuronal receptor for 5-HT in guinea pig ileum with properties similar to 5-HT$_4$ receptor. J. Pharmacol. Exp. Ther. **252:** 1378–1386, 1990.

CRITCHLEY, M. A. E., AND HANDLEY, S. L.: Effects in the X-maze anxiety model of agents acting at 5-HT$_1$ and 5-HT$_2$ receptors. Psychopharmacology **93:** 502–506, 1987.

CROSS, A. J.: Serotonin in Alzheimer-type dementia and other dementing illnesses. Ann. N. Y. Acad. Sci. **600:** 405–417, 1990.

CROSS, A. J.: Serotonin in neurodegenerative disorders. *In* Neuronal Serotonin, ed. by N. N. Osborne and M. Hamon, pp. 231–245, Wiley and Sons Ltd., New York, 1988.

CROSS, A. J., SLATER, P., PERRY, E. K., AND PERRY, R. H.: An autoradiographic analysis of serotonin receptors in human temporal cortex: changes in Alzheimer-type dementia. Neurochem. Int. **13:** 89–96, 1988.

CROW, T. J., CROSS, A. J., COOPER, S. J., DEAKIN, J. F. W., FERRIER, I. N., JOHNSON, J. A., JOSEPH, M. H., OWEN, F., POULTER, M., LOFTHOUSE, R., CORSELLIS, J. A. N., CHAMBERS, D. R., BLESSED, G., PERRY, E. K., PERRY, R. H., AND TOMLINSON B. E.: Neurotransmitter receptors and monoamine metabolites in the brains of patients with Alzheimer-type dementia and depression and suicide. Neuropharmacology **23:** 1561–1569, 1984.

CSANALOSI, I., SCHWEIZER, E., CASE, W. G., AND RICKELS, K.: Gepirone in anxiety: a pilot study. J. Clin. Psychopharmacol. **7:** 31–33, 1987.

CSERNANSKY, J. G., POSCHER, M., AND FAULL, K. F.: Serotonin (5-HT) in schizophrenia. *In* Serotonin in Major Psychiatric Disorders, ed. by E. F. Coccaro and D. L. Murphy, American Psychiatric Press, Washington, D.C., in press, 1992.

CUNNINGHAM, D., HAWTHORN, J., POPLE, A., GAZET, J.-C., FORD, H. T., CHALLONER, T., AND COOMBES, R. C.: Prevention of emesis in patients receiving cytotoxic drugs by GR 38032F, a selective 5-HT$_3$ receptor antagonist. Lancet **1:** 1461–1463, 1987.

CUNNINGHAM, D., TURNER, A., HAWTHORN, J., AND ROSIN, R. D.: Ondansetron with and without dexamethasone to treat chemotherapy-induced emesis. Lancet **2:** 1323, 1989.

CURTIS, C. A. M., WHEATLEY, M., BANSAL, S., BIRDSALL, N. J. M., EVELEIGH, P., PEDDER, E. K., POYNER, D., AND HULME, E. C.: Propylbenzilylcholine mustard labels an acidic residue in transmembrane helix 3 of the muscarinic receptor. J. Biol. Chem. **264:** 489–495, 1989.

CURZON, G.: Serotonergic mechanisms of depression. Clin. Neuropharmacol. **11** (suppl.)**:** S11–S20, 1988.

CURZON, G.: Serotonin and appetite. Ann. N. Y. Acad. Sci. **600:** 521–531, 1990.

CURZON, G., AND KENNETT, G. A.: m-CPP: a tool for studying behavioural responses associated with 5-HT$_{1C}$ receptors. Trends Pharmacol. Sci. **11:** 181–182, 1990.

DABIRÉ, H., BAJJOU, R., CHAOUCHE-TEYARA, K., FOURNIER, B., DE NANTEUIL, G., LAUBIE, M., SAFAR, M., AND SCHMITT, H.: S-14063: a new potent 5-HT$_{1A}$ receptor antagonist devoid of β-adrenoceptor blocking properties. Eur. J. Pharmacol. **203:** 323–324, 1991.

DARMANI, N. A., MARTIN, B. R., PANDEY, U., AND GLENNON, R. A.: Pharmacological characterization of ear-scratch response in mice as a behavioral model for selective 5-HT$_2$ receptor agonists and evidence for 5-HT$_{1B}$ and 5-HT$_2$ receptor interactions. Pharmacol. Biochem. Behav. **37:** 95–99, 1990a.

DARMANI, N. A., MARTIN, B. R., PANDEY, U., AND GLENNON, R. A.: Do functional relationships exist between 5-HT$_{1A}$ and 5-HT$_2$ receptors? Pharmacol. Biochem. Behav. **36:** 901–906, 1990b.

DAVAL, G., VERGÉ, D., BECERRIL, A., GOZLAN, H., SAMPINATO, U., AND HAMON, M.: Transient expression of 5-HT$_{1A}$ receptor binding sites in some areas of rat CNS during postnatal development. Int. J. Dev. Neurosci. **5:** 171–180, 1987.

DAVIES, F. M., DEISZ, R. A., PRINCE, D. A., AND PEROUTKA, S. J.: Two distinct effects of 5-HT on single cortical neurons. Brain Res. **423:** 347–352, 1987.

DAVIS, M., CASSELLA, J. V., AND KEHNE, J. A.: Serotonin does not mediate anxiolytic effects of buspirone in the fear-potentiated startle paradigm: comparison with 8-OH-DPAT and ipsapirone. Psychopharmacology **94:** 14–20, 1988.

DE CHAFFOY DE COURCELLES, D., LEYSEN, J. E., DE CLERK, F., VAN BELLE, H., AND JANSSEN, P. A. J.: Evidence that phospholipid turnover is the signal transducing system coupled to serotonin$_2$ receptor sites. J. Biol. Chem. **260:** 7603–7608, 1985.

DE SOUZA, R. J., GOODWIN, G. M., AND GREEN, A. R.: Antidepressant drugs and ECS attenuate the hypothermia and behavioural syndrome following 8-OH-DPAT administration to rats. Br. J. Pharmacol. **89:** 523P, 1986.

DE VIVO, M., AND MAAYANI, S.: Characterization of the 5-h-HT$_{1A}$ receptor-mediated inhibition of forskolin-stimulated adenylate cyclase activity in guinea pig and rat hippocampal membranes. J. Pharmacol. Exp. Ther. **238:** 248–253, 1986.

DE VIVO, M., AND MAAYANI, S.: Stimulation and inhibition of adenyl cyclase by distinct 5-hydroxytryptamine receptors. Biochem. Pharmacol. **40:** 1551–1558, 1990.

DE VOS, H., CZERWIEC, E., DE BACKER, J.-P., DE POTTER, W., AND VAUQUELIN, G.: [^{3}H]Rauwolscine behaves as an agonist for the 5-HT$_{1A}$ receptors in human frontal cortex membranes. Eur. J. Pharmacol. **207:** 1–8, 1991.

DEAKIN, J. F.: 5-HT$_2$ receptors, depression and anxiety. Pharmacol. Biochem. Behav. **29:** 819–820, 1988.

DEAKIN, J. F.: 5-HT receptor subtypes in depression. *In* Behavioural Pharmacology of 5-HT, ed. by T. Archer, P. Bevan, and A. R. Cools, pp. 179–204, Lawrence Erlbaum Associates, Hillsdale, N.J., 1989.

DELIGANIS, A. V., AND PEROUTKA, S. J.: 5-HT$_{1D}$ receptor agonism predicts antimigraine efficacy. Headache **31:** 228–231, 1991.

DEN BOER, M. O., VILLALON, C. M., AND SAXENA, P. R.: 5-HT$_1$-like receptors in the porcine carotid circulation: do they belong to the 5-HT$_{1D}$ receptor subtype ? Br. J. Pharmacol. **104:** 280P, 1992.

DERKACH, V., SURPRENANT, A., AND NORTH, R. A.: 5-HT$_3$ receptors are membrane ion channels. Nature **339:** 706–709, 1989.

DI CHIARA, G., CAMBA, G., AND SPANO, P. F.: Evidence for inhibition by brain serotonin of mouse killing behaviour in rats. Nature **233:** 272–273, 1971.

DILLON, K. A., GROSS-ISSEROFF, R., ISRAELI, M., AND BIEGON, A.: Autoradiographic analysis of serotonin 5-HT$_{1A}$ receptor binding in the human brain postmortem: effects of age and alcohol. Brain Res. **554:** 56–64, 1991.

DOENICKE, A., BRAND J., AND PERRIN, V. L.: Possible benefit of GR 43175, a novel 5-HT$_1$-like receptor agonist, for the acute treatment of severe migraine. Lancet **1:** 1309–1311, 1988.

DOMPERT, W. U., GLASER, T., AND TRABER, J.: [^{3}H]-TVX Q 7821: identification of 5-HT$_1$ binding sites as target for a novel putative anxiolytic. Naunyn Schmiedebergs Arch. Pharmacol. **328:** 883–892, 1985.

DOURISH, C. T.: Brain 5-HT$_{1A}$ receptors and anxiety. *In* Brain 5-HT$_{1A}$ Receptors: Behavioral and Neurochemical Pharmacology, ed. by Dourish, C. T., Ahlenius, S., and Hutson, P. H., pp. 261–278, Ellis Horwood Ltd., Chichester, United Kingdom, 1987.

DOURISH, C. T., CLARK, M. L., FLETCHER, A., AND IVERSEN, S. D.: Evidence that blockade of post-synaptic 5-HT$_1$ receptors elicits feedings in satiated rats. Psychopharmacology **97:** 54–58, 1989.

DOURISH, C. T., HUTSON, P. H., AND CURZON, G.: Characteristics of feeding induced by the serotonin agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT). Brain Res. Bull. **15:** 377–384, 1985.

DOURISH, C. T., HUTSON, P. H., AND CURZON, G.: Para-chlorophenylalanine prevents feeding induced by the serotonin agonist 8-OH-DPAT. Psychopharmacology **89:** 467–471, 1986a.

DOURISH, C. T., HUTSON, P. H., AND CURZON, G.: Effects of 5-HT depletion and of 5-HT and catecholamine receptor antagonists on 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT)-induced feeding in the rat. Soc. Neurosci. Abstr. **12:** 1190, 1986b.

DOURISH, C. T., HUTSON, P. H., KENNETT, G. A., AND CURZON, G.: 8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) induced hyperphagia: its neural basis and possible therapeutic relevance. Appetite **7** (suppl.): 127–140, 1986c.

DOYLE, V. M., CREBA, J. A., RUEGG, U. T., AND HOYER, D.: Serotonin increases the production of inositol phosphates and mobilises calcium via the 5-HT$_2$ receptor in A7r5 smooth muscle cells. Naunyn Schmiedebergs Arch. Pharmacol. **333:** 98–103, 1986.

DUGOVIC, C., AND WAUQUIER, A.: 5-HT$_2$ receptors could be primarily involved in the regulation of slow-wave sleep in the rat. Eur. J. Pharmacol. **137:** 145–146, 1987.

DUGOVIC, C., WAUQUIER, A., LEUSEN, J. E., MARRANNES, R., AND JANSSEN, P. A. J.: Functional role of 5-HT$_2$ receptors in the regulation of sleep and wakefulness in the rat. Psychopharmacology **97:** 1431–1433, 1989.

DUMUIS, A., BOUHELAL, R., SEBBEN, M., AND BOCKAERT, J.: A 5-HT receptor in the central nervous system, positively coupled with adenylate cyclase, is antagonized by ICS 205-930. Eur. J. Pharmacol. **146:** 187–188, 1988a.

DUMUIS, A., BOUHELAL, R., SEBBEN, M., CORY, R., AND BOCKAERT, J.: A non classical 5-HT receptor positively coupled with adenylate cyclase in the central nervous system. Mol. Pharmacol. **34:** 880–887, 1988b.

DUMUIS, A., GOZLAN, H., SEBBEN, M., ANSANAY, H., RIZZI, C. A., TURCONI, M., MONFERINI, E., GIRALDO, E., SCHIANTARELLI, P., LADINSKY, H., AND BOCKAERT, J.: Characterization of a novel 5-HT$_4$ receptor antagonist of the azabicycloalkyl benzimidazolone class: DAU 6285. Naunyn Schmiedebergs Arch. Pharmacol. **345:** 264–269, 1992.

DUMUIS, A., SEBBEN, M., AND BOCKAERT, J.: BRL 24924: a potent agonist at a non-classical 5-HT receptor positively coupled with adenylate cyclase in colliculi neurons. Eur. J. Pharmacol. **162:** 381–384, 1989a.

DUMUIS, A., SEBBEN, M., AND BOCKAERT, J.: Pharmacology of 5-HT$_{1A}$ receptors which inhibit cAMP production in hippocampal and cortical neurons in primary culture. Mol. Pharmacol. **33:** 178–186, 1988c.

DUMUIS, A., SEBBEN, M., AND BOCKAERT, J.: The gastrointestinal prokinatic benzamide derivates are agonists at the non-classical 5-HT receptor (5-HT$_4$) positively coupled to adenylate cyclase in neurons. Naunyn Schmiedebergs Arch. Pharmacol. **340:** 403–410, 1989b.

DUMUIS, A., SEBBEN, M., MONFERINI, E., NICOLA, M., TURCONI, M., LADINSKY, H., AND BOCKAERT, J.: Azabicylloalkyl benzimidazolone derivatives as a novel class of potent agonists at the 5-HT$_4$ receptor positively coupled to adenylate cyclase in brain. Naunyn Schmiedebergs Arch. Pharmacol. **343:** 245–251, 1991.

EDWARDS, E., ASHBY, C. R., AND WANG, R. Y.: The effect of typical and atypical antipsychotic drugs on the stimulation of phosphoinositide hydrolysis produced by the 5-HT$_3$ receptor agonist 2-methyl-serotonin. Brain Res. **545:** 276–278, 1991a.

EDWARDS, E., HARKINS, K., ASHBY, C. R., AND WANG, R. Y.: Effect of 5-HT$_3$ receptor agonists on phosphoinositides hydrolysis in the rat fronto-cingulate and entorhinal cortices. J. Pharmacol. Exp. Ther. **256:** 1025–1031, 1991b.

EDWARDS, E., HARKINS, K., WRIGHT, G., AND HENN, F. A.: 5-HT$_{1B}$ receptors in an animal model of depression. Neuropharmacology **30:** 101–105, 1991c.

EGLEN, R. M., SWANK, S. R., WALSH, L. K. M., AND WHITING, R. L.: Characterization of 5-HT$_3$ and "atypical" 5-HT receptors mediating guinea-pig ileal contractions in vitro. Br. J. Pharmacol. **101:** 513–520, 1990.

EISON, A. S., YOCCA, F. D., AND GIANUTSOS, G.: Noradrenergic denervation alters serotonin$_2$-mediated behavior but not serotonin$_2$ receptor number in rats: modulatory role of beta adrenergic receptors. J. Pharmacol. Exp. Ther. **246:** 571–577, 1988.

EL MESTIKAWY, S., LAPORTE, A. M., VERGÉ, D., DAVAL, G., GOZLAN, H., AND HAMON, M.: Production of specific anti-rat 5-HT$_{1A}$ receptor antibodies in rabbits injected with a synthetic peptide. Neurosci. Lett. **118:** 189–192, 1990.

ELLIOTT, J. M., AND PHIPPS, S.: Differential effects of monovalent cations on GTP-sensitive states of the 5-HT$_{1A}$ receptor. Br. J. Pharmacol. **105:** 223P, 1992.

ELSWOOD, C. J., BUNCE, K. T., AND HUMPHREY, P. P. A.: Identification of putative 5-HT$_4$ receptors in guinea-pig ascending colon. Eur. J. Pharmacol. **196:** 149–155, 1991.

EMERIT, M. B., MIQUEL, M. C., GOZLAN, H., AND HAMON, M.: The GTP-insensitive component of high-affinity [^{3}H]8-hydroxy-2-(di-n-propylamino)tetralin binding in the rat hippocampus corresponds to an oxidized state of the 5-hydroxytryptamine-1A receptor. J. Neurochem. **56:** 1705–1716, 1991.

ENGEL, G., GÖTHERT, M., HOYER, D., SCHLICKER, E., AND HILLENBRAND, K.: Identity of inhibitory presynaptic 5-hydroxytryptamin (5-HT) autoreceptors in the rat brain cortex with 5-HT$_{1B}$ binding sites. Naunyn Schmiedebergs Arch. Pharmacol. **332:** 1–7, 1985.

ENGEL, G., GÖTHERT, M., HOYER, D., SCHLICKER, E., AND HILLENBRAND, K.: Identity of inhibitory presynaptic 5-hydroxytryptamine (5-HT) autoreceptors in the rat brain cortex with 5-HT$_{1B}$ binding sites. Naunyn Schmiedebergs Arch. Pharmacol. **332:** 1–7, 1986.

ENGEL, G., MULLER-SCHWEINITZER, E., AND PALACIOS, J. M.: 2-[^{125}Iodo]LSD, a new ligand for the characterisation and localisation of 5-HT$_2$ receptors. Naunyn Schmiedebergs Arch. Pharmacol. **325:** 328–336, 1984.

ERIKSSON, E.: Brain neurotransmission in panic disorder. Acta Psychiatr. Scand. **76** (suppl. 335): 31–37, 1987.

ESCHALIER, A., KAYSER, V., AND GUILBAUD, G: Influence of a specific 5-HT$_3$ antagonist on carrageenin-induced hyperalgesia in rats. Pain **36:** 249–255, 1989.

FARGIN, A., RAYMOND, J. R., LOHSE, M. J., KOBILKA, B. K., CARON, M. J., AND LEFKOWITZ, R. J.: The genomic clone G-21 which resembles a beta-adrenergic receptor sequence encodes the 5-HT$_{1A}$ receptor. Nature **335:** 358–360, 1988.

FARGIN, A., RAYMOND, J. R., REAGAN, J. W., COTECCHIA, S., LEFKOWITZ, R. J., AND CARON, M. G.: Effector coupling mechanisms of the cloned 5-HT$_{1A}$ receptor. J. Biol. Chem. **264:** 14848–14852, 1989.

FARROW, J. T., AND VAN VUNAKIS, H.: Binding of d-lysergic acid diethylamide to subcellular fractions from rat brain. Nature **237:** 164–166, 1972.

FARROW, J. T., AND VAN VUNAKIS, H.: Characteristics of d-lysergic acid diethylamide binding to subcellular fractions derived from rat brain. Biochem. Pharmacol. **22:** 1103–1113, 1973.

FAYOLLE, C., FILLION, M.-P., BARONE, P., OUDAR, P., ROUSSELLE, J. C., AND FILLION, G.: 5-Hydroxytryptamine stimulates two distinct adenylate cyclase activities in rat brain: high affinity activation is related to a 5-HT$_1$ subtype different from 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$. Fundam. Clin. Pharmacol. **2:** 195–214, 1988.

FEDERMAN, A. D., CONKLIN, B. R., SCHRADER, K. A., REED, R. R., AND BOURNE, H. R.: Hormonal stimulation of adenylyl cyclase through Gi-protein β-gamma subunits. Nature **356:** 159–161, 1992.

FEIGHNER, J. P., MEREDITH, C. H., AND HENRICKSON, G. A.: A double-blind comparison of buspirone and diazepam in outpatients with generalized anxiety disorder. J. Clin. Psychiatry **43:** 103–107, 1982.

FELDBERG, W., AND MYERS, R. D.: Effects on temperature of 5-hydroxytrypta-

mine, adrenaline and noradrenaline injected into the cerebral ventricles or the hypothalamus of cats. J. Physiol. **173:** 25P, 1964.

FELDER, C. C., KANTERMAN, R. Y., MA, A. L., AND AXELROD, J.: Serotonin stimulates phospholipase A2 and the release of arachidonic acid in hippocampal neurons by a type 2 serotonin receptor that is independent of inositol phospholipid hydrolysis. Proc. Natl. Acad. Sci. USA **87:** 2187–2191, 1990.

FERNANDEZ-GUASTI, A., AHLENIUS, S., HJORTH, S., AND LARSSON, K.: Separation of dopaminergic and serotonergic inhibitory mechanisms in the mediation of estrogen-induced lordosis behavior in the rat. Pharmacol. Biochem. Behav. **27:** 93–98, 1987.

FERNANDEZ-GUASTI, A., ESCALANTE, A., AND AGMO, A.: Inhibitory actions of various 5-HT_{1B} receptor agonists on rat masculine sexual behaviour. Pharmacol. Biochem. Behav. **34:** 811–816, 1989.

FERRARI, M., BAYLISS, E. M., LUDLOW, S., AND PILGRIM, A. J.: Subcutaneous GR43175 in the treatment of acute migraine: an international study. Cephalalgia **9** (suppl. 10): 348, 1989.

FERRARI, M. D.: Treatment of migraine attacks with sumatriptan. J. Med. **325:** 316–321, 1991.

FEUERSTEIN, T. J., AND HERTTING, G.: Serotonin enhances hippocampal noradrenaline release: evidence for facilitatory 5-HT receptors within the CNS. Naunyn Schmiedebergs Arch. Pharmacol. **333:** 191–197, 1986.

FILE, S. E.: Animal models for predicting clinical efficacy of anxiolytic drugs: social behaviour. Neuropsychobiology **13:** 55–62, 1985.

FILLION, G., CECCALDI, P. E., FILLION, M.-P., ERMINE, A., AND TSIANG, H.: Central 5-HT_{1D} receptors decrease in cortex and striatum of rat brain infected by rabies virus. Eur. J. Pharmacol. **183:** 1962, 1990.

FILLION, G., FILLION, M.-P., SPIRAKIS, C., BAHERS, J. M., AND JACOB, J.: 5-HT binding to synaptic membranes from rat brain. Life Sci. **18:** 65–74, 1976.

FISCHETTE, C. T., NOCK, B., AND RENNER, K.: Effects of 5,7-DHT on serotonin$_1$ and serotonin$_2$ receptors throughout the rat central nervous system using quantitative autoradiography. Brain Res. **421:** 263–279, 1987.

FONE, K. C. F., JOHNSON, J. V., BENNETT, G. W., AND MARSDEN, C. A.: Involvement of 5-HT_2 receptors in the behaviors produced by intrathecal administration of selected 5-HT agonists and the TRH analog (CG 3509) to rats. Br. J. Pharmacol. **96:** 599–608, 1989.

FOREMAN, M. M., HALL, J. L., AND LOVE, R. L.: The role of the 5-HT_2 receptor in the regulation of sexual performance of male rats. Life Sci. **45:** 1263–1270, 1989.

FOZARD, J. R.: Functional correlates of 5-HT_1 recognition sites. Trends Pharmacol. Sci. **4:** 288–289, 1983.

FOZARD, J. R.: Neuronal 5-HT receptors in the periphery. Neuropharmacology **23:** 1473–1486, 1984.

FOZARD, J. R.: 5-HT in migraine: evidence from 5-HT receptor antagonists for a neuronal etiology. *In* Migraine: A Spectrum of Ideas, ed. by M. Sandler and G. Collins, pp. 128–196. Oxford University Press, Oxford. United Kingdon, 1985.

FOZARD, J. R.: 5-HT_3 receptors and cytotoxic drug-induced vomiting. Trends Pharmacol. Sci. **8:** 44–45, 1987.

FOZARD, J. R.: Agonists and antagonists of 5-HT_3 receptors. *In* Cardiovascular Pharmacology of 5-Hydroxytryptamine, ed. by P. R. Saxena, D. I. Wallis, W. Wouters, and P. Bevan, pp. 101–115, Kluwer, Dordrecht, The Netherlands, 1990.

FOZARD, J. R., AND GRAY, J. A.: 5-HT_{1C} receptor activation: a key step in the initiation of migraine? Trends Pharmacol. Sci. **10:** 307–309, 1989.

FOZARD, J. R., AND KILBINGER, H.: 8-OH-DPAT inhibits transmitter release from guinea-pig enteric cholinergic neurones by activating 5-HT_{1A} receptors. Br. J. Pharmacol. **86:** 601P, 1985.

FOZARD, J. R., MOBAROCK, A., A. T. M., AND NEWGROSH, G.: Blockade of serotonin receptors on autonomic neurones by (−)cocaine and some related compounds. Eur. J. Pharmacol. **59:** 195–210, 1979.

FRANCÈS, H.: New animal model of social behavioral deficit: reversal by drugs. Pharmacol. Biochem. Behav. **29:** 467–470, 1988a.

FRANCÈS, H.: Psychopharmacological profile of TFMPP. Pharmacol. Biochem. Behav. **31:** 37–41, 1988b.

FRANCÈS, H., AND KHIDICHIAN, F.: Chronic but not acute antidepressants interfere with serotonin (5-HT_{1B}) receptors. Eur. J. Pharmacol. **179:** 173–176, 1990.

FRANCÈS, H., KHIDICHIAN, F., AND MONIER, C.: Increase in the isolation-induced social behavioural deficit by agonists at 5-HT_{1A} receptors. Neuropharmacology **29:** 103–107, 1990.

FRANCÈS, H., AND MONIER, C.: Tolerance to the behavioural effect of serotonergic (5-HT_{1B}) agonists in the isolation-induced social behavioural deficit test. Neuropharmacology **30:** 623–627, 1991.

FRAZER, A., AND HENSLER, J. G.: 5-HT_{1A} receptors and 5-HT_{1A}-mediated responses: effect of treatments that modify serotonergic neurotransmission. Ann. N. Y. Acad. Sci. **600:** 460–475, 1990.

FRAZER, A., MAAYANI, S., AND WOLFE, B. B.: Subtypes of receptors for serotonin. Annu. Rev. Pharmacol. Toxicol. **30:** 307–348, 1990.

FRIEDMAN, E., AND DALLOB, A.: Enhanced serotonin receptor activity after chronic treatment with imipramine or amitriptyline. Commun. Psychopharmacol. **3:** 89, 1979.

FROHLICH, E. D., AND VAN ZWIETEN, P.: Serotonin in cardiovascular regulation. J. Cardiovasc. Pharmacol. **10** (suppl. 3): S1–S138, 1987.

FUJIWARA, Y., NELSON, D. L., KASHIHARA, K., VARGA, E., ROESKE, W. R., AND YAMAMURA, H. I.: The cloning and sequence analysis of the rat serotonin-1A receptor gene. Life Sci. **47:** PL127–PL132, 1990.

FUKUDA, T., SETOGUCHI, M., INABA, K., SHOJI, H., AND TAHARA, T.: The antiemetic profile of Y-25130, a new selective 5-HT_3 receptor antagonist. Eur. J. Pharmacol. **196:** 299–305, 1991.

FULLER, R. W.: Serotonin receptors and neuroendocrine responses. Neuropsychopharmacology **3:** 495–502, 1990.

FUXE, K., AGNATI, L. F., ZOLI, M., BJELKE, B., AND ZINI, I.: Some aspects of the communicational and computational organization of the brain. Acta Physiol. Scand. **135:** 203–216, 1989.

FUXE, K., VON EULER, G., AGNATI, L. F., AND ÖGREN S.-O.: Galanin selectively modulates 5-HT_{1A} receptors in the rat ventral limbic cortex. Neurosci. Lett. **85:** 163–167, 1988.

GADDUM, J. H., AND PICARELLI, Z. P.: Two kinds of tryptamine receptors. Br. J. Pharmacol. Chemother. **12:** 323–328, 1957.

GALZIN, A. M., CHODKIEWICZ, J. P., POIRIER, M. F., LOO, H., ROUX, F. X., REDONDO, A., LISTA A., RAMDINE, R., BLIER, P., AND LANGER, S.: Modulation of the electrically-evoked release of [^{3}H]5-HT in slices of human frontal cortex. Br. J. Pharmacol. **93:** 14, 1989.

GALZIN, A. M., AND LANGER, S. Z.: Modulation of 5-HT release by presynaptic inhibitory and facilitatory 5-HT receptors in brain slices. Adv. Biosci. **82:** 59–62, 1991.

GANDOLFI, O., BARBACCIA, M. L., AND COSTA, E.: Different effects of serotonin antagonists on [^{3}H]mianserin and [^{3}H]ketanserin recognition sites. Life Sci. **36:** 713–721, 1985.

GARDNER, C. R.: Pharmacological studies of the role of serotonin in animal models in anxiety. *In* Neuropharmacology of Serotonin, ed. by A. R. Green, vol. 19, pp. 345–356, Oxford University Press, Oxford, United Kingdom, 1985.

GARDNER, C. R.: Recent developments in 5-HT related pharmacology of animal models in anxiety. Pharmacol. Biochem. Behav. **24:** 1479–1485, 1986.

GARRATT, J. C., KIDD, E. J., WRIGHT, I. K., AND MARSDEN, C. A.: Inhibition of 5-hydroxytryptamine neuronal activity by the 5-HT agonist, DOI. Eur. J. Pharmacol. **199:** 349–355, 1991.

GARTSIDE, S. E., COWEN, P. J., AND HJORTH, S.: Effects of MDL 73005 EF on central pre- and postsynaptic 5-HT_{1A} receptor function in the rat in vivo. Eur. J. Pharmacol. **191:** 391–400, 1990.

GEHLERT, D. R., GACKENHEIMER, S. L., WONG, D. T., AND ROBERTSON, D. W.: Localisation of 5-HT_3 receptors in the rat brain, using [^{3}H]LY-278–584. Brain Res. **553:** 149–154, 1991.

GELDERS, Y., CEULEMANS, D., AND HOPPENBROUWERS, M. L., REYNTJENS, A., MESOTTEN, F.: Ritanserin: a selective serotonin antagonist in chronic schizophrenia. Drugs Future **11:** 391–393, 1986.

GELLER, I., AND HARTMANN, R. J.: Effects of buspirone on operant behavior of laboratory rats and cynomolgus monkeys. J. Clin. Psychiatry **43:** 25–32, 1982.

GERSHON, S. C., AND BALDESSARINI, R. J.: Motor effects of serotonin in the central nervous system. Life Sci. **27:** 1435–1451, 1980.

GILBERT, F., BRAZELL, C., TRICKLEBANK, M. D., AND STAHL, S. M.: Activation of the 5-HT_{1A} receptor subtype increases rat plasma ACTH concentration. Eur. J. Pharmacol. **147:** 431–439, 1988a.

GILBERT, F., AND DOURISH, C. T.: Effects of the novel anxiolytics gepirone, buspirone and ipsapirone on free feeding induced by 8-OH-DPAT. Psychopharmacology **93:** 349–352, 1987.

GILBERT, F., DOURISH, C. T., BRAZELL, C., MCCLUE, S., AND STAHL, S. M.: Relationship of increased food intake and plasma ACTH levels to 5-HT_{1A} receptor activation in rats. Psychoneuroendocrinology **13:** 471–478, 1988b.

GILBERT, F., TRICKLEBANK, M. D., AND STAHL, S. M.: Characterisation of the 5-HT receptor subtype mediating ACTH release in the rat. Br. J. Pharmacol. **91:** 495P, 1987.

GIORDANO, J.: Analgesic profile of centrally administered 2-methylserotonin against acute pain in rats. Eur. J. Pharmacol. **199:** 233–236, 1991.

GIRAL, P. H., MARTIN, P., SOUBRIE, P. H., AND SIMON, P.: Reversal of helpless behavior in rats by putative 5-HT_{1A} agonists. Biol. Psychiatry **23:** 237–242, 1988.

GLASER, T.: Ipsapirone, a potent and selective 5-HT_{1A} receptor ligand with anxiolytic and antidepressant properties. Drugs Future **13:** 429–439, 1988.

GLASER, T., AND TRABER, J.: Binding of the putative anxiolytic TVX Q 7821 to hippocampal 5-hydroxytryptamine binding sites. Naunyn Schmiedebergs Arch. Pharmacol. **329:** 211–215, 1985.

GLAUM, S. R., PROUDFIT, H. K., AND ANDERSON, E. G.: Reversal of the antinociceptive effects of intrathecally administered serotonin in the rat by a selective 5-HT_3 receptor antagonist. Neurosci. Lett. **95:** 313–317, 1988.

GLENNON, R. A.: Involvement of serotonin in the action of hallucinogenic agents. *In* Neuropharmacology of Serotonin, ed. by A. R Green, pp. 253–280, Oxford University Press, Oxford, United Kingdom, 1985.

GLENNON, R. A.: Do classical hallucinogens act as 5-HT_2 agonists or antagonists? Neuropsychopharmacology **3:** 509–517, 1990a.

GLENNON, R. A.: Serotonin receptors: clinical implications. Neurosci. Biobehav. Rev. **14:** 35–47, 1990b.

GLENNON, R. A., NAIMAN, N. A., PIERSON, M. E., TITELER, M., LYON, R. A., HERNDON, J. L., AND MISENHEIMER, B.: Stimulus properties of arylpiperazines: NAN-190, a potential 5-HT_{1A} serotonin antagonist. Drug Dev. Res. **16:** 335–343, 1989.

GLENNON, R. A., NAIMAN, N. A., PIERSON, M. E., TITELER, M., LYON, R. A., AND WEISBERG, E.: NAN-190: an arylpiperazine analog that antagonizes the

stimulus effects of the 5-HT_{1A} agonist 8-OH-DPAT. Eur. J. Pharmacol. **154:** 339–341, 1988.

GLENNON, R. A., RAGHUPATHI, R., BARTYZEL, P., TEITLER, M., AND LEOHNARDT, S.: Binding of phenylalkylamine derivatives at 5-HT_{1C} and 5-HT_2 serotonin receptors: evidence for a lack of selectivity. J. Med. Chem. **35:** 734–740, 1992.

GLENNON, R. A., TITELER, M., AND MACKENNEY, J. D.: Evidence of 5-HT_2 involvement in the mechanism of action of hallucinogenic agents. Life Sci. **35:** 2505–2511, 1985.

GLITZ, D. A., AND POHL, R.: 5-HT_{1A} partial agonists: what is their future? Drugs **41:** 11–18, 1991.

GOA, K. L., AND WARD, A.: Buspirone: a preliminary review of its pharmacological properties and therapeutic efficacy as an anxiolytic. Drugs **32:** 114–129, 1986.

GOBBI, M., CAVANUS, S., MIARI, A., AND MENNINI, T.: Effect of acute and chronic administration of buspirone on serotonin and benzodiazepine receptor subtypes in the rat brain: an autoradiographic study. Neuropharmacology **30:** 313–321, 1991.

GODFREY, P. P., GRAHAME-SMITH, D. J., AND GRAY, J. A.: GABA-B receptor inhibits 5-HT-stimulated inositol phospholipid turnover in mouse cerebral cortex. Eur. J. Pharmacol. **152:** 185–188, 1988a.

GODFREY, P. P., MACCLUE, S. J., YOUNG, M. M., AND HEAL, D. J.: 5-HT-stimulated inositol phospholipid hydrolysis in the mouse cortex has pharmacological characteristics compatible with mediation via 5-HT_2 receptors but this response does not reflect altered 5-HT_2 function after 5,7-DHT lesioning or repeated antidepressant treatments. J. Neurochem. **50:** 730–738, 1988b.

GOLDBERG, H. L., AND FINNERTY, R.: The comparative efficacy of buspirone and diazepam in the treatment of anxiety. Am. J. Psychiatry **136:** 1184–1187, 1979.

GOLDFARB, J.: Electrophysiologic studies of serotonin receptor activation. Neuropsychopharmacology **3:** 435–446, 1990.

GONZALEZ-HEYDRICH, J., AND PEROUTKA, S. J.: Postsynaptic localization of 5-HT_{1D} receptor binding sites in human caudate. Exp. Neurol. **113:** 28–30, 1991.

GOODWIN, G.: The effects of antidepressant treatments and lithium upon 5-HT_{1A} receptor function. Prog. Neuropsychopharmacol. Biol. Psychiatry **13:** 445–451, 1989.

GOODWIN, G. M., DE SOUZA, R. J., AND GREEN, A. R.: Presynaptic serotonin receptor-mediated response in mice attenuated by antidepressant drugs and ECS. Nature **317:** 531–533, 1985a.

GOODWIN, G. M., DE SOUZA, R. J., AND GREEN, A. R.: The pharmacology of the hypothermic response in mice to 8-OH-DPAT: a model of presynaptic 5-HT_1 function. Neuropharmacology **24:** 1187–1194, 1985b.

GOODWIN, G. M., DE SOUZA, R. J., GREEN, A. R., AND HEAL, D. J.: The pharmacology of the behavioral and hypothermic responses of rats to 8-OH-DPAT. Psychopharmacology **91:** 500–505, 1987.

GOODWIN, G. M., DE SOUZA, R. J., WOOD, A. J., AND GREEN, A. R.: Lithium decreases 5-HT_{1A} and 5-HT_2 receptor and alpha-adrenoceptor mediated function in mice. Psychopharmacology **90:** 482–487, 1986.

GOODWIN, G. M., GREEN, A. R., AND JOHNSON, P.: 5-HT_2 receptor characteristics in frontal cortex and 5-HT_2 receptor-mediated head-twitch behavior following antidepressant treatment to mice. Br. J. Pharmacol. **83:** 235–242, 1984.

GOREA, E., AND ADRIEN, J.: Serotonergic regulation of noradrenergic coerulean neurones: electrophysiological evidence for the involvement of 5-HT_2 receptors. Eur. J. Pharmacol. **154:** 285–291, 1988.

GORELICK, D. A.: Serotonin uptake blokers and the treatment of alcoholism. Recent Dev. Alcohol **7:** 267–281, 1989.

GORZALKA, B. B., MENDELSON, S. D., AND WATSON, N. V.: Serotonin receptor subtypes and sexual behavior. Ann. N. Y. Acad. Sci. **600:** 435–445, 1990.

GÖTHERT, M.: Pharmacological, biochemical and molecular classification schemes of serotonin receptors with special reference to the 5-HT_2 class. *In* Progress in Pharmacology and Clinical Pharmacology, ed. by G. Fischer, vol. 7, pp. 3–15, Verlag, New-York, 1990.

GÖTHERT M., SCHLICKER E., FINK K., CLASSEN K.: Effects of RU 24969 on serotonin release in rat brain cortex: further support for the identity of serotonin autoreceptors with 5HT_{1B} sites. Arch. Int. Pharmacodyn. Ther. **288:** 31–42, 1987.

GOUDIE, A. J., AND LEATHLEY, M. J.: Effects of the 5-HT_3 antagonist GR38032F (ondansetron) on benzodiazepine withdrawal in rats. Eur. J. Pharmacol. **185:** 179–186, 1990.

GOUDIE, A. J., LEATHLEY, M., DEANS, C., AND TAYLOR, M. A. I.: Tolerance to the behavioural effects of ipsapirone. Behav. Pharmacol. **1:** 33–44, 1989.

GOZLAN, H., DAVAL, G., VERGÉ, D., STAMPINATO, U., FATTACCINI, C. M., GALLISSOT, M. C., AND EL MESTIKAWY, S.: Aging associated changes in serotonergic and dopaminergic pre- and post-synaptic neurochemical markers in rat brain. Neurobiol. Aging **11:** 437–449, 1990.

GOZLAN, H., EL MESTIKAWY, S., PICHAT, A., GLOWINSKI, J., AND HAMON, M.: Identification of presynaptic serotonin autoreceptors using a new ligand ^{3}H-PAT. Nature **305:** 140–142, 1983.

GOZLAN, H., PONCHANT, M., VERGÉ, D., MÉNARD, F., VANHOVE, H., BEAUCOURT, J. P., AND HAMON, M.: [125-I]-Bolton-Hunter-8-methoxy-2-(N-propyl-N-propylamino)tetralin as a new selective radioligand of 5-HT_{1A} sites in the rat brain. In vitro binding and autoradiographic studies. J. Pharmacol. Exp. Ther. **244:** 751–759, 1988.

GREEN, A. R., JOHNSON, P., AND NIMGAONKAR, V. L.: Increased 5-HT receptor number in brain as a probable explanation for the enhanced 5-HT-mediated behaviour following repeated electroconvulsive shock administration to rats. Br. J. Pharmacol. **80:** 173–177, 1983.

GROSS-ISSEROFF, R., AND BIEGON, A.: Autoradiographic analysis of [^{3}H]imipramine binding in the human brain postmortem: effects of age and alcohol. J. Neurochem. **5:** 528–534, 1988.

GROSS-ISSEROFF, R., SALAMA, D., ISRAELI, M., AND BIEGON, A.: Autoradiographic analysis of [^{3}H]-ketanserin binding in the human brain post-mortem: effect of suicide. Brain Res. **507:** 208–215, 1990.

GUDELSKY, G. A., KOENIG, J. I., AND MELTZER, H. Y.: Thermoregulatory responses to serotonin receptor stimulation in the rat: evidence for opposing roles of 5-HT_2 and 5-HT_{1A} receptors. Neuropharmacology **25:** 1307–1313, 1986.

GUDELSKY, G. A., KOENIG, J. I., AND MELTZER, H. Y.: Selective desensitization of serotonin receptor-mediated hyperthermia by mianserin and other 5-HT antagonists. Neuropharmacology **26:** 707–712, 1987.

GULLIKSON, G. W., LOEFFLER, R. F., AND VIRINA, M. A.: Relationship of serotonin-3 receptor antagonist activity to gastric emptying and motor-stimulating actions of prokinetic drugs in dogs. J. Pharmacol. Exp. Ther. **258:** 103, 1991.

GYLYS, J. A., WRIGHT, R. N., NICOLOSI, W. D., BUYNISKI, J. P., AND CRENSHAW, R. R.: BMY-25801, an antiemetic agent free of D2-dopamine receptor antagonist properties. J. Pharmacol. Exp. Ther. **244:** 830–834, 1988.

HAGAN, R. M., JONES, B. J., JORDAN, C. C., AND TYERS, M. B.: Effect of 5-HT_3 receptor antagonists on responses to selective activation of mesolimbic dopaminergic pathways in the rat. Br. J. Pharmacol. **99:** 227–232, 1990.

HAJ-DAHMANE, S., HAMON, M., AND LANFUMEY, L.: K^+ channel and 5-HT_{1A} autoreceptor interactions in the rat dorsal raphe nucleus: an in vitro electrophysiological study. Neuroscience **41:** 495–505, 1991.

HALASZ, B., AND BANKY, Z.: Serotonergic structures and onset of the circadian corticosterone rhythm. Monogr. Neural Sci. **12:** 148–152, 1986.

HALEEM, D. J., KENNETT, G. A., WHITTON, P. S., AND CURZON, G.: 8-OH-DPAT increases corticosterone but not other 5-HT_{1A} receptor dependent responses more in females. Eur. J. Pharmacol. **164:** 435–443, 1989.

HALL, H., ROSS, S. B., AND SALLEMARK, M.: Effect of destruction of central noradrenergic and serotonergic nerve terminals by systemic neurotoxins on the long-term effect of antidepressants on beta-adrenoceptors and 5-HT_2 binding sites in rat cerebral cortex. J. Neural Transm. **59:** 9–23, 1984.

HALL, M. D., EL MESTIKAWY, S., EMERIT, M. B., PICHAT, L., HAMON, M., AND GOZLAN, H.: [^{3}H]8-Hydroxy-2-(di-n-propylamino)tetralin binding to pre- and postsynaptic 5-hydroxytryptamine sites in various regions of the brain. J. Neurochem. **44:** 1685–1696, 1985.

HAMBLIN, M. W., ARIANI, K., ADRIAENSSENS, P. I., AND CIARANELLO, R. D.: [^{3}H]Dihydroergotamine as a high affinity, slowly dissociating radioligand for 5-HT_{1B} binding sites in rat brain membranes. Evidence for guanine nucleotide regulation of agonist affinity states. J. Pharmacol. Exp. Ther. **243:** 989–1001, 1987.

HAMBLIN, M. W., AND METCALF, M. A.: Primary structure and functional characterization of a human 5-HT_{1D}-type serotonin receptor. Mol. Pharmacol. **40:** 143–148, 1991.

HAMLIN, K. E., AND FISHER, F. E.: The synthesis of 5-hydroxytryptamine. J. Am. Chem. Soc. **73:** 5007–5008, 1951.

HAMON, M., BOURGOIN, S., CHANEZ, C., AND DE VITRY, F.: Do serotonin and other neurotransmitters exert a trophic influence on the immature brain. *In* Developmental Neurobiology, Nestlé Nutrition Workshop Series, ed. by P. Evrard and A. Minkowski, vol. 12, pp. 171–183, Nestec Ltd., Vevey/Raven Press Ltd., New York, 1989.

HAMON, M., EL MESTIKAWY, S., LAPORTE, A. M., KOSCIELNIAK, T., PONCHANT, M., VERGÉ, D., AND GOZLAN, H.: New developments in methods for the visualisation of 5-HT_{1A} and 5-HT_3 receptors in the rat brain. *In* The 2nd International Union of Pharmacology-Satellite Meeting on Serotonin, Elsevier, Amsterdam, Vol. 10, pp. 39, 1990a.

HAMON, M., FATTACCINI, C.-M., ADRIEN, J., GALLISSOT, M.-C., MARTIN, P., AND GOZLAN, H.: Alterations of central serotonin and dopamine turnover in rats treated with ipsapirone and other 5-HT_{1A} agonists with potential anxiolytic properties. J. Pharmacol. Exp. Ther. **246:** 745–752, 1988.

HAMON, M., LANFUMEY, L., EL MESTIKAWY, S., BONI, C., MIQUEL, M. C., BOLANOS, F., SCHECHTER, L., AND GOZLAN, H.: The main features of central 5-HT$_1$ receptors. Neuropsychopharmacology **3:** 349–360, 1990b.

HAMON, M., MALLAT, M., HERBET,A., NELSON,D. L., AUDINOT, M., PICHAT, L., AND GLOWINSKI, J.: [^{3}H]-metergoline: a new ligand for serotonin receptors in rat brain. J. Neurochem. **36:** 613–626, 1981.

HANDLEY, S. L., AND SINGH, L.: Involvement of the locus coeruleus in the potentiation of the quipazine-induced head-twitch response by diazepam and beta-adrenoceptor agonists. Neuropharmacology **25:** 1315–1321, 1986.

HARD, E., AND ENGEL, J.: Effects of 8-OH-DPAT on ultrasonic vocalization and audiogenic immobility reaction in pre-weanling rats. Neuropharmacology **27:** 981–986, 1988.

HAREL-DUPAS, C., CLOEZ, I., AND FILLION, G.: Antagonism by antidepressant drugs of the inhibitory effect of TFMPP on [^{3}H]acetylcholine release in rat or guines-pig hippocampal synaptosomes. Eur. Neuropsychopharmacol. **1:** 157–164, 1991a.

HAREL-DUPAS, C., CLOEZ, I., AND FILLION, G.: The inhibitory effect of TFMPP on [^{3}H]acetylcholine release in guinea pig hippocampal synaptosomes is mediated by a 5-HT_1 receptor distinct from 1A-subtype, 1B-subtype, and 1C-subtype. J. Neurochem. **56:** 221–227, 1991b.

HARRINGTON, M. A., OKSENBERG, D., AND PEROUTKA, S. J.: 5-HT$_{1A}$ receptors are linked to a Gi-adenylate cyclase complex in rat hippocampus. Eur. J. Pharmacol. **154:** 95–98, 1988.

HARRINGTON, M. A., AND PEROUTKA, S. J.: Modulation of 5-HT$_{1A}$ receptor density by non-hydrolysable GTP analogues. J. Neurochem. **54:** 294–299, 1990a.

HARRINGTON, M. A., AND PEROUTKA, S. J.: Differential modulation of 5-HT$_{1D}$ binding sites by GTP and GTP S. Brain Res. **506:** 172–174, 1990b.

HARRINGTON, M. A., SLEIGHT, A. J., PITHA, J., AND PEROUTKA, S. J.: Structural determinants of 5-HT$_{1A}$ versus 5-HT$_{1D}$ receptor binding site selectivity. Eur. J. Pharmacol. **194:** 83–90, 1991.

HARRISSON, J., PEARSON, W. R., AND LYNCH, K. R.: Molecular characterization of α_1 and α_2-adrenoceptors. Trends Pharmacol. Sci. **12:** 62–67, 1991.

HARTIG, P., KAO, H. T., MACCHI, M., ADHAM, N., ZGOMBICK, J., WEINSHANK, R., AND BRANCHEK, T.: The molecular biology of serotonin receptors. An overview. Neuropsychopharmacology **3:** 335–347, 1990a.

HARTIG, P. R.: Molecular biology of 5-HT receptors. Trends Pharmacol. Sci. **10:** 64–69, 1989a.

HARTIG, P. R.: Serotonin 5-hydroxytryptamine-1C receptors: what do they do? *In* Serotonin: Actions, Receptors, Pathophysiology, ed. by E. J. Mylecharane, J. A. Angus, I. S. de la Lande, and P. P. A. Humphrey, pp. 180–187, McMillan Press, London, United Kingdom, 1989b.

HARTIG, P. R., BRANCHEK, T. A., AND WEINSHANK, R. L.: A subfamily of 5-HT$_{1D}$ receptor genes. Trends Pharmacol. Sci. **13:** 152–159, 1992.

HARTIG, P. R., HOFFMAN, B. J., KAUFMAN, M. J., AND HIRATA, F.: The 5-HT$_{1C}$ receptor. Ann. N. Y. Acad. Sci. **600:** 149–167, 1990b.

HARTIG, P. R., KADAN, M. J., EVANS, M. J., AND KROHN, A. M.: [^{125}I]-LSD: a high selectivity ligand for serotonin receptors. Eur. J. Pharmacol. **89:** 321–322, 1983.

HARTO, N. E., BRANCONNIER, R. J., SPERA, K. F., AND DESSAIN, E. C.: Clinical profile of gepirone, a non-benzodiazepine anxiolytic. Psychopharmacol. Bull. **24:** 154–160, 1988.

HAYDON, P. G., MACCOBB, D. P., AND KATER, S. B.: Serotonin selectively inhibits growth cone motility and synaptogenesis of specific identified neurons. Science **226:** 561–564, 1984.

HEAL, D. J., PHILPOT, J., MOLYNEUX, S. J., AND METZ, A.: Intracerebroventricular administration of 5,7-DHT to mice increases both head-twitch response and the number of cortical 5-HT$_2$ receptors. Neuropharmacology **24:** 1201–1205, 1985.

HEDLUND, P., AND FUXE, K.: Chronic imipramine treatment increases the affinity of [^{125}I]galanin binding sites in the tel- and diencephalon of the rat and alters the 5-HT$_{1A}$/galanin receptor interaction. Acta Physiol. Scand. **141:** 137–138, 1991.

HEDLUND, P., VON EULER, G., AND FUXE, K.: Activation of 5-hydroxytryptamine-1A receptors increases the affinity of galanin receptors in di- and telencephalic areas of the rat. Brain Res. **560:** 251–259, 1991a.

HEDLUND, P. B., AGUIRRE, J. A., NARVAEZ, J. A., AND FUXE, K.: Centrally coinjected galanin and a 5-HT$_{1A}$ agonist act synergically to produce vasodepressor responses in the rat. Eur. J. Pharmacol. **204:** 87–95, 1991b.

HENSLER, J., KORACHICH, G. B., AND FRAZER, A.: A quantitative autoradiographic study of serotonin-1a receptor regulation: effect of 5,7-dihydroxytryptamine and antidepressant treatments. Neuropsychopharmacology **4:** 131–144, 1991.

HERRICK-DAVIS, K., AND TITELER, M.: [^{3}H]-Spiroxatrine: a 5-HT$_{1A}$ radioligand with agonist binding properties. J. Neurochem. **50:** 528–533, 1988a.

HERRICK-DAVIS, K., AND TITELER, M.: Detection and characterization of serotonin 5-HT$_{1D}$ receptor in rat and human brain. J. Neurochem. **50:** 1624–1631, 1988b.

HERRICK-DAVIS, K., AND TITELER, M.: Detection and characterization of a 5-HT$_{1D}$ serotonin receptor-GTP binding protein, interaction in porcine and bovine brain. Synapse **3:** 325–330, 1989.

HESKETH, P. J., AND GANDARA, D. R.: *In* Serotonin Antagonists. A New Class of Antiemetic Agents, vol. 83, pp. 613–620, 1991.

HEURING, R. E., AND PEROUTKA, S. J.: Characterization of a novel [^{3}H]5-HT binding site subtype in bovine brain membranes. J. Neurosci. **7:** 894–903, 1987.

HEURING, R. E., SCHLEGEL, R. J., AND PEROUTKA, S. J.: Species variations in RU 24969 interactions with non-5HT$_{1A}$ binding sites. Eur. J. Pharmacol. **122:** 279–282, 1987.

HEWSON, G., LEIGHTON, G. E., HILL, R. G., AND HUGHES, J.: Quipazine reduces food intake in the rat by activation of 5-HT$_2$ receptors. Br. J. Pharmacol. **95:** 598–604, 1988.

HEYM, J., MENA, E. E., AND SEYMOUR, P. A.: SM-3997: A non-benzodiazepine anxiolytic with potent and selective effects on serotonergic neurotransmission. Soc. Neurosci. Abst. **13:** 127, 1987.

HIBERT, M. F., MIR, A. K., MAGHIOROS, G., MOSER, P., MIDDLEMISS, D. N., TRICKLEBANK, M. D., AND FOZARD, J. R.: The pharmacological properties of MDL 73005 EF: a potent and selective ligand at 5-HT$_{1A}$ receptors. Br. J. Pharmacol. **93** (suppl.): 2P, 1988.

HIBERT, M. F., TRUMPP-KALLMEYER, S., BRUINVELS, A., AND HOFLACK, F.: Three-dimensional models of neurotransmitter G-binding protein-coupled receptors. Mol. Pharmacol. **40:** 8–15, 1991.

HIDE, I., KATO, T., AND YAMAWAKI, S.: In vivo determination of 5-HT receptor-stimulated phosphoinositide turnover in rat brain. J. Neurochem. **53:** 556–560, 1989.

HIDE, I., AND YAMAWAKI, S.: Inactivation of presynaptic 5-HT autoreceptors by lithium in rat hippocampus. Neurosci. Lett. **107:** 323–326, 1989.

HIGGINS, G. A., BRADBURY, A. J., JONES, B. J., AND OKLEY, N. R.: Behavioural and biochemical consequences following activation of 5-HT$_1$-like and GABA receptors in the dorsal raphe nucleus of the rat. Neuropharmacology **27:** 993–1001, 1988.

HIGGINS, G. A., JONES, B. J., OAKLEY, N. R., AND TYERS, M. B.: Evidence that the amygdala is involved in the disinhibitory effects of 5-HT$_3$ receptor antagonists. Psychopharmacology **104:** 545–551, 1991a.

HIGGINS, G. A., JORDAN, C. C., AND SKINGLE, M.: Evidence that the unilateral activation of 5-HT$_{1D}$ receptors in the substantia nigra of the guinea pig elicits contralateral rotation. Br. J. Pharmacol. **102:** 305–310, 1991b.

HIGGINS, G. A., KILPATRICK, G. J., BUNCE, K. T., JONES, B. J., AND TYERS, M. B.: 5-HT$_3$ receptor antagonists injected into the area postrema inhibit cisplatin-induced emesis in the ferret. Br. J. Pharmacol. **97:** 247–255, 1989.

HILLEGAART, V.: Functional topography of brain serotonergic pathways in the brain. Acta Physiol. Scand. **142** (suppl. 598): 1–54, 1991.

HILLEGAART, V., AND HJORTH, S.: Median raphe, but not dorsal raphe, application of the 5-HT$_{1A}$ agonist 8-OH-DPAT stimulates rat motor activity. Eur. J. Pharmacol. **160:** 303–307, 1989.

HILLEGAART, V., WADENBERG, M. L., AND AHLENIUS, S.: Effects of 8-OH-DPAT on motor activity in the rat. Pharmacol. Biochem. Behav. **32:** 797–800, 1989.

HIROSE, A., KATO, T., SHIMIZU, H., NAKAMURA, M., AND KATSUBE, J.: The pharmacological properties of SM-3997. Jpn. J. Pharmacol. **40** (suppl.): 114P, 1986.

HJORTH, S.: Hypothermia in the rat induced by the potent serotonergic agent 8-OH-DPAT. J. Neural Transm. **61:** 131–135, 1985.

HJORTH, S.: Single-dose 8-OH-DPAT pretreatment does not induce tachyphylaxis to the 5-HT release-reducing effect of 5-HT$_{1A}$ autoreceptor agonists. Eur. J. Pharmacol. **199:** 237–242, 1991.

HJORTH, S., CARLSSON, A., LINDBERG, P., SANCHEZ, D., WIKSTROM, H., ARVIDSSON, L. E., HACKSELL, U., AND NILSSON, J. L. G.: 8-OH-DPAT, a potent and selective simplified ergot congener with central 5-HT receptor stimulating activity. J. Neural Transm. **55:** 169–188, 1982.

HJORTH, S., AND MAGNUSSON, T.: The 5-HT$_{1A}$ receptor agonist, 8-OH-DPAT, preferentially activates cell bode 5-HT autoreceptors in rat brain in vivo. Naunyn Schmiedebergs Arch. Pharmacol. **338:** 463–471, 1988.

HJORTH, S., AND SHARP, T.: Effect of the 5-HT$_{1A}$ receptor agonist 8-OH-DPAT on the release of 5-HT in dorsal and median raphe-innervated rat brain regions as measured by in vivo microdialysis. Life Sci. **48:** 1779–1786, 1991.

HJORTH, S., AND SHARP, T.: Mixed agonist/antagonist properties of NAN-190 at 5-HT$_{1A}$ receptors: behavioral and in vivo brain microdialysis studies. Life Sci. **46:** 955–963, 1990.

HJORTH, S., AND TAO, R.: The putative 5-HT$_{1B}$ receptor agonist CP-93,129 suppresses rat hippocampal 5-HT release in vivo: comparison with RU 24969. Eur. J. Pharmacol. **209:** 249–252, 1991.

HOFFMAN, B. J., KARPA, M. D., LEVER, J. R., AND HARTIG, P. R.: NI-methyl-2-[125-I]LSD([125-I]MIL), a preferred ligand for serotonin 5-HT$_2$ receptors. Eur. J. Pharmacol. **110:** 147–148, 1985.

HOFFMAN, B. J., AND MEZEY, E.: Distribution of serotonin 5-HT$_{1C}$ receptor mRNA in adult rat brain. FEBS Lett. **247:** 453–462, 1989.

HOFFMAN, B. J., SCHEFFEL, U., LEVER, J. R., KARPA, M. D., AND HARTIG, P. R.: N1-methyl-2-^{125}I-lysergic acid diethylamide, a preferred ligand for in vitro and in vivo characterization of serotonin receptors. J. Neurochem. **48:** 115–124, 1987.

HOLLENBERG, N. K.: Serotonin and vascular responses. Annu. Rev. Pharmacol. Toxicol. **28:** 41–59, 1988.

HOPPENBROUWERS, M. L., VENDEN BUSSCHE, G., AND GELDERS, Y.: Is ritanserin, a serotonin receptor blocker, able to counteract jet lag: a placebo-controlled pilot investigation. Psychopharmacology **96** (suppl.): 245, 1988.

HOYER, D.: Molecular pharmacology and biology of 5-HT$_{1C}$ receptors. Trends Pharmacol. Sci. **9:** 89–94, 1988.

HOYER, D.: Serotonin 5-HT$_3$, 5-HT$_4$, and 5-HT-M receptors. Neuropsychopharmacology **3:** 371–383, 1990.

HOYER, D., ENGEL, G., AND KALKMAN, H. O.: Characterization of the 5-HT$_{1B}$ recognition site in rat brain: binding studies with [^{125}I]-iodocyanopindolol. Eur. J. Pharmacol. **118:** 1–12, 1985a.

HOYER, D., ENGEL, G., AND KALKMAN, H. O.: Molecular pharmacology of 5-HT$_1$ and 5-HT$_2$ recognition sites in rat and pig brain membranes: radioligand binding studies with [^{3}H]5-HT, [^{3}H]8-OH-DPAT, [^{125}I]-iodocyanopindolol, [^{3}H]mesulergine, [^{3}H]ketanserin. Eur. J. Pharmacol. **118:** 13–23, 1985b.

HOYER, D., AND KARPF, A.: [^{125}I]SCH 23982, a selective D1 receptor antagonist, labels with high affinity 5-HT$_{1C}$ sites in pig choroid plexus. Eur. J. Pharmacol. **150:** 181–184, 1988.

HOYER, D., AND MIDDLEMISS, D. N.: Species differences in the pharmacology of terminal 5-HT autoreceptors in mammalian brain. Trends Pharmacol. Sci. **10:** 130–132, 1989.

HOYER, D., AND NELJT, H. C.: Identification of 5-HT$_2$ recognition sites by radioligand binding in NG108–15 neuroblastoma-glioma cells. Eur. J. Pharmacol. **143:** 291–292, 1987.

HOYER, D., AND NELJT, H. C.: Identification of 5-HT$_2$ recognition sites in membranes of N1E-115 neuroblastoma cells by radioligand binding. Mol. Pharmacol. **33:** 303–309, 1988.

HOYER, D., PAZOS, A., PROBST, A., AND PALACIOS, J. M.: Serotonin receptors in the human brain. I. Characterization and autoradiographic localization of

5-HT_{1A} recognition sites. Apparent absence of 5-HT_{1B} recognition sites. Brain Res. **376:** 85–96, 1986a.

HOYER, D., PAZOS, A., PROBST, A., AND PALACIOS, J. M.: Serotonin receptors in the human brain. II. Characterization and autoradiographic localization of 5-HT_{1C} and 5-HT_2 recognition sites. Brain Res. **376:** 97–107, 1986b.

HOYER, D., AND SCHOEFFTER, P.: 5-HT_{1D} receptor-mediated inhibition of forskolin-stimulated adenylate cyclase activity in calf substantia nigra. Eur. J. Pharmacol. **147:** 145–147, 1988.

HOYER, D., AND SCHOEFFTER, P.: 5-HT receptors: subtypes and second messengers. J. Recept. Res. **11:** 197–214, 1991.

HOYER, D., SCHOEFFTER, P., PALACIOS, J. M., KALKMAN, H. O., BRUINVELS, A. T., FOZARD, J. R., SIEGL, H., SEILER, M. P., AND STOLL, A.: SDZ 216–525: a selective, potent and silent 5-HT_{1A} receptor antagonist. Br. J. Pharmacol. **105:** 29P, 1992.

HOYER, D., WAEBER, C., PAZOS, A., PROBST, A., AND PALACIOS, J. M.: Identification of a 5-HT_1 recognition site in human brain membranes different from 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C} sites. Neurosci. Lett. **85:** 357–362, 1988.

HOYER, D., WAEBER, C., SCHOEFFTER, P., PALACIOS, J. M., AND DRAVID, A.: 5-HT_{1C} receptor-mediated stimulation on inositol phosphate production in pig choroid plexus. Naunyn Schmiedebergs Arch. Pharmacol. **339:** 252–258, 1989.

HOYLAND, V. J., SHILLITON, E. E., AND VOGT, M.: The effect of parachlorophenylalanine on the behaviour of cats. Br. J. Pharmacol. **40:** 659–667, 1970.

HUMPHREY, P. P. A., FENIUK, W., PERREN, M. J., BERESFORD, I. J. M., SKINGLE, M., AND WHALLEY, E. T.: Serotonin and migraine. Ann. N. Y. Acad. Sci. **600:** 587–600, 1990.

HUNTER, A. J., HOLE, D. R., AND WILSON, C. A.: Studies into the dual effects of serotonergic pharmacological agents on female sexual behaviour in the rat: preliminary evidence that endogenous 5-HT is stimulatory. Pharmacol. Biochem. Behav. **22:** 5–13, 1985.

HUTSON, P. H., DONOHOE, T. P., AND CURZON, G.: Hypothermia induced by the putative 5-HT_{1A} agonist LY 165 163 and 8-OH-DPAT is not prevented by 5-HT depletion. Eur. J. Pharmacol. **143:** 221–228, 1987.

HUTSON, P. H., DOURISH, C. T., AND CURZON, G.: Neurochemical and behavioural evidence for mediation of the hyperphagic action of 8-OH-DPAT by 5-HT cell body autoreceptors. Eur. J. Pharmacol. **129:** 347–352, 1986.

HUTSON, P. H., DOURISH, C. T., AND CURZON, G.: Evidence that the hyperphagic response to 8-OH-DPAT is mediated by 5-HT_{1A} receptors. Eur. J. Pharmacol. **150:** 361–366, 1988.

IDZIKOWSKI, C., MILLS, F. J., AND GLENNARD, R.: 5-HT_2 antagonist increases human slow wave sleep. Brain Res. **378:** 164–168, 1986.

IMPERATO, A. N., AND ANGELUCCI, L.: 5-HT_3 receptors control dopamine release in the nucleus accumbens of freely moving rats. Neurosci. Lett. **101:** 214–217, 1989.

INNIS, R. B., AND AGHAJANIAN, G. K.: Pertussis toxin blocks 5-HT_{1A} and GABA-B receptor-mediated inhibition of serotoninergic neurons. Eur. J. Pharmacol. **143:** 195–204, 1987.

INNIS, R. B., NESTLER, E. J., AND AGHAJANIAN, G. K.: Evidence for G-protein mediation of serotonin- and GABA$_B$-induced hyperpolarization of rat dorsal raphe neurons. Brain Res. **459:** 27–36, 1988.

INSEL, T. R., ZOHAR, J., BENKELFAT, C., AND MURPHY, D. L.: Serotonin in obsessions, compulsions, and the control of aggressive impulses. Ann. N. Y. Acad. Sci. **600:** 574–586, 1990.

IVERFELDT, K., PETERSON, L-L., BRODIN, E., ÖGREN, S.-O., AND BARTFAI, T.: Serotonin type-2 receptor mediated regulation of substance P release in the ventral spinal cord and the effects of chronic antidepressant treatment. Naunyn Schmiedebergs Arch. Pharmacol. **333:** 1–6, 1986.

IVERSEN, S. D.: 5-HT and anxiety. Neuropharmacology **23:** 1553–1560, 1984.

IVINS, K. J., AND MOLINOFF, P. B.: Serotonin-2 receptors coupled to phosphoinositide hydrolysis in a clonal cell line. Mol. Pharmacol. **37:** 622–630, 1990.

IVINS, K. J., AND MOLINOFF, P. B.: Densensitization and down-regulation of 5-HT_2 receptors in P11 cells. J. Pharmacol. Exp. Ther. **259:** 423–429, 1991.

JACKSON, H. C., AND KITCHEN, I.: Behavioural profiles of putative 5-HT receptor agonists and antagonists in developing rats. Neuropharmacology **28:** 635–642, 1989.

JACOB, J., GIRAULT, J. 5-Hydroxytryptamine. *In* Body temperature. Regulation, Drug effects and Therapeutic implication, ed. by P. Lomax and E. Schonbaum, pp. 183–230, Marcel Dekker, New York and Basel, 1979.

JACOBS, B. L., FORNAL, C. A., RIBEIRO-DO-VALLE, L. E., LITTO, W. J., AND WILKINSON, L. O.: Effects of 8-OH-DPAT on food intake and serotonergic dorsal raphe unit activity in behaving cats. Soc. Neurosci. Abstr. **15:** 1283, 1989.

JAMES, M. D., LANE, S. M., HOLE, D. R., AND WILSON, C. A.: Hypothalamic sites of action of the dual effect of 5-HT on female sexual behaviour in the rat. *In* Behavioral Pharmacology of 5-HT, ed. by P. Bevan, A. R. Cools, and T. Archer, pp. 73–77, Lawrence Erlbaum Associates, Hillsdale, N.J., 1989.

JANOWSKY, A., LABARKA, R., AND PAUL, S. M.: Characterization of neurotransmitter receptor-mediated phosphatidylinositol hydrolysis in the rat hippocampus. Life Sci. **35:** 1953–1961, 1984.

JENKINS, S. W., ROBINSON, D. S., FABRE, L. F., ANDARY, J. J., AND MESSINA, M. E.: Gepirone in the treatment of major depression. J. Clin. Psychopharmacol. **10** (suppl.): 77S–85S, 1990.

JOHANSEN, B., AND BECH, K.: BRL 24924, a 5-hydroxytryptamine type 3 antagonist, and gastric secretion of acide and pepsin in vivo. Digestion **48:** 121–127, 1991.

JOHANSSON, C. E., MEYERSON, B. J., AND HACKSELL, U.: The novel 5-HT_{1A} receptor antagonist (S)-UH-301 antagonizes 8-OH-DPAT-induced effects on male as well as female rat copulatory behaviour. Eur. J. Pharmacol. **202:** 81–87, 1991.

JOHNSSON, A. L., AND FILE, S. E.: 5-HT and anxiety: promises and pitfalls. Pharmacol. Biochem. Behav. **24:** 1467–1470, 1986.

JOHNSSON, A. L., AND FILE, S. E.: Effects of 5-HT_3 antagonists in two animal tests of anxiety. Neurosci. Lett. **32** (suppl.): S44, 1988.

JONES, A. L., HILL, A. S., SOUKOP, M., HUTCHEON, A. W., CASSIDY, J., KAYE, S. B., SIKOBA, K., CARNEY, D. N., AND CUNNINGHAM, D.: Comparison of dexamethazone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. Lancet **338:** 483–487, 1991.

JONES, B. J., COSTALL, B., DOMENEY, A. M., KELLY, M. E., NAYLOR, R. J., OAKLEY, N. R., AND TYERS, M. B.: The potential anxiolytic activity of GR 38032F, a 5-HT_3 receptor antagonist. Br. J. Pharmacol. **93:** 985–993, 1988.

JOUVET, M.: Recherches sur les structures nerveuses et les mécanismes responsables des différentes phases du sommeil physiologique. Arch. Ital. Biol. **100:** 125–206, 1962.

JOUVET, M.: Neurophysiology of the states of sleep. Physiol. Rev. **47:** 117–177, 1967.

JOUVET, M.: Neuropharmacology of the sleep-waking cycle. *In* Handbook of Psychopharmacology: Drug, Neurotransmitters and Behavior, ed. by L. L. Iversen, S. D. Iversen, and S. H. Snyder, vol. 8, pp. 233–281, Plenum Press, New York, 1977.

JULIUS, D.: Molecular biology of serotonin receptors. Annu. Rev. Neurosci. **14:** 335–360, 1991.

JULIUS, D., HUANG, K. N., LIVELLI, T. J., AXEL, R., AND JESSEL, T. M.: The 5-HT_2 receptor defines a family of structurally distinct but functionally conserved serotonin receptors. Proc. Natl. Acad. Sci. USA **87:** 928–932, 1990.

JULIUS, D., LIVELLI, T. J., JESSELL, T. M., AND AXEL, R.: Ectopic expression of the serotonin 1c receptor and the triggering of malignant transformation. Science **244:** 1057–1062, 1989.

JULIUS, D., MACDERMOTT, A. B., AXEL, R., AND JESSEL, T. M.: Molecular characterization of a functional cDNA encoding the serotonin 1c receptor. Science **241:** 558–564, 1988.

KAFI DE ST-HILAIRE, S., HJORTH, S., AND GAILLARD, J. M.: Effects of 8-OH-DPAT on the sleep-waking cycle in the rat. *In* Brain 5-HT_{1A} Receptors: Behavioral and Neurochemical Pharmacology, ed. by Dourish, C. T., Ahlenius, S., and Hutson, P. H., pp. 135–139, Ellis Horwood Ltd., Chichester, United Kingdom, 1987.

KAHN, A. S., VAN PRAAG, H. M., WETZLER, S., ASNIS, G. M., AND BARR, C.: Serotonin and anxiety revisited. Biol. Psychiatry **23:** 189–208, 1988.

KALUS, O., ASNIS, G. M., AND VAN PRAAG, H. M.: The role of serotonin in depression. Psychiatr. Ann. **19:** 348–353, 1989.

KAO, H.-T., OLSEN, M. A., AND HARTIG, P. R.: Isolation and characterization of a human 5-HT_2 receptor clone. Soc. Neurosci. Abstr **15:** 486, 1989.

KATO, R.: Sex-related differences in drug metabolism. Drug Metab. Rev. **3:** 1–32, 1974.

KAUMANN, A. J.: Piglet sinoatrial 5-HT receptors resemble human atrial 5-HT_4-like receptors. Naunyn Schmiedebergs Arch. Pharmacol. **342:** 619–622, 1990.

KAUMANN, A. J., AND FRENKEN, M.: A paradox: the 5-HT_2 receptor antagonist ketanserin restores the 5-HT induced contraction depressed by methysergide in large coronary arteries of calf. Allosteric regulation of 5-HT_2 receptors. Naunyn Schmiedebergs Arch. Pharmacol. **328:** 295–300, 1985.

KAUMANN, A. J., SANDERS, L., BROWN, A. M., MURRAY, K. J., AND BROWN, M. J.: A 5-HT_4 receptor in human right atrium. Naunyn Schmiedebergs Arch. Pharmacol. **344:** 150–159, 1991.

KELLAR, K. J., CASCIO, C. S., BUTLER, J. A., AND KURTZKE, R. N.: Different effects of electroconvulsive shock and antidepressant drugs on serotonin-2 receptors in rat brain. Eur. J. Pharmacol. **69:** 515–518, 1981.

KENDALL, D. D., AND NAHORSKI, S. R.: Temperature-dependent 5-HT-sensitive [^{3}H]spiperone binding to rat cortical membranes: regulation by guanine nucleotide and antidepressant treatment. J. Pharmacol. Exp. Ther. **227:** 429–434, 1983.

KENDALL, D. A., AND NAHORSKI, S. R.: Suppression of 5-HT receptor mediated inositol phospholipid breakdown in brain by chronic antidepressant treatment. Br. J. Pharmacol. **82:** 206P, 1984.

KENDALL, D. A., AND NAHORSKI, S. R.: 5-HT-stimulated inositol phospholipid hydrolysis in rat cerebral cortex slices: pharmacological characterization and effects of antidepressants. J. Pharmacol. Exp. Ther. **233:** 473–479, 1985.

KENNETT, G. A., AND CURZON, G.: Evidence that m-CPP may have behavioural effects mediated by central 5-HT_{1C} receptors. Br. J. Pharmacol. **94:** 137–147, 1988.

KENNETT, G. A., AND CURZON, G.: Potencies of antagonists indicate that 5-HT_{1C} receptors mediate mCPP-induced hypophagia. Br. J. Pharmacol. **103:** 2016–2020, 1991.

KENNETT, G. A., DOURISH, C. T., AND CURZON, G.: Antidepressant-like action of 5-HT_1 agonist and conventional antidepressants in an animal model of depression. Eur. J. Pharmacol. **134:** 265–274, 1987a.

KENNETT, G. A., DOURISH, C. T., AND CURZON, G.: 5-HT_{1B} agonists induce anorexia at a postsynaptic site. Eur. J. Pharmacol. **141:** 429–435, 1987b.

KENNETT, G. A., MARCOU, M., DOURISH, C. T., AND CURZON, G.: Single administration of 5-HT_{1A} agonists decreases 5HT_{1A} presynaptic, but not postsynaptic receptor-mediated responses: relationship to antidepressant-like action. Eur. J. Pharmacol. **138:** 53–60, 1987c.

KENNETT, G. A., WHITTON, P., SHAH, K., AND CURZON, G.: Anxiogenic-like

effects of m-CPP and TFMPP in animal models are opposed by 5-HT_{1C} receptor antagonists. Eur. J. Pharmacol. **164:** 445–454, 1989.

KIDD, E. J., GARRATT, J. C., AND MARSDEN, C. A.: Effects of repeated treatment with DOI on the autoregulatory control of dorsal raphe 5-HT neuronal firing and cortical 5-HT release. Eur. J. Pharmacol. **200:** 131–139, 1991.

KIDD, E. J., LEYSEN, J. E., AND MARSDEN, C. A.: Chronic 5-HT_2 receptor antagonist treatment alters 5-HT_{1A} autoregulatory control of 5-HT release in rat brain, in vivo. J. Neurosci. Methods **34:** 91–98, 1990.

KILBINGER, H., AND WOLF, D.: Effects of 5-HT_4 receptor stimulation on basal and electrically evoked release of acetylcholine from guinea-pig myenteric plexus. Naunyn Schmiedebergs Arch. Pharmacol. **345:** 270–275, 1992.

KILPATRICK, G. J., BUNCE, K. T., AND TYERS, M. B.: 5-HT_3 Receptors. Med. Res. Rev. **10:** 441–475, 1990a.

KILPATRICK, G. J., BUTLER, A., HAGAN, R. M., JONES, B. J., AND TYERS, M. B.: [^{3}H]GR67330, a very high affinity ligand for 5-HT_3 receptors. Naunyn Schmiedebergs Arch. Pharmacol. **342:** 22–30, 1990b.

KILPATRICK, G. J., JONES, B. J., AND TYERS, M. B.: Binding of the 5-HT_3 ligand, [^{3}H]GR 65630, to rat area postrema, vagus nerve and the brains of several species. Eur. J. Pharmacol. **159:** 157–164, 1989.

KILPATRICK, G. J., JONES, B. J., AND TYERS, M. B.: Identification and distribution of 5-HT_3 receptors in rat brain using radioligand binding. Nature **330:** 746–748, 1987.

KLANCNIK, J. M., OBENAUS, A., PHILLIPS, A. G., AND BAIMBRIDGE, K. G.: The effects of serotonergic compounds on evoked responses in the dentate gyrus and CA1 region of the hippocampal formation of the rat. Neuropharmacology **30:** 1201–1209, 1991.

KLODZINSKA, A., JAROS, T., CHOJANACKA-WOJCIK, E., AND MAJ, J.: Exploratory hypoactivity induced by TFMPP and mCPP. J. Neural Transm. **1:** 207–218, 1989.

KOBILKA, B. K., FRIELLE, T., COLLINS, S., YANG-FENG, T., KOBILKA, T. S., FRANCKE, U., LEFKOWITZ, R. J., AND CARON, M. G..: An intronless gene encoding a potential member of the family of receptors coupled to guanine nucleotide regulatory proteins. Nature **329:** 75–79, 1987.

KOE, B. K., LEBEL, L. A., FOX, C. B., AND MACOR, J. E.: Characterization of [^{3}H]CP-96,501 as a selective radioligand for the serotonin 5-HT_{1B} receptor: binding studies in rat brain membranes. J. Neurochem. **58:** 1268–1276, 1992.

KOELLA, W. P.: Serotonin and sleep. *In* Neuronal Serotonin, ed. by N. N. Osborne and M. Hamon, pp. 153–170, John Wiley Ltd., New York, 1988.

KOENING, J. I., GUDELSKY, G. A., AND MELTZER, H. Y.: Stimulation of corticosterone and b-endorphin secretion in the rat by selective 5-HT receptor subtype activation. Eur. J. Pharmacol. **137:** 1–8, 1987.

KOENING, J. I., MELTZER, H. Y., AND GUDELSKY, G. A.: 5-HT_{1A} receptor mediated effects of buspirone, gepirone and ipsapirone. Pharmacol. Biochem. Behav. **29:** 711–715, 1988.

KÖHLER, C., RADESÄTER, A. C., LANG, W., AND CHAN-PALAY, V.: Distribution of serotonin-1A receptors in the monkey and the post-mortem human hippocampal region: a quantitative autoradiographic study using the selective agonist [^{3}H]8-OH-DPAT. Neurosci. Lett. **72:** 43–48, 1986.

KUEMMEL, B., BENEKE, M., KROL, G., SCHOELLNHAMMER, G., AND SPECHTMEYER, H.: Ipsapirone in the treatment of generalized anxiety disorders: results of a phase II vs multicenter trial. Psychopharmacology **96** (suppl.): 353, 1988.

LAI, J., WAITE, S. L., BLOOM, J. W., YAMAMURA, H. I., AND ROESKE, W. E.: The M2 muscarinic acetylcholine receptors are coupled to multiple signaling pathways via pertussis toxin-sensitive guanine nucleotide regulatory proteins. J. Pharmacol. Exp. Ther. **258:** 938–944, 1991.

LAMBERT, J. J., PETERS, J. A., HALES, T. G., AND DEMPSTER, J.: The properties of 5-HT_3 receptors in clonal cell lines studied by patch-clamp techniques. Br. J. Pharmacol. **97:** 27–40, 1989.

LANDSCHULZ, W. H., JOHNSON, P. F., AND MACKNIGHT, S. L.: The leucine zipper: a hypothetical structure common to a new class of DNA binding proteins. Science **240:** 1759–1764, 1988.

LARIJANI, G. E., GRATZ, I., AND AFSHAR, M.: Treatment of postoperative nausea and vomiting with ondansetron: a randomized, double-blind comparison with placebo. Anesth. Analg. **73:** 246–249, 1991.

LARSSON, L.-G., RÉNYI, L., ROSS, S. B., SVENSSON, B., ÄNGEBY-MÖLLER, K.: Differential effects on the responses of functional pre- and postsynaptic 5-HT_{1A} receptors by repeated treatment of rats with the 5-HT_{1A} receptor agonist 8-OH-DPAT. Neuropharmacology **29:** 85, 1990.

LAUDER, J. M., AND KREBS, H.: Serotonin as a differentiation signal in early neurogenesis. Dev. Neurosci. **1:** 15–30, 1978.

LEBARS, D.: Serotonin and pain. *In* Neuronal Serotonin, ed. by N. N. Osborne and M. Hamon, pp. 171–229, John Wiley & Sons Ltd., New York, 1988.

LECHLEITER, J., HELLMISS, R., DUERSON, K., ENNULAT, D., DAVID, N., CLAPHAM, D., AND PERALTA, E.: Distinct sequence elements control the specificity of G protein activation by muscarinic, acetylcholine receptor subtypes. EMBO J. **9:** 4381–4390, 1990.

LEIBUNDGUT, U., AND LANCRANJAN, I.: First results with ICS 205–930 (5-HT_3 receptor antagonist) in prevention of chemotherapy-induced emesis. Lancet **1:** 1198, 1987.

LEONHARDT, S., HERRICK-DAVIS, K., AND TITELER, M.: Detection of a novel serotonin receptor subtype (5-HT_{1E}) in human brain: interaction with a GTP-binding protein. J. Neurochem. **53:** 465–471, 1989.

LEONHARDT, S., AND TITELER, M.: Serotonin 5-HT_2 receptors: two states versus two subtypes. J. Neurochem. **53:** 316–318, 1989.

LESH, K. P., MAYER, S., DISSELKAMP-TIETZE, J., HOH, A., SCHOELLNHAMMER, G., AND SCHULTE, H. M.: Subsensitivity of the 5-HT_{1A} receptor-mediated hypothermic response to ipsapirone in unipolar depression. Life Sci. **46:** 1271–1277, 1990.

LEVY F. O., GUDERMANN, T., BIRNBAUMER, M., KAUMANN, A. J., AND BIRNBAUMER, L.: Molecular cloning of a human gene (S31) encoding a novel serotonin receptor mediating inhibition of adenylyl cyclase. FEBS Lett. **296:** 201-206, 1992.

LEYSEN, J. E.: Problems in in vitro receptor binding studies and identification, and role of serotonin receptor sites. Neuropharmacology **23:** 247–254, 1984a.

LEYSEN, J. E.: Serotonin receptor binding sites: is there pharmacological and clinical significance? Med. Biol. **61:** 139–143, 1984b.

LEYSEN, J. E.: Gaps and peculiarities in 5-HT_2 receptor studies. Neuropsychopharmacology **3:** 361–369, 1990.

LEYSEN, J. E., GEERTS, R., GOMMEREN, W., VERWIN, P. M., AND VAN GOMPEL, P.: Regional distribution of serotonin 2 receptor binding sites in the brain and effects of neuronal lesions. Arch. Int. Pharmacodyn. Ther. **256:** 301–305, 1982a.

LEYSEN, J. E., JANSSEN, P. F. M., AND NIEMEGEERS, C. J. E.: Rapid desensitization and down-regulation of 5-HT_2 receptors by DOM treatment. Eur. J. Pharmacol. **163:** 145, 1989.

LEYSEN, J. E., NIEMEGEERS, C. J. E., TOLLENAERE, J. P., AND LADURON, P. M.: Serotonergic component of neuroleptic receptors. Nature **272:** 168–171, 1978.

LEYSEN, J. E., NIEMEGEERS, J. M., VAN NUETEN, J. M., AND LADURON, P. M.: [^{3}H]ketanserin (R41 468) a selective ligand for serotonin$_2$ receptor binding sites. Mol. Pharmacol. **21:** 301–314, 1982b.

LEYSEN, J. E., VAN COMPEL, P., VERWIMP, M., AND NIEMEGEERS, C. J. E.: Role and localization of serotonin$_2$ receptor binding sites: effects of neuronal lesions in CNS. *In* Receptors: From Molecular Pharmacology to Behavior, ed. by G. Mandel and S. DeFeudis, pp. 373–383, Raven Press, New York, 1983.

LEYSEN, J. E., VAN GOMPEL, P., COMMEREN, W., WOESTENBORGHS, R., AND JANSSEN, P. A. J.: Down regulation of serotonin-S2 receptor sites in rat brain by chronic treatment with the serotonin-S2 antagonists: ritanserin and setoperone. Psychopharmacology **88:** 434–444, 1986.

LIAU, L. M., SLEIGHT, A. J., PITHA, J., AND PEROUTKA, S. J.: Characterization of a novel and potent 5-HT_{1A} receptor antagonist. Pharmacol. Biochem. Behav. **38:** 555–559, 1991.

LIBERT, F., PARMENTIER, M., LEFORT, A., DINSART, C., VAN SANDE, J., MAENHAUT, C., SIMONS, M. J., DUMONT, J. E., AND VASSART, G.: Selective amplification and cloning of four new members of the G protein-coupled receptor family. Science **244:** 569–572, 1989.

LIBERT, F., PASSAGE, E., PARMENTIER, M., SIMONS, M.-J., VASSART, G., AND MATTEI, M.-G.: Chromosomal mapping of A1 and A2 adenosine receptors, VIP receptor, and a new subtype of serotonin receptor. Genomics **11:** 225–227, 1991.

LIMBERGER, N., DEICHER, R., AND STARKE, K.: Species differences in presynaptic serotonin autoreceptors: mainly 5-HT_{1B} but possibly in addition 5-HT_{1D} in the rat, 5-HT_{1D} in the rabbit and guinea-pig cortex. Naunyn Schmiedebergs Arch. Pharmacol. **343:** 353–364, 1991.

LIST, S., AND SEEMAN, P.: Resolution of dopamine and serotonin receptor components of [^{3}H]-spiperone binding to rat brain regions. Proc. Nat. Acad. Sci. USA **78:** 2620–2624, 1981.

LIU, J., CHEN, Y., KOZAK, C. A., AND YU L.: The 5-HT_2 serotonin receptor gene Htr-2 is tightly linked to Es-10 on mouse chromosome 14. Genomics **11:** 231–234, 1991.

LIU, Y. F., AND ALBERT, P. R.: Cell-specific signaling of the 5-HT_{1A} receptor. J. Biol. Chem. **266:** 23689–23697, 1991.

LOISY, C., BEORCHIA, S., CENTONZEV, V., FOZARD, J. R., SCHECHTER, P. J., AND TELL, G. P.: Effects on migraine headache of MDL 72222, an antagonist at neuronal 5-HT receptors: double-blind, placebo-controlled study. Cephalalgia **5:** 79–82, 1985.

LÖSCHER, W., AND CZUCZWAR, S. J.: Evaluation of the 5-HT receptor agonist 8-OH-DPAT in different rodent models of epilepsy. Neurosci. Lett. **60:** 201–206, 1985.

LOWE, J. A., SEEGER, T. J., AND VINICK, F. J.: Atypical antipsychotics—recent findings and new perpectives. Med. Res. Rev. **8:** 457–497, 1988.

LOWTHER, S., DE PAERMENTIER, F., CROMPTON, M. R., AND HORTON, R. W.: 5-HT_{1D} and 5-HT_{1E} binding sites in post-mortem human brain. Br. J. Pharmacol. **102:** 246P, 1991.

LÜBBERT, H., HOFFMAN, B. J., SNUTCH, T. P., VAN DUKE, T., LEVINE, A. J., HARTIG, P. R., LESTER, H. A., AND DAVINSON, N.: cDNA cloning of a serotonin 5-HT_{1C} receptor by electrophysiological assays of mRNA-injected *Xenopus* oocytes. Proc. Natl. Acad. Sci. USA **84:** 4332–4336, 1987a.

LÜBBERT, H., SNUTCH, T. P., DASCAL, N., LESTER, H. A., AND DAVIDSON, N.: Rat brain 5-HT_{1C} receptors are encoded by a 5–6 kbase mRNA size class and are functionally expressed in injected *Xenopus* oocytes. J. Neurosci. **7:** 1159–1165, 1987b.

LUCKI, I.: 5-HT_1 receptors and behavior. Neurosci. Biobehav. Rev. **16:** 83–93, 1992.

LUCKI, I., AND FRAZER, A.: Prevention of the serotonin syndrome in rats by repeated administration of monoamine oxidase inhibitors but not tricyclic antidepressants. Psychopharmacology **77:** 205–211, 1982.

LUCKI, I., NOBLER, M. S., AND FRAZER, A.: Differential actions of serotonin antagonists on two behavioral models of serotonin receptor activation in the rat. J. Pharmacol. Exp. Ther. **228:** 133–139, 1984.

LUCKI, I., WARD, H. A., AND FRAZER, A.: Effect of mCPP on locomotor activity. J. Pharmacol. Exp. Ther. **249:** 155–164, 1989.
LUCKI, I., AND WIELAND, S.: 5-HT_{1A} receptors and behavioral responses. Neuropsychopharmacology **3:** 481–493, 1990.
LUCOT, J. B.: Blockade of 5-HT_3 receptors prevents cisplatin-induced but not motion- or sylazine-induced emesis in the cat. Pharmacol. Biochem. Behav. **32:** 207–210, 1989.
LUCOT, J. B., AND CRAMPTON, G. H.: 8-OH-DPAT suppresses vomiting in the cat elicited by motion, cisplatin or xylazine. Pharmacol. Biochem. Behav. **33:** 627–631, 1989.
LYON, R. A., DAVIS, K. H., AND TITELER, M.: [^{3}H]DOB labels a guanyl nucleotide-sensitive state of cortical 5-HT_2 receptors. Mol. Pharmacol. **31:** 194–199, 1987.
LYON, R. A., TITELER, M., FROST, J. J., AND WHITEHOUSE, P. J., WONG, D. F., WAGNER, H. N., DANNALS, R. F., LINKS, J. M., AND KUHAR, M.: ^{3}H-3-N-methylspiperone labels D2 dopamine receptors in basal ganglia, and S2 serotonin receptors in cerebral cortex. J. Neurosci. **6:** 2941–2949, 1986.
LYON, R. A., AND TITELER, M.: Pharmacology and biochemistry of the 5-HT_2 receptor. *In* The Serotonin Receptors, ed. by E. Sanders-Bush, pp. 59–88, The Humana Press, Clifton, N.J., 1988.
MAHLE, C. D., NOWAK, H. P., MATTSON, R. J., HURT, S. D., AND YOCCA, F. D.: [^{3}H]5-Carboxamidotryptamine labels multiple high affinity 5-HT_{1D}-like sites in guinea pig brain. Eur. J. Pharmacol. **205:** 323–324, 1991.
MALICK, J. B., DOSEN, E., AND BARNETT, A.: Quipazine-induced head-twitch in mice. Pharmacol. Biochem. Behav. **6:** 325–329, 1977.
MALOTEAUX, J. M., LATERRE, E. C., LADURON, P. M., JAVOY-AGID, F., AND AGID, Y.: Decrease of serotonin-2 receptors in temporal cortex of patients with Parkinson's disease and progressive supranuclear palsy. Movement Disord. **3:** 255–262, 1988.
MANN, J. J., ARANGO, V., AND UNDERWOOD, M. D.: Serotonin and suicidal behavior. Ann. N. Y. Acad. Sci. **600:** 476–485, 1990.
MANN, J. J., STANLEY, M., MACBRIDE, P. A., AND MCEWEN, B. S.: Increased serotonin-2 and beta-adrenergic receptor binding in the frontal cortices of suicide victims. Arch. Gen. Psychiatry **43:** 954–959, 1986.
MARAZZITI, D., MACCHI, E., ROTONDO, A., PLACIDI, G. F., AND CASSANO, G. B.: Involvement of serotonin systems in bulimia. Life Sci. **43:** 2123–2126, 1988.
MARCHBANKS, R. M.: Serotonin binding to nerve ending particles and other preparations from rat brain. J. Neurochem. **13:** 1481–1493, 1966.
MARCHBANKS, R. M.: Inhibitory effects of lysergic acid derivative and reserpine on 5-HT binding to nerve endings particle. Biochem. Pharmacol. **16:** 1971–1979, 1967.
MARCINKIEWICZ, M., VERGÉ, D., GOZLAN, H., PICHAT, L., AND HAMON, M.: Autoradiographic evidence for the heterogeneity of 5-HT_1 sites in the rat brain. Brain Res. **291:** 159–163, 1984.
MARCUSSON, J. O., MORGAN, D. G., WINBLAD, B., AND FINCH, C. E.: Serotonin-2 binding sites in human frontal cortex and hippocampus selective loss of S-2 sites with age. Brain Res. **311:** 51–56, 1984.
MARICQ, A. V., PETERSON, A. S., BRAKE, A. J., MYERS, R. M., AND JULIUS, D.: Primary structure and functional expression of the 5-HT_3 receptor, a serotonin-gated channel. Science **254:** 432–437, 1991.
MARKSTEIN, R., HOYER, D., AND ENGEL, G.: 5-HT_{1A} receptors mediate stimulation of adenylate cyclase in rat hippocampus. Naunyn Schmiedebergs Arch. Pharmacol. **333:** 335–341, 1986.
MARTIAL, J., LAL, S., DALPÉ, M., OLIVIER, A., DE MONTIGNY, C., AND QUIRION, R.: Apparent absence of serotonin-1B receptors in biopsied and post-mortem human brain. Synapse **4:** 203–209, 1989.
MARTIN, D. C., INTRONA, R. P., AND ARONSTAM, R. S.: Fentanyl and sufentanil inhibit agonist binding to 5-HT_{1A} receptors in membranes from the rat brain. Neuropharmacology **30:** 323–327, 1991a.
MARTIN, J. V., EDWARDS, E., JOHNSON, J. O., AND HENN, F. A.: Monoamine receptors in an animal model of affective disorder. J. Neurochem. **55:** 1142–1148, 1990a.
MARTIN, K. F., KELLETT, R., AND BUCKETT, W. R.: Membrane stabilising properties of the selective 5-HT_2 receptor agonist, (±)DOI. Eur. J. Pharmacol. **200:** 191–193, 1991b.
MARTIN, K. F., AND MASON, R.: Ipsapirone is a partial agonist at 5-hydroxytryptamine-1A (5-HT_{1A}) receptors in the rat hippocampus: electrophysiological evidence. Eur. J. Pharmacol. **141:** 479–481, 1987.
MARTIN, P., BENINGER, R. J., HAMON, M., AND PUECH, A. J.: Antidepressant-like action of 8-OH-DPAT, a 5-HT_{1A} agonist, in the learned helplessness paradigm: evidence for a postsynaptic mechanism. Behav. Brain Res. **38:** 135–144, 1990b.
MARTIN, P., AND PUECH, A. J.: Is there a relationship between 5-HT_{1B} receptors and the mechanisms of action of antidepressant drugs in the learned helplessness paradigm in rats? Eur. J. Pharmacol. **192:** 193–196, 1991.
MARTIN, P., TISSIER, M. M., ADRIEN, J., AND PUECH, A.: Antidepressant-like effects of buspirone mediated by 5-HT_{1A} post-synaptic receptors in learned helplessness paradigm. Life Sci. **48:** 2505–2511, 1991c.
MARTY, M., DROZ, J. P., POUILLART, P., PAULE, B., BRION, N., AND BONS, J.: GR 38032F, a 5-HT_3 receptor antagonist, in the prophylaxis of acute cisplatin-induced nausea and vomiting. Cancer Chemother. Pharmacol. **23:** 389–391, 1989.
MASSI, M., AND MARINI, S.: Effect of the 5-HT_2 antagonist ritanserin on food intake and on 5-HT-induced anorexia in the rat. Pharmacol. Biochem. Behav. **26:** 333–340, 1987.
MATHESON, G. K., GAGE-WHITE, D., WHITE, G., GUTHRIE, D., ROADES, J., AND DIXON, V.: The effects of gepirone and 1-(2-pyrimidinyl)-piperazine on levels of corticosterone in rat plasma. Neuropharmacology **28:** 329–334, 1989.
MATSUBARA, S., AND MELTZER, H. Y.: Effect of typical and atypical antipsychotic drugs on 5-HT_2 receptor density in rat cerebral cortex. Life Sci. **45:** 1397–1406, 1989.
MATSUDA, T., NAKANO, Y., KANDA, T., IWATA, H., AND BABA, A.: Gonadectomy changes the pituitary-adrenocortical response in mice to 5-HT_{1A} receptor agonists. Eur. J. Pharmacol. **200:** 299–304, 1991.
MATTHEWS, W. D., AND SMITH, C. D.: Pharmacological profile of a model for central serotonin receptor activation. Life Sci. **26:** 1397–1403, 1980.
MAURA, G., BARZIZZA, A., FOLGHERA, S., AND RAITERI, M.: Release of endogenous aspartate from rat cerebellum slices and synaptosomes: inhibition mediated by a 5-HT_2 receptor and by a 5-HT_1 receptor of a possibly novel subtype. Naunyn Schmiedebergs Arch. Pharmacol. **343:** 229–236, 1991.
MAURA, G., FEDELE, E., AND RAITERI, M.: Acetylcholine release from rat hippocampal slices is modulated by 5-HT. Eur. J. Pharmacol. **165:** 173–179, 1989.
MAURA, G., AND RAITERI, M.: Cholinergic terminals in rat hippocampus possess 5-HT_{1B} receptors mediating inhibition of acetylcholine release. Eur. J. Pharmacol. **129:** 333–337, 1986.
MAURA, G., ROCCATAGLIATA, E., ULIVI, M., AND RAITERI, M.: Serotonin-glutamate interaction in rat cerebellum: involvement of 5-HT_1 and 5-HT_2 receptors. Eur. J. Pharmacol. **145:** 31–38, 1988.
MAURER, B. J., CARLOCK, L., WASMUTH, J., AND ATTARDI, G.: Assignment of human dihydrofolate reductase gene to band q23 of chromosome 5 an to related pseudogene phi HD1 to chromosome 3. Somatic Cell. Mol. Genet. **11:** 79–85, 1985.
MAWE, G. M., BRANCHEK, T. A., AND GERSHON, M. D.: Peripheral neural serotonin receptors: identification and characterization with specific antagonists and agonists. Proc. Natl. Acad. Sci. USA **83:** 9799–9803, 1986.
MAY, P. C., MORGAN, D. G., AND FINCH, C. E.: Regional serotonin receptor studies: chronic methysergide treatment induces a selective and dose-dependent decrease in serotonin-2 receptors in mouse cerebral cortex. Life Sci. **38:** 1741–1747, 1986.
MCALLISTER, G., CHARLESWORTH, A., SNODIN, C., BEER, M. S., NOBLE, A. J., MIDDLEMISS, D. N., IVERSEN, L. L., AND WHITING, P.: Molecular cloning of a serotonin receptor from human brain (5HT1E): a fifth 5HT1-like subtype. Proc. Natl. Acad. Sci. USA **89:** 5517–5521, 1992.
MCCALL, R. B., AND AGHAJANIAN, G. K.: Pharmacological characterization of serotonin receptors in the facial motor nucleus: a microiontophoretic study. Eur. J. Pharmacol. **65:** 175–183, 1980.
MCCORMICK, D. A., AND WANG, Z.: Serotonin and noradrenaline excite GABAergic neurones of the guinea-pig and cat nucleus reticularis thalami. J. Physiol. **442:** 235–255, 1991.
MCENTEE, W. J., AND CROOK, T. H.: Serotonin, memory and the aging brain. Psychopharmacology **103:** 143–149, 1991.
MCKEITH, I. G., MARSHALL, E. F., FERRIER, I. N., ARMSTRONG, M. M., KENNEDY, W. N., PERRY, R. M., PERRY, E. K., AND ECCLESTON, D.: 5-HT receptor binding in post-mortem brain from patients with affective disorder. J. Affective Disord. **13:** 67–74, 1987.
MCKENNA, D. J., NAZARALI, A. J., HIMENO, A., AND SAAVEDRA, J. M.: Chronic treatment with (±)DOI, a psychotomimetic 5-HT_2 agonist, downregulates 5-HT_2 receptors in rat brain. Neuropsychopharmacology **2:** 81, 1989.
MCKENNA, D. J., AND PEROUTKA, S. J.: Differentiation of 5-HT_2 receptor subtypes using [^{125}I]-(R)-DOI and [^{3}H]ketanserin. J. Neurosci. **9:** 3482–3490, 1989.
MCKERNAN, R. M., QUIRK, K., JACKSON, R. G., AND RAGAN, I.: Solubilisation of the 5-HT_3 receptor from pooled rat cortical and hippocampal membranes. J. Neurochem. **54:** 924–930, 1990.
MEERT, T. F., AND COLPAERT, F. C.: The effects of agonists and antagonists at putative 5-HT receptor subtypes in the shock-probe conflict procedure. Psychopharmacology **89:** S23, 1986.
MEERT, T. F., AND JANSSEN, P. A.: Psychopharmacology of ritanserin: comparison with chlordiazepoxide. Drug Dev. Res. **18:** 119–144, 1989.
MELLER, E., GOLDSTEIN, M., AND BOHMAKER, K.: Receptor reserve for 5-HT_{1A}-mediated inhibition of serotonin synthesis: possible relationship to anxiolytic properties of 5-HT_{1A} agonists. Mol. Pharmacol. **37:** 231–237, 1990.
MELLER, S. T., LEWIS, S. J., BRODY, M. J., AND GEBHART, G. F.: The peripheral nociceptive actions of intravenously administered 5-HT in the rat requires dual activation of both 5-HT_2 and 5-HT_3 receptor subtypes. Brain Res. **561:** 61–68, 1991.
MELLIN, C., VALLGARDA, J., NELSON, D. L., BJÖRK, L., YU, H., ANDÉN, N.-E., GOÖREGH, I., ARVIDSSON, L.-E., AND HACKSELL, U.: A 3-D model for 5-HT_{1A}-receptor agonists based on stereoselective methyl-substituted and conformationally restricted analogues of 8-hydroxy-2-(dipropylamino)tetralin. J. Med. Chem. **34:** 497–510, 1991.
MELMER, G., SHERRINGTON, R., MANKOO, B., KALSI, G., CURTIS, D., AND GURLING, H. M. D.: A cosmid clone for the 5-HT_{1A} receptor (HTR1A) revels a TaqI RFLP that shows tight linkage to DNA loci D5S6, D5S39, and D5S76. Genomics **11:** 767–769, 1991.
MELTZER, H. Y.: Role of serotonin in depression. Ann. N. Y. Acad. Sci. **600:** 486–499, 1990.
MELTZER, H. Y., AND LOWY, M. T.: The serotonin hypothesis of depression. *In* Psychopharmacology: The Third Generation of Progress, ed. by H. Y. Meltzer, pp. 513–526, Raven Press, New York, 1987.

MENDELSON, S. D., AND GORZALKA, B. B.: 5-HT$_{1A}$ receptors: differential involvement in female and male sexual behavior in the rat. Physiol. Behav. **37:** 345–351, 1986a.

MENDELSON, S. D., AND GORZALKA, B. B.: Serotonin type 2 antagonists inhibit lordosis behaviour in the female rat: reversal with quipazine. Life Sci. **38:** 33–39, 1986b.

MENGOD, G., NGUYEN, H., LE, H., WAEBER, C., LÜBBERT, H., AND PALACIOS, J. M.: The distribution and cellular localization of the 5-HT$_{1C}$ receptor mRNA in the rodent brain examined by in situ hybridation histochemistry. Comparison with receptor binding distribution. Neuroscience **35:** 577–592, 1990.

MENGOD, G., POMPEIANO, M., MARTINEZ-MIR, M. I., AND PALACIOS, J. M.: Localization of the mRNA for the 5-HT$_2$ receptor by in situ hybridization histochemistry. Correlation with the distribution of receptor sites. Brain Res. **324:** 139–143, 1990.

MERLO-PICH, E., AND SAMANIN, R.: Disinhibitory effects of buspirone and low doses of sulpiride and haloperidol in two experimental anxiety models in rats: possible role of dopamine. Psychopharmacology **89:** 125–130, 1986.

METZ, A., GOODWIN, G. M., AND GREEN, A. R.: The administration of baclofen to mice increases 5-HT$_2$-mediated head-twitch behavior and 5-HT$_2$ receptor number in frontal cortex. Neuropharmacology **24:** 357–360, 1985.

METZ, A., AND HEAL, D. J.: In mice repeated administration of electroconvulsive shock or desmethylimipramine produces rapid alterations in 5-HT$_2$ mediated head-twitch responses and cortical 5-HT$_2$ receptor number. Eur. J. Pharmacol. **126:** 159–162, 1986.

MEYER, D. K., HOLLAND, A., LAIS, A., AND SZABO, B.: Effects of p-chloroamphetamine on release of [^{3}H]-GABA from slices of rat caudate-putamen. Eur. J. Pharmacol. **196:** 189–195, 1991.

MEYERSON, B. J., AND MALMNAS, C. O.: Brain monoamines and sexual behavior. *In* Biological Determinants of Sexual Behavior, ed. by J. S. Hutchinson, pp. 521–554, Wiley and Sons Ltd., New York, 1978.

MICZEK, K. A., AND DONAT, P.: Brain 5-HT system and inhibition of aggressive behaviour. *In* Behavioural Pharmacology of 5-HT, ed. by P. Bevan, A. R. Cools and T. Archer, pp. 117–144, Lawrence Erlbaum Assoc., Hillsdale, N.J., 1989.

MIDDLEMISS, D. N.: Stereoselective blockade at [^{3}H]5HT binding sites and at the 5-HT autoreceptor by (−)propranolol. Eur. J. Pharmacol. **101:** 289–293, 1984.

MIDDLEMISS, D. N., BREMER, M. E., AND SMITH, S. M.: A pharmacological analysis of the 5-HT receptor mediating inhibition of 5-HT release in the guinea pig frontal cortex. Eur. J. Pharmacol. **157:** 101–107, 1988.

MIDDLEMISS, D. N., PALMER, A. N., EDEL, N., AND BOWEN, D. W.: Binding of the novel serotonin agonist 8-hydroxy-2-(di-n-propylamino)-tetralin in normal and Alzheimer brain. J. Neurochem. **46:** 993–996, 1986.

MIDDLETON, J. P., RAYMOND, J. R., WHORTON, A. R., AND DENNIS, V. W.: Short-term regulation of Na^+/K^+ ATPase by recombinant 5-HT$_{1A}$ receptor expressed in HeLa cells. J. Clin. Invest. **86:** 1799–1805, 1990.

MILBURN, C. M., AND PEROUTKA, S. J.: Characterization of [^{3}H]quipazine binding to 5-HT$_3$ receptors in rat brain membranes. J. Neurochem. **52:** 1787–1792, 1989.

MILN, R. J., AND HEEL, R. C.: Ondanetron—therapeutic use as an antiemetic. Drug **41:** 574–595, 1991.

MINER, W. D., SANGER, G. J., AND TURNER, D. H.: Comparison of the effect of BRL 24924, metoclopramine and domperidone on cisplatin-induced emesis in the ferret. Br. J. Pharmacol. **88:** 374P, 1986.

MINER, W. D., AND SANGER, G. J.: Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine M-receptor antagonism. Br. J. Pharmacol. **88:** 497–499, 1986.

MINER, W. D., SANGER, G. J., AND TURNER, D. H.: Evidence that 5-HT$_3$ receptors mediate cytotoxic drug and radiation-evoked emesis. Br. J. Cancer **56:** 159–162, 1987.

MIQUEL, M.-C., EMERIT, M. B., BOLANOS, F. J., SCHECHTER, L. E., GOZLAN, H., AND HAMON, M.: Physicochemical properties of serotonin 5-HT$_3$ binding sites solubilized from membranes of NG 108–15 neuroblastoma-glioma cells. J. Neurochem. **55:** 1526–1536, 1990.

MIQUEL, M. C., EMERIT, M. B., GOZLAN, H., AND HAMON, M.: Involvement of tryptophan residue(s) in the specific binding of agonists/antagonists to 5-HT$_3$ receptors in NG108–15 clonal cells. Biochem. Pharmacol. **42:** 1453–1456, 1991.

MITA, T., HANADA, S., NISHINO, N., KUNO, T., NAKAI, H., YAMADORI, T., MIZOI, Y., AND TANAKA, C.: Decreased serotonin S2 and increased dopamine D2 receptors in chronic schizophrenics. Biol. Psychiatry **21:** 1407–1414, 1986.

MITTMAN, S. M., AND GEYER, M. A.: Effects of 5-HT$_{1A}$ agonists on locomotor and investigatory behaviors in rat differ from those of hallucinogens. Psychopharmacology **98:** 321–329, 1989.

MIZUTA, T., AND SEGAWA, T.: Chronic effects of imipramine and lithium on postsynaptic 5-HT$_{1A}$ and 5-HT$_{1B}$ sites and on presynaptic 5-HT$_3$ sites in rat brain. Jpn. J. Pharmacol. **47:** 107–113, 1988.

MIZUTA, T., AND SEGAWA, T.: Chronic effects of imipramine and lithium on 5-HT receptor subtypes in rat frontal cortex, hippocampus and choroid plexus: quantitative receptor autoradiographic analysis. Jpn. J. Pharmacol. **50:** 315–326, 1989.

MOLDERINGS, G. J., FINK, K., SCHLICKER, E., AND GÖTHERT, M.: Inhibition of noradrenaline release via presynaptic 5-HT$_{1B}$ receptors of the rat vena cava. Naunyn Schmiedebergs Arch. Pharmacol. **336:** 245–250, 1987.

MOLDERINGS, G. J., AND GÖTHERT, M.: Mutual interaction between presynaptic α_2-adrenoceptors and 5-HT$_{1B}$ receptors on the sympathetic nerve terminals of the rat inferior vena cava. Naunyn Schmiedebergs Arch. Pharmacol. **341:** 391–397, 1990.

MOLDERINGS, G. J., LIKUNGU, J., AND GÖTHERT, M.: Inhibition of noradrenaline release from the sympathetic nerves of the human saphenous vein via presynaptic 5-HT receptors similar to the 5-HT$_{1D}$ subtype. Naunyn Schmiedebergs Arch. Pharmacol. **342:** 371–377, 1990.

MOLINEAUX, S. M., JESSEL, T. M., AND AXEL, R.: 5-HT$_{1C}$ receptor a prominent serotonin receptor subtype in the central nervous system. Proc. Natl. Acad. Sci. USA **86:** 6793–6797, 1989.

MONTERO, D., DE FELIPE, M. C., AND DEL RIO, J.: Acute or chronic antidepressants do not modify [^{125}I]cyanopindolol binding to 5-HT$_{1B}$ receptors in rat brain. Eur. J. Pharmacol. **196:** 327–329, 1991.

MORGAN, D. G., MAY, P. C., AND FINCH, C. E.: Dopamine and serotonin systems in human and rodent brain: effects of age and neurodegenerative disease. J. Am. Geriatr. Soc. **35:** 334–345, 1987.

MORINAN, A.: Reduction in striatal 5-HT turnover following chronic administration of ethanol to rats. Alcohol Alcohol. **2:** 53–60, 1987.

MÖRK, A., AND GEISLER, A.: 5-HT receptor agonists influence calcium-stimulated adenylate cyclase activity in the cerebral cortex and hippocampus of the rat. Eur. J. Pharmacol. **175:** 237–244, 1990.

MOS, J., OLIVIER, B., BLOETJES, K., AND POTH, M.: Drug-induced facilitation of sexual behaviour in the male rat: behavioural. *In* Psychoneuroendocrinology of Growth and Development, ed by A. K. Slob and M. J. Baum, pp. 221–232, Bussum, Medicom Europe, The Netherlands, 1990.

MOS, J., VAN DER HEYDEN J. A. M., AND OLIVIER B.: Behavioral effects of 5-HT$_3$ antagonists in animal models for aggression, anxiety and psychosis. *In* Behavioral Pharmacology of 5-HT, ed. by P. Bevan, A. R. Cools and T. Archer, pp. 389–397, Lawrence Erlbaum Associates, Hillsdale, N.J., 1989.

MOSER, P., TRICKLEBANK, M. D., MIDDLEMISS, D. N., MIR, A. K., HIBERT, M., AND FOZARD, J. R.: Characterization of MDL 73005EF as a 5-HT$_{1A}$ selective ligand and its effects in animal models of anxiety: comparison with buspirone, 8-OH-DPAT and diazepam. Br. J. Pharmacol. **99:** 343–349, 1990.

MURAMATSU, M., CHAKI, S., USUKI-ITO, C., AND AIHARA, H.: Attenuation of serotonin-induced suppression of [^{3}H]-acetylcholine release from rat cerebral cortex by minaprine: possible involvement of the serotonin-2 receptor and K^+ channel. Neurochem. Int. **16:** 301–307, 1990.

MURAMATSU, M., TAMAKI-OHASHI, J., USUKI, C., ARAKI, H., AND AIHARA, H.: Serotonin-2 receptor-mediated regulation of release of acetylcholine by minaprine in cholinergic nerve terminal of hippocampus of rat. Neuropharmacology **27:** 603–609, 1988a.

MURAMATSU, M., TAMAKI-OHASHI, J., USUKI C., ARAKI H., CHAKI, S., AND AIHARA, H.: 5-HT$_2$ antagonists and minaprine block the 5-HT-induced inhibition of dopamine release from rat brain striatal slices. Eur. J. Pharmacol. **153:** 89–95, 1988b.

MURPHY, D. L.: Neuropsychiatric disorders and the multiple human brain serotonin receptor subtypes and subsystems. Neuropsychopharmacology **3:** 457–471, 1990.

MURPHY, D. L., MUELLER, E. A., HILL, J. L., TOLLIVER, T. J., AND JACOBSEN, F. M.: Comparative anxiogenic, neuroendocrine and other physiologic effects of mCPP given intravenously or orally to healthy volunteers. Psychopharmacology **98:** 275–282, 1989.

MYERS, R. D.: Serotonin and thermoregulation: old and new views. J. Physiol. (Paris) **77:** 505–513, 1981.

NAKADA, M. T., WIECZOREK, C. M., AND RAINBOW, T. C.: Localization and characterization by quantitative autoradiography of [^{125}I]LSD binding sites in rat brain. Neurosci. Lett. **49:** 13–18, 1984.

NELJT, H. C., KARPF, A., SCHOEFFTER, P., ENGEL, G., AND HOYER, D.: Characterisation of 5-HT$_3$ recognition sites in membranes of NG 108–15 neuroblastoma-glioma with [^{3}H]ICS 205–930. Naunyn Schmiedebergs Arch. Pharmacol. **337:** 493–499, 1988a.

NELJT, H. C., TE DUIS, I. J., AND VIJVERBERG, H. P. M.: Pharmacological characterisation of serotonin 5-HT$_3$ receptor-mediated electrical response in cultured mouse neuroblastoma cells. Neuropharmacology **27:** 301–307, 1988b.

NELSON, D. R., AND THOMAS, D. R.: [^{3}H]BRL 43694 (granisetron), a specific ligand for 5-HT$_3$ binding sites in rat brain cortical membranes. Biochem. Pharmacol. **38:** 1693–1695, 1989.

NEMEROFF, C. M., CUGHLIN, S. R., HANDLEY, D. A., AND MOSKOWITZ, M. A.: Stimulation of aortic smooth muscle cell mitogenesis by serotonin. Proc. Natl. Acad. Sci. USA **83:** 674–678, 1986.

NEWBERRY, N. R.: 5-HT$_{1A}$ receptors activate a potassium conductance in rat ventromedial hypothalamic neurones. Eur. J. Pharmacol. **210:** 209–212, 1992.

NEWMAN, M. E., BEN-ZEEV, A., AND LERER, B.: Chloroamphetamine did not prevent the effects of chronic antidepressants on 5-HT inhibition of forskolin-stimulated adenylate cyclase in rat hippocampus. Eur. J. Pharmacol. **207:** 209–213, 1991.

NEWMAN, M. E., DRUMMER, D., AND LERER, B.: Single and combined effects of desimipramine and lithium on serotonergic receptor number and second messenger function in rat brain. J. Pharmacol. Exp. Ther. **252:** 826–831, 1990.

NEWMAN, M. E., AND LERER, B.: Chronic electroconvulsive shock and desipramine reduce the degree of inhibition by 5-HT and carbachol of forskolin-stimulated adenylate cyclase in rat hippocampal membranes. Eur. J. Pharmacol. **148:** 257–260, 1988a.

NEWMAN, M. E., AND LERER, B.: Effects of lithium and desipramine administration on agonist-stimulated inositol phosphate accumulation in rat cerebral cortex. Biochem. Pharmacol. **37:** 1991–1996, 1988b.

NEWMAN, M. E., MISKIN, I., AND LERER, B.: Effects of single and repeated electroconvulsive shock administration and inositol phosphate accumulation in rat brain slices. J. Neurochem. **49:** 19–23, 1987.

NEWMAN, M. E., SHAPIRA, B., AND LERER, B.: Regulation of 5-HT_{1A} receptor function in rat hippocampus by short- and long-term administration of 5-HT_{1A} agonists and antidepressants. J. Pharmacol. Exp. Ther. **260:** 16–20, 1992.

NICKLAUS, K. J., MCGONIGLE, P., AND MOLINOFF, P. B.: [^{3}H]SCH 23390 labels both dopamine$_1$ and 5-HT_{1C} receptors in the choroid plexus. J. Pharmacol. Exp. Ther. **247:** 343–348, 1988.

NORMAN, A. B., BATTAGLIA, G., AND CREESE, I.: [^{3}H]WB 4101 labels the 5-HT_{1A} receptor subtype in rat brain. Mol. Pharmacol. **28:** 487–494, 1985.

NORTH, R. A., AND UCHIMURA, N.: 5-Hydroxytryptamine acts at 5-HT_2 receptors to decrease potassium conductance in rat nucleus accumbens neurons. J. Physiol. **417:** 1–12, 1989.

NOWAK, G., AND DULINSKI, J.: Effect of repeated treatment with ECS on serotonin receptor density and turnover in the rat cerebral cortex. Pharmacol. Biochem. Behav. **38:** 691–694, 1991.

NUTT, D. J., AND GEORGE, D. T.: Serotonin and anxiety. Neurobiol. Anxiety **3:** 189–221, 1990.

O'DELL, S. J., LA HOSTE, G. J., WIDMARK, C. B., SHAPIRO, R. M., POTKIN, S. G., AND MARSHALL, J. F.: Chronic treatment with clozapine or haloperidol differentially regulates dopamine and serotonin receptors in rat brain. Synapse **6:** 146–153, 1990.

O'DOWD, B. F., LEFKOWITZ, R. J., AND CARON, M. G.: Structure of the adrenergic and related receptors. Annu. Rev. Neurosci. **12:** 67–83, 1989.

O'NEILL, C., COWBUM, R. F., WIEHAGER, B., ALAFUZOFF, I., WINDBLAND, B., AND FOWLER, C. J.: Preservation of 5-hydroxytryptamine-1A receptor-G protein interactions in the cerebral cortex of patients with Alzheimer's disease. Neurosci. Lett. **133:** 15–19, 1991.

OAKEY, R. J., CARON, M. G., LEFKOWITZ, R. J., AND SELDIN, M. F.: Genomic organization of adrenergic and serotonin receptors in the mouse: linkage mapping of sequence-related genes provides a method for examining mammalian chromosome evolution. Genomics **10:** 338–344, 1991.

OAKLEY, N. R., JONES, B. J., TYERS, M. B., COSTALL, B., AND DOMENEY, A. M.: The effect of GR 38032F on alcohol consumption in the marmoset. Br. J. Pharmacol. **95:** 870P, 1988.

ODAKAKI, Y., KOYAMA, T., MATSUBARA, S., MATSUBARA, R., AND YAMASHITA, I.: Effects of chronic lithium treatment on serotonin binding sites in rat brain. J. Psychiatr. Res. **24:** 271–277, 1990.

OFFORD, S. J., ORDWAY, G. A., AND FRAZER, A.: Application of [^{125}I]iodocyanopindolol to measure 5-HT_{1B} receptors in the brain of the rat. J. Pharmacol. Exp. Ther. **244:** 144–153, 1988.

ÖGREN, S. O., AND FUXE, K.: Intraventricular injections of galanin counteract development of head twitches induced by the 5-HT_2 agonist DOB. Acta Physiol. Scand. **136:** 297–298, 1989.

OKADA, F., TOKUMITSU, Y., AND NOMURA, Y.: Pertussis toxin attenuates 5-HT_{1A} receptor-mediated inhibition of forskolin-stimulated adenylate cyclase activity in rat hippocampal membranes. J. Neurochem. **52:** 1566–1569, 1989.

OKAMOTO, T., MURAYAAMA, Y., HAYASHI, Y., INAGAKI, M., OGATA, E., AND NISHIMOTO, I.: Identification of a Gs activator region of the beta-adrenergic receptor that is autoregulated via protein kinase A-dependent phosphorylation. Cell **67:** 723–730, 1991.

OKSENBERG, D., AND PEROUTKA, S. J.: Antagonism of 5-HT_{1A} receptor-mediated modulation of adenylate cyclase activity by pindolol and propranolol isomers. Biochem. Pharmacol. **37:** 3429–3433, 1988.

OLIVIER, B., MOSS, J., TULP, M., SCHIPPER, J., AND BEVAN, P.: Modulatory action of serotonin in aggressive behaviour. *In* Behavioral Pharmacology of 5-HT, ed. by P. Bevan, A. R. Cools, and T. Archer, pp. 89–115, Lawrence Erlbaum Associates, Hilladale, N.J., 1989.

OLPE, H. R., AND SCHELLENBERG, A.: The sensitivity of cortical neurons to serotonin: effect of chronic treatment with antidepressants, serotonin uptake inhibitors and monoamine-oxidase-blocking drugs. J. Neural Transm. **51:** 233–244, 1981.

OLPE, H. R., SCHELLENBERG, A., AND JONES, R. S. G.: The sensitivity of hippocampal pyramidal neurons to serotonin in vitro: effect of prolonged treatment with clorgyline or clomipramine. J. Neural Transm. **60:** 265–271, 1984.

ORTMANN, R., BISCHOFF, S., RADEKE, E., BUECH, O., AND DELINI-STULA, A.: Correlations between different measures of antiserotonin activity of drugs. Study with neuroleptics and serotonin receptor blockers. Naunyn Schmiedebergs Arch. Pharmacol. **321:** 265–270, 1982.

OSBORNE, N. N., AND HAMON, M.: Neuronal Serotonin, John Wiley & Sons Ltd., New York, 1988.

OUADID, H., SEGUIN, J., DUMUIS, A., BOCKAERT, J., AND NARGEOT, J.: Serotonin increases calcium current in human atrial myocytes via the newly described 5-hydroxytryptamine-4 receptors. Mol. Pharmacol. **41:** 346–351, 1991.

OWENS, M. J., EDWARDS, E., AND NEMEROFF, C. B.: Effects of 5-HT_{1A} receptor agonists on hypothalamo-pituitary-adrenal axis activity and corticotropin-releasing factor containing neurons in the rat brain. Eur. J. Pharmacol. **190:** 113–122, 1990.

PALACIOS, J. M., AND DIETL, M. M.: Autoradiographic studies of serotonin receptors. *In* The Serotonin Receptors, ed. by E. Sanders-Bush, pp. 89–138, Humana Press, Clifton, N.J., 1988.

PALACIOS, J. M., MARKSTEIN, R., AND PAZOS, A.: Serotonin-1C sites in the choroid plexus are not linked in a stimulatory or inhibitory way to adenylate cyclase. Brain Res. **380:** 151–154, 1986.

PALACIOS, J. M., WAEBER, C., BRUINVELS, A. T., AND HOYER, D.: Direct visualization of serotonin-1D receptors in the human brain using a new iodinated radioligand. Mol. Brain Res. **13:** 175–179, 1992.

PALACIOS, J. M., WAEBER, C., MENGOD, G., AND HOYER, D.: Autoradiography of 5-HT receptors: a critical appraisal. Neurochem. Int. **18:** 17–25, 1991.

PANDEY, S. C., ISAAC, L., DAVIS, J. M., AND PANDEY, G. N.: Similar effects of treatment with desipramine and electroconvulsive shock on 5-hydroxytryptamine 1A receptors in rat brain. Eur. J. Pharmacol. **202:** 221–225, 1991.

PANGALIA-RATU LANGI, E. A., AND JANSSEN, A. A. I.: Ritanserin in the treatment of generalized anxiety disorders: a placebo-controlled trial. Hum. Psychopharmacol. **3:** 207–212, 1988.

PANICKER, M. M., PARKER, I., AND MILEDI, R.: Receptors of 5-HT_{1C} subtype expressed from cloned DNA mediate the closing of K^+ membrane channels encoded by brain mRNA. Proc. Natl. Acad. Sci. USA **88:** 2560–2562, 1991.

PAPE, H.-C., AND MCCORMICK, D. A.: Noradrenaline and serotonin selectively modulate thalamic burst firing by enhancing a hyperpolarization-activated cation current. Nature **340:** 715–718, 1989.

PARSONS, A. A.: 5-HT receptors in human and animal cerebrovasculature. Trends Pharmacol. Sci. **12:** 310–315, 1991.

PAZOS, A., CORTÉS, R., AND PALACIOS, J. M.: Quantitative autoradiographic mapping of serotonin receptors in the rat brain. II. Serotonin-2 receptors. Brain Res. **346:** 231–249, 1985a.

PAZOS, A., HOYER, D., DIETL, M. M., AND PALACIOS, J. M.: Autoradiography of serotonin receptors. *In* Neuronal Serotonin, ed. by N. N. Osborne and M. Hamon, pp. 507–543, Wiley & Sons Ltd., New York, 1988.

PAZOS, A., HOYER, D., AND PALACIOS, J. M.: The binding of serotonergic ligands to the porcine choroid plexus: characterization of a new type of serotonin recognition site. Eur. J. Pharmacol. **106:** 539–546, 1985b.

PAZOS, A., AND PALACIOS, J. M.: Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. Brain Res. **346:** 205–230, 1985.

PAZOS, A., PROBST, A., AND PALACIOS, J. M.: Serotonin receptors in the human brain. III. Autoradiographic mapping of serotonin-1 receptors. Neuroscience **21:** 97–121, 1987a.

PAZOS, A., PROBST, A., AND PALACIOS, J. M.: Serotonin receptors in the human brain. IV. Autoradiographic mapping of serotonin-2 receptors. Neuroscience **21:** 123–139, 1987b.

PEDIGO, N. W., YAMAMURA, H. I., AND NELSON, D. L.: Discrimination of multiple [^{3}H]5-HT binding sites by the neuroleptic spiperone in rat brain. J. Neurochem. **36:** 220–226, 1981.

PELLOW, S., JOHNSTON, A. L., AND FILE, S. E.: Selective agonists and antagonists for 5-hydroxytryptamine receptor subtypes, and interactions with yohimbine and FG 7142 using the elevated plus-maze test in the rat. J. Pharm. Pharmacol. **39:** 917–928, 1987.

PERALTA, E. G., ASHKENAZI, A., WINSLOW, J. W., RAMACHANDRAN, J., AND CAPON, D. J.: Differential regulation of Pi hydrolysis and adenyl cyclase by muscarinic receptor subtypes. Nature **334:** 434–437, 1988.

PEROUTKA, S. J.: Pharmacological differentiation and characterization of 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C} binding sites in rat frontal cortex. J. Neurochem. **47:** 529–540, 1986.

PEROUTKA, S. J.: 5-hydroxytryptamine receptor subtypes. Pharmacol. Toxicol. **67:** 373–383, 1990.

PEROUTKA, S. J.: Cortical and striatal variations in drug competition studies with putative 5-HT_{1D} binding sites. Brain Res. **553:** 206–210, 1991a.

PEROUTKA, S. J.: VI. Serotonin receptor subtypes and neuropsychiatric diseases: focus on 5-HT_{1D} and 5-HT_2 receptor agents. Pharmacol. Rev. **43:** 579–586, 1991b.

PEROUTKA, S. J.: Serotonin Receptor Subtypes: Basic and Clinical Aspects, John Wiley & Sons Ltd., New York, 1991c.

PEROUTKA, S. J., AND HAMICK, A.: [^{3}H]Quipazine labels 5-HT_2 recognition sites in rat cortical membranes. Eur. J. Pharmacol. **148:** 297–299, 1988.

PEROUTKA, S. J., HAMIK, A., HARRINGTON, M. A., HOFFMAN, A. J., MATHIS, C. A., PIERCE, P. A., AND WANG, S. S. H.: (R)-(−)-[77Br]4-bromo-2,5-dimethoxyamphetamine labels a novel 5-HT binding site in brain membranes. Mol. Pharmacol. **34:** 537–542, 1988.

PEROUTKA, S. J., LEBOVITZ, R. M., AND SNYDER, S. H.: Serotonin receptor binding sites affected differentially by guanine nucleotides. Mol. Pharmacol. **16:** 700–708, 1979.

PEROUTKA, S. J., LEBOVITZ, R. M., AND SNYDER, S. H.: Two distinct central serotonin receptors with different physiological functions. Science **212:** 827–829, 1981.

PEROUTKA, S. J., AND MCCARTHY, B. G.: Sumatriptan (GR 43175) interacts selectively with 5-HT_{1B} and 5-HT_{1D} binding sites. Eur. J. Pharmacol. **163:** 133–136, 1989.

PEROUTKA, S. J., MCCARTHY, B. G., AND GUAN X-M.: 5-Benzyloxytryptamine: a relatively selective 5-$HT_{1D/1B}$ agent. Life Sci. **49:** 409–418, 1991.

PEROUTKA, S. J., AND SNYDER, S. H.: Multiple serotonin receptors: differential binding of [^{3}H]5-HT, [^{3}H]LSD and [^{3}H]spiroperidol. Mol. Pharmacol. **16:** 687–695, 1979.

PEROUTKA, S. J., AND SNYDER, S. H.: Long-term antidepressant treatment decreases spiroperidol-labelled serotonin receptor binding. Science **210:** 86–90, 1980.

PEROUTKA, S. J., AND SNYDER, S. H.: [^{3}H]Mianserin: differential labeling of

serotonin$_2$ and histamine1 receptors in rat brain. J. Pharmacol. Exp. Ther. **216:** 142–148, 1981.

PERRIN, V. L., FARKKILA, M., GOASGUEN, J., DOENICKE, A., BRAND, J., AND TFELT-HANSEN, P.: Overview of initial clinical studies with intravenous and oral GR43175 in acute migraine. Cephalalgia **9** (suppl. 9): 63–72, 1989.

PETERS, J. A., AND LAMBERT, J. J.: Electrophysiology of 5-HT$_3$ receptors in neuronal cell lines. Trends Pharmacol. Sci. **10:** 172–173, 1989.

PIERCE, P. A., AND PEROUTKA, S. J.: Antagonism of 5-HT$_2$ receptor-mediated phosphatidylinositol turnover by d-LSD. J. Pharmacol. Exp. Ther. **247:** 918–925, 1988.

PIERCE, P. A., AND PEROUTKA, S. J.: Evidence for distinct 5-HT$_2$ binding site subtypes in cortical membrane preparations. J. Neurochem. **52:** 656–658, 1989.

PIPER, D., UPTON, N., THOMAS, D., AND NICHOLASS, J.: The effects of the 5-HT$_3$ receptor receptor antagonists BRL 43694 and GR 38032F in animal behavioral models of anxiety. Br. J. Pharmacol. **94:** 314P, 1988.

PLAZNIK, A., KOSTOWSKY, W., AND ARCHER, T.: Serotonin and depression: old problems and new data. Prog. Neuropsychopharmacol. Biol. Psychiatry **13:** 623–633, 1989.

POST, C., MINOR, B. G., DAVIES, M., AND ARCHER, T.: Analgesia induced by 5-HT receptor agonists is blocked or reversed by noradrenaline depletion in rats. Brain Res. **363:** 18–27, 1986.

PRANZATELLI, M. R.: Regulation of 5-HT$_2$ receptors in rat cortex. Studies with a putative selective agonist and an antagonist. Biochem. Pharmacol. **42:** 1099–1105, 1991.

PRANZATELLI, M. R., AND PLUCHINO, R. S.: The relation of central 5-HT$_{1A}$ and 5-HT$_2$ receptors: low dose agonist-induced selective tolerance in the rat. Pharmacol. Biochem. Behav. **39:** 407–413, 1991.

PRATT, G. D., AND BOWERY, N. G.: The 5-HT$_3$ receptor ligand [^{3}H]BRL 43694 binds to presynaptic sites in the nucleus tractus solitarius of the rat. Br. J. Pharmacol. **97:** 414P, 1989.

PRATT, G. D., BOWERY, N. G., KILPATRICK, G. J., LESLIE, R. A., BARNES, N. M., NAYLOR, R. J., JONES, B. J., NELSON, D. F., PALACIOS, J. M., SLATER, P., AND REYNOLDS, J. M.: Consensus meeting agrees distribution of 5-HT$_3$ receptors in mammalian hindbrain. Trends Pharmacol. Sci. **11:** 135–137, 1990.

PRITCHETT, D. B., BACH, A. W., WOZNY, M., TALEB, O., DAL TOSO, R., SHIH, J. C., AND SEEBURG, P. H.: Structure and functional expression of cloned rat serotonin 5-HT$_2$ receptor. EMBO J. **7:** 4135–4140, 1988.

PUCILOWSKI, O., AND KOSTOWSKI, W.: Aggressive behavior and the central serotonergic systems. Behav. Brain Res. **9:** 33–48, 1983.

QUIK, M., AND AZMITIA, E.: Selective destruction of the serotonergic fibers of the formix fimbria and cingulum bundle increases 5-HT$_1$ but not 5-HT$_2$ receptors in rat midbrain. Eur. J. Pharmacol. **90:** 377–384, 1983.

RADJA, F., DAVAL, G., EMERIT, M. B., GALLISSOT, M. C., HAMON, M., AND VERGÉ, D.: Selective irreversible blockade of 5-HT$_{1A}$ and 5-HT$_{1C}$ receptor binding sites in the rat brain by 8-MeO-2′-chloro-PAT: a quantitative autoradiographic study. Neuroscience **31:** 723–733, 1989.

RADJA, F., DAVAL, G., HAMON, M., AND VERGÉ, D.: Pharmacological and physicochemical properties of pre- versus postsynaptic 5-hydroxytryptamine 1A receptor binding sites in the rat brain: a quantitative autoradiographic study. J. Neurochem. **58:** 1338–1346, 1992.

RAKEL, R. E.: Long term buspirone therapy for chronic anxiety: a multicenter international study to determine safety. Southern Med. J. **83:** 194–198, 1990.

RAMSON, R. W., ASARCH, K. B., AND SHIH, J. C.: [^{3}H]-1-(2-(4-Aminophenyl)ethyl)-4-(3-trifluoromethylphenyl)piperazine: a selective radioligand for 5-HT$_{1A}$ receptors in rat brain. J. Neurochem. **46:** 68–75, 1986.

RAPPORT, M. M.: Serum vasoconstrictor (serotonin): presence of creatinine in the complex. A proposed structure of the vasoconstrictor principle. J. Biol. Chem. **180:** 961–969, 1949.

RAPPORT, M. M., GREEN, A. A., AND PAGE, I. H.: Purification of the substance which is responsible for vasoconstrictor activity of serum. Fed. Proc. **6:** 184, 1947.

RAPPORT, M. M., GREEN, A. A., AND PAGE, I. H.: Serum vasoconstrictor (serotonin): isolation and characterization. J. Biol. Chem. **176:** 1243–1251, 1948.

RAUSH, J. L., RUEGG, R., AND MOELLER, F. G.: Gepirone as a 5-HT$_{1A}$ agonist in the treatment of major depression. Psychopharmacology **26:** 169–171, 1990.

RAYMOND, J. R.: Protein kinase C induces phosphorylation and desensitization of the human 5-HT$_{1A}$ receptor. J. Biol. Chem. **266:** 14747–14753, 1991.

RAYMOND, J. R., ALBERTS, F. J., MIDDLETON, J. P., LEFKOWITZ, R. J., CARON, M. G., OBEID, L. M., AND DENNIS, V. W.: 5-HT$_{1A}$ and histamine H1 in HeLa cells stimulate phosphoinositide hydrolysis and phosphate uptake via distinct G protein pools. J. Biol. Chem. **266:** 372–379, 1991.

RAYMOND, J. R., FARGIN, A., LOHSE, M. J., REGAN, J. W., SENOGLES, S. E., LEFKOWITZ, R. J., AND CARON, M. G.: Identification of the ligand-binding subunit of the human 5-hydroxytryptamine-1A receptor with N-(p-azido-m-[125-I]iodophenethyl)spiperone, a high affinity radioiodinated photoaffinity probe. Mol. Pharmacol. **36:** 15–21, 1989a.

RAYMOND, J. R., FARGIN, A., MIDDLETON, J. P., GRAFF, J. M., HAUPT, D. M., CARON, M. G., LEFKOWITZ, R. J., AND DENNIS, V. W.: The human 5-HT$_{1A}$ receptor expressed in HeLa cells stimulates sodium-dependent phosphate uptake via protein kinase C. J. Biol. Chem. **264:** 21943–21950, 1989b.

REISER, G., AND HAMPRECHT, B.: Serotonin raises the cyclic GMP level in a neuronal cell line via 5-HT$_3$ receptors. Eur. J. Pharmacol. **172:** 195–198, 1989.

REISINE, T. D., FIELDS, J. Z., YAMAMURA, M. I., BIRD, E. D., IVERSEN, L. L., SCHREINER, P. S., AND ENNA, S. J.: Neurotransmitter receptor abnormalities in Parkinson's disease. Life Sci. **21:** 335–344, 1977.

REYNOLDS, D. J. M., ANDREWS, P. R. L., LESLIE, R. A., HARWEY, J. M., GRASBY, P. M., AND GRAHAME-SMITH, D. G.: Bilateral abdominal vagotomy abolishes binding of [^{3}H]BRL 43694 in ferret dorsovagal complex. Br. J. Pharmacol. **98:** 692P, 1989a.

REYNOLDS, D. J. M., LESLIE, R. A., GRAHAME-SMITH, D. G., AND HARVEY, J. M.: Localization of 5-HT$_3$ receptor binding sites in human dorsal vagal complex. Eur. J. Pharmacol. **174:** 127–130, 1989b.

REYNOLDS, G. P., ARNOLD, L., ROSSOR, M. N., IVERSEN, L. L., MOUNTJOY, C. Q., AND ROTH, M.: Reduced binding of [^{3}H]ketanserin to cortical 5-HT$_2$ receptors in senile dementia of the Alzheimer type. Neurosci. Lett. **44:** 47–51, 1984.

REYNTJENS, A., GELDERS, Y., HOPPENBROUWERS, M.-L., AND VEN DEN BUSSCHE, G.: Thymostenic effects of ritanserin (R55667), a centrally acting serotonin-S2 receptor blocker. Drug Dev. Res. **8:** 205–211, 1986.

RICHARDSON, B. P.: Serotonin and nociception. Ann. N. Y. Acad. Sci. **600:** 511–520, 1990.

RICHARDSON, B. P., AND BUCCHEIT, K. H.: The pharmacology, distribution and function of 5-HT$_3$ receptors. *In* Neuronal Serotonin, ed. by N. N. Osborne and M. Hamon, pp. 465–506, John Wiley Ltd., New York, 1988.

RICHARDSON, B. P., AND ENGEL, G.: The pharmacology and function of 5-HT$_3$ receptors. Trends Neurosci. **9:** 424–428, 1986.

RICKELS, K., WEISNAN, K., NORSTAD, N., SINGER, M., STOLTZ, D., BROWN, A., AND DANTON, I.: Buspirone and diazepam in anxiety: a controlled study. J. Clin. Psychiatry **43:** 81–86, 1982.

RITTENHOUSE, P. A., BAKKUM, E. A., HERBERT, G., BETHEA, C. L., AND VAN DE KAR, L. D.: Serotonin receptor subtypes mediating neuroendocrine responses to DOI. Pharmacologist **32:** 185, 1990.

RITTENHOUSE, P. A., BAKKUM, E. A., AND VAN DE KAR, L. D.: Evidence that the serotonin agonists, DOI, increases renin secretion and blood pressure through both central and peripheral 5-HT$_2$ receptors. J. Pharmacol. Exp. Ther. **259:** 58–65, 1991.

ROBINSON, D. S., ALMS, D. R., SHROTRIYA, R. C., MESSINA, M., AND WICKRAMARATNE, P.: Serotonergic anxiolytics and treatment of depression. Psychopathology **22** (suppl. 1): 27–36, 1989.

ROPERT, N., AND GUY, N.: Serotonin facilitates GABAergic transmission in the CA1 region of rat hippocampus in vitro. J. Physiol. **441:** 121–136, 1991.

ROTH, B. L., CHUANG, D. M., AND COSTA, E.: On a bovine brain peptide functioning as putative ligand for 5-HT$_2$ recognition sites. Fed. Proc. **43:** 1092, 1984.

ROTH, B. L., AND CIARANELLO, R. D.: Chronic mianserin treatment decreases 5-HT$_2$ receptor binding without altering 5-HT$_2$ receptor mRNA levels. Eur. J. Pharmacol. **207:** 169–172, 1991.

ROTH, B. L., DECKER, L., AND HERKENHAM, M.: An autoradiographic study of mianserin-induced down regulation of serotonin (5HT$_2$ and 5HT$_{1C}$) receptors. Biol. Psychiatry **25:** 42A, 1989.

ROTH, B. L., HAMBLIN, M., AND CIARANELLO, R. D.: Regulation of 5-HT$_2$ and 5-HT$_{1C}$ serotonin receptor levels—methodology and mechanisms. Neuropsychopharmacology **3:** 427–433, 1990.

ROTH, B. L., HAMBLIN, M. W., AND CIARANELLO, R. D.: Developmental regulation of 5-HT$_2$ and 5-HT$_{1C}$ mRNA and receptor levels. Dev. Brain Res. **58:** 51–58, 1991.

ROTH, B. L., NAKAKI, T., CHUANG, D. M., AND COSTA, E.: 5-Hydroxytryptamine-2 receptors coupled to phospholipase C in rat aorta: modulation of phosphoinositide turnover by phorbol ester. J. Pharmacol. Exp. Ther. **238:** 480–485, 1986.

ROTH, B. L., NAKATI, T., CHUANG, D. M., AND COSTA, E.: Evidence for an endocoid for the 5-HT$_2$ recognition site. *In* Endocoids, ed. by H. Lal, F. Labella, and J. Lane, pp. 473–476, Alan R. Liss, Inc., New York, 1985.

ROY, A., AND LINNOILA, M.: Suicidal behavior, impulsiveness and serotonin. Acta Psychiatr. Scand. **78:** 529–535, 1988.

RUBENSTEIN, R. C., LINDER, M. E., AND ROSS, E. M.: Selectivity of the β-adrenergic receptor among Gs, Gi's, and Go: assay using recombinant α subunits in reconstituted phospholipid vesicles. Biochemistry **30:** 10769–10777, 1991.

RYDELEK-FITZGERALD, L., TEITLER, M., FLETCHER, P. W., ISMAIEL, A. M., AND GLENNON, R. A.: NAN-190: agonist and antagonist interactions with brain 5-HT$_{1A}$ receptors. Brain Res. **532:** 191–196, 1990.

SADZOT, B., BARABAN J. M., GLENNON, R. A., LYON, R. A., LEONHARDT, S., JAN, C. R., AND TITELER, M.: Hallucinogenic drug interactions at human brain 5-HT$_2$ receptors: implications for treating LSD-induced hallucinogenesis. Psychopharmacology **98:** 495–499, 1989.

SAHIN-ERDEMLI, I., SCHOEFFTER, P., AND HOYER, D.: Competitive antagonism by recognized 5-HT$_2$ receptor antagonists at 5-HT$_{1C}$ receptors in pig choroid plexus. Naunyn Schmiedebergs Arch. Pharmacol. **344:** 137–142, 1991.

SANDERS-BUSH, E.: The Serotonin Receptors. Humana Press, Clifton, N.J., 1988a.

SANDERS-BUSH, E.: 5-HT receptors coupled to phosphoinositide hydrolysis. *In* The Serotonin Receptors, ed. by E. Sanders-Bush, pp. 181–198, Humana Press, Clifton, NJ, 1988b.

SANDERS-BUSH, E.: Adaptative regulation of central serotonin receptors linked to phosphoinositide hydrolysis. Neuropsychopharmacology **3:** 411–416, 1990.

SANDERS-BUSH, E., AND BREEDING, M.: Putative selective 5-HT$_2$ antagonists

block serotonin 5-HT$_{1C}$ receptors in the choroid plexus. J. Pharmacol. Exp. Ther. **247:** 169–173, 1988.

SAXENA, P. R., AND VILLALON, C. M.: 5-Hydroxytryptamine: a chameleon in the heart. Trends Pharmacol. Sci. **12:** 223–227, 1991.

SAXENA, P. R., WALLIS, D. I., WOUTERS, W., AND BERAN, P.: The Cardiovascular Pharmacology of 5-Hydroxytryptamine, Kluwer, Dordrecht, The Netherlands, 1989.

SCHACHTER, M., GODFREY, P. P., MINCHIN, M. C. W., MACCLUE, S. J., AND YOUNG, M. M.: Serotonergic agonists stimulate inositol lipid metabolism in rabbit platelets. Life Sci. **37:** 1641–1647, 1985.

SCHECHTER, L. E., BOLANOS, F. J., GOZLAN, H., LANFUMEY, L., HAJ-DAHMANE, S., LAPORTE, A. M., FATTACCINI, C. M., AND HAMON, M.: Alterations of central serotonergic and dopaminergic neurotransmission in rats chronically treated with ipsapirone: biochemical and electrophysiological studies. J. Pharmacol. Exp. Ther. **255:** 1335–1347, 1990.

SCHECHTER, L. E., AND SIMANSKY, K. J.: DOI exerts an anorexic action that is blocked by 5-HT$_2$ antagonists in rats. Psychopharmacology **94:** 342–346, 1988.

SCHILDKRAUT, J. J.: The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am. J. Psychiatry **122:** 509–522, 1965.

SCHIPPER, J., AND TULP, M. T. M.: Serotonin autoreceptors in guinea pig cortex slices resemble to 5-HT$_{1D}$ binding site. Soc. Neurosci. Abstr. **14:** 221.8, 1988.

SCHLEGEL, J. R., AND PEROUTKA, S. J.: Nucleotide interactions with 5-HT$_{1A}$ binding sites directly labeled by [^{3}H]-8-OH-DPAT. Biochem. Pharmacol. **35:** 1943–1949, 1986.

SCHLICKER, E., FINK, K., GÖTHERT, M., HOYER, D., MOLDERINGS, G., ROSCHKE, I., AND SCHOEFFTER, P.: The pharmacological properties of the presynaptic serotonin autoreceptor in the pig brain cortex conform to the 5-HT$_{1D}$ receptor subtype. Naunyn Schmiedebergs Arch. Pharmacol. **340:** 45–51, 1989.

SCHMIDT, A. W., AND PEROUTKA, S. J.: Three-dimensional steric molecular modeling of the 5-HT$_3$ receptor pharmacophore. Mol. Pharmacol. **36:** 505–511, 1989.

SCHMIDT, A. W., AND PEROUTKA, S. J.: Quantitative molecular analysis predicts 5-HT$_3$ receptor binding affinity. Mol. Pharmacol. **38:** 511–516, 1990.

SCHNEIDER, H. P., AND MCCANN, S. M.: Mono- and indolamines and control of LH secretion. Endocrinology **86:** 1127–1133, 1970.

SCHNUR, S. L., SMITH, E. R., LEE, R. L., MAS, M., AND DAVIDSON, J. M.: A component analysis of the effects of DPAT on male rat sexual behavior. Physiol. Behav. **45:** 897–901, 1989.

SCHOEFFTER, P., AND HOYER, D.: Centrally acting hypotensive agents with affinity for 5-HT$_{1A}$ binding sites inhibit forskolin-stimulated adenylate cyclase activity in calf hippocampus. Br. J. Pharmacol. **95:** 975–985, 1988.

SCHOEFFTER, P., AND HOYER, D.: 5-Hydroxytryptamine 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors mediating inhibition of adenylate cyclase activity. Pharmacological comparison with special reference to the effects of yohimbine, rauwolscine and some beta-adrenoceptor antagonists. Naunyn Schmiedebergs Arch. Pharmacol. **340:** 285–292, 1989a.

SCHOEFFTER, P., AND HOYER, D.: How selective is GR 43175? Interactions with functional 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$, 5-HT$_{1D}$ receptors. Naunyn Schmiedebergs Arch. Pharmacol. **340:** 135–138, 1989b.

SCHOEFFTER, P., AND HOYER, D.: 5HT-induced endothelium-dependent relaxation of pig coronary arteries is mediated by 5-HT receptors similar to the 5-HT$_{1D}$ receptor subtype. J. Pharmacol. Exp. Ther. **252:** 387–395, 1990.

SCHOEFFTER, P., WAEBER, C., PALACIOS, J. M., AND HOYER D.: The 5-hydroxytryptamine 5-HT$_{1D}$ receptor subtype is negatively coupled to adenylate cyclase in calf substantia nigra. Naunyn Schmiedebergs Arch. Pharmacol. **337:** 602–608, 1988.

SCHOTTE, A., AND LEYSEN, J. E.: Identification of 5-HT$_2$ receptors, α_1-adrenoceptors and amine release sites in rat brain by autoradiography with [^{125}I]7-amino-8-iodo-ketanserin. Eur. J. Pharmacol. **172:** 99–106, 1989.

SCHWEIZER, E. E., AMSTERDAM, J. D., RICKELS, K., KAPLAN, M., AND DOBRA, M.: Open trial of buspirone in the treatment of major depressive disorder. Psychopharmacol. Bull. **22:** 183–185, 1986.

SCIULLO, A., BLUET-PAJOT, M. T., MOUNIER, F., OLIVER, C., SCHMIDT, B., AND KORDON, C.: Changes in anterior pituitary hormone levels after serotonin-1A receptor stimulation. Endocrinology **127:** 567–571, 1990.

SEGAL, M., AZMITIA, E. C., AND WHITAKER-AZMITIA, P. M.: Physiological effects of selective 5-HT$_{1A}$ and 5-HT$_{1B}$ ligands in rat hippocampus: comparison to 5-HT. Brain Res. **502:** 67–74, 1989.

SELLERS, E. M., HIGGINS, G. A., AND SABELL, M. B.: 5-HT and alcohol abuse. Trends Pharmacol. Sci. **13:** 69–75, 1992.

SELLERS, E. M., KAPLAN, H. L., LAWRIN, M. O., SOMER, G., NARANJO, C. A., AND FRECKER, R. C.: The 5-HT$_3$ antagonist GR 38032F decrease alcohol consumption in rats. Soc. Neurosci. Abstr. **14:** 41, 1988.

SEUWEN, K., MAGNALDO, I., AND POUYSSÉGUR, J.: Serotonin stimulates DNA synthesis in fibroblasts acting through 5-HT$_{1B}$ receptors coupled to a Gi-protein. Nature **335:** 254–256, 1988.

SEUWEN, K., AND POUYSSÉGUR, J.: Serotonin as a growth factor. Biochem. Pharmacol. **3:** 985–990, 1990.

SHARP, T., BRAMWELL, S. R., LAMBERT, P., AND GRAHAME-SMITH, D. G.: Effect of short- and long-term administration of lithium on the release of endogenous 5-HT in the hippocampus of the rat in vivo and in vitro. Neuropharmacology **30:** 977–984, 1991.

SHARPLEY, A. L., GREGORY, C. A., SOLOMON, R. A., AND COWEN, P. J.: Slow wave sleep and 5-HT$_2$ receptor sensitivity during maintenance tricyclic antidepressant treatment. J. Affective Disorders **19:** 273–277, 1990a.

SHARPLEY, A. L., SOLOMON, R. A., FERNANDO, A. I., DA ROZA DAVIS, J. M., AND COWEN, P. J.: Dose-related effects of selective 5-HT$_2$ receptor antagonists on slow wave sleep humans. Psychopharmacology **101:** 568–569, 1990b.

SHEARD, M. H.: The effect of pCPA on behavior in rats: relation to brain serotonin and 5-HIAA. Brain Res. **15:** 524–528, 1969.

SHEARMAN, M. S., AND STRANGE, P. G.: Guanine nucleotide effects on agonist binding to serotonin$_2$ receptors in rat frontal cortex. Biochem. Pharmacol. **37:** 3097–3102, 1988.

SHEEHAM, D. V., ZAK, J. P., MILLER, J. A., AND FANOUS, B. S. L.: Panic disorder: the potential role of serotonin reuptake inhibitors. J. Clin. Psychiatry **49** (suppl.): 30–36, 1988.

SHENKER, A., MAAYANI, S., WEINSTEIN, H., AND GREEN, J. P.: Enhanced serotonin-stimulated adenylate cyclase activity in membranes from adult guinea pig hippocampus. Life Sci. **32:** 2335–2342, 1983.

SHENKER, A., MAAYANI, S., WEINSTEIN, H., AND GREEN, J. P.: Two 5-HT receptors linked to adenylate cyclase in guinea pig hippocampus are discriminated by 5-carboxamidotryptamine and spiperone. Eur. J. Pharmacol. **109:** 427–429, 1985.

SHENKER, A., MAAYANI, S., WEINSTEIN, H., AND GREEN, J. P.: Pharmacological characterization of two 5-hydroxytryptamine receptors coupled to adenylate cyclase in guinea pig hippocampal membranes. Mol. Pharmacol. **31:** 357–367, 1987.

SHEPHERD, J. K., AND RODGERS, R. J.: 8-OH-DPAT specifically enhances feeding behaviour in mice: evidence from behavioural competition. Psychopharmacology **101:** 408–413, 1990.

SHIGERI, Y., WATANABE, S., AND FUJIMOTO, M.: Dibutyryl-cAMP increases functions of 5-hydroxytryptamine-2 receptors, but not of β-adrenergic receptors, in a clonal cell line of rat neurotumor RT4. J. Cell. Physiol. **150:** 28–33, 1992.

SHIMIZU, H., HIROSE, A., TATSUMO, T., NAKAMURA, M., AND KATSUBE, J.: Pharmacological properties of SM-3997: a new anxioselective anxiolytic candidate. Jpn. J. Pharmacol. **45:** 493–500, 1987.

SIDHU, A., SULLIVAN, M., KOHOUT, T., BALEN, P., AND FISHMAN, P. H.: D1 dopamine receptors can interact with both stimulatory and inhibitory guanine nucleotide binding proteins. J. Neurochem. **57:** 1445–1451, 1991.

SIETNIEKS, A., AND MAYERSON, B. J.: Progesterone enhancement of LSD and levo-5-hydroxytryptophan stimulation of the copulatory response in female rat. Neuroendocrinology **36:** 462–467, 1983.

SIJBESMA, H., SCHIPPER, J., AND DE KLOET, E. R.: The anti-aggressive drug eltoprazine preferentially binds to 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor subtypes in rat brain: sensitivity to guanine nucleotides. Eur. J. Pharmacol. **187:** 209–223, 1990.

SIJBESMA, H., SCHIPPER, J., MOLEWUK, H. E., BOSCH, A. I., DE AND KLOET, E. R.: 8-OH-DPAT increases the activity of adenylate cyclase in the hippocampus of freely-moving rats. Neuropharmacology **30:** 967–975, 1991.

SILLS, M. A., WOLFE, B. B., AND FRAZER, A.: Determination of selective and non selective compound for the 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors subtypes in rat frontal cortex. J. Pharmacol. Exp. Ther. **231:** 480–487, 1984.

SINISCALCHI, A., BEANI, L., AND BIANCHI, C.: Different effects of 8-OH-DPAT, a 5-HT$_{1A}$ receptor agonist, on cortical acetylcholine release, electrocortigram and body temperature in guinea pigs and rats. Eur. J. Pharmacol. **175:** 219–223, 1990a.

SINISCALCHI, A., BEANI, L., AND BIANCHI, C.: Influence of chronic chlorimipramine treatment of the serotonergic modulation of acetylcholine release from guinea pig caudate nucleus slices. Neuropharmacology **29:** 1091–1093, 1990b.

SINTON, C. M., AND FALLON, S. L.: Electrophysiological evidence for a functional differentiation between subtypes of the 5-HT$_1$ receptor. Eur. J. Pharmacol. **157:** 173–181, 1988.

SLEIGHT, A. J., CERVENKA, A., AND PEROUTKA, S. J.: In vivo effects of sumatriptan (GR 43175) on extracellular levels of 5-HT in the guinea pig. Neuropharmacology **29:** 511–513, 1990.

SLEIGHT, A. J., MARSDEN, C. A., PALFREYMAN, M. G., MIR, A. K., AND LOVENBERG, W.: Chronic MAO A and MAO B inhibition decreases the 5-HT$_{1A}$ receptor-mediated inhibition of forskolin-stimulated adenylate cyclase. Eur. J. Pharmacol. **154:** 255–261, 1988.

SMITH, D. B., NEWLANDS, E. S., RUSTIN, G. J. S., BEGENT, R. H. J., HOWELLS, N., MACQUADE, B., AND BAGSHAWE, K. D.: Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin-containing chemotherapy. Lancet **338:** 487–490, 1991.

SMITH, L. M., AND PEROUTKA, S. J.: Differential effects of 5-hydroxytryptamine-1A selective drugs on the 5-HT behavioural syndrome. Pharmacol. Biochem. Behav. **24:** 1513–1516, 1986.

SMITH, W. L., CALLAHAN, E. M., AND ALPHIN, R. S.: The emetic activity of centrally administered cisplatin in cats and its antagonism by zacopride. J. Pharm. Pharmacol. **40:** 142–143, 1988.

SOUBRIÉ, P.: Reconciling the role of central serotonin neurons in human and animal behavior. Behav. Brain Sci. **9:** 319–354, 1986.

SPARKES, R. S., LAN, N., KLISAK, I., MOHANDAS, T., DIEP, A., KOJIS, T., HEINZMANN, C., AND SHIH, J. C.: Assignment of a serotonin 5-HT$_2$ receptor gene (HTR2) to human chromosome 13q14-q21 and mouse chromosome 14. Genomics **9:** 461–465, 1991.

SPROUSE, J. S., AND AGHAJANIAN, G. K.: Electrophysiological responses of serotoninergic dorsal raphe neurons to 5-HT$_{1A}$ and 5-HT$_{1B}$ agonists. Synapse **1:** 3–9, 1987.

SPROUSE, J. S., AND AGHAJANIAN, G. K.: Responses of hippocampal pyramidal

cells to putative serotonin 5-HT_{1A} and 5-HT_{1B} agonists: a comparative study with dorsal raphe neurons. Neuropharmacology **27:** 707–715, 1988.

SPROUSE, J. S., MCCARTY, D. R., AND DUDLEY, M. W.: Inhibition of dorsal raphe cell firing by MDL 73005 EF: relationship to 5-HT_{1A} receptor binding. Soc. Neurosci. Abstr. **16:** 1034, 1990.

STANLEY, M., AND MANN, J. J.: Increased serotonin-2 binding sites in frontal cortex of suicide victims. Lancet **1:** 214–216, 1983.

STEIN, R., PINKAS-KRAMARSKI, R., AND SOKOLOVSKY, M.: Cloned M1 muscarinic receptors mediate both adenylcyclase inhibition and phosphoinositide turnover. EMBO J. **7:** 3031–3035, 1988.

STERNBACH, H.: The serotonin syndrome. Am. J. Psychiatry **148:** 705–713, 1991.

STEVENS, L. T., AND LEE, F. S.: Action of intermittent pressure and of defibrinated blood upon blood vessels of frog and terrapin. Johns Hopkins Biol. Studies **3:** 99, 1884.

STOCKMEIER, C. A., AND KELLAR, K. J.: In vivo regulation of the serotonin-2 receptors in rat brain. Life Sci. **38:** 117–127, 1986.

STOTT, J. R. R., BARNES, G. R., WRIGHT, R. J., AND RUDDOCK, J. S.: The effect on motion sickness and oculomotor function of GR 38032F, a 5-HT_3 receptor antagonist with anti-emetic properties. Br. J. Pharmacol. **27:** 147–157, 1989.

STRADER, C. D., SIGAL, I. S., AND DIXON, R. A.: Structural basis of beta-adrenergic receptor function. FASEB J. **3:** 1825–1832, 1989.

STRANGE, P. G., AND PEROUTKA, S. J.: States and subtypes of the 5-HT_2 serotonin receptor: interpretation of the data. J. Neurochem. **54:** 1085–1086, 1990.

STRATFORD, C. A., TAN, G. L., HAMBLIN, M. W., AND CIARANELLO, R. D.: Differential inactivation and G protein reconstitution of subtypes of [^{3}H]5-HT binding sites in brain. Mol. Pharmacol. **34:** 527–536, 1988.

STRUHL, K.: Helix-turn-helix, zinc-finger, and leucine-zipper motifs for eukaryotic transcriptional regulatory proteins. Trends Pharmacol. Sci. **14:** 137–140, 1989.

STUTZMANN, J. M., EON, B., DARCHE, F., LUCAS, M., RATAUD, J., PIOT, O., BLANCHARD, J. C., AND LADURON, P. M.: Are 5-HT_2 antagonists endowed with anxiolytic properties in rodents? Neurosci. Lett. **128:** 4–8, 1991.

STUTZMANN, J. M., EON, B., ROUX, M., LUCAS, M., BLANCHARD, J. C., AND LADURON, P. M.: RP 62203, a 5-HT_2 antagonist, enhances slow wave sleep in rats. Eur. J. Pharmacol. **183:** 1394, 1990.

SUFKA, K. J., AND GIORDANO, J.: Analgesic effects of S and R isomers of the novel 5-HT_2 receptor antagonists ADR-851 and ADR-882 in rats. Eur. J. Pharmacol. **204:** 117–119, 1991.

SUMNER, M. J., AND HUMPHREY, P. P. A.: 5-HT_{1D} binding sites in porcine brain can be subdivided by GR 43175. Br. J. Pharmacol. **98:** 29–31,,1989.

SVENSSON, K., LARSSON, K., AHLENIUS, S., ARVIDSSON, L-E., AND CARLSSON, A.: Evidence for a facilitatory role of central 5-HT in male mouse sexual behavior. *In* Brain 5HT_{1A} Receptors: Behavioral and Neurochemical Pharmacology, ed. by C. T. Dourish, S. Ahlenius, and P. H. Hutson, pp. 199–210, Ellis Horwood Ltd., Chichester, United Kingdom, 1987.

TANAKA, H., SHIMIZU, H., KUMASAKA, Y., HIROSE, A., TATSUNO, T., AND NAKAMURA, M.: Autoradiographic localisation and pharmacological characterization of [^{3}H]tandospirone binding sites in the rat brain. Brain Res. **546:** 181–189, 1991.

TAYLOR, D. P., AND HYSLOP, D. K.: Chronic administration of buspirone down-regulates 5-HT_2 receptor binding sites. Drug Dev. Res. **24:** 93–105, 1991.

TAYLOR, D. P., AND MOON, S. L.: Buspirone and related compounds as alternative anxiolytics. Neuropeptides **19** (suppl.): 15–19, 1991.

TEITLER, M., LEONHARDT, S., WEISBERG, E. L., AND HOFFMAN, B. J.: 4-[^{125}I] iodo-(2, 5-dimethoxy)phenylisopropylamine and [^{3}H]ketanserin labelling of 5-HT_2 receptors in mammalian cells transfected with a rat 5-HT_2 cDNA: evidence for multiple states and not multiple 5-HT_2 receptor subtypes. Mol. Pharmacol. **38:** 594–596, 1990.

TENEN, S. S.: The effects of p-chlorophenylalanine, a serotonin depletor, on avoidance acquisition, pain sensitivity and related behaviour in the rat. Psychopharmacology **10:** 204–219, 1967.

TFELT-HANSEN, P., BRAND, J., AND DANO, P.: Early clinical experience with subcutaneous GR43175 in acute migraine: an overview. Cephalalgia **9** (suppl. 9): 73–77, 1989.

TITELER, M., HERRICK, K., LYON, R. A., MACKENNEY, J. D., AND GLENNON, R. A.: [^{3}H]DOB: a specific agonist radioligand for 5-HT_2 receptors. Eur. J. Pharmacol. **117:** 145–146, 1987.

TITELER, M., LYON, R. A., DAVIS, K. H., AND GLENNON, R. A.: Role of [^{3}H] DOB, a 5-HT_2 agonist radioligand. Biochem. Pharmacol. **36:** 3265–3271, 1985.

TOHDA, M., NAKAMURA, J., HIDAKA, H., AND NOMURA, Y.: Inhibitory effects of KN-62, a specific inhibitor of Ca/calmodulin-dependent protein kinase II, on serotonin-evoked Cl- current and 36Cl- efflux in *Xenopus* oocytes. Neurosci. Lett. **129:** 47–50, 1991a.

TOHDA, M., AND NOMURA, Y.: Biphasic effects of mianserin and desipramine on serotonin-evoked current and Cl- efflux in *Xenopus* oocytes. Eur. J. Pharmacol. **200:** 305–310, 1991.

TOHDA, M., SAKUMA, I., AND NOMURA, Y.: The slow cyclic GMP increase caused by serotonin in NG 108–15 cells is not inhibited by antagonists of known serotonin receptors: possible existence of a new receptor subtype coupled with membrane-bound guanylate cyclase. J. Neurochem. **57:** 714–717, 1991b.

TOHDA, M., TAKASU, T., AND NOMURA, Y.: Effects of antidepressants on serotonin-evoked current in *Xenopus* oocytes injected with rat brain mRNA. Eur. J. Pharmacol. **166:** 57–63, 1989.

TOLLEFSON, G. D.: Serotonin and alcohol: interrelationships. Psychopathology **22** (suppl. 1): 37–48, 1989.

TORTELLA, F. C., ECHEVARRIA, E., PASTEL, R. H., COX, B., AND BALCKBURN, T. P.: Suppressant effects of selective 5-HT_2 antagonists on rapid eye movement sleep in rat. Brain Res. **485:** 294–300, 1989.

TRABER, J., AND GLASER, T.: 5-HT_{1A} receptor-related anxiolytics. Trends Pharmacol. Sci. **8:** 432–437, 1987.

TRABER, J., SCHUURMAN, T., AND BENZ, U.: A comparison of the serotonergic anxiolytics buspirone, gepirone, ipsapirone, SM-3997, their common metabolite 1-PP and diazepam in animal models of anxiety. Psychopharmacology **96** (suppl.): 352, 1988.

TREISER, S., AND KELLAR, K. J.: Lithium effects on serotonin receptors in rat brain. Eur. J. Pharmacol. **64:** 183–185, 1980.

TRICKLEBANK, M. D.: The motor and discriminative stimulus properties of 8-OH-DPAT and their relationship to activation of the putative 5-HT_{1A} receptor. *In* Brain 5-HT_{1A} Receptors: Behavioral and Neurochemical Pharmacology, ed. by C. T. Dourish, S. Ahlenius, and P. H. Hutson, pp. 140–151, Ellis Horwood Ltd., Chichester, United Kingdom, 1987.

TRICKLEBANK, M. D.: Interactions between dopamine and 5-HT_2 receptors suggest new treatments for psychosis and drug addiction. Trends Pharmacol. Sci. **10:** 127–129, 1989.

TRICKLEBANK, M. D., MIDDLEMISS, D. N., AND NEILL, J.: Pharmacological analysis of the behavioural thermoregulatory effects of the putative 5-HT_1 receptor agonist RU 24969 in the rat. Neuropharmacology **25:** 877–886, 1986.

TSUTSUMI, M., AND SANDERS-BUSH, E.: 5-HT-induced transferrin production by choroid plexus epithelial cells in culture: role of 5-HT_{1C} receptor. J. Pharmacol. Exp. Ther. **254:** 253–257, 1990.

TSUTSUMI, M., SKINNER, M. K., AND SANDERS-BUSH, E.: Transferrin gene expression and synthesis by cultured choroid plexus epithelial cells. J. Biol. Chem. **264:** 9626–9631, 1989.

TUOMISTO, J., AND MANNISTO, P.: Neurotransmitter regulation of anterior pituitary hormones. Pharmacol. Rev. **37:** 249–332, 1985.

TWAROG, B. M., AND PAGE, J. H.: Serotonin content of some mammalian tissues and urine and a method for its determination. J. Physiol. **175:** 157–161, 1953.

TYERS, M. B.: A review of the evidence supporting the anxiolytic potential of 5-HT_2 receptor antagonists. *In* Behavioural Pharmacology of 5-HT, ed. by P. Bevan, A. R. Cools, and T. Archer, pp. 353–358, Laurence Erlbaum Associates, Hillsdale, N.J., 1989.

TYERS, M. B., COSTALL, B., DOMENY, A. M., JONES, B. J., KELLY, M. E., NAYLOR, R. J., AND OAKLEY, N. R.: The anxiolytic activities of 5-HT_2 antagonists in laboratory animals. Neurosci. Lett. **29:** 868, 1987.

UPHOUSE, L., MONTANEZ, S., RICHARDS-HILL, R., CALDAROLA-PASTUSZKA, M., AND DROGE, M.: Effects of the 5-HT_{1A} agonist, 8-OH-DPAT, on sexual behaviors of the proestrous rat. Pharmacol. Biochem. Behav. **39:** 635–640, 1991a.

UPHOUSE, L., SALAMANCA, S., AND CALDOROLA-PASTUSZKA, M.: Gender and estrous cycle differences in the response to the 5-HT_{1A} agonist 8-OH-DPAT. Pharmacol. Biochem. Behav. **40:** 901–906, 1991b.

VAN DE KAR, L. D.: Neuroendocrine pharmacology of serotonergic neurons. Annu. Rev. Pharmacol. Toxicol. **31:** 289–320, 1991.

VAN DE KAR, L. D., CARNES, M., MASLOWSKI, R. J., BONADONNA, A. M., RITTENHOUSE, P. A., KUNIMOTO, K., PIECHOWSKI, R. A., AND BETHEA, C. L.: Neuroendocrine evidence for denervation supersensitivity of serotonin receptors: effects of the 5-HT agonist RU 24969 on corticotropin, corticosterone, prolactin and renin secretion. J. Pharmacol. Exp. Ther. **251:** 428–434, 1989a.

VAN DE KAR, L. D., LORENS, S. A., URBAN, J. H., AND BETHEA, C. L.: Effect of selective serotonin agonists and 5-HT_2 antagonist on prolactin secretion. Neuropharmacology **28:** 299–305, 1989b.

VAN DER HEYDEN, J. A. M.: Modulation of the 5-HT system and antipsychotic activity. *In* Behavioural Pharmacology of 5-HT, ed. by P. Bevan, A. R. Cools, and T. Archer, pp. 205–223, Lawrence Erlbaum Associates, Hillsdale, N.J., 1989.

VAN DEN HOOFF, P., AND GALVAN, M.: Electrophysiology of the 5-HT_{1A} ligand MDL 73005 EF in the rat hippocampal slice. Eur. J. Pharmacol. **196:** 291–298, 1991.

VAN DER MAELEN, C. P., AND AGHAJANIAN, G. K.: Intracellular studies showing modulation of facial motoneuron excitability by serotonin. Nature **287:** 346–347, 1980.

VAN DER MAELEN, C. P., MATHESON, G. K., WILDERMAN, R. C., AND PATTERSON, L. A.: Inhibition of serotonergic dorsal raphe neurons by systemic and iontophoretic administration of buspirone, a non-benzodiazepine anxiolytic drug. Eur. J. Pharmacol. **129:** 123–130, 1986.

VAN PRAAG, H. M., ASNIS, G. M., KAHN, R. S., BROWN, S. L., KORN, M., FRIEDMAN, J. M., AND WETZLER, S.: Monoamines and abnormal behavior: a multi-aminergic perspective. Br. J. Psychiatry **157:** 723–734, 1990.

VAN WIJNGAARDEN, I., TULP, M. T., AND SOUDIJN, W.: The concept of selectivity in 5-HT receptor research. Eur. J. Pharmacol. **188:** 301–312, 1990.

VANHOUTTE, P. M.: Serotonin and the Cardiovascular Systems, Raven Press, New York, 1985.

VARRAULT, A., LEVIEL, V., AND BOCKAERT, J.: 5-HT_{1A}-sensitive adenylyl cyclase of rodent hippocampal neurons: effets of antidepressant treatments and chronic stimulation with agonists. J. Pharmacol. Exp. Ther. **257:** 433, 1991.

VERGÉ, D., DAVAL, G., MARCINKIEWICZ, M., PATEY, A., EL MESTIKAWY, S., GOZLAN, H., AND HAMON, M.: Quantitative autoradiography of multiple 5-

HT_1 receptors subtypes in the brain of control and 5,7-DHT treated rats. J. Neurosci. **6:** 3474–3482, 1986.

VERGÉ, D., DAVAL, G., PATEY, A., GOZLAN, H., EL MESTIKAWY, S., AND HAMON, M.: Presynaptic 5-HT autoreceptors on serotonergic cell bodies and/or dendrites but not terminals are of the $5\text{-}HT_{1A}$ subtype. Eur. J. Pharmacol. **113:** 463–464, 1985.

VETULANI, J., BEDNARCZYK, B., REICHENBERG, K., AND ROSKOSZ, A.: Head twitches induced by LSD and quipazine: similarities and differences. Neuropharmacology **19:** 155–158, 1980.

VETULANI, J., LEBRECHT, U., AND PILC, A.: Enhancement of responsiveness of the central serotonergic system and serotonin-2 receptor density in rat frontal cortex by electroconvulsive treatment. Eur. J. Pharmacol. **76:** 81–85, 1981.

VIALLI, M., AND ERSPAMER, V.: Cellule enterocromaffini e cellule basigranulose acidofile nei vertebrati. Z. Zellforsch. Mikrosk. Anat. **19:** 743, 1933.

VILLALON, C. M., DEN BOER, M. O., HEILIGERS, J. P. C., AND SAXENA, P. R.: Further characterization, by use of tryptamine and benzamide derivatives, of the putative $5\text{-}HT_4$ receptor mediating tachycardia in the pig. Br. J. Pharmacol. **102:** 107–112, 1991.

VOIGT, M. M., LAURIE, D. J., SEEBURG, P. H., AND BACH, A.: Molecular cloning and characterization of a rat brain cDNA encoding a 5-hydroxytryptamine-1B receptor. EMBO J. **10:** 4017–4023, 1991.

WAEBER, C., DIETL, M. M., HOYER, D., AND PALACIOS, J. M.: $5\text{-}HT_1$ receptors in the vertebrate brain. Regional distribution examined by autoradiography. Naunyn Schmiedebergs Arch. Pharmacol. **340:** 486–494, 1989a.

WAEBER C., DIETL, M. M., HOYER, D., PROBST, A., AND PALACIOS, J. M.: Visualization of a novel serotonin recognition site ($5\text{-}HT_{1D}$) in the human brain by autoradiography. Neurosci. Lett. **88:** 11–16, 1988a.

WAEBER, C., DIXON, K., HOYER, D., AND PALACIOS, J. M.: Localisation by autoradiography of neuronal $5\text{-}HT_2$ receptors in the mouse CNS. Eur. J. Pharmacol. **151:** 351–352, 1988b.

WAEBER, C., HOYER, D., AND PALACIOS, J. M.: $5\text{-}HT_2$ receptors in the human brain, autoradiographic visualisation using [^{3}H]ICS 205–930. Neuroscience **31:** 393–400, 1989b.

WAEBER, C., HOYER, D., AND PALACIOS, J. M.: GR 43175: A preferential $5\text{-}HT_{1D}$ agent in monkey and human brains as shown by autoradiography. Synapse **4:** 168–170, 1989c.

WAEBER, C., AND PALACIOS, J. M.: $5\text{-}HT_1$ receptor binding sites in the guinea pig superior colliculus are predominantly of the $5\text{-}HT_{1D}$ class and are presynaptically located on primary retinal afferents. Brain Res. **528:** 207–211, 1990.

WAEBER, C., AND PALACIOS, J. M.: Serotonin-1 receptor binding site in the human basal ganglia are decreased in Huntington's chorea but not in Parkinson's disease: a quantitative in vitro autoradiography study. Neuroscience **32:** 337–347, 1989.

WAEBER, C., SCHOEFFTER, P., HOYER, D., AND PALACIOS, J. M.: The serotonin $5\text{-}HT_{1D}$ receptor: a progress review. Neurochem. Res. **15:** 567–582, 1990a.

WAEBER, C., SCHOEFFTER, P., PALACIOS, J. M., AND HOYER, D.: $5\text{-}HT_{1D}$ receptors in guinea-pig and pigeon brain: radioligand binding and biochemical studies. Naunyn Schmiedebergs Arch. Pharmacol. **340:** 479–485, 1989d.

WAEBER, C., SCHOEFFTER, P., PALACIOS, J. M., AND HOYER, D.: Molecular pharmacology of $5\text{-}HT_{1D}$ recognition sites: radioligand binding studies in human, pig and calf brain membranes. Naunyn Schmiedebergs Arch. Pharmacol. **337:** 595–601, 1988c.

WAEBER, C., ZHANG, L., AND PALACIOS, J. M.: $5\text{-}HT_{1D}$ receptors in the guinea pig brain: pre- and postsynaptic localizations in the striatonigral pathway. Brain Res. **528:** 197–206, 1990b.

WAJDA, I. J., BANAY-SCHWARTZ, M., MAIGAULT, I., AND LAJTHA, A.: Modulation of the serotonin S2-receptor in brain after chronic lithium. Neurochem. Res. **11:** 949–957, 1986.

WALTER, A. E., HOGER, J. H., LABARCA, C., YU, L., DAVIDSON, N., AND LESTER, H. A.: Low molecular weight messenger RNA encodes a protein that controls serotonin-$5\text{-}HT_{1C}$ and acetylcholine M1 receptor sensitivity in *Xenopus* oocytes. J. Gen. Physiol. **98:** 399–417, 1991.

WANDER, T. J., NELSON, A., OKAZAKI, H., AND RICHELSON, E.: Antagonism by neuroleptics of $5\text{-}HT_{1A}$ and $5\text{-}HT_2$ receptors of normal human brain in vitro. Eur. J. Pharmacol. **143:** 279–282, 1987.

WANG, S. H., MATHIS, C. A., AND PEROUTKA, S. J.: R(−)-2,5-Dimethoxy-4-bromoamphetamine [^{77}Br]R(−)DOB: a novel radioligand which labels a 5-HT binding site subtype. Psychopharmacology **94:** 431–432, 1988.

WATLING, K. J., ASPLEY, S., SWAIN, C. J., AND SANDERS, J.: [^{3}H]Quaternised-ICS 205–930 labels $5\text{-}HT_3$ binding sites in rat brain. Eur. J. Pharmacol. **149:** 397–398, 1988.

WATSON, N. V., AND GORZALKA, B. B.: DOI-induced inhibition of copulatory behavior in male rats—reversal by $5\text{-}HT_2$ antagonists. Pharmacol. Biochem. Behav. **39:** 605, 1991.

WEINSHANK, R. L., ZGOMBICK, J. M., MACCHI, M. J., BRANCHEK, T. A., AND HARTIG, P. R.: Human serotonin 1D receptor is encoded by a subfamily of two distinct genes: $5\text{-}HT_{1D\alpha}$ and $5\text{-}HT_{1D\beta}$. Proc. Natl. Acad. Sci. USA **89:** 3630–3634, 1992.

WEINSTEIN, H., AND OSMAN, R.: On the structural and mechanistic basis of function, classification, and ligand design for 5-HT receptors. Neuropsychopharmacology **3:** 397–409, 1990.

WEISS, S., SEBBEN, M., KEMP, D. E., AND BOCKAERT, J.: Serotonin $5\text{-}HT_1$ receptors mediate inhibition of cyclic AMP production in neurons. Eur. J. Pharmacol. **120:** 227–230, 1986.

WEISSMANN, D., MACH, E., OBERLANDER, C., DEMASSEY, Y., AND PUJOL, J. F.: Evidence for hyperdensity of $5\text{-}HT_{1B}$ binding sites in the substantia nigra of the rat after 5,7-DHT intraventricular injection. Neurochem. Int. **9:** 191–200, 1986.

WEISSMANN-NANOPOULOS, D., MACH, E., MAGRE, J., DEMASSEY, Y., AND PUJOL, J. F.: Evidence for the localization of $5\text{-}HT_{1A}$ binding sites on serotonin containing neurons in the raphe dorsalis and the raphe centralis nuclei of the rat brain. Neurochem. Int. **7:** 1061–1072, 1985.

WELNER, S. A., DE MONTIGNY, C., DESROCHES, J., DESJARDINS, P., AND SURANYI-CADOTTE, B. E.: Autoradiographic quantification of $5\text{-}HT_{1A}$ receptors in rat brain following antidepressant drug treatment. Synapse **4:** 347–352, 1989.

WESEMANN, W., AND WEINER, N.: Circadian rhythm of serotonin binding in rat brain. Progr. Neurobiol. **35:** 405–428, 1990.

WETZLER, S., KAHN, R. S., ASNIS, G. M., KORN, M., AND VAN PRAAG, H. M.: Serotonin receptor sensitivity and aggression. Psychiatr. Res. **37:** 271–279, 1991.

WEYDERT, A., CLOEZ-TAYARANI, I., FILLION, M.-P., SIMON-CHAZOTTES, D., GUENET, J.-L., AND FILLION, G.: Molecular cloning of two partial serotonin $5\text{-}HT_{1D}$ receptor sequences in mouse and one in guinea pig. C. R. Acad. Sci., 319, 929–935.

WHITAKER-AZMITIA, P. M., LAUDER, J. M., SHEMMER, A., AND AZMITIA, E. C.: Postnatal changes in serotonin$_1$ receptors following prenatal alterations in serotonin levels: further evidence for functional fetal serotonin$_1$ receptors. Dev. Brain Res. **33:** 285–289, 1987.

WHITE, S. M., KUCHARIK, R. F., AND MOYER, J. A.: Effects of serotoniergic agents on isolation-induced aggression. Pharmacol. Biochem. Behav. **39:** 729–736, 1991.

WHITTON, P., AND CURZON, G.: Anxiogenic-like effect of infusing mCPP into the hippocampus. Psychopharmacology **100:** 138–140, 1990.

WIELAND, S., AND LUCKI, I.: Antidepressant-like activity of $5\text{-}HT_{1A}$ agonists measured with the forced swim test. Psychopharmacology **101:** 497–504, 1990.

WIERNSPERGER, N.: Serotonin $5\text{-}HT_2$ receptors and brain circulation. J. Cardiovasc. Pharmacol. **16** (suppl.): S20–S24, 1990.

WILKINSON, L. O., AND DOURISH, C. T.: Serotonin and animal behavior. *In* Serotonin Receptor Subtypes: Basic and Clinical Aspects, ed. by S. Peroutka, pp. 147–210, John Wiley & Sons Ltd., New York, 1991.

WILMOT, C. A., AND SZEPANIK, A. M.: Effects of acute and chronic treatments with clozapine and haloperidol on serotonin-2 and dopamine-2 receptors in the rat brain. Brain Res. **487:** 288–298, 1989.

WITZ, P., AMLEIKY, N., PLASSAT, J. L., MAROTEAUX, L., BORELLI, E., AND HEN, R.: Cloning and characterization of a *Drosophila* serotonin receptor that activates adenylate cyclase. Proc. Natl. Acad. Sci. USA **87:** 8940–8944, 1990.

WOLF, W. A., AND KUHN, D. M.: The 5-HT transporter is an additional site of action for the 5-HT agonists RU 24969 and TFMPP. Neurochem. Int. **19:** 39–44, 1991.

WONG, D. F., WAGNER, H. N., DANNALS, R. F., LINKS, J. M., FROST, J. J., RAVERT, H. T., WILSON, A. A., AND KUHAR, M. J.: Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. Science **226:** 1393–1396, 1984.

WONG, D. T., ROBERTSON, D. W., AND REID, L. R.: Specific [^{3}H]LY-278584 binding to $5\text{-}HT_3$ recognition sites in rat cerebral cortex. Eur. J. Pharmacol. **166:** 107–110, 1989.

WOUTERS, W., JANSSEN, C. G. M., VAN DUN, J., THIJSSEN, J. B. A., AND LADURON, P. M.: In vitro labelling of serotonin-S2 receptors: synthesis and binding characteristics of [^{3}H]7-aminoketanserin. J. Med. Chem. **29:** 1663–1668, 1986a.

WOUTERS, W., VAN DUN, J., AND LADURON, P. M.: 7-amino-8-[^{125}I]-X iodoketanserin ([^{125}I]amik): a high selective serotonin-S2 receptor ligand. Biochem. Pharmacol. **35:** 3199–3202, 1986b.

XIONG, W., AND NELSON, D. L.: Characterization of a [^{3}H]5-HT binding site in rabbit caudate nucleus that differs from the $5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, $5\text{-}HT_{1C}$ and $5\text{-}HT_{1D}$ subtypes. Life Sci. **45:** 1433–1442, 1989.

YAGALOFF, K. A., GUILLERMINA, L., VAN DYKE, T., LEVINE, A. J., AND HARTIG, P. R.: Serotonin $5\text{-}HT_{1C}$ receptors are expressed at high density on choroid plexus tumors from transgenic mice. Brain Res. **385:** 389–394, 1986.

YAGALOFF, K. A., AND HARTIG, P. R.: [^{125}I]LSD binds to a novel serotonergic site on rat choroid plexus epithelial cells. J. Neurosci. **5:** 3178–3183, 1985.

YAGALOFF, K. A., AND HARTIG, P. R.: Solubilisation and characterization of the $5\text{-}HT_{1C}$ site from pig choroid plexus. Mol. Pharmacol. **29:** 120–125, 1986.

YAKEL, J. L., AND JACKSON, M. B.: $5\text{-}HT_3$ receptors mediate rapid responses in cultured hippocampus and a clonal cell line. Neuron **1:** 615–621, 1988.

YAMADA, J., SUGIMOTO, Y., AND HORISAKA, K.: The evidence for the involvement of $5\text{-}HT_{1A}$ receptor in 5-HT syndrome induced in mice by tryptamine. Jpn. J. Pharmacol. **51:** 421–424, 1989.

YAMADA, J., SUMIMOTO, Y., AND HORISAKA, K.: The behavioral effects of 8-OH-DPAT in mice. Eur. J. Pharmacol. **154:** 299–304, 1988.

YAP, C. Y., AND TAYLOR, D. A.: Involvement of $5\text{-}HT_2$ receptors in the wet dog shake behavior induced by 5-HTP in the rat. Neuropharmacology **22:** 801–804, 1983.

YATES, M., LEAKE, A., CANDY, J. M., FAIRBAIRN, A. F., MCKEITH, I. G., AND FERRIER, I. N.: $5\text{-}HT_2$ receptor changes in major depression. Biol. Psychiatry **27:** 489–496, 1990.

YI, S-J., GIFFORD, A. N., AND JOHNSON, K. M.: Effect of cocaine and $5\text{-}HT_3$ receptor antagonists on 5-HT induced [^{3}H]dopamine release from rat striatal synaptosomes. Eur. J. Pharmacol. **199:** 185–189, 1991.

YOCCA, F. D.: Neurochemistry and neurophysiology of buspirone and gepirone: interactions at presynaptic and postsynaptic 5-HT_{1A} receptors. J. Clin. Psychopharmacology **10:** 6S–12S, 1990.

YOCCA, F. D., HYSLOP, D. K., SMITH, D. W., AND MAAYANI, S.: BMY 7378, a buspirone analog with high affinity selectivity and low intrinsic activity at the 5-HT_{1A} receptor in rat and guinea pig hippocampal membranes. Eur. J. Pharmacol. **137:** 293–294, 1987.

YOCCA, F. D., IBEN, L., AND MELLER, E.: Lack of receptor reserve (RR) at postsynaptic 5-HT_{1A} receptors linked to adenylyl cyclase (AC) in rat hippocampus (HP). Soc. Neurosci. Abst. **16:** 1034, 1990a.

YOCCA, F. D., AND MAAYANI, S.: 5-HT receptors linked to adenylyl cyclase activity in mammalian brain. Ann. N. Y. Acad. Sci. **600:** 212–223, 1990.

YOCCA, F. D., WRIGHT, R. N., MARGRAF, R. R., AND EISON, A. S.: 8-OH-DPAT and buspirone analogs inhibit the ketanserin-sensitive quipazine-induced head shake response in rats. Pharmacol. Biochem. Behav. **35:** 251–254, 1990b.

YOUNG, R., AND GLENNON, R. A.: Second generation anxiolytics and serotonin. *In* 5-HT Agonists comme Psychoactive Drugs, ed. by Rech and Gudelsky, pp. 239–258, NPP Press, Ann Arbor, MI, 1988.

YOUNG, R., AND JOHNSON, D. N.: Anxiolytic-like activity of R(+)- and S(−)zacopride in mice. Eur. J. Pharmacol. **201:** 151–155, 1991.

YU, L., NGUYEN, H., LE HUONG, BLOEM, L. J., KOZAK, C. A., HOFFMAN, B. J., SNUTCH, T. P., LESTER, H. A., DAVIDSON, N., AND LÜBBERT, H.: The mouse 5-HT_{1C} receptor contains eight hydrophobic domains and is X-linked. Mol. Brain Res. **11:** 143–149, 1991.

ZAK, J. P., MILLER, J. A., SHEEHAM, D. V., AND FANOUS, B. S. L.: The potential role of serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder. J. Clin. Psychiatry **49** (suppl.): 23–90, 1988.

ZELMAN, F. P., AND SCHWAB, E. F.: Characterization of a novel serotonin receptor subtype (5-HT_{1S}) in rat CNS: interaction with a GTP binding protein. J. Neurochem. **57:** 2092–2099, 1991.

ZELMAN, F. P., SCHWAB, E. F., MURPHY, R. M., AND BEHBEHANI, M. M.: Identification of a novel 5-HT_1 binding site in rat spinal cord. Neurochem. Int. **16:** 507–513, 1990.

ZGOMBICK, J. M., BECK, S. G., MAHLE, C. D., CRADDOCK-ROYAL, B., AND MAAYANI, S.: Pertussis toxin-sensitive guanine nucleotide-binding protein(s) couple adenosine A1 and 5-HT_{1A} receptors to the same effector systems in rat hippocampus: biochemical and electrophysiological studies. Mol. Pharmacol. **35:** 484–494, 1989.

ZIFA, E., HERNANDEZ, J., FAYOLLE, C., AND FILLION, G.: Postnatal development of 5-HT_1 receptors: [^{3}H]5-HT binding sites and 5-HT induced adenylate cyclase activations in rat brain cortex. Dev. Brain Res. **44:** 133–140, 1988.

ZILLES, K., RATH, M., SCHLEICHER, A., GLASER, T., AND TRABER, J.: Ontogenesis of serotonin (5-HT) binding sites in the choroid plexus of the rat brain. Brain Res. **380:** 201–203, 1986.

ZOHAR, J., AND INSEL, T. R.: Obsessive-compulsive disorders: psychobiological approaches to diagnosis, treatment and pathophysiology. Biol. Psychiatry **22:** 667–687, 1987.