Structure and Function of Serotonin 5-HT_2 Receptors

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INTRODUCTION

One of at least seven known subtypes of serotonin (5-hydroxytryptamine [5-HT_2]) receptors is the 5-HT_2 receptor. The molecular cloning of these subtypes has unequivocally defined receptor subtypes and confirmed the existence of 5-HT receptor subtypes found by earlier pharmacological, biochemical, and physiological studies. The 5-HT_2 receptors are integral membrane proteins that elicit a cellular response to serotonin in conjunction with a guanosine triphosphate binding protein (G-protein) and an effector enzyme (Shih et al. 1991). The 5-HT_2 receptors are known to activate the inositol triphosphate (IP_3)/diacylglycerol second messenger system via enzymatic cleavage of polyphosphoinositol by phospholipase C, which ultimately results in increased calcium ion levels in the cell (Conn and Sanders-Bush 1986; Pritchett et al. 1988).

The 5-HT_2 receptors are found in the brain cortical regions and may be involved in depression and suicide (Meltzer and Lowy 1987; Sternbach 1991). In addition, 5-HT_2 receptors are targets for hallucinogenic drugs that also implicate 5-HT_2 receptors as being important in mental health (Glennon, this volume; Pierce and Peroutka 1989; Sadzot et al. 1989). Outside the brain, 5-HT_2 receptors are found in platelets and smooth muscle tissue and play a role in blood pressure and in hypertension (Vanhoutte 1982). The 5-HT_2 receptors are of great interest for their multifaceted actions in the body and the importance of their function for mental and physical health.

This chapter presents the background of the research leading up to the identification and cloning of 5-HT_2 receptors and the current molecular knowledge of the 5-HT_2 receptor, with an emphasis on the structure and functions of these receptors.

BACKGROUND

Many fields of research contributed to the formation of receptor theory and the identification of 5-HT_2 receptors. Studies of hallucinogenic drugs and antipsychotic drugs provided information that led directly to the identification and cloning of 5-HT_2 receptors. Hallucinogenic drugs have been used for millennia in human culture, and scientific analysis of their chemical properties and functions began in this century. In 5-HT receptor research, lysergic acid diethylamide (LSD) has made an invaluable contribution. Hofmann first synthesized LSD and discovered its profound psychological properties (Hofmann 1975). The effects of LSD were recognized to be related to the effects of mescaline, a compound from the peyote cactus that has been used traditionally by Native Americans in religious ceremonies (Schultes 1938, 1972). LSD and mescaline present two basic structural types of hallucinogenic drugs: indoleamines (LSD) and phenylalkylamines (mescaline). Hofmann later isolated psilocybin and psilocin, the active ingredients of hallucinogenic mushrooms, and discovered that these compounds also were indolealkylamines (Schultes and Hofmann 1973). The shared indolealkylamine structure of hallucinogenic drugs and serotonin suggested that they acted through identical or similar physical mechanisms that were unknown at the time.

Concurrent with the early studies of hallucinogenic drugs was the development of a class of compounds known as antipsychotics. These drugs, exemplified by chlorpromazine and haloperidol, greatly reduced psychosis in mental patients and also were able to counteract LSD-induced psychosis (Shoichet and Solursh 1969). The observations of the structure and actions of hallucinogens and the actions of antipsychotics produced information indicating that specific functions of the, brain can be altered by specific drugs. The question then was how the drugs exert these effects.

Now it is clear that the actions of these drugs are explained by the existence of specific receptors at the neuronal surface. Early studies of receptors used isolated tissue systems such as the guinea pig ileum, where two types of serotonin receptors were identified: the D- and M-type receptors (Gaddum and Picarelli 1957). Much work also was done using electrophysiological methods to measure electrical responses of neurons to neurotransmitters and drugs such as LSD and chlorpromazine. The breakthrough technique of radioligand binding analysis occurred in the early 1970s and led to detailed pharmacological analyses of receptors and

identification of different receptor subtypes based on pharmacological specificities of individual receptors. Peroutka and Snyder (1979) first identified 5-HT_1 and 5-HT_2 receptors using [^{3}H]serotonin, [^{3}H]LSD, and [^{3}H]spiperone as radiolabels. Since that time, at least eight different 5-HT receptor subtypes have been identified by pharmacological analysis. The classification of 5-HT receptors by pharmacological methods now has been confirmed, and the pharmacological definitions are known to have been extremely accurate.

MOLECULAR CLONING OF 5-HT RECEPTORS

Today all 5-HT receptors that were identified by radioligand analysis have been cloned. (Table 1 summarizes the cloned G-protein-coupled 5-HT receptors and some of their molecular and functional properties.) The 5-HT_{1C} receptor was the first serotonin receptor cloned and identified (Julius et al. 1988). This receptor was cloned by using messenger ribonucleic acid (mRNA) extracts in conjunction with the *Xenupus* oocyte expression system to provide the basis for a functional assay. The 5-HT_2 receptor was cloned next, using a hybridization approach with a probe derived from the 5-HT_{1C} receptor (Pritchett et al. 1988).

The 5-HT_{1A} receptor was cloned by screening a genomic deoxyribonucleic acid (DNA) library with a probe derived from the ß-adrenergic receptor (P-AR). The isolated clone was called G-21, and its identity was unknown; it was later identified as the 5-HT_{1A} receptor (Fargin et al. 1988). The list of cloned receptors now includes the 5-HT_{1D}, 5-HT_{1B}, 5-HT_{1E} (also cloned as S31), and three 5-HT receptors from ***Drosophila.*** Another 5-HT receptor that has been cloned is the 5-HT_3 receptor (Maricq et al. 1991). It is not a member of the G-protein-coupled receptor family but a member of the ligand-gated ion channel receptor family.

The gene structures of several of the serotonin receptors have been determined, including the 5-HT_{1A}, 5-HT_{1D}, 5-HT_2, and ***Drosophila*** 5-HT receptors. Of considerable interest is that 5-HT_{1A}, receptors, 5-HT_{1D}, receptors, and two of the three *Drosophila* receptors are intronless genes, whereas the 5-HT_2 receptor and one of the *Drosophila* receptors contain multiple introns. These observations raise questions concerning the relationship and evolution of serotonin receptors and G-protein receptors in general.

TABLE 1. *Biochemical properties of cloned G-protein-coupled 5-HT receptors*

Receptor	No. Amino Acids	No. Introns	Second Messenger	Species
5-HT_{1A}	421 (human) 422 (rat)	0	cAMP ↓, K^+ channel, IP_3	Human, rat
5-HT_{1B}	390 (human) 386 (rat, mouse)	0	cAMP ↓	Human, rat, mouse
5-HT_{1D}	377	0	cAMP ↓	Human, dog
5-HT_{1E} (S31)	365	0	cAMP ↓	Human
5-HT_{1C}	459 (mouse), 460 (rat)	Has introns; no. not available	IP_3	Human, rat, mouse
5-HT_2	471	2	IP_3	Human, rat, mouse, hamster
5-HT-Dro_1	564	0	cAMP ↑	*Drosophila*
5-HT-Dro_{2A}	834	0	cAMP ↓	*Drosophila*
5-HT-Dro_{2B}	645	4	cAMP ↓	*Drosophila*

Traditionally, classification of receptors has been along lines of shared ligands, for example, the serotonin, acetylcholine, or gamma aminobutyric acid (GABA) receptors. However, molecular cloning of receptors has demonstrated clearly that protein structural relations are not reflected in ligand specificities of receptors. For example, 5-HT acts on the G-protein-coupled receptors and the 5-HT_3 receptor coupled with an ion channel. The observation that a receptor's functional and evolutionary relationship to other receptors cannot be determined by shared ligands is reinforced by the demonstration of the intronless nature of some 5-HT receptors.

Further evidence arose from the molecular cloning of the human and mouse 5-HT_2 receptor genes (Chen et al. 1992; Yang et al. 1992). The 5-HT_2 receptor genes contain three exons for the coding region of the receptor (figure 1). This was the first demonstration of an intron containing the 5-HT receptor gene: The 5-HT_{1A}, 5-HT_B, 5-HT_D, and 5-HT_E receptors are intronless. The 5-HT_{1C}, (Yu et al. 1991) and 5-HT_2 receptors have a high degree of sequence homology, and both contain introns. On the other hand, 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D}, receptors are intronless, as is the ß-AR. The intronless 5-HT receptors are clearly more closely related to the P-AR than to the 5-HT_{1C}, and 5-HT_2, receptors, based on sequence homology and gene structure, but share activating ligand 5-HT with the 5-HT_{1C}, and 5-HT_2, receptors, not the more closely related P-AR.

Thus, in many cases the use by two receptors of the same activating ligand is seen as a convergent evolution that does not reflect a common ancestral source gene. More anomalies are presented by the structures of *Drosophila* 5-HT receptor genes when evolutionary relationships are examined. Three *Drosophila* 5-HT receptors have been cloned. The primary structures of these genes indicate that they are more closely related to the intronless 5-HT/ß-AR group, but one of these three genes in *Drosophila* contains introns. The intron organization is different from that of the 5-HT_2 gene. The questions concerning 5-HT gene structure and functional and evolutionary relationships—when and where introns were acquired or lost-are open and amenable to further study.

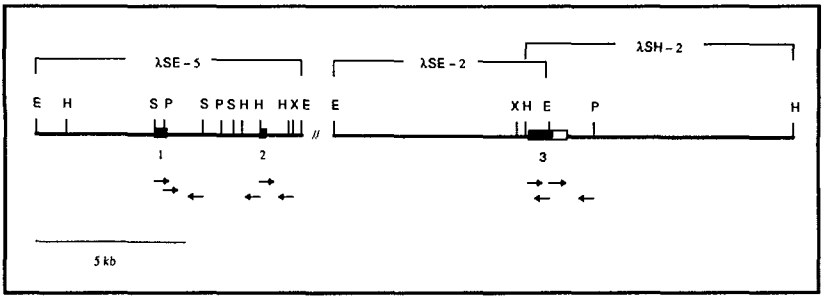

FIGURE 1. *Partial structural map of the human 5-HT$_2$ receptor gene. λ-Clones designated λSE-5, λSE-2, and λSH-2 were isolated from λ-phage genomic DNA libraries. The filled boxes are the three exon coding regions, and the open box is the untranslated region. '//' represents the intron gap between the genomic clones. Arrows indicate the start sites and direction of sequencing. The restriction enzyme sites are as follows: E = EcoRI; X = XbaI; S = SmaI; P = PstI; H = HindIII.*

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FUNCTIONAL STRUCTURE OF 5-HT RECEPTORS

Except for the 5-HT$_3$ receptor, 5-HT receptors are members of the G-protein-coupled family of integral membrane receptor proteins. These receptors show seven hydrophobic regions that are believed to traverse the lipid bilayer seven times analogously to bacteriorhodopsin (BR) and rhodopsin. This topological structure acts as the major determinant for the functional three-dimensional (3-D) structure. The receptors are classified into three main domains: the extracellular domain, which includes the amino terminal and three extracellular loops between membrane spanning regions; the transmembrane domain (TMD), consisting of the seven hydrophobic α-helices that span the membrane; and the intracellular domain, comprising the carboxy terminal and three cytoplasmic loops between the TMDs.

Experimental evidence indicates that the TMDs form the binding sites for agonists and antagonists and that certain TMD residues are necessary for allbsteric activation of the G-protein and signal transduction. The cyroplasmic loops two and three are implicated in G-protein coupling and

are necessary for activation of the G-protein and conferring the specific G-protein/receptor coupling. Most of the knowledge of the structure and function of the G-protein receptors comes from studies of adrenergic and muscarinic receptors. The general principles of their structure and function mentioned above are expected to be true also for 5-HT receptors and other G-protein receptors, but as yet little work has been done on the 5-HT receptors. The authors' laboratory has begun an analysis of the rat 5-HT_2 receptor using site-directed mutagenesis and the known primary structures of 5-HT_2 receptors from different species.

MUTAGENESIS OF ASPARTIC ACID RESIDUES IN THE 5-HT_2 RECEPTOR-G-PROTEIN COUPLING

Three aspartic acid (Asp) residues of the rat 5-HT_2 receptor were mutated to asparagine (Asn) residues to determine the role of the negatively charged aspartate on receptor function. The mutated residues were Asp- 120, Asp-l 55, and Asp- 172. The effects of the mutations were analyzed by using [^{125}I]-LSD for radioligand binding studies to determine agonist and antagonist binding properties and by measuring agonist-stimulated [^{3}H]polyphosphoinositol formation in the mutant and wild-type receptors.

The results indicate that Asp-120 is necessary for the activation of second messengers through the G-protein. Mutation of this residue in the second TMD abolishes 5-HT-stimulated phosphoinositol (PI) turnover. This mutation also confers a loss of affinity for 5-HT and (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) binding to the receptor, comparable with the loss of affinity seen in wild-type receptors caused by the presence of guanosine triphosphate (GTP) that induces uncoupling of the receptor G-protein complex and a lower affinity state for agonist. The effect of GTP on the binding of 5-HT and DOI is greatly reduced in this mutation. Little difference is seen in DOI and 5-HT binding in the presence of GTP, whereas the wild-type receptor affinity is greatly reduced because of the presence of GTP. These results are consistent with Asp- 120 being necessary for G-protein/receptor allostericity where the receptor activates the G-protein and the G-protein/receptor complex confers the high-affinity agonist binding state to the receptor. When uncoupled because of GTP, the receptor exhibits lower affinity agonist binding. The Asp-120 mutation is seen as an uncoupled mutant that is unable to activate second messenger production because of its inability to allosterically modulate the G-protein. This uncoupling may be caused by

a loss of allosteric effects conferred by the loss of the negatively charged aspartate, rather than the loss of a direct interaction between Asp-120 and the G-protein, because the position of Asp-120 in the lipid bilayer TMD of the protein makes a direct contact unlikely.

The result of this mutation correlates well with mutagenesis of the P-AR, α-adrenergic receptor (α-AR), and muscarinic receptors where the cognate Asp in the TMD of these receptors also played the same role. The conserved structure of G-protein receptors where an aspartic acid occurs in the hydrophobic second TMD suggests that this is an allosteric feature retained by all members of the G-protein-coupled receptor family.

AGONIST-BINDING SITE

Mutagenesis implicates Asp-155 in the third TMD as being necessary for high-affinity agonist and antagonist binding. Mutation of this residue to Asn causes a profound loss of binding affinity for the agonists 5-HT and DOI, as determined by competition for [^{125}I]-LSD binding, and also decreases antagonist affinity. Phosphoinositide turnover is not abolished in this mutant, and GTP-sensitive binding is retained. The role of this negative amino acid in the hydrophobic third TMD is presumably to act as a counter ion for the amine group of the ligands. As a negative amino acid, Asp-155 acts as one of the epitopes for ligand binding but not as a determinant for G-protein coupling.

These observations parallel those seen for the adrenergic receptors and the muscarinic receptor. The conserved nature of the Asp residue in the third TMD in receptors for amine-containing ligands (e.g., adrenergic, muscarinic, dopaminergic, and serotonergic receptors) and its absence in receptors whose ligands do not contain aliphatic amines, support a conserved role in binding in the aliphatic amine receptors such as the 5-HT$_2$ receptor.

Another putative binding epitope for 5-HT association with the 5-HT$_2$ receptor is serine (Ser)-239 in the fifth TMD. The difference in primary structure of the rat and human 5-HT$_2$ receptors has been advantageous in examining this possibility. The human 5-HT$_2$ receptor and rat receptor are highly homologous in their amino acid structure. Both contain Ser-239, but one of the three differences in the TMD sequence is seen at position 242 in the fifth TMD, where the human receptor expresses a Ser and the rat receptor expresses an alanine (Ala). The Ser-239 is predicted

to act as a hydrogen-bonding site for serotonin's 5-hydroxyl group in both rat and human 5-HT_2 receptors.

Ser-242 of the human receptor presents another possible hydrogen bond donor, whereas Ala-242 of the rat receptor does not. The helical structure of the fifth TMD indicates that a hydroxy group at the 4-position of the indole ring could interact with Ser-242 of the human receptor with the same geometry as 5-HT interacting with Ser-239. Therefore, a 4-hydroxyl serotonin analog should bind with higher affinity to the human receptor than to the rat receptor.

The hallucinogenic drugs 4-hydroxydimethyltryptamine (psilocin) and 5-hydroxydimethyltryptamine (bufotenin), both amino-dimethylated analogs of 5-HT, were used to examine this possibility. Psilocin bound to human receptors with a fifteenfold higher affinity than to rat receptors, whereas bufotenin bound to both species' receptors with equal affinity (less than twofold difference in dissociation constants). These results indicate the hydoxyl substituents serve as binding epitopes and that Ser-239 associates with 5-hydroxy groups as in serotonin.

The human receptor with the Ser-242 can bind 4-hydroxytryptamines such as psilocin with high affinity, but other 5-HT_2 receptors that express Ala-242 do not. These results are also consistent with observations concerning the adrenergic receptors and their interactions with ligand hydroxy groups. The conservation of hydroxyl-containing amino acids in the fifth TMD of receptors for agonists, with hydroxyl substituents (e.g., serotonin), but not in those without, also supports this analysis.

TOPOLOGICAL STRUCTURE

The role of Asp-172 at the interface of the third TMD and the second cytoplasmic loop is not clearly defined by mutagenesis to asparagine. This mutation reduces the binding affinity of agonists and antagonists; decreases the magnitude of GTP-induced binding affinity changes, but does not abolish it; and does not abolish 5-HT-stimulated PI production. These results could be interpreted to indicate that Asp-172 may serve as an epitope for the ligand amine groups as suggested for Asp-155. However, the inconsistency of mutagenesis results in other G-protein receptors indicates Asp-172 may serve another role in 5-HT_2 receptor structure. When mutated, cognate aspartic acids sometimes abolish second messenger stimulation and sometimes do not, depending on the,

receptor. Asp-172 and its cognates are found in virtually all G-protein receptors, regardless of the structure of their ligand, in a three amino acid motif of Asp-Arg-Tyr (aspartic acid-arginine-tyrosine [DRY]). Some opsin proteins express the functionally analogous motif of Glu-Arg-Tyr (ERY).

It is possible that this motif serves as a topological determinant for the positioning of the third TMD in the lipid bilayer. Charged amino acids have been shown to serve this function in other membrane proteins (Boyd and Beckwith 1989). Mutation of Asp-172 would thus result in a changed topography and affect the global 3-D structure of the receptor. This mutation would account for lowered affinities seen for ligand binding and can account for the loss of G-protein coupling in some receptors but not others. The global changes induced by this mutation would slightly change the binding site geometry, conferring the observed lower affinity binding. In some receptors the topological difference would affect G-protein coupling, whereas in others such as the 5-HT_2 receptor the change would not affect such a coupling. Different receptors couple with different G-proteins, so this interpretation is consistent with the known properties of G-proteins and the nature of membrane protein topological determinants.

FUTURE

It is evident that 5-HT_2 receptors and other G-proteins are structurally complex and that the mutagenesis studies of these receptors and proteins have just begun to address their structure-function relationship. Many more studies combining mutagenesis with biophysical investigations can reveal the molecular mechanisms of their function. Currently, mutagenesis yields the most information regarding the structure of the receptors and provides the most easily accessible, although indirect but powerful, method to study the structure and function of 5-HT receptors.

Biophysical studies that can provide direct information concerning structure and function are hampered by the unavailability of purified receptor preparations. For example, fluorescent ligand studies using purified reconstituted ß-AR have shown the binding site to reside in the hydrophobic TMD of the receptor, a finding consistent with the results of mutagenesis. Because of the low percentage of 5-HT_2 receptor protein expressed in brain tissues, the receptors are difficult to purify in any large quantity. To overcome this problem, alternate expression systems need

to be developed in microorganisms such as yeast or bacteria to provide ample source materials for purification.

Detailed knowledge of the structure and function of the 5-HT_2 receptor obtained by a variety of methods will provide a basis for designing new therapeutic agents for treating diseases associated with 5-HT_2 receptors.

The isolation of the carrier deoxyribonucleic acid (cDNA) and genomic clones of 5-HT_2 receptors provides more than just a basis for the study of their molecular structure and function. The possibility that polymorphisms in 5-HT_2 receptor genes may contribute to disease states can be examined. Any polymorphisms in the gene can be examined using cDNA or gene probes. If a polymorphism is found to be associated with a disease state, then the DNA sequences can provide possible diagnostic tools for these states.

The most exciting future project is the regulation of the 5-HT_2 receptor gene expression. The promoter region of a gene consists of the core promoter, enhancer, and repressor. The core promoter is the region controlling the transcription of the gene and is regulated by enhancers or repressors. These DNA sequences bind specific protein transcription factors to fine-tune gene expression. An example of such gene expression regulatory factor is SP-1 proteins known to be active in the regulation of monoamine oxidase A gene expression,

Researchers are at an exciting point where they can use molecular biological techniques to investigate the mechanisms for regulation of the 5-HT_2 receptor gene. It is now possible to investigate whether hallucinogenic agents play a role in the gene expression by influencing either cis-element or *trans*-element.

Moreover, it is interesting to note that there may be tissue-specific elements in the 5-HT_2 receptor promoter. Once brain-specific elements are identified, it would be possible to manipulate the expression of the receptor only in the brain to better understand the function of brain 5-HT_2 receptors and their relation to hallucinogenic effects. This new knowledge will help researchers to design therapeutic agents that are brain specific. Any mutations in this region may affect the expression of the receptor and contribute to diseases. The molecular cloning of the 5-HT_2 receptor gene allows many possibilities to be examined and can contribute to the knowledge and treatment of mental disease or other serotonin-related illnesses.

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