The $5$-HT$_{1A}$ Receptor: From Molecular Characteristics to Clinical Correlates

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1. Introduction and Historical Perspective

The past decade has seen a remarkable growth in our understanding of the pharmacology and physiology of the various receptors for serotonin (5-hydroxytryptamine, 5-HT). Since 1979, when radioligand binding techniques were used to distinguish subtypes of 5-HT binding sites (Peroutka and Snyder, 1979), no less than ten subtypes of 5-HT receptors have been characterized (Richardson and Engel, 1986; Bradley et al., 1986; Mawe et al., 1986; Heuring and Peroutka, 1987; Dumuis et al., 1988b; Leonhardt et al., 1989; Conner and Monsour, 1990). However, the biochemical characterization of these receptors has been hampered by the lack of selective radioligands and/or cell lines expressing single well-characterized receptor subtypes.

Nowhere have the difficulties been more apparent than with the 5-HT$_{1A}$ receptor. Despite active development of radioligands (Gozlan et al., 1983, 1988a; Norman et al., 1985; Dompert et al., 1985; Moon and Taylor, 1985; Glaser and Traber, 1985; Ransom et al., 1986a; Cossery et al., 1987; Nelson et al., 1987; Herrick-Davis and Titeler, 1988; Gallagher and Wang, 1988), photoaffinity labels (Ransom et al., 1986b; Emerit et al., 1987; Gozlan et al., 1988b), and solubilization protocols (Asarch and Shih, 1987; Gozlan et al., 1987; El Mestikawy et al., 1988), attempts to purify the receptor were largely unsuccessful until recently (El Mestikawy et al., 1989). Fortunately, molecular biology techniques have proved to be powerful adjuncts to classic biochemical and pharmacological approaches to the characterization of this receptor subtype. The genes encoding this receptor have been cloned from human and rat by two different groups using low-stringency cross-hybridization (Kobilka et al., 1987b; Fargin et al., 1988; Albert et al., 1990).
Since this receptor is apparently well conserved among mammalian species (Hoyer, 1989), cloning and expression of the 5-HT\textsubscript{1A} receptor from other species such as hamster, guinea pig, and pig will undoubtedly soon follow.

The story of the initial cloning of the 5-HT\textsubscript{1A} receptor gene is fascinating, both from a point of historical perspective and from the remarkable insight which has been gained regarding the larger family of genes encoding G-protein-coupled receptors. This receptor was first cloned in 1987 by Brian Kobilka and colleagues. They had cloned first the hamster \(\beta_2\)-adrenergic receptor (\(\beta_2\)-AR) in collaboration with the group of Richard Dixon and Catherine Strader at Merck (Dixon et al., 1986), followed by the human \(\beta_2\)-AR (Kobilka et al., 1987a). They next sought to clone the human \(\beta_1\)-AR from a genomic library by low-stringency cross-hybridization using the full-length \(\beta_2\)-AR sequence as a probe. A single minor cross-hybridizing species termed \(\beta_2\)-AR was obtained. Like the \(\beta_2\)-AR gene, \(\beta_2\)-AR was intronless. This DNA was determined to encode a putative protein product with striking sequence and structural similarities to \(\beta_2\)-AR and rhodopsin (Figure 5.1), sharing particular sequence identity (41\%) with the \(\beta_2\)-AR in the putative transmembrane domains. However, this DNA was found not to encode an adrenergic receptor. In fact, initial studies in \textit{Xenopus} oocytes failed to reveal ligand binding or second messenger functions.Remarkably, the \(\beta_2\)-AR was subsequently cloned in a fortuitous fashion by using \(\beta_2\)-AR to probe a human placental library (Frielle et al., 1987).

In mid-1988, the \(\beta_2\)-AR DNA was transfected into COS-7 African green monkey kidney cells in order to screen for binding with adrenergic ligands. Although no specific binding was obtained with \(^{3}H\)epinephrine or \(^{3}H\)rauwolscine, specific binding with the \(\beta\)-AR partial agonist ligand \(^{125}\)I[cyanopindolol was obtained in these cells by displacing with the \(\beta\)-AR antagonist propranolol (Fargin et al., 1988). However, saturation studies with \(^{125}\)I[cyanopindolol revealed only a moderate affinity (\(\approx 10\) nM), more consistent with a 5-HT\textsubscript{1A} receptor subtype (Hoyer et al., 1985a,b). Binding studies with the specific agonist 5-HT\textsubscript{1A} receptor ligand \(^{3}H\)8-dihydroxy-2-(di-n-propylamino)tetratin (\(^{3}H\)8-OH-DPAT) subsequently confirmed that clone G-21 encodes the human 5-HT\textsubscript{1A} receptor (Fargin et al., 1988; Raymond, 1989a). The identification of the protein encoded by G-21 using two “typical” \(\beta\)-AR ligands (cyanopindolol and propranolol) further illustrates the remarkable overlap in both the structure and functions of these members of the family of G-protein-coupled receptors.

2. Pharmacology

In 1979 Peroutka and Snyder used radioligand binding techniques to distinguish between two subtypes of 5-HT recognition sites in the central nervous system. According to their convention, 5-HT\textsubscript{1} binding sites are labeled by \(^{3}H\)5-HT, displaying nanomolar affinity for 5-HT. 5-HT\textsubscript{2}