Preface

It has been nearly 20 years since the last Humana Press book devoted to serotonin (5-hydroxytryptamine; 5-HT) receptors has appeared. Since then, the field of 5-HT receptors has undergone a revolution due to the discovery of many additional 5-HT receptors. Although 5-HT was chemically elucidated in 1948 by Page and colleagues (Rapport et al., 1948) and 5-HT receptors initially classified in 1957 (Gaddum and Picarelli, 1957), the complexity of 5-HT pharmacology was not fully appreciated until the late 1970s and early 1980s when many putative 5-HT receptors were identified by radioligand binding studies (e.g., 5-HT1A, 5-HT2, 5-HT1E and so on) (Leysen et al., 1979; Hamon et al., 1980; Peroutka et al., 1981; Leonhardt et al., 1989). The first 5-HT receptors were cloned in 1988 (Fargin et al., 1988; Julius et al., 1988) and the discovery of 14 distinct human 5-HT receptors since then ushered in the era of 5-HT receptor molecular biology (Kroeze et al., 2003). The cloning and sequencing of 5-HT receptors has also revealed the presence of post-transcriptionally modified mRNA species (RNA editing) (Burns et al., 1997) as well as naturally occurring mutations and their relations to various diseases (e.g., single nucleotide polymorphisms; SNPs) (Arranz et al., 1995).

The identification of the amino acid sequences of 5-HT receptors has allowed us to predict how 5-HT and related agonists bind to and activate 5-HT receptors (Shapiro et al., 2000; Shapiro et al., 2002). The hope has been that this information will lead, eventually, to the development of novel, subtype-selective 5-HT receptor agonists and antagonists (Kroeze et al., 2002).

The first several chapters of The Serotonin Receptors: From Molecular Pharmacology to Human Therapeutics are aimed at reviewing our knowledge of the molecular and structural biology of 5-HT receptors, followed by our current understanding of 5-HT receptor pharmacology. The elucidation of the sequences of 5-HT receptors has also facilitated the development of highly selective tools for mapping the distribution of 5-HT receptors. These tools include selective 5-HT receptor antibodies and hybridization probes. The use of these biochemical probes has revealed an unexpected complexity in both the cellular and subcellular distribution of 5-HT receptors.

The next few chapters describe the anatomical, cellular, and subcellular distribution of 5-HT receptors. Because of the plethora of receptors and receptor subtypes, however, it has been exceedingly difficult to identify the physiological role of various 5-HT receptors using pharmacological tools. A powerful approach
to elucidating the physiological role of 5-HT receptors was to use mice in which 5-HT receptors were deleted (e.g., knockout mice); the first 5-HT receptor knockouts were reported in 1994 (Saudou et al., 1994) and, since then, nearly all 5-HT receptors have been “knocked-out”—typically with novel phenotypes (Tecott et al., 1995; Brunner et al., 1999).

The final chapters review our understanding the physiological role(s) of 5-HT receptors based mainly on studies performed in genetically engineered mice. This book represents our collective attempts to provide the reader with a “snapshot” of the 5-HT receptor field circa 2006. The scope of the book is vast, proceeding from the genomic to the therapeutic. Because it is unlikely that any reader will devote the time to reading the entire book cover-to-cover, each chapter has been designed to represent a complete review of the particular field. Thus, each chapter begins with a short introduction to 5-HT receptors and then proceeds to review the particular subfield in depth. Not surprisingly, therefore, the enterprising reader will find some overlap between various introductory sections.

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References


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