

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-HT_{1A}, 5-HT₂, 5-HT_{1E} 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 knock-outs 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.

Acknowledgments

I would like to especially thank Mr. Jon Evans who has tirelessly collected, edited, and collated the finished chapters and who has done most of the “leg work” associated with this book. Without Jon’s devotion to this task, the book would never have been completed. Any omissions and errors are my sole responsibility. I would also like to thank my wife Judith and my daughter Rachel for their warmth and understanding during the gestation of this book. Lastly, I dedicate this book to “beings throughout the ten directions—hands palm-to-palm.”

Bryan L. Roth, MD, PhD

References

- Arranz M, Collier D, Sodhi M, Ball D, Roberts G, Price J, Sham P, and Kerwin R. Association between clozapine response and allelic variation in 5-HT_{2A} receptor gene. *Lancet* 1995;346:281–282.
- Brunner D, Buhot MC, Hen R, and Hofer M. Anxiety, motor activation, and maternal-infant interactions in 5HT_{1B} knockout mice. *Behav Neurosci* 1999;113:587–601.
- Burns CM, Chu H, Rueter SM, Hutchinson LK, Canton H, Sanders-Bush E, and Emeson RB. Regulation of serotonin-2C receptor G-protein coupling by RNA editing [see comments]. *Nature* 1997;387:303–308.
- Fargin A, Raymond JR, Regan JW, Cotecchia S, Lefkowitz RJ, and Caron MG. The genomic clone G-21 which resembles a beta-adrenergic receptor sequence encodes the 5-HT_{1A} receptor. *Nature* 1988;335:358–360.
- Gaddum JH and Picarelli ZP. Two kinds of tryptamine receptors. *Br J Pharmacol* 1957;12:323–328.

Hamon M, Nelson DL, Herbert A. and Glowinski J. Multiple receptors for serotonin in the rat brain. *Adv Biochem Psychopharmacol* 1980;21:223–233.

Julius D, MacDermott AB, Axel R, and Jessell TM. Molecular characterization of a functional cDNA encoding the serotonin 1c receptor. *Science* 1988;241:558–564.

Kroeze WK, Kristiansen K, and Roth BL. Molecular biology of serotonin receptors structure and function at the molecular level. *Curr Top Med Chem* 2002;2:507–528.

Kroeze WK, Sheffler DJ, and Roth BL. G-protein-coupled receptors at a glance. *J Cell Sci* 2002;116:4867–9.

Leonhardt S, Herrick-Davis K, and Titeler M. Detection of a novel serotonin receptor subtype (5-HT1E) in human brain: interaction with a GTP-binding protein. *J Neurochem* 1989;53:465–471.

Leysen JE, Gommeren W, Laduron PM, et al. Distinction between dopaminergic and serotonergic components of neuroleptic binding sites in limbic brain areas. *Biochem Pharmacol* 1979;28:447–448.

Peroutka SJ, Lebovitz RM, and Snyder SH. Two distinct serotonin receptors with distinct physiological functions. *Science* 1981;212:827–829.

Rapport MM, Green AA, and Page IH. Crystalline serotonin. *Science* 1948;108:329.

Saudou F, Amara DA, Dierich A, et al. Enhanced aggressive behavior in mice lacking 5-HT1B receptor. *Science* 1994;265:1875–1878.

Shapiro DA, Kristiansen K, Kroeze WK, and Roth BL. Differential modes of agonist binding to 5-hydroxytryptamine(2A) serotonin receptors revealed by mutation and molecular modeling of conserved residues in transmembrane region 5. *Mol Pharmacol* 2000;58:877–886.

Shapiro DA, Kristiansen K, Weiner DM, Kroeze WK, and Roth BL. Evidence for a model of agonist-induced activation of 5-HT2A serotonin receptors which involves the disruption of a strong ionic interaction between helices 3 and 6. *J Biol Chem* 2002;18:18.

Tecott LH, Sun LM, Akana SF, et al. Eating disorder and epilepsy in mice lacking 5-HT2c serotonin receptors [see comments]. *Nature* 1995;374:542–546.

The Serotonin Receptors

From Molecular Pharmacology to Human Therapeutics

Roth, B.L. (Ed.)

2006, XVIII, 618 p. 82 illus., 5 illus. in color., Hardcover

ISBN: 978-1-58829-568-2

A product of Humana Press