

PREFACE

Dopamine neurotransmission has been the subject of research for nearly half a century. However, it was not until 1987, when it was implicated with the reinforcing effects of cocaine, that the dopamine transporter (DAT) was thrust into the scientific spotlight and became a pharmacological target for the development of a potential medication for one of the most addictive drugs known. At this time a surge in biological, chemical, and pharmacological investigations directed toward understanding the DAT occurred, spearheaded primarily by the National Institute on Drug Abuse. To date, the development of a clinically useful therapeutic agent for cocaine addiction has been elusive, but tremendous scientific advances have been made toward understanding the DAT and its role in a variety of neurological disease states and disorders. This includes Parkinson's disease, schizophrenia, attention-deficit/hyperactivity disorder, Tourette's syndrome, and drug abuse. Although, according to SciFinder Scholar the annual number of research publications focused on dopamine-uptake inhibitors peaked in 2001,⁶ the annual output of research publications concerning all aspects of the DAT is increasing continually. This clearly illustrates the importance of the DAT in neuroscience and as a pharmacological target for neurotherapeutic agents.

Like many similar substances, our interest in the DAT began in the early 1990s. Our focus was directed toward the synthesis and development of selective dopamine-uptake inhibitors as potential medications for cocaine addiction. During the course of our studies we have learned a great deal about the structure-activity relationships of the DAT. In addition, we have serendipitously gained a greater understanding of both the serotonin and norepinephrine transporters. Moreover, recent discoveries which suggest that the DAT may be affected indirectly by other drugs of abuse (e.g., nicotine and cannabinoids) have led to additional investigations into the neurochemistry of these systems.

Overall, our understanding of the DAT and dopaminergic systems has increased dramatically over the past decade, and that level of understanding is being elevated by new discoveries every day. When training new researchers in such a rapidly developing field, it has been difficult to find background materials that would provide a

foundation that was sufficiently broad but detailed enough to furnish a basic understanding of the biological, chemical, and pharmacological aspects of the DAT. Although there were excellent reviews of specific subject material in many areas, a single comprehensive source of DAT biology, chemistry, and pharmacology was not available. This spawned the idea that a book that reviewed significant advances in the various fields of the DAT would be highly valuable to new as well as experienced researchers in the field.

The book is organized to summarize the significant biological, chemical, and pharmacological developments that have led to our current understanding of the DAT. Most of the research and discoveries presented here are derived from efforts directed toward understanding the pharmacological mechanisms of cocaine as well as medication development for cocaine dependence. However, these studies have contributed significantly toward the elucidation of general DAT function. In Part I the focus is on important biological developments. Chapters 1 to 5 are authoritative reviews written by eminent scientists in the areas of DAT function, pathological conditions, DAT cloning, DAT molecular structure, and DAT electrochemical characterization. Part II deals with the medicinal chemistry of DAT inhibitory ligands and substrates. Chapters 6 to 11 are written by pioneering medicinal chemists in this area. Chemical syntheses and various structure-activity relationships of important classes of dopamine-uptake inhibitors and dopamine releasers are discussed. Finally, in Part III, the reader is directed to pharmacological discoveries that have provided extraordinary insight into the role of the DAT in normal neurological function as well as in disease states. Chapters 12 to 14 are written by leading researchers in the fields of DAT imaging, *in vitro* studies, and *in vivo* behavioral studies.

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The editors dedicate the book to all the postdoctoral researchers, graduate students, technicians, and undergraduate students who have, and will, contribute to the research efforts of our laboratories. Their hard work and dedicated efforts have been, and will continue to be, vital to the success of our research program. The editors would also like to thank Dr. Stacey Lomenzo for technical assistance in assembling the manuscript.

On August 29, 2005, Hurricane Katrina dealt our program a devastating blow. Our University of New Orleans laboratories were shut down for nearly eight months as electricity was restored, mold was eradicated, and repairs were made. Many of our personnel lost their homes and were scattered around the country. At a time when careers were in jeopardy with no clear view of recovery, it was a great comfort to have the sympathy and support of both the scientific and administrative communities of the National Institutes of Health and the National Institute on Drug Abuse. It is with sincere appreciation that we acknowledge the National Institute on Drug Abuse for financial support of our research (DA11528).

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