Dopamine and Glutamate in Psychiatric Disorders

EDITED BY

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HUMANA PRESS

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Humana Press Totowa, New Jersey

999 Riverview Drive, Suite 208
Totowa, New Jersey 07512

humanapress.com

Production Editors: Mark J. Breaugh and Amy Thau

Cover design by Patricia F. Cleary

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This publication is printed on acid-free paper. ∞
ANSI Z39.48-1984 (American National Standards Institute) Permanence of Paper for Printed Library Materials.

Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

eISBN:1-59259-852-8

Library of Congress Cataloging-in-Publication Data

Dopamine and glutamate in psychiatric disorders / edited by Werner J.Schmidt and Maarten E.A. Reith.

p. cm. Includes bibliographical references and index.

ISBN 1-58829-325-4 (alk. paper)

1. Neuropsychiatry. 2. Dopamine--Pathophysiology. 3.Glutamate--Pathophysiology. 4. Neurotransmitter receptors. I. Schmidt,Werner J. II. Reith, Maarten E.A.

RC347.D674 2005

616.8--dc22

2005001495

PREFACE

Among the medical disciplines, psychiatry has for a long time held a special position separate from natural sciences. This may be rooted in the old philosophical problem of the mind–body dichotomy. Accordingly, psychiatry, with its focus on the mind, developed separately from natural sciences, which were concerned with the body. Thus, psychiatry laid out its own hypotheses, constructs, and methods. The substrate of the mind is formed by neuronal networks, and neurobiology as a natural science discipline developed on its own, focusing primarily on neuronal mechanisms, from computationally integrated networks all the way down to electrical, cellular, and molecular processes underlying neuronal communication. In the last decades, psychiatry has moved from psychoanalytical to biological approaches. Biological psychiatry has completely changed the treatment of psychoses, allowing outpatient treatment of psychotics who previously would have been locked up inside psychiatric institutions; more recently, neurotic symptomology is also being treated more and more by chemical approaches. In the meantime, neurobiology has been revolutionized by new techniques, among which the development of molecular biological tools is of primary importance. Now psychiatry and neurobiology are approaching each other, and our knowledge about the neurobiological basis of mental functions is increasing rapidly. *Dopamine and Glutamate in Psychiatric Disorders* is dedicated to fostering interactions between the two disciplines.

One could highlight two approaches to understanding psychiatric diseases within the realm of neurobiological and natural sciences. Psychiatric diseases can be regarded from a molecular genetic point of view, i.e., to be genetically caused by, or at least be susceptible to, a predisposition, with proteins being the end product of the genetic machinery. This view equates a psychiatric disease to a proteinopathy. In this sense Parkinson's disease can be regarded as a synucleinopathy, Alzheimer's disease as a tauopathy, and so forth. A book could easily be filled summarizing this type of knowledge. Another approach is to first study the biological properties and functions of proteins we know play an important role in mental processes. Thus, dopamine and glutamate receptors can be singled out as crucial targets for endogenous transmitters known to play a role in pychoses or other complex psychiatric diseases. The molecular biology of such receptors, their subtypes and subunits could also easily fill a book. *Dopamine and Glutamate in Psychiatric Disorders* wishes to focus on the combination of these approaches. We plan to address the basic molecular mechanisms, but psychiatric diseases will be primarily regarded as "synaptic or extrasynaptic diseases," taking into account changes in dopamine and glutamate neurotransmission that can occur by communication through synaptic connections between neurons as well as by longer-range action through the extracellular space, sometimes referred to as volume transmission. This approach has led to effective medications in the past, for example, antipsychotics and antidepressants. In turn, the pharmacotherapy of psychiatric diseases has significantly contributed to concepts and hypotheses about neuronal dysfunctions underlying these diseases, such as the dopamine hypothesis of schizophrenia, or the monoamine-deficiency hypothesis of depression. However, better treatments are still badly needed. For example, antipsychotics, even the newer atypicals, have undesirable side effects; antidepressants, including the newer

Prozac-type, develop their therapeutic effect too slowly and offer no therapeutic help to a large percentage of depressed patients. Drug development is still an urgent priority.

Dopamine and Glutamate in Psychiatric Disorders reviews our progress in the field of dopamine and glutamate in psychiatric diseases. It includes both basic and clinical approaches and should be of interest to both basic scientists working at the bench on dopamine or glutamate neurotransmission and clinicians treating psychiatric diseases. In addition, graduate students and advanced undergraduates seeking a comprehensive overview of the field of dopamine and glutamate in psychiatric disorders will be interested in the book.

There is a fine line between symptoms of psychosis and symptoms of mood disorder. The latter can be secondary to an underlying psychosis; conversely, psychotic symptoms such as phobia can accompany depression. To make matters more complicated, many disorders that are targets for antidepressant treatment, such as obsessive compulsive phobic states, acute panic attacks, social phobias, and bulimia, are now considered to be clinical anxiety disorders rather than manifestations of an underlying depression. *Dopamine and Glutamate in Psychiatric Disorders* addresses many of these diseases originating in the central nervous system. Stress, as it is intricately related to depression, is also covered, as well as addiction, which is considered by many to be another brain disease, if not in origin, then created by repeated drug use.

Each chapter of *Dopamine and Glutamate in Psychiatric Disorders* summarizes the prevalence and symptoms of the disease, covers involvement of dopamine and/or glutamate systems with emphasis on findings with new molecular approaches, such as transgenic knockout or knockin mice and newer analytical techniques, such as brain imaging, and describes future directions and possibilities for new therapy development.

Werner J. Schmidt, PhD
Maarten E. A. Reith, PhD

ACKNOWLEDGMENT

We thank Mrs. Daniela Binder for her excellent secretarial assistance. Without her help, the production of this book would not have been possible.

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I DOPAMINE

1
Dopamine Receptors

Kim A. Neve

1. INTRODUCTION

Beginning with the initial suggestion that antipsychotic neuroleptic drugs block dopamine receptors *(1)*, and continuing with the demonstration that the affinity of antipsychotic drugs for dopamine receptors is highly correlated with clinical potency *(2,3)*, and that the density of [^{3}H]neuroleptic-labeled dopamine receptors is enhanced in postmortem brain tissue of schizophrenics *(4)*, the study of dopamine receptors has been inextricably linked with hypotheses for the mechanism of action of antipsychotic drugs and the etiology of schizophrenia. As described in other chapters in this volume, the role of dopamine in numerous other neuropsychiatric disorders, such as parkinsonism, attention deficit hyperactivity disorder, and addiction, has made consideration of the properties of dopamine receptor subtypes important for attempts to provide improved pharmacological treatments for these disorders. This chapter summarizes the molecular cloning of the five mammalian dopamine receptor subtypes, and reviews their structural, pharmacological, signaling, and regulatory properties.

2. DOPAMINE RECEPTOR SUBTYPES

2.1. Classification Into D1 and D2 Receptor Subfamilies

Although the existence of a receptor for dopamine was suggested indirectly by the effect of blockade of those receptors on dopamine turnover *(1)*, more direct evidence for such a receptor came in 1972 with the identification of dopamine-stimulated adenylate cyclase activity and cyclic adenosine monophosphate (AMP) accumulation first in retina *(5)*, and subsequently in rat neostriatum *(6)* and other basal forebrain nuclei including the nucleus accumbens and olfactory tubercle *(7)*. Importantly, the dopamine-stimulated adenylate cyclase was inhibited by antipsychotic drugs such as chlorpromazine, haloperidol, and fluphenazine much more potently than by drugs without antipsychotic or extrapyramidal actions such as imipramine and promethazine *(6–9)*. Dopamine receptors were first identified by radioligand binding in 1975 using both [^{3}H]dopamine and [^{3}H]haloperidol to label the receptors *(10–12)*, followed shortly by the synthesis and characterization of [^{3}H]spiperone *(13–15)*, still perhaps the most commonly used radioligand for D2-like dopamine receptors because of its high affinity and selectivity for the receptors.

From: *Dopamine and Glutamate in Psychiatric Disorders*
Edited by: W. J. Schmidt and M. E. A. Reith © Humana Press Inc., Totowa, NJ

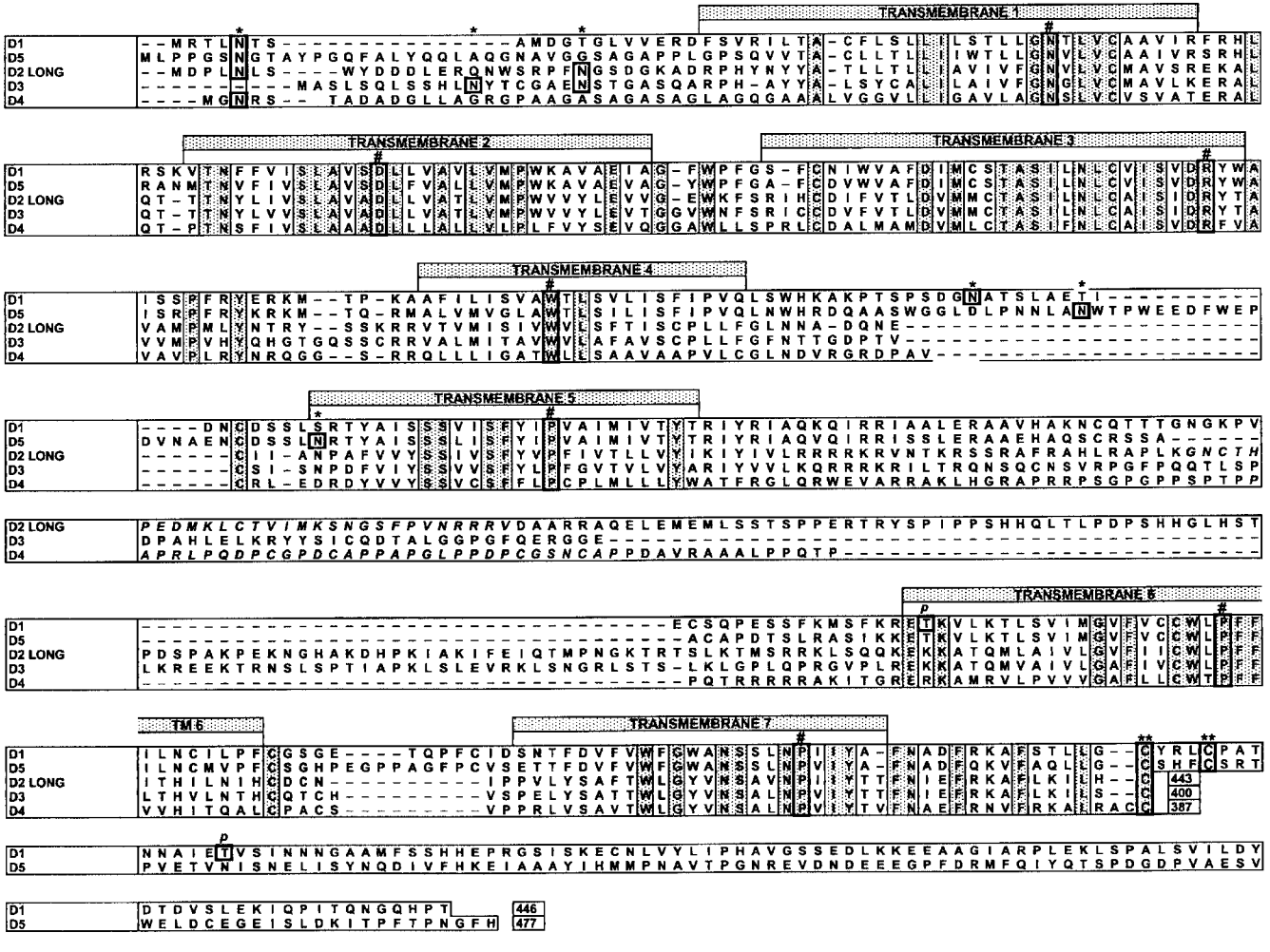
TRANSMEMBRANE 1
TRANSMEMBRANE 2
TRANSMEMBRANE 3
TRANSMEMBRANE 4
TRANSMEMBRANE 5
TRANSMEMBRANE 6
TM 6
TRANSMEMBRANE 7
D1
D5
D2 LONG
D3
D4

Fig. 1.

Two seminal papers in 1978 and 1979 summarized several lines of evidence that are inconsistent with the notion of a single type of dopamine receptor *(16,17)*. For example, the pharmacological profiles of dopamine-stimulated adenylate cyclase and the dopamine receptor identified by radioligand binding studies differ in key ways; in particular, domperidone and substituted benzamide derivatives, such as metoclopramide and sulpiride, that are potent inhibitors of radioligand binding are weak antagonists of dopamine-stimulated adenylate cyclase *(18–20)*, and butyrophenone antipsychotic drugs, such as spiperone and haloperidol, are also less potent inhibitors of enzyme activity than would be predicted based on their binding affinity *(21)*. Furthermore, dopamine-stimulated adenylate cyclase was shown to be physically distinct from the receptor predominantly labeled by most of the dopamine receptor radioligands in use at that time. Thus, dopamine does not stimulate adenylate cyclase activity in the anterior pituitary *(16)*, a tissue with abundant binding of several dopamine receptor ligands *(15,21)*, and axon terminal-sparing lesions of the cell bodies in the neostriatum (kainic acid) and substantia nigra (6-hydroxydopamine) selectively abolish or spare, respectively, dopamine-stimulated adenylate cyclase *(22–24)*. Data such as these led to the proposal that dopamine receptors belong to two subtypes, with the D1 subtype being coupled to adenylate cyclase and having low affinity for dopamine, ergots, such as bromocriptine, and substituted benzamine antagonists, and the D2 subtype being unassociated with adenylate cyclase, having high affinity for dopamine, substituted benzamide derivates, and butyrophenone antipsychotic drugs, and serving as the autoreceptor that regulates dopamine release *(17)*. This classification is still valid, with the major modifications to it being the recognition that, rather than being uncoupled from adenylate cyclase, D2 receptors are coupled to inhibition of adenylate cyclase *(25)*, and the fulfillment of the prediction that subcategories of D1 and D2 receptors would be discerned *(17)*; that is, D1 (henceforth referred to as D1-like) and D2 (D2-like) receptors are subfamilies, rather than subtypes.

2.2. *Molecular Cloning of Dopamine Receptor Subtypes*

The molecular cloning of a rat D2 receptor cDNA, reported in December of 1988 *(26)*, was the first step in the cloning of five dopamine receptor subtypes, all of which were discovered by 1991. As this work has been reviewed in detail elsewhere *(27)*, in this chapter I will summarize the cloning of the human receptors (Fig. 1). The cloning of the rat cDNA was rapidly followed by isolation of cDNA encoding the human D2 receptor, with four reports appearing in 1989 *(28–31)*. The first unanticipated result of the cloning of the dopamine receptors was the observation by all four of these reports that the D2 receptor gene product is alternatively spliced to produce long ($D2_L$; gene accession no. NM_000795) and short ($D2_S$; NM_016574) variants, 443 and 414 amino acids long, respectively. The variants differ by the presence or absence of an alternatively spliced

Fig. 1. Amino acid sequence-alignment of the human dopamine receptors. Positions that are conserved among all five subtypes are shaded. Residues that are marked with a dark border and a symbol above the alignment include the most highly conserved residue in each transmembrane domain (#), predicted sites of *N*-linked glycosylation (*), predicted sites of palmitoylation (**), and experimentally determined sites of phosphorylation (*p*). The alternatively spliced insert in $D2_L$ and the tandem repeat in the D4.2 variant are in italicized font.