

Apomorphine and Other Dopaminomimetics

Volume 1
BASIC PHARMACOLOGY

Editors
Gian Luigi Gessa
Giovanni Umberto Corsini

Apomorphine and Other Dopaminomimetics

Volume 1

Basic Pharmacology

Editors

Gian Luigi Gessa, M.D.

Giovanni Umberto Corsini, M.D.

Institute of Pharmacology

University of Cagliari

Cagliari, Italy

Raven Press ■ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

© 1981 by Raven Press Books, Ltd. All rights reserved. This book is protected by copyright. No part of it may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior written permission of the publisher.

Made in the United States of America

International Standard Book Number 0-89004-667-0

Library of Congress Catalog Number 81-40610

Great care has been taken to maintain the accuracy of the information contained in the volume. However, Raven Press cannot be held responsible for errors or for any consequences arising from the use of the information contained herein.

Materials appearing in this book prepared by individuals as part of their official duties as U.S. Government employees are not covered by the above-mentioned copyright.

Raven Press ■ New York

Preface

Apomorphine was discovered in 1869 as a by-product of morphine, and has for many years been considered primarily for its emetic properties—in spite of its ability to produce other peripheral and central actions. In addition to its morphine-like actions, apomorphine exerts cardiovascular and hypotensive effects, selectively alters gastric motility, and induces a variety of stereotyped behaviors. Increased attention was given to apomorphine when it was found to have sedative properties, which made it a valuable aid in treating agitated patients, and in 1951 when Schwab described its usefulness in the treatment of Parkinson's disease.

The popularity of apomorphine, however, is linked to that of dopamine, which has also been considered a "cinderella" drug among neurotransmitters. The relationship of apomorphine to dopamine was clarified significantly by Ernst in 1967, whose studies indicated the existence of structural similarities between the two drugs, thus explaining the dopaminergic nature of apomorphine's effects. Apomorphine has since been known as a specific tool for the study of dopamine function in animals and humans. Research focusing in this direction has led to the development of several analogs with dopaminergic properties and of newly synthesized agonists, which have proven to be valuable pharmacological agents with a myriad of useful therapeutic applications.

Apomorphine and Other Dopaminomimetics is a two-volume set which organizes the material in this field into basic and clinical research. *Volume 1: Basic Pharmacology* is a comprehensive treatise on various aspects of the use of apomorphine and related dopaminomimetics to disclose central and peripheral roles of dopamine in regulating physiological functions such as motor activity, sleep, wakefulness, food intake, hormonal control, blood pressure, and diuresis. *Volume 2: Clinical Pharmacology* deals with the clinical aspects of dopamine agonists in relation to schizophrenic and affective disorders, Parkinson's disease and dyskinesias, sleep, pituitary hormone interactions, aging, and arterial pressure control.

These two volumes represent the establishment of apomorphine as an invaluable tool in basic and clinical research in the neurosciences, and will be of interest to pharmacologists as well as neuroscientists.

Acknowledgments

This volume is based on presentations from a symposium entitled "Clinical Pharmacology of Apomorphine and Other Dopaminomimetics," held in Villasimius, Italy in September 1980. We would like to thank the Fidia Research Laboratories of Abano Terme (Italy), who were the principal sponsors of the congress, and also Sandoz Ltd. of Basel (Switzerland) and Milan (Italy) for their contribution. Further, for the expert organization and smooth running of the symposium we wish to thank Dr. Cristina Schirato of Fidia Research Laboratories, and Miss Anne Farmer, whose assistance was also greatly appreciated in the publishing of this book.

Contributors

G. W. Arana

*Department of Psychiatry
Mailman Research Center
McLean Hospital
115 Mill Street
Belmont, Massachusetts 02178*

A. Argiolas

*Institute of Pharmacology
University of Cagliari
Via Porcell 4
09100 Cagliari, Italy*

L.-E. Arvidsson

*Department of Organic Pharmaceutical
Chemistry
Uppsala, Sweden*

G. Baggio

*Chair of Pharmacology and Pharmacognosy
University of Modena
Via G. Campi 287
41100 Modena, Italy*

Ross J. Baldessarini

*Department of Psychiatry
Mailman Research Center
McLean Hospital
115 Mill Street
Belmont, Massachusetts 02178*

A. Barbeau

*Department of Neurobiology
Clinical Research Institute of Montreal
110 Pine Avenue West
Montreal, Quebec, Canada H2W 1R7*

B. S. Bunney

*Departments of Pharmacology and Psychiatry
Yale University School of Medicine
New Haven, Connecticut 06510*

A. Campbell

*Department of Psychiatry
Mailman Research Center
McLean Hospital
115 Mill Street
Belmont, Massachusetts 02178*

M. O. Carruba

Department of Pharmacology

School of Medicine

University of Milan

Via Vanvitelli 32

20129 Milan, Italy

Miguel Casas Brugué

Hospital de la Sta

Cruz y San Pablo

Av. San Antonio M. Claret 167

Barcelona 25, Spain

Franca Cerrito

Institute of Pharmacology

Catholic University

Via Pineta Sacchetti 644

00168 Rome, Italy

A. Chéramy

Groupe NB

Inserm U14

Collège de France

11, place Marcelin Berthelot

75231 Paris Cedex 5, France

M. F. Chesselet

Groupe NB

Inserm U114

Collège de France

11, place Marcelin Berthelot

75231 Paris Cedex 5, France

Wai Yiu Cheung

Department of Biochemistry

St. Jude Children's Research Hospital

Memphis, Tennessee 38101

Yvonne Clement-Cormier

Department of Pharmacology

University of Texas Medical School

Houston, Texas 77025

E. Costa

Laboratory of Preclinical Pharmacology

National Institute of Mental Health

St. Elizabeth's Hospital

Washington, D.C. 20032

G. De Giorgio

Institute of Clinical Medicine V

University of Rome

00100 Rome, Italy

G. Di Chiara

*Institute of Pharmacology
University of Cagliari
Via Porcell 4
09100 Cagliari, Italy*

Valerie B. Domesick

*Department of Anatomy
Harvard Medical School and McLean Hospital
115 Mill Street
Belmont, Massachusetts 02178*

Guy M. Everett

*Department of Pharmacology
University of California
San Francisco, California 94143*

P. Falaschi

*Institute of Clinical Medicine V
University of Rome
00100 Rome, Italy*

F. Ferrari

*Chair of Pharmacology and Pharmacognosy
University of Modena
Via G. Campi 287
41100 Modena, Italy*

W. Ferrari

*Institute of Pharmacology
University of Modena
Via G. Campi 287
41100 Modena, Italy*

G. Frajese

*Institute of Clinical Medicine V
University of Rome
00100 Rome, Italy*

W. Fratta

*Institute of Pharmacology
University of Cagliari
09100 Cagliari, Italy*

S. Gentleman

*Laboratory of Preclinical Pharmacology
National Institute of Mental Health
St. Elizabeth's Hospital
Washington, D.C. 20032*

G. L. Gessa

*Institute of Pharmacology
University of Cagliari
Via Porcell 4
09100 Cagliari, Italy*

J. Glowinski

*Groupe NB
Inserm U114
Collège de France
11, place Marcelin Berthelot
75231 Paris Cedex 5, France*

Margaret E. Gnegy

*Department of Pharmacology
University of Michigan Medical School
Ann Arbor, Michigan 48109*

Michel Goiny

*Department of Pharmacology
Karolinska Institutet
Box 60400
S-104 01 Stockholm, Sweden*

Leon I. Goldberg

*Department of Pharmacological and Physiological Sciences
University of Chicago
Chicago, Illinois 60637*

M. Goldstein

*Department of Psychiatry
New York University Medical Center
New York, New York 10016*

A. A. Grace

*Departments of Pharmacology and Psychiatry
Yale University School of Medicine
New Haven, Connecticut 06510*

S. Guarini

*Institute of Pharmacology
University of Modena
Via G. Campi 287
41100 Modena, Italy*

U. Hacksell

*Department of Organic Pharmaceutical Chemistry
Uppsala, Sweden*

Ingeborg Hanbauer

*Section on Biochemical Pharmacology
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland 20205*

M. Harding

*Department of Psychiatry
Mailman Research Center
McLean Hospital
115 Mill Street
Belmont, Massachusetts 02178*

Mario Herrera-Marchitz

*Department of Psychology
University of Stockholm
S-104 01 Stockholm, Sweden*

S. Hjorth

*Department of Pharmacology
University of Göteborg
Box 33031
S-400 33 Göteborg, Sweden*

T. Hokfelt

*Department of Histology
Karolinska Institute
S-104 01 Stockholm 60, Sweden*

D. W. Hommer

*Departments of Pharmacology and Psychiatry
Yale University School of Medicine
New Haven, Connecticut 06510*

J. L. Imbs

*Institute of Pharmacology
Faculty of Medicine
11, rue Humann
67000 Strasbourg, France*

S. Imperato

*Institute of Pharmacology
University of Cagliari
Via Porcell 4
09100 Cagliari, Italy*

P. Jenner

*University Department of Neurology
Institute of Psychiatry
King's College Hospital Medical School
Denmark Hill, London SE5 8AF, United Kingdom*

F. Jolicœur

*Department of Neurobiology
Clinical Research Institute of Montreal
110 Pine Avenue West
Montreal, Quebec, Canada H2W 1R7*

Jai D. Kohli

*Department of Pharmacological and Physiological Sciences
University of Chicago
Chicago, Illinois 60637*

N. S. Kula

*Department of Psychiatry
Mailman Research Center
McLean Hospital
115 Mill Street
Belmont, Massachusetts 02178*

Samarthji Lal

*Department of Psychiatry
Montreal General Hospital
Montreal, Quebec, Canada*

Pierre Laduron

*Department of Biochemical Pharmacology
Janssen Pharmaceutica
B-2340 Beerse, Belgium*

J. S. Lamont

*Department of Chemistry
Northeastern University
Boston, Massachusetts 02115*

S. J. Law

*Department of Chemistry
Northeastern University
Boston, Massachusetts 02115*

P. Lindberg

*Organic Chemistry Unit
Department of Pharmacology
S-400 33 Göteborg, Sweden*

P. Mantegazza

*Department of Pharmacology
School of Medicine
University of Milan
Via Vanvitelli 32
20129 Milan, Italy*

K. Markey

*Department of Psychiatry
New York University Medical Center
New York, New York 10016*

C. D. Marsden

*University Department of Neurology
Institute of Psychiatry
King's College Hospital Medical School
Denmark Hill, London SE5 8AF, United Kingdom*

Guido Maura

*Institute of Pharmacology and Pharmacognosy
University of Genova
Via Capo S. Chiara 5
16146 Genova, Italy*

Maurizio Memo

*Section on Biochemical Pharmacology
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland 20205*

M. Morelli

*Institute of Pharmacology
University of Cagliari
Via Porcell 4
09100 Cagliari, Italy*

N. H. Neff

*Laboratory of Preclinical Pharmacology
National Institute of Mental Health
St. Elizabeth's Hospital
Washington, D.C. 20032*

John L. Neumeyer

*Department of Chemistry
Northeastern University
Boston, Massachusetts 02115*

J. L. G. Nilsson

*Department of Organic Pharmaceutical
Chemistry
Uppsala, Sweden*

M. C. Olinas

*Laboratory of Preclinical Pharmacology
National Institute of Mental Health
St. Elizabeth's Hospital
Washington, D.C. 20032*

M. Parenti

*Laboratory of Preclinical Pharmacology
National Institute of Mental Health
St. Elizabeth's Hospital
Washington, D.C. 20032*

R. D. Pinnock

*Department of Physiology and Pharmacology
University of Southampton
Southampton SO9 3TU, United Kingdom*

M. L. Porceddu

*Institute of Pharmacology
University of Cagliari
09100 Cagliari, Italy*

Maurizio Raiteri

*Institute of Pharmacology and Pharmacognosy
University of Genova
Via Capo S. Chiara 5
16146 Genova, Italy*

C. Reavill

*University Department of Neurology
Institute of Psychiatry
King's College Hospital Medical School
Denmark Hill, London SE5 8AF, United Kingdom*

J. F. Rehfeld

*Department of Chemistry
University of Aarhus
Aarhus, Denmark*

T. D. Reisine

*Groupe NB
Inserm U114
Collège de France
11, place Marcelin Berthelot
75231 Paris Cedex 5, France*

S. Ricciardi

*Department of Pharmacology
School of Medicine
University of Milan
Via Vanvitelli 32
20129 Milan, Italy*

F. Rioux

*Departments of Physiology and Pharmacology
Faculty of Medicine
University of Sherbrooke
Sherbrooke, Quebec, Canada J1H 5N4*

A. Rocco

*Institute of Clinical Medicine Y
University of Rome
00100 Rome, Italy*

D. Rondeau

*Department of Psychiatry
Moncton University
Moncton, New Brunswick, Canada E1A 3E9*

D. Sanchez

*Organic Chemistry Unit
Department of Pharmacology
S-400 33 Göteborg, Sweden*

M. Sandrini

*Institute of Pharmacology
University of Modena
Via G. Campi 287
41100 Modena, Italy*

M. Schmidt

*Institute of Pharmacology
Faculty of Medicine
11, rue Humann
67000 Strasbourg, France*

J. J. Schwartz

*Institute of Pharmacology
Faculty of Medicine
11, rue Humann
67000 Strasbourg, France*

*Medical College of Pennsylvania
3300 Henry Avenue
Philadelphia, Pennsylvania 19129*

G. Serra

*Institute of Pharmacology
University of Cagliari
Via Porcell 4
09100 Cagliari, Italy*

L. R. Skirboll

*Department of Histology
Karolinska Institutet
S-104 01 Stockholm 60, Sweden*

Ennio Stefanini

*Department of Pharmacology
University of Texas Medical School
Houston, Texas 77025*

S. St.-Pierre

*Departments of Physiology and Pharmacology
Faculty of Medicine
University of Sherbrooke
Sherbrooke, Quebec, Canada J1H 5N4*

U. Svensson

*Department of Organic Pharmaceutical
Chemistry
Uppsala, Sweden*

A. H. Tissari

Institute of Pharmacology

*University of Cagliari
Via Porcell 4
09100 Cagliari, Italy*

Glenn Treisman

*Department of Pharmacology
University of Michigan Medical School
Ann Arbor, Michigan 48109*

Urban Ungerstedt

*Department of Pharmacology
Karolinska Institutet
S-104 01 Stockholm 60, Sweden*

Kerstin Uvnäs-Wallensten

*Department of Pharmacology
Karolinska Institutet
Box 60400
S-104 01 Stockholm 60, Sweden*

Benjamin Weiss

*Department of Pharmacology
Medical College of Pennsylvania
3300 Henry Avenue
Philadelphia, Pennsylvania 19129*

H. Wikström

*Organic Chemistry Unit
Department of Pharmacology
S-400 33 Göteborg, Sweden*

G. N. Woodruff

*Departments of Physiology and Pharmacology
University of Southampton
Southampton SO9 3TU, United Kingdom*

APOMORPHINE AND OTHER DOPAMINOMIMETICS

APOMORPHINE AND OTHER DOPAMINOMIMETICS

Volume 1: Basic Pharmacology

APOMORPHINE AND OTHER DOPAMINOMIMETICS

Volume 1: Basic Pharmacology

Volume 2: Clinical Pharmacology

Contents

Volume 1: Basic Pharmacology

Introductory Issues

- 1 Historical Highlights of the Chemistry, Pharmacology, and Early Clinical Uses of Apomorphine

John L. Neumeyer, Samarthji Lal, and Ross J. Baldessarini

- 19 Peptides and the Basal Ganglia

F. Jolicoeur, D. Rondeau, S. St.-Pierre, F. Rioux, and A. Barbeau

Basic Research on Dopaminergic Transmission

- 27 The Anatomical Basis for Feedback and Feedforward in the Striatonigral System

Valerie B. Domesick

- 41 Substantia Nigra as an Efferent Station for Dopaminergic Behavioural Syndromes Arising in the Striatum

G. Di Chiara, M. Morelli, A. Imperato, and M. L. Porceddu

- 65 The Coexistence of Dopamine and a CCK-Like Peptide in a Subpopulation of Midbrain Neurons: Immunocytochemical and Electrophysiological Studies

L. R. Skirboll, T. Hokfelt, A. A. Grace, D. W. Hommer, J. F. Rehfeld, K. Markey, M. Goldstein, and B. S. Bunney

- 79 Effects of Opiates on Dopamine Release in the Cat Caudate Nucleus *In Vivo*

M. F. Chesselet, A. Chéramy, T. D. Reisine, and J. Glowinski

- 85 Are Apomorphine, Bromocriptine, and the Methylxanthines Agonists at the Same Dopamine Receptor?

Urban Ungerstedt, Mario Herrera-Marschitz, and Miguel Casas Brugue

- 95 Dopamine Receptor: A Unique Site with Multiple Postsynaptic Localization

Pierre Laduron

- 105 New Evidence for Dopamine Receptors in Synaptosomes Controlling Dopamine Synthesis

A. H. Tissari and G. L. Gessa

- 117 Brain Dopamine and Premature Ejaculation: Results of Treatment with Dopamine Antagonists

P. Falaschi, A. Rocco, G. De Giorgio, G. Frajese, W. Fratta, and G. L. Gessa

- 123 Do Presynaptic Dopamine Autoreceptors Exist?

Franca Cerrito, Guido Maura, and Maurizio Raiteri

- 133 Opposite Changes in DA-Autoreceptors Sensitivity Induced by Chronic Antidepressants and Neuroleptics

G. Serra, A. Argiolas, and G. L. Gessa

Modulation of Dopamine Receptor Function

- 143 Intraneuronal Translocation of Modulators: A Regulatory Mechanism for Interneuronal Communication
E. Costa
- 147 Calmodulin: An Intracellular Ca^{2+} Mediator and Modulator
Wai Yiu Cheung
- 161 Interaction of CaM and Guanyl Nucleotides in the Stimulation of Rat Striatal Adenylate Cyclase Activity
Margaret E. Gnegy and Glenn Treisman
- 171 Long-Term Modulation of Dopamine Receptor Sensitivity: Participation of Calmodulin
Ingeborg Hanbauer and Maurizio Memo
- 179 Effects of Antipsychotic Dopamine Antagonists and Polypeptide Hormones on Calmodulin
Benjamin Weiss and Mary Sellinger-Barnette
- 193 Modulation of Dopamine Receptors by Opiates
N. H. Neff, M. Parenti, S. Gentleman, and M. C. Olanas
- 201 The Dopamine Receptor Complex: Biochemical Consequences of Supersensitivity Induced by Treatment with 6-Hydroxydopamine or Morphine
M. Parenti, S. Gentleman, M. C. Olanas, and N. H. Neff

Pharmacology of Dopamine Agonists

- 209 Apomorphine and Related Aporphines as Probes of the Dopamine Receptor
John L. Neumeyer, S. J. Law, and J. S. Lamont
- 219 Preclinical Studies of the Pharmacology of Apomorphine
R. J. Baldessarini, G. W. Arana, N. S. Kula, A. Campbell, and M. Harding
- 229 Puzzles of the Mechanism of Action of Bromocriptine
C. Reavill, P. Jenner, and C. D. Marsden
- 241 Some Central Actions of ADTN—A Potent Dopamine Receptor Agonist
G. N. Woodruff and R. D. Pinnock
- 253 3-PPP—A Centrally Acting DA-Autoreceptor Agonist
S. Hjorth, A. Carlson, H. Wikström, P. Lindberg, D. Sanchez, U. Hacksell, L. E. Arvidson, U. Svensson, and J. L. G. Nilsson
- 261 Pemoline: A Specific Long-Acting Dopaminomimetic Drug
Guy M. Everett
- 265 Renal Vascular Effects of Dopaminomimetics
J. L. Imbs, M. Schmidt, and J. Schwartz
- 273 Agonists and Antagonists of Peripheral Pre- and Post-Synaptic Dopamine Receptors: Clinical Implications
Leon J. Goldberg and Jai D. Kohli

- 285 Diuretic Effect of Dopaminomimetic Agents
G. Baggio, F. Ferrari, S. Guarini, M. Sandrini, and W. Ferrari
- 297 Detection and Characterization of Dopamine Receptors in Dog Area Postrema
Ennio Stefanini and Yvonne Clement-Cormier
- 303 Dopamine Agonists and Food Intake
M. O Carruba, S. Ricciardi, and P. Mantegazza
- 311 Dopaminergic Control of Gastrointestinal Hormones
Kerstin Uvnäs-Wallensten and Michel Gojny
- 319 Subject Index

Historical Highlights of the Chemistry, Pharmacology, and Early Clinical Uses of Apomorphine

John L. Neumeyer, *Samarthji Lal, and **Ross J. Baldessarini

Section of Medicinal Chemistry, Northeastern University, Boston, Massachusetts 02115; *Department of Psychiatry, Montreal General Hospital, Douglas Hospital and McGill University, Montreal, Quebec, Canada; **Departments of Psychiatry, Harvard Medical School and Mailman Research Center, McLean Hospital, Belmont, Massachusetts 02178

INTRODUCTION

Apomorphine (APO) was first prepared in 1869. Its pharmacology and even its clinical actions were extensively evaluated between 1869 and 1900. Many of its potentially useful actions in neuropsychiatric and other patients had been virtually forgotten or abandoned until the post-DOPA era and the explosive surge of interest in dopamine (DA) systems a century later.

Other chapters in this collection presuppose some familiarity with the chemistry and pharmacology of apomorphine and its congeners, and do not emphasize the rich early clinical history of apomorphine. Thus, we have prepared a brief historically oriented summary as a background for other chapters.

CHEMISTRY

The chemistry of apomorphine (APO) [2] is closely linked to chemical studies involving morphine [1], although apomorphine has little pharmacologic similarity to the narcotic analgesic from which its name was derived (Fig. 1). As early as 1869 Mathiessen and Wright (81) noted that an acid treatment of morphine yields (-)apomorphine. This conversion consists of dehydration of morphine followed by a skeletal rearrangement, whereby four of the five asymmetric centers in morphine are destroyed. However, carbon atom 9 in morphine, corresponding to the 6a carbon of APO, retains its configuration and results in a levo-rotating product. Codeine [3] and thebaine [5] undergo similar acid-catalyzed rearrangements to give the corresponding aporphines, apocodeine [4] and morphothebaine [6] (Fig. 1).

Supported in part by USPHS Awards MH-31154, MH-34006, MH-47370 and NS-15439, and an award from MRC-Canada. The manuscript was prepared by Mila Cason. Translation of Harnack (62) was assisted by Hartmut Stauss and Nora S. Kula.

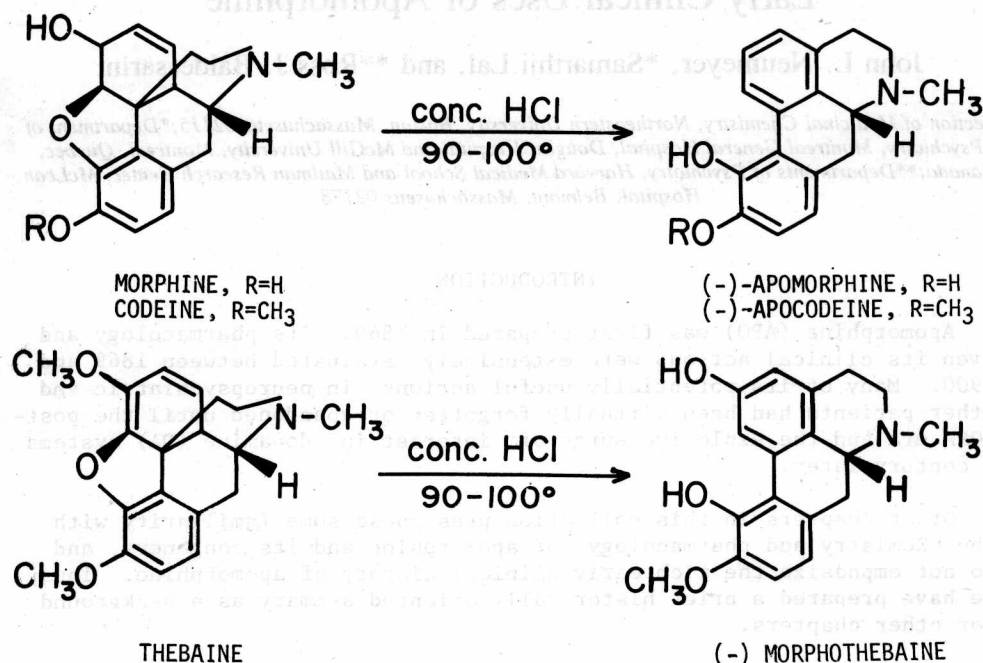


Fig. 1. Interconversion of the opioids morphine, codeine and thebaine to the aporphines (-)apomorphine, (-)apocodeine, and (-)morphothebaine.

The structure of APO was elucidated by Pschorr et al. in 1902 (99) and its absolute configuration was determined to be *Rectus* at carbon 6a (6aR) via a stereoselective degradation by Corrodi and Hardegger in 1955 (28). The determination of its crystal structure by Giesecke in 1973 confirmed both the structure and the stereochemistry of APO (54). In 1970, a century after the first preparation of APO, the total synthesis of (+)APO was carried out via a multistep process from isoquinoline and vanillin by Neumeyer et al. (91). Racemic APO was resolved into 6aR and 6aS enantiomers in 1974 by Saari et al. (104), who established that dopaminergic and emetic activity reside principally in the 6aR (*levo-rotatory*) isomer.