Apomorphine and Other Dopaminomimetics

Volume 1
BASIC PHARMACOLOGY

Editors
Gian Luigi Gessa
Giovanni Umberto Corsini

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Raven Press ■ New York

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

Made in the United States of America

International Standard Book Number 0–89004–667–0
Library of Congress Catalog Number 81–40610

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.

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Volume 1: Basic Pharmacology

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Volume 1: Basic Pharmacology
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Apomorphine and Other Dopaminomimetics, Vol. 1: Basic Pharmacology, edited by G. L. Gessa and G. U. Corsini, Raven Press, New York © 1981.

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

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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.

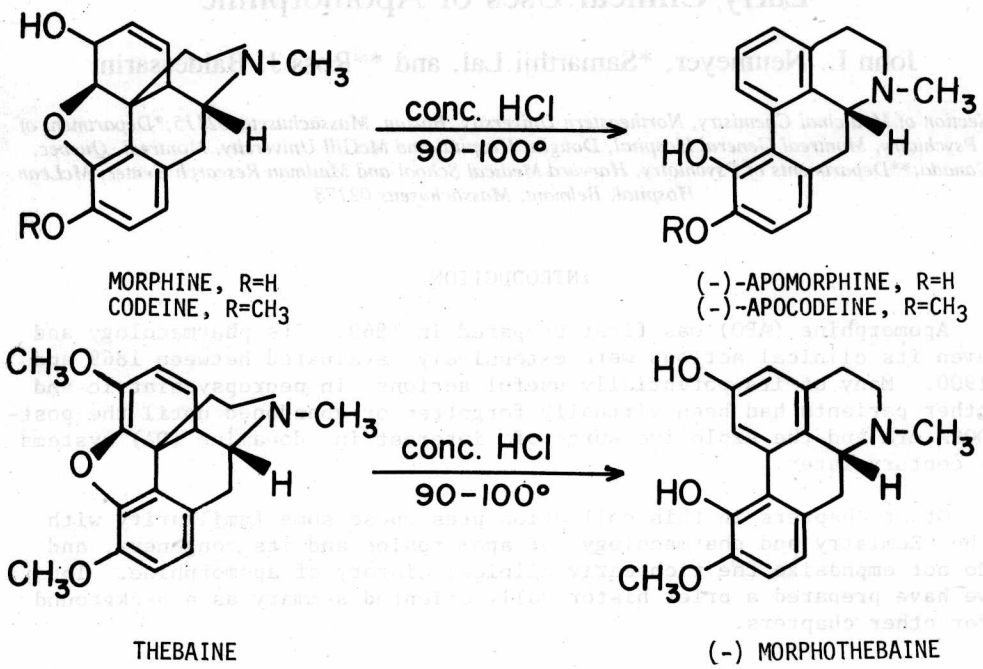

Fig. 1. Interconversion of the opioids morphine, codeine and thebaine to the aporphines (-)apomorphine, (-)apocodeine, and (-)morphothebaine.

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.