Handbook of

Drug and Chemical Stimulation of the Brain

Behavioral, Pharmacological and Physiological Aspects

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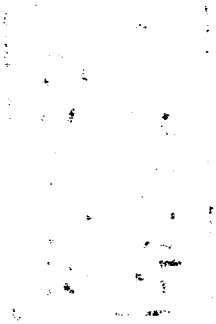
VAN NOSTRAND REINHOLD COMPANY
NEW YORK CINCINNATI TORONTO LONDON MELBOURNE

MEDICAL ECONOMICS BOOK DIVISION, INC.
ORADELL, NEW JERSEY



Van Nostrand Reinhold Company Regional Offices:
New York Cincinnati Chicago Millbrae Dallas

Van Nostrand Reinhold Company International Offices:
London Toronto Melbourne

Library of Congress Catalog Card Number: 74-10564
ISBN: 0-442-25622-1

Manufactured in the United States of America

Published by Van Nostrand Reinhold Company
450 West 33rd Street, New York, N.Y. 10001

Published simultaneously in Canada by Van Nostrand Reinhold Ltd.

15 14 13 12 11 10 9 8 7 6 5 4 3 2 1

Library of Congress Cataloging in Publication Data

Myers, Robert D 1931–
Handbook of drug and chemical stimulation of the brain.

1. Psychopharmacology. I. Title. [DNLM: 1. Brain –Drug effects. 2. Stimulation, Chemical. WL300 M996h]
RM315.M93 615'.78 74-10564
ISBN 0-442-25622-1

Preface

Ever since its inception in 1969, my intent in writing this book has been to present a comprehensive and up-to-date survey of the world's literature that pertains to the direct action of a drug or other chemical on the brain. Since experiments using the method of chemical stimulation have blossomed forth so readily in the past few years, this is indeed an appropriate time to take stock and review the exciting endeavors in this field and their present status.

Many of the research papers which are based on the application of a chemical to cerebral tissue have made substantial advances to our overall understanding of brain function. As such, they should be brought to light in the perspective of their own specific discipline. In view of this, it is my frank hope that this survey will be of value to every student interested in any of the intriguing issues of brain function, whether he be an inquisitive beginner or an established neuroscientist.

Each chapter is organized on a functional basis according to major physiological and behavioral systems. In this way, the facts which can be gleaned from the text should bring to the academician and clinician alike a keen awareness of the unique way in which a given chemical or drug can affect a distinct cerebral structure. A worker in one field of physiology, psychology, pharmacology or medicine hopefully will become cognizant of the enterprising activity of a worker in an entirely different area even though both may utilize the same experimental means to an end.

This book also seeks to point out some of the directions that a researcher may take in the future. In every chapter, the care and controls that are necessary in this proliferating field are emphasized so as to help the reader make a sensible interpretation of the series of isolated observations about a specific topic. Inasmuch as instances of controversy are not uncommon, I have attempted to evaluate critically the source of discrepancy which often rests simply in a difference in laboratory procedure.

In addition to the recent studies describing the action that a drug exerts on a specific cerebral structure, the early research reports of the German, Swiss and Japanese workers at the turn of the century are included. Since an attempt has

been made to include every pertinent paper written on this topic, any omission from the reference citations is certainly unintentional. Should the reader be aware of any paper which ought to be incorporated in the future version of this survey, I would be most grateful if the information is forwarded to me.

In general, a rule of thumb was followed to exclude from either the text or the master summary tables an abstract or summary written for the proceedings of a meeting, a conference, symposium or colloquium. Ordinarily, such an abstracted account is characterized by insufficient experimental detail, an inadequate analysis of the results or another shortcoming. Obviously, arbitrary exceptions to this rule had to be made. Although the basic reference list was completed in 1971, I have nevertheless included as many reports published in 1972 as possible.

I am deeply indebted to a great number of individuals who contributed in so many diverse ways to every aspect of this book. It is truly a pleasure to thank my professional colleagues and friends, both in England and America, who shared their valuable ideas on this subject, gave of their own personal insights and who offered the most salutary criticisms. My technicians and several other members of my laboratory staff kindly participated in the tracking down of articles, the redrawing of figures, and the reading and proofreading of the manuscript. Many authors not only gave generous permission to use their figures but often forwarded their own photographs or line drawings. The cooperation of the librarians and their various staff members of Purdue University, Indiana University Medical Center, National Institute for Medical Research (London), U.C.L.A. Brain Information Service, and University College (London) is deeply appreciated.

My secretary, Miss Jorga Fielder, typed the final draft of the book in its entirety with never-ending patience and a willingness for which I am sincerely grateful. Each of my four children always extended an amicable and helping hand whenever and in whatever direction it was needed. Finally, the cheerful and untiring efforts of my wife in typing the initial drafts, collating the references, in attending to hundreds of inconspicuous details and in offering inestimable encouragement have made this book possible.

R. D. MYERS

Lafayette, Indiana

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1 Principles of Chemical Stimulation of the Brain

"To deride the hope of progress is the ultimate fatuity, the last word in poverty of spirit and meanness of mind. There is no need to be dismayed by the fact that we cannot yet envisage a definitive solution of our problem, a resting-place beyond which we need not try to go . . ." P. B. MEDAWAR (1972)

I. INTRODUCTION

The incomparable challenge inherent in the manifold mysteries of brain function has led to one of the most fascinating experimental endeavors in all of the neurosciences. Essentially this widespread quest has centered on a prodigious attempt to "decode" the chemical fabric of a discrete collection of neurons. The logistics of such a decoding enterprise rests on the fundamental principle that an artificial alteration of the biochemical environment of a distinct region of the brain will produce a specific functional change in an animal. If such a change is evoked and is clearly repeatable, the response must make immutable sense in terms of the anatomy of the nervous system. In fact, the reaction to an alteration in the local chemical milieu of the brain may correspond directly with the acknowledged function of that morphological area. Or it may not correspond with the general knowledge about the structure which has been derived from the more traditional neurological approaches based on ablation or electrical stimulation.

Admittedly, any new method whereby a compound is applied directly to brain tissue, particularly of a wide-awake and behaving animal, is open to criticism. As we shall see in Chapter 2, the vast number of bench-top problems attendant to the technique itself is impressive. However, Sir Peter Medawar's statement at the heading of this chapter reflects with great insight the spirit in which the experimental evidence of an encoded functional system should be examined. The progress has been painfully slow and often obfuscated by an experimental or technical limitation rather than by an impoverished theoretical viewpoint. But the hope of understanding the neurochemical attribute of each of the complex

networks of neurons is notably profound, particularly if the concepts based on chemical stimulation are linked together with those derived from other experimental sources including those of histochemistry, transmitter dynamics and drug action.

In a word then, the overall purpose of this decoding endeavor is to contribute to the neuroscientist's goal of unraveling the mechanisms and even perhaps the circuitry that underlie the intricate processing of information of which the vertebrate brain is so capable. The chemical signal which triggers a response, the chemical reaction which inhibits that response, the balance and the interplay between the two, and the action which an individual substrate may have on another chemical system—all of these constitute a part of the questions raised when one stimulates the brain with a chemical substance.

II. WHY CHEMICAL STIMULATION?

The rationale upon which the laboratory usage of chemical stimulation of the brain is based can be subdivided into two major parts. The first is concerned with the anatomical locus and cellular mechanism of any of the endogenous humoral factors. These substances that occur naturally in brain tissue include the biogenic amines, peptides, and steroids. A second and entirely different purpose centers on the localization of a possible central site of action of a chemical or drug that is administered systemically. From behavioral observations, many of these artificially synthesized compounds appear superficially to exert a direct effect on some part of the central nervous system. On the basis of these two fundamental points and because of the attractive analogies that can often be drawn with the responses evoked by electrical stimulation of brain tissue (Myers, 1971a), the theoretical principles and procedures of chemical stimulation have evolved.

A. Definition

In the broad context of general physiology, we shall use the term chemical stimulation to apply to any class of neuronal events that is brought about when an endogenous or synthetic substance is applied locally within a given structure of the brain. Although a multitude of compounds may affect nervous tissue in a way that is not necessarily excitatory in the sense of membrane physiology, the reaction observed by the scientist is indicative of a local perturbation of that tissue reached or touched upon by the chemical.

For example, some of the endogenous hormones, when deposited in the brain, appear to inhibit, rather than stimulate neural elements in a manner similar to that of electrical current. Moreover, certain drugs act to hyperpolarize or depolarize a neuron by altering the flux of cations across the axonal membrane. Still other compounds may either block or enhance the action of a transmitter

substance or another humoral factor that is released into the synaptic cleft between two or more nerve cells. Rather than compartmentalizing the effect of a locally applied substance into functional categories, which in themselves would often be *ad hoc* and arbitrary, the term chemical "stimulation" is retained in this book for descriptive purposes.

B. Comparison with Ablation and Electrical Stimulation

Defying all reason is a question that is argued rather vehemently in some circles by a few investigators. Is chemical stimulation "more physiological" or "less physiological" than some other laboratory procedure used in the exploration of brain function? Plainly, at the very moment when an experimental neurosurgeon enters the cranium, a nonphysiological state is created. Beyond this, the logic of the debate degenerates into a matter of relativity. The implantation or insertion of any device into any part of the brain results in a pathological circumstance. Taking the question of relative "physiological-ness" a step further, almost any neurobiological technique, except perhaps a skull X-ray, can interfere to some degree with normal function. Even the ingestion of an ordinary pill by mouth is viewed as unphysiological by certain naturopathic practitioners, who happily are in the minority.

Scientists who utilize the method of chemical stimulation ordinarily follow certain principles of neuroanatomy and exercise basic neuropharmacological controls. By staying within these principles, this approach to studying the brain can be as valid as any other that seeks a specific functional answer in the realm of an unknown cerebral process. If performed properly, the analytical exploration of a reaction of a given structure to a chemical can supplement in a very vital way the information that is already known from other studies of that region. In the broad purview of stimulating tissue that is intrinsically excitable, the topical application of a chemical does permit a fine grain resolution of the characteristics of a collection of neurons that are seemingly delegated to a specific function. Why is this so?

First, on the basis of the biochemistry of cortical and subcortical structures, we know that endogenous substances such as amines, amino acids and hormones are present in varying concentrations in separate parts of the brain (e.g., Hebb, 1970; McEwen *et al.*, 1972). Second, cytochemical studies of individual fiber systems show that individual amine pathways are laid down anatomically in unique patterns (e.g., Fuxe *et al.*, 1966; Shute and Lewis, 1967). Third, the membrane of an individual neuron that lies contiguous to another possesses a special sensitivity to different molecules, as demonstrated by the technique of iontophoresis. Logically, one can deduce that within a single collection of neurons each cell possesses: (a) distinct chemoreceptors; (b) the capacity to convey an impulse to another cell by virtue of the release of an endogenous

substance; or (c) a mechanism in the form of the release of a humoral factor for altering the depolarization threshold of an adjacent cell.

What happens when we either ablate this collection of neurons or pass electrical current through it? These events can be conceptualized by considering a schematic representation portrayed in Fig. 1-1 of a hypothetical collection of nerve cells in an unspecified area of the mammalian brain. Let us assume that three separate pathways traverse this structure. Pathway A is excitatory and mediated by an excitatory substance at synapses A_1 and A_2 to stimulate functional system

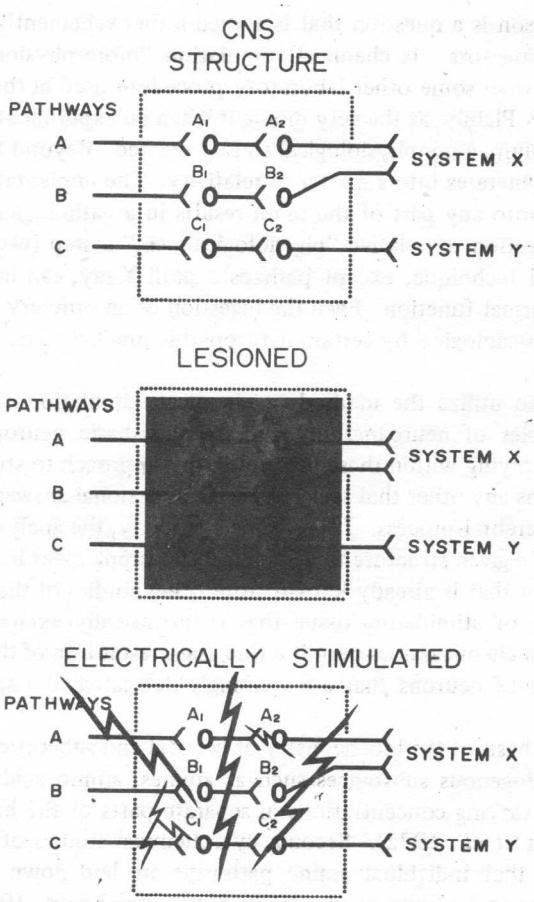

Fig. 1-1 A hypothetical structure in a mammalian central nervous system (CNS). Three separate pathways mediated by three individual sets of synapses traverse this structure. When the structure is lesioned (*middle*), all of the pathways are transected and the synapses are destroyed. When electric current is passed through the structure (*bottom*), all of the pathways are excited homogeneously in an undifferentiated manner.