ADVANCES IN BEHAVIORAL PHARMACOLOGY

Volume 1

Edited by

TRAVIS THOMPSON AND P. B. DEWS

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Advances in Behavioral Pharmacology

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Contents

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Preface

Behavioral pharmacology has grown from its modest beginnings in the 1950s to a substantial scientific enterprise. Numerous journals report the results of individual investigations, and volumes appear from time to time dealing with one or another aspect of behavioral pharmacology. There remains the chasm separating the individual research report from the integrated volume dealing with a single aspect of behavioral pharmacology. The field has reached such a point in its development that efforts to synthesize knowledge in subdomains of a behavioral pharmacology are in order. It was with this need in mind that the Advances in Behavioral Pharmacology series was created.

This series will provide synthetic and analytic review of significant areas of behavioral pharmacology, prepared by those most competent and knowledgeable in the respective fields.

As the term suggests, behavioral pharmacology is concerned with behavioral actions of drugs. Neurochemical and neurophysiological actions of drugs generally fall outside the domain intended to be included in this series. As the fields of behavioral pharmacology and neuropharmacology develop, from time to time papers bridging the two domains will be included in the Advances series. Actions of drugs on mental or emotional states generally fall outside the domain as well. Thus, while the series will include papers dealing with human behavioral pharmacology, the analysis will be limited to *behavioral* actions of drugs, and so will generally not include investigations at other levels of analysis. Reviews will be concerned with behavioral mechanisms of drug action. They will represent in-depth analyses, rather than summarizing research literature. Papers in the Advances are selective and critical in their treatment and deal with topics in depth as opposed to providing broad and superficial reviews.

The Editors are keenly aware of the relative youth of behavioral pharmacology. Thus, in the present volume, papers have been included providing both an historical background and a brief review of the current (and anticipated future) of the discipline. The reviews of the behavioral pharmacology of specific classes of compounds, as well as specific mechanisms of action included in this volume, are intended to be prototypic of the contents of subsequent volumes.

The Editors are deeply indebted to the authors of Volume I, both for their carefully and thoughtfully prepared manuscripts and for their indulgence in the delays in completing this volume. Finally, the editors wish to thank the staff of Academic Press for their confidence in support of this exciting new enterprise.

Travis Thompson
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Behavioral Pharmacology of the Tetrahydrocannabinols

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I. INTRODUCTION

For thousands of years man has used various preparations of the *Cannabis* plant (*Cannabis sativa*) to produce effects on the central nervous system. Yet, there are few well-controlled studies on the behavioral pharmacology of cannabis preparations appearing in the literature before the early 1960s. Although there are several reasons for the lack of scientific study of the pharmacological effects of cannabis preparations, among the most important reasons were that the active ingredients in the plant were not identified, so that their concentration varied from one preparation to another, and that objective methods for the study of drugs affecting the central nervous system were only beginning to be developed, particularly with respect to the objective measurement of behavior. The establishment of 1-Δ^9-*trans*-tetrahydrocannabinol (Δ^9-THC) as the major behaviorally active constituent of marijuana and its total synthesis (Gaoni & Mechoulam, 1964; Isbell, Gorodetzsky, Jasinski, Claussen, Spulak, & Korte, 1967; Mechoulam & Gaoni, 1965), the discovery and total synthesis of a second active constituent (Fahrenholtz, Lurie, & Dierstead, 1966; Petrzilka & Sikemeier, 1967; Taylor, Lenard, & Shvo, 1966), 1-Δ^8-*trans*-tetrahydrocannabinol (Δ^8-THC), and the application of operant conditioning techniques to the study of drug effects (Dews, 1955; Ferster & Skinner, 1958), mark the beginning of intensive investigation of the behavioral pharmacology of cannabis constituents.

II. DIFFICULTIES IN STUDYING THE BEHAVIORAL EFFECTS OF CANNABIS PREPARATIONS

A. Purity of Preparations Derived from *Cannabis sativa*

Marijuana refers to a preparation from the leaves, stems, flowers, and seeds of the plant *Cannabis sativa.* Marijuana is usually used by burning the dry plant parts in a cigarette and inhaling the smoke. Marijuana often contains less than

1% of the active tetrahydrocannabinols (THCs), although some preparations may contain as much as 7% THCs (Doorenbos, Fetterman, Quimby & Turner, 1971). Hashish, which is the dried resin from the flowering tops of the plant, may contain much higher concentrations of THCs. The concentration of THCs in the plant parts is variable, generally decreasing in the order of resin, flowers, and leaves with very little in the stems, roots and seeds. Thus, the concentration of THCs in a particular plant preparation varies not only with the genetic make-up of the plant, but also with the relative amount of each of the plant parts in the preparation. Until these facts became known, it was difficult to estimate dosages used in the early behavioral studies on marijuana. Since the orderly relationship existing between the dose of the drug and the magnitude of its effects is fundamental to quantitative pharmacological study, it is not too surprising that little progress was made until synthetic THCs became available to scientific investigators.

B. Solubility Problems

Neither Δ^9-THC nor Δ^8-THC is water soluble, making it necessary to administer these THCs in suspensions or in special solvents. Some of these vehicles have pharmacological effects of their own. For example, both Δ^8- and Δ^9-THC are quite soluble in ethyl alcohol; in fact it is sometimes recommended that stock solutions of THCs be kept in alcohol to prevent decomposition (Pars & Razdan, 1971). However, because ethyl alcohol effects behavior and because ethanol is exceedingly irritating to tissue on parenteral injection (Goodman & Gilman, 1970), the usefulness of this vehicle is limited.

THCs are also soluble in dimethyl sulfoxide (Bergel, 1965). This vehicle has been used successfully in a number of studies on the behavioral effects of THCs, especially when the desired concentrations are too high to make the use of suspensions practical (McMillan, Ford, Frankenheim, Harris, & Harris, 1972). Disadvantages of dimethyl sulfoxide as a solvent for THCs include the unpleasant odor it imparts to laboratory animals injected with it and the ease with which it crosses tissue barriers, such as the skin, thereby endangering laboratory personnel (David, 1972).

Various suspending agents have also been used successfully as THC vehicles. Some investigators have suggested the use of aqueous suspensions of Tween® 80 (Waller, 1971). In our laboratories we have found Triton X-100® to be an excellent suspending agent, which does not produce behavioral effects after intramuscular injections in pigeons (McMillan *et al.*, 1972) at concentrations as high as 20% (by volume in aqueous solution). Care should be taken to shake these suspensions immediately before use. If the suspension is shaken by hand for a few seconds and then placed in a sonicator for several minutes before injection, a homogeneous suspension can be obtained. Recently Dewey, Jenkins, O'Rourke, and Harris (1972b) have utilized an albumin suspension as a THC