Edited by Arnold J. Friedhoff

CATECHOLAMINES AND BEHAVIOR · 2

Neuropsychopharmacology

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PLENUM PRESS • NEW YORK AND LONDON

Library of Congress Cataloging in Publication Data

Main entry under title:

Catecholamines and behavior.

Includes bibliographies and indexes.
CONTENTS: v. 1. Basic neurobiology. — v. 2. Neuropsychopharmacology.
1. Catecholamines. 2. Psychopharmacology. I. Friedhoff, Arnold J. [DNLM: 1. Behavior — Drug effects. 2. Catecholamines — Physiology. QV129 C357]
QP981.C25C37 599'.01'88 75-11697
ISBN 0-306-38412-4 (v. 2)

A Division of Plenum Publishing Corporation
227 West 17th Street, New York, N.Y. 10011

United Kingdom edition published by Plenum Press, London
A Division of Plenum Publishing Company, Ltd.
Davis House (4th Floor), 8 Scrubs Lane, Harlesden, London, NW10 6SE, England

Printed in the United States of America

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Neuropsychopharmacology

Volume 1: Basic Neurobiology

Volume 2: Neuropsychopharmacology

Preface

This volume is intended to provide students and investigators of brain–behavior relationships with an understanding of the current concepts of the role of catecholamines in the regulation of behavior. Catecholamines are now believed to be modulators or transmitters in systems regulating a number of important aspects of behavioral function. The present intense interest in catecholamines is reflected by the large number of scientific reports dealing with these compounds. Even those reports which are relevant to behavior are staggering in number. The contributors to this book have drawn on the salient literature, as well as on their own work, with a view toward clarifying relationships between the basic neurobiology of catecholaminergic neural systems and normal and abnormal behavioral function. Current work in this field is heavily dependent on the use of psychotropic drugs to produce model behavioral states, or as biological probes. As a result psychopharmacological studies are generously represented. In the last chapter of Volume 2 the editor has attempted to further relate and develop the material in the two volumes from the conceptual and theoretical standpoint.

New York AJF

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Chapter 1

The Role of Catecholamines in Animal Learning and Memory*

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1. DEFINITIONS

1.1. Catecholamines

Since the locus of learning and memory is presumably within the CNS, we will consider only the two catecholamines (CA) which are important putative CNS neurotransmitters in mammals, dopamine (DA) and norepinephrine (NE). We exclude epinephrine, which is found chiefly in the peripheral nervous system (PNS), because little CNS pharmacological work has been done with it, although recent evidence suggests that it may function as a CNS neurotransmitter (Hökfelt *et al.*, 1974; Koslow and Schlumpf, 1974).

1.2. Learning and Memory

For the purposes of this chapter, we will use an empirical definition of learning: the process by which experience or practice leads to a relatively

* During the preparation of this chapter David A. Gorelick was supported by NIH training grant 5T5 GM 1674 from the National Institute of General Medical Sciences; Thomas R. Bozewicz was supported by NIMH grant MH 06418.

permanent change in behavior (Kimble, 1961). Thus, we exclude from consideration changes in behavior which are due to factors other than experience, e.g., maturation, senescence, or nutrition, or factors which are not relatively permanent, e.g., sensitization or fatigue. As so defined, the concept of learning includes that of memory, since the former could not occur without the latter. However, we will reserve the word "learning" for the acquisition of behavioral change and use the word "memory" to refer to the persistence of learning over time so that it can be expressed in later behavior. Memory can be subdivided into three separate processes: (i) consolidation, the entry of the information into storage, (ii) retention, the storage process itself, and (iii) retrieval, the bringing of the information out of storage.

2. PROBLEMS OF SPECIFICITY

2.1. Behavioral Specificity

In any behavioral experiment, the learning process is not observed directly. What is observed is a change in the behavior or performance of an animal in a particular task. Such a change can be caused not only by learning, but also by changes in other processes which contribute to the performance of the behavior, such as perception, motivation, or motor ability. A behavioral change can be attributed to learning only after establishing its independence from changes in other behavioral processes. This is particularly important when studying the relation between CA and learning, because CA play a role in many behavioral processes besides learning (see other chapters of these volumes).

Two types of control experiments are important in ruling out effects on behavioral processes other than learning. One type is to show that the treatment used to affect behavior does not affect the particular perceptual, motivational, and motor variables used in that experiment. This is usually done by showing that conditioned or spontaneous behavior involving these variables is unaffected. The other type of control experiment is to show that the behavioral effect of the treatment is consistent even when completely different variables are used. Examples of such variables include, for perception, the sensory modality of the conditioned stimulus (CS); for motivation, the type of reinforcement; for motor ability, the response requirements of the task. Ideally, one should parametrically alter these variables to ensure that they are equivalent in their ability to control the animal's behavior.

An experimental example may help clarify how a change in behavior can be attributed to learning by use of proper controls. Cooper *et al.* (1973)

trained rats in a discriminated shuttlebox escape/avoidance task. The task involved presenting the rat with a CS, in this case a light plus a tone, followed after 10 sec by an unconditioned stimulus (UCS), continuous 0.8 mA electric shock to the feet. If the rat made a conditioned response (CR), crossing to the other side of the shuttlebox within 10 sec of CS onset, the UCS was avoided. A CR made after UCS onset resulted in escape from the UCS. Rats given a 6-hydroxydopamine (6-OHDA) treatment which decreased brain CA levels during training made significantly fewer avoidance responses than did control rats given saline. Does this difference in performance reflect a difference in learning because of altered brain CA levels?

One alternate possibility is that the treatment altered the perceptual process. A rat whose vision was impaired would obviously do poorly in a task involving a visual CS. A general visual perceptual deficit could be ruled out by showing that unconditioned responses to a visual CS, e.g., orienting, photophobic, visual cliff, or startle responses, were not impaired by the treatment. Another necessary control would be to show that similar behavioral effects were obtained when using CS of different sensory modalities, e.g., auditory or tactile. Since CS of different modalities may differ in the extent to which they can control behavior, a parametric comparison should be done. The finding of a consistent effect with different stimulus modalities would suggest that the treatment's behavioral effect was not due to visual impairment.

Another possibility is that the treatment altered motivation. If an electric shock were less painful or produced less fear in a treated rat, the rat would be less motivated to exert effort to avoid or escape the shock. One way to rule out a specific deficit of fear motivation would be to test the effect of the treatment on different unconditioned responses (UCR) elicited by the UCS, e.g., freezing, jumping, squealing. Another way would be to use completely different aversive UCS such as an air blast or sudden loud noise, instead of electric shock. The use of other motivational states, such as hunger, thirst, or sex, provides a further necessary control to ensure that the treatment is not affecting this process. Each type of motivation used should be tested parametrically to ensure that equivalent motivational states are induced in the animal. The finding of a consistent effect with different levels and types of reinforcers would suggest that the treatment's behavioral effects were not due to a motivational alteration.

A third possibility is that the treatment affected motor ability. A rat could have learned the appropriate CR but still be unable to perform it because of a motor deficit. This possibility could be ruled out by showing that the treatment does not affect similar responses when made spontaneously or as UCR. Cooper *et al.* (1973) found that neither spontaneous motor activity in an activity cage nor crossings in the shuttlebox between trials (no CS

present) were affected by the treatment. Another necessary control would be to show that the treatment has similar behavioral effects on tasks requiring different types of responses. Some important comparisons would be between tasks requiring active *vs.* passive responses and between tasks requiring a certain response rate or latency for a correct response (strict requirements) *vs.* tasks with broader requirements such as making a correct choice (e.g., discrimination task). The finding of a consistent effect on tasks with these different response requirements would suggest that the treatment's behavioral effects were not due to alteration of motor ability. Cooper *et al.* (1973) found that their treatment did not affect the acquisition of a one-trial passive avoidance task. This difference in behavioral effect between active (shuttlebox) and passive avoidance tasks suggests that the treatment does not affect learning, but does have some effect on the ability to make this type of active learned response. This effect appears to be limited to learned responses because, as mentioned above, unconditioned and spontaneous active motor responses were not affected by the treatment. Another explanation for the absence of a deficit on the passive avoidance task may be that this task is not of equivalent difficulty to the active task. If the passive task were much easier to learn than the active (as suggested by the fact that significant learning occurs in one trial), the lower level of CA activity remaining after the treatment might still be sufficient to maintain performance without a deficit.

The time at which a treatment is active in relation to the time the behavior is measured affects the behavioral specificity of the results (McGaugh, 1973). Only experiments where the treatment is active during training (acquisition) can provide information about learning, *per se*. A key criterion for the occurrence of a learning effect is whether the behavioral change persists after the effects of the experimental treatment have worn off, since learning, by definition, must involve a relatively permanent change in behavior. However, there are several difficulties in interpreting such results. A learning effect might occur but not be reflected in later behavior because of state dependency effects, i.e., an impairment of performance because of the difference in "brain states" during training and during later performance caused by the treatment (Overton, 1974). A behavioral change may persist after training and yet not be due to an effect of the treatment on learning. Instead, the treatment might have altered other behavioral variables during training (e.g., arousal, number of reinforcements received) in such a way as to change later behavior. Experiments where the treatment is active only immediately (seconds to hours) after training can provide information about consolidation and retention. However, possible state-dependency effects must be controlled (Wright, 1974). Information about retention alone can be provided by experiments where the treatment is active a sufficient time (days) after acquisition and before later performance