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Advances in Behavioral Pharmacology

VOLUME 4

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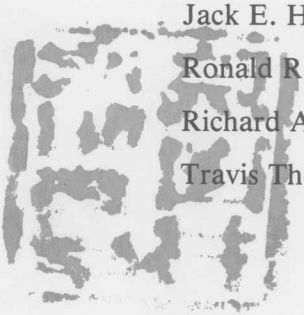

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Erratum
Advances in Behavioral Pharmacology, Volume 3

JAMES E. BARRETT and JONATHAN L. KATZ

The following line should be inserted between the fifth and sixth lines above the heading "B. Second-Order Schedules" on page 130:

These findings further emphasize the natural complementarity that exists be-

The sentence in its entirety *should read*: These findings further emphasize the natural complementarity that exists between behavioral pharmacology and the experimental analysis of behavior and also dramatically illustrate that the behavioral effects of drugs are determined by many of the same environmental variables that affect behavior.

Contents of Previous Volumes

Advances in Behavioral Pharmacology

VOLUME 4

Contents

Behavioral Mechanisms of Drug Dependence[1]

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[1]The introductory section of this article is based on an articled published in *Behavioral pharmacology of human drug dependence* (NIDA Research Monograph 37) edited by T. Thompson and C. E. Johanson, U.S. Govt. Printing Office, Washington, D.C., 1981.

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I. INTRODUCTION

A. The Search for Common Processes

The search for a more thorough understanding of the basic common processes underlying drug dependence has been thwarted by the lack of a conceptual map of the terrain. Investigators have been in the position of the crew in Lewis Carroll's *The Hunting of the Snark*. The Bellman brought a map purporting to show the elusive Snark's location; however, once the voyage was underway, the crew discovered the map was completely blank. All too often those of us in the field of drug dependence find ourselves floating in an uncharted conceptual sea, zigging and zagging in search of a common causal process. It would be as naive to suppose that all forms of drug abuse would have a single common causal mechanism as it would be to believe that all forms of heart disease have a common cause. Instead, it is more reasonable to suppose that, just as there are similarities in the symptoms in various forms of heart disease, there are also similarities in various forms of drug dependence. However, in both cases one cannot expect the normal controlling mechanisms to have gone awry in precisely the same ways. It must be assumed there is a relatively limited number of variables, whose weightings differ among forms of substance abuse, which interact to produce the various states of dependence.

A second problem facing the field has been the absence of a unit of analysis and a metric for assessing the control drugs exercise over the behavior of the user. It wasn't until the mid-1960s that the control over objectively measurable behavior was suggested as a criterion for the dependence-producing properties of drugs. Finally, we have struggled to develop more objective ways of assessing behavioral consequences of the drugs which are self-administered, and to provide a consistent framework within which to interpret those effects. Thus, like Janus's two faces, these two opposite facing problems of drug dependence have oriented investigators in opposite directions. Behavioral pharmacologists have treated drug self-administration and the study of other behavioral effects of drugs as only nominally related. People in the drug treatment community have focused primarily on the adverse consequences of drug dependence, with little interest in drug self-administration, per se. As we shall see presently, the two have finally come face to face.

Drug dependence involves a cluster of processes in which a state is pro-

duced by repeated self-administration of a drug, such that the drug user will engage in substantial amounts of behavior leading specifically to further administration of the drug, and will continue to administer the drug even when this requires the sacrifice of other important reinforcers (Kalant, Engel, Goldberg, Griffiths, Jaffe, Krasnegor, Mello, Mendelson, Thompson, & VanRee, 1978). An understanding of drug dependence requires knowledge of the factors responsible for development, maintenance, and elimination of drug self-administration and of the effects of the self-administered drug on other ongoing bio-behavioral processes. We are interested, therefore, not only in how a drug comes to serve as a potent reward exercising extensive behavioral control, but in how the drug influences the subjects' ability to meet environmental demands. The aspects of an animal or person's behavioral functioning which are altered by a drug are the drug's *locus of action.* The processes which account for the drug's behavioral effects are the *mechanisms of action.*

B. Behavioral Mechanisms of Drug Action

In the natural sciences, there is broad agreement concerning what the term mechanism means. The mechanism by which oxygen is transferred from the atmosphere into the blood stream involves the gradients of partial pressure of oxygen and carbon dioxide in the alveoli of the lung and in the bloodstream. The degree to which oxygen and carbon dioxide are exchanged has to do with differential pressure gradients. Thus, we refer to a general physical principle of gradients of partial pressure of gases across a membrane in specifying the mechanism. Similarly, when we ask what the mechanism is by which a plant turns toward the sun, reference is made to a general set of principles having to do with differential rate of elongation of cells along the brightly illuminated and the shaded side of the stem of the plant. Auxins migrate toward the side of the stem nearest the sun, reducing the rate of growth of the long cells toward the sun relative to the rate of the cell growth away from the sun. The consequence is the turning of the stem due to differential rate of cell growth. These examples seem clear enough. A "mechanism" refers to a description of a given phenomenon in terms of more general principles.

In pharmacology, the notion of mechanism of action is intertwined with the concept of locus of action. Claude Bernard (1856) conducted several experiments elucidating these two concepts. In one study, he examined the site of the paralytic action of curare. Using a nerve-muscle preparation, Bernard showed that if a muscle were stimulated directly, the muscle would contract. However, even though the nerve continued to conduct stimuli along its axons, if the nerve itself were stimulated, the muscle would not

contract. Therefore, Bernard concluded that the site of action of curare must be at the myoneural junction. In a conceptually related experiment, Bernard studied the mechanism by which carbon monoxide causes asphyxiation. Bernard knew it was necessary for oxygen to be carried to the tissues by the bloodstream. Moreover, he knew that when an animal was placed under a bell jar filled with carbon monoxide, the animal was asphyxiated. In a series of elegant experiments, he demonstrated that carbon monoxide has a differential and selective affinity for hemoglobin, which was the active element responsible for the distribution of oxygen to the tissues. Bernard's experiment was critically important for the development of the concept of mechanism of action, because he demonstrated that carbon monoxide altered a normal function of hemoglobin which was responsible for oxygenation of tissues. Thus, the term "mechanism" in pharmacology, as in other areas of the natural sciences, refers to a description of a phenomenon in terms of some more general set of scientific principles. The fact that in pharmacology, most of the mechanisms to which we have customarily referred have been reductionistic, does not necessarily carry special significance. To a degree, this has been a fortuitous historical development which has become entangled with unwarranted tenacity in our theoretical fabric.

Nearly all modern biological scientists subscribe to a *constitutive reductionistic* view, i.e., the assumption that the composition of organisms is exactly the same as that found in the inorganic world and that none of the processes encountered in living organisms conflicts with those of known molecular phenomena (Mayer, 1981). However, *explanatory reductionism,* as is commonly asserted, has serious limitations. According to this view, the actions of a drug administered to an organism would not be adequately described until an account is provided at the most molecular level (i.e., presumably biophysical). A fundamental problem with this position is that events at subcellular levels may have little direct bearing on *integrated function* of larger levels of biological organization within a living organism. A drug at a given dosage which diminishes an organism's execution of a learned performance under one set of reinforcement contingencies may have little effect on performance regulated by other contingencies. A molecular explanation of drug action would not deal adequately with the functional organization of operant behavior. Moreover, the effects of most interactions among systems of all kinds in nature decrease in strength with distance between levels (e.g., biochemical to physiological, physiological to behavioral). As an analysis moves from one level of organization to another, the dynamic features at a given level are often nearly independent of the detailed structure of the various subsystems at a lower level of organization.