Bacterial Chemotaxis As A Model Behavioral System

Distinguished Lecture Series of the Society of General Physiologists

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Daniel E. Koshland, Jr.

Department of Biochemistry
University of California
Berkeley, California

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Preface

The understanding of behavior has been approached in past eras through witchcraft, religion, philosophy, and psychiatry. Today we stand at the threshold of the chemical era. We no longer explain melancholia by the ghosts of Hamlet but by the imbalance of hormones. Euphoria is not described in iambic pentameter but in terms of neurotransmitters. And suicidal impulses are more effectively treated by lithium therapy than the psychoanalyst's couch.

One purpose of this volume is to describe the simplest behavioral system and one that is undoubtedly the most advanced in biochemical understanding. Bacteria migrate toward chemicals that are good for them, such as nutrients, and away from chemicals that are toxic. This behavioral response, called chemotaxis, is shared with almost all living species including man, who is attracted to perfume and repelled by rotting food. The bacterium has receptors on its surface like our eyes and ears, a primitive information processing system not unlike our neurons, and a motor response. The manner in which this tiny organism responds to external stimuli is fascinating in itself.

Interesting as any one system may be, it assumes more interest if it is relevant to other species as well. Although it is an exaggeration to say "if you've seen one cell, you've seen them all," biochemists have learned that nature cleverly repeats patterns so that the most primitive cell has much in common with the most complex organism. In neurobiology this makes it possible for us to gain insights into the human brain from studies on the biochemistry of the bacterium, the neural organization of the fly, the visual system of frogs, the aggressiveness of rats, and the language of apes. Therefore, a second purpose of this volume is to emphasize those features of the bacterial system that are relevant to all species and provide windows into the interpretation of more complex behavior. Thus in one part I discuss the strategy of receptors to maximize information gathering and in another section the relation of bacterial behavior to the genetics of schizophrenia.

Bridging the gap between general interest and scientific accuracy is an enormous challenge, particularly in a rapidly developing field. In this volume the first two chapters and the last one are written in language understandable to the educated layman. In the middle chapters the language is designed for an individual with biological training, although it is hoped that a dedicated scientist from other disciplines could follow the logic. To provide both an up-to-date overview for the general reader and current developments for the specialist, the device of references to primary literature has been utilized. In this way it is hoped that reference to original data will not impede the flow of the narrative.

To some the suggestion that behavior can be reduced to chemistry is a sacrilege, the replacement of romance and mystery by the language of receptors and electrical circuits. I have spent the last eight years in this area and hope to spend many more, and to me there is no greater adventure and no more profound mystery than the understanding of the human brain. If this book provides some insight into the extraordinarily clever devices that nature has devised to process sensory information, it will have fulfilled its goal. The bacterium, like a Matisse painting, illustrates with elegant simplicity the essentials of behavior; to some it may also illuminate the beauty of nature's designs.

Daniel E. Koshland, Jr.
Berkeley, California
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Glossary

E refers to enzyme.
R refers to receptor.
C refers to chemoeffector.
S refers to substrate.
T subscript refers to total of a species, e.g. $R_T = R + RC$.
$\underline{X}$ refers to instantaneous value of response regulator.
$\overline{X}$ refers to average value of X over time.
X_{SS} refers to steady state value of X.
X_0 refers to value of X at $t = 0$.
X_∞ refers to value of X after adaptation is complete (relatively long time).
Rate constants are defined in Figs. 31 and 33.
Genetic nomenclature is defined in Fig. 18.

Acknowledgment

The author is grateful to the Society of General Physiologists for the honor of their Distinguished Lectureship and more importantly for providing the catalytic spark to create this book. I am also grateful to the Harvard Department of Biological Sciences for their hospitality on the sabbatical leave that made this endeavor possible.

The author's research in chemotaxis and behavior has been greatly stimulated by his collaboration with imaginative and enthusiastic colleagues too numerous to mention here. Their names and signal contributions are recorded in the bibliography.

Contents

I.

Introduction

From the witch doctors of ancient times to the gossip magazines of today, behavior is a phenomenon which fascinates all of us. Admittedly, antisocial behavior makes more news than "good" behavior; but the two are interrelated, both in the intellectual analysis of behavior and the rewards and punishments society and evolution devise to induce acceptable behavior. Developments of modern science are daily defining behavior in more precise terms. This has not in any way lessened controversy but has moved it to different grounds. As the data from biochemistry and neurobiology accumulate, it is inevitable that questions of nature and nurture, of chemical predestination vs. free will, and of normal and abnormal behavior will be cast in different terms than in previous more philosophical and less scientific eras.

The *Oxford Dictionary* defines behavior in two ways: (a) "Mode of conducting oneself, deportment" and (b) "The way in which an organism, organ, or substance acts in response to a stimulus." The study of behavior will be devoted to both of these areas, which overlap. The first definition has the flavor of an anthropomorphic societal response; whereas the second is applicable to all species as well as the individual cell. The latter is more scientific, hence easier to place on an objective basis. However, both types of behavior may have similar chemical components, and there are no easy lines of demarcation between instinctive and learned behavior or between complex and simple stimuli. Some of our "reasoned" behavioral responses to apparently complex stimuli may be highly conditioned by heredity, and some of our instantaneous responses to simple stimuli may be developed by careful training programs.

For these reasons, analysis of behavior can proceed on a number of different levels such as good and bad, which requires a philosophical value system, or nature and nurture, which requires the science of genetics. The ambiguity in terms used to describe behavior may be decreased and our understanding increased by the examination of the behavior and biochemistry of simple species. This book will examine one such species in detail and then discuss what extrapolations can be made to other levels of biological organization.

It is of particular importance in studying behavior to disentangle the overtones of a value system from the fundamentals of scientific measurements. The second definition of behavior previously listed does not ascribe any positive or negative overtones to the description of behavior. When behavior in higher species is discussed, we use terms such as altruism, courtship, and learning, which can easily be construed to be inherently good or necessarily complex. But such assumptions are frequently unwarranted. Thus, learning can be defined as the modification of behavior based on experience, and such definition can apply to a goldfish's response to electric shock as well as to a grammar school education.

It does not follow that learning at the level of the bacterium involves the same mechanisms as human cognitive processes just because they fit into the same definition. But it would be a mistake to deduce that learning in man must have fundamentally different mechanisms from simpler species just because it is more complex. Similarly, poets and novelists may use altruism to denote a type of commendable behavior. But scientists can define it as "any behavior which benefits others to the detriment of the individual performing the act." Such a definition would inevitably include instinctive acts such as cries of fear which alert others to a danger, as well as deliberative acts such as diving into a river to save a drowning child. The science of behavior, therefore, must be careful in its definitions and must make a clear distinction between the discovery and understanding of behavior on a scientific basis and the value judgments which society must construct in order to reward "good behavior."

This book, therefore, will approach the subject of behavior by describing a simple system in which value judgments do not impinge. It will then discuss the relationship of this system to higher systems in which such value judgments may be inescapable.

For our simple behavioral system we have chosen the phenomenon of bacterial chemotaxis. Chemotaxis is defined as movement toward or away from chemicals and is a ubiquitous biological phenomenon. From bacteria which migrate toward nutrients, to man who is pleased by the odor of a good meal, the movement of organisms in response to chemical stimuli is universal. Individual cells as well as complex mammals respond to chemical attractants. Insects respond to sex lures. White blood cells, which devour bacteria, are attracted to them by chemicals which the bacteria excrete. Of all chemotactic systems, the bacterial one is perhaps easiest to study and it has the good fortune that the complete organism is also a single cell.

II.

Brief Description of the System

Bacterial chemotaxis was discovered by Pfeffer (176) and Englemann (68) in the 1880s and the phenomenon has been studied intensively in a number of laboratories in recent times. Workers from the laboratories of Adler, Berg, Dahlquist, Hazelbauer, Macnab, Ordal, Parkinson, Simon, Taylor, and our own have made major contributions to recent literature. Pfeffer demonstrated that bacteria would swim toward certain chemicals that were termed attractants and away from other chemicals termed repellents and were completely insensitive to many other chemicals. One kind of experiment he performed is illustrated in Fig. 1 taken from his notebook. He placed a capillary containing an attractant in a beaker containing uniformly distributed bacteria. After an appropriate interval of time, he examined the capillary under the microscope and observed that the bacteria swam into the capillary in numbers far in excess of what would be expected by simple random motion. He also observed that some attractants were more powerful than others, and that certain molecules even appeared to repel the bacteria from entering the capillary.

Since his initial studies, a wide variety of bacterial species have been examined for their chemotactic ability of which the most widely investigated are the gram-negative bacteria *Escherichia coli* and *Salmonella typhimurium*. Although the two organisms on which most work has been done are gram-negative bacteria, studies on other species such as *Bacillus subtilis,* which is gram-positive, and phototactic bacteria, which contain chlorophyll, have also been

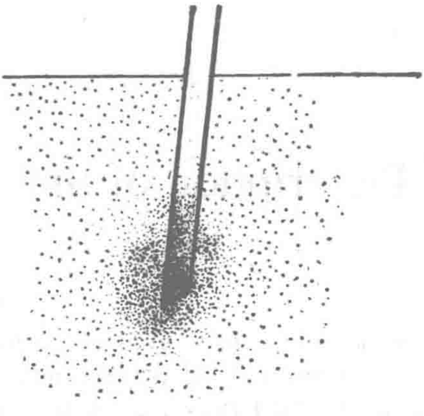

FIG. 1. Bacteria accumulating in a capillary. Original schematic drawing by Pfeffer showing bacteria swimming into capillary that contains an attractant. Bacteria were originally observed in the microscope, but they can be determined quantitatively by emptying the capillary contents into a nutrient solution and counting the bacterial growth (4).

shown to have chemotactic mechanisms very similar to those of the gram-negatives. These other species frequently provide special opportunities, e.g. the gram-positives have a membrane more permeable to cyanine dyes and also help establish the generality of the mechanism observed in the gram-negatives.

In general, attractants are usually nutrients, and repellents are usually toxic or indicators of toxic conditions. The bacteria swim toward molecules that aid in their survival and away from molecules that are deleterious. They ignore molecules that are useless to them. Hence, the bacterial chemotaxis system operates as a rudimentary pain and pleasure system to reward favorable and discourage unfavorable migration.

From what is known, bacterial sensing is organized in conceptual outline rather similarly to the organization of higher species. A schematic illustration of a sensory transduction system which applies to man, as well as bacteria, is shown in Fig. 2. The receptors that receive signals from the external environment are located in the

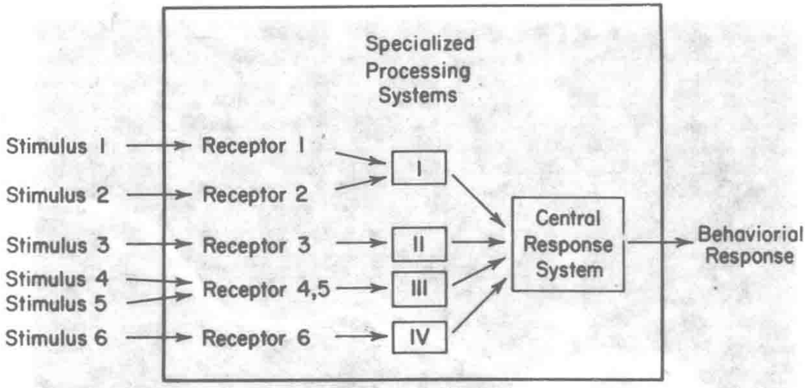

FIG. 2. A generalized scheme of a signaling system. Stimuli 1, 2, and 3 represent chemicals, sound, light, and so forth, which act to modify receptor proteins which are designed to be specific for one or more stimuli. Receptors 4 and 5 are used to illustrate a receptor that can be stimulated by stimuli 4 and 5. The receptor transmits the signal to a specialized processing system, which is then transmitted to a central processing system. Receptors 1 and 2 are seen to act at the same specialized processing system I. The specialized system could be the visual, the gustatory, etc., or the special chemical pathways described below. The processed signal then generates a motor response to result in a behavioral pattern.

membrane of the bacteria, which is on its periphery. The signal is then processed by a sensory apparatus within the cell which has been shown to involve approximately a dozen proteins. Some of these proteins are in the membrane and the rest in the cytoplasm of the bacterium. The output from this processing system is a motor response. This response involves a signal to the bacterial flagella either to tumble and hence change direction or to suppress tumbling and continue on in the same direction. By altering the frequency of tumbling, the bacterium can thus direct its migration. This simple system has been selected by evolution to optimize its properties and allows the bacterium to be responsive to changes in its environment.

The description of this simple system has been made possible by a variety of techniques. Biochemical approaches have been used for

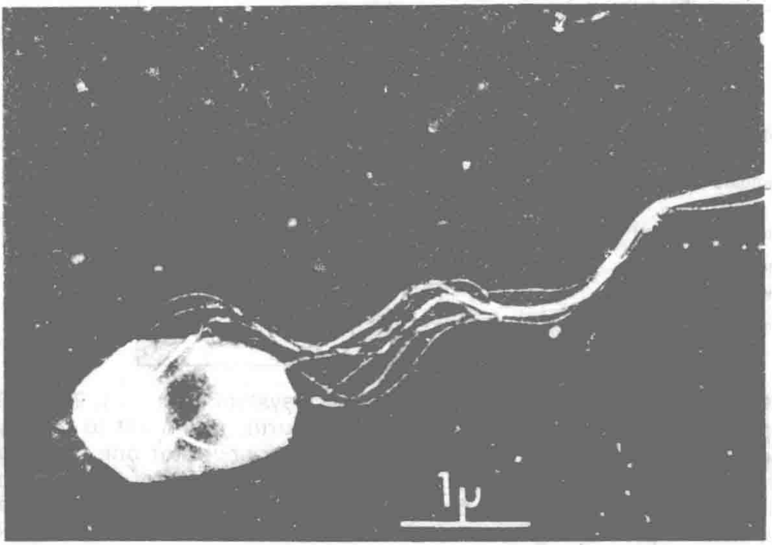

FIG. 3. Electron micrographs of *S. typhimurium*. (*E. coli* looks essentially the same.) (**A**): Bacterium with flagella in a bundle. (**B**): Bacterium with flagella spread out.

isolating receptors and for identifying enzymes of the processing machinery. Genetic manipulations have been utilized to determine the genes involved in the sensory processing system. Special analytical techniques have been developed which allow this sensory system to be monitored quickly and easily. Genetic engineering has made the system amenable to study in ways impossible in higher species. Finally, these techniques have been utilized individually and in combination to understand the complex feedback loops which make this processing possible. (Recent reviews on the subject can be found in refs. 3,5,34,81,106,107,109,111,126,127,172,206,243.)

Figure 3 shows two pictures of *S. typhimurium* bacteria taken in the electron microscope. The bacteria are from 2 to 5 μm long and from 1 to 2 μm in diameter. Their surface contains several layers of membrane in which the flagella are embedded. These flagella are shown in an unorganized form in Fig. 3B, and coalesced in a bundle