Perception of behavioral chemicals

D. M. Norris, editor

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PERCEPTION OF BEHAVIORAL CHEMICALS

edited by

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Preface

Perception is the resultant impression which an organism, human, forms of its environment, or a portion thereof, based on sensory input from stimuli. This book addresses how we perceive our environment via two-fifths of our sensory input (i.e., smell and taste). Our understandings of smell and taste have been the poorer among the recognized senses. This volume seeks to increase significantly the knowledge of these senses relative to that of the other stimulant modalities. Perception in the chemical senses is updated in both the aquatic and terrestrial environments, and in organisms ranging from bacteria to humans. These perceptions are analysed especially in terms of behavioral, physiological, biochemical and biophysical parameters that distinguish the individual that is experiencing the stimulus from those individuals of the species that are not so stimulated. We attempt especially to increase the understanding of the physicochemical mechanisms of energy transduction and transfer that allow a chemical stimulus to be perceived. The attempted emphasis on fundamental physicochemical aspects of perceptions in the chemical senses is based on the conclusion that our understanding should now surpass the level at which its aroma only tells us that a rose is a rose. Understanding the mechanism of perception of stimulus is now, if not before, important to optimal use of the chemical senses by humans. Efficient use of olfaction and taste, after all, is important in the most basic activities of organisms: nutrient intake, defense against parasites and predators, reproduction and detection of inanimate threats (e.g., fire and poisonous gases) in the environment.

This effort, like most, falls short of its goals, but it hopefully provides a fresh foundation from which progress may develop. We have sought to stimulate thought and experimental efforts to understand better the chemical senses. We sought not to create dogmas that inhibit new energies.

However incomplete our recorded understandings of smell and taste, they are now adequate to allow much management of two-fifths of our recognized perceptions of the environment. Our capabilities for altering these perceptions are formidable. Applications of these abilities hopefully can include the clinical correction of abnormal human perceptions in smell and taste that threaten survival or markedly decrease the quality of life, and will not be limited to such uses as enabling our perception of the garbage dump as an odorous flower garden - if we close our eyes!

Dale Melvin Norris
Editor

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Chapter 1

THE ROLE OF PROTEINS IN CHEMICAL PERCEPTION IN BACTERIA

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"Wisdom, whose lessons have been represented as so hard to learn by those who never were at her school, only teaches us to extend a simple maxim universally known. And this is, not to buy at too dear a price."

Henry Fielding (1749), in "The History of Tom Jones"

1. BACTERIAL CHEMOTAXIS: A MODEL FOR CHEMICAL PERCEPTION

The relative simplicity of the bacteria makes them especially well suited to an investigation of the molecular mechanisms of chemical perception. Bacterial chemotaxis, which is a migrational response to perceived chemicals, shares the essential elements of chemosensory systems with higher organisms (Koshland, 1977; Hazelbauer, 1977). Specific receptors on the cell surface bind chemical affectors (i.e., messengers) that are present in the environment. The energy in many receptor-affector complexes is transduced into a signal that can be transmitted through the membrane. The organism processes the signal, and may make a response appropriate to the stimulus. The bacterium has a rudimentary memory and is capable of potentiation and adaptation (Koshland, 1979b). It accomplishes this in a single cell, without the complexity imposed by a highly differentiated neural network. The ease with which bacterial mutants in chemotaxis can be selected adds a powerful tool for probing such neurosensory processes. The combined application of genetic and biochemical techniques has been responsible for the rapid progress made toward elucidation of the mechanism of bacterial chemotaxis.

This chapter seeks to provide a brief overview of the known biochemical mechanisms of genetic and biochemical techniques has been responsible for the rapid progress made Most of the discussed studies concern the closely related gram-negative bacteria, *Salmonella typhimurium* and *Escherichia coli**, but some references are also made to the gram-positive species, *Bacillus subtilis*. For additional information regarding chemotaxis the reader is referred to several recent reviews (Adler, 1975; Hazelbauer and Parkinson, 1977; Koshland, 1979a; Macnab, 1978; Springer et al., 1979) and an excellent monograph (Koshland, 1980). We anticipate that elucidation of the mechanisms of bacterial chemotaxis will reveal principles of sensory transduction that are important in other neurosensory systems. Experience has shown that themes expressed in simple organisms have been improvised upon in more complex organisms.

1.1. *Chemicals and other stimuli perceived*

Bacteria are attracted to some chemicals and repelled by others. Attractants usually are nutrients and repellents frequently are harmful substances, but there are numerous exceptions. Approximately eight common amino acids, most of which are acidic or uncharged polar molecules, are attractants for *S. typhimurium* and *E. coli* (Mesibov and Adler, 1972; Melton et al., 1978; Clarke and Koshland, 1979). These are the majority of amino acids that these bacteria can utilize as a sole nitrogen source (Gutnick et al., 1969). A variety of sugars and sugar derivatives also are attractants (Adler et al., 1973). The best sugar attractants can serve as a sole carbon source for vigorous growth (Adler et al., 1973; Gutnick et al., 1969). However, it is not necessary for sugars or any nutrients to be metabolized to be attractants. For example, *E. coli* mutant W4690 is strongly

*This chapter uses a new common nomenclature for the homologous *che* genes in *S. typhimurium* and *E. coli* (Koshland, 1980). *S. typhimurium che* genes previously designated *P, Q, T, U* and *X* are now designated *A, Y, Z, C* and *B*, respectively. For *E. coli, cheX* has been replaced by *cheR*.

attracted to galactose but it lacks three enzymes that are essential for the metabolism of galactose (Adler, 1969).

The receptor complement deployed by bacteria for chemotaxis to amino acids and sugars is designed to sample selected compounds among the variety of metabolizable substances that are present. In the natural environment this capability evidently ensures adequate guidance to nutrients without the expenditure of cellular resources to synthesize chemotactic systems for all amino acids and sugars.

Malate (Melton et al., 1978), citrate (Kihara and Macnab, 1979) and divalent cation-citrate complexes (Ingolia and Koshland, 1979) are attractants for *S. typhimurium*. Oxygen and the alternative electron acceptors, nitrate, fumarate and trimethylamine oxide, also are attractants (Engelmann, 1881; Beijerinck, 1893; Baracchini and Sherris 1959; Adler, 1966; Taylor et al., 1979). The synthetic sweetners, saccharin, cyclamate and dulcin, are not attractants. Gymnemic acid, which blocks sweet perception in man, does not affect taxis toward D-glucose in *E. coli* (Adler et al., 1973). Cyclic AMP and other nucleotides, which are involved in chemotaxis in more complex organisms such as the slime mold *Dictyostelium discoideum*, are not affectors for *E. coli* (Adler et al., 1973).

Repellents of *E. coli* include the aliphatic amino acids (leucine, isoleucine and valine), short-chain fatty acids, benzoate, indole and salicylate (Tso and Adler, 1974). Although most are harmful to bacteria, repellents are not all toxic, and harmful substances are not all repellents. Phenol is toxic to both *S. typhimurium* and *E. coli* but it is a repellent only for *S. typhimurium* (Lederberg, 1956; Tsang et al., 1973).

Bacteria respond to other environmental stimuli such as light (Clayton, 1964; Harayama and Iino, 1977); extremes of temperature (Maeda et al., 1976; Miller and Koshland, 1977b) and pH (Tso and Adler, 1974) repel them. Some are oriented by the earth's magnetic field (Blakemore, 1975). An unidentified sex pheromone attracts Hfr cells to F^- *S. typhimurium* (Bezdek and Soska, 1972). There are also a variety of artificial perturbations of bacteria that induce a behavioral response. Intense blue light (Macnab and Koshland, 1974; Taylor and Koshland, 1975) and membrane active agents such as anesthetics, uncouplers and ionophores alter behavior in *B. subtilis* (Ordal and Goldman, 1976; Miller and Koshland, 1977a, 1980) and *S. typhimurium* (Taylor et al., 1979). Such perturbants may be rarely, if ever, encountered in natural environments, but they are useful for probing the mechanisms of chemotaxis.

1.2. *Behavioral response to affectors*

The earliest systematic studies of chemotaxis used assays in which a capillary filled with attractant was inserted into a culture of bacteria (see Berg, 1975). As the attractant diffused out of the capillary it created a gradient to which the bacteria responded (Figure 1). Julius Adler (1966) initiated modern studies of chemotaxis by quantitating the capillary assay and using a defined minimal-salts medium. Many additional insights into behavior came from microscopic observations of individual bacteria.

Peritrichous bacteria such as *Escherichia, Salmonella* and *Bacillus* swim in approximately straight lines (runs) interrupted occasionally by tumbles when the bacteria appear

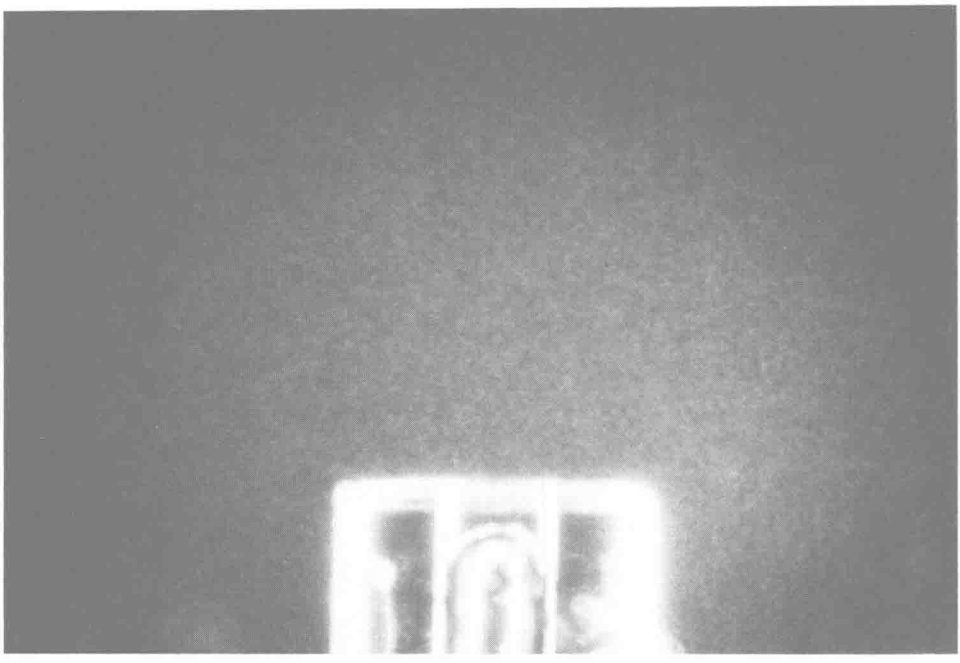

Figure 1. Capillary assay for chemotaxis. *S. typhimurium* in anaerobic medium accumulated at the mouth of a capillary filled with oxygen.

to jiggle in place. After each tumble the cells swim off in a different direction (Berg and Brown, 1972; Macnab and Koshland, 1972; Ordal and Goldman, 1975). In normal swimming, brief tumbles occur at an average frequency of about once per second, yielding a three-dimensional random walk motility pattern (Berg and Brown, 1972).

Bacteria swim by rotating their helical flagella like propellers (Silverman and Simon, 1974a). In *S. typhimurium* there are between four and nine flagella that are distributed randomly over each cell's surface. As a cell begins swimming, hydrodynamic forces collect the flagella into a synchronous bundle that pushes the cell body from behind (Anderson, 1975; Macnab, 1977). Tumbling is initiated by reversing the direction in which the flagella are rotated (Larsen et al., 1974b); this causes the flagellar bundle to unravel (Macnab and Koshland, 1974). Bacteria such as *Pseudomonas citronellolis*, which has a single polar flagellum, back up when flagellar rotation is reversed (Taylor and Koshland, 1974). The brief reversal results in a direction change analogous to tumbling in peritrichous bacteria. The energy for motility is derived from the protonmotive force (an electrochemical potential across the plasma membrane) and not from ATP, the energy currency in muscle (Larsen et al., 1974a; Manson et al., 1977).

E. coli and *S. typhimurium* respond to gradients so shallow that the difference in affector concentration over the length of a bacterium (2 μm) is less than 0.01% (Macnab and Koshland, 1972). This difference is insignficant relative to the statistical fluctuations in the distribution of affector molecules at a concentration of 10^{-6} M. Instead of relying upon comparison of stimuli detected simultaneously, a bacterium compares the present with the immediate past. The swimming of the cell is essential in this transposition from a

gradient in space to a gradient in time, because it results in an ability to compare affector concentrations at sites separated by many times the cell's length. The cell's discrimination problem is thus reduced considerably, and the problem posed by inhomogeneities in the gradient is diminished. If an increase in attractant or decrease in repellent is detected, tumbling is suppressed and the bacterium continues to swim in the favorable direction. If there is an unfavorable change in the concentration of affector the bacterium slightly increases its tumbling frequency to improve its chances of moving in a favorable direction. This mechanism is surprisingly effective; theoretical treatments indicate that bacteria could migrate up a steep gradient of attractant at a velocity up to 50% of their swimming speed (Dahlquist et al., 1976; Macnab, 1980).

The temporal characteristics of the chemotactic mechanism led to the development of a temporal assay for quantifying the response to attractants (Spudich and Koshland, 1975). If attractant is instantaneously added to the medium, all bacteria sense the addition and suppress tumbling, irrespective of the direction in which they are swimming. The bacteria swim smoothly (without tumbling) for seconds or minutes, depending on the strength of the stimulus, and then relax back to a normal tumbling frequency. By using a mutant of *S. typhimurium* that normally has a constantly tumbling motility, Spudich and Koshland (1975) were able to detect the end of a smooth response easily (Figure 2). The time required for half of the bacteria to return to a normal tumbling frequency is a quantitative measure of the response.

Bacteria in a temporal gradient of affector display aspects of behavior not readily

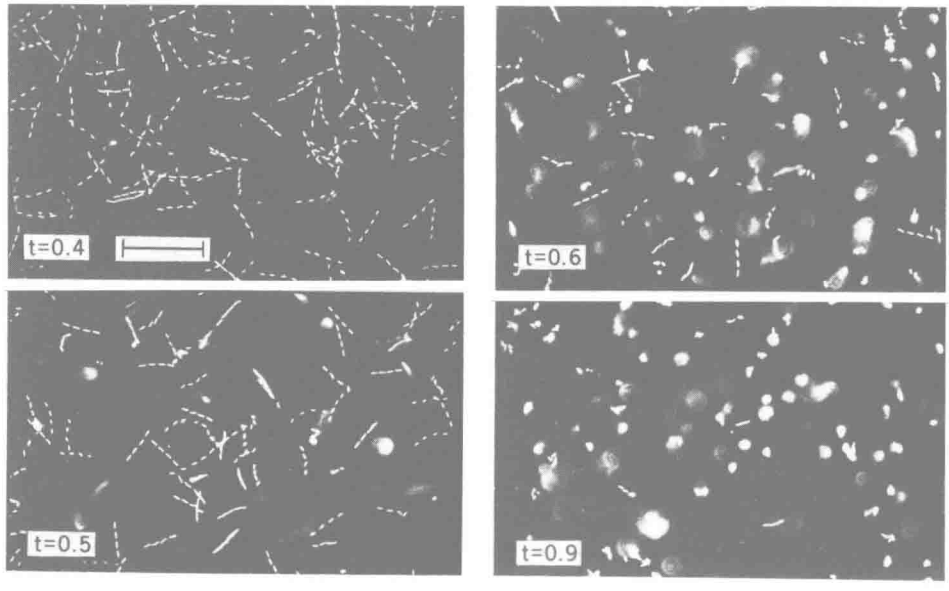

Figure 2. The temporal assay for chemotaxis. Serine (0.02 mM) was added to *S. typhimurium* ST171 and the motility photographed with a stroboscopic lamp and 0.8 s exposure at the indicated times. As the assay progressed, fewer bacteria were swimming smoothly (tracks), and more returned to the constantly tumbling motility (splotches) that is characteristic of ST171 before stimulation. (Spudich and Koshland, 1975).

revealed by other assay methods. The return to normal motility after a step increase in affector concentration represents adaptation to the new affector concentration (Macnab and Koshland, 1972). Simultaneous stimulation with two affectors may elicit a response less than, or greater than, the sum of the responses caused individually by the affectors; these phenomena correspond to desensitization and potentiation, respectively (Rubik and Koshland, 1978).

2. PROPERTIES OF THE CHEMORECEPTORS

Chemoreceptors in bacteria, as in other organisms, are proteins. In *E. coli* there are about 25 receptors for attractants and possibly 10 receptors for repellents (Adler, 1975; Hazelbauer and Parkinson, 1977). *S. typhimurium* probably has a similar number of receptors. Some of these receptors have been isolated and characterized, others have been identified by competition studies measured with a behavioral assay; thus the evidence for each is not equally strong. The best characterized are receptors for D-ribose, D-galactose and maltose (Aksamit and Koshland, 1972; Willis and Furlong, 1974; Anraku, 1968; Kellerman and Szmelcman, 1974; Hazelbauer, 1975a). In each case the purified receptor has a molecular weight between 30 000 and 40 000 and is a monomer with one sugar-binding site (Zukin et al., 1977b; Hazelbauer and Parkinson, 1977). There may be specific structural similarities between these sugar receptors and other soluble binding proteins for ligand transport (Parsons and Hogg, 1973; Quiocho et al., 1977). Definitive structural information from X-ray crystallography will soon be available for direct comparison of receptors for ligand transport and chemotaxis in *E. coli* (Quiocho et al., 1979).

Although some of the earlier competition studies (Mesibov and Adler, 1972; Adler et al., 1973) suggested a broad specificity for many chemoreceptors, it is now clear that receptors are highly specific for ligands. This is evident in Table 1 which shows that

TABLE 1

BINDING OF SUBSTRATES TO THE D-GALACTOSE AND L-SERINE RECEPTORS IN *S. TYPHIMURIUM*

D-Galactose Receptor*		L-Serine Receptor**	
Substrate	Dissociation constant (M)	Substrate	Dissociation constant (M)
D-Galactose	$2 \cdot 10^{-7}$	L-Serine	$5 \cdot 10^{-6}$
D-Glucose	$1 \cdot 10^{-7}$	L-Homoserine	$1.5 \cdot 10^{-2}$
D-Arabinose	$4 \cdot 10^{-5}$	L-Alanine	$4 \cdot 10^{-2}$
Lactose	$6 \cdot 10^{-4}$	α-Aminoisobutyrate	$> 10^{-1}$
D-Fucose	$6 \cdot 10^{-3}$	D-Serine	$> 10^{-2}$
Methyl-β-D-galactoside	No binding	Glycine	$> 10^{-2}$
D-Ribose	No binding	Isoserine	$> 10^{-2}$
D-Allose	No binding		

*From Zukin et al., 1977b.
**From Clarke and Koshland, 1979.

D-glucose and D-galactose bind with high affinity to the galactose receptor with dissociation constants of 10^{-7} M. These hexoses differ only by inversion at the C-4 position. Sugars with slightly greater differences in structure (D-arabinose, lactose and D-fucose) have affinities 1000-fold less (Koshland, 1980). Other sugars do not bind appreciably to the galactose receptor. The serine receptor shows nearly absolute specificity for L-serine. Even L-alanine and L-homoserine bind so weakly to the serine receptor that these interactions are of no physiological significance. Considering the specificity of these and other isolated receptors, it will be surprising if olfactory and gustatory chemoreceptors in man are not similarly specific.

2.1. *Location of the chemoreceptors*

In the envelope of the gram-negative bacterium, the plasma membrane is surrounded by the cell wall or peptidoglycan, a thin, rigid layer that maintains cell shape and prevents lysis in a hypotonic environment. The outer membrane adheres to the peptidoglycan and is the first permeability barrier encountered by molecules entering the cell. Hydrophilic pores in the outer membrane freely admit polar molecules smaller than about 600 daltons (Nikaido and Nakae, 1979). Between the inner membrane and the cell wall is an aqueous layer of uncertain, and perhaps variable, dimensions that is known as the periplasm. The chemoreceptors are located in the periplasm, or in the surface of the plasma membrane that is in contact with the periplasm. Thus the receptors are protected and retained inside the cell wall but are still exposed to environmental stimuli. The relatively high (10^{-3}-10^{-4} M) concentration of receptors must have a significant effect in retaining attractant in the periplasm when the attractant concentration in the external environment is very low (Silhavy et al., 1975; Willis and Furlong, 1974). At attractant concentrations of 10^{-6} M, which bacteria readily detect, there would be, on the average, about one molecule of free attractant in the periplasm of each bacterium, if the receptors were absent. If there were only a few receptors in the periplasm, perception of affectors would obviously be a hit or miss proposition; the response would be drastically affected by local fluctuations. The retention of attractant by the high concentration of receptors buffers against these local fluctuations.

The best characterized receptors, the maltose-, ribose- and galactose-binding proteins described above, are all periplasmic and are readily released from the bacterium by osmotic shock (Heppel, 1969). All known periplasmic chemoreceptors are sugar receptors and have a dual role as chemoreceptors and as receptors for the active transport of the sugars (Aksamit and Koshland, 1974; Hazelbauer, 1975a; Hazelbauer and Adler, 1971). However, periplasmic binding proteins for amino acid transport appear not to function as chemoreceptors (Ordal et al., 1978; Schellenberg, 1978). In fully induced bacteria about 10^4 copies of each periplasmic protein are present (Strange and Koshland, 1976). This is an appropriate number of receptors to balance the cell's need for efficient detection against the space requirements for 40 different receptors (Berg and Purcell, 1977; Koshland, 1980).

The glucose and mannitol chemoreceptors are representative of another class of sugar receptors that are hydrophilic but attached to the surface of the plasma membrane (Adler

and Epstein, 1974). These chemoreceptors also have a dual role and are the sugar-specific component of Enzyme II in the phosphotransferase active-transport system.

The high affinity serine and aspartate chemoreceptors of *S. typhimurium* and *E. coli* are integral membrane proteins and are not involved in transport of these amino acids (Clarke and Koshland, 1979). Terminal oxidases and reductases are also integral proteins which function as chemoreceptors. In an aerobic environment *E. coli* and *S. typhimurium* utilize oxygen as the electron acceptor for the electron transport system. Under anaerobic conditions these bacteria are able to use nitrate, fumarate or trimethylamine oxide as alternate electron acceptors for a modified electron transport system; all four of the electron acceptors are attractants and the receptor for chemotaxis is, in each case, the terminal oxidase or reductase of the appropriate electron transport pathway (Taylor et al., 1979; Laszlo and Taylor, 1980). It appears that the receptor for the light response in *S. typhimurium* and *E. coli* is a flavoprotein component of the electron transport system (Macnab and Koshland, 1974; Taylor and Koshland, 1975, 1976; Koshland et al., 1976; Taylor et al., 1979).

No chemoreceptors for repellents have been isolated or characterized. Indeed, it is not yet clearly established that all repellents act via specific receptors. Uncouplers, respiratory inhibitors and ionophores which decrease the membrane protonmotive force in *B. subtilis* and *S. typhimurium* also induce a tumbling response similar to that elicited by repellents (Ordal and Goldman, 1975, 1976; Miller and Koshland, 1977a, 1980; Taylor et al., 1979). Some of the known repellents, such as short-chain fatty acids, are known to alter the protonmotive force and it is conceivable that certain repellent responses might reflect changes in the protonmotive force rather than binding to a specific receptor. However, when Snyder, Stock and Koshland (personal communication) investigated this possibility in *S. typhimurium* they did not find a correlation between repellent-induced changes in the protonmotive force and the behavioral response. The receptors for the tactic response to pH and temperature have not been identified, although Maeda and Imae (1979) proposed that the high-affinity L-serine receptor is the temperature receptor.

2.2. *The relationship between receptor and response*

The chemotactic response is largely determined by the binding characteristics of the receptor proteins; the response time is proportional to the change in affector bound. Using the known constants for the dissociation of ribose and allose from the purified ribose receptor, Spudich and Koshland (1975) computed the theoretical response assuming it is proportional to the change in receptor occupancy. The predicted response curve drawn on this basis is a good approximation of the chemotactic responses to ribose and allose measured in vivo (Figure 3). Similar observations have been made for the receptors for galactose (Strange and Koshland, 1976; Zukin et al., 1977b) and maltose (Hazelbauer, 1975a). Because the response is independent of the time rate of change, chemotactic stimuli administered sequentially should be additive. Spudich and Koshland (1975) confirmed this by demonstrating that the sum of the responses to two sequential increases in serine concentration equalled the response to a single step increase that achieved the same final concentration.