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CHEMOSENSORY RESPONSES TO AMINO ACIDS AND CERTAIN AMINES BY THE CILIATE *TETRAHYMENA*: A FLAT CAPILLARY ASSAY

M. LEVANDOWSKY, T. CHENG, A. KEHR, J. KIM, L. GARDNER, L. SILVERN, L. TSANG, G. LAI, C. CHUNG, AND E. PRAKASH

Haskins Laboratories of Pace University, 41 Park Row, New York, New York 10038

ABSTRACT

An assay for chemosensory responses by the ciliate *Tetrahymena thermophila* is described that uses glass capillaries with a rectangular cross-section (inner dimensions, $20 \times 2 \times 0.2$ mm). These have optical and geometrical properties permitting convenient observation of cell behavior within the capillaries.

Washed cells, starved for 12 h, accumulated preferentially in capillaries containing L-methionine, L-leucine, L-cysteine, L-histidine, L-histamine, cimetidine, agmatine, and berenil at concentrations of 10^{-3} *M* or less. They avoided capillaries containing tripelennamine, diphenhydramine, and pentamidine at these concentrations. It is argued that the actual response thresholds are much lower than the concentrations put into the capillaries, since cells respond to the gradient of the diffusing chemical.

L-Isoleucine, itself inert, blocked the response to L-leucine but not to L-methionine, L-cysteine, or L-histidine. L-Ethionine and l-homocysteine caused accumulation but not L-cysteine or DL-cystathionine. L-Cystine did not block the response to L-cysteine.

Cells accelerated when entering a capillary where accumulation occurred. On reaching the interior they swam more slowly and uniformly, and with fewer turns or stops than in control capillaries lacking the chemical signal, or when outside of the capillaries. Cells were inhibited from leaving both control and test capillaries, possibly because of accumulated wastes or secretions in the surrounding medium.

INTRODUCTION

Chemical senses have been analyzed extensively in bacteria (Adler, 1975; Koshland, 1980) and the cellular slime molds (Mato and Konijn, 1979), and are probably ubiquitous among motile microorganisms (Levandowsky and Hauser, 1978). Among ciliate protozoa, chemosensory responses have been much studied in *Paramecium* (Van Houten *et al.*, 1981) and *Blepharisma* (Miyake, 1980). The genus *Tetrahymena*, easily grown in chemically defined media and the subject of numerous genetic and biochemical studies, appears particularly promising for the analysis of the mechanisms of these responses. Csaba and Lantos (1973, 1975) demonstrated enhanced phagocytosis by starved *Tetrahymena* cells in the presence of low levels of serotonin and other vertebrate neurohormones. Ueda, Kobatake, and their colleagues (Ueda and Kobatake, 1977; Ataka *et al.*, 1978; Tanabe *et al.*, 1980) described dispersion or accumulation in response to a number of chemicals, particularly those producing a bitter taste in humans, and related these responses to interactions with membrane lipids and membrane potential as measured with fluorescent dyes. Almagor *et al.* (1981) adapted capillary methods which have been used with bacteria (Adler, 1975) and flagellates (Sjoblad *et al.*, 1978; Spero, 1984). They demonstrated responses to methionine and leucine, and related these to the influence of those chemicals on swimming behavior.

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We describe another assay method based on capillaries with a rectangular cross section. These have optical and geometrical properties which permitted detailed observations of behavior within them. We also extend the results of Almager *et al.* to include other amino acids and certain amines.

Materials and Methods

Organisms and culture methods

Tetrahymena thermophila (CU strain 307, mating type BIV) was obtained from Dr. Lea Bleyman and cultured at room temperature in autoclaved HTM medium: (gm/100 ml H_2O) dextrin 0.8; yeast autolysate (Difco) 0.5; liver concentrate (Sigma) 0.06; casein hydrolysate (Hycase, Sheffield) 0.6; morpholinopropane sulfonic acid (MOPS) 0.1; pH adjusted to 7.0 with NaOH.

Starvation pretreatment

Three to six day old cultures (late log phase, approximately 2×10^5 cells/ml) were harvested and washed twice by gentle centrifugation (2 min in a clinical centrifuge followed by resuspension in distilled H_2O), then recentrifuged and resuspended in starvation medium (S) (mg/100 ml H_2O): $CaCl_2$ $2H_2O$ 15.0; Na_2EDTA 60.0; N-tris (hydroxymethyl) methyl-glycine (TRICINE) 18.0; adjusted to pH 7.0 with NaOH. (A somewhat more complex medium, containing also magnesium, sodium, and potassium salts was used in early experiments, but later work showed these were not required for the chemosensory response). After starvation in S for at least 6 h, cells were washed once in distilled H_2O as before and resuspended in S and allowed to stand at least an hour before use in an experiment. During the starvation period the cells underwent metamorphosis to the faster-swimming dispersal form (Nelson and DeBault, 1978). In this assay significant chemosensory responses were seen only with the starved dispersal form, and never with well-fed cells.

The behavior of starved, washed cells appeared to be quite sensitive to the presence of trace contaminants. In preliminary studies it was found that the presence of Na_2EDTA or other organic ligands was desirable for normal swimming behavior. Salt solutions lacking this, made up with samples of glass-distilled water from six different laboratories of the New York–New Haven area, collected and transported in clean glass or plastic containers, resulted in abnormal swimming behavior such as swimming backward or in circles; this problem could be cured by addition of appropriate amounts of Na_2EDTA and $CaCl_2$ H_2O (see Discussion section).

Capillaries, glassware, and plasticware

Borosilicate glass capillaries ("microslides," Vitro Dynamics Inc., P. O. Box 285, Rockaway, NJ 07866) with rectangular cross-section and inner dimensions (mm) 20. $\times$ 2. $\times$ 0.2 were used. Before use, both new and used capillaries were cleaned by soaking overnight in concentrated H_2SO_4. Before and after soaking they were boiled in several changes of distilled H_2O. Capillaries cleaned in this manner yielded best results.

Glassware and plasticware used for these experiments were kept segregated and washed separately from other labware, using Alconox detergent and many rinses in hot water, followed by soaking in distilled H_2O. New or only slightly used plastic dishes tended to inhibit cell motility (see also Wolfe and Colby, 1981); this problem could be eliminated by soaking the dishes overnight in concentrated H_2SO_4, but concentrated HCl, NaOH 5 *N* or 10% Na_2EDTA were not effective (see Discussion).

Assay method

Capillaries were filled with S medium (control capillaries) or with S and a solute to be tested (test capillaries), by touching one end to the fluid, allowing the latter to be rapidly drawn in by capillarity. Properly cleaned capillaries fill very quickly. Capillaries were handled with clean forceps. Filled capillaries were then placed in a plastic dish with 40 mm inner diameter (the top half of a Corning 35-mm tissue culture dish) containing 3 ml of a cell suspension, diluted to approximately 25,000 cells/ml. Two capillaries, test and control, were placed in each dish and gently submerged to lie flat and parallel on the dish bottom, with ends separated by several mm from each other and from the sides of the dish. It should be noted that both ends of the capillary are open in this assay, in contrast to the capillary assays commonly used with bacteria (Adler, 1975).

Experiments were done at 28°C. Below 25°C the chemosensory response was never detected. Results of replicate experiments done in the dark and in various light regimes appeared to be the same.

After 5 min, capillaries were removed with forceps, gently blotted on the outside with tissue, and placed in a dry plastic dish. Behavior of organisms swimming inside the capillaries was observed with the microscope. Then the dish with the two capillaries was floated for 1 min on a hot water bath (65–75°C). The heat-killed cells in each capillary were then counted.

Six replicate assays of each concentration of the test chemical were done in each experiment. Experiments were then repeated several times with different cell preparations. Cells were also checked in a control experiment for response to 10^{-3} *M* L-methionine or L-histamine before being used to test other compounds. Purest available reagent grade commercial chemicals were used.

RESULTS

Statistical aspects.

To establish a statistical base line we did experiments in which no chemical cue was tested, but rather both capillaries in each dish contained only the salts solution S. Table I shows data for ten replicate experiments with the same cell preparation. These data appear inconsistent with a simple statistical model in which each cell "decides" independently of others whether to enter one or the other of the two identical capillaries. Such a model would predict a binomial distribution in which the great differences between the two capillaries in trials 1, 2, 3, 6, and 9 would be very improbable. This great variability may perhaps be due to cell interactions, in which case the assumption of statistical independence of the cells is not valid. Thus, standard parametric tests for significance are probably inappropriate.

Table II shows the effect of introducing 10^{-3} *M* L-methionine into one of the capillaries in each dish. Though there is great variability in both absolute numbers

TABLE I

Numbers of cells entering pairs of identical capillaries in replicate trials

Trial number	1	2	3	4	5	6	7	8	9	10
Capillary 1	228	34	164	78	75	238	120	158	135	212
Capillary 2	92	199	91	82	96	157	76	172	240	200

TABLE II

Response to L-methionine in six replicate trials

Trial number	1	2	3	4	5	6
Test capillary: S medium + 10^{-3} *M*						
Methionine	225	568	637	852	468	347
Control capillary: S medium	211	385	227	132	273	179

and ratios of cells in test and control capillaries, the former always had more cells than the latter in a given dish, and it is clear that they accumulated preferentially in the presence of 10^{-3} *M* methionine. By the nonparametric sign test, the probability of the data in Table II occurring by chance is less than .016. Because of high variability, of unknown origin, we adopted the sign test as a conservative measure of statistical significance, and each experiment was therefore done in six or more replicates. This was repeated with several different cell preparations before we accepted a response as significant.

Amino acid responses

Of 23 common amino acids tested, only four elicited significant responses by the above criterion (Table III). The L forms of methionine, leucine, histidine, and cysteine were active at 10^{-3}, 10^{-4}, and sometimes lower molar levels. Others tested and found inert were the L forms of alanine, arginine, asparagine, aspartic acid, cystine, glutamic acid, glutamine, glycine, isoleucine, lysine, ornithine, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, and valine. In an abstract of preliminary results (Levandowsky *et al.*, 1982) we had reported responses to several of the latter also, but in subsequent experiments these were not significant by the above criterion.

TABLE III

Response to amino acids, amines, and their antagonists

Molar concentration	10^{-3}	10^{-4}	10^{-5}
Amino acids			
L-methionine	+	+	+*
L-histidine	+	+	+*
L-leucine	+	+	+*
L-cysteine	+	0	0
Amines			
L-histamine 2HCl	+	+	+*
Agmatine SO_4	+	+	+*
Histamine and diamine antagonists			
Cimetidine HCl	+	+	0
Berenil	–	+	+
Tripelenamine HCl	–	0	0
Diphenhydramine HCl	–	–	0
Pentamidine isethionate	–	–	0

+ = accumulation (more cells in test capillary).
– = dispersion (fewer cells in test capillary).
* = effect true only in some experiments.
0 = response not significant (see text).

Specificity of amino acid responses

Isoleucine was usually inert (in a few preparations slight accumulation occurred at 10^{-3} *M*). When added to the background, so that 10^{-3} *M* L-isoleucine was present in both control and test capillaries, and in the surrounding fluids, it blocked the response to leucine but not to methionine, cysteine, or histidine.

Several methionine analogs were tested. DL-Ethionine elicited a strong response in the same range as methionine, but not seleno-DL-methionine. DL-Homocysteine, a cysteine analog, was active in the same range as L-cysteine, but L-cystine and DL-cystathionine were inert. L-Cystine added to the background at 10^{-3} *M* did not block the response to either cysteine or methionine.

Histamine and the diamines

L-Histamine HCl (Table III) elicited a somewhat stronger aggregation response than histidine, over the same concentration range. Because of certain biochemical similarities, discussed below, we also tested a group of diamines. Of these, only agmatine proved active, causing aggregation in the same range as histamine and the four amino acids. Diaminopropane, putrescine, spermidine, spermine, and cadaverine were inactive.

Antihistamines and diamine antagonists

We examined several antihistamines, as well as anti-parasite drugs which are antagonists to both histamine and polyamines (see Discussion). Of these, the H-2 antihistamine cimetidine and the trypanocide Berenil (diminazene aceturate) elicited aggregation at 10^{-3} *M*. Dispersion (fewer cells in the test capillary) occurred with the H-1 antihistamines tripelennamine and diphenhydramine, and with the polyamine antagonist pentamidine.

Behavioral basis of the responses

Using an ocular micrometer and a stopwatch we measured swimming speed and turning frequency of individual cells selected arbitrarily by following the first cell to swim past a line on the ocular micrometer grid in a given time. Tables IV and V show differences in swimming behavior in the test capillary and elsewhere.

A basic element in the repertoire of swimming behavior of starved *T. thermophila* cells, and the most important one for getting cells into the capillary during a five minute experimental period, consists simply of straight or nearly straight "runs" punctuated by turns. Unlike *Paramecium, T. thermophila* does not usually stop, but often slows down during the turn.

On entering a test capillary containing an attractant, cells immediately accelerated and swam rapidly without turns for 4–8 mm. On reaching the midregion of the

TABLE IV

Average swimming speed (mm/s, $\pm 2\sigma$) in a typical experiment

1. Midregion of test capillary	.44 ± 0.3 (n = 10)
2. Entering the test capillary	.72 ± 0.4 (n = 10)
3. Midregion of control capillary	.58 ± 0.4 (n = 10)
4. Entering control capillary	.50 ± .03 (n = 10)
5. Outside capillaries	.49 ± .05 (n = 10)

TABLE V

Average time between turns or stops (s, ± 2σ) in a typical experiment

Middle of test capillary	8.2 ± 1.2 (n = 20)
Middle of control capillary	4.8 ± 1.1 (n = 20)
Outside of capillaries	4.2 ± 1.0 (n = 20)

capillary they swam more slowly and uniformly than elsewhere, with fewer turns than in the control capillary or outside of the capillaries (Tables IV, V). On attempting to leave, cells in both the test and control capillaries tended to stop and turn more frequently in a zone near the end of the capillary, and in some cell preparations appeared virtually unable to leave once they had entered either the test or the control capillary.

When cells inside the capillary swam into the wall they usually just "reflected" like billiard balls, at an equal angle, without slowing down. These were not counted as turns in the observations.

In summary: outside the test capillary, where there was no added chemical cue, the cells moved in a series of small, relatively fast "runs." There was a large variability in individual speed and turning frequency, and the overall impression was of a jerky, erratic searching behavior. At the entrance to the test capillary, where there is a gradient of diffusing chemical signals, they suddenly and dramatically accelerated and swam up the gradient to the midregion of the capillary. This appears to be the main factor causing greater accumulation in the test capillary than in the control during the five minute duration of the experiment. In the midregion, where the chemical concentration was presumably constant, they slowed down and turned less frequently than outside, and the overall impression was of a very uniform, even motion, with few turns or stops. On attempting to swim out of either test or control capillary, their motion became jerky and irregular, with many stops and turns. In some cell preparations they seemed to be unable to leave. Since this occurred also in the control capillary, this was probably the effect of wastes or cell secretions in the fluid outside, which had cells in it for at least an hour before the experiment began.

DISCUSSION

Responses to methionine and leucine were also studied by Almagor *et al.* (1981), using the WH-52 strain of *T. thermophila* and a somewhat different capillary assay method, as well as microscopic observation to record motility in various attractant concentrations. The latter method detected responses at much lower levels than the capillary method. As they note, organisms responding to a gradient of a diffusing chemical would initially encounter a much lower concentration than that originally placed in the capillary. Thus capillary assays, though convenient and meaningful, are relatively insensitive and overestimate the response threshold by at least an order of magnitude. Similar conclusions have been drawn regarding capillary assays of bacterial chemosensory assays (Hazelbauer and Adler, 1971). Our capillary assays and those of Almagor *et al.* appear to be similar in sensitivity.

Ordinary capillaries with a circular cross section present difficulties however, when they are submerged in the cell suspension it is difficult to determine whether cells swimming at a given focal depth are inside the capillaries. Furthermore, when they are removed from the medium, fluid-filled capillaries act as lenses, and cells swimming

inside them are extremely difficult to watch with the microscope. These problems do not arise with the rectangular capillaries used in this assay.

The abnormal behavior in the absence of organic ligands such as Na_2EDTA, noted in the materials and methods section, may be due to heavy metals leaching from glass or plastic containers (Bernhard, 1977). Inhibition of cell motility (sticking to the bottom) in new, untreated plastic dishes probably stems from surface charge-related hydrophobic interactions between cells and the plastic surface (Kitamura, 1982; D. Rittshoff, pers. comm.).

It would be interesting to know whether the WH-52 strain used by Almagor *et al.* also responds to cysteine, histidine, and the amines listed in Table III. There is a great deal of biochemical variation among morphologically indistinguishable members of this group (Nanney, 1980), and one would like to know whether sensory responses are a conservative or a variable feature. As noted above, we had indications in early experiments of responses to other amino acids, notably tyrosine, phenylalanine, arginine, and serine, but these did not appear consistently in subsequent experiments. Such inconsistency could have various explanations, one of which is a latent sensitivity to these compounds that is not always expressed. This deserves further study.

Amines and amino acids may serve as useful ecological signals for food. Thus, Fuzessery *et al.* (1978) suggested a correlation between the spiny lobster's chemosensitivity to very low levels of taurine and the latter's particular value as a potential food indicator in the marine environment. In the case of *Tetrahymena,* a freshwater phagotroph, there are numerous laboratory studies of feeding behavior (Nilsson, 1979), but virtually no field studies of its natural history—its natural diet is, strictly speaking, unknown. In the lab it is usually grown on living or dead bacteria or yeast, or in defined or undefined liquid media containing precipitated particles. Histamine is a common waste product of bacterial decomposition, particularly of plant tissues (Guggenheim, 1951), and agmatine is an amine restricted to certain plants and bacteria. Beyond these hints, we have no clues yet regarding the adaptive value of responses to this particular set of amino acids and amines.

From a comparative, phylogenetic point of view the histamine response is of particular interest. Csaba and Lantos (1975) found that low levels of histamine and two histamine antagonists also stimulated phagotrophy in their GL strain. The positive (accumulation) response to the drug cimetidine, used to block the H-2 histamine receptor in treating ulcers, probably reflects its structural similarity to histamine (the presence of an imidazole group).

Tripelennamine and diphenhydramine on the other hand, drugs used to block histamine H-1 receptors in treating allergy and cold symptoms, gave rise to a negative (dispersion) response. Though they are antihistamines, these do not resemble histamine structurally and lack the imidazole group, but do have pharmacological and chemical affinities to local anesthetics of the cocaine family. The mode of action of the latter is thought to involve, among other possibilities, alteration of the physical properties of the cell membrane. We think it likely that some chemosensory responses of *Tetrahymena* will prove to be due to binding of the signal molecule to specific membrane-bound or intracellular receptor molecules, probably proteins, but some responses may be simply due to non-specific changes in physicochemical properties of the membrane. This was indicated by studies in which negative (repulsion) responses to various hydrophobic chemicals and to bitter substances were correlated with changes in membrane fluidity (Ataka *et al.,* 1978; Tanabe *et al.,* 1980).

Berenil (diminazene aceturate) and pentamidine are known mainly as anti-trypanosomal drugs. It appears that these and a number of other anti-trypanosomal and anti-malarial drugs are inhibitors of both histamine N-methyl transferase and also

diamine oxidase (Duch *et al.,* 1984). This link between histamine and the diamines is not yet understood, but appears promising as a pharmacological principle. Further analysis of the *Tetrahymena* response to such compounds would be desirable and might yield useful information on clinically important questions.

Chemosensory responses to amino acids are phylogenetically widespread, being found in bacteria (Adler, 1975; Koshland, 1980), algae (Hauser *et al.,* 1975; Sjoblad *et al.,* 1978), many invertebrates (*e.g.,* Ache, 1972) and vertebrates (*e.g.,* Caprio, 1978). In catfish, L-cysteine was the most effective olfactory stimulus tested (Caprio, 1978). Amino acids also act as excitatory transmitters in the brain and may be involved in some forms of epilepsy (Croucher *et al.,* 1982). In particular, L-cysteine may function as a transmitter in the brain (Watkins and Evans, 1981).

We have also found responses by *T. thermophila* to several other chemical groups, including neurotransmitters and hormones. Preliminary accounts of this work and of studies of the ionic requirements of the chemosensory response have appeared (abstracts: Levandowsky *et al.,* 1982; Gardner and Levandowsky, 1983; Tsang and Levandowsky, 1983).

The possibility of homologies between *Tetrahymena* responses to amino acids and amines, and those in higher organisms is intriguing. In addition to its evolutionary interest, this would suggest the practical possibility of using this organism as a model system to investigate chemosensory mechanisms, profiting from the ease with which it can be grown in mass culture, and the possibilities of genetic analysis.

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