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Richard C. Lewis

University of Arkansas at Little Rock

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Role of Olfaction in "Taste-Aversion" to PTC in Mice

RICHARD C. LEWIS
Department of Health Sciences
University of Arkansas at Little Rock
Little Rock, Arkansas 72204

ABSTRACT

The objective of most taste research involving choice is to eliminate from the experiment all cues to the animal except those that are strictly gustatory. Among those potentially confounding cues, one of the most obvious is olfaction, although it often remains uncontrolled in taste experiments.

The present report clearly demonstrates the role played by olfaction in a discrimination experiment with C₅₇Bl/6 and CFW mice as regards their response to phenylthiocarbamide (PTC) when paired with water. The results have implications for conclusions drawn by other investigators who have attributed differences in PTC sensitivity in mice to taste alone.

INTRODUCTION

The mouse strains CFW and C57Bl/6 differ in their acceptance of the bitter sugar derivative sucrose octaacetate (SOA). CFW mice avoid dilute solutions of SOA when offered in a choice with water, while C57Bl/6 mice accept all concentrations of this compound (Warren & Lewis, 1970). In evaluating the basis of this differential response to SOA, these strains were also tested with the bitter compounds quinine hydrochloride (QHC1), propylthiouracil (PROP), and phenylthiocarbamide (PTC). The responses of these strains to QHC1, PROP, and PTC were unlike the dramatic differences observed with SOA, although a significant difference in acceptability did occur with PTC (Lewis, 1971).

Although PTC has been widely used in studies of taste in man (Blakeslee, 1932; Barnicot et al., 1951; Allison and Blumberg, 1959) as well as mice (Hoshishima et al., 1962; Klein and DeFries, 1970), its odor makes it of questionable value in experiments designed to elicit taste discrimination. Skude (1963) found that two-thirds of the human subjects he tested for PTC thresholds reported elevated thresholds when their nostrils were plugged with cotton. Fisher (1967) suggests that PTC is such an odorous substance that determinations of taste thresholds with this compound may be artifactual in that olfaction and not taste is being measured. These considerations, plus the suggestions of previous investigators that the role of olfaction in taste tests should be controlled (Parr, 1934; Gessel and Fisher, 1968), led this investigator to examine the differential response to PTC with mice that had their olfactory bulbs removed (bulbectomized) and thereby rendered anosmic.

METHODS AND MATERIALS

Twenty CFW mice (10 bulbectomized, 5 sham operated, 5 control) and eighteen C57Bl/6 mice (8 bulbectomized, 5 sham operated, 5 control) were tested for their acceptance of PTC by a modification of Richter's two-bottle choice method (Richter and Clisby, 1941). In lieu of bottles, the fluid containers were calibrated 25 ml burettes with tips modified into narrow drinking spouts. The potential confounding effects of mice adopting side or burette preferences were controlled by rotating the position and contents of the burettes so that over any 96 hour period the PTC was presented to the mice in each of the four possible combinations of side and burette for 24 hours at a time. The concentration of the PTC was elevated by approximately one-third of a molar log unit every two days. Percent consumption of PTC was determined over a 48 hour period to control for side preferences. Possible development of burette preferences were controlled by requiring that significant between-strain differences be obtained on two successive 48 hour measures. All between-strain comparisons were made by the nonparametric Mann-Whitney 2-tailed U test.

Bulbectomies were performed by suction. The skin of the skull was cut and connective tissue was scraped from the surface of the frontal and nasal bones with a scalpel. The skull was opened by use of a Foredom drill, using a .05 inch bit. Three holes were made just anterior to the nasofrontal suture in a triangular fashion so that they

met along their arcs to form a roughly circular opening of three to four millimeters in diameter at the posterior portion of the nasal bone. In addition to suctioning as much of the olfactory bulbs as possible, a microscalpel was used to scrape the posterior surface of the cribriform plate of the ethmoid bone to ensure that all olfactory connections were severed. Before the skin of the skull was stitched together, Gel-Foam was placed in the cavity to aid in the clotting process.

Sham-operated mice were anesthetized, the skin on the skull was cut, the bone was scraped, and three holes were drilled through the skull in the same position as in the experimental mice. No tissue was removed from the brains of these animals with the possible exception of small bits of the olfactory bulbs being damaged when the drill bit pierced the nasal bone.

RESULTS

All sham-operated mice of both strains avoided PTC at lower concentrations than did any of the bulbectomized mice. Since the five sham-operates in each strain also show no differences when compared with their five respective control mice, the shams have been incorporated into the control or "intact" group.

Intact CFW mice differ significantly from intact C57Bl/6 mice in their acceptance of PTC (Table 1). A comparison of intact and anosmic mice of each strain also shows that intact mice avoid PTC at lower concentrations than do the respective bulbectomized mice; however, when comparison is made between the bulbectomized mice of each strain all differences disappear, even though these mice continue to drink some of the PTC solution at concentrations near saturation.

To better understand the significance of this lack of difference between bulbectomized mice, it is instructive to compare the absolute responses to PTC by these two strains. For this purpose rejection of PTC is defined as that concentration at which a mouse consumes less than 30% of his total fluid intake in the form of PTC solution. The "rejection concentrations" for each of the mice in the group can then be averaged for comparison with other groups. A comparison of rejection concentrations shows that while bulbectomized CFW mice consume PTC solutions 25 times as concentrated as those consumed by their intact counterparts, bulbectomized C57Bl/6 mice accept PTC solutions only six times as concentrated as those accepted by C57Bl/6 control mice.

DISCUSSION

The absence of any difference in acceptance of PTC between bulbectomized CFW and C57Bl/6 mice would suggest that their gustatory responses to PTC are similar. The basis of the significant between-strain difference in intact mice can then be attributed to a differential olfactory response. In addition to the between-strain differences found for intact mice, this conclusion is supported by the fact that rejection concentrations in each strain are significantly higher in bulbectomized mice when compared with their respective control group. Further, the finding that CFW control mice are 25 times as

Richard C. Lewis

sensitive to PTC as are anosmic CFW mice, while control C57Bl/6 mice are only six times as sensitive as their anosmic counterparts, leads to the conclusion that intact C57Bl/6 mice are relatively unresponsive to the odor of PTC.

This conclusion takes on more meaning in the light of two studies (Hoshishima et al., 1962; Klein and DeFries, 1970) in which it was concluded that C57Bl/6 mice were less sensitive to the taste of PTC than were other strains of mice. All mice in these two studies, however, possessed an intact sense of smell. The present study corroborates the data but does not support the conclusion of the two papers cited above. It is the olfactory and not the gustatory sense of intact C57Bl/6 mice that accounts for its relatively low level of aversion to PTC in solution.

Certifying that bulbectomized mice are fully anosmic is an extremely difficult task, but support for the effectiveness of the bulbectomies in these experiments was derived from an unexpected source, that of daily total fluid consumption. In bulbectomized mice a sudden and significant drop in fluid intake occurred at the PTC concentrations of .05% and 0.1%. At these concentrations, bulbectomized mice of each strain consumed only half of their normal fluid volume over this four day period, only to resume a normal value of fluid intake at the next higher concentration.

These data suggest the following explanation. Bulbectomized mice accepted considerably more PTC over the duration of the experiment than did control mice. Control mice first reduced their consumption of PTC below 50% of their total fluid intake at a concentration of .0005%, while bulbectomized mice were still consuming equal amounts of water and PTC solution at .02% PTC. It is suggested that this PTC load taken on by bulbectomized mice was sufficient to induce a low-level poisoning or at least a general malaise which served as the stimulus to produce a conditioned aversion to the fluid being offered in the burettes (Garcia and Ervin, 1968). Since PTC solutions could not be discriminated from water at these concentrations on the basis of taste alone, both solutions were avoided. This avoidance of both burettes and reduction in total fluid intake would not occur if the animals were able to smell the PTC. At 0.2% PTC all bulbectomized mice show a clear rejection of PTC and also a return to a normal volume of fluid consumption.

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Table 1. Percent of total fluid intake comprised of PTC solution when offered in a choice with water for each of four groups of mice. Comparisons below are by Mann-Whitney two-tailed U tests and are coded by using letters (A through D) associated with the mouse groups in the upper half of the table.

Concentration of PTC (%)		.0002	.0005	.001	.002	.005	.01	.02	.05	.1	.2	
Mean % Acceptance	A. Intact CFW	10	56.3	46.8	44.0	39.5	19.3	7.0	2.6	2.4	-	-
	B. Intact C ₅₇ Bl/6	10	52.1	47.2	46.6	40.2	33.5	20.5	10.6	4.6	-	-
	C. Anosmic CFW	10	51.0	46.6	47.6	47.5	51.0	49.9	53.7	45.9	28.7	4.9
	D. Anosmic C ₅₇ Bl/6	8	48.8	47.8	55.0	51.1	49.5	50.6	51.8	37.9	21.0	3.3
COMPARISONS												
Value of U and level of significance	A vs B	> 30	> 30	> 30	> 30	19	9	2	-	-	-	
		--	--	--	--	.05	.01	.01	-	-	-	
	A vs C	> 30	> 30	> 30	> 30	11	3	0	0	-	-	
		--	--	--	--	.01	.01	.01	.01	-	-	
	B vs D	> 20	> 20	15	17	2	3	0	0	-	-	
		--	--	.05	.05	.01	.01	.01	.01	-	-	
	C vs D	> 30	> 30	19	27	> 30	> 30	> 30	21	27	24	
		--	--	.05	--	--	--	--	--	--	--	