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Increased Sensitivity of Taste and Smell in Cystic Fibrosis

Abstract. Cystic fibrosis is consistently accompanied by the ability to taste and smell salt, sweet, sour, and bitter substances in solution at concentrations much more dilute than those at which the substances are detectable by normal persons. These abnormal thresholds are not affected by the administration of carbohydrate-active steroids.

It has been previously reported that (i) patients with adrenal insufficiency exhibit an increased taste sensitivity for all four modalities of taste (salt, sweet, sour, and bitter) (*1–3*); (ii) thresholds for the corresponding smells are lower in these patients (*4*); and (iii) treatment with carbohydrate-active steroids results in the return of taste and smell thresholds to normal levels, whereas treatment with deoxycorticosterone acetate has no effect on either type of threshold (*1–4*). Because abnormalities in sweat electrolytes in cystic fibrosis are similar to those in untreated adrenal insufficiency, we decided to study taste and smell thresholds in cystic fibrosis and to explore the effect of adrenal cortical hormones on the senses of taste and smell in this syndrome.

Eleven patients, 6 to 20 years old, with cystic fibrosis were studied. All met the usual diagnostic criteria for cystic fibrosis, exhibiting chronic lung disease with obstructive emphysema, steatorrhea, and elevated sweat-electrolyte concentrations. All the patients remained in an air-conditioned ward and ate a normal diet.

Taste was evaluated by measuring the detection threshold in a manner which has been described elsewhere (*1*). Smell was evaluated by a similar technique. The test substance in solution, varying from 0.00006 to 300 mmole/lit., or glass-distilled water was placed approximately 1 to 2 cm below the subject's external nares. The subject was asked to sniff each fluid vigorously, once, for 2 to 4 seconds. Comparison of the fluids—two samples of water and one of test solution—was made after each group of three fluids had been smelled. Threshold was defined as the lowest concentration of test substance which evoked two successive positive responses followed by two consecutive negative responses at the next lower concentration.

The detection thresholds for taste and smell for each patient with cystic fibrosis are presented in Table 1. The median detection thresholds and the ranges of response are indicated for the patients and for normal volunteers 6 to 65 years old. As in the normal volunteers, the median taste-detection thresholds for NaCl, KCl, $NaHCO_3$, and sucrose are all similar (0.3 to 0.1 mmole/lit.) in the group of patients, whereas the values for HCl and urea are quite different (0.006 and 0.8 mmole/lit., respectively). Ten of the 11 patients with cystic fibrosis showed a markedly increased ability to detect all substances. They could detect substances at concentrations 40 to 13,000 times more dilute than the concentrations at which these could be detected by the normal volunteers. In one patient (D.S., age 6) the responses for both taste and smell fell within the normal range. In ten of the 11 patients the range of taste responses did not overlap the range of responses in the normal volunteers, and similarly, in nine of the 11 there was no overlap in the smell responses. Smell thresholds in these patients generally were ten times lower than corresponding taste thresholds.

Since the sensitivity for taste and smell in patients with adrenal insufficiency returns to normal after treatment with carbohydrate-active steroids, four of the patients in our study (C.T., J.B., P.R., and M.D.) were given prednisolone alone (20 mg/day) for 5 days. The values for detection thresholds for taste and smell after treatment are essentially the same as those for

Table 1. Detection thresholds for taste and smell in 11 patients with cystic fibrosis, compared with thresholds in normal volunteers. All patients were Caucasian, and all but D.S. were males. ∞, Inability to smell the substance at any concentration tested.

Patient	Age (yr)	Detection thresholds for taste (mmole/lit.)						Detection thresholds for smell (mmole/lit.)					
		NaCl	KCl	$NaHCO_3$	Sucrose	HCl	Urea	NaCl	KCl	$NaHCO_3$	Sucrose	HCl	Urea
L.R.	13	0.001			0.1	0.00006	0.008	0.001			0.001	0.00006	0.008
B.B.	20	.3	0.5	0.3	.3	.03	.3	∞	300	300	∞	∞	∞
D.B.	13	.3			.1	.03	.8	0.01			0.01	0.01	0.08
C.T.	8	.01			.01	.0006	.8	.001			.1	.01	30
J.B.	9	.1	.01	.01	.01	.0006	.08	.1			.001	.00006	0.008
D.S.	6	60			30	3	150	∞			∞	∞	∞
J.L.	9	0.1			0.1	0.006	0.8	0.6			0.5	0.006	12
P.R.	8	.01			.001	.0006	.008	.01			.001	.00006	0.008
M.D.	8	.01			.1	.06	.08	.001			.01	.00006	.008
R.R.	9	.01			.001	.006	.008	.001			.001	.00006	.008
M.H.	9	.1	.3	.1	.1	.01	.8	.3	0.3	0.1	.1	.006	.8
							*Medians**						
Patients		.1	.3	.1	.1	.006	.8	.01			.01	.006	.08
Normal volunteers:													
$N = 28$		12 (6–60)	21 (6–60)	12 (6–60)	12 (6–60)	3 (0–6)	120 (90–150)						
$N = 8$								∞ (∞–150)	∞ (∞–150)	∞ (∞–150)	∞ (∞–150)	∞ (∞–150)	∞ (∞–150)

* Ranges in parentheses.

thresholds prior to treatment. One of these patients (J.B.) was also given deoxycorticosterone alone (10 mg/day), for 5 days. The detection thresholds after treatment with this drug were essentially the same as those prior to treatment, despite changes in serum sodium and potassium concentrations and a gain in body weight.

Thus we found that thresholds for the basic modalities of taste and for corresponding smells were lowered in cystic fibrosis. Sensitivity of taste in the patients was roughly 100 times (range 40 to 13,000 times) that of normal subjects; sensitivity of smell in the patients was roughly 10,000 times (range 10^3 to 10^8 times) that of normal subjects.

Whereas, after treatment with carbohydrate-active steroids, taste and smell thresholds for all test substances returned to normal in patients with adrenal insufficiency, no significant change was noted among patients with cystic fibrosis. Treatment with deoxycorticosterone alone did not alter the abnormal threshold in patients with adrenal insufficiency or in the one patient with cystic fibrosis who received it. These results call attention to another set of findings common to these two groups. Concentrations of sodium and chloride in the sweat of patients with untreated adrenal insufficiency and in patients with cystic fibrosis are abnormally high (*5–7*). After treatment with deoxycorticosterone or adrenal cortical extract the sweat-electrolyte concentration in patients with Addison's disease returns to normal levels (*5*). It has been reported that after restriction of sodium intake and treatment with deoxycorticosterone or 9α-fluorohydrocortisone the sweat-chloride concentration in patients with "fully manifest" cystic fibrosis does not return to normal levels (*7*). Changes in serum sodium and potassium concentrations do not alter taste or smell thresholds in patients with either adrenal insufficiency or cystic fibrosis.

No satisfactory explanation can be found for the normal taste and smell threshold exhibited by patient D.S. In view of the subjective nature of the test and the youth of the patient it is possible that there was some misunderstanding of the test instructions, which resulted in inaccuracy of threshold measurements. This patient was also the only female in the group. It is possible that not all patients with cystic fibrosis respond in like manner. That patient B.B. exhibited a normal smell threshold while exhibiting an abnormal taste threshold may be related to an acute exacerbation of this patient's severe chronic pansinusitis at the time of testing.

The mechanisms by which these phenomena occur are not clear. The underlying defect may reside in (i) the specialized end organ—that is, the taste bud or olfactory hair cell; in (ii) the cranial nerves that conduct the impulse —the 7th, 9th, or 1st; or in (iii) the brain itself. Preliminary data suggest no consistent gross abnormalities in the electroencephalographic responses or in the ulnar nerve conduction velocities of patients with cystic fibrosis (*8*), whereas these responses are abnormal in animals and patients with adrenal insufficiency (*8, 9*). Thus, the taste bud or olfactory hair cell—the end organs themselves—may be the site of the sensory abnormality in cystic fibrosis, whereas a general alteration in nervous system activity may be the basis of the sensory abnormality in adrenal insufficiency (*4*).

Taste and smell thresholds for NaCl and other modalities in a variety of acute and chronic debilitating diseases were comparable to those observed in healthy subjects (*1, 3, 8*). Cystic fibrosis is the second disease state (adrenal insufficiency was the first) in which a consistently abnormal threshold for taste and smell has been found.

These phenomena may lead to a better understanding of cystic fibrosis and of the physiology of taste and smell.

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Penicillinase Production in Some Bacilli

Abstract. Penicillinase production in strains of bacillus in which such production is constitutive, as well as in strains in which it is inducible, was found to be a function of the type of penicillin to which the organism was exposed. A repressive effect in two constitutive strains was noted. An increase in the level of penicillinase produced by the constitutive strains was noted for some of the penicillins.

It has long been known that a specific hydrolytic enzyme, penicillinase, is elaborated by certain micoorganisms in response to exposure to penicillin (*1*). While the same organisms produce penicillinase without having been exposed to this antibiotic, the basal level is much lower than the maximum observed when an organism is exposed to any of a large number of penicillins. In *Bacillus cereus* this has been observed to be a 300-fold (*2*) and 800-fold (*3*) increase.

Penicillinase is a clear-cut example of an inducible enzyme—that is, one that is produced in increased quantities in response to specific chemical stimuli. Penicillinase production is enhanced by several penicillins (*3, 4*). Mutants of *B. cereus* which produce penicillinase at a very high level without the stimulus of an added penicillin have been isolated (*5*). The level actually observed is higher than the maximum induced level so far observed in the closely related strains in which production of the enzyme is not constitutive. We report here the results of studies made to determine the effects of certain penicillins on penicillinase production in both inducible and constitutive strains of bacilli.

The penicillins used were benzyl penicillin (G), 6-aminopenicillanic acid (APA), 6-*N*-α-(phenoxy)pentanoylaminopenicillanic acid (PPA), 6-*N*-α-(*o*-benzy-*p*-chlorophenoxy) propionylaminopenicillanic acid (BCP, 6-*N*-α-(*p*-benzyloxyphenoxy)-propionylaminopenicillanic acid (BPP) (*6*), and cephalosporin C (CC). The microorganisms used were *B. cereus* [strains 5/B (NCTC 9946), 569/H (NCTC 9945), and 569 (NRRL 569)] and *B. subtilis* (strain ATCC 6633). Strains 5/B and 569/H are constitutive producers of penicillinase; the other two are strains in which production can be induced.

Suitable quantities of a casein hydrolyzate medium (CH/C) (*7*) were inoculated, usually by wire-loop transfer of the appropriate organism from an