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Insulin Iontophoresis in Cystic Fibrosis (38858)

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(Introduced by Q. T. Smith)

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Search for the abnormal gene product(s) responsible for the clinical findings in cystic fibrosis (CF) has occurred on various fronts. A humoral factor (or factors) found in CF and obligate heterozygotes that affects ciliary activity in several organisms as well as ion, sugar, and amino acid transport has been reported (1). Despite these recent observations, increased sweat chloride remains the most constant and clearly defined abnormality in CF (2). A CF "effect" has been obtained by microperfusion of CF sweat into isolated sweat glands of controls but could not be obtained by subcutaneous injection (3). It is probable, therefore, that the CF "factor" acts luminally on exocrine gland ducts (3, 4). Since an insulin involvement in CF has been noted (5–8), and because the CF "factor" in sweat and saliva appears to be due to some action on the luminal surface of duct cells, we decided to examine the effect of insulin iontophoresis on the sweat chloride concentration of CF subjects, controls, and obligate heterozygotes.

Materials and Methods. A modification of the iontophoresis technique of Gibson and Cooke (9) as described in detail by Hansen *et al.* (10) was used. After pilocarpine iontophoresis for 5 min on both arms of a subject, the areas were swabbed with distilled, deionized water and dried with gauze. Insulin (Injection, USP Lilly Iletin 80 U/cc) was applied to the area previously iontophoresed on one arm and the vehicle without insulin [1.6% glycerin (w/v) and 0.2% phenol (w/v) per cc of distilled water] to the other. After 10 min of iontophoresis the test areas were swabbed thoroughly with distilled, deionized water and dried. Sweat was then collected from the test areas for 30 min and chloride in the sweat determined by titration with a Cotlove chloridometer (10).

Data were recorded in terms of meq of chloride/liter of sweat. We tested the null hypothesis that meq/liter (treatment) = meq/liter (vehicle) with a matched pair (both arms of the same person) Student's t test.

Results and Discussion. The results are summarized in Table I. Sweat chloride values after iontophoresis of pilocarpine and the insulin vehicle were within the expected values for the three groups after pilocarpine iontophoresis alone. In the control sample no decrease in sweat chloride concentration was found after insulin intophoresis in comparison with the vehicle alone. However, a decrease in sweat chloride concentration was noted in both the CF ($P < 0.005$) and heterozygote ($P < 0.01$) samples.

Several observations in the CF literature appear to coincide with an involvement of insulin. For example: (a) abnormal glucose tolerance, defective insulin release, and an increased risk for diabetes mellitus occur in CF (5–7); (b) decreased urinary excretion of insulin occurs in CF and carriers (8); (c) a major effect of insulin is stimulation of the pentose phosphate pathway (PPP) and abnormalities of this pathway in CF erythrocytes have been reported (11); (d) a primary action of insulin is on sugar, amino acid, and ion transport; serum, saliva and sweat from CF patients and carriers have been shown to affect the transport of these substances across cells (4, 12); (e) maintenance of membrane potential is thought to be affected by insulin (13); abnormal membrane potential has been reported in CF sweat gland ducts (14); and (f) insulin is found in parotid saliva (15) and whole saliva (16); a salivary "factor" has been demonstrated in several CF bioassay systems (1, 4).

Too little is known about insulin action, cystic fibrosis, or sweat gland physiology to favor one or another of these relationships at this time. However, it is known that glutathione, glutathione reductase (GR), and NADP(H) are important in the inactivation of insulin (17). Data from this laboratory

TABLE I. EFFECT OF IONTOPHORESIS OF INSULIN ON SWEAT CHLORIDE IN CONTROLS, CYSTIC FIBROSIS PATIENTS, AND PARENTAL HETEROZYGOTES.

		meq Cl^-/liter in Sweat		
	N	Vehicle Mean ± SE	Insulin Mean ± SE	P^a
CF	12	79.70 ± 3.59	68.07 ± 3.29	<0.005
Control	18	14.81 ± 2.39	14.47 ± 2.66	>0.25
Heterozygotes	11	16.03 ± 2.34	11.52 ± 1.28	<0.01

[a] P values are based on each individual's sweat chloride response to insulin vs the insulin vehicle using a matched-pair Student's t test.

concerning red blood cell (rbc) PPP (11), rbc glutathione and GR (18), white blood cell GR (19), and serum GR (16) differences in CF, carriers, and controls and now differential sweat gland response to insulin suggest that this area of intermediary metabolism may be a fruitful one for CF research. Of particular interest is the conclusion of Kaiser (14) that reduced transmembrane hydrogen ion secretion is a major factor in sweat glands leading to the abnormalities in CF. Previously, we had suggested (11) that the transposition of hydrogen ions between NADP and NADPH during oxidoreductions involving the PPP in duct cells may be a link between intermediate metabolic defects and observed ion abnormalities in CF. In any case, the reported effect of iontophoresed insulin on sweat chloride transport may be important from the point of view of sweat gland function as well as CF. To our knowledge, prior to this report, no statement concerning a role of insulin on sweating has been reported.

Summary. Insulin and its vehicle without insulin were administered separately by iontophoresis to patients with cystic fibrosis (CF), obligate heterozygotes, and healthy controls. The resultant sweat chloride concentration after treatment with both preparations was compared in each individual. No difference after the two treatments was found in the control sample. A decrease in sweat chloride concentration after insulin iontophoresis in comparison with the vehicle was observed in both the CF ($P < 0.005$) and heterozygote ($P < 0.01$) samples. These observations suggest an involvement of insulin in CF and a possible role of insulin in sweat gland function.

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