Water secretion and embryological layers in cystic fibrosis

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ABSTRACT – Cystic fibrosis primarily affects tissues containing secretory epithelia, but not all of them become diseased. The distribution of clinical disease corresponds closely to the effect on net anion-linked water secretion, which is reduced across epithelia of endodermal and mesodermal origin but not those of ectodermal origin. Although the gene is expressed in all secretory epithelia, its effects on water secretion are bypassed in those of ectodermal origin.

Cystic fibrosis is associated with abnormal ion transport across secretory epithelia [1–11]. However, its pathogenesis is still unclear. Some structures have relatively dehydrated luminal contents and secretions, while others do not; the former develop clinical disease while the latter are spared [12]. These two groups have been separated into mucous and serous secreting tissues, but this does not explain why, for example, the pancreas is affected and the parotid is not, although both secrete mucus-containing fluids with similar protein concentrations [2,7]. However, in cystic fibrosis the parotid secretes water normally but the pancreas does not.

In most epithelia, water secretion is linked to anion secretion. Cholinergic, cyclic adenosine monophosphate (cAMP) mediated and, in some tissues, cyclic guanosine monophosphate (cGMP) mediated agents cause epithelial cells to secrete chloride and bicarbonate ions through specific channels in the luminal membrane. These agents also cause a net epithelial secretion of water and electrolytes. Some tissues such as the stomach and the kidney have alternative mechanisms. Although the epithelial lining of the stomach secretes bicarbonate in response to cAMP mediated agents, the volume of gastric secretion is mainly influenced by acid secretion from specialised oxyntic cells with a specific transport mechanism, the proton pump. Similarly water enters the nephron by glomerular ultrafiltration rather than by anion-linked secretion. With the exception of those tissues, the effect of the cystic fibrosis gene product on net water secretion appears to vary in epithelia from different embryological layers. This variation corresponds closely to the distribution of clinical disease.

Ectodermal structures with secretory epithelia include the sweat, lacrimal and parotid glands, and the breast. In patients with cystic fibrosis these do not become diseased and there is no clinical evidence of inadequate water secretion, such as a sicca syndrome. Physiological stimuli provoke a normal volume of secretion, with normal sodium and chloride concentrations in tears at high flow rates, parotid saliva and milk, but not in sweat, owing to the reduced chloride permeability of sweat ducts [2, 13, 14]. Cholinergic drugs also cause cystic fibrosis patients to secrete both sweat and parotid saliva normally [2]. However, cAMP mediated agents such as ß agonists, which normally provoke sweat formation, have no effect in cystic fibrosis patients, in spite of a normal rise in intracellular cAMP [15]. The defective cAMP mediated response cannot be of physiological importance in sweat secretion, since the latter is normal in patients with cystic fibrosis, but does indicate, like abnormal sweat electrolyte concentrations, expression of the gene in sweat glands.

In contrast, in cystic fibrosis patients most of the mesodermal and endodermal structures that contain secretory epithelia have relatively dehydrated luminal contents and secretions [2, 12, 16, 17]. They may develop clinical disease associated with obstruction of their lumina [18], and they do not respond normally to physiological or pharmacological stimuli that promote water and ion secretion. Seminal fluid volume is decreased from one-third to half [16]. Cervical mucus is dryer than normal and does not change around the time of ovulation when an increase in water and electrolyte content and decreased viscosity would normally occur [17]. Basal pancreatic water and electrolyte secretion is severely reduced, as is also the expected increase on stimulation by secretin and pancreozymin [5–7]. The volumes of biliary secretion and airway water secretion have not been studied. However, respiratory mucus from cystic fibrosis patients is dryer than that from normal subjects and from patients with other chronic respiratory disease, and water evaporation through the upper airway mucosa is reduced in cystic fibrosis [12, 19].

Pancreatic stimulation studies also suggest abnormal intestinal water secretion in cystic fibrosis [5–7]. They rely on quantifying the fluid and electrolytes aspirated from an isolated length of bowel between the ampulla of Vater and the upper jejunum, and assume that any changes result from pancreatic and biliary secretion

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alone. However, these results could be influenced by intestinal water and electrolyte transport, particularly if the reduction of water absorption caused by secretin and pancreozymin in the upper jejunum of normal subjects [20] also occurs in the duodenum. That this may be so is suggested by stimulation studies in two other conditions: the Schwachman–Diamond syndrome (familial pancreatic dysplasia with achylia, cyclic neutropenia, short stature and metaphyseal dysostosis), where bicarbonate and enzyme secretion is reduced as expected from the pancreatic abnormality, but net water secretion is normal [5–7], and pancreatitis, where the volume obtained by duodenal aspiration exceeds that obtained by direct cannulation of the ampulla of Vater by a ratio of 2.3 to 1 [21]. In cystic fibrosis patients, however, net water secretion is reduced, which implies that both pancreatic and intestinal water transport are abnormal.

The salivary glands, stomach and kidney are not usually clinically affected. However, when salivary disease occurs it affects the submaxillary gland, and pathological studies show changes in the sublingual glands of 80% of cystic fibrosis patients [18]. Unlike the parotid, which is unaffected, these glands are endodermal, and their secretory responses to reflex stimulation and cholinergic agents are reduced in cystic fibrosis [2]. The alternative mechanisms for water transport of the stomach and kidney appear intact in cystic fibrosis but both organs show other abnormalities that suggest expression of the gene. Although gastric acid secretion itself appears normal, the volume of gastric juice secreted after stimulation by pentagastrin is lower in cystic fibrosis patients [22]. This could reflect an absence of bicarbonate linked secretion, which has not yet been studied. The glomerular filtration rate is normal in cystic fibrosis, but renal sodium transport is not [23].

These observations suggest that the effect of cystic fibrosis on water secretion differs in epithelia of ectodermal origin and those of endodermal or mesodermal origin. Reduced secretion in cystic fibrosis has been related to an abnormal response to cAMP mediated agents [24], although the main human disease due to defective action of the cAMP pathway, familial pseudohypoparathyroidism [25], has no features in common with cystic fibrosis. Absent cAMP mediated anion-linked secretion in all the epithelia studied [3, 5–11, 15], together with increased sodium absorption, which has been demonstrated across the airway [3], proximal renal tubule [23] and, possibly, the intestine [8], may explain the relative dehydration of some secretions in cystic fibrosis, but not the fact that ectodermal epithelia can secrete water normally while epithelia of endodermal or mesodermal origin cannot. The ability to secrete water correlates better with the differing effects of cystic fibrosis on the response to cholinergic agents, to which sweat glands and parotid glands respond normally, while non-parotid salivary glands and the intestine do not.

Thus, although the dysfunctional product of the cystic fibrosis gene is expressed in all epithelia, its effect on water secretion under physiological conditions, and its ability to cause disease, is bypassed in the two organs with alternative mechanisms and in those of ectodermal origin. This raises the hope that the same might be achieved pharmacologically in other epithelia.

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References

1. Sato, K. (1984) Differing luminal potential difference of cystic fibrosis and control sweat secretory coils *in vitro*. *American Journal of Physiology*, **247**, R646–9.
2. Quinton, P. M. (1984) Exocrine glands. In *Cystic fibrosis* (ed. L. M. Taussig) pp338–75. New York: Thieme-Stratton.
3. Boucher, R. C., Cotton, C. U., Gatzy, J. T. *et al.* (1988) Evidence for reduced Cl permeability and increased Na permeability in cystic fibrosis human primary cell cultures. *Journal of Physiology*, **405**, 77–103.
4. Widdicombe, J. H. and Barthelson, R. A. (1988) Altered chloride transport across primary cultures of tracheal epithelium in cystic fibrosis. In *Cellular and molecular basis of cystic fibrosis* (ed. G. Mastella and P. M. Quinton) pp 377–82. San Francisco: San Francisco Press.
5. Hadorn, B., Zoppi, G., Shmerling, D. H. *et al.* (1968) Quantitative assessment of exocrine pancreatic function in infants and children. *Journal of Pediatrics*, **73**, 39–50.
6. Wong, L. T. K., Turtle, S. and Davidson, A. G. F. (1982) Secretin pancreozymin stimulation test and confirmation of the diagnosis of cystic fibrosis. *Gut*, **23**, 744–50.
7. Kopelman, H., Durie, P., Gaskin, K. *et al.* (1985) Pancreatic fluid secretion and protein hyperconcentration in cystic fibrosis. *New England Journal of Medicine*, **312**, 329–34.
8. Berschneider, H. M., Knowles, M. R., Azizkhan, R. G. *et al.* (1988) Altered intestinal chloride transport in cystic fibrosis. *Faseb Journal*, **2**, 2625–9.
9. Taylor, C. J., Baxter, P. S., Hardcastle, J. and Hardcastle, P. T. (1988) Failure to induce secretion in jejunal biopsies from children with cystic fibrosis. *Gut*, **29**, 957–62.
10. Baxter, P. S., Wilson, A. J., Read, N. W. *et al.* (1989) Abnormal jejunal potential difference in cystic fibrosis. *Lancet*, **i**, 464–6.
11. Goldstein, J. L., Nash, N. T., Al-Bazzaz, F. *et al.* (1988) Rectum has abnormal ion transport but normal cAMP binding proteins in cystic fibrosis. *American Journal of Physiology*, **254**, C719–24.
12. Johansen, P. G., Anderson, C. M. and Hadorn, B. (1968) Cystic fibrosis of the pancreas: a generalised disturbance of water and electrolyte movement in exocrine tissues. *Lancet*, **i**, 455–60.
13. Botelho, S. Y., Goldstein, A. M. and Rosenlund, M. L. (1973) Tear sodium, potassium, chloride and calcium at various flow rates: children with cystic fibrosis and unaffected siblings with and without corneal staining. *Journal of Pediatrics*, **83**, 601–6.
14. Alpert, S. E. and Cormier, A. D. (1983) Normal electrolyte and protein content in milk from mothers with cystic fibrosis: an explanation for the initial report of elevated milk sodium concentration. *Journal of Pediatrics*, **102**, 77–80.
15. Sato, K. and Sato, F. (1984) Defective beta adrenergic response of cystic fibrosis sweat glands *in vivo* and *in vitro*. *Journal of Clinical Investigation*, **73**, 1763–71.
16. Rule, A. H., Kopito, L. and Schwachman, H. (1970) Chemical analysis of ejaculates from patients with cystic fibrosis. *Fertility and Sterility*, **21**, 515–20.
17. Kopito, L. E., Kosansky, H. J. and Schwachman, H. (1973) Water and electrolytes in cervical mucus from patients with cystic fibrosis. *Fertility and Sterility*, **24**, 512–6.
18. Oppenheimer, E. H. and Esterly, J. R. (1975) Pathology of cystic fibrosis: review of the literature and comparison with 146 autopsied cases. *Perspectives in Pediatric Pathology*, **2**, 241–78.

19. Primiano, F. P., Saidel, G. M., Montague, F. W. *et al.* (1988) Water vapour and temperature dynamics in the upper airways of normal and cystic fibrosis subjects. *European Respiratory Journal*, **1**, 407–14.
20. Dollinger, H. C., Raptis, S., Rommel, K. and Pfeiffer, E. F. (1982) Effects of secretin and cholecystokinin-pancreozymin on water, electrolyte and glucose absorption in human jejunum: a comparison between different hormone preparations. *Research in Experimental Medicine* (Berlin), **180**, 215–21.
21. Denyer, M. E. and Cotton, P. B. (1979) Pure pancreatic juice studies in normal subjects and patients with chronic pancreatitis. *Gut*, **20**, 89–97.
22. Fieber, M., Meschede, R. and Tolckmitt, W. (1975) Acidität und peptische aktivität des magensafts bei gesunden und mucoviscidosis-kranken kindern. *Zeitschrift Kinderheilkunde*, **120**, 199–209.
23. Assael, B. M., Marra, G., Tirelli, A. S. *et al.* (1986) Renal function in cystic fibrosis. *International Journal of Pediatric Nephrology*, **4**, 213–6.
24. Editorial (1989) Towards the biochemical defect in cystic fibrosis. *Lancet*, **ii**, 1433.
25. Spiegel, A. M., Gierschik, P., Levine, M. A. and Downs, R. W. (1985) Clinical implications of guanine nucleotide-binding proteins as receptor-effector couplers. *New England Journal of Medicine*, **312**, 26–33.