model with regular measurements of surface and upper-ocean salinity from merchant vessels and moored or drifting profiling instruments, for which suitable devices must be developed quickly.

Clearly, long-term, high-quality hydrographic measurements are also necessary. The data on which Dickson *et al.* based their analysis were collected by various national fisheries or other research programmes, many of which are no longer running. But annual oceanographic monitoring following each winter's convection is an important component of World Ocean Circulation Experiment (WOCE). CONVEX-91 (a British contribution to WOCE), from which Read *et al.* draw their data, shows that colder, fresher waters are still migrating through the deeper North Atlantic. The further intensive observations of the North Atlantic planned for 1994–97 under WOCE should provide a new basis for models connecting air–sea fluxes, oceanic convection, North Atlantic variability and the large-scale meridional overturning of the global ocean. □

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CYSTIC FIBROSIS

ATP and chloride conductance

Jeffrey J. Wine and Samuel C. Silverstein

CYSTIC fibrosis results from mutations in the gene for the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel that is controlled in complicated and ill-understood ways[1]. CFTR is a member of a large family of transmembrane transport proteins that are predicted to have 12 membrane-spanning regions and two nucleotide-binding domains; it also uniquely possesses a large, highly charged cytosolic region containing numerous phosphorylation consensus sites. In accord with predictions from structural data, opening of CFTR channels requires both phosphorylation and binding of ATP[2].

Why is the regulation of this channel so complex? On page 79 of this issue[3], Quinton and Reddy report that in human sweat-duct cells activated by cyclic AMP, nonhydrolysable ATP analogues can stimulate chloride conductance via CFTR and that intracellular ATP levels of 5 mM are needed to maintain normal levels of chloride conductance. They put forward a new and important idea — that CFTR is sensing either the energy charge of the cell [(ATP + 1/2 ADP)/(ATP + ADP + AMP)] or the cellular ATP concentration itself, and that one or both of these factors regulates ion transport by CFTR.

Human sweat ducts are tiny organs which are difficult to study. Their usefulness is that, of any tissue, they express among the highest levels of CFTR on their luminal surface and have one of the highest chloride conductances; such conductance is absent in ducts afflicted with cystic fibrosis[4]. By permeabilizing the basolateral membrane of the duct with a bacterial toxin that creates large pores, the cytosolic levels of nucleotides can be altered and the chloride conductance of the luminal membrane measured. Under these conditions, Quinton and Reddy found that levels of ATP many times higher than the K_m for activating the cAMP-dependent protein kinase PKA did not produce appreciable increases in conductance. But after about 1 mM of ATP, which alone did not increase chloride conductance, the conductance rose steeply up to 10 mM of ATP, the highest concentration used. With the ATP level held at 0.5–1.0 mM to maintain phosphorylation of CFTR, large increases in conductance were produced by 5 mM additions of any four different non- or poorly hydrolysable analogues of ATP, whereas AMP was inhibitory.

These results are surprising. Previous experiments with excised patches expressing recombinant CFTR suggested that opening of CFTR in such patches requires hydrolysis of ATP, and concentrations for half-maximal activation were only about 260 μM ATP[2]. There are, however, several differences in the conditions under which the two experiments were carried out. CFTR was endogenous to the ducts but recombinant in the excised-patch experiments, and magnesium, an essential cofactor for ATP hydrolysis, was held at different concentrations. Moreover, bath chloride was replaced with gluconate in the duct experiments, and whereas pores formed by the bacterial toxin should allow free diffusion of the ATP analogue used, the duct apparently retained most of its metabolic machinery and cytosolic structure so that actual concentrations of nucleotides at the cytosolic face of the apical membrane may differ from those in the bath. For example, bath ADP, which inhibited CFTR opening in excised patches[5], stimulated opening in the duct. This was presumably because the permeabilized duct retains adenylate kinase, and thus the ability to form ATP and ADP. Moreover, the intact duct cells retain phosphatases capable of dephosphorylating the regulatory domain of CFTR. Such phosphatases are presumably less readily available in excised patches. Clearly, all these differences must be addressed experimentally before the results can be directly compared.

Taking Quinton and Reddy's observations at face value, it seems difficult to reconcile them with a mechanism that depends purely upon hydrolysis. Here, other recent experiments that hint at complexities in the ATP-regulation of CFTR and related channels come to mind. If ADP (and AMP?) directly inhibit CFTR channel opening[5], and if ADP and AMP are present at significant concentrations in the permeabilized duct, increased levels of ATP will be needed for conductance. Some clues to what is going on might also be provided from studies of P-glycoprotein (MDR1), an integral membrane protein related to CFTR, which confers multi-drug resistance upon cells in which it is expressed[6]. P-glycoprotein can apparently function either as a chloride channel activated by swelling, or as a transporter of a wide range of lipid-soluble compounds[7]. Opening of the P-glycoprotein channel is stimulated by allosteric ATP binding[8], but transport requires ATP hydrolysis[9]. The protein cannot simultaneously carry out both functions[8].

Quinton and Reddy's experiments will mean that even more attention is focused on mechanisms of CFTR regulation, on whether CFTR has several functions, and, if it does, whether they are distinct and use ATP differently. Numerous efforts are now underway to provide rational treatments for cystic fibrosis, and these issues are of great relevance in unravelling the pathophysiology of the disease. □

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