A Dual Role for Purinergic Agonists: Closer to Effective Treatment for Cystic Fibrosis?

A review of: Mall MA, Wissner T, Gonska D, *et al*. 2000 Inhibition of amiloride-sensitive epithelial Na(+) absorption by extracellular nucleotides in human normal and cystic fibrosis airways. Am J Respir Cell Mol Biol 23(6):755–761

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THE CLINICAL MANIFESTATIONS of cystic fibrosis (CF) result from defective CFTR gene product that functions as a Cl^- channel and a regulator of other ion transporters. The primary target for novel therapies in CF is the respiratory epithelium that, in CF patients, manifests a combination of linked electrophysiological defects (impaired Cl^- secretion and increased Na^+ absorption) associated with CFTR dysfunction. Following much dispute over precisely how these ion transport abnormalities result in airway obstruction and recurrent bronchitis in CF, recent evidence supports the hypothesis that diminished Cl^- secretion and excessive Na^+ absorption can deplete the volume of liquid lining airway surfaces in CF (1). This primary event can explain how mucus is then trapped in the airways, precipitating a chain of events resulting in chronic lung infection. If the ion transport abnormality in CF can be reversed therapeutically, lung disease could potentially be prevented or treated. A recent study by Mall and others (2) investigated the effects of a class of potential therapeutic agents, 5'-triphosphate nucleotides, on sodium hyperabsorption across normal and cystic fibrosis airways in humans. They measured changes in short circuit current across freshly excised nasal membranes from healthy controls (undergoing reconstructive surgery) and CF subjects (nasal polypectomy). Both adenosine 5'-triphosphate (ATP) and uridine 5'-triphosphate (UTP), when added to the luminal side of the membranes, induced prolonged, reversible inhibition of Na^+ transport. These agents were about half as effective as the sodium channel blocker, amiloride, which inhibits all current passing through the sodium channel, ENaC. ATP and UTP were equally effective in blocking Na^+ transport in CF and normal tissues. In addition, they showed that the ATP and UTP effect could be blocked by buffering changes in intracellular Ca^{2+}, suggesting that $[Ca^+]$ rather than protein kinase C mediates the purinoceptor-induced inhibition of Na^+ transport.

These studies confirm, in freshly excised human tissues, earlier work that showed inhibition of Na^+ transport by ATP and UTP in cultured human bronchi from CF and normal subjects (3) and respiratory epithelia from other species (4, 5). The Ca^{2+} dependence of the effect on Na^+ transport agrees with previous studies of human and porcine airways (3, 4). The importance of these studies lies in the confirmation of this class of agents as excellent candidates for treatment of patients with CF. Purinergic agonists were previously known to stimulate Cl^- secretion in CF airways through non-CFTR dependent pathways, but the confirmation that sodium hyperabsorption can also be inhibited suggest that both of the ion transport abnormalities associated with CFTR dysfunction can be countered by these agents. Studies with nebulized UTP showed near-normalization of mucociliary clearance rates in CF patients (6). Longer-acting analogues of these compounds are currently undergoing clinical trials in this patient population.

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3. Devor D C, Pilewski J M 1999 UTP inhibits Na+ absorption in wild-type and DeltaF508 CFTR-expressing human bronchial epithelia. Am J Physiol 276(4 Pt 1):C827–837
4. Inglis S K, Collett A, McAlroy H L, Wilson S M, Olver R E 1999 Effect of luminal nucleotides on Cl-secretion and Na+ absorption in distal bronchi. Pflugers Arch 438(5):621–627
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