Technology Summary

Metabolically Stable Analogues of Ursodeoxycholic Acid as a Treatment for Diarrheal Disease

Introduction

The global impact of diarrheal disease: Diarrhoeal diseases represent a huge global burden. In developing countries infectious diarrhoea kills 2.5 million children annually while in Western societies diarrhea is a feature of many intestinal disorders including infectious diseases (ID), inflammatory bowel diseases (IBD), irritable bowel syndrome (IBS), celiac disease, and a number of conditions associated with bile acid malabsorption. It has been estimated by the American Gastroenterological Association that ID, IBD and IBS alone represent an annual cost to the US economy of more than $9.6 billion (€17 billion in Europe) in terms of healthcare and lost work hours. Diarrhoea is also a prominent and dose-limiting side effect of many chemotherapeutic agents, thereby limiting their therapeutic efficacy. However, despite the prevalence and impact of diarrheal diseases on global health there is still a lack of specific and effective therapeutics and no drugs to treat diarrhea directly at the level of dysregulated fluid transport currently exist.

Intestinal fluid movement occurs across the epithelial cells and is driven by ion transport processes that establish osmotic gradients. In the intestine, Cl⁻ ion secretion is the primary driving force for fluid secretion and direct modulation of the molecular components of the epithelial secretory pathway therefore represents a logical approach for the development of new therapeutics for diarrheal disease. However, drugs that act specifically in this fashion are not yet available.

Technology

Analysis of the effects of UDCA and 6-MUDCA on Cl⁻ secretion in vitro and in vivo. Cl⁻ secretory responses to prototypical secretagogues, carbachol (CCh) and forskolin (FSK), were measured as changes in Isc across voltage-clamped T84 colonic epithelial cells or ex vivo mouse colon. A) UDCA and 6-MUDCA were equipotent in inhibiting Cl⁻ secretory responses to CCh in T84 cells while B) intraperitoneal injection of UDCA (100 mg/kg) to mice enhanced responses to both CCh and FSK. C) In contrast, treatment of mice with 6-MUDCA potently inhibited agonist-induced colonic secretory responses.
Metabolically stable analogues of ursodeoxycholic acid for treatment of diarrheal diseases.

Ursodeoxycholic acid (UDCA) has been used in Traditional Chinese Medicine for 1000’s of years in treatment of a variety of ailments. More recently UDCA has found a place in Western medicine for treatment of liver disorders and it is currently under investigation for a possible therapeutic role in several other conditions. RCSI studies have revealed a novel role for UDCA in inhibiting colonic epithelial Cl secretion, suggesting it might also be useful in treating diarrhea. However, counter-intuitive to its antisecretory actions in vitro, when it is used in clinical practice UDCA has the tendency to cause diarrhea. Our data suggest that this is likely due to the fact that in vivo UDCA is rapidly metabolised in the colon to lithocholic acid (LCA) which, in contrast to UDCA, we have found to enhance epithelial secretory capacity. This invention provides a new method to treat diarrhoeal diseases through the use of metabolically stable analogues of UDCA that cannot be converted to LCA in the colon.

Applications

Metabolically stable analogues of UDCA, typified by 6-methyl-UDCA (6-MUDCA), exert potent antisecretory effects on colonic epithelial cells in vitro and in vivo. Further RCSI studies have identified these antisecretory actions as being mediated at the molecular level through inhibition of specific transport proteins that comprise the epithelial Cl secretory pathway. Thus, stable derivatives of UDCA may represent a new class of antidiarrheal drug that acts directly at the level of the epithelial Cl secretory mechanism.

Advantages

UDCA is already used extensively to treat liver disease and is known to be very safe with few side effects. Stable analogues of UDCA have already been synthesised elsewhere and, on the basis of our data, these compounds may provide the first class of anti-diarrheal drugs that act directly at the level of epithelial secretory processes.

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<th>Feature</th>
<th>Benefit</th>
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<td>Directly targets intestinal epithelial secretion</td>
<td>Avoids unnecessary side effects of indirect treatments eg constipation, bloating, central effects, etc</td>
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<td>Potentially useful in treating a wide range of diarrhoeal diseases of different causes</td>
<td>Large potential market</td>
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<td>Several stable analogues of UDCA already exist</td>
<td>Facilitates development</td>
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<td>Unlike vaccines and oral rehydration solutions, drugs are easily portable and do not require refrigeration.</td>
<td>These are essential factors when considering distribution of a new therapeutic for diarrhoeal disease in developing countries.</td>
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