Anionophores: A Novel Approach to Cystic Fibrosis Treatment

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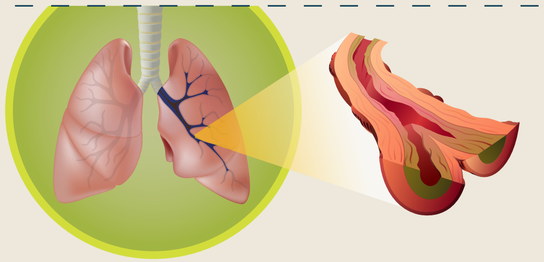
Abstract

Cystic fibrosis (CF) is caused by mutations in the gene encoding a chloride channel known as the CF transmembrane conductance regulator (CFTR). This study aimed to look for synthetic anion carrier molecules, known as anionophores, that could be delivered to a patient's cell membrane to perform the same function as the missing CFTR. From the 22 anionophores tested, four anionophores facilitated anion transport in CF cells, and they enhanced anion transport in cells with the F508 deletion, the most prevalent CFTR mutation associated with CF, when used in with lumacaftor and ivacaftor, with minimal toxicity. The findings confirm that anionophores can be used to restore anion transport, offering a promising therapeutic approach for CF.



Introduction

Mutations in the CFTR gene cause a characteristic defect in epithelial ion transport that plays a central role in the pathogenesis of CF.
Currently, few drugs have been authorized for the treatment of CF.
However, the vast number of disease-causing variations and their rarity may restrict the utility of these drugs.
Recently, anion selective ionophores, anionophores, have been studied and a number of synthetic anionophores have been reported.
This study focuses on the potential biological application of anionophores in CF therapy.

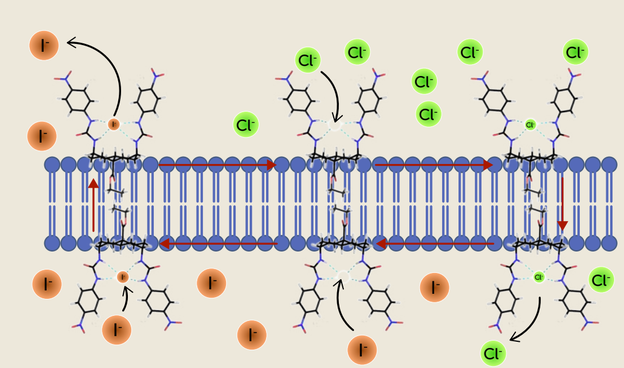
Study question

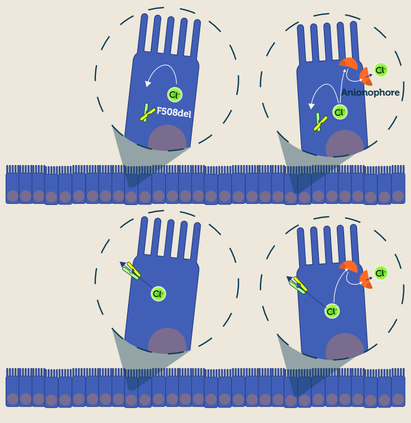
Can anionophores imitate CFTR functioning and restore ion transport, thereby offering a general treatment for CF?

Methodology

- 22 test compounds were screened using a halide-sensitive fluorophore yellow fluorescent protein.
- Compounds were tested using cells coexpressing F508del-CFTR in conjunction with the clinically approved CFTR drugs, lumacaftor and ivacaftor
- The cytotoxicity of these anionophores was also investigated.

Results





- Three compounds were found to have anion transport activity similar to or greater than that of a previously found anionophore.
- All four compounds were efficient at transporting anions in and out of lung cells grown in a lab dish.
- When applied in conjunction with lumacaftor and ivacaftor, all four drugs enhanced anion transport in cells with the F508 defect.

The compounds exhibited minimal toxic levels.

Conclusion

Synthetic anionionophores successfully mimic CFTR behavior in CF cells and can be useful in CF treatment, when added clinically authorized drugs

References

1 P. Davis, D. N. Sheppard and B. D. Smith, 2007. *Chem. Soc. Rev.*, 36, 348-357.
2 P. A. Gale, J. T. Davis and R. Quesada, 2017. *Chem. Soc. Rev.*, 46, 2497-2519
3 C. Jiang, E. R. Lee, M. B. Lane, Y.-F. Xiao, D. J. Harris and S. H. Cheng, 2001. *Am. J. Physiol. Lung Cell Mol. Physiol.*, 281, L1164-L1172.
4 B. Shen, X. Li, F. Wang, X. Yao and D. Yang, 2012. *PLoS ONE*, 7, e34694.
5 F. Ratjen, S. C. Bell, S. M. Rowe, C. H. Goss, A. L. Quittner and A. Bush, 2015. *Nat. Rev. Dis. Primers,* 1, 15010.

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