Transrectal potentiel difference in F508del-CFTR mice: an additional tool to evaluate in vivo ion transport in cystic fibrosis

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Objectives:

Cystic fibrosis is characterized by increased absorption of sodium and a decrease or absence of chloride secretion by epithelia. These disorders can be evaluated *in vivo* in mice and humans, by measuring the potential difference across the nasal mucosa. The aim of this work is to evaluate the transport defects in another target tissue such as rectal mucosa, used as representative of the digestive tract.

Methods:

Mice homozygous for the F508del mutation, constructed in a genetic background FVB/129, were examined in comparison to wild congeners and heterozygous congeners for the mutation. The measurement of rectal potential difference (RPD) was performed under general anesthesia in animals aged 12 to 16 weeks (n: 5/5/11 homozygous for F508del/wild type/heterozygous). During testing, the animal was placed supine on a hot plate at ~ 37°C and a dual channel catheter was inserted against the rectal wall 0.5 cm from the anal opening. One lane of the catheter was used to measure the RPD between the surface of the rectum and the subcutaneous space, taken as a reference. In the other lane, buffered solutions were infused at a constant rate of 12 µl / min. We recorded under continuous perfusion successively the baseline in the presence of physiological saline and after addition of amiloride (10^{-4} M) and barium (5×10^{-3} M) to block the transport of sodium and potassium respectively. The secretion of chloride was then triggered by imposing a gradient favorable to chloride efflux, obtained by replacing chloride solution by gluconate, and through the addition of forskolin (10^{-5} M), an activator of adenylate cyclase. At the end of the experiment, animals received antidotes and were placed in a shaded room until awakening.

Results:

F508del mice show disorders of ion transport characteristic of the disease. Indeed, a hyperpolarization in baseline conditions was observed in mice with F508del mean voltage values (± SEM) significantly different from those measured in wild-type animals (-33.5 ± 2.8 mV and -20.8 ± 1.8 mV; F508del and wild-type respectively, $p < 0.001$). The response to amiloride, also reflecting a lack of sodium transport, was significantly different between the two groups (39.8 ± 3.3 mV and 19.9 ± 2.0 mV, $P < 0.001$). Chloride secretion in F508del animals was reduced to almost one third of that measured in wild-type animals (-4.2 ± 0.4 mV and -9.4 ± 0.9 mV, $p < 0.001$). Intermediate values for both the conductance of sodium and for chloride conductance were observed in the heterozygous group.

Discussion and conclusion:

These results confirm that the rectal mucosa is a target tissue to study *in vivo* the function of CFTR. They encourage us to use the DPR as a tool for assessing potential therapeutic molecules in cystic fibrosis.