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Effect of Potentiator VX-770 on the Kinetics of Disease-Associated Mutant CFTR Channels ZULEYHA YUKSEK, ZOIA KOPEIKIN, SILVIA BOMPADRE, University of Missouri — CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) is a Cl- channel whose malfunction results in the genetic disease CF. One of the most common CF-associated mutations is the deletion of Phe 508 (ΔF508) resulting in channels with poor membrane expression and impaired function. Several functional abnormalities were demonstrated: infrequent openings, shorter locked-open time, reduced resident-time for the ATP molecule bound in the first nucleotide binding domain NBD1. Recently, the drug VX-770 was approved for clinical use, which increases the activity of ΔF508-CFTR. We studied the effect of VX-770 on the functional defects associated with ΔF508-CFTR: the Po of the channels is increased 12x due to the increase of opening rate and open time. Response to ATP analogues is decreased when channels are treated in conjunction with VX-770, suggesting that the potentiator by itself repairs gating defects. The potentiation effect was observed for temperature-corrected channels as well as channels treated with corrector VX-809. The shorter locked-open time of hydrolysis-deficient mutants is prolonged by VX-770 suggesting a stabilizing effect on the NBD dimer. The ATP resident time at NBD1, reflecting a partial NBD dimer configuration, is not affected by VX-770.

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