Location of a Common Inhibitor Binding Site in the Cytoplasmic Vestibule of the Cystic Fibrosis Transmembrane Conductance Regulator Chloride Channel Pore*

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Chloride transport by the cystic fibrosis transmembrane conductance regulator (CFTR) Cl⁻ channel is inhibited by a broad range of organic anions that enter the channel pore from its cytoplasmic end, physically occluding the Cl⁻ permeation pathway. These open channel blocker molecules are presumed to bind within a relatively wide pore inner vestibule that shows little discrimination between different large anions. The present study uses patch clamp recording to identify a pore-lining lysine residue, Lys-95, that acts to attract large blocker molecules into this inner vestibule. Mutations that remove the fixed positive charge associated with this amino acid residue dramatically weaken the blocking effects of five structurally unrelated open channel blockers (glibenclamide, 4,4'-dinitrostilbene-2,2'-disulfonic acid, lonidamine, 5-nitro-2-(3-phenylpropyl)pyrrolamino)benzoic acid, and tauroliothocholate-3-sulfate) when applied to the cytoplasmic face of the membrane. Mutagenesis of Lys-95 also induced amino acid side chain charge-dependent rectification of the macroscopic current-voltage relationship, consistent with the fixed positive charge on this residue normally acting to attract Cl⁻ ions from the intracellular solution into the pore. These results identify Lys-95 as playing an important role in attracting permeant anions into the channel pore inner vestibule, probably by an electrostatic mechanism. This same electrostatic attraction mechanism also acts to attract larger anionic molecules into the relatively wide inner vestibule, where these substances bind to block Cl⁻ permeation. Thus, structurally diverse open channel blockers of CFTR appear to share a common molecular mechanism of action that involves interaction with a positively charged amino acid side chain located in the inner vestibule of the pore.

Cystic fibrosis results from mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), an epithelial cell Cl⁻ channel (1, 2). CFTR is a member of the ATP-binding cassette family of membrane transport proteins (3) but appears to be unique within this family by functioning as an ion channel rather than some kind of active transporter protein. The CFTR protein contains 12 transmembrane (TM) α-helices that are presumed to form the pore region by which Cl⁻ ions cross the membrane (4, 5). Indeed, recent functional evidence implicates TMs 1 and 6 as playing key roles in forming the pore and interacting with Cl⁻ ions to determine the functional permeation properties (6).

Functional evidence suggests that permeant anions bind to several discrete sites within the CFTR channel pore (7–11), consistent with the identification of three separate Cl⁻ binding sites within a CIC Cl⁻ channel crystal structure (12). These binding sites may be involved in attracting Cl⁻ ions into the CFTR pore (13) and in coordinating ion-ion interactions that are necessary for rapid ion movement through the pore (14, 15). Site-directed mutagenesis studies implicate the positively charged amino acid side chains of Lys-95 (in TM1) (6) and Arg-334 (in TM6) (13, 16) as contributing to Cl⁻ ion binding sites inside the pore.

Chloride ion binding sites within the CFTR pore may also be sites at which certain substances bind to occlude the pore and inhibit Cl⁻ permeation (17–19) by a so-called “open channel block” mechanism. A diverse range of large organic anions have been shown to inhibit the Cl⁻ transport function of CFTR by such a mechanism (20, 21), for example sulfonylureas (19, 22, 23) and related substances (24), aryldiminozobenzoates (17, 25, 26), disulfonic stilbenes (27), indazoles (18), and conjugated bile salts (28). CFTR channel blockers are the subject of considerable scientific and clinical interest (29). These structurally diverse open channel blocker molecules share an apparently similar mechanism of action characterized by entry into the channel pore exclusively or preferentially from its intracellular end in a manner that is facilitated by negative membrane voltages and impeded by Cl⁻ ions on the opposite side of the membrane. The sidedness of action shown by these open channel blockers has led to the suggestion that the CFTR pore has a wide inner vestibule that shows little discrimination between anions, allowing electrodiffusional entry of a structurally diverse range of negatively charged molecules (19, 22, 27, 30).

However, despite numerous studies showing that the apparent affinity of different blockers can be altered by mutations within the putative pore region (17, 18, 25, 31, 32), the location of blocker binding site(s) and the number of such sites within the pore inner vestibule remain unknown.

The present study seeks to identify the molecular mechanism of action of CFTR open channel blockers and also to understand the biophysical significance of the structural features of the CFTR pore that makes it susceptible to the effects of such blockers.

EXPERIMENTAL PROCEDURES

Experiments were carried out on baby hamster kidney cells transiently transfected with wild type or mutant forms of human CFTR (6, 33). Patch clamp recording from inside-out membrane patches excised from these...
cells was performed as described previously (14, 33). Following patch excision, CFTR channels were activated by exposure of the cytoplasmic face of the patch to the protein kinase A catalytic subunit (20 nM) plus MgATP (1 mM). Activated channels were then "locked" in the open state by the addition of 2 mM sodium pyrophosphate (11, 33, 34). Initially, both intracellular (bath) and extracellular (pipette) solutions contained 150 mM NaCl, 2 mM MgCl₂, and 10 mM TES. To study the effects of open channel blockers, 150 mM sodium gluconate was substituted for NaCl in the pipette solution. All solutions were adjusted to pH 7.4 with NaOH. Given voltages have been corrected for liquid junction potentials calculated using pCLAMP8 software (Axon Instruments, Union City, CA).

CFTR inhibitors were added to the patch clamping chamber from stock solutions made up in normal bath solution. These stocks were made fresh every 3 h and stored in the dark at 4 °C until use. All chemicals were obtained from Sigma-Aldrich except for the protein kinase A catalytic subunit (Promega, Madison, WI). Glibenclamide, lonidamine, and 5-nitro-2-(3-phenylpropylamino)benzoic acid (NPPB) were initially solubilized in Me₂SO. Final Me₂SO concentrations in the experimental chamber were < 0.1%. At this concentration Me₂SO had no apparent effect on CFTR macroscopic currents, which is in agreement with prior reports from several laboratories (22, 25, 31, 35, 36). To isolate blocker-channel interactions as much as possible from blocker-Cl⁻ interactions that are known to affect the block of CFTR by many intracellular anions (14, 17–19, 22, 28), experiments were carried out using a low extracellular Cl⁻ concentration (4 mM).

Current traces were filtered at 100–200 Hz using an eight-pole Bessel filter, digitized at 250 Hz-1 kHz, and analyzed using pCLAMP8 software (Axon Instruments). Macroscopic current-voltage (I-V) relationships were constructed using depolarizing voltage ramp protocols (27, 37). Background (leak) currents recorded before the addition of the protein kinase A catalytic subunit were subtracted digitally, leaving uncontaminated CFTR currents (14, 37). Rectification of the I-V relationship was quantified (Fig. 1) as the "rectification ratio", the slope conductance at 50 mV as a fraction of that at 50 mV, as described previously (16).

For channel inhibition by glibenclamide, concentration-inhibition relationships (Fig. 2B) were fitted by an equation of the form shown in Equation 1,

\[
\text{Fractional unblocked current} = \frac{1}{1 + \left(\frac{[\text{glibenclamide}]}{K_d}\right)^{nH}}
\]

(Eq. 1)

where \(K_d\) is the apparent blocker dissociation constant and \(nH\) the slope factor or Hill coefficient. The relative effects of other blockers on wild type and mutant CFTR channels were compared only at a single concentration of blocker that caused >50% inhibition of wild type CFTR without the addition of excessive amounts of vehicle to the experimental chamber. In these cases, the \(K_d\) was simply approximated according to Equation 2,
\[
\frac{B}{(1/(I/I_0)) - 1}
\]  
(Eq. 2)

where \(B\) is the concentration of blocker, \(I\) the current amplitude in the presence of blocker, and \(I_0\) the control, unblocked current.

Experiments were performed at room temperature, 21–24 °C. Mean values are presented as mean ± S.E.

RESULTS

Charge-dependent Role of Lys-95 in Determining the Shape of the Current-Voltage Relationship—Previously it has been shown that mutagenesis of Arg-334 in TM6 causes inward rectification of the current-voltage relationship and that the degree of rectification is dependent on the side chain charge of the amino acid residue present at this position (13, 16). This phenomenon was ascribed to the location of Arg-334 in the outer vestibule of the pore, where its fixed charge acts electrostatically to attract \(\text{Cl}^-\) ions from the extracellular solution (13, 16). Conversely, removal (by mutagenesis) of another positively charged residue within the pore, Lys-95 in TM1, caused strong outward rectification of the \(I-V\) relationship (6) (Fig. 1). In a striking parallel with previous findings involving Arg-334 (13, 16), mutagenesis of Lys-95 had a strongly charge-dependent effect on \(I-V\) rectification (Fig. 1); the charge-conservative K95R, like wild type CFTR, showed a practically linear \(I-V\) relationship, whereas all of the other mutations, and especially the charge-reversing K95E, caused significant outward rectification. Although all of the results shown in Fig. 1 come from currents recorded after locking the channels open with PPi, identical rectification was observed prior to PPi treatment in all cases (data not shown), indicating that current rectification is not the result of voltage-dependent channel gating. Consideration of the overall net charge at these two amino acid positions (95 and 334) yields a continuum of the \(I-V\) relationship shape (Fig. 1C), which is consistent with these two positively charged residues playing analogous roles in attracting intracellular and extracellular \(\text{Cl}^-\) ions, respectively, into the channel pore.

Interaction of Open Channel Blockers with Lys-95—Because
Lys-95 appears to play a role in attracting intracellular Cl\(^-\) ions into the CFTR channel pore, I next addressed whether this positively charged residue is also involved in attracting large intracellular anions into the putative inner pore vestibule. As shown in Fig. 2, inhibition of macroscopic CFTR current by glibenclamide, a potent intracellular open channel blocker, was greatly weakened in K95Q as compared with wild type. Consistent with previous reports (19, 22, 23, 38), intracellular glibenclamide blocked wild type CFTR in a voltage-dependent manner, with a \(K_d\) of 12.6 \(\mu\)M at \(-100\) mV (Fig. 2, B and C) and an \(n_H\) of between 0.91 and 1.11 at different voltages. In K95Q, the \(K_d\) at this voltage was increased to 107 \(\mu\)M, an increase of \(-8.5\)-fold. Furthermore, glibenclamide block of K95Q appeared only weakly dependent on voltage (Fig. 2C). Thus, the positively charged side chain of Lys-95 appears to be important in attracting negatively charged glibenclamide molecules into the channel pore, particularly at negative voltages that facilitate glibenclamide movement into the pore and across part of the transmembrane electric field.

To investigate the role played by Lys-95 in attracting glibenclamide molecules into the pore, glibenclamide inhibition of other CFTR mutants was examined (Fig. 3). These results, using a number of different amino acid substitutions of Lys-95, strongly suggest that side chain charge at this position is important in controlling the apparent affinity of glibenclamide block; the apparent \(K_d\) at \(-100\) mV was not affected in the charge-conservative K95R but was significantly increased in charge-neutralizing mutants (K95A, K95C, K95Q) and most strongly increased in the charge-reversing K95E mutant. Whereas it is likely that introduction of a negatively charged amino acid side chain at any point along the permeation pathway could impede the entry of negatively charged substances such as glibenclamide, the results with mutants in which the positive charge is removed are consistent with Lys-95 normally playing an electrostatic role in attracting anionic substances such as glibenclamide into the channel pore from its intracellular end.

The blocking effects of other structurally unrelated open

**Fig. 4.** Mutagenesis of Lys-95 weakens the inhibitory effects of structurally diverse open channel blockers. A, example leak-subtracted current-voltage relationships for wild type and K95Q-CFTR following maximal channel activation with the protein kinase A catalytic subunit and PPI. In each case, currents were recorded before (control) and after the addition of different CFTR channel blockers to the intracellular solution, namely 4,4′-dinitrostilbene-2,2′-disulfonic acid (DNDS) (100 \(\mu\)M), lonidamine (100 \(\mu\)M), NPPB (50 \(\mu\)M), or tauroliothocholate-3-sulfate (TLCS) (50 \(\mu\)M). B, mean fraction of control current remaining \((I/I_0)\) after the addition of these concentrations of blockers in wild type (○) and K95Q (●) as a function of membrane potential. Values are means of data from 3–6 patches.
channel blockers on wild type and K95Q-CFTR are compared in Fig. 4. Four well characterized anionic CFTR open channel blockers from different chemical families were chosen, namely the disulfonic stilbene 4,4′-dinitrostilbene-2,2′-disulfonic acid (27), the indazole lonidamine (18), the arylaminobenzoate NPPB (25, 31), and the conjugated bile salt tauroliothocholate-3-sulfate (28). As shown in Fig. 4, all of these substances caused potent, voltage-dependent inhibition of wild type CFTR currents when added to the intracellular solution. In contrast, at the same concentrations each of these substances had only weak inhibitory effects on K95Q-CFTR. Indeed, a simplistic quantitative analysis of the blocking effects of these substances at the single concentration studied (see “Experimental Procedures”) suggested that the $K_d$ at $-100$ mV was increased by a factor of at least 25-fold in each case. Although this provides a rough approximation only, particularly as the estimated $K_d$ was far greater than the concentration of blocker actually used in the case of K95Q, it does suggest that the blocking effects of each of these substances is in fact considerably more sensitive to mutagenesis of Lys-95 than are the blocking effects of glibenclamide. Thus Lys-95 appears to play a central role in conferring sensitivity to these open channel blockers on the CFTR pore.

**DISCUSSION**

The results presented here support a major role for Lys-95 in attracting both permeant and blocking ions into the CFTR channel pore from its intracellular end. The proposed function of Lys-95 is shown in schematic form in Fig. 5. The fixed positive charge of the lysine side chain attracts $\text{Cl}^-$ ions from the intracellular solution into an inner vestibule of the channel pore (Fig. 5A). This role is directly analogous to that suggested previously for another fixed positive charge, that of the arginine side chain of Arg-334, in attracting extracellular Cl$^-$ ions into an outer pore vestibule (13) (Fig. 5A). Removal of the fixed charge at position 95 reduces anion entry from the intracellular solution, leading to diminished anion efflux and an outwardly rectified current-voltage relationship, whereas removal of the positive charge at position 334 reduces anion entry from the extracellular solution and causes inward rectification. The analogous roles of these two positively charged amino acid side chains is supported by the continuum of current-voltage relationship shapes that result from modifying the charge at these two positions (Fig. 1C). The importance of this anion attraction in the normal permeation mechanism is underscored by the finding that the unitary Cl$^-$ conductance of CFTR is reduced by removal of the fixed charge at position 95 (6) or 334 (13, 15). The proposed locations of Lys-95 and Arg-334, in pore inner and outer vestibules, respectively, implies that a short, narrow section of the pore between these residues contributes a major barrier to anion flux; this section may also contain the anion selectivity filter that includes the TM6 residue Phe-337 (39, 40).

Mutation of Lys-95 also alters the sensitivity of CFTR to diverse open channel blockers applied to the intracellular solution (Figs. 2–4). The most likely explanation is that the positively charged lysine side chain exerts the same kind of attractive force on large intracellular anions as it does on intracellular Cl$^-$ ions (Fig. 5B). As indicated by the relative effect of different amino acid substitutions at this position on block by intracellular glibenclamide (Fig. 3), the interaction between Lys-95 and intracellular blockers is most likely to be of an electrostatic nature. This would be consistent with both the apparent electrostatically attractive interaction between Lys-95 and intracellular Cl$^-$ ions (see above) and the previous finding that the blocking effects of glibenclamide are at least partly dependent on its negative charge (22). The fact that removal of the positive charge at this position greatly weakens block by a diverse range of intracellular anionic blockers (Fig. 4) suggests that these substances share a common molecular mechanism of action, i.e. they are attracted into a relatively wide inner vestibule of the pore due to an electrostatic attraction conferred by the fixed positive charge of the lysine side chain, and that the interaction with Lys-95 and perhaps other pore-lining residues is strong enough to confer a long residency time within the pore (relative to the short residency time of permeating Cl$^-$ ions), leading to occlusion of the pore and an overall decrease in the rate of Cl$^-$ permeation.

Although it was not possible to analyze the effects of other blockers in the same way, the present data suggest that mutagenesis of Lys-95 has a greater effect on block by 4,4′-dinitrostilbene-2,2′-disulfonic acid, lonidamine, NPPB or tauroliothocholate-3-sulfate than it does on glibenclamide. At least two factors may contribute to this apparent discrepancy. First, the large glibenclamide molecule may interact simultaneously with Lys-95 and other sites in the pore (24, 32) in the same way in which different parts of the glibenclamide molecule have been proposed to bind to different regions of the sulfonylurea receptor (41), such that mutagenesis of Lys-95 leaves some aspects of the binding site unperturbed. Secondly, it has been proposed that glibenclamide may have multiple inhibitory effects on CFTR (23), and such different inhibitory actions may show different dependences on the presence of a positively charged amino acid side chain within the pore inner vestibule. In contrast, the very low sensitivity of K95Q to other open channel blockers suggests that Lys-95 plays a dominant role in coordinating binding of these substances within the pore.

The schematic presented in Fig. 5, which is derived from experiments examining both Cl$^-$ permeation and open channel block, reflects a simple structural model of CFTR Cl$^-$ channel function. It is proposed that the pore contains a relatively short, narrow selectivity filter region that contributes the main
resistance to Cl\textsuperscript{−} ion flow. This central selectivity region is flanked by positive charges that attract Cl\textsuperscript{−} ions to the narrow region, increasing their local concentration and facilitating rapid Cl\textsuperscript{−} flux through the pore. This model places Lys-95 in TM1 at the intracellular end of the selectivity region and Arg-334 in TM6 at its extracellular end, providing further support for the proposed role of these two TM regions in forming the pore and determining its functional properties (6). Alignment of the TM regions of CFTR indicate that both of these residues are in the extracellular half of their respective membrane-spanning α-helices (4, 6), implying that the narrow selectivity region is relatively short and resides near the outer face of the membrane. The pore contains a wide inner vestibule, as proposed from previous functional studies (19, 22, 27). The same attractive forces that concentrate Cl\textsuperscript{−} ions in this inner vestibule also attract larger anions that can be accommodated in this wide part of the pore, leading to occlusion of the pore and open channel block (Fig. 5C). The apparently simple electrostatic interaction between the fixed charge of Lys-95 in the pore inner vestibule and negatively charged organic blocker molecules may explain the finding that a diverse range of organic anions act as open channel blockers of the CFTR pore when applied to the intracellular solution (20, 21). Conversely, other large anions that cannot approach close to this positive charge, for example because of steric constraints, may be ineffective as open channel blockers of CFTR. It is also possible that those substances included in the present study show favorable interactions with other parts of the pore walls that do not occur with similarly sized organic anions that are less effective blockers. The fact that most Cl\textsuperscript{−} channel blockers show little specificity between different classes of Cl\textsuperscript{−} channels (20, 42) may indicate that a similarly simple interaction as that proposed with the positive charge of Lys-95 in the CFTR pore underlies the interaction between these blockers and other structurally unrelated Cl\textsuperscript{−} channel pores.

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