The mechanism by which inositol 3,4,5,6-tetrakisphosphate (Ins(3,4,5,6)P₄) regulates chloride (Cl⁻) secretion was evaluated in the colonic epithelial cell line T84 using whole cell voltage clamp techniques. Our studies focused on the calcium-dependent chloride conductance (gClCa) that was activated either by mobilizing intracellular calcium (Ca²⁺) stores with thapsigargin or by introduction of the autonomous, autophosphorylated calmodulin-dependent protein kinase II (CaMKII) into the cell via the patch pipette. Basal concentrations of Ins(3,4,5,6)P₄ (1 μM) present in the pipette solution had no significant effect on Cl⁻ current; however, as the concentration of the polyphosphate was increased there was a corresponding reduction in anion current, with near complete inhibition at 8–10 μM Ins(3,4,5,6)P₄. Corresponding levels are found in cells after sustained receptor-dependent activation of phospholipase C. The Ins(3,4,5,6)P₄-induced inhibition of gClCa was isoform specific; neither Ins(1,3,4,5)P₄, Ins(1,3,4,6)P₄, Ins(1,4,5,6)P₃, nor Ins(1,3,4,5,6)P₅ induced current inhibition at concentrations of up to 100 μM. Annexin IV also plays an inhibitory role in modulating gClCa in T84 cells. When 2 μM annexin IV was present in the pipette solution, a concentration that by itself has no effect on gClCa, the potency of Ins(3,4,5,6)P₄ was approximately doubled. The combination of Ins(3,4,5,6)P₄ and annexin IV did not alter the in vitro activity of CaMKII. These data demonstrate that Ins(3,4,5,6)P₄ is an additional cellular signal that participates in the control of salt and fluid secretion, pH balance, osmoregulation, and other physiological activities that depend upon gClCa activation. Ins(3,4,5,6)P₄ metabolism and action should also be taken into account when designing treatment strategies for cystic fibrosis.

Transcellular Cl⁻ fluxes are pivotal to the control of salt and fluid secretion, pH balance, osmoregulation, cardiac function, and volume-dependent metabolic effects (1–5). The physiologic importance of Cl⁻ transport is reflected by both the diversity of the Cl⁻ channels that are expressed in eukaryotic cells as well as by the many intracellular signaling pathways that regulate them, including Ca²⁺ and cAMP. In cystic fibrosis, epithelia are defective in cAMP-regulated transport (6–15).

Experimental Procedures

Materials—Ins(1,4,5,6)P₄ was synthesized according to the scheme presented in Scheme 1. A solution of (−)−3,4,5,6-tetrabenzylmyo-inositol (I) (23) (708 mg, 1.31 mmol) in dimethylformamide (3 ml) was mixed with disopropylethylamine (0.5 ml) and methoxymethylene chloride (0.25 ml). The mixture was stirred at 55 °C for 24 h, diluted with hexane-ethyl acetate (20 ml), and extracted three times with water (10 ml). The organic phase was concentrated to dryness under vacuum, and the residue was chromatographed on silica gel (hexane-acetone, 10:1) to give the fully protected derivative II (660 mg, 80%). ¹H NMR (toluened₆): δ 7.2–6.9 (m, Ph), 4.8–4.69 (m, 8H), 4.62 (d, J = 6.7 Hz, 1H), 4.49 (d, J = 6.6 Hz, 1H), 4.40 (d, J = 11.7 Hz, 1H), 3.31 (d, J = 11.6 Hz, 1H), 1.46 (tr, J = 2.4 Hz, 1H), 3.97 (m, 2H), 3.36 (dd, J = 2.4, 10.0 Hz, 1H), 3.27 (1 H, CH₃). The abbreviations used are: PLC, phospholipase C; ATP, γS, adenosine 5'-O-(3-thiotriphosphate); NMDG, N-methyl-D-glucamine; CaMKII, Ca²⁺/calmodulin-dependent kinase II; 1CₐClCa, Ca²⁺-dependent chloride current; gClCa, Ca²⁺-dependent chloride conductance.

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2 Inositol polyphosphates are abbreviated according to IUPAC nomenclature, where Ins represents myo-inositol, and the phosphate substituents are as indicated (i.e. Ins(1,4,5,6)P₄ represents inositol 1,4,5,6-tetrakisphosphate).
(s, 3H), 3.24 (tr, J = 9.2 Hz, 1H), 3.15 (s, 3H), 3.04 (dd, J = 2.4, 9.8 Hz, 1H). The foregoing amount of the derivative II was dissolved in methanol: tetrahydrofuran (10:1, 10 ml) and subjected to hydrogenolysis under atmospheric pressure at room temperature over Pd/C catalyst (100 mg, 10% Pd). After 12 h, the catalyst was filtered off, and the filtrate was concentrated to give the tetritol (284 mg, 100%). Tetrizole (585 mg, 8 equivalents) and 2-((N,N-diethylamino)-5,6-benzo-1,3,2-dioxaphosphane (1.2 g, 4.8 equivalents) were added at room temperature, 8 equivalents) and 2-((N,N-diethylamino)-5,6-benzo-1,3,2-dioxaphosphane (1.2 g, 4.8 equivalents) were added at room temperature and extracted with aqueous sodium carbonate and water (5 ml). The organic fraction was concentrated to dryness and chromatographed on silica gel (chloroform:acetone, 7:2) to give the fully protected tetrakisphosphate IV (349 mg, 34%). The derivative IV (215 mg, 0.22 mmol) was subjected to hydrogenolysis in the presence of Pd/C catalyst (50 mg, 10% Pd) in methanol solution (4 ml) for 12 h at room temperature. The catalyst was filtered off, the residue was redissolved in water, extracted twice with chloroform (5 ml), and left in the aqueous solution at 4 °C for 48 h to remove the methoxymethylene groups. The mixture was left at room temperature for 48 h and subsequently treated with a solution of m-chloroperbenzoic acid (1.605 g, 50% content) in water, extracted twice with chloroform (5 ml), and left in the aqueous solution at 4 °C for 48 h to remove the methoxymethylene groups. The solution was freeze-dried to give a white solid. The solid was redissolved in water, and the solution was titrated with NaOH to pH 11. This solution was freeze-dried a second time to give pure tetrakisphosphate V as an off-white solid (137 mg, 92%, δ 5.90° (c 1.05, H2O). The spectral data (H and 31P NMR) of this sample were: H NMR (300 MHz, D2O, octasodium salt) δ 4.21 (q, J = 9.8 Hz, 1H), 4.16 (tr, J = 2.7 Hz, 1H), 4.04 (dtr, J = 9.3, 7.6 Hz, 1H), 3.89 (tr, J = 9.4 Hz, 1H), 3.78 (dd, J = 2.4, 7.4, 9.8 Hz, 1H), 3.54 (dd, J = 3.0, 9.5 Hz, 1H), 3.35 (m, J = 2.4, 7.8, 9.4 Hz, 1H), 2.71 ppm. 31P NMR (121 MHz, D2O, octasodium form) δ 4.87, 4.38, 2.78 ppm. EIMS (negative ion) m/z 489.8 (M-1). In some experiments we confirmed that Ins(3,4,5,6)P4 purchased from Sigma also inhibited the T84 Ca2+-dependent Cl− conductance. Ins(1,3,4,5)P4 was obtained from Calbiochem. Ins(1,3,4,6)P4, a kind gift of Desai et al., was synthesized as described previously (24). Ins(3,4,5,6)P4 was purchased from Sigma.

Annexin IV was purified from frozen rat lung using calcium-dependent binding to phenyl-Sepharose and fast protein liquid chromatography as described previously (25, 26).

Preparation of Activated CaMKII—The multifunctional Ca2+-calmodulin-dependent protein kinase II (CaMKII) purified from Electrophorus electricus, was aliquoted, stored at −80 °C in 25 ml Tris-HCl (pH 7.4), 1 mM EGTA, 100 mM NaCl, and 3% glycerol. The kinase was prepared for the electrophysiological experiments according to previously published methodology (6, 27–29) and delivered to the cell interior via inclusion in the patch pipette solution. The purified kinase was thawed and made autonomous by the incubation of 100 μg CaMKII with 600 μM calmodulin, 500 μM ATPγS, and 1 mM CaCl2 for 10 min at 4 °C immediately before the patch-clamp experiments were performed. The reaction was terminated by the addition of 20 mM EDTA. The mixture was diluted 5-fold with the pipette buffer solution and kept on ice for a maximum period of 3 h. In experiments in which cells were dialyzed with the activated kinase, 5 μl of activated kinase solution (approximately 20 μg/ml) was sandwiched between kinase-free pipette solution. Failure to prefill the tip of the pipette with kinase-free solution resulted in a significant reduction in the rate of seal formation.

Electrophysiological Studies—Cells from the Cl−-secretory cell line T84 were obtained from Dr. Raymond Frizzell (University of Alabama, Birmingham) and were subcultured and plated at a density of 5 × 104 cells/ml in human placental collagen-coated 35-mm tissue culture dishes. Whole cell electrophysiological studies were carried out on single, subconfluent cells, 1–6 days following plating (size ranged from 15 to 20 mm in diameter) using the techniques of Hamill et al. (30). The pipette solution contained (in mM): 40 N-methyl-D-glucamine (NMDG)-Cl, 100 NMDG-glutamate, 10 HEPS, 1 mM MgATP, 1 MgCl2, 5 EGTA, 0.5 CaCl2 (20 mM calculated free Ca2+), pH was adjusted to 7.2 with NMDG-OH. ATP was added to the pipette solution and the pH readjusted immediately prior to the experiments. The bath solution contained (in mM): 140 NMDG-Cl, 2 MgCl2, 2 CaCl2, 10 HEPS (pH 7.3) with NMDG-OH. Solution osmolarities were determined by vapor pressure osmometry (Wescor, Logan, UT). The osmolarity of the pipette and bath solutions was approximately 280 mosm. These solutions did not give rise to a spontaneous increase in basal currents as has been reported by Worrell et al. (31) for T84 cells in similar studies. In the presence of intracellular CaMKII, current activation developed with time after the establishment of the whole cell configuration. Variation in the concentration of kinase in the pipette tip and length of time the kinase was incubated in the activating thophosphorylation mixture affected the temporal response of Cl− current activation. In saline control experiments, pipette filling was performed using an identical protocol; however, under these conditions 5 μl of protein-free dialysis solution (20 mM Na2PO4, 154 mM NaCl (pH 7.4)) or the thophosphorylation mixture was used in place of the protein-containing solutions.

Whole cell currents were elicited by applying hyperpolarizing and depolarizing voltage pulses from a holding potential of −40 mV to potentials between −110 and +110 mV using an EPC-7 patch-clamp amplifier (List Electronics, Darmstadt). Experiments were performed at room temperature. Current amplitudes for a given experimental condition are given for the most depolarized voltage of +110 mV. Data are expressed as means ± S.E. with the number of experiments in parentheses. The statistical significance of the results was assessed using a paired Student’s t-test analysis.

RESULTS

Effect of Ins(3,4,5,6)P4 upon Whole Cell Ca2+-stimulated Cl− Currents—In whole cell experiments on T84 cells, Cl− was the major permeant ionic species in both the pipette and bath solutions. The equilibrium potential (ECl) for Cl− was −31 mV. The cells had an average capacitance of 37.2 ± 0.8 picofarad (n = 121).

The direct effect of Ins(3,4,5,6)P4 upon Ca2+-dependent Cl− current was first examined when intracellular Ca2+ levels were elevated by adding the Ca2+-ATPase inhibitor thapsigargin to the pipette solution. Current amplitude at +110 mV increased from a basal level of 179 ± 39 pA (n = 11) to 1,326 ± 175 pA (n = 6) following maximum thapsigargin stimulation (Fig. 1).

The current potential of the thapsigargin-induced current was −26 ± 3 mV (n = 6), indicating that the current was Ca2+-selective. The thapsigargin-induced increase in ICa,Cl was inhibited completely in the presence of Ins(3,4,5,6)P4 (10 μM) in pipette solution. This concentration is the level attained in receptor-activated T84 cells (19). A similar effect of Ins(3,4,5,6)P4 upon ICa,Cl current activation was brought about by the Ca2+-ionophore A23187 (data not shown). These data provide the first direct electrophysiological demonstration that Ins(3,4,5,6)P4 can inhibit a Ca2+-dependent Cl− current.

Effect of Ins(3,4,5,6)P4 upon Whole Cell Ca2+ Currents Stimulated by Autonomous CaMKII—Ca2+-dependent Cl− current activation in epithelial cells has been shown to be independent of the cystic fibrosis transport regulator and is mediated through the multifunctional CaMKII (6, 32, 33). The dependence on Ca2+-calmodulin can be circumvented by introducing activated, autonomous kinase into the cell via the pipette solution (34). Fig. 2A illustrates whole cell currents obtained over time in the presence of autonomous CaMKII. Current activation reached a maximum of 3,417 ± 109 pA (n = 10) over a period of 12–15 min. Zero current potential following maximal activation was −16.5 ± 0.3 mV (n = 16), indicating that the current was predominantly Ca2+-selective. A shift in zero current potential of 43 ± 2.7 mV (n = 3) in the depolarizing
direction was obtained when all but 4 mmol of the extracellular Cl$^-$ was replaced by the impermeant anion, glutamate. The anion channel inhibitor DIDS (500 μM) produced an 82 ± 4% (n = 3) inhibition in current amplitude at 110 mV, further confirming that the current was Cl$^-$ selective. Fig. 2B illustrates the absence of current activation when activated kinase was introduced intracellularly in the presence of Ins(3,4,5,6)P$_4$ (10 μM). These data also indicate that the mechanism by which Ins(3,4,5,6)P$_4$ inhibits Ca$^{2+}$-dependent Cl$^-$ channels is independent of any perturbation of Ca$^{2+}$ mobilization itself. Currents in the presence of Ins(3,4,5,6)P$_4$ (10 μM) and thapsigargin or activated CaMKII were not significantly different from currents measured in the absence of an activation stimulus (see Table I). These data indicate that the low basal current levels in the absence of other permeant cations were insensitive to Ins(3,4,5,6)P$_4$.

$I_{\text{Cl, Ca}}$ was allowed to develop over time in the presence of the autonomous kinase in the pipette solution. Once current amplitude had reached a steady state, Ins(3,4,5,6)P$_4$ (10 μM) was added to the bath solution (Fig. 3). Exposure of the voltage-clamped cell to externally applied Ins(3,4,5,6)P$_4$ failed to produce current inhibition, indicating that the inhibitory effect of Ins(3,4,5,6)P$_4$ on $I_{\text{Cl, Ca}}$ was specific to the interior of the cell and that Ins(3,4,5,6)P$_4$ binds specifically to a site on the cytoplasmic side of the plasma membrane.

Specificity of Inhibition of Cl$^-$ Channels by Ins(3,4,5,6)P$_4$—The specificity of the Ins(3,4,5,6)P$_4$-induced inhibition of $I_{\text{Cl, Ca}}$ was examined using Ins(1,3,4,5,6)P$_5$ and the three naturally occurring tetrakisphosphate isomers Ins(1,3,4,5)P$_4$, Ins(1,3,4,6)P$_4$, and Ins(1,4,5,6)P$_4$ (Fig. 4). None of these alternative isomers had any significant effect at levels of up to 100 μM, which is 10-fold greater than the maximally effective concentration of Ins(3,4,5,6)P$_4$. These data illustrate the specificity of the Ins(3,4,5,6)P$_4$ response.

Under conditions of basal cellular PLC activity, the level of Ins(3,4,5,6)P$_4$ is approximately 1 μM; the sustained activation of PLC can increase levels of the polyphosphate to 10 μM (19). The inhibitory effect of Ins(3,4,5,6)P$_4$ on $I_{\text{Cl, Ca}}$ was determined over the concentration range of 0.1–15 μM (Fig. 5A). At 1 μM,
**Table I**

<table>
<thead>
<tr>
<th>Intracellular solution</th>
<th>Current</th>
<th>pA</th>
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<tbody>
<tr>
<td>ATP (1 mM)</td>
<td>90 ± 20 (3)</td>
<td></td>
</tr>
<tr>
<td>ATP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ CaMKII</td>
<td>3,417 ± 49 (10)</td>
<td></td>
</tr>
<tr>
<td>+ Ins(3,4,5,6)P&lt;sub&gt;4&lt;/sub&gt;</td>
<td>89 ± 49 (3)</td>
<td></td>
</tr>
<tr>
<td>+ Ins(1,3,4,5)P&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3,095 ± 295 (3)</td>
<td></td>
</tr>
<tr>
<td>+ Ins(1,4,5,6)P&lt;sub&gt;4&lt;/sub&gt;</td>
<td>2,864 ± 485 (3)</td>
<td></td>
</tr>
<tr>
<td>+ Ins(1,3,4,5,6)P&lt;sub&gt;5&lt;/sub&gt;</td>
<td>2,495 ± 54 (3)</td>
<td></td>
</tr>
<tr>
<td>+ Ins(1,3,4,5,6)P&lt;sub&gt;5&lt;/sub&gt;</td>
<td>3,425 ± 463 (3)</td>
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</table>

* Insitol polyphosphate concentration.

Ins(3,4,5,6)P<sub>4</sub> had no effect on I<sub>Cl,Ca</sub>. Between 3 and 5 μM, Ins(3,4,5,6)P<sub>4</sub> inhibited Cl<sup>-</sup> current by about 15%, after which there was a precipitous drop in the dose-response curve, with near complete inhibition by 8–10 μM (Fig. 5). The data did not fit a single-site binding curve, suggesting that more than one Ins(3,4,5,6)P<sub>4</sub> binding site was present. Ins(3,4,5,6)P<sub>4</sub> purchased from Sigma also blocked I<sub>Cl,Ca</sub>, although with a slightly lower affinity, with 50% inhibition at approximately 8 μM (n = 3).

Annexin IV is distributed in close association with apical membranes of Cl<sup>-</sup>-secretory epithelial cells (29). Previous studies demonstrated that annexin IV acts as an endogenous, negative regulatory element in I<sub>Cl,Ca</sub> activation (34). We therefore investigated the possible interplay between annexin IV and I<sub>Cl,Ca</sub> inhibition. In the presence of 2 μM annexin IV (a concentration that does not itself induce I<sub>Cl,Ca</sub>, inhibition, see Fig. 6B) the I<sub>Cl,Ca</sub> response was potentiated in the dynamic range of the curve. At 8 μM I<sub>Cl,Ca</sub> annexin IV increased the extent of inhibition by 60%.

Ins(3,4,5,6)P<sub>4</sub> and Annexin IV Do Not Directly Affect CaMKII Activity—The inhibition of CaMKII-dependent current activation by Ins(3,4,5,6)P<sub>4</sub> and annexin IV raised the possibility of direct inhibition of the enzyme. The direct in vitro interaction of Ins(3,4,5,6)P<sub>4</sub> and annexin IV with CaMKII was evaluated. As shown in Fig. 6, in the presence of Ca<sup>2+</sup>, neither Ins(3,4,5,6)P<sub>4</sub> nor annexin IV, alone or in combination, inhibited CaMKII activity, as determined by autophosphorylation activity. These data demonstrate that Ins(3,4,5,6)P<sub>4</sub> inhibition of I<sub>Cl,Ca</sub> is not through direct interaction with the kinase.

**DISCUSSION**

There are several sites at which the complex process of transepithelial Cl<sup>-</sup> secretion can be regulated, including Cl<sup>-</sup> channels directly, K<sup>+</sup> channels, and the Na-K-2Cl cotransporter (3, 4). The present study used electrophysiological techniques to gain insight into our understanding of the mechanistic basis of a recent report (19) that cell-permeant Ins(3,4,5,6)P<sub>4</sub> inhibits Ca<sup>2+</sup>-dependent Cl<sup>-</sup> secretion across T84 monolayers. We demonstrate that Ins(3,4,5,6)P<sub>4</sub> attenuates CaMKII-activated g<sub>Cl,Ca</sub>.

Ins(3,4,5,6)P<sub>4</sub>-induced I<sub>Cl,Ca</sub> inhibition was highly specific. Half-maximal inhibition of I<sub>Cl,Ca</sub> was observed at 5–7 μM Ins(3,4,5,6)P<sub>4</sub>. At a concentration of 8–10 μM, Ins(3,4,5,6)P<sub>4</sub>-induced inhibition of I<sub>Cl,Ca</sub> was complete. In contrast, Ins(1,3,4,5,6)P<sub>5</sub> and three I<sub>Cl</sub><sub>P</sub> isomers (Ins(1,3,4,5)P<sub>4</sub>, Ins(1,3,4,5,6)P<sub>4</sub>, and Ins(1,4,5,6)P<sub>4</sub>) were all without effect at 100 μM, which is well in excess of the concentrations of these isomers measured in either stimulated or unstimulated cells (35). The absence of an effect of Ins(1,3,4,5,6)P<sub>5</sub> on I<sub>Cl,Ca</sub> is consistent with its proposed role as an inactive precursor pool (17, 18).

In unstimulated T84 cells, the cellular concentration of Ins(3,4,5,6)P<sub>4</sub> is estimated to be 1 μM (19). We found that intracellular concentrations of Ins(3,4,5,6)P<sub>4</sub> in the concentration range of 1 μM did not have a significant effect upon g<sub>Cl,Ca</sub> (Fig. 6) The receptor-mediated activation of PLC leads to a progressive increase in intracellular levels of Ins(3,4,5,6)P<sub>4</sub> which can continue for over 30 min, at which point the levels of Ins(3,4,5,6)P<sub>4</sub> may be greater than 10 μM (17, 19). Our data therefore provide a mechanistic explanation for the earlier observation that sustained receptor activation almost completely prevents calcium from activating Cl<sup>-</sup> secretion from T84 cells (19). The physiological significance of this phenomenon may be to protect against the potentially deleterious consequences that could otherwise arise from a sustained secretion of salt and fluid from intestinal epithelium. In addition to osmoregulation and the control of salt secretion, it will be of interest to determine the range of cell types in which this novel modulation of I<sub>Cl,Ca</sub> by Ins(3,4,5,6)P<sub>4</sub> occurs, since it could have an impact on several other important physiological processes that depend upon calcium-regulated Cl<sup>-</sup> channel activity, e.g. pH balance, volume-dependent metabolic effects, and cardiac electrical activity (1–5). Because of the relatively slow rate of Ins(3,4,5,6)P<sub>4</sub> metabolism in vivo, the effects of this polyphosphate may continue some considerable time after the termination of the agonist response that elevated I<sub>Cl,Ca</sub> levels (19). Such desensitization may be considered to be heterogeneous, since the subsequent elevation of calcium by a second PLC-linked agonist will, by itself, be unable to bypass the inhibitory effect of Ins(3,4,5,6)P<sub>4</sub>.

Examination of the concentration dependence of the Ins(3,4,5,6)P<sub>4</sub>-induced I<sub>Cl,Ca</sub> inhibition revealed a precipitous decrease in Cl<sup>-</sup> current when the Ins(3,4,5,6)P<sub>4</sub> concentration was increased over a relatively narrow concentration range from 5 to 8 μM. This steep concentration dependence strongly suggests a cooperative interaction. The inhibitory effect of Ins(3,4,5,6)P<sub>4</sub> was potentiated by annexin IV, a protein that is most prominently expressed in epithelia (29) and which is also an endogenous inhibitor of I<sub>Cl,Ca</sub> (34). When a physiologically relevant concentration of annexin IV (2 μM) (36) was introduced into T84 cells, no effect was observed on CaMKII-dependent g<sub>Cl,Ca</sub>. When the same concentration of annexin was combined
with Ins(3,4,5,6)P₄, the degree of ICl,Ca inhibition was potentiated. The demonstration of this synergy provides a focal point for further elucidation of the intracellular Ins(3,4,5,6)P₄ binding site and the molecular characterization of Cl⁻ channel regulation. Furthermore, our data suggest that the precise potency of Ins(3,4,5,6)P₄ in vivo will depend upon the prevailing level of annexin IV. It will be important to unravel the processes that regulate the interconversion of Ins(3,4,5,6)P₄ and Ins(1,3,4,5,6)P₅ through the 1-kinase/1-phosphatase substrate cycle (18). A receptor-dependent increase in the net rate of dephosphorylation of Ins(1,3,4,5,6)P₅ to Ins(3,4,5,6)P₄ accompanies activation of PLC (18). Pharmacological intervention in this metabolic cycle should be considered as a possible approach to ameliorate the consequences of secretory defects such as cystic fibrosis. In this way the inhibitory activities of Ins(3,4,5,6)P₄ upon chloride conductance could be avoided, which could improve the therapeutic potential of activating PLC-mediated Ca²⁺-dependent salt and fluid secretion. Alternative approaches could include the design of inactive Ins(3,4,5,6)P₄ analogues that compete for the Ins(3,4,5,6)P₄ targets.

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Inhibition of Chloride Conductance by Inositol Tetrakisphosphate


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Inositol 3,4,5,6-Tetrakisphosphate Inhibits the Calmodulin-dependent Protein Kinase II-activated Chloride Conductance in T84 Colonic Epithelial Cells

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