Curcumin Stimulates Cystic Fibrosis Transmembrane Conductance Regulator Cl\(^{-}\) Channel Activity*

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Compounds that enhance either the function or bio-
synthetic processing of the cystic fibrosis trans-
membrane conductance regulator (CFTR) Cl\(^{-}\) channel may be of value in developing new treatments for cystic fi-
brosis (CF). Previous studies suggested that the herbal
extract curcumin might affect the processing of a com-
mon CF mutant, CFTR-ΔF508. Here, we tested the hy-
pothesis that curcumin influences channel function.
Curcumin increased CFTR channel activity in excised,
inside-out membrane patches by reducing channel
closed time and prolonging the time channels remained
open. Stimulation was dose-dependent, reversible, and
greater than that observed with genistein, another com-
ponent that stimulates CFTR. Curcumin-dependent
stimulation required phosphorylated channels and the
presence of ATP. We found that curcumin increased
the activity of both wild-type and ΔF508 channels. Adding
curcumin also increased Cl\(^{-}\) transport in differentiated
non-CF airway epithelia but not in CF epithelia. These
results suggest that curcumin may directly stimulate
CFTR Cl\(^{-}\) channels.

Cystic fibrosis (CF)\(^1\) results from mutations in the gene
encoding the CFTR Cl\(^{-}\) channel (1). The most common CF
mutation (ΔF508) causes defective protein folding, and as a
result CFTR is targeted for degradation rather than progress-
ning to the cell membrane (2). Other CF-associated mutations
disrupt CFTR function by a variety of mechanisms, including
some that prevent normal biosynthesis or impair CFTR Cl\(^{-}\)
channel function in the cell membrane. Knowledge of how
mutations disrupt function has encouraged development of
compounds that correct CFTR-ΔF508 processing and/or stimu-
late CFTR activity for those channels in the cell membrane (3).
This effort has been spurred on by the suggestion that even a
fraction of normal CFTR activity may be enough to prevent
disease; studies in non-CF humans and in mice bearing tar-
geted alterations of the CFTR gene suggest that that 5–10% of
wild-type CFTR levels may be sufficient to prevent lung disease
in humans and intestinal disease in mice (4–7). Two additional
discoveries support the feasibility of a pharmacologic approach.
First, although the Cl\(^{-}\) channel activity of CFTR-ΔF508 and
several other CF-associated mutants is reduced, they do retain
significant Cl\(^{-}\) channel activity (2, 8, 9). Second, defective
processing of CFTR-ΔF508 can be partially corrected by reduc-
ing the incubation temperature or adding chemical chaperones
(8, 9).

In pursuit of this strategy, a recent study found that curcu-
mun partially corrected the processing defect of CFTR-ΔF508 in
heterologous cells (10). Moreover, administering curcumin to
mice homozygous for the ΔF508 mutation corrected the char-
acteristic defect in voltage across the nasal epithelium,
whereas nasal voltage was unaltered in null mice. Curcumin
administration also improved weight gain in CFTR-ΔF508 an-
imals. However, three more recent studies did not find an effect
of curcumin on CFTR-ΔF508 processing (11–13).

Given the potential value of agents that modify CFTR func-
tion and/or processing and given differences in the reported
effects of curcumin, we asked if curcumin might stimulate
CFTR Cl\(^{-}\) channel activity. Earlier studies had suggested that
a very small amount of CFTR-ΔF508 may reach the cell surface
in mouse intestinal and airway epithelia (14, 15). Thus, an
agent that stimulates CFTR-ΔF508 activity might increase Cl\(^{-}\)
transport independent of alterations in mutant protein proc-
essing. Likewise, if an agent produced even a small correction
in CFTR-ΔF508 processing, then increasing its channel activity
would further augment the physiologic consequences. Our in-
terest in curcumin stimulation of CFTR was also piqued by the
earlier suggestion (10, 12) that curcumin exhibits structural
similarities to other compounds that may bind directly to CFTR
and stimulate its activity; examples include genistein, apige-
nin, benzo[clquinoliziniums, and benzimidazolones (16–20).
Therefore, we tested the hypothesis that curcumin stimulates
the activity of wild-type and ΔF508 CFTR Cl\(^{-}\) channels.

EXPERIMENTAL PROCEDURES

Cells and Expression Systems—For patch clamp studies, wild-type
and mutant CFTR were transiently expressed in HeLa cells using a
hybrid vaccinia virus system as described previously (21). For studies of
CFTR phosphorylation, COS-7 cells were electroporated with pcDNA3-CFTR (22).

 Cultures of human airway epithelia were obtained from non-CF and
CF bronchus (ΔF508/ΔF508) and cultured at the air-liquid interface as
described previously (23). Epithelia were used at least 14 days after
seeding when they were well differentiated with a surface consisting of
ciliated cells, goblet cells, and other non-ciliated cells (23). These dif-
ferentiated epithelium retain the functional properties of airway epithelia
including transepithelial electrolyte transport.
Curcumin Stimulates CFTR

Using Chamber Studies—Transepithelial current was measured as described previously (24) using a submucosal solution that contained (in mM): 135 NaCl, 1.2 MgCl₂, 1.2 CaCl₂, 2.4 K₃PO₄, 0.6 KH₂PO₄, 5 dextrose, and 5 HEPES, pH 7.4, and a mucosal solution that was the same except that NaCl was replaced by sodium gluconate to generate a transepithelial Cl⁻ concentration gradient. After measuring base-line current, we sequentially added amiloride (10⁻⁴ M), 4,4’-disothiocyanostilbene-2,2’-disulfonic acid (10⁻⁴ M), and the CAMP agonist forskolin (10⁻⁴ M) plus 3-isobutyl-1-methyloxanthine (10⁻⁴ M) to the mucosal solution followed by submucosal bumetanide (10⁻⁴ M).

CFTR Phosphorylation—48 h after transfection, COS cells were washed three times with ice-cold phosphate-buffered saline and solubilized for 1 h at 4 °C with ice-cold lysis buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1% Nonidet P-40 and protease inhibitors) (22). Soluble proteins were centrifuged for 15 min at 15,000 × g at 4 °C. Proteins in soluble supernatant were immunoprecipitated overnight at 4 °C with anti-CFTR antibodies (24-1 from R&D Systems, Minneapolis, MN, and MM3-4 and M3A7 from Upstate Technologies, Charlottesville, VA). The antibody-protein complex was precipitated with protein A-agarose (Pierce). Immunoprecipitated CFTR was washed three times with ice-cold lysis buffer containing detergent and once with lysis buffer without detergent. Pellets were then phosphorylated with 40 nm catalytic subunits of PKA (Promega, Madison, WI) and [γ⁻³²P]ATP (6000 cpm/μl, PerkinElmer Life Sciences) in the indicated concentrations of curcumin or the Me₂SO vehicle control. Phosphorylation was stopped by dilution into 100× volume of lysis buffer and cAMP-dependent protein kinase inhibitor (PKI) (10 μM) (Promega). Proteins were separated by SDS-PAGE, stained, destained, dried, and exposed to phosphor screens (Amersham Biosciences). Radioactivity was quantitated using the ImageQuant program (Amersham Biosciences).

Patch Clamping—We studied excised, inside-out membrane patches using the methods described previously (25, 26). The pipette (extracellular) solution contained, in mM: 140 N-methyl-d-glucamine, 2 MgCl₂, 5 CaCl₂, 100 l-aspartic acid, and 10 Tricine, pH 7.3, with HCl. The bath (intracellular) solution contained 140 N-methyl-d-glucamine, 3 MgCl₂, 1 CsEGTA, and 10 Tricine, pH 7.3, with HCl. Following patch excision, channels were activated with the catalytic subunit of PKA (80 units/ml) and ATP. Holding voltage was −40 mV for macro-patch experiments and −80 mV for single-channel experiments. Experiments were performed at 23–26 °C.

An Axopatch 200A amplifier (Axon Instruments, Inc., Union City, CA) was used for voltage clamping and current recording. The pCLAMP software package (version 8.1, Axon Instruments, Inc.) was used for data acquisition and analysis. Recordings were low pass Bessel-filtered at 10 kHz and stored using a digital tape recorder. Replayed recordings were low pass-filtered at 100 Hz using an 8-pole Bessel filter (Model 900, Frequency Devices, Inc., Haverhill, MA) and digitized at 250 Hz for macropatch recordings. Single-channel recordings were low pass-filtered at 700 Hz and digitized at 7 kHz. Single-channel analysis was performed as described previously (27, 28) with a burst width of 20 ms. Events < 15 ms in duration were removed.

Reagents—Curcumin was obtained from Sigma (catalog no. C7727, lot no. 093K0795) and Fluka Chemika (Seelze, Germany, product no. 28260, lot no. 455335/142403356); we obtained similar results with both. Curcumin was dissolved in Me₂SO prior to use and added directly to experiments without intermediate dilution in aqueous buffers. As we began our patch clamp experiments with curcumin, we noticed that when a curcumin solution was placed in a plastic syringe reservoir and gravity fed through a 50-cm length of 0.58-mm diameter polyethylene tubing (Clay Adams® Intramedic), the color of the solution emerging when a curcumin solution was placed in a plastic syringe reservoir and gravity fed through a 50-cm length of 0.58-mm diameter polyethylene tubing (Clay Adams® Intramedic), the color of the solution emerging was less yellow than the starting material. Absorbance spectra of the samples showed a peak at 418 nm, consistent with curcumin, and after perfusion through the tubing more than 70% of the peak disappeared. Therefore, we prepared curcumin and added it directly to the cells or chambers in all studies. We were not able to study concentrations > 50 μM because of poor solubility. For prolonged exposure, curcumin was dissolved in Me₂SO, diluted into culture medium at 1:1000, and added to the submucosal surface for 3, 6, or 18 h.

Data—Data are shown as means ± S.E. unless otherwise indicated. p values <0.05 were considered statistically significant.

RESULTS

Curcumin Stimulates CFTR in Excised Membrane Patches—To learn whether curcumin could stimulate CFTR, we added it to the cytosolic surface of excised, inside-out membrane patches containing many CFTR channels. We added curcumin dissolved in Me₂SO directly to the cytosolic bath solution, because when we applied it through a perfusion system it adsorbed to the tubing, and we observed no effect on current (see “Experimental Procedures”). Curcumin stimulated a large, reversible increase in Cl⁻ channel activity (Fig. 1A). Stimulation required the presence of ATP and only occurred in channels that had been phosphorylated by PKA (not shown).

As the curcumin dose increased, the current response increased (Fig. 1B). Previous studies showed that highly phosphorylated channels (those studied in the presence of PKA) have an altered response to the channel activator genistein and to ATP concentration (29, 30). Therefore, we also examined the effect of curcumin on highly phosphorylated channels (i.e. in the presence of PKA). Adding curcumin after removing PKA stimulated current with an apparent EC₅₀ of 2.2 ± 1.1 μM (squares, EC₅₀ 2.2 ± 1.1 μM, n = 4; stimulation of 50 μM curcumin is less than that of 10 μM, p < 0.05) or ATP alone following removal of PKA (circles, EC₅₀ 9.1 ± 2.4 μM, n = 6). Vehicle control indicates addition of the Me₂SO buffer with no curcumin (with addition of 50 μM curcumin, the Me₂SO concentration was 1%).

Curcumin Inhibits PKA Activity—Finding that 50 μM curcumin stimulated less current than 10 μM curcumin in highly phosphorylated channels raised the possibility that curcumin might inhibit channel activity. Such behavior was reported for genistein, which stimulated CFTR currents at low micromolar concentrations and inhibited currents at concentrations above 20 μM (29, 31). Alternatively, curcumin might alter PKA activity. To test for a direct effect of curcumin on PKA, we asked whether it inhibited PKA phosphorylation of CFTR. We found that as the curcumin concentration increased, CFTR phosphorylation fell (Fig. 2). Curcumin has also been reported to inhibit protein kinase C activity (32). The reduced PKA activity may explain, in part, the decreasing current in response to high curcumin concentrations in the presence of PKA. However, we cannot exclude the possibility that high curcumin concentrations have a small direct inhibitory effect on CFTR.

Curcumin Stimulates CFTR-Δ508—To learn whether curcumin stimulates CFTR-ΔF508, we cultured cells at 27 °C to allow mutant channels to reach the cell surface (8, 9). When we...
then excised membrane patches, we found that even though the amount of current was less than with wild-type channels, 10 \( \mu \text{M} \) curcumin stimulated current (Fig. 3).

Curcumin Increases Channel Opening and Slows Channel Closing—To understand how curcumin increases current, we examined the response of single channels. Fig. 4A shows an example. Curcumin augmented activity by elevating \( P_o \) (Fig. 4B). The increase resulted from both a prolongation of burst duration and a reduction in interburst interval. Curcumin did not alter single-channel current amplitude.

Curcumin and Genistein Do Not Have Additive Effects—As noted previously (10, 12), curcumin has some structural similarities to genistein and other compounds that stimulate CFTR activity. Therefore, we compared the effects of genistein and curcumin and found that 10 \( \mu \text{M} \) curcumin generated a greater current increase than 10 \( \mu \text{M} \) genistein (Fig. 5). To further explore the mechanism by which curcumin stimulates CFTR, we added curcumin and genistein together. Instead of additive effects, genistein reduced the magnitude of curcumin-stimulated current. These results suggest that the two compounds might have related binding sites.

Curcumin Acutely Increases \( \text{Cl}^- \) Current in Differentiated Non-CF Airway Epithelia—To learn whether curcumin stimulates epithelial \( \text{Cl}^- \) transport, we measured the transepithelial \( \text{Cl}^- \) current across well differentiated human airway epithelia. As observed previously, cAMP agonists increased \( \text{Cl}^- \) current in non-CF but not CF epithelia (Fig. 6A and B). We found that curcumin slowly increased \( \text{Cl}^- \) current in non-CF epithelia, but it failed to alter current in CF epithelia. These results are consistent with curcumin stimulation of CFTR. Ten \( \mu \text{M} \) curcumin had little effect (Fig. 6B), even though this concentration stimulated substantial activity in isolated CFTR \( \text{Cl}^- \) channels (Fig. 1B). The difference may relate to different access to CFTR channels in the two systems, different levels of CFTR phosphorylation, variable adsorption, or other factors.

Our patch clamp studies showed that curcumin only stimulated activity after channels had been phosphorylated. In the

![Figure 2](http://www.jbc.org/)

**Fig. 2.** Curcumin inhibits PKA phosphorylation of CFTR. A, immunoprecipitated CFTR phosphorylated with PKA and \( [\gamma-^{32}\text{P}] \text{ATP} \) in the presence of indicated concentrations of curcumin. Bands B and C refer to partially and fully glycosylated CFTR, respectively. B, total counts in bands B and C expressed as percent of counts in the presence of the Me\(_2\)SO vehicle control alone. \( n = 5 \) separate experiments.

![Figure 3](http://www.jbc.org/)

**Fig. 3.** Curcumin stimulates CFTR-\( \Delta F508 \) channels. A, example of effect of curcumin on current in a membrane patch containing multiple CFTR-\( \Delta F508 \) channels. Bars indicate presence of 10 \( \mu \text{M} \) curcumin and 1 mM ATP plus 80 units/ml PKA applied to the cytosolic surface of the patch. B, effect of adding curcumin on current. ATP (1 mM) and PKA (80 units/ml) were present in all conditions. Circles indicate individual experiments, and squares and bars indicate mean ± S.E. Asterisk indicates \( p < 0.05 \). WT, wild type.

![Figure 4](http://www.jbc.org/)

**Fig. 4.** Effect of curcumin on single-channel properties of CFTR. A, example of single-channel tracing in the presence and absence of 10 \( \mu \text{M} \) curcumin. ATP (1 mM) and PKA (80 units/ml) were present throughout. For purposes of illustration, the traces were filtered at 100 Hz. o, open; c, closed. B, effect of curcumin (10 \( \mu \text{M} \)) on CFTR gating including open-state probability (\( P_o \)), burst duration (\( BD \)), and interburst interval (\( IBI \)). Data are from six paired experiments in five patches. Circles indicate individual experiments, and squares and bars indicate mean ± S.E. Asterisks indicate \( p < 0.05 \) (Wilcoxon signed rank test). Single-channel amplitude was 8.3 ± 0.1 picosiemens under control conditions and 8.9 ± 0.5 picosiemens with curcumin (\( n = 4 \)).
epithelial studies, CFTR has a basal level of phosphorylation and activity (33, 34) that would allow curcumin to stimulate transepithelial Cl\(^{-}\)/H\(^{+}\) current. We found that curcumin stimulated less current than cAMP agonists, and adding curcumin and cAMP agonists together generated no more current than cAMP agonists alone (Fig. 6C). We obtained similar results measuring bumetanide-sensitive current (Fig. 6C), which provides an assay of total CFTR-dependent transepithelial Cl\(^{-}\)/H\(^{+}\) transport (23).

We also tested the effect of more prolonged curcumin addition. Curcumin had little effect on Cl\(^{-}\)/H\(^{+}\) current in non-CF epithelia (Fig. 7). CF epithelia (ΔF508/ΔF508) developed no bumetanide-sensitive current even after incubation with a range of curcumin concentrations and exposure for 3 and 6 h (not shown) or 18 h (Fig. 7).

**DISCUSSION**

In these studies, we focused on the acute response to curcumin and found that it stimulates CFTR Cl\(^{-}\) channel activity. Stimulation was dose-dependent and reversible and occurred with both wild-type and ΔF508 channels. Curcumin also stimulated CFTR activity in differentiated human airway epithelia.

Finding that curcumin stimulated CFTR in excised, inside-out membrane patches suggests that it might interact directly with CFTR. Although our data do not allow us to determine the molecular mechanism, they do provide some initial suggestions. We found that curcumin only stimulated phosphorylated CFTR, and its potency increased when applied to highly phosphorylated channels. Moreover, stimulation occurred at curcumin concentrations that partially inhibit PKA phosphorylation of CFTR. These results suggest that the primary mechanism probably does not directly involve the R domain (35, 36). The lack of effect on single-channel current amplitude also suggests that major changes in the anion pore were probably not responsible. Nevertheless, we cannot exclude the possibility that curcumin induced structural changes in the R domain or membrane-spanning domains that somehow influenced channel function. However, because of its effects on gating, we favor the hypothesis that curcumin altered nucleotide binding domain (NBD)-dependent regulation. Curcumin reduced the duration of the closed state; this gating step is determined by nucleotide concentration, nucleotide structure, and NBD amino acid sequence (35, 36). Curcumin also prolonged the burst duration, a gating step influenced by NBD mutations and by interventions that alter NBD enzymatic activity.
In speaking about the mechanism of stimulation, we can also compare curcumin to other compounds that stimulate CFTR. Earlier studies noted that the biphenolic compound curcumin shares some structural features with flavones (apigenin), isoflavones (genistein), benzimidazolones (NS004), and benzoi[quinolizinium compounds that increase channel activity (16–20, 37). In addition, the monophenolic compound capsaicin was reported to stimulate CFTR (38). Like curcumin, genistein and capsaicin also prolonged the burst duration and reduced the interburst interval (29, 38, 39). Although the mechanism(s) by which these compounds stimulate is not with certainty, some work suggests that genistein interacts with the CFTR NBDs to alter gating (31, 40–42). Our finding that genistein and curcumin do not have additive effects and, with certainty, some work suggests that genistein interacts with the CFTR NBDs to alter gating (31, 40–42).

Our results highlight some potential difficulties in assessing the effect of curcumin. Curcumin adsorption to plastic and solubility were concerns. Curcumin stimulated the CFTR Cl⁻ channel. Curcumin inhibited PKA activity. Like genistein, curcumin might inhibit current at high concentrations. Also previous studies suggested curcumin may enhance processing of CFTR-ΔF508 (10). Given the variety of these effects, which might be compounded by methodological differences between laboratories, it is perhaps not surprising to see differences in reports about the activities of curcumin.

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