Functional Characterization of a Cloned Human Kidney Na\(^+\):HCO\(_3\)\(^-\) Cotransporter*

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Functional properties of a cloned human kidney Na\(^+\):HCO\(_3\)\(^-\) cotransporter (NBC-1) were studied in cultured HEK-293 cells that were transiently transfected with NBC-1 cDNA. The Na\(^+\):HCO\(_3\)\(^-\) cotransporter activity was assayed as the Na\(^+\) and HCO\(_3\)\(^-\) dependent pH\(_i\) recovery from intracellular acidosis with the use of the pH-sensitive dye 2',7' bis(2-carboxyethyl)-5(6)-carboxyfluorescein. In acid-loaded cells and in the presence of amiloride (to block Na\(^+\)/H\(^+\) exchange), switching to a Na\(^+\)-containing solution (115 mM) resulted in rapid pH\(_i\) recovery only in the presence of HCO\(_3\). This recovery was completely abolished by 300 μM 4,4’-diisothiocyanostilbene-2,2’-disulfonic acid. Replacing the Na\(^+\) with Li\(^+\) (115 mM) caused significant HCO\(_3\)-dependent, DIDS-sensitive pH\(_i\) recovery from intracellular acidosis, with Li\(^+\) showing lower affinity than Na\(^+\). Potassium (K\(^+\)) had no affinity for the Na\(^+\):HCO\(_3\) cotransporter. The Na\(^+\)-dependent HCO\(_3\) cotransporter was abolished in the presence of 0.2 mM harmaline. The Na\(^+\):HCO\(_3\) cotransporter could also function in Na\(^+\)(OH\(^-\)) cotransport mode, although only at high external pH (7.8). Based on functional similarities with the mammalian kidney experiments, we propose that NBC-1 is the proximal tubule Na\(^+\):HCO\(_3\) cotransporter.

The majority of the filtered load of HCO\(_3\) is reabsorbed in the kidney proximal tubule via the luminal Na\(^+\)/H\(^+\) exchanger NHE-3 (1–4). The exit of HCO\(_3\) across the basolateral membrane of proximal tubule is via the Na\(^+\):HCO\(_3\) cotransporter (5–8). The Na\(^+\):HCO\(_3\) cotransporter (NBC)\(^1\) mediates an electroneutral process with a stoichiometry of 3 eq of HCO\(_3\) per Na\(^+\) (9, 10). Recent studies have indicated that the actual ionic mechanism involves the cotransport of Na\(^+\), HCO\(_3\), and CO\(_2\) in a 1:1:1 ratio (11). In addition to reabsorption of HCO\(_3\) in proximal tubule, NBC also plays an important role in cell pH regulation in several tissues, including brain, liver, heart, and lung (12–17).

Functional studies support the presence of more than one NBC isofrom as judged by direction and stoichiometry of the cotransporter. In kidney, NBC activity leads to cell acidification, whereas in other tissues (such as liver and heart) its function leads to cell alkalinization (5–8, 13, 14). Furthermore, NBC has a stoichiometry of 3 eq of HCO\(_3\) per Na\(^+\) ion in the kidney (9, 10) but shows a stoichiometry of 2 eq of HCO\(_3\) per Na\(^+\) in other tissues (12).

We recently cloned and functionally expressed a human kidney Na\(^+\):HCO\(_3\) cotransporter (18). In addition to the kidney, the Na\(^+\):HCO\(_3\) cotransporter (called here NBC-1) is highly expressed in pancreas, with detectable levels in brain (18). The human NBC-1 (18) shows 80% homology to the amphibian Na\(^+\):HCO\(_3\) cotransporter (19). Both the human NBC-1 (18) and the amphibian NBC (19) mediate Na\(^+\)-dependent HCO\(_3\) cotransport in a DIDS-sensitive manner. The purpose of the current study was to examine the functional properties of the human kidney NBC. Accordingly, cultured HEK-293 cells were transiently transfected with the NBC-1 cDNA and studied.

**EXPERIMENTAL PROCEDURES**

**Cell Culture Procedures**—HEK-293 cells were cultured in Dulbecco’s modified Eagle’s medium containing 100 units/ml penicillin-G and supplemented with 10% fetal bovine serum. Cultured cells were incubated at 37 °C in a humidified atmosphere of 5% CO\(_2\) in air. The medium was replaced every other day.

**Transient Transfection**—Cultured HEK-293 cells were plated on coverslips and transfected at 60% confluence with 8 μg of the full-length human NBC-1 cDNA construct (in the cloning/expression vector pCMV.SPORT1) by calcium phosphate-DNA coprecipitation (20). Cells were assayed 44–52 h after transfection.

**Intracellular pH Measurement**—Changes in intracellular pH (pH\(_i\)) were monitored using the acetoxyethyl ester of the pH-sensitive fluorescent dye 2',7'-bis(2-carboxyethyl)-5(6)-carboxyfluorescein (BCECF-AM) as described (21–23). HEK-293 cells were grown to confluence on coverslips and incubated in the presence of 5 μM BCECF in a Na\(^+\)-free solution consisting of 115 mM tetramethylammonium-Cl and 25 mM KHCO\(_3\), pH 7.4 (solution A, Table I). pH\(_i\) was measured at a thermostatically controlled holding chamber (37 °C) in a Delta Scan dual excitation spectrofluorometer (Photon Technology International, South Brunswick, NJ). The monolayer was then perfused with the appropriate solutions (Table I). The fluorescence ratio at excitation wavelengths of 500 and 450 nm was utilized to determine intracellular pH values in the experimental groups by comparison with the calibration curve that was generated by KCl/gluconate technique. The fluorescence emission was recorded at 525 nm. The Na\(^+\)-HCO\(_3\) cotransporter activity was determined as the initial rate of the DIDS-sensitive, Na\(^+\)-dependent pH\(_i\) recovery (dpH/dt, pH/min) in a HCO\(_3\)-containing solution following an acid load induced by NH\(_4\)/NH\(_3\) withdrawal. The experiments were performed in the presence of 1 mM amiloride to block the Na\(^+\)/H\(^+\) exchanger activity. The experiments were repeated in the absence of HCO\(_3\), CO\(_2\), and bubbled with O\(_2\) to determine whether NBC can mediate Na\(^+\)-OH\(^-\) (hydroxyl) cotransport. The dpH/dt was calculated by fitting to a linear equation the first 2 min of the time course of intracellular pH recovery. Correlation coefficients for these linear fits averaged 0.984 ± 0.004.

**Materials**—Dulbecco’s modified Eagle’s medium was purchased from Life Technologies, Inc. BCECF-AM was from Molecular Probes Inc. Nigericin, DIDS, amiloride, and other chemicals were purchased from Sigma.

**Statistics**—Results are expressed as means ± S.E. Statistical significance between experimental groups was determined by Student’s t test or by one-way analysis of variance.
RESULTS

Na\(^+\) and HCO\(_3\)^– Dependence of the Cloned Human Kidney NBC (Influx Mode)—In the first series of experiments, cells were incubated and loaded with BCECF in Na\(^+\)-free solution (solution A, Table I), exposed to NH\(_4\)\(^+\) for 10 min (solution B, Table I), and acid-loaded by switching to an NH\(_4\)\(^+\)-free solution (solution A, Table I). The base-line pH\(_i\) in sodium-free solution was 7.11 ± 0.02. In the presence of 1 mM amiloride (to block Na\(^+\)/H\(^+\) exchange), transferring to a Na\(^+\)-free (115 mM) and HCO\(_3\)^–-containing solution (solution C, Table I) resulted in rapid pH\(_i\) recovery from acidosis in transfected cells (Fig. 1A), which was completely inhibited by 300 \(\mu M\) DIDS. The rate of pH\(_i\) recovery was 0.190 ± 0.013 pH/min in transfected cells (n = 5). This recovery was HCO\(_3\)^–-dependent, as shown by lack of significant pH\(_i\) recovery in the absence of HCO\(_3\)^– (solution D, Table I) (Fig. 1B). In HCO\(_3\)^–-free solution, pH\(_i\) recovery was 0.015 ± 0.003 pH/min in transfected cells (p < 0.001 versus HCO\(_3\)^–-containing solution, n = 5). Nontransfected cells showed little Na\(^+\)-dependent HCO\(_3\)^– cotransport (Fig. 1C) with pH\(_i\) recovery of 0.017 ± 0.002 pH/min (p < 0.001 versus transfected cells, n = 5).

Na\(^+\) and HCO\(_3\)^– Dependence of NBC (Efflux Mode)—NBC activity in transfected cells was also measured in the efflux mode. As shown in Fig. 2, switching the cells from a Na\(^+\) and HCO\(_3\)^–-containing medium (solution C, Table I) to a Na\(^+\)-free solution (solution A, Table I) resulted in rapid cell acidification,\(^2\) with ΔpH of 0.27 pH unit (n = 3). This cell acidification was reversible, with pH\(_i\) returning to base line upon switching back to the Na\(^+\)-containing solution (solution A, Table I) (Fig. 2A), with ΔpH of 0.31 pH unit (n = 3). The pH\(_i\) recovery back to base line was completely inhibited in the presence of 300 \(\mu M\) DIDS (Fig. 2A) (n = 3). Neither cell acidification nor pH\(_i\) recovery were observed in the absence of HCO\(_3\)^– (Fig. 2B), indicating the dependence of the transporter on Na\(^+\) and HCO\(_3\)^–. Taken together with Fig. 1, these studies indicate that the cloned cDNA encodes a Na\(^+\):HCO\(_3\)^– cotransporter.

Interaction of Lithium (Li\(^+\)) with the Cloned NBC—The ability of NBC to mediate Li\(^+\):HCO\(_3\)^– cotransport was next tested. As shown in Fig. 3A, exposing the cells to a Li\(^+\)-containing solution (solution E, Table I) caused significant recovery from intracellular acidosis. Switching from the Li\(^+\)-containing solution to the Na\(^+\)-containing solution (solution A, Table I) further increased the rate of pH\(_i\) recovery (Fig. 3A). At comparable concentrations, Na\(^+\) cotransport was next tested.

**TABLE I**

Composition of experimental solutions

Concentrations are in mM. Solutions (A, B, C, E, F) were bubbled with 5% CO\(_2\), 95% O\(_2\); solution D was gassed with 100% O\(_2\). The pH was adjusted to 7.40 with tris(hydroxymethyl)aminomethane.

| Compound       | A    | B    | C    | D    | E    | F    |
|----------------|------|------|------|------|------|------|
| NaCl           | 115  | 25   | 15   |      |      |      |
| KCl            |      | 115  |      |      |      |      |
| LiCl           |      |      | 115  |      |      |      |
| Tetramethylammonium-Cl | 115 | 75   | 115  |      |      |      |
| K\(_2\)HCO\(_3\) | 25   | 25   | 25   | 25   | 25   | 25   |
| K\(_2\)HPO\(_4\) | 0.8  | 0.8  | 0.8  | 0.8  | 0.8  | 0.8  |
| K\(_2\)HPO\(_4\) | 0.2  | 0.2  | 0.2  | 0.2  | 0.2  | 0.2  |
| CaCl\(_2\)      | 1    | 1    | 1    | 1    | 1    | 1    |
| MgCl\(_2\)      | 1    | 1    | 1    | 1    | 1    | 1    |
| Hepes          | 10   | 10   | 10   | 10   | 10   | 10   |
| NH\(_4\)Cl      | 40   |      |      |      |      |      |

\(^2\) For the Na\(^+\):HCO\(_3\)^– cotransporter to work in the efflux mode, the cells were loaded with a high sodium-containing solution (140 mM) for 30 min as compared with regular solution (Table I, solution A), which has 115 mM sodium. Although the difference between the sodium concentrations in the two solutions is only 25 mM, we observe that NBC can function in the efflux mode only at higher Na\(^+\) concentration, indicating that incubation with high Na\(^+\) solution increases intracellular Na\(^+\) and therefore allows for the Na\(^+\):HCO\(_3\)^– cotransporter to function in the efflux mode.

**FIG. 1.** Na\(^+\) and HCO\(_3\)^– dependence of the cloned human kidney NBC (influx mode). Transfected cells were acid loaded by NH\(_4\)\(^+\) withdrawal and monitored for pH\(_i\) recovery. A, in Na\(^+\) and HCO\(_3\)^–-containing solution, in the presence of 300 \(\mu M\) DIDS (n = 5); B, in HCO\(_3\)^–-free Na\(^+\)-containing solution (n = 4); C, nontransfected cells were exposed to Na\(^+\)- and HCO\(_3\)^–-containing solution (n = 5). Amiloride, 1 mM, was present to block Na\(^+\)/H\(^+\) exchange.
acidic pH (nadir pH of 6.282 ± 0.039 and 6.32 ± 0.027 for Li⁺ and Na⁺ experiments, respectively, p > 0.05, n = 4) the rate of pHᵢ recovery caused by Na⁺ was 4-fold higher than Li⁺ (Fig. 3, A and B) (pHᵢ recovery was 0.185 ± 0.003 pH/min in the presence of Na⁺ and 0.045 ± 0.003 in the presence of Li⁺, p < 0.001, n = 4 for each group). The Li⁺-dependent HCO₃⁻ cotransport was completely inhibited in the presence of 300 μM DIDS (Fig. 3C) and was not detected in nontransfected cells (Fig. 3D). These results indicate that Li⁺ can substitute for Na⁺ on NBC, with Li⁺ showing lower rates in mediating HCO₃⁻ transport. This is in contrast to the proximal tubule luminal NHE, where Li⁺ has much stronger affinity than Na⁺ (1).

Inhibition of the Cloned NBC by Harmaline—The purpose of the next series of experiments was to examine the interaction of harmaline with NBC. As indicated in Fig. 4, the presence of 0.2 mM harmaline completely blocked the Na⁺-dependent pHᵢ recovery in HCO₃⁻-containing media (the experiments were performed in the presence of 1 mM amiloride to block Na⁺/H⁺ exchange). The inhibition by harmaline was reversible as shown by recovery from cell acidosis upon switching to a harmaline-free solution (Fig. 4). pHᵢ recovery from acidosis was 0.184 ± 0.005 pH/min in the absence of harmaline and 0.007 ± 0.002 in the presence of harmaline (p < 0.001, n = 4 for each group). pHᵢ recovery upon removal of harmaline was 0.178 ± 0.006 pH/min (n = 4).

Effect of External pH on the Cloned NBC—NBC in rabbit...
kidney cortex is absolutely dependent on HCO$_3^-$ (24) and does not demonstrate any affinity for OH$^-$ whereas in colon it can also accept OH$^-$ (25). To examine the interaction of human kidney NBC with OH$^-$, cells were transfected and assayed for pH$_i$ recovery from an acid load in the presence of varying pH$_o$ and the absence of HCO$_3^-$ (A). Na$^+$-dependent pH$_i$ recovery at pH$_o$ 7.40 ($n$ = 5). B, Na$^+$-dependent pH$_i$ recovery at pH$_o$ 7.80 in the presence of 300 µM DIDS ($n$ = 4) or its vehicle ($n$ = 5). Nontransfected cells were exposed to Na$^+$ at pH$_o$ 7.80 in the absence (C) ($n$ = 4) or presence of 300 µM DIDS (D) ($n$ = 3). Fig. 5E shows the Na$^+$-dependent and Na$^+$-independent pH$_i$ recovery at pH$_o$ 7.8 in transfected cells.

To examine the Na$^+$-dependent pH$_i$ recovery at pH$_o$ 7.8 further, transfected cells were acidified and then switched to a Na$^+$-free solution at pH$_o$ 7.8. The rate of Na$^+$-independent pH$_i$ recovery at pH$_o$ 7.8 was 0.027 ± 0.004 pH/min ($p$, 0.009 versus Na$^+$-free pH$_o$ 7.8 solution, $n$ = 5 for each group), consistent with Na$^+$:OH$^-$ cotransport.

Interaction of potassium (K$^+$) with the cloned NBC. A K$^+$-
sponse in the brain (18). NBC-1 mRNA was not detected in the
absence of amiloride, intracellular pH returns to base-line
cotransport (Fig. 3). This is very similar to the NBC in basolateral membranes of rabbit
kidney proximal tubule (11, 29) and is opposite to the luminal
NHE, which has much higher affinity for Li+ than Na+ (1).

The human kidney NBC was completely inhibited in the presence
of harmaline (Fig. 4) and DIDS (Fig. 1), indicating that it has an inhibitory profile similar to the mammalian NBC in
basolateral membranes of rat or rabbit kidney proximal

DISCUSSION

The results of current experiments indicate that the cloned human kidney Na+:HCO3- cotransporter (NBC-1) accepts Na+
and HCO3- and is inhibited by DIDS (Figs. 1 and 2). The results
further indicate that Li+ can substitute for Na+ on NBC-1,
with Li+ showing decreased capacity to mediate HCO3-
dependent pH recovery compared with Na+ (Fig. 3). NBC-1 is
inhibited by DIDS and harmaline (Fig. 4) and can accept OH-
in place of HCO3-, with HCO3- showing much higher affinity
than OH- (Fig. 5). NBC does not function in K+::HCO3-
cotransport mode (Fig. 6).

We recently cloned the human kidney NBC-1 (18). Based on the
deduced amino acid sequence, the cDNA encodes a protein
with a molecular mass of ~116 kDa. Northern blot analysis
reveals that NBC-1 encodes a 7.6-kilobase mRNA that is highly
expressed in kidney and pancreas, with lower levels of expression
in the brain (18). NBC-1 mRNA was not detected in the liver,
lung, and heart (18) despite functional studies indicating the
presence of Na+::HCO3- cotransport in these tissues. These
results strongly suggest that the Na+::HCO3- cotransport in
these latter tissues might be another isoform from this family.

The human kidney NBC cDNA is highly homologous with the
amphibian kidney NBC and shares striking similarities at both
structural and functional levels with that cotransporter (19).

We have cloned rat NBC-1 and examined its mRNA distribu-
tion in different tissues as well as various nephron segments
(28). Rat NBC-1 is highly expressed in kidney and brain but
shows low levels of expression in stomach and colon (28).
Nephron segment distribution studies revealed that NBC-1 is
predominantly expressed in proximal tubules (28).

The results in Fig. 1 demonstrate that the Na+::HCO3-
cotransport does not mediate complete pH recovery from acidosis
to baseline values in the presence of amiloride. Whereas in the
absence of amiloride, intracellular pH returns to base-line
values (data not shown), further studies are needed to determine
whether NHE activity is indeed essential for complete
pH recovery from acidosis.

The results of Fig. 3 demonstrate the interaction of Li+ with
NBC and indicate that the human kidney NBC can accept Li+
in place of Na+, with Li+::HCO3- cotransport demonstrating
lower transport rate than Na+::HCO3- cotransport (Fig. 3). This
is very similar to the NBC in basolateral membranes of rabbit
kidney proximal tubule (11, 29) and is opposite to the luminal
NHE, which has much higher affinity for Li+ than Na+ (1).

The human kidney NBC was completely inhibited in the presence
of harmaline (Fig. 4) and DIDS (Fig. 1), indicating that it has an inhibitory profile similar to the mammalian NBC in
basolateral membranes of rat or rabbit kidney proximal

characteristics of Na+::HCO3- Cotransport

FIG. 6. Interaction of K+ with the
cloned NBC. A, transfected cells were
acidified and then exposed to a K+ (solution F, Table I) or Na+-containing solution
(solution C, Table I) (n = 4). B, the
rate of pH recovery caused by Na+ or K+
addition in the same monolayer (n = 4).
HCO3- was present during the duration of
the experiment. Amiloride, 1 mM, was
present to block possible K+/
H+ exchange.
OH⁻ demonstrating much lower Na⁺-dependent transport rates than HCO₃⁻ (Fig. 5). These results are in agreement with functional studies in rabbit colon, indicating lower affinity of NBC for OH⁻ (25). The rabbit kidney NBC on the other hand shows absolute dependence on HCO₃⁻ and does not demonstrate any affinity for OH⁻ (24). It is worth mentioning that functional studies in rabbit kidney cortex were performed at physiologic pH (pH₇.4) (24). As such, the affinity of rabbit kidney cotransporter for OH⁻ at external pH values similar to current experiments (i.e. pH₇.8) remains unknown.

Kidney NBC functions in an outwardly directed mode under physiologic conditions (5–8), resulting in trans-vectorial transport of HCO₃⁻ from lumen to blood. As such, the physiologic significance of Na⁺:OH⁻ cotransport mode remains speculative, as carbonic anhydrase activity in the kidney proximal tubule cells couples the CO₂ with OH⁻ to generate HCO₃⁻, thereby diminishing the concentration of intracellular OH⁻. We propose that the physiologic significance of Na⁺:OH⁻ cotransport mode may be in the colon, where secretion of acid into the lumen via NHE-3 may not lead to the reabsorption of HCO₃⁻, as the luminal [HCO₃⁻] is negligible (34), but rather results in generation of intracellular OH⁻. The Na⁺:OH⁻ cotransporter will then exit the cell across the basolateral membrane, thereby regulating cell pH.

In conclusion, based on functional properties (Figs. 1–6) and nephron segment distribution studies (28), we propose that NBC-1 is the kidney proximal tubule Na⁺:HCO₃⁻ cotransporter.

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