Distribution of sodium transporters and aquaporin-1 in the human choroid plexus

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Praetorius, Jeppe, and Søren Nielsen. Distribution of sodium transporters and aquaporin-1 in the human choroid plexus. Am J Physiol Cell Physiol 291: C59–C67, 2006. First published February 14, 2006; doi:10.1152/ajpcell.00433.2005.—The choroid plexus epithelium secretes electrolytes and fluid in the brain ventricular lumen at high rates. Several channels and ion carriers have been identified as likely mediators of this transport in rodent choroid plexus. This study aimed to map several of these proteins to the human choroid plexus. Immunoperoxidase-histochemistry was employed to determine the cellular and subcellular localization of the proteins. The water channel, aquaporin (AQP) 1, was predominantly situated in the apical plasma membrane domain, although distinct basolateral and endothelial immunoreactivity was also observed. The Na+/K+-ATPase α1-subunit was exclusively localized apically in the human choroid plexus epithelial cells. Immunoreactivity for the Na+/K+–2Cl– cotransporter, NKCC1, was likewise confined to the apical plasma membrane domain of the epithelium. The Cl−/HCO3– exchanger, AE2, was localized basolaterally, as was the Na+-dependent Cl−/HCO3– exchanger, NCCB, and the electroneutral Na+-HCO3– cotransporter, NBCn1. No immunoreactivity was found toward the Na+-dependent acid/base transporters NHE1 or NBCe2. Hence, the human choroid plexus epithelium displays an almost identical distribution pattern of water channels and Na+ transporters as the rat and mouse choroid plexus. This general cross species pattern suggests central roles for these transporters in choroid plexus functions such as cerebrospinal fluid production.

immunohistochemistry; metabolism; cerebrospinal fluid secretion

THE CHOROID PLEXUS EPITHELIUM secretes a major fraction of the cerebrospinal fluid (CSF) to the lumen of the ventricular system (see Ref. 4 for review). Studies of the mammalian choroidal plexus suggest that the pivotal event in CSF secretion is the active ouabain-sensitive transport of Na+ from the epithelial cell to the CSF mediated by the apically positioned Na+/K+-ATPase (5, 20). The apical Na+/K+/2Cl– cotransporter, NKCC1 (30), seems to contribute to Na+ secretion, because bumetanide inhibits CSF formation when applied apically (2, 10, 14). At the same time, NKCC1 would enrich the CSF with K+ to feed the apical Na+/K+-ATPase. NKCC1 may alternatively take up ions from the CSF as part of regulatory cell volume increase (44). Cl– is secreted through electrogenic mechanisms, likely involving one or more Cl– channels (15). Water would, in turn, follow by a transcellular pathway, i.e., through the water channel AQP1 (27–29) and possibly through a paracellular pathway from the interstitium to the slightly hyperosmolar CSF.

The basolateral Na+ and H2O entry mechanisms in the choroid plexus epithelium are not fully understood. The mRNA encoding the Na+/H+ exchanger, NHE1, has been demonstrated in the choroid plexus of rat (12), and amiloride-sensitive Na+ transport has been detected (25). However, Na+/H+ exchange seems of less importance in vitro compared with a basolateral Na+– and CO2/HCO3–-dependent mechanism that was shown to be sensitive to DIDS (21), an inhibitor of many Cl– and HCO3– transporters/channels. Another line of evidence for the involvement of HCO3– transporters in the CSF production is that carbonic anhydrase inhibition reduced secretion by ~50% (40). This was originally interpreted as the effect of inhibiting only cytosolic carbonic anhydrase and that most if not all secreted HCO3– was formed inside the epithelial cells of the choroid plexus. However, recent studies imply that at least some of the HCO3– transporters of the SLC4a family (as AE2, and electrogenic NBC) are functionally and physically coupled to both intracellular carbonic anhydrase II and external plasma membrane-bound forms of the carbonic anhydrase (36, 37). High transport rate seems to depend on the local formation of HCO3– or perhaps CO3–2−. It has been suggested that the basolateral uptake of Na+ may be mediated by a Na+-dependent Cl–/HCO3– exchanger, the NBCe2 (5). This transporter is DIDS sensitive and expressed extensively in the basolateral plasma membrane domain of the epithelial cell in both rat and mouse choroid plexus (32) and to much lesser extent in other epithelial tissues (unpublished observations). This transporter exists in at least two forms, rat brain (rb)1- and rb2NCBE, in rats (7). The molecular difference between these variants is found in the COOH terminal, where the rb2NCBE contains a PDZ domain.

Two additional HCO3– transporters have been identified in the basolateral plasma membrane domain in the rodent choroid plexus: an Na+-independent Cl–/HCO3– exchanger, AE2, and an electroneutral Na+-HCO3– cotransporter, NBCn1 (32). The epithelial AE2 was actually first cloned from the rat choroid plexus (18) and serves as a base extruder to maintain intracellular pH. AE2 may well contribute to DIDS-sensitive basolateral Cl– uptake in the choroid plexus. This certainly would explain the inhibition by this drug of the Cl– flux (6). However, DIDS may also inhibit CSF production partly by its action on the basolateral NBCe, which may be an important Na+ entry mechanism. The epithelial NBCn1 is more likely to help counteract intracellular acidosis in the choroid plexus (3) than being a major player in the transepithelial movement of Na+ and HCO3– because of its low DIDS sensitivity.

The human choroid plexus is thought to secrete CSF by similar mechanisms as the rodent tissue; however, no previous

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studies have addressed the molecular basis for the transport in humans. Therefore, we investigated the expression patterns of aquaporin (AQP) 1, the Na\(^{+}\)-K\(^{+}\)-ATPase, NCBE, NKCC1, NHE1, AE2, NBCn1, and NBCe2 proteins in the human choroid plexus by immunohistochemistry.

**METHODS**

**Antibodies.** Seven of the applied primary antibodies were previously validated in rodents, and the characterization of two additional antibodies is reported in the current study. Table 1 compares the amino acid composition of the immunizing rat peptides with the corresponding human sequences of AQP1 (27), AE2 (38), the rb1 variant of NCBE (32), the rb2 variant of human NCBE (22 COOH-terminal amino acid), and NBCn1 (41). These antibodies are all polyclonal and were raised in rabbits. For AQP1, a 22 COOH-terminal amino acid epitope identical to the peptide used by Terris et al. (39) was used for immunization of rabbits. The serum was affinity purified and displayed identical labeling patterns as the previous antibody, and tissue labeling was prevented by a peptide preabsorption test (data not shown). Monoclonal anti-α1 Na\(^{+}\)-K\(^{+}\)-ATPase antibodies were made using chicken soleus muscle as the immunogen. The antibody was first used by Kashgarian and coworkers (13). The corresponding human sequences of AQP1 (27), AE2 (38), the rb1 terminal amino acid (34), human NBCe2 (73 COOH-terminal amino acids (3)), and rat NKCC1 (454 COOH-terminal or 200 NH2-terminal amino acids (17)) antibodies. The human NHE1 COOH terminal is 88% identical to rat NHE1 immunogen. The corresponding human NKCC1 COOH terminal is 96% identical to the rat NKCC1, and the human NH2-terminal was 79% identical to rat NKCC1.

**Immunohistochemistry.** Human IV ventricle choroid plexus was obtained postmortem after informed consent from relatives or donated tissue according to the Danish guidelines for use of human material. In the first case, from which all shown images originate, the young male individual was hospitalized after noncerebral physical trauma and knowingly did not suffer from chronic diseases. The history of the individuals donating organs for science and education is unknown to Dr. Thomas Hasselbalch, but the donors all knew they did not suffer from chronic diseases.

**RESULTS**

**Immunolocalization of the Na\(^{+}\)-K\(^{+}\)-ATPase and AQP1 to the human choroid plexus.** Figure 1A shows that Na\(^{+}\)-K\(^{+}\)-ATPase α1 immunoreactivity was confined to the apical plasma membrane domain of the epithelial cells of the human choroid plexus. No other structures of the choroid plexus were stained by the antibody. Human kidney sections were stained with the antibody in parallel to the choroid plexus as positive controls.

**Table 1. Comparison of immunizing peptides and corresponding human epitope**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Species</th>
<th>Amino Acid Sequences</th>
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<tbody>
<tr>
<td>AQP1</td>
<td>Rat</td>
<td>GQQVEYDLLADDINSVEMKPK</td>
</tr>
<tr>
<td>AE2</td>
<td>Human</td>
<td>CEGVDEYENMPV</td>
</tr>
<tr>
<td>rb2NCBE</td>
<td>Rat</td>
<td>IESRKEKKSADSGGVYRTCTL</td>
</tr>
<tr>
<td>NBCn1</td>
<td>Human</td>
<td>EDPSKKYMDAETSL</td>
</tr>
<tr>
<td>rb1NCBE</td>
<td>Human</td>
<td>DNSKEKSSRFPSKSSPS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DNSKXKSSFPSSKXIES</td>
</tr>
</tbody>
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AQP1, aquaporin-1; AE2, Cl\(^{-}\)/HCO\(_3\)\(^{-}\) exchanger; rb, rat brain; NCBE, Na\(^{+}\)-dependent Cl\(^{-}\)/HCO\(_3\)\(^{-}\) exchanger; NBCn1, Na\(^{+}\)-HCO\(_3\)\(^{-}\) cotransporter. Interspecies differences in amino acids are shown in bold.
The AQP1 labeling of the choroid plexus epithelium was primarily apical, although there was distinct but less intense staining of the basolateral plasma membrane domain (Fig. 2A). The AQP1 labeling was readily prevented by preabsorbing the antibody with the immunizing peptide, as shown in Fig. 2B. With less diluted antibody, endothelial labeling was observed as well (Fig. 2C). Human kidney sections were stained in parallel to the choroid plexus as positive controls and displayed immunolabeling of the thin ascending limbs of Henle’s loop (Fig. 2D) and of the apical and basolateral membrane domains of proximal tubules (Fig. 2E). The capillaries of renal corpuscles were also labeled.

Fig. 1. Immunolocalization of the Na\(^+\)-K\(^+\)-ATPase to the human choroid plexus. A: semithin sections of formaldehyde-fixed human choroid plexus were labeled with an antibody against the \(\alpha_1\)-subunit of the Na\(^+\)-K\(^+\)-ATPase. Vent, 3rd ventricle; Int, interstitium; Ep, epithelium. B: sections of human kidney were stained in parallel to the choroid plexus to serve as positive control. TAL, thick ascending limbs of Henle’s loop; ThL, thin limbs of Henle’s loop; CD, collecting ducts; VR, vasa recta. Bars indicate 50 \(\mu\)m.

Fig. 2. Immunolocalization of aquaporin (AQP) 1 to the human choroid plexus. A: human choroid plexus sections were labeled with an anti-AQP1 antibody. B: a similar section was incubated with the same antibody dilution after overnight preabsorption by the immunizing peptide. C: human choroid plexus was stained with less diluted primary antibody. Cap, capillary. Human kidney sections were stained in parallel to the choroid plexus sections to serve as positive control. D: immunostaining in the renal inner medulla. E: staining in the renal cortex. ReCo, renal corpuscles; PxT, proximal tubules; BIV, blood vessel. Bars indicate 50 \(\mu\)m.
Immunolocalization of NKCC1 and NHE1 to the human choroid plexus. Both the anti-NH2-terminal and anti-COOH-terminal antibodies localized NKCC1 to the human choroid plexus (Fig. 3, A and C, respectively). The labeling was primarily observed corresponding to the apical plasma membrane domains of the epithelial cells. However, weak nuclear and cytosolic labeling was observed with the anti-NH2-terminal antibody (Fig. 3A). Sections of human kidney stained in parallel to the choroid plexus also stained with the anti-NH2-terminal antibody, as shown in Fig. 3B. The labeling was most intense apically in the collecting ducts of the inner medulla. Immunolabeling of the renal cortex with an anti-NHE1 antibody revealed basolateral staining in distal tubules and collecting ducts (Fig. 3D), whereas there were no NHE1 immunoreactivity in the choroid plexus (Fig. 3E).

Immunolocalization of NCBE to the human choroid plexus with two antibodies. Figure 4A, left, demonstrates that the anti-rb1NCBE antibody recognizes the immunizing peptide by immunoblotting. Furthermore, labeling of MDCK cells revealed that the antibody reacts with proteins expressed by both rb1NCBE- and rb2NCBE-transfected cells, but not with protein of untransfected MDCK cells. The cellular labeling was visualized in the plane of the nuclei. It is noted that the labeling seemed closer associated with the plasma membrane domain in rb1NCBE-transfected cells than in rb2NCBE-transfected cells. The anti-rb2NCBE antibody also recognizes the corresponding immunizing peptide by immunoblotting (Fig. 4B, left). The anti-rb2NCBE antibody did not react with proteins of rb1NCBE-transfected cells or untransfected cells. However, the antibody did recognize proteins of the rb2NCBE-transfected cells. Again, the anti-NCBE immunoreactivity was observed mainly intracellularly.

The two anti-NCBE antibodies were then applied to localize the proteins in the human choroid plexus. Figure 4C shows the labeling using the rb1NCBE of the basolateral plasma membrane domain of the choroid plexus epithelium. The basal part of the cell seems more intensely stained than the lateral part. In Fig. 4D, the anti-rb2NCBE antibody was applied and revealed a similar staining pattern. As shown in Fig. 4E, preabsorption with the immunizing peptide prevented anti-rb1NCBE labeling. Peptide preabsorption also prevented rb1NCBE labeling (data not shown).

Immunolocalization of AE2, NBCn1, and NBCe2 to the human choroid plexus. Figure 5A demonstrates that AE2 immunolabeling was restricted to the basolateral plasma membrane domain of the choroid plexus epithelial cells. Also, NBCn1 staining was observed corresponding to the basolateral domain (Fig. 5B). The labeling seemed more intense along the basal than the lateral part of this domain. As shown in Fig. 5C, preabsorbing the antibody with the immunizing peptide
prevented labeling. In particular areas of the same human choroid plexus, the NBCn1 labeling was observed at the apical plasma membrane domain (Fig. 5D). This labeling was also abolished by peptide preabsorption, and no basolateral labeling was observed in these areas. The area with apical NBCn1 staining was estimated to cover 10% of the IV ventricle choroid plexus. Staining of human choroid plexus with antibodies did not reveal NBCe2 immunoreactivity, although human kidney controls and mouse choroid plexus did label with the antibody (data not shown).

**DISCUSSION**

In this study, we aimed to localize transport proteins that are thought to play major roles in the CSF formation by the choroid plexus. A summary of the findings is shown in Fig. 6. Similar studies have previously been undertaken using rodent tissue, revealing almost identical localization of the selected transporters.

The Na\(^+\)-K\(^+\)-ATPase was first demonstrated in human choroid plexus by enzyme histochemistry (24). Interestingly, the
ouabain-inhibitable and K⁺-dependent ATPase activity was detected at the basolateral surface. To our knowledge, there are no other reports to support this finding. In contrast, every functional and immunohistochemical animal study since then, as well as the present report on human tissue, has localized the Na⁺-K⁺-ATPase to the apical plasma membrane of the choroid plexus epithelium (20, 23). Thus the vast majority of evidence from studies on rodents lead to the current concept that the Na⁺-K⁺-ATPase is driving the secretion of CSF by pumping Na⁺ and net positive charge directly in the ventricular cavities. This creates the electrical gradient for Cl⁻ and HCO₃⁻ from the epithelial cell to the CSF.

The Na⁺ transporter, NKCC1, seems also to be mainly associated with the apical plasma membrane in the human choroid plexus. This is in line with reports on the rodent choroid plexus (30, 44) and a recent study of human choroid plexus (11). Interestingly, one antibody also revealed intracellular immunoreactivity. This was also observed in the referred work by Johanson and coworkers on human choroid plexus (11). It remains uncertain whether this staining represents an intracellular pool of NKCC1 to be mobilized, as observed for the renal NKCC2 protein (22), or merely reflects unspecific labeling.

The NKCC inhibitor, bumetanide, inhibited Na⁺ secretion, thus indicating that NKCC1 supplies the CSF with Na⁺ and at the same time supplies the CSF with K⁺ to sustain the apical Na⁺-K⁺-ATPase (2, 14). In contrast, the same inhibitor was applied to show the involvement of NKCC2 in regulatory volume increase after exposure to hypertonic media, suggesting an inward transport under such conditions (44). The driving forces for NKCC1 transport can be estimated based on the Nernst equation and previously reported concentrations of Na⁺, K⁺, and Cl⁻ inside rat choroid plexus cells and in the CSF (26). The high intracellular concentration of Na⁺ (and Cl⁻) and the relatively low K⁺ concentration in CSF would result in an outward transport by NKCC1 in contrast to all other epithelia expressing this transporter. Despite the fact that minor changes in the ionic concentrations would change the net direction of transport, the aforementioned effect of bumetanide on CSF secretion in vivo provides compelling evidence for significant outward transport through NKCC1.

Nielsen and coworkers (27) showed that AQP1 was expressed in the apical plasma membrane in large quantities in the rat choroid plexus and that it was also localized to the basolateral membrane and to endothelia, although in less abundance. In contrast to earlier studies on the human choroid plexus reporting only apical immunoreactivity (8, 19), we find an identical AQP1 labeling pattern in humans and rodents. The finding is especially interesting considering the lack of other

Fig. 5. Immunolocalization of Cl⁻/HCO₃⁻ exchanger (AE2) and Na⁺-HCO₃⁻ cotransporter (NBCn1) to the human choroid plexus. A: human choroid plexus sections were labeled with an anti-AE2 antibody. B: choroid plexus sections were stained with an anti-NBCn1 antibody. C: a similar section was incubated with the same antibody dilution after overnight preabsorption by the immunizing peptide. D: one region of the human choroid plexus section shown in B stained differently with the anti-NBCn1 antibody. Bars indicate 50 μm.
water-transporting aquaporins in a tissue with such high secretory rate (31). Although water may pass paracellularly from the blood side to the CSF, it is feasible that the transcellular water transport occurs mainly through basolateral and apical AQP1 in humans and rodents. Both processes would be driven by the relative luminal hyperosmolarity and may be very similar to the transport processes of the renal proximal tubules. Both of these tissues displayed greatly reduced transepithelial water flux in AQP1 knockout mice, even though compensatory mechanisms and altered gradients seem to partially counteract for the lack of AQP1 (28, 29, 35).

NCBE is a DIDS-sensitive NaHCO₃ importer that likely also extrudes Cl⁻ (42). Similarly to the current localization for the human tissue, it was found to be highly expressed in the basolateral membrane of rat and mouse choroid plexus epithelium (32). It was speculated that NCBE could be a major Na⁺ entry route in the choroid plexus epithelium, since the secretion of Na⁺ (proportional to the production of CSF) is not only sensitive to basolateral pH but also toward the HCO₃⁻ concentration (9) and is inhibited by basolateral application of the inhibitor DIDS (21). Recently, such DIDS-sensitive Na⁺- and CO₂/HCO₃⁻-dependent base uptake was demonstrated in isolated rat choroid plexus (3).

The anti-rb1NCBE antibody clearly recognizes both forms of NCBE when expressed in culture cells, whereas the anti-rb2NCBE antibody specifically binds the rb2NCBE form. This may well be explained by the overlap in sequences between the two COOH termini. Although the entire length of the rb2NCBE peptide is specific to the COOH terminal of rb2NCBE, the rb1NCBE peptide is not entirely specific to rb1NCBE. Actually, the first 14 and the last amino acid of this peptide are also found near the COOH terminal of rb2NCBE, and only two amino acids are thus different from rb2NCBE. Interestingly, the rb2 form of NCBE seemed to be largely retained within cytosolic structures when analyzed in transfected MDCK cells (and in HEK293 cells, not shown). This was found with both anti-COOH-terminal antibodies and contradicts the previously described subcellular distribution of NCBE in transgenic 3T3 cells (7). However, in the present report, both of our antibodies clearly stained the basolateral plasma membrane in human choroid plexus, as also observed in the native rat and mouse tissue by immunogold electron microscopy (32). Possibly, the rb2NCBE form needs accessory proteins expressed by the choroid plexus to obtain effective plasma membrane trafficking. Again, this contradicts the suggestion by the referred study by Giffard et al. (7) that rb2NCBE was more closely associated with the plasma membrane than rb1NCBE because of the presence of a PDZ domain of rb2NCBE. Further studies are clearly warranted to clarify this issue.

In other epithelia, NHE1 is involved in setting intracellular pH or maintaining cell volume, rather than participating in transepithelial Na⁺ movement. Nevertheless, application of amiloride to the blood side of the choroid plexus was repeatedly shown to inhibit Na⁺ flux in the CSF (5, 25). Thus NHE was suggested as a major Na⁺ entry route in the choroid plexus epithelium. Interestingly, amiloride also abolished the HCO₃⁻-induced increase in transepithelial Na⁺ flux (26), suggesting that an NHE mediated Na⁺ entry for the enhanced secretion. In contrast, an in vitro study found that amiloride has little effect on Na⁺-dependent pH recovery in the choroid plexus in the presence of CO₂/HCO₃⁻ (21), suggesting that the Na⁺/H⁺ exchanger plays a minor role in maintaining the intracellular pH in these cells. Although NHE1 mRNA and amiloride-sensitive Na⁺-dependent acid extrusion have been demonstrated in the choroid plexus in the absence of CO₂/HCO₃⁻ (12), the NHE1 protein has not been detected by antibody methods (1). In the present study, we fail to uncover NHE1 immunoreactivity in the human choroid plexus despite the positive staining in the renal control tissue. It is of some importance to confirm the molecular nature of this transporter possibly by applying several different anti-NHE antibodies to tissue sections or by studying the effect of amiloride on CSF formation in NHE1 knockout mice. Furthermore, the NCBE and NBCn1 should be tested systematically for amiloride sensitivity.

The AE2 is normally an epithelial base extruder and is involved in HCO₃⁻ reabsorption in, e.g., the distal renal tubules and collecting ducts. With the basolateral localization in the choroid plexus that we also found in the human tissue, AE2 is not likely to participate in HCO₃⁻ secretion but may well support apical Cl⁻ secretion by loading this ion in the cells from the basolateral side, as suggested by the effect of basolateral DIDS on transepithelial Cl⁻ flux and CSF formation (6). AE2 may also serve cell volume regulatory functions in concert with the NHE1 or protect the cells against alkalization.

NBCn1 was, like AE2 and NCBE, localized to the basolateral membrane of the human choroid plexus. This was also reported in rodents in an earlier study (32). Bouzinova et al. (3) showed that a large fraction of the pH recovery from acid load was mediated by DIDS-insensitive NaHCO₃ cotransport. These results together with the DIDS insensitivity of NBCn1 is...
suggestive of a major role in protection of the choroid plexus epithelium against acidification rather than sustaining apical Na\(^+\) and HCO\(_3\)\(^-\) secretion. The occasional apical immunoreactivity may unbalance normal regional differences in choroid plexus acid/base regulation with both apical or basolateral NBCn1 forms, as described in kidney tubules (33, 41). Alternatively, the labeling could represent cross-reactivity of the antibody with other membrane proteins. Hence, the epithelial cells of the choroid plexus express several acid/base transporters at the basolateral surface, and this may indicate that many distinct such mechanisms are needed to meet challenges such as systemic acid/base disturbances. Indeed, the cells seem capable of maintaining nearly normal intracellular pH despite acidosis and alkalosis (26).

The intracellular pH value in the choroid plexus is not well enough established. Our in vitro data on intracellular pH in rat choroid plexus by fluorescence imaging (BCECF) indicates a resting intracellular pH of 7.38 in the presence of CO\(_2\)/HCO\(_3\)\(^-\) (3). This is quite different from the reported intracellular pH of 7.05 by the in vivo [\(^{14}\)C]methionine method (26) but relatively close to the intracellular pH value of 7.3 obtained with the benzoxate method on primary cultures (21). In our hands, there is only a small chemical gradient for HCO\(_3\)\(^-\) in the cell, and the inward Na\(^+\) gradient would determine the direction and turnover of NaHCO\(_3\) transporters even under acid/base disturbances. Thus the basolateral NBCn1 and NCBE are most likely to transport inward.

The electrogenic NaHCO\(_3\) cotransporter from rat and mouse choroid plexus, NBCe2, could not be found in the human choroid plexus. The antibody was directed against a large fraction of the predicted intracellular human COOH terminal. The lack of NBCe2 immunoreactivity may rely either on the actual absence of NBCe2 from the human tissue (thereby representing the only known molecular difference between humans and rodents) or on the expression of masked or alternatively spliced COOH terminals of the human NBCe2, which is not recognized by the antibody.

The quite similar distribution of transporters in the human and rodent choroid plexus encourage further investigations of this fascinating epithelium. Hence, studies of rodent choroid plexus transporters and CSF formation would seem highly relevant for human physiology as well. During hydrocephalus and brain edema, the CSF production by the choroid plexus is reduced, e.g., measured as decreased Cl\(^-\) secretion (16). In a recent review, Weaver and colleagues (43) suggested that the net transport direction in hydrocephalus even may be reversed. Hence, it would be of high importance to define any molecular changes underlying this functional change in the choroid plexus as changes in abundance or localization of, e.g., the Na\(^+\)-K\(^+\)-ATPase. Such work might enable the targeted development of drugs to ameliorate states of increased water contents in the brain parenchyma or in the CSF.

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