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Expression of the non-erythroid Rh glycoproteins in mammalian tissues

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Abstract

A novel family of proteins, the Mep/AMT/Rh glycoprotein family may mediate important roles in transmembrane ammonia transport in a wide variety of single-celled and multicellular organisms. Results from our laboratory have examined the expression of the non-erythroid proteins, Rh B Glycoprotein (Rhbg) and Rh C glycoprotein (Rhcg), in a wide variety of mammalian tissues. In the kidney, Rhbg and Rhcg are present in distal nephron sites responsible for ammonia secretion. In the mouse kidney, Rhbg immunoreactivity is exclusively basolateral and Rhcg immunoreactivity is exclusively apical, whereas in the rat kidney Rhcg exhibits both apical and basolateral expression. Chronic metabolic acidosis increases Rhcg expression in the outer and inner medulla of the rat kidney; these changes, at least in the outer medullary collecting duct, involve changes in total cellular protein expression in both principal and intercalated cell and changes in its subcellular localization. In the liver, Rhbg is present in the basolateral plasma membrane of the perivenous hepatocyte and Rhcg is present in bile duct epithelia. In the gastrointestinal tract, Rhbg and Rhcg exhibit cell-specific, axially heterogeneous, and polarized expression. These patterns of expression are consistent with Rhbg and Rhcg mediating important roles in mammalian ammonia biology. The lack of the effect of chronic metabolic acidosis on Rhbg expression raises the possibility that Rhbg may function either as ammonia sensing-protein or that it may mediate roles other than ammonia transport.

Keywords

Rh glycoprotein; Mouse; Rat; Kidney; Liver; Stomach; Instestinal tract

1. Introduction

A wide variety of evidence suggests that the Mep/AMT/Rh glycoprotein family mediates important roles in ammonia [1] metabolism and transport. Three mammalian members of this

[1]The term ammonia is used to refer to the combination of the two molecular species, NH_3 and NH_4^+. When referring specifically to the molecular species NH_3, we specifically state "NH_3", and when referring to NH_4^+ we specifically state "NH_4^+."

family are known, Rh A glycoprotein (RhAG/Rhag), Rh B Glycoprotein (RhBG/Rhbg) and Rh C Glycoprotein (RhCG/Rhcg). RhAG is an erythroid-specific protein present in the Rh complex of erythrocytes [1,2]. Both heterologous expression studies and studies using erythrocytes from RhAG-null individuals show that RhAG can transport ammonia [3-7]. Rhbg and Rhcg are non-erythroid Rh glycoproteins [8,9]. Functional studies has confirmed that both Rhbg and Rhcg transport ammonia, although different studies have identified differing affinities for the two molecular forms of ammonia, NH_3 and NH_4^+, and whether transport is electroneutral or electrogenic [10-16]. In this review, we will concentrate on the expression of Rhbg and Rhcg in the kidney, liver and gastrointestinal tract.

2. Expression in the mouse kidney

The kidney is a major site of ammonia metabolism and transport. Ammonia is produced by the proximal tubule and is preferentially secreted into the luminal fluid [17,18]. Apical secretion is probably mediated by NHE-3 [19], although a mechanism independent of NHE-3 may be operable [20]. Ammonia is reabsorbed by the medullary thick ascending limb of the loop of Henle predominantly via transport by the apical Na^+-K^+-$2Cl^-$ cotransporter, NKCC-2 [18]. Ammonia is then secreted by the collecting duct into the luminal fluid through mechanisms that appear, in general, to involve net NH_3 transport [18]. Approximately 80% of total urinary ammonia is secreted between the micropuncturable distal tubule and the tip of the collecting duct [17,21].

The initial cloning of Rhbg and Rhcg reported that their mRNA was expressed in the kidney and that they exhibited substantial predicted secondary structural homology with the Mep/AMT family of proteins [8,9]. Thus, it was postulated that Rhbg and Rhcg might be important in renal ammonia metabolism [8,9]. Shortly thereafter, we generated antibodies directed against the cytoplasmic carboxyl-terminus of Rhbg and Rhcg that we used to examine mouse renal Rhbg and Rhcg expression [22]. Immunoblot analysis confirmed that the mouse kidney expressed both proteins. Rhbg exhibited basolateral labeling in the connecting segment (CNT) and in the majority of initial collecting tubule (ICT) and cortical collecting duct (CCD) cells. In the outer medullary collecting duct (OMCD) and inner medullary collecting duct (IMCD) only a subpopulation of cells exhibited basolateral immunoreactivity. Essentially similar findings were reported by others in the rat kidney [23]. Colocalization of Rhbg with cell-type specific markers demonstrated Rhbg immunoreactivity in CNT cells, A-type intercalated cells, non-A, non-B cells and in CCD and ICT principal cells. In the ICT and CCD, A-type intercalated cells, but not B-type intercalated cells, expressed basolateral Rhbg immunoreactivity. In the OMCD and IMCD, only intercalated cells exhibited Rhbg immunoreactivity. Rhcg was expressed in the same epithelial cells, with the exception that mouse OMCD principal cells expressed Rhcg, but did not express detectable Rhbg. RhCG immunoreactivity was apical, thereby complementing the basolateral Rhbg expression. These findings suggested that Rhbg and Rhcg mediate cell-specific roles in ammonia transport and/or signaling.

3. Functional characterization of collecting duct ammonia transport

The observation of ammonia transporter family members in apical and basolateral membranes of collecting duct cells suggested that they would contribute to transepithelial ammonia secretion. Several studies have shown that collecting ducts secrete ammonia, and that the rate of secretion parallels the transepithelial NH_3 gradient, and is independent of the transepithelial NH_4^+ gradient [18,24]. Although the Na^+-K^+-$2Cl^-$ cotransporter, NKCC1, is present in the collecting duct, it does not contribute significantly to ammonia secretion [25]. Thus, ammonia secretion involves net NH_3 transport in parallel with active H^+ secretion. Net NH_3 transport can indicate either passive NH_3 diffusion across lipid bilayers, facilitated NH_3 transport or NH_4^+/H^+ exchange.

We examined whether collecting duct ammonia transport involved passive lipid-phase diffusion or specific transport activities by reasoning that the rate of diffusive transport would be proportional to the ammonia concentration, whereas transporter-mediated transport would exhibit saturable kinetics [26]. To examine the mechanisms of collecting duct ammonia transport we used the mIMCD-3 collecting duct cell line grown on permeable support membranes, enabling separate apical and basolateral plasma membrane domains, and we quantified uptake of the ammonia analog, [^{14}C]methylammonia ([^{14}C]MA). Basolateral MA transport exhibited both diffusive and transporter-mediated components. Transporter-mediated uptake predominated at concentrations below ~7.0 mM, exhibited a K_m for MA of ~4.6 mM and was competitively inhibited by ammonia with a K_i of ~2.1 mM. This basolateral transport activity was not mediated by Na^+-K^+-ATPase, Na^+-K^+-$2Cl^-$ cotransporter, K^+ channels or KCC proteins, and did not involve Na^+ or K^+. Altering membrane potential did not alter transport, consistent with electroneutral transport. Changing the H^+ gradient altered transport in a pattern consistent with either NH_4^+/H^+ exchange or facilitated NH_3 transport. Finally, mIMCD-3 cells expressed basolateral Rhbg immunoreactivity. Thus, the mIMCD-3 collecting duct cell exhibits a basolateral transport activity consistent with facilitated NH_3 transport or NH_4^+/H^+ exchange and likely to be mediated by Rhbg.

We then examined apical ammonia transport [27]. Apical MA transport exhibited both diffusive and saturable, transporter-mediated kinetics. The apical transport activity had a K_m of ~7.0 mM and ammonia was a competitive inhibitor with a K_i of ~4.3 mM. Transport activity was bidirectional, linked to H^+ gradients, unaltered by membrane voltage, did not involve Na^+ or K^+, and was not mediated by H^+-K^+-ATPase, Na^+-K^+-AT-Pase or Na^+/H^+ exchange. Finally, mIMCD-3 cells expressed apical Rhcg. These results identify that the renal collecting duct mIMCD-3 cell has an apical transport activity consistent with facilitated NH_3 transport or NH_4^+/H^+ exchange, and possibly mediated by Rhcg.

Thus, the major components of both apical and basolateral ammonia transport across the mIMCD-3 collecting duct cell is via specific, transporter-mediated mechanisms likely to involve Rhbg and Rhcg. The lower affinity of the apical transporter is consistent with luminal ammonia concentrations being higher than interstitial ammonia concentrations. Moreover, the affinity of Rhcg for ammonia is less than that of Rhbg [10]. The identification that the apical and basolateral transport activities were compatible with net NH_3 transport,

either facilitated NH_3 transport or NH_4^+/H^+ exchange, is consistent with findings that bacterial ammonia transporter family member, AmtB, is an NH_3 transporter [28-30]. However, there was trans-stimulation of the apical transport activity, suggesting an NH_4^+/H^+ exchange transport activity which can also function in an NH_4^+/NH_4^+ exchange mode [27]. More important, however, is that collecting duct apical and basolateral ammonia transport occurs via a saturable and inhibitable, transporter-mediated mechanism.

4. Localization of Rhbg and Rhcg in the rat kidney

Because a substantial component of studies examining ammonia metabolism has been performed in the rat, we examined rat renal Rhbg and Rhcg expression [31]. Similar to others [23, 32], we confirmed rat renal expression of mRNA and protein for both Rhbg and Rhcg. Rhbg and Rhcg immunoreactivity in the rat kidney was similar to that observed in the mouse [22], with one significant difference, that rat renal epithelial cells expressing RhCG immunoreactivity expressed both apical and basolateral RhCG immunoreactivity [31]. Thus, at least in the rat, Rhcg might contribute to both apical and basolateral ammonia transport.

5. Effect of chronic metabolic acidosis on the rat renal Rhbg and Rhcg

We then examined the effects of chronic metabolic acidosis on rat renal Rhbg and Rhcg expression [31]. Chronic metabolic acidosis was induced using HCl ingestion for 1 week; control animals were pair-fed. After 1 week, rats exhibited mild metabolic acidosis and had substantial increases in urinary ammonia excretion.

Chronic metabolic acidosis was associated with several changes. Rhcg protein expression was increased significantly in both the outer and inner medulla. OMCD and IMCD intercalated cells protruded into the tubule lumen and had a sharper, more discrete band of apical Rhcg immunoreactivity, as compared to a flatter cell profile and a broader RhCG band in control kidneys. Rhcg mRNA expression in the outer and inner medulla was not significantly altered, suggesting the increased Rhcg protein expression involved post-transcriptional regulation. Renal cortical Rhcg protein expression and immunoreactivity were not significantly altered. These findings suggest that chronic metabolic acidosis increases the medullary shunting of ammonia through mechanisms that include changes in Rhcg expression.

Renal Rhbg protein and mRNA expression were unchanged in the cortex, outer and inner medulla in response to chronic metabolic acidosis, and we observed no changes in Rhbg immunolabel [31]. This lack of change, combined with observation that genetic ablation of Rhbg in the mouse does not detectably alter renal ammonia metabolism [33], raises the possibility that Rhbg expression is not essential for renal ammonia metabolism.

6. Changes in the subcellular localization of Rhcg in response to chronic metabolic acidosis

Changes in the subcellular localization of ion transporters are a common regulatory mechanism involved in collecting duct transport. Accordingly, we examined the effect of chronic metabolic acidosis on the subcellular localization of Rhcg in the OMCD in the inner

stripe [34]. We used immunogold electron microscopy and morphometric analyses of RhCG expression.

Under basal conditions, Rhcg was expressed in the apical plasma membrane, the basolateral plasma membrane and in subcellular compartments in both the intercalated cell and the principal cell [34]. Intercalated cell Rhcg expression was greater than in the principal cell, consistent with observations by light microscopy [22,32]. Chronic metabolic acidosis increased intercalated cell apical plasma membrane Rhcg expression approximately fourfold. Total cellular Rhcg in the intercalated cell increased significantly, but only by ~30% above control levels. The quantitatively predominant mechanism was an increase in the proportion of total cellular Rhcg that was present in the apical plasma membrane. Under control conditions, 20% of Rhcg was in the apical plasma membrane, and in chronic metabolic acidosis this increased ~3-fold to 58%. There was an equivalent decrease in the proportion of total cellular Rhcg in the intracellular compartment. Thus, chronic metabolic acidosis increased apical plasma membrane Rhcg expression through two mechanisms, increased total cellular Rhcg and a relative redistribution of Rhcg from intracellular sites to the apical plasma membrane, and redistribution was the quantitatively greater mechanism.

Chronic metabolic acidosis also altered principal cell Rhcg expression [34]. Apical plasma membrane Rhcg increased approximately fourfold, similar to that observed in intercalated cells. Total cellular Rhcg increased approximately 2.5-fold, contributing the majority of the increase in apical Rhcg expression. Apical plasma membrane Rhcg increased from 20% to 32% of total cellular Rhcg, and the proportion of RhCG present in the intracellular compartment decreased by a similar amount. Thus, changes in both total cellular expression and the subcellular localization contribute to increased apical plasma membrane expression in the principal cell, but, in contrast to the intercalated cell, the increase in total cellular expression is the quantitatively predominant mechanism. The cellular mechanisms regulating Rhcg expression may differ in the OMCDi intercalated and principal cell.

Chronic metabolic acidosis also increased principal cell basolateral Rhcg expression. This increase paralleled the increase in total cellular Rhcg expression, and did not appear to involve changes in the subcellular distribution of Rhcg. The mechanism(s) regulating principal cell basolateral Rhcg expression appear to differ from those regulating apical expression in the intercalated and principal cell.

7. Rhbg and Rhcg expression in liver

The liver is critically important for normal ammonia metabolism. If the liver does not adequately metabolize ammonia, whether as a result of acute or chronic liver disease, portasystemic shunting, or because ammonia production exceeds hepatic ammonia metabolic capacity, hyperammonemia can develop and can lead to encephalopathy. There are two ammonia-metabolic pathways in the liver [35]. Periportal and midzonal hepatocytes metabolize ammonia through the urea cycle and produce urea. This is a high-capacity, low-affinity pathway, with an affinity for ammonia of ~3600 μM [36]. Perivenous hepatocytes metabolize ammonia to glutamine; this is a low-capacity, high-affinity pathway with ammonia affinity of ~110 μM [36].

We showed that Rhbg is specifically expressed in the sinusoidal membrane of the perivenous hepatocyte [37]. This localization was confirmed using histologic identification of the central vein and by colocalizing Rhbg with glutamine synthetase, the rate-limiting enzyme for perivenous hepatocyte ammonia metabolism. These observations suggest that Rhbg may be involved in high-affinity hepatic perivenous hepatocyte ammonia metabolism. The observation that genetic absence of Rhbg does not cause hyperammonemia [33] either suggests that Rhbg-mediated ammonia transport is not necessary for perivenous hepatocyte ammonia metabolism or that periportal/midzonal hepatocyte ammonia metabolism can maintain normal ammonia metabolism during unstressed states.

The mouse liver also expresses Rhcg [37]. We demonstrated mRNA expression using real-time RT-PCR and protein expression using immunoblot analyses. Immunohistochemical studies identified Rhcg expression, although at low levels, in bile duct epithelial cells. Rhcg expression in this site may explain the high ammonia level in bile [38].

8. Rhbg and Rhcg expression in the gastrointestinal tract

In addition to the liver, the entire gastrointestinal tract is an important site for ammonia metabolism. Our studies identified Rhbg and Rhcg expression throughout the mouse intestinal tract [39]. In the stomach, both Rhbg and Rhcg are expressed in the fundus and forestomach. In the forestomach, all nucleated squamous epithelial cells expressed Rhbg, whereas only the stratum germinativum expressed Rhcg. In the fundus, zymogenic cells expressed apical Rhbg and basolateral Rhcg; parietal and mucous cells did not express detectable Rhbg and Rhcg. In the duodenum, jejunum, ileum and colon villous epithelial cells, but not mucous or crypt cells, expressed Rhbg and Rhcg, with apical Rhcg and basolateral Rhbg immunoreactivity. Thus, Rhbg and Rhcg may function cooperatively in gastrointestinal tract ammonia transport.

9. Conclusion

Rhbg and Rhcg are widely expressed in mammalian tissues important in ammonia metabolism. In the kidney, Rhbg and Rhcg are expressed in distal nephron sites critically important for ammonia secretion, and Rhcg expression is regulated by chronic metabolic acidosis. This regulation involves multiple levels of control, including post-transcriptional regulation of protein expression and changes in subcellular localization. Rhbg and Rhcg are also widely expressed in both the liver and intestinal tract, suggesting that these proteins may play important roles in enterohepatic ammonia metabolism.

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