Evidence for the Existence of a Sodium-dependent Glutathione (GSH) Transporter

EXPRESSION OF BOVINE BRAIN CAPILLARY mRNA AND SIZE FRACTIONS IN XENOPUS LAEVIS OOCYTES AND DISSOCIATION FROM γ-GLUTAMYLTRANSEPTIDASE AND FACILITATIVE GSH TRANSPORTERS*

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Our laboratory previously has shown apparent carrier-mediated glutathione (GSH) uptake across the blood-brain barrier (BBB) in two animal models. In the present study, when Xenopus oocytes were injected with bovine brain capillary mRNA expression of intact GSH, uptake was observed after 3 days. When total mRNA was converted to cDNA and subfractionated with subsequent cRNA injection into oocytes, three distinct fractions (5, 7–8, and 11–12) expressed carrier-mediated intact GSH transport. Northern blot analysis established that these fractions (5, 7–8, and 11–12) expressed carrier-mediated intact GSH transport. Our laboratory previously has shown apparent carrier-mediated glutathione (GSH) uptake across the blood-brain barrier (BBB) in two animal models. In the present study, when Xenopus oocytes were injected with bovine brain capillary mRNA expression of intact GSH, uptake was observed after 3 days. When total mRNA was converted to cDNA and subfractionated with subsequent cRNA injection into oocytes, three distinct fractions (5, 7–8, and 11–12) expressed carrier-mediated intact GSH transport. Northern blot analysis established that these fractions (5, 7–8, and 11–12) expressed carrier-mediated intact GSH transport. In conclusion, we have identified three distinct sized transcripts from bovine brain capillary mRNA which express GSH transport: one fraction which can be dissociated unequivocally from both GGT and RcGshT for the first time and which may account for uptake of GSH against its electrochemical gradient at the BBB.

Inherited disorders of GSH metabolism cause severe neurological defects. GSH is a key factor in defense against hydrogen peroxide and other reactive metabolites and also may act as a neuromodulator (1–3). GSH is present in whole brain and in brain endothelium in millimolar levels (4). Endothelial cells, constituting the blood brain barrier (BBB), play a vital role in overall GSH metabolism, although the mechanisms are not clearly understood, especially with respect to the potential role of uptake and the responsible carriers. We recently obtained evidence that GSH transport is present in the BBB in the rat and in the perfused guinea pig brain, which is developmentally regulated (5–7). This transport system differed in substrate specificity from the known neutral amino acid carriers (5, 6).

Uptake of GSH was saturable and was inhibited by organic anions consistent with a carrier-mediated process. Brain perfusion studies further showed transendothelial transport of GSH into the brain and partial inhibition of uptake into endothelium by addition of BSP-GSH (7) and removal of sodium from the perfusion medium. If GSH uptake is to have physiologic significance and therapeutic potential, a driving force is required to overcome the steep electrochemical gradient from plasma to endothelial cell cytoplasm. The previous results support the possible existence of a luminal Na+-dependent GSH transporter for uptake and abluminal transporter for efflux of GSH in brain endothelium. However, in other systems, such as kidney, as well as in brain, it has been argued that GSH uptake does not exist and that nearly all apparent GSH uptake depends on the breakdown of GSH initiated by GGT (8).

Since GGT and GSH transporter(s) are functional at the BBB, we decided to see if these activities could be resolved by size fractionation and oocyte expression and if a Na+-dependent GSH uptake could be demonstrated unequivocally. We have recently cloned two liver transporters and demonstrated that the sodium-independent, BSP-GSH insensitive rat canicular GSH transporter (RcGshT), but not rat sinusoidal GSH transporter (RsGshT), was present in brain (9, 10). Therefore, an additional goal was to determine if a putative sodium-dependent GSH transporter could be separated from RcGshT.

EXPERIMENTAL PROCEDURES

35S-Labeled isotopes (glutathione, 145 Ci/mm; cysteine, 600 Ci/mmol) and [glycine-2-3H]glutathione (1000 Ci/mmol) were obtained from DuPont NEN. Chemicals and buffer reagents were obtained from Sigma. BSP-GSH was synthesized in the laboratory as described previously (9).

RNA Isolation, Size Fractionation, Oocyte Preparation, and Transport—Capillaries from bovine calf brain were isolated according to the method of Triguero et al. (11). Poly(A)1 RNA from bovine brain capillaries and microinjection of mRNA (and cRNA) into state 5 or 6 defolliculated Xenopus oocytes was performed essentially following the protocol described for rat liver in our previous publications (9, 12). The cDNA library was constructed in the plasmid vector pSPORT1, using the Superscript protocol (Life Technologies, Inc.). Briefly, total RNA was isolated from bovine capillary preparation using acid guanidinium thiocyanate method. Purified poly(A)1 RNA was reverse-transcribed

†This work was supported by Veterans Administration medical research funds and National Institutes of Health Grants DK30312 and DK48522. Part of this work was presented at the Annual Meeting of the Society of Neuroscience, Nov. 11–16, 1995, San Diego, CA (Kannan, R., Yi, J. R., Tang, D., Li, Y., Zlokovic, B. V., and Kaplowitz, N. (1995) Soc. Neurosci. Abstr. 21, 1428). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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§The abbreviations used are: BBB, blood-brain barrier; GGT, γ-glutamyltranspeptidase; BSP-GSH, sulfobromophthalein-glutathione; RcGshT, rat canicular GSH transporter; RsGshT, rat sinusoidal GSH transporter; HPLC, high pressure liquid chromatography; kb, kilobase(s); DTT, dithiothreitol; SAAM, simulation analysis and modeling.
into cDNA by avian myeloblastosis virus reverse transcriptase and Sal I sites of the vector sPORT1, respectively, and 13 cDNA libraries were obtained, each with approximately 1.0–2.0 × 10^6 transformants. The cDNA inserts in this vector are flanked by T7 and SP6 RNA promoters at the 3’ and 5’ ends, respectively, allowing sense and antisense transcription.

Aliquots (1 μl) of the plasmid pool (20 μl) prepared from each fraction’s cDNA library were used to transform Escherichia coli DH 5α strain. Plasmid DNA was purified from fraction 3–15 transformants and linearized with NotI and transcribed in vitro with T7 RNA polymerase in the presence of GppGpp cap using a protocol supplied with riboprobe transcription system (Promega). The complementary RNAs (cRNAs) were injected into Xenopus oocytes (3 ng/oocyte) which were then analyzed for expression of GSH transport 3 days after injection. Water-injected oocytes served as controls. The activity of individual fractions for GSH uptake was compared with that of total mRNA-injected oocytes under GGT-inhibited (1 mM acivicin, 30 min) or uninhibited conditions. GSH uptake in active fractions was determined in the presence of Na^+ (NaCl medium) or absence of Na^+ (sucrose medium or choline chloride medium). In some experiments, effect of BSP-GSH (2 mM) on GSH uptake in fraction 7 cRNA-injected oocytes was examined by Northern blot analysis. Similarly, Northern blot analysis was also performed with radiolabeled full-length cDNA probe of the cloned rat sinusoidal transporter cDNA (10). Presence or absence of GGT in the isolated active fractions was examined by Northern blot analysis using a full-length human kidney GGT clone kindly provided by Dr. Henry J. Forman (USC School of Pharmacy).

RESULTS

Uptake of GSH by Brain Capillary mRNA-injected Oocytes and Molecular Forms of Uptake—Bovine and guinea pig brain capillary mRNA-injected oocytes expressed uptake of GSH 3 days after injection. Fig. 1 shows the uptake of [35S]GSH in the presence of 10 mM GSH in bovine and guinea pig capillary poly(A)^+ RNA-injected oocytes incubated for 1 h. GSH uptake is expressed as nanomoles/oocyte/h. The 1-h incubation period was chosen from pilot studies on the linearity of uptake as a function of time (not shown), and all subsequent uptake and inhibitory studies were conducted at the linear part of the curve (1 h). To determine the ion requirements of uptake, the studies were performed either in a medium containing NaCl (NaCl medium) or in which NaCl is replaced by sucrose isosmotically (12). The brain capillary mRNA-injected oocytes showed a significant uptake of GSH for both species as compared with water-injected controls (Fig. 1). Replacement of NaCl with sucrose resulted in ~49% and 36% inhibition in uptake in bovine capillary mRNA and guinea pig capillary mRNA-injected oocytes, respectively. The molecular form of uptake of GSH as determined by HPLC (13) was predominately performed by electrophoresing RNAs on 6.7% formaldehyde, 1% agarose gels which was then blotted onto a nylon membrane and hybridized with a 32P-labeled 1.3-kb insert of a subclone of RcGshT cDNA corresponding to nucleotides 1132–2623. Blots were subsequently washed under high stringency. Similarly, Northern blot analysis was also performed with radiolabeled full-length cDNA probe of the cloned rat sinusoidal transporter cDNA (10). Presence or absence of GGT in the isolated active fractions was examined by Northern blot analysis using a full-length human kidney GGT clone kindly provided by Dr. Henry J. Forman (USC School of Pharmacy).
and GGT transcripts. As shown in Fig. 2, 11–12 were examined for the presence or absence of RcGshT brain and in brain capillaries. The active fractions 5, 7–8, and 11 from bovine brain capillaries (not shown). Thus, the organs (10); in the present studies, we also found no RsGshT (2.7 kb) was found only in rat liver and not in brain or other blots probed for RsGshT, the sinusoidal transporter, transcript contain the RcGshT transcript. On the other hand, in Northern blot analysis of fraction 7 (see above, Fig. 2), supporting evidence for the dissociation of fraction 7 from GGT-mediated degradation and resynthesis was obtained in additional studies. Net uptake of GSH in fraction 7 cRNA-injected oocytes was similar under GGT-inhibited conditions (for example, uptake measurements in the presence or absence of acivicin at 0.05 mM GSH (0.17 ± 0.02 and 0.15 ± 0.03 nmol/oocyte/h, respectively) and at 2 mM GSH (1.23 ± 0.11 and 1.16 ± 0.20 nmol/oocyte/h, respectively) were not significantly different from each other). The molecular form of uptake in 35S- and 3H-double-labeled experiments in fraction 7 cRNA-injected oocytes was predominantly intact GSH with both isotopes in the presence or absence of acivicin (Fig. 4), and the ratios of the 35S/3H in GSH peak in natural GSH (93 ± 2%).

Evidence for Multiple GSH Transporters in Brain Capillary mRNA by Size Fractionation Studies—Bovine poly(A)" RNA was converted to cDNA, subjected to size fractionation and library construction, and cDNA prepared from transformants produced from aliquots of each library was injected into oocytes. Fig. 2 shows GSH transport activity expressed by each fraction with 10 mM GSH in the incubation medium. The uptake was highly reproducible when aliquots of plasmid pools of each cDNA size fraction were expressed in two oocyte preparations. Uptake determinations performed with either 1 mM GSH (not shown) or 10 mM GSH in NaCl medium identified three separate fractions expressing intact GSH transport (as confirmed by HPLC). Considering the difference in amount of cDNA versus poly(A)" RNA injected, fractions 5, 7–8, and 11–12 showed 10–25-fold enrichment in expressed activity versus total RNA.

Northern Blot Analysis of RcGshT and GGT Transcripts in Brain Capillaries and Brain Capillary Size Fractions—Organ distribution studies in the rat had previously shown that RcGshT transcript is present in all tissues examined including the brain (9). We now have obtained evidence for the presence of RcGshT in the brain capillaries. Northern blot analysis of mRNA from bovine brain capillaries and rat liver (used as a positive control) identified an identical size single 4.0-kb transcript when hybridized with a 1.3-kb cDNA subclone of RcGshT (not shown). Brain capillary mRNA from the rat and guinea pig also contained the transcript for RcGshT (not shown). Since isolated capillaries likely contain adherent astroglia, this finding cannot be taken as definitive proof that endothelial cells contain the RcGshT transcript. On the other hand, in Northern blots probed for RsGshT, the sinusoidal transporter, transcript (2.7 kb) was found only in rat liver and not in brain or other organs (10); in the present studies, we also found no RsGshT transcript in bovine brain capillaries (not shown). Thus, the above results show that RcGshT transcript is present in whole brain and in brain capillaries. The active fractions 5, 7–8, and 11–12 were examined for the presence or absence of RcGshT and GGT transcripts. As shown in Fig. 2, left inset, among the active fractions 5, 7, and 11, only fraction 5 hybridized with the cDNA probe of RcGshT. RsGshT was not found in brain capillary fractions. Exclusion of GGT-mediated hydrolysis and resynthesis was provided by Northern blot analysis of fraction 7 with a full-length human kidney GGT probe. While transcript for GGT could be detected in whole bovine brain, it was absent in fraction 7 (Fig. 2, right inset). As expected from its known size, GGT transcript was found in fraction 11.

Identification of Na+ Dependence of GSH Transport, Inhibitor Specificity, and Kinetics—Fig. 3 shows GSH uptake at 0.05 mM GSH (Fig. 3A) and 2 mM GSH (Fig. 3B), in oocytes injected with cDNA from fractions 7 and 11. Uptake was studied in NaCl and choline chloride-containing media, and the oocytes were pretreated with acivicin. Fraction 7 showed a significant inhibition in GSH uptake when NaCl medium was replaced by a medium containing choline chloride at both GSH concentrations while fraction 11 did not show any significant difference in uptake in both media. We also confirmed that fraction 5, consistent with the finding that it contained RcGshT (see above), expressed sodium-independent transport (not shown).

BSP-GSH at 2 mM concentration caused a significant inhibition of GSH uptake in fraction 7 cRNA-injected oocytes. Thus, in 1-h incubation experiments in NaCl medium with 0.05 mM and 2 mM GSH, BSP-GSH inhibited GSH uptake by ~90% and 39%, respectively.

In addition to demonstrating the absence of GGT in fraction 7 (see above, Fig. 2), supporting evidence for the dissociation of fraction 7 from GGT-mediated degradation and resynthesis was obtained in additional studies. Net uptake of GSH in fraction 7 cRNA-injected oocytes was similar under GGT-inhibited or uninhibited conditions (for example, uptake measurements in the presence or absence of acivicin at 0.05 mM GSH (0.17 ± 0.02 and 0.15 ± 0.03 nmol/oocyte/h, respectively) and at 2 mM GSH (1.23 ± 0.11 and 1.16 ± 0.20 nmol/oocyte/h, respectively) were not significantly different from each other). The molecular form of uptake in 35S- and 3H-double-labeled experiments in fraction 7 cRNA-injected oocytes was predominantly intact GSH with both isotopes in the presence or absence of acivicin (Fig. 4), and the ratios of the 35S/3H in GSH peak in
cells in the presence or absence of acivicin corrected for spill-over (1.112 and 1.104, respectively) were also very similar to that of the incubation medium (1.091). Furthermore, HPLC analysis of uptake of [35S]cysteine (150 mM unlabeled cysteine in 10 mM DTT) showed that nearly all the radioactivity was associated with cysteine and no conversion to GSH had taken place in the 1-h incubation period (not shown). Thus, breakdown and resynthesis could not account for apparent GSH uptake.

Fig. 5 shows the kineticsof uptake of GSH in oocytes injected with cRNA from fraction 7 versus water controls. Oocytes were injected with water or cRNA, and uptake was carried out 3 days later. The incubation medium (NaCl medium) contained 2 μCi of labeled GSH and varying concentrations of unlabeled GSH, and uptake was studied for 1 h. The data in the open circles represent net uptake after subtraction of the water controls, shown as closed circles. The net data points (mean ± S.E., n = 3) were fitted with SAAM using the Michaelis-Menten equation which showed a high affinity component (inset) with a $K_m$ of $0.40 \pm 0.19 \text{ mM}$ ($V_{max} = 0.57 \pm 0.21 \text{ nmol/oocyte/h}$) and a sigmoid low affinity component with a $K_m$ of $10.8 \pm 3.1 \text{ mM}$ ($V_{max} = 7.66 \pm 0.27 \text{ nmol/oocyte/h}$) and a Hill coefficient of $n = 2$. In view of a predominant sodium-dependent component (Fig. 3), kinetics were not performed in Na+-free medium to establish if the small Na+-independent component in fraction 7 is saturable. This analysis has been postponed until completion of cloning so that more meaningful information can be obtained on the kinetics of the sodium-independent component of the isolated Na+-GSH cotransporter.

**DISCUSSION**

Uptake of GSH in oocytes expressing brain capillary mRNA has been demonstrated in this study for the first time. Three distinct GSH transporter activities have been identified based on size fractionation, one of which corresponds to the previously cloned sodium independent rat canalicular GSH transporter. One of the remaining two GSH transporter activities...
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was found to be Na⁺-dependent and exhibited both high affinity and low affinity GSH transport. This also is the first unequivocal demonstration of a sodium-dependent transporter by expressing its mRNA in a heterologous cell which normally does not express it and therefore provides the strongest evidence to date that sodium-dependent GSH transporter exists.

Because of the widely held view that GSH is broken down by ecto GGT and resynthesized to GSH within the cell (14), we have ensured that GGT (and dipeptidase) mediated breakdown, constituent amino acid uptake and GSH resynthesis were negligible, and uptake of labeled GSH in brain capillary mRNA and size fraction cRNA-injected oocytes was due to its transport in intact form. This was achieved by several approaches. (a) GSH transport studies were carried out under conditions of GGT inhibition by acivicin. (b) Molecular forms of uptake in capillary mRNA or cRNA-injected oocytes were determined by HPLC to be predominantly GSH with or without GGT inhibition. (c) In uptake experiments with oocytes expressing the novel sodium-dependent GSH transporter, double-labeled GSH was employed to exclude breakdown and resynthesis: the isotope ratio of GSH taken up was nearly identical with that of the medium in the presence or absence of acivicin. (d) Transport of [³⁵S]cysteine examined under conditions of GSH uptake (1-h incubation, 18°C, NaCl medium, GGT inhibition) showed that radioactivity taken up was predominantly cysteine, and no conversion to GSH was evident by HPLC. (e) Finally, it was unequivocally shown that the fraction expressing Na⁺-dependent GSH transporter did not contain a transcript for GGT in Northern blot analysis when probed with a full-length GGT clone. The existence of Na⁺/GSH cotransport has been suggested from physiological studies in cells or membrane vesicles of the kidney, intestine, and lung (15–17) as well as our own brain perfusion studies (7). However, controversy has surrounded the validity of these observations, others suggesting that even a small fraction of GGT escaping inhibition or impurities in radiolabel could account for the findings as hydrolysis, sodium amino acid co-transport, and intracellular GSH resynthesis (18). Thus, our expression in oocytes of a Na⁺-dependent GSH transport which can be dissociated from GGT unequivocally supports the existence of such a system.

The exact localization of the GSH transporters is not clear at the present time, but some speculations can be made. RcGshT, one of the transporters identified in the brain, is a Na⁺-independent, low affinity, BSP-GSH insensitive GSH transporter. Since its function is as an effluxer under physiological conditions, its presence in the whole brain and brain capillaries would suggest that it is probably different from the luminal brain endothelial GSH transporter, which was shown to be Na⁺-dependent and BSP-GSH sensitive in our in situ brain perfusion studies (7). RcGshT may function to efflux GSH from the endothelial cells of the BBB to the parenchyma. Since astrocytes are known to efflux GSH at a high rate (19), RcGshT may also serve to efflux astrocyte GSH. Support for this view was obtained in our studies confirming GSH transport in cultured neonatal rat astrocytes and demonstrating the presence of RcGshT transcript by Northern blot analysis.²

GSH transport at the BBB can be envisioned to proceed by endothelial uptake at the luminal pole that is Na⁺-dependent. This system has the possibility of being concentrative so that low plasma GSH (10–20 μM) can lead to net accumulation of GSH in endothelial cells, due to the likely coupling to the entry of sodium. At the same time, the GGT-γ-glutamyl cycle could provide another mechanism for handling luminal GSH and maintaining brain GSH homeostasis. The relative importance of these two mechanisms is not known and may depend on species, age, or other factors. Furthermore, redundancy of mechanisms for maintenance of such a vital defense factor in brain would not be surprising.

The apparent GSH transport activity expressed by fraction 11 will need further characterization. Since GGT is present in this fraction, the possibility of breakdown and resynthesis will need to be rigorously evaluated. The molecular form taken up in the presence of acivicin was intact GSH, and cysteine was not incorporated into GSH in oocytes expressing fraction 11.² No hybridization signal was observed when this fraction was probed with RsGshT and RcGshT, which suggests that this is not another family member of either and also that alternate processing is unlikely. Thus, a novel, previously undescribed sodium-independent GSH transporter is suggested.

In summary, we have demonstrated for the first time that mRNA of GSH transporters other than the two we previously have cloned from rat liver exist, indicating that there are multiple GSH transporters which may have cell-specific expression and may govern uptake or efflux of GSH. Also, we have shown for the first time that brain capillaries express a sodium-dependent GSH transporter and that its apparent activity cannot be explained by the commonly held view of the combination of breakdown of GSH, sodium-dependent amino acid uptake, and GSH resynthesis; this provides the strongest evidence heretofore available of the occurrence of a sodium-dependent GSH transporter. Furthermore, the presence of sodium gradient-driven uptake of GSH provides a physiologic driving force for net GSH transport against the electrochemical gradient.

Acknowledgments—The assistance of Aravind Mittur in double label HPLC analysis and Murad OoKhtens, Ph.D., and the mathematical modeling component of the USC Center for Liver Diseases in kinetic analysis is gratefully acknowledged.

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J. Biol. Chem. 1996, 271:9754-9758. doi: 10.1074/jbc.271.16.9754

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