学位論文

Immunoreactivity of urate transporters, GLUT9 and URAT1, is located in epithelial cells of the choroid plexus of human brains

香川大学大学院医学系研究科
医学専攻

植村直哉

Neuroscience Letters 659 (2017) 99–103

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research paper

Immunoreactivity of urate transporters, GLUT9 and URAT1, is located in epithelial cells of the choroid plexus of human brains

Naoya Uemura[a,b], Ryuta Murakami[a,1], Yoichi Chiba[a,1], Ken Yanase[a,b], Ryuji Fujihara[a], Masato Mashima[a,c], Koichi Matsumoto[a], Machi Kawauchi[a], Gotaro Shirakami[b], Masaki Ueno[a,*]

[a] Department of Pathology and Host Defense, Faculty of Medicine, Kagawa University, Kagawa 761-0793, Japan
[b] Department of Anesthesiology, Faculty of Medicine, Kagawa University, Kagawa 761-0793, Japan
[c] Department of Perinatology and Gynecology, Faculty of Medicine, Kagawa University, Kagawa 761-0793, Japan

ARTICLE INFO

Keywords:
Choroid plexus
GLUT9
URAT1
Urate transporter

ABSTRACT

It has been suggested that urate plays a protective role in neurons, while hyperuricemia is correlated with atherosclerosis and cardiovascular disease. However, whether there is a system that directly transports urate into the brain remains to be clarified. In this study, the localization of glucose transporter 9 (GLUT9) and urate transporter 1 (URAT1), which are known to be representative reabsorptive urate transporters, was immunohistochemically examined in autopsied human brains. Immunoreactivity of GLUT9 was observed on the apical side of the cytoplasm of epithelial cells in the choroid plexus and in the cilia of ependymal cells of the human brain. Immunoreactivity of URAT1 was observed on the basolateral side of the cytoplasm of epithelial cells in the choroid plexus. In addition, immunoreactivity of GLUT9 and URAT1 was not observed in microvessels of the human brains. The choroid plexus and renal proximal tubule were similar in having a polarized distribution of these two transporters with the two transporters on opposite membranes, but the two transporters' distribution differs between the choroid plexus and the kidney in terms of which membrane (apical/basal) expresses which transporter. These findings support the hypothesis of the direct transport of intravascular urate into the central nervous system through the choroid plexus.

1. Introduction

A higher serum level of urate, the end product of purine metabolism in humans, has been pointed out to be a risk factor for hypertension, gout, renal diseases, vascular diseases, and metabolic syndrome [1,2]. On the other hand, it has been proposed that urate has possible neuroprotective effects. Urate, a peroxynitrite scavenger, inhibits central nervous system (CNS) inflammation, blood-CNS barrier permeability changes, and tissue damage in a mouse model of multiple sclerosis [3]. A higher serum level of urate has also been shown to be associated with the decreased incidence and slower progression of Parkinson's disease [4,5]. It is known that patients with gout have a lower risk of developing dementia [6]. Accordingly, it is very likely that urate has a neuroprotective effect, probably due to its antioxidant property [7].

GLUT9 was initially reported to transport glucose or fructose [8,9]. In addition, Doblado and Moley [10] reported that GLUT9 may transport both fructose and urate. However, at present, GLUT9 is thought to primarily transport urate [11–13]. Multiple urate transporters in the kidney are involved in the regulation of serum uric acid levels. Renal urate reabsorption is mainly mediated by urate transporter 1 (URAT1) on the apical side of the renal proximal tubular cells, and GLUT9 on the basolateral side [11,14–16]. In addition, the ATP-binding cassette transporter, sub-family G, member 2 (ABCG2), has also been identified as a urate transporter for secretion into tubules [2,16,17]. Thus, the existence of separate transport pathways for urate reabsorption and secretion across the epithelia is indicative of the bidirectional nature of transepithelial urate flux. Recently, the roles of urate in the CNS have been attracting attention. The uric acid concentration in cerebrospinal fluid (CSF) was reported to be 0.25 mg/100 mL [18]. The localization of urate transporters in the CNS remains to be clarified. URAT1 immunoreactivity was reported to be observed in ependymal cells of the mouse brain [19]. In addition, a recent immunohistochemical and in situ hybridization study showed that GLUT9 was localized in ependymal cells, neurons, and capillaries in the murine brain [20]. ABCG2 has been reported to be localized to the blood-brain barrier (BBB) not only in mouse and rat [21,22] but also in human [23,24] brains. In

* Corresponding author at: Department of Pathology and Host Defense, Faculty of Medicine, Kagawa University, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan.
E-mail address: masaueno@med.kagawa-u.ac.jp (M. Ueno).
[1] These authors equally contributed to this study.

http://dx.doi.org/10.1016/j.neulet.2017.09.001
Received 12 July 2017; Received in revised form 30 August 2017; Accepted 1 September 2017
Available online 07 September 2017
0304-3940/

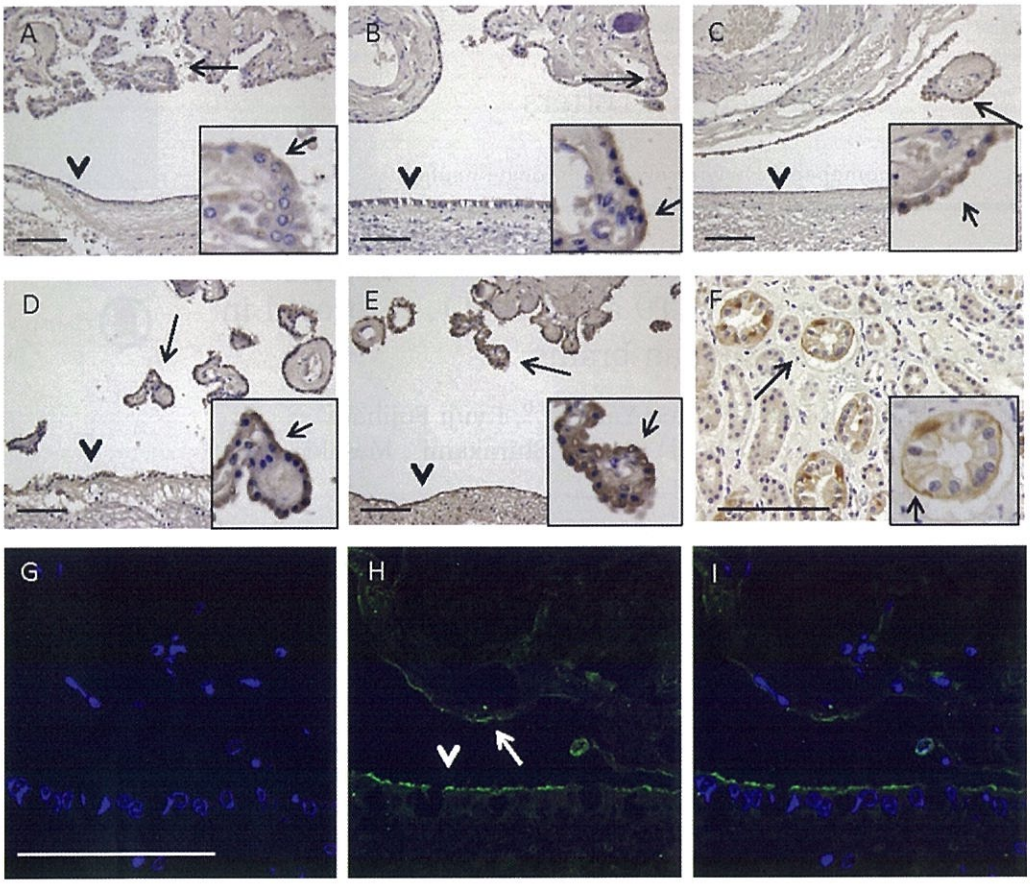

Fig. 1. Immunoreactivity of GLUT9 in sections from 5 human brains (A–E) and one kidney (F), and representative immunofluorescent images (G–I) are shown. Immunoreactivity of GLUT9 is observed in the epithelial cells of the choroid plexus (A–E: arrow), in the ependymal cells (A–E: arrowhead), and in renal proximal tubule cells (F: arrow). Enlarged images in insets indicate that the immunoreactivity is mainly located on the apical side of the cytoplasm in epithelial cells of the choroid plexus (A–E), and in the basal cytoplasmic membrane of renal proximal tubule cells (F: arrow). Immunofluorescent signals of GLUT9 (green) are mainly observed on the apical side of the cytoplasm in epithelial cells of the choroid plexus (H: arrow) and on the apical side of the cytoplasm, especially cilia, of the ependymal cells (H: arrowhead). G shows nuclear stain with TO-PRO-3, and I shows the merged image. Scale bars indicate 100 μm.

addition, ABCG2 was recently shown to be localized in the choroid plexus epithelium as well as capillaries in murine brains [19].

Transporters must be located in cerebral microvessels, epithelial cells of the choroid plexus, and/or ependymal cells to transport intravascular urate into the brain parenchyma. However, it remains to be fully clarified which urate transporters are located in the CNS, especially in the human brain. As the localization of GLUT9 and URAT1, two primary urate transporters, in the human brain remains to be clarified, the localization of GLUT9 and URAT1was immunohistochemically investigated in epithelial cells of the choroid plexus and ependymal cells as well as microvessels, using autopsied human brains.

2. Materials and methods

Human brain samples (n = 5) were obtained at autopsy from 5 patients with or without neurological abnormalities in Kagawa University Hospital, as previously reported [25]. The main diagnosis of each case was established according to the clinical and autopsy findings [25]. This study using human brains was approved by the institutional ethics committee of the Faculty of Medicine, Kagawa University. The brains were fixed in 10% formalin and processed for immunohistochemical examination. The brain samples were embedded in paraffin and sectioned at a 4-μm thickness. The antibodies used in this study were rabbit antibodies for GLUT9 (1:300, ab104623, Abcam, Cambridge, UK) [26], URAT1 (1:1000, LifeSpan BioSciences (LSBio), Seattle, WA, USA), and URAT1 (1:1000, Medical & Biological Laboratories (MBL), Nagoya, Japan) [27]. Before incubation with the antibodies for GLUT9 or URAT1 (MBL), antigen retrieval was performed by heating sections in 10 mM sodium citrate buffer (pH 6) at 95 °C for 20 min or 125 °C for 5 min in a pressure boiler, respectively. Before incubation with the antibodies for URAT1 (LSBio), antigen retrieval was performed by heating sections for 20 min in 1 mM ethylenediaminetetraacetic acid (EDTA) buffer (pH 9). After treatment with hydrogen peroxide and blocking with 2% bovine serum albumin in PBS for 30 min, the sections were incubated with the primary antibodies at 4 °C overnight. Staining was achieved with a Simple Stain kit (Nichirei, Tokyo, Japan) and developed with 3,3′-diaminobenzidine tetrahydrochloride (DAB) and hydrogen peroxide (Nichirei) at room temperature for 5–7 min. The sections were counterstained with hematoxylin. For fluorescent immunostaining, the sections were incubated overnight with a rabbit antibody for GLUT9 (1:300, Abcam) or URAT1 (1:1000, LifeSpan BioSciences), followed by incubation at RT for 60 min in Alexa Fluor 488- or Alexa Fluor 594-conjugated anti-rabbit IgG (1:200, Molecular Probes, Eugene, OR, USA), respectively. The sections were then incubated for 60 min at RT in Monomeric Cyanine Nucleic Acid Stain (TO-PRO-3, Molecular Probes, Eugene, OR, USA), which was diluted to 2.5 μM in PBS. The fluorescent signals were viewed under a confocal microscope (Carl Zeiss LSM700, Oberkochen, Germany). As a control experiment, we performed an identical immunohistochemical procedure with omission of the primary antibody.

3. Results

Immunohistochemical examination using the antibody for GLUT9 showed weak (Fig. 1A–C) or clear (Fig. 1D, E) immunoreactivity in the epithelial cells of the choroid plexus and weak immunoreactivity in the ependymal cells, but not in cerebral microvessels, in all 5 of the human brains (Fig. 1A–E). In addition, very clear immunoreactivity of GLUT9 was observed in the basal cytoplasmic membrane of renal proximal tubule cells (Fig. 1F). Representative immunofluorescent images of GLUT9 in the human brains indicated that the immunoreactivity of GLUT9 was localized on the apical side of the cytoplasm of epithelial cells in the choroid plexus and on the apical side of the cytoplasm of

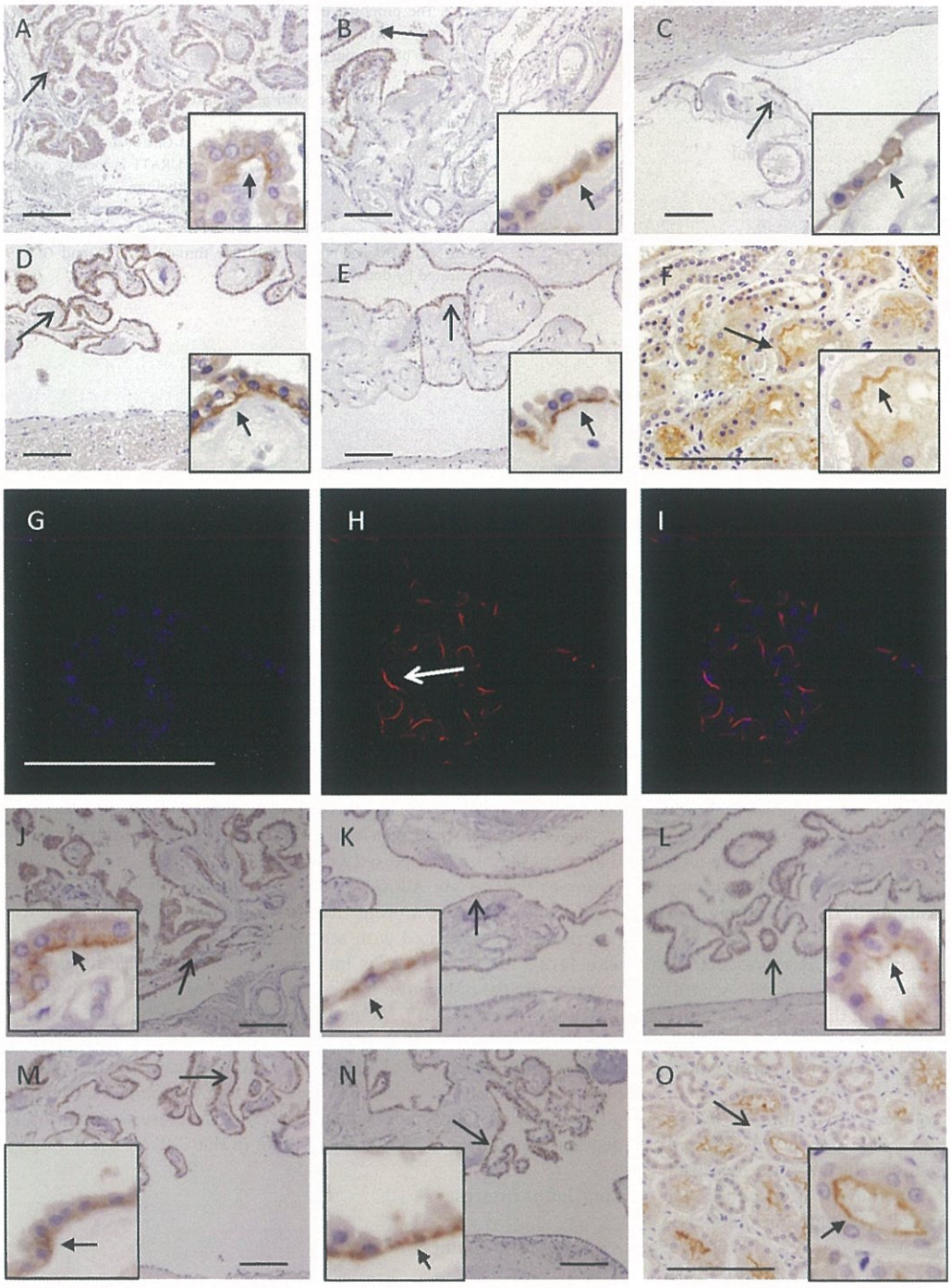

Fig. 2. Immunoreactivity of URAT1 (LSBio) in sections from 5 human brains (A–E) and one kidney (F), and representative immunofluorescent images (G–I) are shown. In addition, immunoreactivity of URAT1 (MBL) in sections from 5 human brains (J–N) and one kidney (O) is shown. Immunoreactivity of URAT1 (LSBio) is observed in the epithelial cells of the choroid plexus (A–E: long arrow) and in renal proximal tubule cells (F: long arrow). Enlarged images in insets indicate that the immunoreactivity is mainly located on the basal side of the cytoplasm in epithelial cells of the choroid plexus (A–E: short arrow), and on the apical cytoplasmic membrane of renal proximal tubule cells (F: short arrow). Immunofluorescent signals of URAT1 (red) are mainly observed on the basolateral side of the cytoplasm in epithelial cells of the choroid plexus (H: long arrow). G shows nuclear stain with TO-PRO-3, and I shows the merged image. In addition, immunoreactivity of URAT1 (MBL) is observed in the epithelial cells of the choroid plexus (J–N: long arrow) and in renal proximal tubule cells (O: long arrow). Enlarged images in insets indicate that the immunoreactivity is mainly located on the basal side of the cytoplasm in epithelial cells of the choroid plexus (J–N: short arrow), and on the apical cytoplasmic membrane of renal proximal tubule cells (O: short arrow). Scale bars indicate 100 μm.

ependymal cells, especially cilia, but not in microvessels (Fig. 1G–I).

Immunohistochemical examination using the antibody for URAT1 (LSBio) showed clear immunoreactivity on the basal or lateral side of the cytoplasm of epithelial cells in the choroid plexus, but not on microvessels, in all 5 of the human brains (Fig. 2A–E). In addition, very clear immunoreactivity of URAT1 (LSBio) was observed on the apical side of the cytoplasmic membrane (brush border) of renal proximal tubule cells (Fig. 2F). Representative immunofluorescent images for URAT1 (LSBio) in the human brains indicated that immunoreactivity of URAT1 was localized on the basolateral side of the cytoplasm of epithelial cells in the choroid plexus (Fig. 2G–I). Immunohistochemical examination using another antibody for URAT1 (MBL) also showed clear immunoreactivity on the basal or lateral side of the cytoplasm of epithelial cells in the choroid plexus, but not on microvessels, in all 5 of the human brains (Fig. 2J–N). Although immunoreactivity of URAT1 was not clear in ependymal cells at the lateral ventricular wall (Fig. 2), that was observed in ependymal cells at the third ventricular wall (data not shown). Very clear immunoreactivity of URAT1 (MBL) was observed on the apical side of the cytoplasmic membrane (brush border) of renal proximal tubule cells (Fig. 2O). Based on these immunohistochemical findings, the proposed distribution of these urate reabsorptive transporters, GLUT9 and URAT1, in the apical/basal membrane of the renal proximal tubule and the choroid plexus epithelial cells is schematically shown in Fig. 3.

4. Discussion

These findings using the human brain indicate that

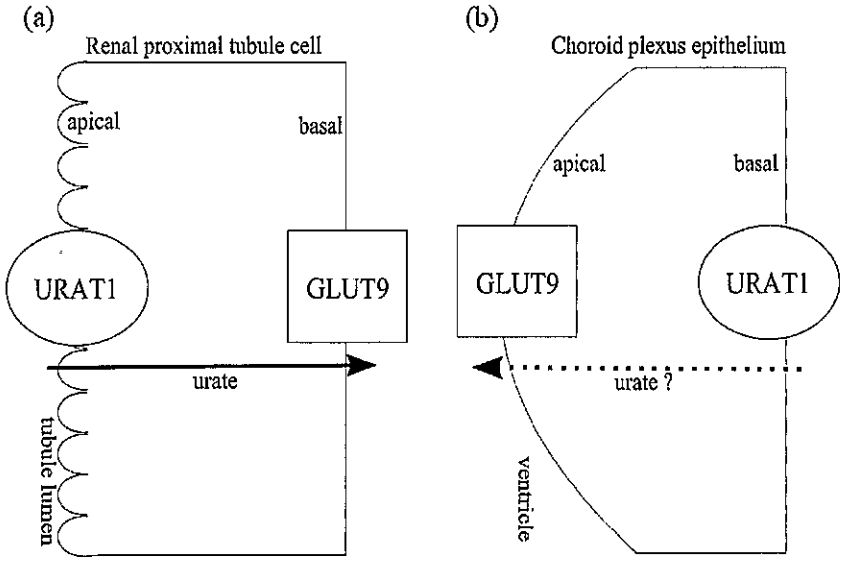

Fig. 3. The proposed immunohistochemical distribution of the two urate reabsorptive transporters, GLUT9 and URAT1, in apical/basal membrane of the renal proximal tubule cell (a) and the choroid plexus epithelium (b) is schematically shown. (a) URAT1 is located on the apical membrane of the renal proximal tubule cell, while GLUT9 is located on the basal membrane. Urate is reabsorbed from the tubule lumen into the vessel through URAT1 and GLUT9 in the proximal tubule cell (indicated by solid arrow). (b) URAT1 is located on the basal membrane of the choroid plexus epithelium, while GLUT9 is located on the apical membrane. From the immunohistochemical findings, it is expected that urate is transported from the choroid plexus parenchyma into the ventricle through URAT1 and GLUT9 (indicated by dotted arrow).

immunoreactivity of GLUT9 was observed on the apical side of the cytoplasm of epithelial cells in the choroid plexus and on the apical side of the cytoplasm of ependymal cells, especially cilia. In addition, immunoreactivity of URAT1 was localized on the basolateral side of the cytoplasm of epithelial cells in the choroid plexus by immunohistochemistry with two kinds of anti-URAT1 antibodies. In addition, as with previous reports [15,16], immunoreactivity of GLUT9 and URAT1 was observed in basal and apical cytoplasmic membranes of renal proximal tubule cells, respectively. The findings also suggest the reliability of the specificity of these antibodies. The antibodies for GLUT9 [26] and URAT1 (MBL) [27] had already been used for immunohistochemistry. The difference in the staining intensity among samples may be partially due to the differences in the lengths of storage of the samples in paraffin blocks or variations in the background pathological conditions.

At present, GLUT9 and URAT1 are recognized as representative reabsorptive urate transporters in the kidney [11,13,15,16]. Accordingly, it is likely that the localization of GLUT9 on the apical side of the cytoplasm and that of URAT1 on the basolateral side of the cytoplasm of epithelial cells in the choroid plexus contribute in a coordinated manner to transport intravascular urate into the ventricle through the choroid plexus. It is interesting that the polarized distribution of GLUT9 and URAT1 in the epithelial cells of the choroid plexus. The choroid plexus and kidney proximal tubule are similar in having a polarized distribution of these two transporters with the two transporters on opposite membranes, but the two transporters' distribution differs between the tissue in terms of which membrane (apical/basal) expresses which transporter (Fig. 3). On the contrary, in the mouse brain, immunoreactivity of GLUT9 and URAT1 was reported in ependymal cells but not in epithelial cells of the choroid plexus [19,20]. The discrepancy regarding the localization of urate transporters between humans and mice may be due to the differences in the expression level of the transporters between them, the antibodies used, or the fixative used. In addition, it was reported that GLUT9 on the brain microvessel can be detected only in the methacarn-fixed tissue [20]. Accordingly, it is likely that no immunoreactivity of GLUT9 on microvessels in autopsied human brains may not be non-expression of GLUT9, but loss of antigenicity by formalin fixation. On immunoreactivity of URAT1 in ependymal cells of mice, it was reported that URAT1 localization is restricted to the ependymal cells that line the upper part of the ventral third ventricle, showing that expression levels of URAT1 differ between ventricles [19]. In this study, although URAT1 immunoreactivity was not clear in ependymal cells at the lateral ventricular wall, that was observed in ependymal cells at the third ventricular wall. Accordingly, the difference of expression levels of URAT1 between ventricles was also confirmed in the human brain.

Two distinct N-terminal isoforms, GLUT9a and GLUT9b, are generated by alternative ends within *SLC2A9* transcripts. GLUT9a and GLUT9b differ in membrane targeting. In the human kidney, GLUT9a is expressed on the basolateral membrane of proximal tubule cells with GLUT9b on the apical membrane of collecting ducts [16,28]. The immunohistochemical findings in the kidneys indicated that the antibody for GLUT9 (ab104623, Abcam) used in this study recognized both GLUT9a and GLUT9b variants, as shown in a previous paper [26].

Together with these previous results, the present findings suggest that urate may be transported via GLUT9 and URAT1 at the choroid plexus as well as via ABCG2 at the microvessels [24] in the human brain. Urate may play a protective role in neurons [29,30], while hyperuricemia is correlated with atherosclerosis and cardiovascular disease [1,2]. Recently, there is increasing evidence indicating that an excessive intake of fructose induces hypertension, fatty liver, diabetes, and renal diseases [31]. Actually, fructose is metabolized in cells, generating urate [32]. We previously reported that GLUT5 and GLUT8, fructose transporters, were located in epithelial cells of the choroid plexus and ependymal cells [25,33]. Accordingly, combined evaluation of the intracerebral localization of urate and fructose transporters is necessary to understand the roles of urate in the CNS.

Conflict of interest

There is no conflict of interest.

Acknowledgements

This study was supported by JSPS KAKENHI 17K08788 (M.U.) and 17K15896 (N.U.) of Japan. The authors thank Ms. K. Yasutomi and Ms. Ueda for editorial assistance.

References

[1] M. Jin, F. Yang, I. Yang, Y. Yin, J.J. Luo, H. Wang, X.F. Yang, Uric acid, hyperuricemia and vascular diseases, Front. Biosci. 17 (2012) 656–669.
[2] A. Brandstätter, C. Lamina, S. Kiechl, S.C. Hunt, S. Coassin, B. Paulweber, F. Kramer, M. Summerer, J. Willeit, T.D. Adams, F. Kronenberg, Sex and age interaction with genetic association of atherogenic uric acid concentrations, Atherosclerosis 210 (2010) 474–478.
[3] D.C. Hooper, S. Spitsin, R.B. Kean, J.M. Champion, G.M. Dickson, I. Chaudhry, H. Koprowski, Uric acid, a natural scavenger of peroxynitrite, in experimental allergic encephalomyelitis and multiple sclerosis, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 675–680.

[4] X. Chen, G. Wu, M.A. Schwarzschild, Urate in Parkinson's disease: more than a biomarker? Curr. Neurol. Neurosci. Rep. 12 (2012) 367–375.
[5] K.C. Simon, S. Eberly, X. Gao, D. Oakes, C.M. Tanner, I. Shoulson, S. Fahn, M.A. Schwarzschild, A. Ascherio, Parkinson study G., Mendelian randomization of serum urate and Parkinson disease progression, Ann. Nuerol. 76 (2014) 862–868.
[6] J.Y. Hong, T.Y. Lan, G.J. Tang, C.H. Tang, T.J. Chen, H.Y. Lin, Gout and the risk of dementia: a nationwide-based cohort study, Arthritis Res. Ther. 17 (2015) 139, http://dx.doi.org/10.1186/s13075-015-0642-1.
[7] M.K. Kutzing, B.L. Firestein, Altered uric acid levels and disease states, J. Phamacol. Exp. Ther. 324 (2008) 1–7.
[8] M.O. Carayannopoulos, A. Schlein, A. Wyman, M. Chi, C. Keembiyehetty, K.H. Moley, GLUT9 is differentially expressed and targeted in the preimplantation embryo, Endocrinology 145 (2004) 1435–1443.
[9] A.R. Manolescu, R. Augustin, K. Moley, C. Cheeseman, A highly conserved hydrophobic motif in the exofacial vestibule of fructose transporting SLC2A proteins acts as a critical determinant of their substrate selectivity, Mol. Membr. Biol. 24 (2007) 455–463.
[10] M. Doblado, K.H. Moley, Facilitative glucose transporter 9, a unique hexose and urate transporter, Am. J. Physiol. Endocrinol. Metab. 297 (2009) E831–835.
[11] N. Anzai, K. Ichida, P. Jutabha, T. Kimura, E. Babu, C.J. Jin, S. Srivastava, K. Kitamura, I. Hisatome, H. Endou, H. Sakurai, Plasma urate level is directly regulated by a voltage-driven urate efflux transporter URATv1 (SLC2A9) in humans, J. Biol. Chem. 283 (2008) 26834–26838.
[12] S. Bilbert, S.K. Hess, D. Firsow, B. Thorens, K. Geering, J.-D. Horisberger, O. Bonny, Mouse GLUT9: evidences for a urate uniporter, Am. J. Physiol. Renal Physiol. 297 (2009) F612–F619.
[13] B. Clemençon, B.P. Lüscher, M. Fine, M.U. Baumann, D.V. Surbek, O. Bonny, M.A. Hediger, Expression, purification, and structural insights for the human uric acid transporter, GLUT9, using the *Xenopus laevis* oocytes system, PLoS One 9 (2014) e108852.
[14] A. Enomoto, H. Kimura, A. Chairoungdua, Y. Shigeta, P. Jutabha, S.H. Cha, M. Hosoyamada, M. Takeda, T. Sekine, T. Igarashi, H. Matsuo, Y. Kikuchi, T. Oda, K. Ichida, T. Hosoya, K. Shimokata, T. Niwa, Y. Kanai, H. Endou, Molecular identification of a renal urate anion exchanger that regulates blood urate levels, Nature 417 (2002) 447–452.
[15] N. Anzai, P. Jutabha, S. Amonpatumrat-Takahashi, H. Sakurai, Recent advances in renal urate transport: characterization of candidate transporters indicated by genome-wide association studies, Clin. Exp. Nephrol. 16 (2012) 89–95.
[16] A.K. Mandal, D.B. Mount, The molecular physiology of uric acid homeostasis, Annu. Rev. Physiol. 77 (2015) 323–345.
[17] O.M. Woodward, ABCG2: the molecular mechanisms of urate secretion and gout, Am. J. Physiol. Renal Physiol. 309 (2015) F485–F488.
[18] C. Carlsson, S.J. Dencker, Cerebrospinal uric acid in alcoholics, Acta Neurol. Scandinav. 49 (1973) 39–46.
[19] N.H. Tomioka, M. Nakamura, M. Doshi, Y. Deguchi, K. Ichida, T. Morisaki, M. Hosoyamada, Ependymal cells of the mouse brain express urate transporter 1 (URAT1), Fluids Barriers CNS 10 (2013) 31, http://dx.doi.org/10.1186/2045-8118-10-31.
[20] N.H. Tomioka, Y. Tamura, T. Takada, S. Shibata, H. Suzuki, S. Uchida, M. Hosoyamada, Immunohistochemical and in situ hybridization study of urate transporters GLUT9/URATv1, ABCG2, and URAT1 in the murine brain, Fluids Barriers CNS 13 (2016) 22, http://dx.doi.org/10.1186/s12987-016-0046-x.
[21] T.M. Do, M.S. Noel-Hudson, S. Ribes, C. Besengez, M. Smimova, S. Cistemino, M. Buyse, F. Calon, G. Chimin, H. Chacun, J.M. Schermann, R. Farinotti, F. Bourasset, ABCG2- and ABCG4-mediated efflux of amyloid-β peptide 1–40 at the mouse blood-brain barrier, J. Alzheimers Dis. 30 (2012) 155–166.
[22] V.S. Narang, C. Fraga, N. Kumar, J. Shen, S. Throm, C.F. Stewart, C.M. Waters, Dexamethasone increases expression and activity of multidrug resistance transporters at the rat blood-brain barrier, Am. J. Physiol. Cell Physiol. 295 (2008) C440–C450.
[23] M. Daood, C. Tsai, M. Ahdab-Barmada, J.F. Watchko, ABC transporter (P-gp/ABCB1, MRP1/ABCC1 BCRP/ABCG2) expression in the developing human CNS, Neuropediatrics 39 (2008) 211–218.
[24] K. Matsumoto, Y. Chiba, R. Fujihara, H. Kubo, H. Sakamoto, M. Ueno, Immunohistochemical analysis of transporters related to clearance of amyloid-β peptides through blood-cerebraospinal fluid barrier in human brain, Histochem. Cell Biol. 144 (2015) 597–611.
[25] M. Ueno, N. Nishi, T. Nakagawa, Y. Chiba, I. Tsukamoto, T. Kusaka, T. Miki, H. Sakamoto, F. Yamaguchi, M. Tokuda, Immunoreactivity of glucose transporter 5 is located in epithelial cells of the choroid plexus and ependymal cells, Neuroscience 260 (2014) 149–157.
[26] P.J. Stanirowski, D. Szukiewicz, M. Pyzlak, N. Abdalla, W. Sawicki, K. Cendrowski, Impact of pre-gestational and gestational diabetes mellitus on the expression of glucose transporters GLUT-1, GLUT-4 and GLUT-9 in human term placenta, Endocrine 55 (2017) 799–808.
[27] A. Tojo, K. Asaba, S. Kinugasa, Y. Ikeda, Y. Shintani, M. Fukayama, M. Nangaku, The reduced expression of proximal tubular transporters in acquired Fanconi syndrome with κ light chain deposion, Med. Mol. Morphol. 49 (2016) 48–52.
[28] T. Kimura, M. Takahashi, K. Yan, H. Sakurai, Expression of SLC2A9 isoforms in the kidney and their localization in polarized epithelial cells, PLoS One 9 (2014) e84996.
[29] E. Méndez-Hernández, J. Salas-Pacheco, L. Ruano-Calderón, A. Téllez-Valencia, J. Cisneros-Martinez, M. Barraza-Salas, O. Arias-Carrión, Lower uric acid linked with cognitive dysfunction in the elderly, CNS Neurol. Disord. Drug Targets 14 (2015) 564–566.
[30] L. Llull, C. Laredo, A. Renú, B. Pérez, E. Vila, V. Obach, X. Urra, A. Planas, S. Amaro, Á. Chamorro, Uric acid therapy improves clinical outcome in women with acute ischemic stroke, Stroke 46 (2015) 2162–2167.
[31] R.J. Johnson, L.G. Sanchez-Lozada, T. Nakagawa, The effect of fructose on renal biology and disease, J. Am. Soc. Nephrol. 21 (2010) 2036–2039.
[32] P. Bjornstad, M.A. Lanaspa, T. Ishimoto, T. Kosugi, S. Kume, D. Jalal, D.M. Maahs, J.K. Snell-Bergeon, R.J. Johnson, T. Nakagawa, Fructose and uric acid in diabetic nephropathy, Diabetologia 58 (2015) 1993–2002.
[33] R. Murakami, Y. Chiba, K. Tsuboi, K. Matsumoto, M. Kawauchi, R. Fujihara, M. Mashima, K. Kanenishi, T. Yamamoto, M. Ueno, Immunoreactivity of glucose transporter 8 is localized in the epithelial cells of the choroid plexus and in ependymal cells, Histochem. Cell Biol. 146 (2016) 231–236.