Drug deliver by utilization of tissue specific transportes.

1999 Fiscal Year Final Research Report Summary

Drug deliver by utilization of tissue specific transportes.

Research Project

Project/Area Number

10470510

Research Category

Grant-in-Aid for Scientific Research (B)

Allocation Type

Single-year Grants

Section

一般

Research Field

応用薬理学・医療系薬学

Research Institution

KANAZAWA UNIVERSITY

Principal Investigator

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1998 – 1999

Keywords

transporter / pharmacokinetics / drug delivery / organic cation / monocarboxylic acid / P-glycoprotein / Blood-brain barrier / Carnitine

Research Abstract

Various transporters that mediate membrane transport of drugs as well as physiological compounds were clarified by molecular cloning of the genes and their functional analysis by gene expression systems. The obtained results are as follows :
1. Novel transporter family OCTNs were molecularly cloned and their transport functions were analyzed by transfection of the gene to HEK293 cells. Human and mouse OCTN2 transported physiologically important carnitine in a sodium dependent manner. JVS mice that show systemic carnitine deficiency(SCD) syndrome had a mutation in OCTN2 gene with loss of carnitine transport function. Furthermore, various mutations in OCTN2 gene were identified in patients who show the SCD syndrome. From these results, it was clarified that OCTN2 is a physiologically important camitine transporter and its mutation leads to the SCD. Interestingly, OCTN2 and its isoform OCTN1 transported organic cations in a sodium independent manner. Accordingly, OCTNs are unique transporters which have are multifunctionality by transporting carnitine and organic cations in the distinct mechanisms.

2. Molecular characterization of the transporter for monocarboxylic acids at the blood-brain barrier (BBB) was performed. Monocarboxylic acid transporter MCT-1 gene was expressed at the BBB and was found to play important role in the transport of organic weak acids by the in vitro cultured cells and in vivo studies.
3. Multiple efflux mechanisms for new quinolone antibacterial agent were found to be expressed at the BBB. They are P-glycoprotein and unknown transporters sensitive to anionic compounds. These multiple efflux transporters seem to restrict the brain distribution of quinolones and other drugs, resulting in a low distribution into the central nervous system.
These lines of studies provide new insight of the siginificance of membrane transporters and new strategy to control disposition of drugs by focusing on the transporters function present in various tissues.

Research Products (36 results)

All Other

All Publications

[Publications] J. Nezu: "Primary systemic carnitine deficiency is caused by mutations in a gene encoding sodium ion-dependent carnitine transporter"Nature Genet. 21. 91-94 (1999)

[Publications] K. Yokogawa: "Decreased tissue distribution of L-carnitine in juvenile visceral sieatosis mice"J. Pharmacol. Exp. Ther.. 289. 224-230 (1999)

[Publications] H. Yabuuchi: "Novel membrane transporter OCTN1 mediates multispecific, bidirectional and pH-dependent transport of organic cations"J. Pharmacol. Exp. Ther.. 289. 768-773 (1999)

[Publications] K. Yokogawa: "Characteristics of L-carnitine transport in cultured hepatoma HLF cells from man"J. Pharm Pharmcol. 51. 935-940 (1999)

[Publications] K. Yokogawa: "Loss of wild-type carrier-mediated L-carnitine transport activity in hepatocytes of juvenile visceral steatosis mice"Hepatology. 30. 997-1001 (1999)

[Publications] R. Ohashi: "Nat-dependent carnitine transport by OCTN2 and its pharmacological and toxicological relevance"J. Pharmacol. Exp. Ther. 291. 778-784 (1999)

[Publications] A. Koizumi: "Genetic epidemiology on carnitine transporter OCTN2 gene in a Japanese population and phenotype characterizations in Japanese pedigrees with primary systemic carnitine deficiency"Human Molecular Genetics. 8. 2247-2254 (1999)

[Publications] M. Murata: "Carrier-mediated lung distribution of HSR-903, a new quinolone antibacterial agent"J. Pharmacol. Exp. Ther.. 289. 79-84 (1999)

[Publications] H. Sasabe: "Differences in the hepatobililary transport of two quinolone antibiotics, grepufloxacin and lomefloxacin, in the rat"Baiopharm. Drug Dispos. 20. 151-158 (1999)

[Publications] M. Murata: "Efflux transport of a new quinolone antibacterial agent, HSR-903, across the blood-brain barrier"J. Pharmacol. Exp. Ther.. 290. 51-57 (1999)

[Publications] M. Kawahara: "Physiologically based phrmacokinetics of digoxin in mdrla knockout mine"J. Pharm. Sci.. 88. 1281-1287 (1999)

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[Publications] Y. Kido: "Functional clarification of HCT1-mediated transport of monocarboxylic acids at the blood-brain barrier of rats using in vitro cultured in vivo BUI studies"Pharm. Res.. 17. 55-62 (2000)

[Publications] T. Hirohashi: "The function and expression of multidrug resistance-associated protein (MRP) family in human colon odenocarcinoma cells (Caco-2)"J. Pharmacol. Exp. Ther.. 292. 265-270 (2000)

[Publications] A. Tsuji: "An introduction to the blood-brain barrier"Cambridge University Press. (1998)

[Publications] A. Tsuji: "Membrane transporters as drug targets"Kluwer Academic/Plenum Publications. (1999)

[Publications] N. Hashimoto, F. Suzuki, I. Tamai, H. Nikaido, M. Kuwajima, J. Hayakawa and A. Tsuji.: "Gene-dose effect on carnitine transport activity in embryonic fibroblasts of JVS mice as a model of human carnitine transporter deficiency."Biochem. Pharmacol.. 55. 1729-1732 (1998)

[Publications] I. Tamai, R. Ohashi, J. Nezu, H. Yabuuchi, A. Oku, M. Shimane, Y. Sai and A. Tsuji.: "Molesular and funcrional identification of sodium ion-dependent, high affinity human carnitine transporter OCTN2."J. Biol. Chem.. 273. 20378-20382 (1998)

[Publications] H. Yabuuchi, I. Tamai, K. Morita, T. Kouda, K. Miyamoto, E. Takeda and A. Tsuji: "Hepatic sinusoidal membrane transport of anionic drugs mediated by anion transporter Npt1."J. Pharmacol. Exp. Ther.. 286. 1391-1396 (1998)

[Publications] H. Sasabe, A. Tsuji and Y. Sugiyama.: "Carrier-mediated mechanism for the biliary excretion of the quinolone antibiotic grepafloxacin and its glucuronide in rats."J. Pharmacol. Exp. Ther.. 284. 1033-1039 (1998)

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[Publications] M. Kawahara, T. Nanbo and A. Tsuji.: "Physiologically based pharmacokinetic prediction of p-phenylbenzoic acid disposition in the pregnant rat."Biopharm. Drug Dispos.. 19. 445-453 (1998)

[Publications] J. Nezu, I. Tamai, A. Oku, R. Ohashi, H. Yabuuchi, N. Hashimoto, H. Nikaido, Y. Sai, A. Koizumi, Y. Shoji, G. Takada, T. Matsuishi, M. Yoshino, H. Kato, T. Ohura, G. Tsujimoto, J. Hayakawa, M. Shimane and A. Tsuji.: "Primary systemic carnitine deficiency is caused by mutations in a gene encoding sodium ion-dependent carnitine transporter."Nature Genet.. 21. 91-94 (1999)

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