Molecular mechanism of blood-brain barrier transport of drugs.

1998 Fiscal Year Final Research Report Summary

Molecular mechanism of blood-brain barrier transport of drugs.

Research Project

Project/Area Number

09672221

Research Category

Grant-in-Aid for Scientific Research (C)

Allocation Type

Single-year Grants

Section

一般

Research Field

Biological pharmacy

Research Institution

KANAZAWA UNIVERSITY

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Project Period (FY)

1997 – 1998

Keywords

Blood-brain barrier / transporter / carrier-mediated transport / drug delivery / drug disposition / P-glycoprotein / monocarboxylic acid / beta-amino acid

Research Abstract

Various transport systems equipped in brain capillary endothelial cells (BECEC) that form blood-brain barrier (BBB) were characterized as follows :
1.beta-amino acid transport system : beta-amino acids such as beta-alanine and taurine were transported across the blood-brain barrier by specific carrier-mediated transport mechanisms that is energized by sodium ion gradient in a chloride ion sensitive manner. The transporter function was found bcth at the luminal and abluminal membranes of BCEC, indicating that both of influx and efflux of beta-amino acids across the BBB are regulated such transporter(s).
2.Substrate specificity of adsorptive-mediated endocytosis at the BBB was further investigated using primary cultured bovine BCEC.By newly synthesizing cationic-derived peptide with various lipophilicity, isoelectric point and molecular size, the optimal structure for the mechanism was speculated.
3.Molecular characterization of the transporter for monocarboxylic acids such as lactic acid has been performed. Monocarboxylic acid transporter MCT-1 gene was expressed in the BCEC and was found to functionally play important role in transport of organic weak acids at the BBB by the in vitro cultured cells and in vivo BUl studies.
4.Multiple brain efflux mechanisms for new quinolone antibacterial agent, HSR-903 were found to be functionally expressed at the BBB.They are P-glycoprotein and unknown transporter sensitive to anionic compounds. These multiple efflux transporters seem to restrict brain distribution of HSR-903, resulting in a low toxicity in the central nervous system.
These lines of studies provide new insight of the function of BBB and imply new strategy to control brain distribution of drugs by focusing on the transporters functioning at the blood-brain barrier.

Research Products (6 results)

All | Other

All | Publications (6 results)

[Publications] I.Tamai et al.: "Structure-internalization relationship for adsorptine-mediated endocytosis of basic peptides at the blood-brain barrier" J.Pharmacol.Exp.Ther.280. 410-415 (1997)

[Publications] J.Komura et al.: "Brain-to-blood active transport of P-alamine across the blood-lrain bavier." FEBS Lett.400. 131-135 (1997)

[Publications] T.Wakamiya et al.: "Design and Synthesis of peptides passing though the blood-brain barrier" Bull.Chem.Soc.Jpn.71. 699-709 (1998)

[Publications] Tamai I.et al.: "Structure-internalization relationship for adsorptive-mediated endocytosis of basic peptides at the blood-brain barrier." J.Pharmcol.Exp.Ther.280. 410-415 (1997)

[Publications] Komura J.et al.: "Brain-to-blood active transport of beta-alanine across the blood-brain barrier." FEBS Lett.400. 131-135 (1997)

[Publications] Wakamiya T.et al.: "Design and synthesis of peptides passing through the blood-brain barrier." Bull.Chem.Soc.Jpn.71. 699-709 (1998)

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