論　文　内　容　の　要　旨
Synopsis of Thesis

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論文題名 Title	Structure–activity characteristics of phenylalanine analogs selectively transported by L-type amino acid transporter 1 (LAT1) (L型アミノ酸トランスポーター1 (LAT1)により選択的に輸送されるフェニルアラニン類似体の構造活性特性)

論文内容の要旨

〔目　的(Purpose)〕

Targeted drug delivery aims to deliver drugs to specific sites within the body at effective concentrations, maximizing therapeutic effects while minimizing adverse reactions due to drug accumulation at non-target sites. The recent focus on transporter-targeted drug delivery leverages transporters that are predominantly expressed in target tissues. Drugs are designed to be substrates of these transporters, enabling selective delivery to specific tissues. Among these transporters, L-type amino acid transporter 1 (LAT1, SLC7A5) is particularly promising for targeted drug delivery, given its tissue-specific expression profile. As an isoform of the amino acid transport system L, LAT1 transports large neutral amino acids with branched or aromatic side chains. Another isoform, LAT2 (SLC7A8), shares similar substrate selectivity but also transports smaller neutral amino acids. While LAT2 is ubiquitously distributed in normal tissues, particularly in renal proximal tubules and small intestinal epithelium, LAT1 is highly expressed in various cancers and is also present in the blood–brain barrier (BBB) and placental barrier. Numerous LAT1-targeted compound delivery for the brain and tumors have been investigated, their LAT1 selectivity often remains ambiguous despite high LAT1 affinity. This study assessed the LAT1 selectivity of phenylalanine (Phe) analogs, focusing on their structure–activity characteristics.

〔方法ならびに成績(Methods/Results)〕

We first used inhibition experiments to explore the structural preferences for LAT1 affinity among halogenated phenylalanines. We then conducted quantitative analyses to assess LAT1 affinity (K_i), selectivity (K_i ratio of LAT2 to LAT1), and transport velocity (V_{max} of efflux) of these Phe analogs, aiming to delineate the structural features critical for LAT1-targeted compound delivery. Subsequent *in vivo* experiments further validated the role of LAT1 selectivity in the biodistribution of the compounds.

We discovered that 2-iodo-L-phenylalanine (2-I-Phe), with an iodine substituent at position 2 in the benzene ring, markedly improves LAT1 affinity and selectivity compared to parent amino acid Phe, albeit at the cost of reduced transport velocity. L-Phenylglycine (Phg), one carbon shorter than Phe, was found to be a substrate for LAT1 with a lower affinity, exhibiting a low level of selectivity for LAT1 equivalent to Phe. Notably, (*R*)-2-amino-1,2,3,4-tetrahydro-2-naphthoic acid (bicyclic-Phe), with an α-methylene moiety akin to the α-methyl group in α-methyl-L-phenylalanine (α-methyl-Phe), a known LAT1-selective compound, showed similar LAT1 transport maximal velocity to α-methyl-Phe, but with higher LAT1 affinity and selectivity. *In vivo* studies revealed tumor-specific accumulation of bicyclic-Phe, underscoring the importance of LAT1-selectivity in targeted delivery.

〔総　括(Conclusion)〕

We advocate for a development strategy that optimizes LAT1 affinity, selectivity, and transport efficiency in targeted compound delivery. A standout candidate, bicyclic-Phe, emerged for its high LAT1 affinity, selectivity, and transport velocity, making it a promising option for targeted delivery in both tumors and the brain. These insights are instrumental in designing LAT1-targeted drug delivery systems that can selectively accumulate in tumors or the brain, maximizing therapeutic efficacy while minimizing side effects in non-target tissues.

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

L型アミノ酸トランスポーター1（LAT1）は、大型中性アミノ酸の輸送を担う膜タンパク質であり、悪性腫瘍および正常組織では血液脳関門に存在するため、薬物送達の標的として検討されてきた。LAT1標的化合物は、これまで親和性の観点から評価されてきたが、LAT1選択性については十分な検討がなされてこなかった。本研究は、LAT1基質であるフェニルアラニン誘導体の構造活性相関解析により、LAT1選択性の構造基盤を検討した。その結果、側鎖ベンゼン環の2位の嵩高さ、α-メチル基およびα-メチレン基がLAT1選択性を賦与することを明らかにした。特にα-メチレン基を有する(*R*)-2-amino-1,2,3,4-tetrahydro-2-naphthoic acidは、親和性、輸送速度の点からもLAT1標的化合物創製の優れた骨格構造となることを示した。加えて、in vivo検討において、腫瘍特異的送達におけるLAT1選択性の意義を実証している。

本研究は、系統的な構造活性相関解析によりLAT1選択性の構造基盤を明らかにしたものであり、学位の授与に値すると考える。