FULL TEXT LINKS

SpringerLink FULL-TEXT ARTICLE

Mol Neurobiol. 2021 Feb;58(2):647-657. doi: 10.1007/s12035-020-02143-6. Epub 2020 Oct 1.

L-Citrulline Level and Transporter Activity Are Altered in Experimental Models of Amyotrophic Lateral Sclerosis

Asmita Gyawali # [1], Shashi Gautam # [1], Seung Jae Hyeon [2], Hoon Ryu [2 3], Young-Sook Kang [4]

Affiliations

Affiliations

1 College of Pharmacy and Drug Information Research Institute, Sookmyung Women's University, Seoul, Republic of Korea.
2 Laboratory for Brain Gene Regulation and Epigenetics, Center for Neuroscience, Korea Institute of Science and Technology, Seoul, 02792, Republic of Korea.
3 Boston University Alzheimer's Disease Center Department of Neurology, Boston University School of Medicine, Boston, MA, 02183, USA.
4 College of Pharmacy and Drug Information Research Institute, Sookmyung Women's University, Seoul, Republic of Korea. yskang@sm.ac.kr.
# Contributed equally.

PMID: 33000451 DOI: 10.1007/s12035-020-02143-6

Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease caused by the death of the neurons regulating the voluntary muscles which leads to the progressive paralysis. We investigated the difference of transport function of L-citrulline in ALS disease model (NSC-34/hSOD1^{G93A}, MT) and a control model (NSC-34/hSOD1^{wt}, WT). The [^{14}C]L-citrulline uptake was significantly reduced in MT cells as compared with that of control. The Michaelis-Menten constant (K_m) for MT cells was 0.67 ± 0.05 mM, whereas it was 1.48 ± 0.21 mM for control. On the other hand, the V_{max} values for MT and control were 10.9 ± 0.8 nmol/mg protein/min and 18.3 ± 2.9 nmol/mg protein/min, respectively. The K_m and V_{max} values showed the high affinity and low capacity for MT as compared with control. Moreover, the uptake of [^{14}C]L-citrulline was significantly inhibited by 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid (BCH) and harmaline which is the inhibitor of the large neutral amino acid transporter1 (LAT1) in NSC-34 cell lines. Furthermore, [^{14}C]L-citrulline uptakes took place in Na^+-independent manner. It was also inhibited by the neutral amino acids such as citrulline and phenylalanine. Likewise, L-dopa, gabapentin, and riluzole significantly inhibited the [^{14}C]L-citrulline uptake. It shows the competitive inhibition for L-dopa in ALS cell lines. On the other hand, [^{14}C]L-citrulline uptake in the presence of riluzole showed competitive inhibition in WT cells, whereas it was uncompetitive for MT cells. The small interfering RNA experiments showed that LAT1 is involved in the [^{14}C]L-citrulline uptake in NSC-34 cell lines. On the other hand, in the examination of the alteration in the expression level of LAT1, it was significantly lower in MT cells as compared with that of control. Similarly, in the spinal cord of ALS, transgenic mice revealed a slight but significant decrease in LAT1 immunoreactivity in motor neurons of ALS mice compared with control. However, the LAT1 immunoreactivity in non-motor neurons and in astrocytes was relatively increased in the spinal cord gray matter of ALS mice. The experimental evidences of our results suggest that the change of transport activity of [^{14}C]L-citrulline may be partially responsible for the pathological alteration in ALS.

Keywords: Amyotrophic lateral sclerosis (ALS); Carrier mediated transporter; L-citrulline; LAT1 (large neutral amino acid transporter 1); Motor neuron disease; NSC-34 cells.

Related information

MedGen
PubChem Compound (MeSH Keyword)

LinkOut – more resources

Full Text Sources
Springer

Medical
Genetic Alliance
MedlinePlus Health Information

Research Materials
NCI CPTC Antibody Characterization Program

Miscellaneous
NCI CPTAC Assay Portal