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The Molecular Mechanism of Intestinal Levodopa Absorption and Its Possible Implications for the Treatment of Parkinson's Disease

Drugs cannot cause more dopamine to be made by the both when depletion exists. The body need the nutrients it requires to make more dopamine.

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Depletion on an optimal diet represents a relative nutritional deficiency of one or more of the nutrients dopamine is made from.

ABSTRACT

Levodopa (L-DOPA) is the naturally occurring precursor amino acid for dopamine and the main therapeutic agent for neurologic disorders due to dopamine depletion, such as Parkinson's disease. L-DOPA absorption in small intestine has been suggested to be mediated by the large neutral amino acids transport machinery, but the identity of the involved transporters is unknown. Clinically, coadministration of L-DOPA and dietary amino acids is avoided to decrease competition for transport in intestine and at the blood-brain barrier. L-DOPA is routinely coadministered with levodopa metabolism inhibitors (dopa-decarboxylase and cathechol-*O*-methyl transferase inhibitors) that share structural similarity with levodopa. In this systematic study involving *Xenopus laevis* oocytes and Madin-Darby canine kidney epithelia expression systems and ex vivo preparations from wild-type and knockout mice, we identified the neutral and dibasic amino acids exchanger (antiporter) $b^{0,+}$AT-rBAT (SLC7A9-SLC3A1) as the luminal intestinal L-DOPA transporter. The major luminal cotransporter (symporter) B^0AT1 (SLC6A19) was not involved in levodopa transport. L-Leucine and L-arginine competed with levodopa across the luminal enterocyte membrane as expected for $b^{0,+}$AT-rBAT substrates, whereas dopa-decarboxylase and cathechol-*O*-methyl transferase inhibitors had no effect. The presence of amino acids in the basolateral compartment mimicking the postprandial phase increased transepithelial levodopa transport by stimulating basolateral efflux via the antiporter LAT2-4F2 (SLC7A8-SLC3A2). Additionally, the aromatic amino acid uniporter TAT1 (SLC16A10) was shown to play a major role in L-DOPA efflux from intestinal enterocytes. These results identify the molecular mechanisms mediating small intestinal levodopa absorption and suggest strategies for optimization of delivery and absorption of this important prodrug.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder mainly caused by dopamine depletion in the substantia nigra, clinically manifested by symptoms including its hallmark, the trias of bradykinesia, resting tremor, and rigidity (Nyholm and Lennernas, 2008; Ahlskog, 2011; Hickey and Stacy, 2011). Since its introduction in 1968, levodopa (L-dihydroxyphenylalanine, L-DOPA) is the major therapeutic agent in treating PD (Poewe et al., 2010). After passing the blood-brain barrier (BBB), levodopa is converted into dopamine by the dopa-decarbocylase (DDC) (Nyholm and Lennernas, 2008). To prevent levodopa metabolism prior to its transport across the BBB, orally administered levodopa is given in combination with a DDC inhibitor (e.g., carbidopa or benserazide) (Hollingworth et al., 2011). It may be additionally combined with a cathechol-*O*-methyltransferase (COMT) inhibitor (such as entacapone) to avoid levodopa methylation into 3-*O*-methyldopa.

Levodopa is a large neutral amino acid (AA) structurally very similar to the aromatic AAs L-phenylalanine (Phe) and L-tyrosine (Tyr). Levodopa is believed to compete with other neutral AAs for its active transport across the BBB, as well as across small intestine enterocytes. In the brain, levodopa has been suggested to be transported by the neutral AA heterodimeric transporter LAT1-4F2hc (SLC7A5-SLC3A2) (Uchino et al., 2002; Morimoto et al., 2008; Ahlskog, 2011). Intestinal levodopa transport has also been suggested to be mediated by neutral AA transporters (Lennernas et al., 1993), but the identity of the transporters involved in its intestinal absorption is still unknown. Several AA and peptide transporters located at the luminal and basolateral enterocyte membrane have been shown to be responsible for neutral AA absorption (Broer, 2008; Verrey et al., 2009; Broer and Palacin, 2011). B^0AT1 (SLC6A19) is the major transporter for neutral AAs in the apical enterocyte membrane (Broer et al., 2004; Kleta et al., 2004; Camargo et al., 2005; Romeo et al., 2006). The neutral and dibasic AA exchanger (antiporter) $b^{0,+}$AT-rBAT (SLC7A9-SLC3A1) is the

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ABBREVIATIONS: AA, amino acid; BBB, blood-brain barrier; COMT, cathechol-*O*-methyl transferase; DDC, dopa-decarboxylase; L-DOPA, levodopa; PCR, polymerase chain reaction; PD, Parkinson's disease.