Efficient Transport and Biotransformation of Dipeptide-like Tyrosine/Phenylalanine-Conjugated Phenolic Amide Esters in THP-1 Cells and PBMCs: A Potential Means for Transporting Compounds Inside Monocytes/Macrophages

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***Background*:** Recent studies suggest that dipeptide-like tyrosine/phenylalanine-conjugated phenolic amide compounds may contain several biological activities, including anti-inflammatory activity. However, there is currently no information about their transport and biotransformation in monocytes/macrophages involved in inflammation process.

***Objective*:** The objective of this study was to investigate cell transport and biotransformation of the phenolic amides and esters in monocyte/macrophage-like cells.

***Methods*:** Cell transport and biotransformation of the phenolic amides and esters (*N*-coumaroylphenylalanine, *N*-caffeoylphenylalanine, *N*-feruloylphenylalanine, *N*-coumaroyltyrosine, *N*-caffeoyltyrosine, *N*-feruloyltyrosine, and their *O*-methyl esters) were investigated in THP-1 cells and PBMCs using HPLC, cellular, and kinetics methods.

***Results*:** In THP-1 cells, the phenolic amides were not transported significantly, but their *O*-methyl esters were transported significantly ($P < 0.02$). Also, the transport of the esters was found to be sodium-independent and pH-dependent. Among the tested esters, *N*-feruloylphenylalanine-*O*-methyl ester showed the highest uptake (K_m of 25 µM), and the uptake was inhibited by PepT1/2 substrate and blocker (GlySar and enalapril) in THP-1 cells. Particularly, enalapril competitively inhibited the uptake with K_i of 560 µM. The data also showed that *N*-feruloylphenylalanine-*O*-methyl ester and *N*-feruloyltyrosine-*O*-methyl ester could be biotransformed into parent phenolic amides in THP-1 cells. Similarly, these ester compounds were also found to be transported and biotransformed in PBMCs.

***Conclusion*:** The data suggest that dipeptide-like tyrosine/phenylalanine-conjugated phenolic amide esters may be transported and biotransformed in THP-1 cells and PBMCs.

Keywords: Dipeptide-like tyrosine, phenylalanine-conjugated phenolic amide esters, bioactives, nutraceuticals, transport, biotransformation, PepT2, THP-1 cells, PBMCs.