

Triphenylphosphonium moiety modulates proteolytic stability and potentiates neuroprotective activity of antioxidant tetrapeptides in vitro

Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2018 Akhmadishina, Garifullin, Petrova, Kamalov and Abdullin. Although delocalized lipophilic cations have been identified as effective cellular and mitochondrial carriers for a range of natural and synthetic drug molecules, little is known about their effects on pharmacological properties of peptides. The effect of triphenylphosphonium (TPP) cation on bioactivity of antioxidant tetrapeptides based on the model opioid YRFK motif was studied. Two tetrapeptide variants with L-arginine (YRFK) and D-arginine (YrFK) were synthesized and coupled with carboxyethyl-TPP (TPP-3) and carboxypentyl-TPP (TPP-6) units. The TPP moiety noticeably promoted YRFK cleavage by trypsin, but effectively prevented digestion of more resistant YrFK attributed, respectively, to structure-organizing and shielding effects of the TPP cation on conformational variants of the tetrapeptide motif. The TPP moiety enhanced radical scavenging activity of the modified YRFK in a model Fenton-like reaction, whereas decreased reactivity was revealed for both YrFK and its TPP derivative. The starting motifs and modified oligopeptides, especially the TPP-6 derivatives, suppressed acute oxidative stress in neuronal PC-12 cells during a brief exposure similarly with glutathione. The effect of oligopeptides was compared upon culturing of PC-12 cells with CoCl₂, L-glutamic acid, or menadione to mimic physiologically relevant oxidative states. The cytoprotective activity of oligopeptides significantly depended on the type of oxidative factor, order of treatment and peptide structure. Pronounced cell-protective effect was established for the TPP-modified oligopeptides, which surpassed that of the unmodified motifs. The protease-resistant TPP-modified YrFK showed the highest activity when administered 24 h prior to the cell damage. Our results suggest that the TPP cation can be used as a modifier for small therapeutic peptides to improve their pharmacokinetic and pharmacological properties.

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Keywords

Antioxidant activity, Aromatic-cationic oligopeptides, Cytoprotection, Fenton reaction, Neuronal cells, Oxidative damage, Protease stability, Triphenylphosphonium compounds

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