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Extended Abstract

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Evaluation of biological activity of certain peptide derivatives of Cyclencarboxymethylen and L-DOPA

Lili Arabuli, University of Georgia, Czech Republic
E-mail: l.arabuli@ug.edu.ge

The most advantage of the macrocyclic polyamines is their unique capacity to bind some biologically important metals (Zn, Cu, Co, Fe) and their role was dramatically increased as behaviour models for enzymes and other metalloproteins. The modification of macrocyclic polyamine receptor molecules with additional ligands (arms) enables to interact with nucleobase, sugar and other biomolecules moieties for a more efficient multipoint recognition, as well as for thermodynamic stabilization of the ternary complexes in aqueous solution. Cyclen, cyclam, their derivatives and metallo complexes are proposed as good candidates to cross blood-brain barrier and with low toxicity as potential neuroprotective or neurorescue agents in the treatment of Alzheimer's disease. In addition, cyclen derivatives showed antibacterial, anti-HIV and anti-malarial activities. On the other hand, polyphenolic compounds, like coumarins and its derivatives are able to bind transition metal ions and inhibit hydroxyl radical and hydrogen peroxide formation produced by Fenton's reactions. Polyphenol derivatives (or metabolites) were found to have numerous therapeutic applications, such as central nervous system stimulants, antitumor and anti-HIV therapy, antibacterial, anticoagulants etc. We prepared cyclencarboxymethylen and L-3, 4-dihydroxyphenylalanine (L-DOPA) derivatives with His-rich dipeptides (cyclen-His-His, cyclen-Asp-His, cyclen-Glu-His, Dopa-His-His, Dopa-Asp-His, Dopa-Glu-His, Dopa-His-His-Dopa, Dopa-Asp-His-Dopa, Dopa-Glu-His-Dopa, Dopa-Glu-His-Dopa and Dopa-cyclen) via solid phase synthesis strategy and identified using 1H-NMR and MALDI-TOF MS. The new DOPA and cyclen (1, 4, 7-10-(carboxymethyl)- tetraazacyclo-dodecane) oligopeptide derivatives were tested for their biological activity evaluation, such as antioxidant, antimicrobial, anticancer, antidiabetic, etc. activities using their different concentration levels. The cytotoxicity and genotoxicity of new compounds were also studied. L-3,4-Dihydroxyphenylalanine [2-amino-3-(3,4-dihydroxyphenyl) propanoic acid (L-DOPA) is a natural constituent of animal and plant tissue derived from post-translational modification of the amino acid tyrosine. L-DOPA is modified during metabolism to catecholamine neurotransmitters, noradrenaline and adrenaline, which are characterized by different biological activities. L-DOPA has been the first drug of choice in the therapy of Parkinson's disease that is a progressive neurodegenerative disorder involving the loss of dopaminergic neurons of substantia nigra pars compacta. The social and economic impact of these diseases is very high due to the progressive aging of the population. This review focuses on the biological effect of LDOPA, as well as on the synthesis of L-DOPA derivatives and their application in central nervous system diseases. Among them, L-DOPA-containing peptides (L-DOPA-Pep) show important biological and pharmacological activities. For example, L-DOPA analogues of the alpha-factor interact with models of the G protein-coupled receptor, inhibit the oxidation of low-density lipoproteins, and are used for improving L-DOPA absorption in long-term treatment of Parkinson's disease and as skin moisturizer in cosmetic compositions. Moreover, L-DOPA residues in proteins provide reactive tools for the preparation of adhesives and coatings materials. Usually, L-DOPA-Pep is prepared by traditional liquid or solid state procedures starting from simple amino acids. Recently, selective side-chain modifications of pre-formed peptides have also been reported both for linear and branched peptides. Here, we describe the recent advances in the synthesis of L-DOPA and dopa-peptidomimetics and their biological and pharmacological activities, focusing the attention on new synthetic procedures and biological mechanism of actions. There is consensus that amelioration of the motor symptoms of Parkinson's disease is most effective with L-DOPA (levodopa). However, this necessary therapeutic step is biased by an enduring belief that L-DOPA is toxic to the remaining substantia nigra dopaminergic neurons by itself, or by specific metabolites such as dopamine. The concept of L-DOPA toxicity originated from pre-clinical studies conducted mainly in cell culture, demonstrating that L-DOPA or its derivatives damage dopaminergic neurons due to oxidative stress and other mechanisms. However, the in vitro data remain controversial as some studies showed neuroprotective, rather than toxic action of the drug. The relevance of this debate needs to be considered in the context of the studies conducted on animals and in clinical trials that do not provide convincing evidence for L-DOPA toxicity in vivo. This review presents the current views on the pathophysiology of Parkinson's disease, focusing on mitochondrial dysfunction and oxidative/proteolytic stress, the factors that can be affected by L-DOPA or its metabolites. We then critically discuss the evidence supporting the two opposing views on the effects of L-DOPA in vitro, as well as the animal and human data. We also address the problem of inadequate experimental models used in these studies. L-DOPA remains the symptomatic 'hero' of Parkinson's disease. Whether it contributes to degeneration of nigral dopaminergic neurons, or is a 'scapegoat' for explaining undesirable or unexpected effects of the treatment, remains a hotly debated topic.

Bottom Note: *This work is partly presented at EuroScicon congress on Biochemistry, Molecular Biology & Allergy* October 11 - 12, 2018 Amsterdam, Netherlands