

Synthesis of creatine derivatives for the treatment of creatine deficiency disorders

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Creatine plays an essential role in the energetic metabolism and serves dual purpose: under normal conditions, it provides high-energy phosphate to the cellular ATPases; under conditions of higher energy requirements or of ischemia, it provides an energy reserve to postpone anoxic depolarization. The main drawback of creatine is due to its hydrophilic nature and consists in its poor crossing of both the blood-brain barrier and the cell plasma membrane, that creatine crosses using a specific transporter, CrT1. The lack of creatine in the brain is mainly due to three severe diseases, CDS (Creatine Deficiency Syndromes), among which CrT1 deficiency is currently an incurable disease, as administered creatine is not able to reach the brain since the transporter is not functional. This project describes the synthesis and biological studies of some creatine derivative compounds which are able to cross biological membranes in an independent way from the CrT1. There can be two different approaches for this purpose: 1) creatine lipophilic derivatives able to cross lipid-rich biological membranes without using the CrT1. This strategy consists in the synthesis of a modified creatine that is more lipophilic than creatine itself, a diacetyl-creatine ethylester. 2) creatine derivatives in which creatine is linked to a carrier able to use a different transporter from CrT1. This strategy consists in the synthesis of a chimeric molecule composed of creatine and a sugar in order to utilize the glucose transporters in the brain. The following biological tests have been carried out: 1. Stability determination by means of mass spectrometry analysis; 2. Study of the neuroprotective effect; 3. Biochemical tests to measure the concentration of creatine and phosphocreatine in the tissue.

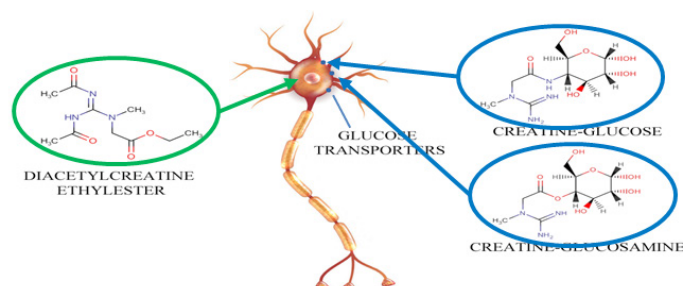


Figure : Two different kind of prodrugs have been synthesized in order to carry the creatine molecules across the neurons membranes: one exploiting its lipophilic nature and the other one utilize alternative transporters instead of SLC6A8

Biography

Maria Arkel is a 3rd year PhD student, working on organic synthesis of biomolecules, particularly creatine derivatives, and their characterization by means of HPLC and mass spectrometry. Her research fields also include biological tests on amino acid derivatives and peptide synthesis.

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