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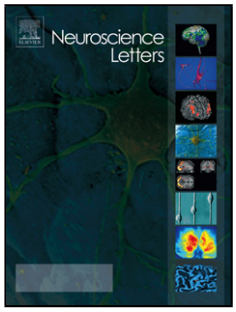

Title: Di-acetyl creatine ethyl ester, a new creatine derivative for the possible treatment of creatine transporter deficiency

Authors: Enrico Adriano, Maurizio Gulino, Maria Arkel, Annalisa Salis, Gianluca Damonte, Nara Liessi, Enrico Millo, Patrizia Garbati, Maurizio Balestrino

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Di-acetyl creatine ethyl ester, a new creatine derivative for the possible treatment of creatine transporter deficiency

Enrico Adriano [1], Maurizio Gulino [1], Maria Arkel [3,4], Annalisa Salis [2,4], Gianluca Damonte [3,4],Nara Liessi [4] Enrico Millo[3,4],Patrizia Garbati [5], Maurizio Balestrino [1*].

[1] Department of Neuroscience, Ophthalmology, Genetics, Maternal-Infantile Sciences, University of Genova, Largo Paolo Daneo 3, 16132 Genova, Italy
[2] Department of Hearth Environmental and Life Science (DISTAV) University of Genova, Corso Europa 26, 16132 Genova, Italy
[3] Department of Experimental Medicine, Section of Biochemistry, University of Genova, Viale Benedetto XV 1, 16132 Genova, Italy
[4] Center of Excellence for Biomedical Research, University of Genova, Viale Benedetto XV 5, 16132 Genova, Italy

[5] Ospedale Policlinico San Martino, Genova, Italy
* Corresponding Author E-mail: mbalestrino@neurologia.unige.it, Tel: +390103537040, Address: Largo Paolo Daneo 3, 16132 Genoa, Italy

Highlights

- We ideated and synthesized di-acetyl creatine ethyl ester (DAC), a new very lipophilic creatine derivative
- In in vitro tests, DAC was able to counter the irreversible suppression of synaptic transmission that is caused by block of the creatine transporter
- Moreover, it was able to increase the concentration of creatine despite block of the creatine transporter
- DAC was active in the micromolar range, a significant innovation compared to all other creatine-derived compounds, which need to be administered in millimolar concentrations.
- DAC opens a promising pathway for possible treatment of the incurable hereditary condition where creatine transporter deficiency is malfunctioning

ABSTRACT

Creatine is pivotal in energy metabolism of the brain. In primary creatine deficiency syndromes, creatine is missing from the brain. Two of them (AGAT and GAMT deficiency) are due to impaired creatine synthesis, and can be treated by creatine supplementation. By contrast, creatine transporter deficiency cannot be treated by such supplementation, since creatine crossing of biological membranes (plasma membrane and blood-brain barrier) is dependent on its transporter. This problem might be overcome by modifying the creatine molecule to allow it to cross biological membranes independently of its transporter. Thus, we designed and synthesized di-acetyl creatine ethyl ester (DAC), a compound that should cross biological membranes independently of the transporter due to its very high lipophilicity. We investigated its ability to increase intracellular creatine levels even after block of creatine transporter, and to counter cell damage induced by transporter block. In our experiments after block of the creatine transporter, DAC was able both to prevent electrophysiological failure and to increase intracellular creatine. Interestingly, it did so in micromolar concentrations, at variance with all the other creatine derivatives that we know of.

KEYWORDS: creatine, creatine derivatives, creatine transporter deficiency, di-acetyl creatine ethyl ester.