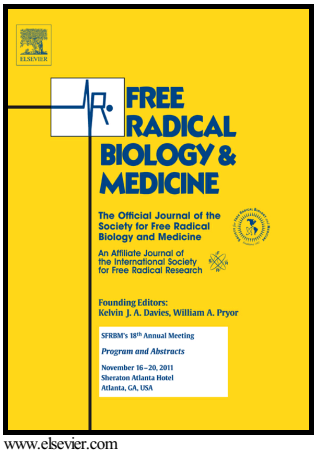
N-acetylcysteine ethyl ester as GSH enhancer in human primary endothelial cells: a comparative study with other drugs

Daniela Giustarini, Federico Galvagni, Isabella Dalle Donne, Aldo Milzani, Filiberto Maria Severi, Annalisa Santucci, Ranieri Rossi



www.elsevier.com

PII: S0891-5849(18)31105-5
DOI: https://doi.org/10.1016/j.freeradbiomed.2018.08.013
Reference: FRB13877

To appear in: *Free Radical Biology and Medicine*

Received date: 21 June 2018
Revised date: 10 August 2018
Accepted date: 12 August 2018

Cite this article as: Daniela Giustarini, Federico Galvagni, Isabella Dalle Donne, Aldo Milzani, Filiberto Maria Severi, Annalisa Santucci and Ranieri Rossi, *N*-acetylcysteine ethyl ester as GSH enhancer in human primary endothelial cells: a comparative study with other drugs, *Free Radical Biology and Medicine,* https://doi.org/10.1016/j.freeradbiomed.2018.08.013

N-acetylcysteine ethyl ester as GSH enhancer in human primary endothelial cells: a comparative study with other drugs

Daniela Giustarini[1*], Federico Galvagni[2], Isabella Dalle Donne[3], Aldo Milzani[3], Filiberto Maria Severi[4], Annalisa Santucci[2] and Ranieri Rossi[1]

[1]Department of Medicine, Surgery and Neurosciences, University of Siena, Via A. Moro 2, I-53100, Siena, Italy

[2]Department of Biotechnology, Chemistry and Pharmacy, University of Siena, Via A. Moro 2, I-53100, Siena, Italy

[3]Department of Biosciences, Università degli Studi di Milano, via Celoria 26, I-20133 Milan, Italy

[4]Department of Molecular and Developmental Medicine, Via delle Scotte, University of Siena, Siena, Italy.

*Correspondence to: Daniela Giustarini, Department of Life Sciences, Laboratory of Pharmacology and Toxicology, University of Siena, via A. Moro 4, I-53100, Siena, Italy Tel.: +39-0577-234198. Fax: +39 0577 234476. E-mail: giustarini@unisi.it

Abstract

Several drugs are currently in use as glutathione (GSH) enhancers in clinical, pre-clinical and experimental research. Here we compare the ability of *N*-acetylcysteine (NAC), 2-oxothiazolidine-4-carboxylic acid (OTC), glutathione ethyl ester (GSH-EE) and *N*-acetylcysteine ethyl ester (NACET) to increase the intracellular concentration of GSH using primary human umbilical vein endothelial cells (HUVEC) as in vitro model. Our experiments highlighted that NACET is largely the most efficient molecule in increasing the intracellular levels of GSH, cysteine, and γ-glutamylcysteine. This is because NACET is lipophilic and can freely cross plasma membrane but, inside the cell, it is de-esterified to the more hydrophilic NAC, which, in turn, is trapped into the cell and slowly transformed into cysteine. The higher availability of cysteine is matched by an increase in GSH synthesis, cysteine availability being the rate limiting step for this reaction. Surprisingly, the increase in GSH concentration was not linear but peaked at 0.5 mM NACET and gradually decreased when cells were treated with higher concentrations of NACET. We