Nitric oxide inhibits adipogenesis by S-nitrosation of CCAAT/enhancer-binding protein β

Astrid SCHRAMMEL1,*, Marion MUSSBACHER2, Heike STESSSEL1, Antonius C. F. GORREN3 and Bernd MAYER1
1Department of Pharmacology and Toxicology, University of Graz, Austria; 2Department of Vascular Biology and Thrombosis Research, Center of Physiology and Pharmacology, Medical University of Vienna, Austria

Background: Within the last decades the prevalence of adipositas, obesity and associated diseases has been escalating world-wide highlighting the need for development of effective therapeutic concepts. 3T3-L1 adipocytes share many similarities with primary fat cells and represent a reliable in vitro model of adipogenesis. The aim of the present study was to investigate the effect of nitric oxide on adipocyte differentiation.

Methods: Adipogenesis was experimentally induced with a mixture of insulin, dexamethasone, and 3-isobutyl-1-methylxanthine in the absence and presence of increasing concentrations of S-nitroso-glutathione (GSNO) and diethylenetriamine NONOate (DETA/NO). After 7 days cells were harvested and analyzed for protein and triglyceride content as well as for mRNA and protein expression of early and late transcription factors and markers of terminal differentiation.

Results: GSNO exerted a prominent anti-adipogenic effect evident as reduced cellular triglyceride and protein content as well as decreased mRNA and protein expression of late transcription factors (e.g. peroxisome proliferator-activated receptor γ) and markers of terminal differentiation (e.g. leptin). By contrast, GSNO did not affect mRNA and protein expression of C/EBPβ, which represents a pivotal early transcription factor of adipogenesis. Differentiation was also inhibited by the NO donor DETA/NO. Biotin switch experiments showed significantly increased S-nitrosation of C/EBPβ variants liver-enriched transcriptional activator protein*, liver-enriched transcriptional activator protein, and liver-enriched inhibitory protein. Moreover, transcriptional activity of C/EBPβ was significantly reduced by the NO donor.

Discussion: Our data demonstrate that posttranslational S-nitrosative modification of C/EBPβ accounts for the anti-adipogenic effect of NO, suggesting that S-nitrosation represents an important physiological concept to control fat cell maturation.

*Corresponding author e-mail: astrid.schrammel-gorren@uni-graz.at