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Title: Biological effects of nanostructured lipid carriers

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Body: Nanostructured lipid carriers (NLC) are a type of drug delivery system offering improved performance in terms of drug loading and long-term stability. Our aims were to test mechanisms of NLC uptake into endothelial cells (EC) and evaluate possible biologic effects of these compounds. NLC were prepared with triglycerides Miglyol and Softisan and egg-phosphatidylcholine (1:1 by weight) by the double emulsion technique. Cultured mouse lung microvascular endothelial cells (LMVEC) were incubated with curcumin-loaded NLC and uptake was quantified as fluorescence detected in the cell homogenate or by FACS. To test biologic effects, we challenged human LMVEC with thrombin with or without NLC and measured endothelial permeability as flux rate of fluorescent albumin across endothelial monolayers grown on transwell inserts. Alterations were tested in thrombin-induced Extracellular-Regulated Kinase (ERK) activation by immunoblotting and endothelial actin remodelling by fluorescence microscopy. Finally, NLC were delivered intravenously as pre-treatment in a mouse model of hydrochloric acid (HCl) aspiration lung injury. Using cultured mouse LMVEC we observed that NLC are incorporated into cells more efficiently when caveolin-1, the structural protein of caveolar vesicles, is expressed. Upon challenge of cultured EC with thrombin, NLC attenuated the permeability increase, activation of ERK, cytokine production and actin stress fiber formation. In the HCl-aspiration model, NLC attenuated the increase in bronchoalveolar lavage protein content, inflammatory cells and histological alterations. Conclusion: systemically delivered NLC are taken up by EC via caveolae and have endothelial-protective effects of potential relevance to acute lung injury.