The Antiatherogenic Effect of DiNAC: Experimental Findings Supporting Immunomodulation as a New Treatment for Atherosclerosis Related Diseases

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ABSTRACT

Inflammatory processes in the arterial wall are important in atherogenesis. The present review discusses the development of DiNAC as a potential new treatment modality for atherosclerosis related diseases. DiNAC, N,N’-diacetyl-L-cystine, is the disulphide dimer of N-acetyl cysteine, NAC. It was selected as an immunomodulating drug candidate due to its ability to modify contact sensitivity/delayed type hypersensitivity (CS/DTH) reactions in vivo. Initial structure-activity relationship (SAR) studies indicated that an intact disulfide bridge was essential for this effect. Antioxidants, like probucol and some close analogs with two sulphurs in close proximity (but not disulphides), were also found to have similar effects on CS/DTH reactions. These antioxidants have antiatherosclerotic effects, while structurally related compounds without sulphurs do not. Therefore, it was hypothesized that DiNAC might also possess antiatherosclerotic effects. This was investigated in WHHL rabbits and mice. In both species, DiNAC had antiatherosclerotic activity similar to that of probucol. The effect of DiNAC was not due to an alteration of lipid metabolism. Impaired endothelium mediated relaxation is known to be associated with atherosclerosis. DiNAC was shown to reverse this process in WHHL rabbits with advanced atherosclerosis, probably due to an action on the vessel wall itself that is not related to the extent of atherosclerosis or to plasma lipid levels. Preliminary data from a clinical investigation in hypercholesterolemic subjects suggest that DiNAC is likely to have similar effects also in patients. Taken together, these findings suggest immunomodulation to be a potential new therapy for atherosclerosis related diseases. DiNAC may represent a new treatment modality for such diseases.