The role of nicotinamide N- methyltransferase (NNMT) in anti-inflammatory and anti-atherosclerotic action of nicotinic acid in mouse model of accelerated atherosclerosis

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Introduction

Nicotinic acid (**NicA**) is the most effective HDL- raising drug, but it has additional anti-inflammatory properties, that seems to be independent of its effect on lipid profile. NicA has ability to attenuate endothelial dysfunction in patients with metabolic syndrome or coronary artery disease [2,4,5], it also prevents the expression of adhesion molecules and MCP-1 release in animal models [6]. It is possible, that many of this actions are connected with 1-methylnicotinamide (**MNA**), synthesized by nicotinamide N-methyltranspherase (NNMT). MNA was considered as an inactive metabolite of NicA. Recent studies, however, has revealed antiatherothrombotic [1] and anti- inflammatory [3] activities of MNA, linked to COX/PGI_2 pathway.

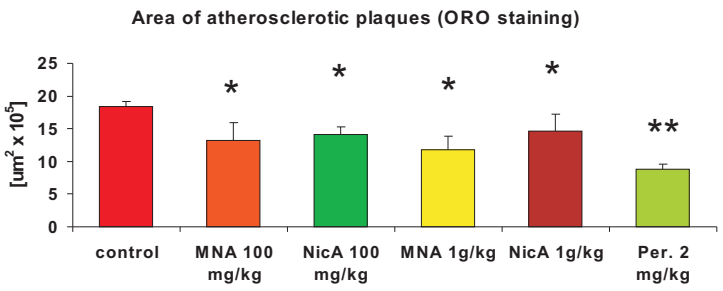
1. Chlopicki,S. et al, 2007 Br.J.Pharmacol., 152, 230-239. **2.** Lee,J.M. et al, 2009 J.Am.Coll.Cardiol., 54, 1787-1794. 3. Przygrodzki,T. et al, 2010 Eur.J.Pharmacol., 640, 157-162. **4.** Thoenes,M. et al, 2007 Int.J.Clin.Pract., 61, 1942-1948. **5.** Warnholtz,A. et al, 2009 Atherosclerosis, 204, 216-221. **6.** Wu,B.J. et al, 2010 Arterioscler.Thromb.Vasc.Biol., 30, 968-975.

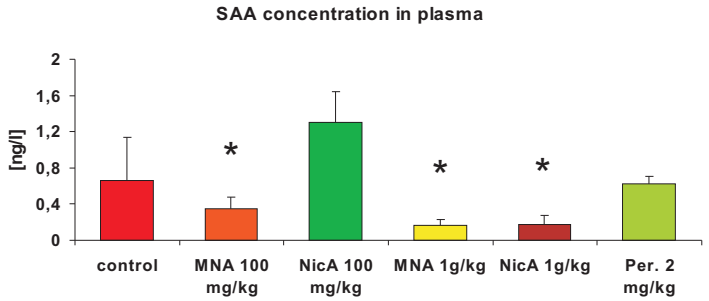
The aim of this study

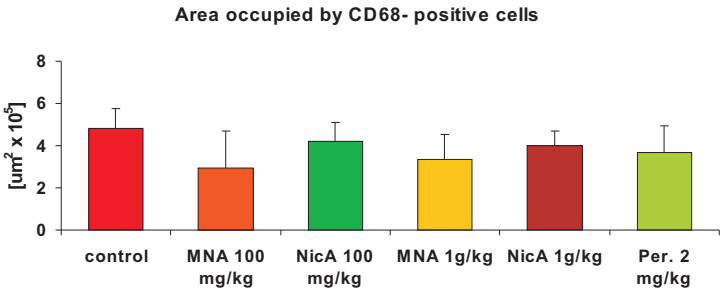
The aim of this study was firstly: to compare the antiatherosclerotic and anti-inflammatory activity of NicA, MNA (100 mg/kg and 1 g/kg) and ACE-I perindopril (2 mg/kg) given for 2 months to ApoE/LDLR$^{-/-}$ mice fed with high-cholesterol diet, and secondly: to examine the concentration of endogenous MNA in plasma taken from NicA- treated groups.

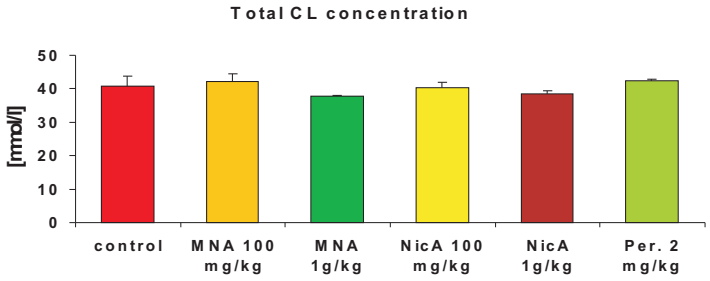
Materials and methods

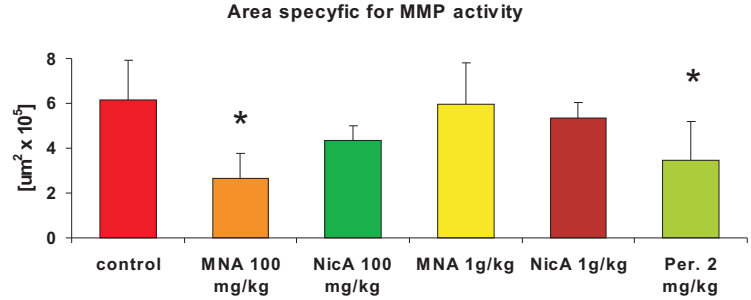
Plaque progression (ORO), macrophage content (CD68 IHC) and MMP activity (zymography) were examined inside aortic roots using standardized *cross- section* protocol. Endogenous NicA metabolites concentrations (LC/MS), SAA (ELISA) and total cholesterol concentration (spectophotometry) were measured in plasma taken from ApoE/LDLR$^{-/-}$ mice.

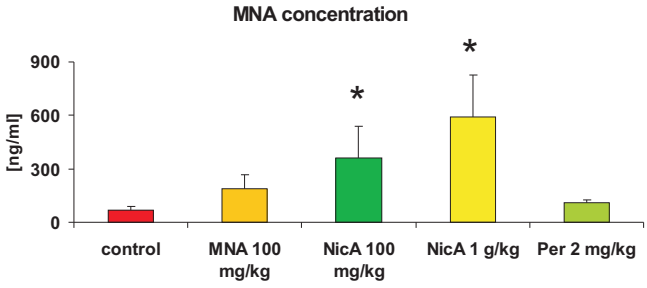












Results

NicA, MNA and perindopril reduced the area of atherosclerotic lesions and plasma concentration of SAA without changing the concentration of totCL. MNA and perindopril also lowered MMP activity in the plaque area and macrophage accumulation. The concentration of endogenous MNA was elevated during atherothrombotic progression in NicA- treated groups, probably as a result of higher NNMT activity in liver.

Summary

Exogenous MNA displays anti-atherosclerotic activity comparable with NicA, suggesting MNA-dependent mechanisms in NicA antiatheroclerotic action. High concentrations of endogenous MNA during atherosclerosis suggest, that NNMT-MNA pathway may have a regulatory role in atherosclerosis.

Acknowledgements

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