The impact of anti-inflammatory action of N-stearoylethanolamine on the development of atherosclerosis in spontaneously hypertensive rats given a cholesterol rich diet

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Introduction: N-stearoylethanolamine (NSE) is a naturally occurring saturated NAE which possesses anti-inflammatory, hypoglycemic and antitoxic properties. NSE had membranotropic action, and could influence the lipid profile of tissues and inhibit platelets *in vitro*. Taking into account the role of lipid metabolism changes and inflammation in atherogenesis we aimed to study the effect of NSE on the atherosclerotic changes in aorta and blood coagulation of rats.

Methods: The model of atherosclerosis was based on **a** cholesterol rich diet (CRD) of spontaneously hypertensive rats (SHR). Female rats (n = 30) with genetically determined hypertension proven by direct measurement of blood pressure were fed the CRD (5 % of cholesterol) during 2 months. A control group of SHR (n = 10) received standard pellet diet, 10 rats received CRD and 10 rats were given CRD with daily *per os* application of NSE at a dose of 50 mg/kg of body weight. Atherosclerotic changes in blood vessels of rats were proven by histological analysis. Platelet aggregation rate, partial activated thromboplastin time (APTT) and fibrinogen concentration were determined by standard methods. Level of protein C (PC) was measured using chromogenic substrate S2366 (p-Glu-Pro-Arg-pNa). Statistical analysis was performed using the Mann-Whitney test.

Results: Dietary cholesterol overload caused the disturbance of the lipoprotein profile of rat blood plasma, with an increase of plasma LDL content of almost 2 times and 15% growth of HDL compared to the control group that was not changed by NSE action. CRD rats had higher fibrinogen concentration, increased rate of platelet aggregation, decreased level of anticoagulant PC and huge edema of the subendothelial layer and a disruption of the middle shell integrity of the aorta. Platelet aggregation speed increased in CRD-rats (52.5 ± 4.1%/min) and was slightly normalized under the action of NSE (40 ± 8.3 against 35 ± 9%/min in controls). Fibrinogen concentration (2.75 ± 0.7 versus 1.9 ± 0.5 mg/ml in controls) and clotting time in APTT-test were not changed by NSE application. However, the level of anticoagulant PC that was decreased in CRD-rats (65 ± 16 versus 100 ± 11% in controls) was normalized under the action of NSE (92 ± 17%). While normalizing the thickness of the aorta wall (0.135 ± 0.06 in CRD, 0.105 ± 0.02 mm in CRD + NSE versus 0.093 ± 0.016 mm in controls), NSE did not change the cholesterol-induced inclusions within aorta media (2.8 ± 1.7 in CRD, 3.3 ± 0.8 in CRD + NSE versus 1.9 ± 1.0% in controls).

Discussion: Anti-inflammatory action of NSE changes the atherogenic processes in CRD-rats, mainly protecting the PC from consumption during the inflammatory process and reducing edema of the aorta. However hematological parameters (including clotting time in APTT-test and fibrinogen concentration) changed independently on NSE application. Anti-aggregatory action of NSE on platelets can be a result of direct action on platelets or the consequence of its anti-inflammatory action.

Conclusions: During atherogenesis induced by CRD in this animal model, NSE demonstrated valuable anti-inflammatory action protecting the rats during atherogenesis. However it cannot be assumed to be an antithrombotic or antiatherogenic agent because it was unable to influence hemostasis directly.

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