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EFFECTS OF SIMVASTATIN IN A RABBIT MODEL OF ATHEROSCLEROSIS: ROLE OF HO-1/CO-CGMP PATHWAY AND RELATED ANTI-OXIDATIVE ENZYME EXPRESSION

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Objectives Clinical and experimental observations indicated that HMG-CoA reductase inhibitors (statins) have pleiotropic effects. The present study was designed to elucidate the status of cyclic adenosine monophosphate (c-GMP), Cyclooxygenase-2 (COX-2),

Carbon Monoxide Haemoglobin (COHb) and haem oxygenase-1 (HO-1) to the antoxidative effects of Simvastatin in the hypercholesterolemic rabbit.

Methods Twenty four male Japanese white (JW) rabbits weighing approximately 2.0 kg were used in this study. The animals were randomised into three groups of eight animals each: one control group and other two groups which were maintained on high-cholesterol diet (HCD) for 24 weeks. After 8 weeks on this diet, the animals were divided into two groups: non-treated group and simvastatin group; the animals were euthanised with an overdose of sodium pentobarbital at the end 24th week. The aorta were excised, placed in ice-cold sterile saline, and cleaned of connective tissue. Blood was taken through cardiac puncture and plasma was used for biochemical assay of lipid peroxides. Levels of HbCO, COX-2 and cGMP were measured by Enzyme-Linked Immunosorbent Assay (ELISA) kits. HO-1mRNA in arterial were analysed using Real Time Quantitative PCR methods, and expression of MMP-9 protein was measured by immunohisto-chemical assay, serum malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were also measured.

Results Twenty-four weeks of atherogenic diet significantly increased the levels of MDA cytotoxic (19.72±2.60 vs 14.24 ±1.87 ng/ml control group), and SOD (1.31±0.45 vs 7.92±1. μg/ml control), cGMP (18.66±1.47 vs 12.54±1.45 nmol/l control group) decreased in serum;

HO-1mRNA expression of non-treated group is no different than the control group (1.75±1.02 vs 1.34±0.63), but is showing the tendency to increase (3.22±1.67vs 1.75±1.02 non-treated group, p=0.062) after treatment with Simvastatin. SOD, NO and cGMP were as well as increased ($p<0.01$ or $p<0.05$), but MMP-9 and HbCO (56.12±11.67 vs 101.0±41.55 μg/ml non-treated group) decreased significantly than the non-treated group ($p<0.01$ or $p<0.05$) after treatment with Simvastatin. Simvastatin partially restored the HO-1, SOD and NO, decreased MDA and HbCO levels, but to COX-2(67.69±6.39 vs 68.90±9.04 U/l non-treated group), no differences among groups were observed.

Conclusions Atherosclerosis induced an oxidative damage and simvastatin had significant anti-atherogenic and anti-oxidation effects in an animal model with rabbits fed a hypercholesterolemic diet, maybe it mediated by HO-1, restoring the SOD and NO levels and reducing cytotoxic MDA levels.