NITRIC OXIDE-DONATING STATINS DISPLAY ANTI-INFLAMMATORY AND HEALING ACTIVITIES IN MODELS OF CARDIOVASCULAR DISEASES

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There is evidence that inhibitors of 3-hydroxy-3-methylglutary CoA reductase, so-called "statins" have pharmacological properties that depend on mechanisms involving activation of endothelial nitric oxide synthase (eNOS). In the attempt to enhance the "non-lipid" properties of statins we have modified their chemical structure to incorporate a NO-donating moiety. Here we describe the profile of one prototype compound, the derivative of pravastatin NCX 6550 (NCX) in models and biomarkers relevant to cardiovascular disorders.
Unlike pravastatin, NCX counteracted noradrenaline-induced contraction in rat aorta (EC50= 14μM) and inhibited smooth muscle cell proliferation (IC50= 2.2 μM). In conditions of vascular dysfunction such as aorta of hypertensive rats (SHR) and internal human mammary artery, NCX markedly improved endothelium-dependent relaxation to Ach. In SHR, NCX reduced systolic blood pressure by 12% at 48 mg/kg orally over repeated treatment.
In severe hypercholesterolemic LDLR-/- mice, NCX was more effective than pravastatin in decreasing IL-6, TNFalpha and sVCAM. In atherosclerotic ApoE-/- mice, NCX reduced plasma MCP-1 levels and splenocyte adhesion to arterial segments concomitant with inhibition of endothelial ICAM espression. In normoglycaemic or STZ-diabetic mice, following unilateral limb ischemia, NCX stimulated reparative angiogenesis and improved limb reperfusion better than pravastatin, thus leading to a higher rate of foot salvage. These effects were associated with mobilization of endothelial progenitor cells (EPC) from bone marrow to the peripheral circulation. In *in vitro* migratory assays, high glucose reduced EPC motility towards SDF-1. This deficit was corrected by pre-incubating EPC with NCX, whereas the effect of pravastatin was partial. In $eNOS^{-/-}$ mice, which typically show impairment in post-ischemic reparative angiogenesis, NCX was able to rescue the deficit and promote faster healing, whereas pravastatin was ineffective. These findings indicate that the NO moiety improves the therapeutic potential of statins for the treatment of peripheral vascular disease.
Overall, from the data available NCX appears to possess properties which contribute significantly to make it effective on multiple pathological mechanisms such as those underlying atherosclerosis, vascular complications associated with diabetes and peripheral ischemia. The NO-donating statins appear therefore to be an opportunity of enhanced therapeutic benefits over the currently used statins.