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1-Methylnicotinamide (MNA) prevents endothelial dysfunction in hypertriglyceridemic and diabetic rats

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Abstract:
For many years, 1-methylnicotinamide (MNA), a primary metabolite of nicotinamide, has been considered inactive. Recently however, it has been discovered that MNA possesses anti-thrombotic and anti-inflammatory activity. In the present study we investigated whether chronic administration of MNA to hypertriglyceridemic or diabetic rats would reverse endothelial dysfunction characterized by the impairment of nitric oxide (NO)-dependent vasodilatation.
Hypertriglyceridemia in rats was induced by fructose-rich (60%) diet, while diabetes was induced by streptozotocin injection (70 mg/kg). After eight weeks, in hypertriglyceridemic or diabetic rats treated or non-treated with MNA (100 mg/kg), we analyzed the magnitude of endothelium-dependent or endothelium-independent vasodilatation in aorta induced by acetylcholine or S-nitroso-N-acetyl-penicilamine (SNAP), respectively, as well as plasma concentration of: cholesterol, triglycerides, glucose, HbA_{1c}, fructosamine, peptide C, endogenous MNA and its metabolites (M2PY, M4PY).
In diabetic rats plasma concentration of glucose, HbA_{1c} and fructosamine was elevated (402.08 ± 19.01 *vs*. 82.06 ± 5.41 mg/dl, $p < 0.001$; 9.55 ± 0.56 *vs*. 4.93 ± 0.24%, $p = 0.052$ and 2.53 ± 0.10 *vs*. 1.14 ± 0.06 mmol DTF/mg protein, $p < 0.001$ in diabetic and control rats, respectively). In hypertriglyceridemic rats plasma concentration of triglycerides was elevated (4.25 ± 0.27 *vs*. 1.55 ± 0.12 mmol/l, $p < 0.001$ in hypertriglyceridemic and control rats, respectively). In both models the NO-dependent vasodilatation in aorta induced by acetylcholine was significantly impaired as compared to control rats, while the response to SNAP was largely preserved. In hypertriglyceridemic rats, 4 weeks of treatment with MNA (100 mg/kg, *po*) resulted in a three to six-fold increase in endogenous levels of MNA and its metabolites (M2PY and M4PY), the fall in triglycerides concentration in plasma (from 4.25 ± 0.27 to 2.22 ± 0.14 mmol/l, $p < 0.001$), and the preservation of the NO-dependent vasodilatation. In diabetic rats chronic treatment with MNA also prevented the impairment of NO-dependent vasodilatation, while it displayed only a mild effect on hyperglycemia and did not lower triglycerides concentration.
In summary, MNA treatment decreased plasma triglycerides concentration in hypertriglyceridemic, but not in diabetic rats, while it prevented the development of endothelial dysfunction in aorta in both of these models. Accordingly, the ability of MNA to reverse endothelial dysfunction seems to be independent of its hypolipemic activity.

Key words:
1-methylnicotinamide, hypertriglyceridemia, diabetes, endothelium, NO, endothelial dysfunction