Leucine Amplifies the Effects of Nicotinic Acid on Hyperlipidemia and Atherosclerosis in LDLRKO-Mice

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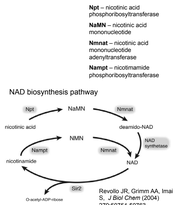
524-P Abstract

Nicotinic acid (NA) is an effective treatment for dyslipidemias, but its use is limited due to poorly tolerated adverse effects (vasodilation and flushing). Since NA serves as a source of nicotinamide adenine dinucleotide (NAD+), some of these effects appear to be mediated by Sirt1-activation. Leucine (Leu) also acts as a Sirt1/AMPK activator, and amplifies the effects of other compounds converging on this pathway, thereby reducing the necessary concentrations. We recently found leucine to synergize with NA on AMPK/Sirt1 activation and increase fatty acid oxidation in hepatocytes and myotubes and to, reduce lipid accumulation and increase life span in C. elegans. We have now tested the interactive effects of Leu and sub therapeutic doses of NA on hyperlipidemia and atherosclerosis in vivo. LDL receptor knockout mice (LDLRKO), a mouse model of atherosclerosis, were fed an atherogenic western diet (WD, 0.21% cholesterol (by weight), 40% calories from fat) and randomized to control (WD), WD + Leu (24g/kg diet), WD + Leu + NA (50 mg/kg diet), WD + Leu + NA (250 mg/kg diet), or WD + NA (1000 mg /kg diet, ~equivalent to low therapeutic human dose of 1500 mg/day) for 10 weeks. Leucine combined with sub-therapeutic NA (50 and 250 mg/kg diet) reduced total cholesterol and cholesterol esters up to ~28% ($p<0.01$), and plasma triglycerides by ~30% ($p<0.01$) at 4 and 8 weeks. Moreover, the Leu/NA combinations decreased atherosclerotic lesion size and lipid area at study conclusion, as well as aortic macrophage infiltration by ~50% ($p<0.001$). All these effects were comparable to the therapeutic NA dose (1000 mg/kg diet). Thus, Leu amplifies the effects of NA on hyperlipidemia and atherosclerosis in LDLRKO mice, thereby decreasing the necessary concentration of NA by 80% without loss of efficacy. This dose reduction may diminish the NA's adverse effects. Accordingly, this combination may provide the basis for a useful therapeutic alternative for hyperlipidemia and atherosclerosis.

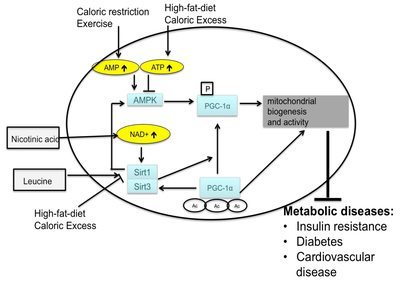
Introduction

Nicotinic acid (NA), a form of vitamin B3, is used in high concentration (up to 2000 mg/day) as an effective treatment for dyslipidemias, and may reduce atherosclerotic plaque progression and thereby prevent coronary heart disease. However, its use is limited due to the poorly tolerated adverse effects such as vasodilation and flushing (1). In addition to its lipid-lowering effects, NA is also a source of NAD^+ by entering the biosynthesis pathway, and thus also a a direct activator of Sirt1 (2, 3).



The branched-chain amino acid leucine (Leu) also activates Sirt1 by lowering the activation energy for NAD^+, thus mimicking the effects of caloric restriction, and coactivates and amplifies the effects of other sirtuin activators at low concentrations (4, 5). We recently found leucine to synergize with NA to stimulate the AMPK/Sirt1 pathway resulting in increased fatty acid oxidation in hepatocytes and myotubes. Moreover, leu combined with NA reduced lipid accumulation and increased lifespan in *C. elegans* (6).

Accordingly, this study was designed to evaluate interactions of leucine and sub-therapeutic doses of NA on hyperlipidemia and atherosclerosis in LDL-receptor knockout (LDLRKO)-mice, a mouse model of atherosclerosis.



Metabolic diseases:
- Insulin resistance
- Diabetes
- Cardiovascular disease

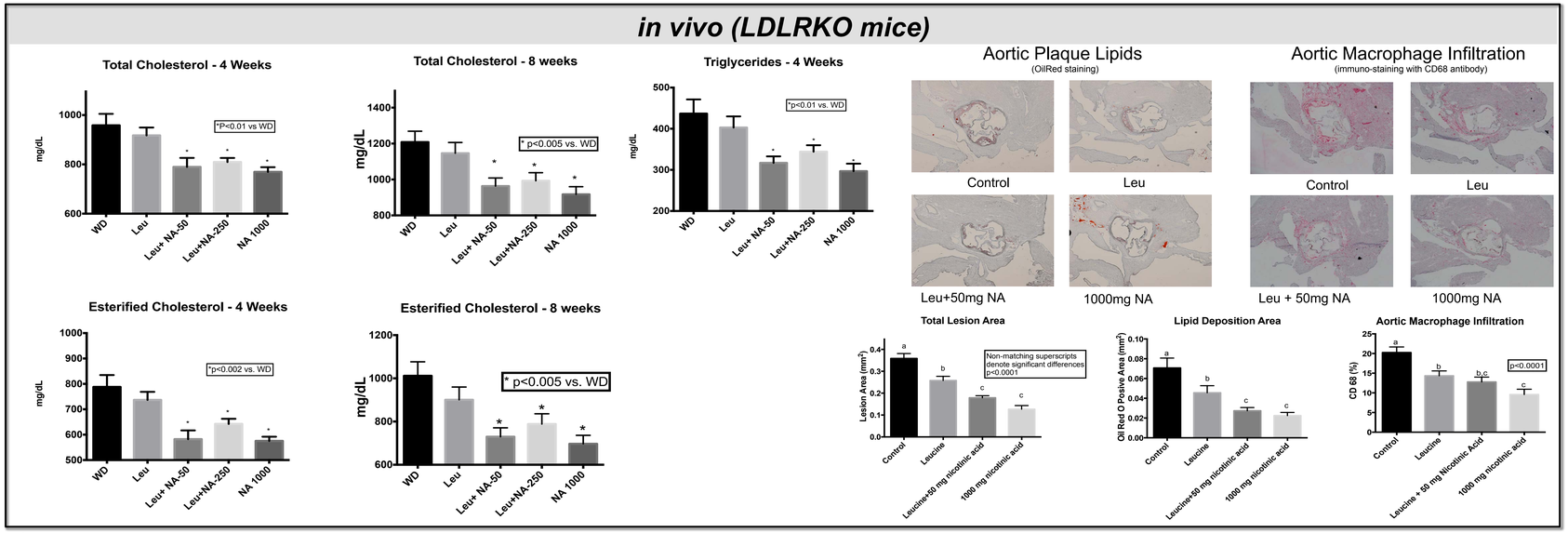
Materials & Methods

Animals: LDL receptor knockout (LDLRKO) mice (n=10/group) were fed an atherogenic western diet (WD) containing 0.21% cholesterol (by weight) and 40% calories from fat for 4 followed by the treatment period for 8 weeks.

Treatment groups:

1. Control WD
2. WD + Leucine (24 g/kg diet; a two-fold increase over control levels)
3. WD + Leucine + 50 mg nicotinic acid/kg diet
4. WD + Leucine + 250 mg nicotinic acid/kg diet
5. WD + 1000 mg nicotinic acid/kg diet
   (equivalent to a low therapeutic dose in humans of ~1500 mg/day)

Results



Conclusions

- ✧ Low dose nicotinic acid (50 and 250 mg/kg diet, 95 and 75% dose reductions) combined with leucine significantly improved hyperlipidemia and hypercholesterolemia comparable to the therapeutic dose of NA (1000 mg/kg diet)
- ✧ The NA-Leu combinations decreased atherosclerotic lesion size, lipid deposition area and aortic macrophage infiltration comparable to the therapeutic dose
- ✧ Leucine enables a marked nicotinic acid dose reduction, potentially reducing adverse effects and expanding therapeutic utility

References

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