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

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Materials & Methods

Animals: LDL-receptor knockout (LDLRKO) mice (n=10/group) 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 + 50 mg nicotinic acid/kg diet, WD + Leu + NA 500 mg/kg diet, WD + Leu + NA 1000 mg/kg diet, and WD + Leu + NA 2000 mg/kg diet, equivalent to the Therapeutic Human dose of NA (1000 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 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 to reduce lipid accumulation and increase lifespan in C. elegans. We have now tested the interactive effects of Leu and sub-therapeutic doses of NA on hyperlipidemia and atherosclerosis in LDLRKO mice, thereby decreasing the necessary concentration of NA by 80% without decreasing total cholesterol and triglycerides.

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 direct activator of Sirt1 (2, 3).

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.

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 weeks followed by the treatment period for 8 weeks.

Treatment groups:

1. Control WD
2. WD + Leucine (24g/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

1. 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)
2. The NA-Leu combinations decreased atherosclerotic lesion size, lipid deposition area and aortic macrophage infiltration comparable to the therapeutic dose
3. Leucine enables a marked nicotinic acid dose reduction, potentially reducing adverse effects and expanding therapeutic utility

References

2. Revollo JR, Grimm AA, Imai S. Nicotinic acid serves as a source of nicotinamide adenine dinucleotide (NAD+), some of these effects appear to be mediated by Sirt1 activation. Leucine also acts as a Sirt1/AMPK activator, and amplifies the effects of other compounds converging on this pathway, thereby reducing the necessary concentration of NA by 80% without decreasing total cholesterol and triglycerides.

Nicotinic acid (NA) is an effective treatment for dyslipidemias, but its use is limited due to poorly tolerated adverse effects (vasodilation and flushing). Nicotinic acid (NA), a form of vitamin B3, is used in high concentration (up to 2000 mg/day) as an effective treatment for hyperlipidemia and hypercholesterolemia comparable to the therapeutic dose of NA (1000 mg/kg diet) with only mild adverse effects on lipid-lowering effects, NA is also a source of NAD+ by entering the biosynthesis pathway, and thus also a direct activator of Sirt1 (2, 3).

1. Control WD
2. WD + Leucine (24g/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)