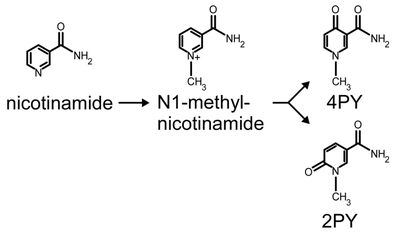
Cleveland Clinic Terminal metabolites of niacin, a component of cereal fortification, are associated with vascular inflammation and residual cardiovascular disease risk

Marc Ferrell, Zeneng Wang, James Anderson, Marco Witkowski, Xinmin Li, Joseph DiDonato, Naseer Sangwan, W. H. Wilson Tang, Stanley Hazen

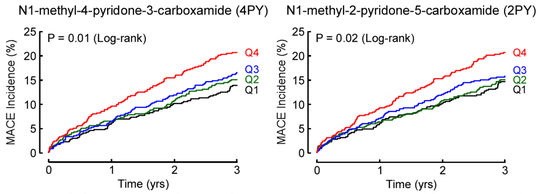
Cardiovascular and Metabolic Sciences

Abstract



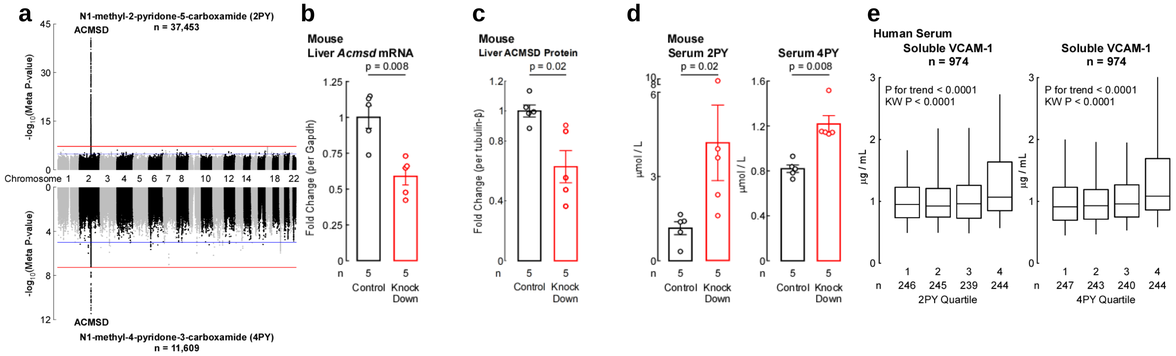
- Niacin (nicotinamide/vitamin B3) is an essential vitamin required for adequate synthesis of NAD (nicotinamide adenine dinucleotide).
- The United States mandates niacin fortification in cereals, and niacin dietary supplements are popular.
- Excess dietary niacin is converted to the metabolites 2PY and 4PY
- 4PY provokes vascular inflammation via VCAM-1 expression *in vitro* and *in vivo*

Niacin metabolites 2PY and 4PY are associated with incident CVD risk



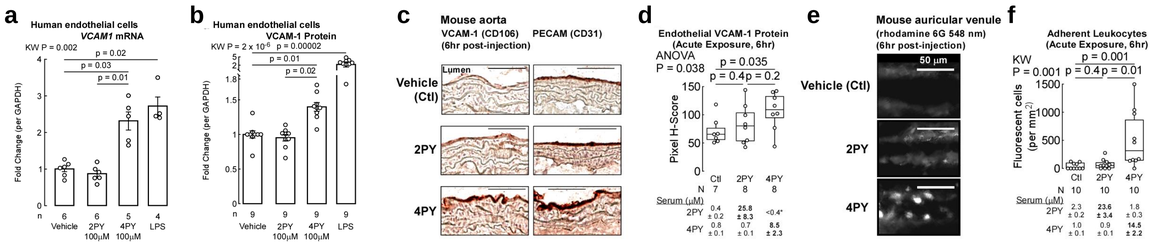
- Incidence of major adverse cardiovascular events vs quartiles of 2PY and 4PY in a prospective cohort study.
- The highest quartile of 2PY/4PY levels is shown in red.

A genetic variant within *ACMSD* is associated with 2PY, 4PY, and VCAM-1



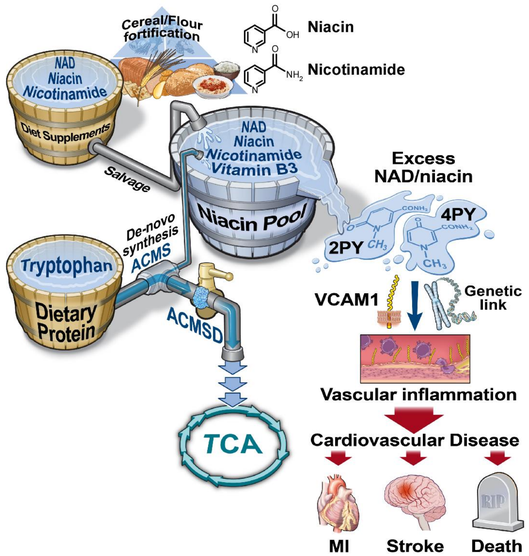
- (a) Genome-wide association analysis revealed an association between *ACMSD* (rs10496731) and 2PY and 4PY.
- (b-c) *Acmsd* knockdown in mice elevated circulating 2PY and 4PY
- (d) Phenome-wide association analysis revealed rs10496731 is also associated with circulating VCAM-1 levels (n = 106,000; P = 3.6 x 10^{-18})
- (e) 2PY and 4PY levels are correlated with circulating VCAM-1

Niacin metabolite 4PY enhances VCAM-1 expression and function *in vivo*



- (a-b) 4PY, but not 2PY, elevates VCAM-1 expression in human endothelial cells
- (c-d) 4PY provokes VCAM-1 expression in mouse aortic endothelium
- (e-f) 4PY induces leukocyte adhesion to vascular endothelium in mice

Conclusions



- Dietary protein and fortified cereals contribute to the niacin pool
- Excess niacin is converted to the metabolites 2PY and 4PY
- 4PY provokes vascular inflammation via VCAM-1 expression

Acknowledgements

- Additional Authors: James R. Hilser, Jaana A. Hartiala, Hooman Allayee
- Funding: R01HL103866, P01HL147823, R01HL133169, R01HL148110