NAD+

The Science of Life Extension

Presented by

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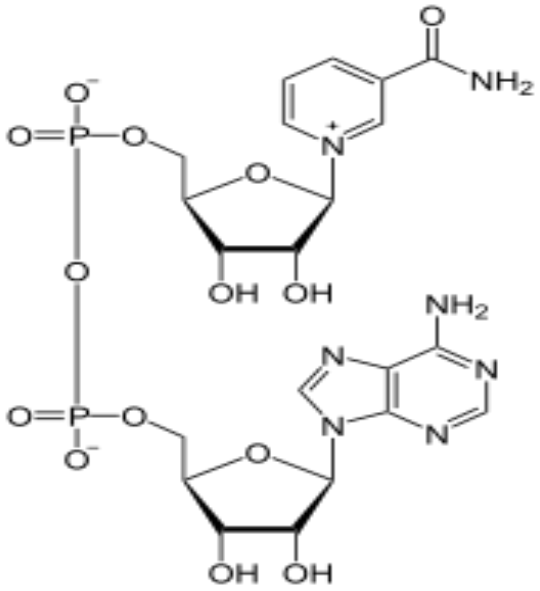
What is NAD+ anyway?

And, why is it so important?



NAD+ (Nicotinamide adenine dinucleotide) is a coenzyme
found inside of every cell in the body and is essential to sustain life!

NAD+ is needed for REDOX chemical reactions

(**Red**uction & **Ox**idation)

NPJ Aging Mech Dis. 2016; 2: 16017 doi: 10.1038/npjamd.2016.17

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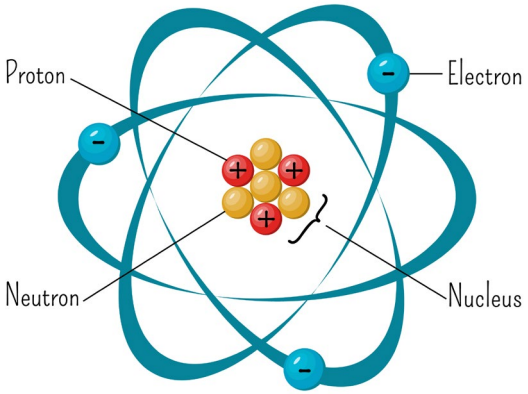
NAD+ transfers electrons

NAD+ picks up electrons to become NADH (reduction).

Then, NADH drops off electrons to become NAD+ again (oxidation).

This drives
ENERGY and METABOLISM



LEO the Lion says GER
Lose electrons is oxidation
Gain electrons is reduction

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NAD+ declines as we age

- Supporting energy & metabolism
- Supporting healthy blood sugar
- Supporting healthy DNA
- ***What can we do!?***

PLoS One. 2011 Apr 26;6(4):e19194. doi: 10.1371/journal.pone.0019194.
Biogerontology. 2017; 18(4): 447–476. doi: 10.1007/s10522-017-9685-9
Handb Exp Pharmacol. 2011; 206: 125–162. doi: 10.1007/978-3-642-21631-2_7
EMBO J. 2006 Mar 22; 25(6): 1305–1314. doi: 10.1038/sj.emboj.7601015

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Nicotinamide Riboside

Precursor to making NAD+!

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Nicotinamide Riboside (NR)

www.nature.com/scientificreports

OPEN

Safety and Metabolism of Long-term Administration of NIAGEN (Nicotinamide Riboside Chloride) in a Randomized, Double-Blind, Placebo-controlled Clinical Trial of Healthy Overweight Adults

Received: 26 March 2019
Accepted: 21 June 2019
Published online: 05 July 2019

Dietrich Conze[1], Charles Brenner[2] & Claire L. Kruger[1]

Nicotinamide riboside (NR) is a newly discovered nicotinamide adenine dinucleotide (NAD^+) precursor vitamin. A crystal form of NR chloride termed NIAGEN is generally recognized as safe (GRAS) for use in foods and the subject of two New Dietary Ingredient Notifications for use in dietary supplements. To evaluate the kinetics and dose-dependency of NR oral availability and safety in overweight, but otherwise healthy men and women, an 8-week randomized, double-blind, placebo-controlled clinical trial was conducted. Consumption of 100, 300 and 1000 mg NR dose-dependently and significantly increased whole blood NAD^+ (i.e., 22%, 51% and 142%) and other NAD^+ metabolites within 2 weeks. The increases were maintained throughout the remainder of the study. There were no reports of flushing and no significant differences in adverse events between the NR and placebo-treated groups or between groups at different NR doses. NR also did not elevate low density lipoprotein cholesterol or dysregulate 1-carbon metabolism. Together these data support the development of a tolerable upper intake limit for NR based on human data.

The NAD^+ co-enzymes NAD^+, NADH, $NADP^+$ and NADPH are the central regulators of metabolism. They are required for fuel oxidation, ATP generation, gluconeogenesis, ketogenesis, production of pentose phosphates, heme, lipids, steroid hormones and detoxification of free radical species[1,2]. NAD^+ is also a consumed substrate of enzymes that polymerize and/or transfer ADPribose, form cyclic ADPribose (cyclic ADPribose synthetases) and deacylate protein lysine substrates (sirtuins) with production of acyl-ADPribosyl products. Poly(ADPribose) polymerases (PARPs) signal DNA damage in order to assemble repair machinery, while cyclic ADPribose synthetases produce second messengers that mobilize calcium ions from intracellular stores, and sirtuins influence gene expression and protein activities by virtue of reversing protein post-translational modifications[3]. In light of

"Consumption of 100, 300 and 1000mg of NR dose-dependently and significantly increased whole blood NAD+ (i.e., 22%, 51% and 142%) and other NAD+ metabolites within 2 weeks"

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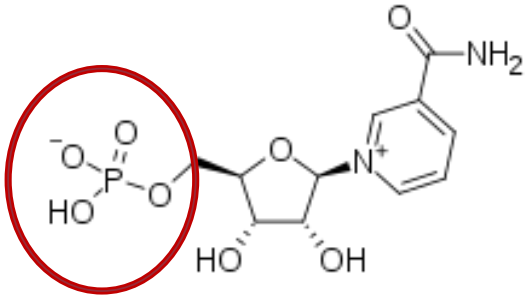
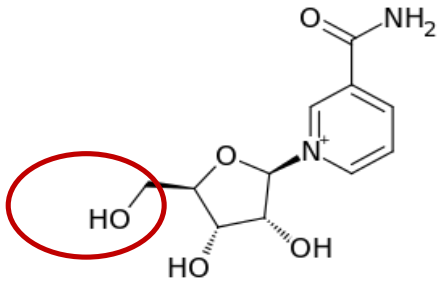
But, there are choices…NR or NMN?

Nicotinamide mononucleotide (NMN) versus Nicotinamide riboside (NR)





- NMN is the immediate precursor to making NAD+
- Then why choose NR?

Ratajczak, J., Joffraud, M., Trammell, S. *et al.* NRK1 controls nicotinamide mononucleotide and nicotinamide riboside metabolism in mammalian cells. *Nat Commun* **7,** 13103 (2016) doi:10.1038/ncomms13103

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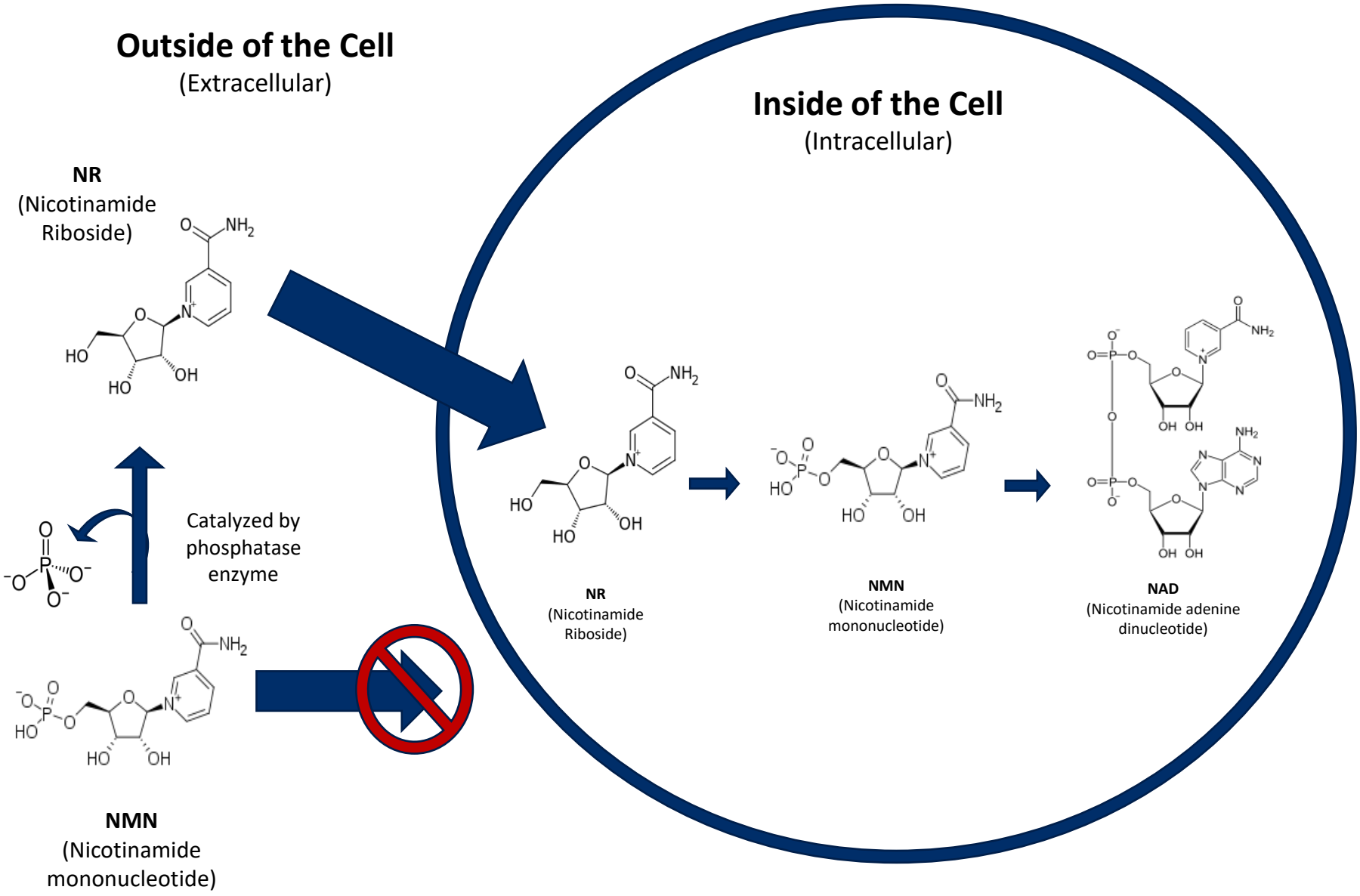

Ratajczak, J., Joffraud, M., Trammell, S. *et al.* NRK1 controls nicotinamide mononucleotide and nicotinamide riboside metabolism in mammalian cells. *Nat Commun* **7,** 13103 (2016) doi:10.1038/ncomms13103

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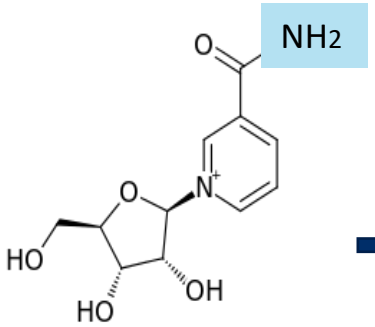
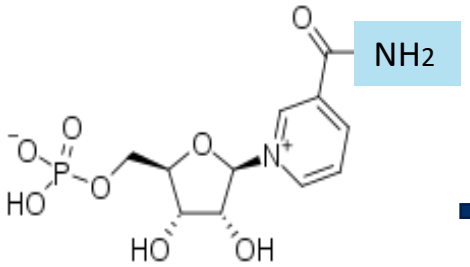
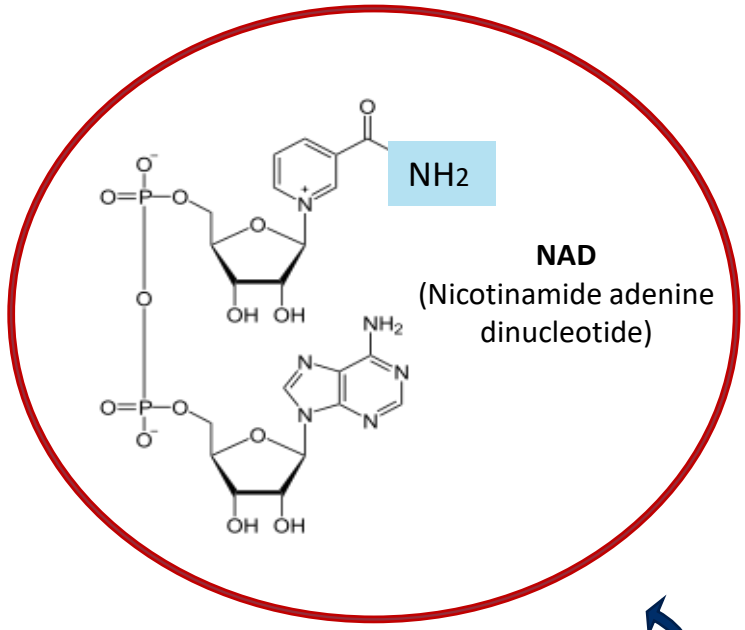
Why not just supplement with Niacin?



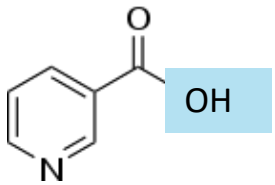
NR
(Nicotinamide Riboside)



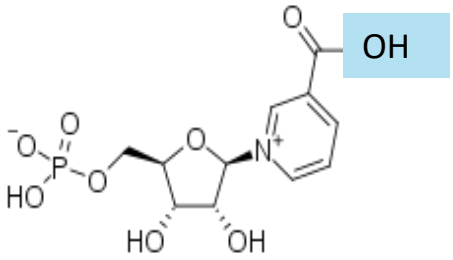
NMN
(Nicotinamide mononucleotide)



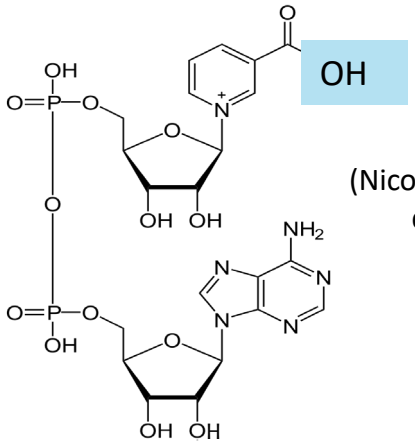
NAD
(Nicotinamide adenine dinucleotide)



Niacin
(Nicotinic acid)



NAMN
(Nicotinic acid mononucleotide)



NAAD
(Nicotinic acid adenine dinucleotide)

https://lpi.oregonstate.edu/mic/vitamins/niacin

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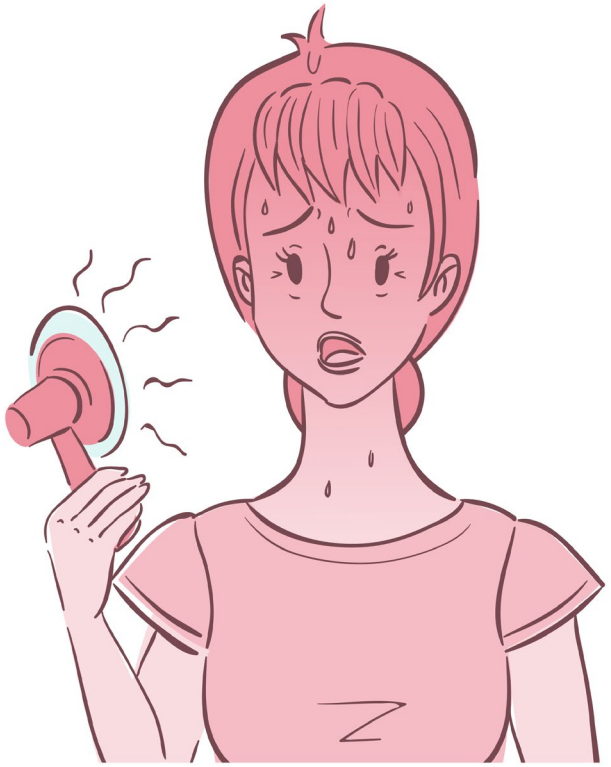
And…Niacin may cause ***Flushing***

Nicotinamide Riboside (NR) does NOT cause Flushing!

- The niacin receptors in the skin known as GPR109A causes the

  Flushing Effect of Niacin

- ***Nicotinamide Riboside (NR) does not activate GPR109A***



Maciejewski-Lenoir, D. *et al.* Langerhans Cells Release Prostaglandin D2 in Response to Nicotinic Acid. *J Invest Dermatol.* Vol 126, Issue 12 (Dec 2006) doi.org/10.1038/sj.jid.5700586

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What about just taking NADH?

J Nutr Sci Vitaminol, **52**, 142–148, 2006

Comparison of Metabolic Fates of Nicotinamide, NAD$^+$ and NADH Administered Orally and Intraperitoneally; Characterization of Oral NADH

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Laboratories of Food Science and Nutrition, Department of Life Style Studies, School of Human Cultures, The University of Shiga Prefecture, 2500 Hassakacho, Hikone, Shiga 522–8533, Japan

(Received April 21, 2005)

Summary Since NADH has been implicated in medication for some symptoms and as a possible supplement for health, we characterized the metabolic fate of NADH orally given to mice by comparing with those of nicotinamide (Nam), NAD$^+$ and NADH intraperitoneally or orally administered. Mice were individually housed in metabolic cages, and divided into two sets of four groups. Within each set, one group was intraperitoneally or orally administered saline and the other three groups received intraperitoneal or oral administration of a pharmacological dose of Nam, NAD$^+$ or NADH (5 μmol/mouse). Twenty-four hour urine samples for the day before and days 1 to 4 after administration were collected and analyzed for Nam and its metabolites. When mice were administered saline alone, urinary excretion of Nam and its metabolites, such as nicotinamide *N*-oxide (Nam *N*-oxide), N^1-methylnicotinamide (MNA), N^1-methyl-2-pyridone-5-carboxamide (2-Py), and N^1-methyl-4-pyridone-3-carboxamide (4-Py), was unchanged from day 0 to day 4. Intraperitoneal injection of Nam, NAD$^+$ and NADH produced significant increases in urinary excretion of Nam and its metabolites. Similar results were obtained when Nam and NAD$^+$ were given orally. On the other hand, oral administration of NADH did not bring about an increase in urinary excretion of Nam and its metabolites, suggesting that NADH in digestive organs has been decomposed to a compound(s) that cannot yield Nam. In fact, incubation of NADH at acidic pH to mimic the stomach resulted in rapid conversion of NADH to an unknown compound. Better understanding of the fate of oral NADH is needed for its therapeutic and supplemental use.

Key Words NADH, NAD$^+$, oral administration, intraperitoneal administration, mouse

Reduced nicotinamide adenine dinucleotide (NADH) and its oxidized form (NAD$^+$) in cells are synthesized

activation of tyrosine hydroxylase (*8*), which is the rate-limiting step of dopamine biosynthesis (*9*), and the

Concern with ***Absorption***

May not survive the stomach acid!

"In fact, incubation of NADH at acidic pH to mimic the stomach resulted in rapid conversion of NADH to an unknown compound"

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