Nicotinamide Riboside

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A number of studies confirmed that measurable, biological effects on NAD^+ levels can be achieved by oral NR supplementation, with no serious adverse effects. Significant increase of NAD^+ levels by NR administration have been reported in whole-blood, liver, skeletal muscles, and brown adipose tissue, but not in the brain and white adipose tissue. The observed differences may be explained by differential expression of Nmrk (nicotinamide ribose kinases, NMRK1 and NMRK2) in the specific tissues. The literature gives some suggestions for the dosing of NR to achieve a desired clinical outcome. NR is considered as a safe supplement as no severe side effects are reported, as otherwise seen with other NAD^+ precursers such as flushing, pruritus, hyperglycemia, hyperuricemia, or increased enzyme activity in the liver or muscles.

Keywords: Nicotinamide riboside ; bioavailability ; stability ; pharmacokinetic profile ; half-life of NR ; nicotinamide adenine dinucleotide (NAD+) ; supplementation ; safety

1. Introduction

Oral bioavailability of nicotinamide riboside (NR) is highly variable among individuals. Interindividual variation can be explained in part by different uptake potential in the intestinal system. Also, NR may be degraded in the gut or be metabolised in the liver, and therefore explain low bioavailability in other tissues.

2. Bioavailability

The **bioavailability of Nicotinamide Riboside (NR)** can be tested by measuring nicotinamide adenine dinucleotide (NAD^+) levels or other relevant biomarkers such as nicotinic acid adenine dinucleotide (NAAD) in the cells of the target tissue or in the blood. Throughout numerous observations in a wide variety of mammalian cell lines including liver, skeletal muscles, and brown adipose tissue, NR was documented to enhance NAD^+ levels [1]. Conversely, the NAD^+ levels did not significantly increase in the brain or white adipose tissue [1]. It was suggested that the observed differences are caused due to differential Nmrk expression in the specific tissues. While Nmrk1 is expressed ubiquitously, Nmrk2 is mainly expressed in cardiac and skeletal muscles, but also detectable in the liver and brown adipose tissue which might explain the better ability of these tissues to respond to NR. On the other hand, NR is very unstable in the blood, which makes it difficult to measure and detect. Despite its instability, the development of reliable methods for collection, processing, and measuring has enabled the determination of the pharmacokinetic profile of orally administered NR. The study conducted in both healthy human volunteers and mice reported that an NR dose of 1000 mg twice daily (2000 mg in total) can significantly increase steady-state, whole-blood levels of NAD^+ (up to 2.7 fold after one dose) [2] and effectively stimulate NAD^+ metabolism [3],[2],[4]. The studies also confirmed that measurable, biological effects on NAD^+ levels can be achieved by chronic oral NR supplementation with no serious adverse effects [3],[4]. Specifically, there were no severe side effects reported such as flushing, pruritus, hyperglycemia, hyperuricemia, or increased enzyme activity in the liver or muscle [2],[4],[5] . However, the blood NAD^+ response did not appear to correlate with the absorption pattern of NR and the peak in NAD^+ increase was reached after 9 days [4]. Furthermore, it was suggested that repeated dosing would be required to prevent wide fluctuations in body levels of NR due to a relatively short elimination half-life of NR observed in several subjects; however, continuous blood levels of NAD^+ suggest that twice-daily or even once-daily dosing of NR may be sufficient to achieve a desired clinical outcome [4].

On the other hand, the apparent oral bioavailability of a 1000 mg dose of NR was highly variable among individuals [4]. The instability of NR in blood samples observed across several studies [4],[6] could be one contributing factor, although it cannot completely explain the observed variability. Another proposed explanation was the NR hydrophilicity [7] since NR is expected to exhibit low passive permeability across the human intestinal mucosa [4]. Additionally, the interindividual variation in the transport mechanism of NR in the intestinal system might also affect the oral absorption of NR. Furthermore, it was proposed that NR can be degraded to NAM in the gut, whereas, another study showed that NR is

metabolized to NAM in the liver and might explain low bioavailability in other tissues [8]. Subsequently, NAM can be absorbed and converted to NMN, and further metabolized to NAD^+ or dephosphorylated to NR. In this case, the degradation of NR to NAM in the gut, which presumably involves purine nucleoside phosphorylase in mammalian and bacterial cells, may be the variable step involved in the oral intake of NR [9]. Furthermore, multiple pathways for the conversion of NR to NAD^+ were identified in a study with male human subjects and C57Bl6/J mice [2]. Interestingly, as a response to NR, a remarkable increase (45-fold) in NAAD was reported [2] indicating another possible conversion pathway of the NR to NAD^+. These studies suggest that causes in the variable oral bioavailability might be revealed with further investigation of NR metabolism and transport.

References

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