

Podcast Episode 7: Current status of NAD+, NMN, NR

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Teaser

Hey everyone! Welcome to the new episode of the Life Extension Podcast – technology & magic, society & business. Most people engaged in life extension practices have already heard about biochemical compounds called NMN and NR, which can be taken as nutritional supplements, similar to vitamins. Scientists and suppliers of supplements are claiming that taking NMN and NR might be beneficial for health and life-span. Continue to listen to this episode for an evaluation of those claims. I will explain the role of NAD, NMN, and NR in our cells and scientific hypotheses regarding their impact on health and longevity. I will present you with the current status of scientific research and clinical trials, and compare this with marketing claims by supplement suppliers. Last, I will provide my opinion as an informed consumer, if one should take NMN and NR supplements. Insights from this podcast will provide you with some grounding in a field where hard science, business interests, and magical beliefs are intermingling.

What is NAD, NMN, NR

This episode is about the current status of NAD+, NMN, and NR. As you are listening to a podcast about life extension, you have probably heard these abbreviations before. NAD+ is a coenzyme, playing an important role in cell metabolism. David Sinclair in his book “Lifespan” has popularized research on NAD+ and its role in sirtuin activity, which he believes to be one out of three important longevity pathways. Sirtuins are enzymes, which function as epigenetic regulators, meaning they are responsible to switch genes on and off, while at the same time assuming a role in DNA repair. According to Sinclair aging is caused by the “repeated shuffling of sirtuins between genes and sites of broken DNA and back again”. In this process information gets lost, and “over time, the wrong genes come on at the wrong time and in the wrong place.” (Sinclair 2019: 60). Sinclair calls this the information theory of aging. Sinclair’s research and commercial interests focus on the development of NAD+ boosters, mainly NMN and NR, which are metabolic precursors of NAD+. NAD+ is present in all cells of the body, but levels are dramatically declining with age, either because more NAD+ is consumed for tasks countering aging, or because the organism’s capability to recycle NAD+ declines with age. So again, this molecular pathway is roughly: NR makes NMN outside of the cell. NMN enters the cell and is converted into NAD+. NAD+ among other tasks is then used to build new sirtuins, which are needed in DNA repair processes.

From an evolutionary point of view, Sinclair writes that longevity pathways “evolved to protect the body during times of adversity by activating survival mechanisms. When they are activated, either by low-calorie or low amino-acids diets, or by exercise, organisms become healthier, disease resistant, and longer lived. Molecules (like NMN or NR) ...can mimic the benefits of low-calorie diets and exercise and extend the lifespan of diverse organisms.” (Sinclair 2019: 129).

Science hypothesis about the role of NAD in longevity

Based on my short review of academic articles on NMN and NR, the 2 most active research teams seem to be the one around David Sinclair from Harvard University, as well as a team from Washington University. There is also research going on in Japan and in China. Research teams hypothesize that oral administration of NR and NMN would increase NAD+ levels in cells and as a result would have beneficial effects on age-related disease conditions.

Status of research: preclinical and clinical trials

Trials targeted to confirm this hypothesis have multiplied during the last years. Trials are mostly small and short-term, and are first conducted at cell level in vitro, meaning more or less in the petri dish of a laboratory. Then other preclinical trials are conducted with living organisms - those relatively well understood like yeast, worms, flies, and mice. Only when safety, bioavailability, and efficacy are confirmed, will clinical trials be conducted involving humans.

What I understood from reading the most recent academic research papers, the status of current research is the following:

NAD+ levels in animal tissue cells are declining with age and this may be related to an increase of age-related disease conditions (Yoshino 2018).

Short-term studies did not give any indication that the administered doses of NR and NMN had any toxic effects (Mills 2016, Yaku 2018).

Oral administration of NR and NMN seems to be well absorbed and leads to high bioavailability of NAD+ in cells of many tissues in animal organisms (Trammel, Mills 2016, Dollerup 2018). But it is not clear yet, if bioavailability in humans works in the same way as in animal organisms in all tissues.

Indications that the administration of NR or NMN could be an efficient therapeutic intervention against many age-related disease conditions were found in a number of trials involving mice (Yoshino 2018).

Another trial found that the administration of NMN leads to an improvement of fertility in aged female mice (Bertoldo 2020).

Life span of yeast, worms, and flies was extended through administration of NAD boosters. The same has not been proven in other animals so far.

Human trials have established safety in the framework of short-term studies and specific dosage, but have only just started to look at efficacy.

One trial found an increase in NAD+ in muscle tissue after administering NR to humans, as well as a reduction of inflammation markers. But it did not find evidence that NAD+ levels were declining in muscle and brain only due to aging, differently from mice (Elhassan 2019)

The risk that boosting NAD+ could drive tumor growth cannot be excluded yet (Yoshino 2018).

Downstream mechanisms of NAD⁺ supplementation leading to beneficial health effects are not well understood. As NAD⁺ is playing a factor in many molecular processes which interact in complex ways, much more research will be required to clearly establish cause and effect relations between NAD⁺ boosters and age-related disease conditions (Yoshino 2018)

The first very small human trial on efficacy of NMN was completed in April 2021 and demonstrated a small increase in muscle insulin sensitivity (Yoshino 2021), but did not have any influence on other markers.

Marketing claims of NMN/NR supplement suppliers

Based on those carefully formulated statements of scientists, which were made in very narrow research frameworks and remain clearly inconclusive at this point in time, commercial suppliers of NMN and NR supplements are formulating their own stories addressed at supplement buyers. In fact, the research papers do not at all say what the marketing people say, but marketing people refer to those science statements when promising wide-ranging health benefits to buyers of their products.

For example, a supplier of NMN as supplement claims that NMN should be part of a healthy balanced diet, and that it boosts the body's longevity gene. It also helps against loss in quality of life, naturally increases energy, also naturally fights against the effects of aging, and maintains health as we age. NMN is claimed to strengthen the immune system, or to provide fuel to the nervous system, as well as to mitochondria, the body's powerhouses.

Another provider claims that his product helps to increase energy and performance, incl athletic performance, it promotes memory and concentration, helps with fatigue and sleep deficit, increases the oxygen supply to your cells, but also acts as a powerful antioxidant. Last but not least it improves your mood and helps with jet-lag.

Sometimes a marketing message uses frightening science words like NAD⁺ depletion, DNA strand breaks, oxidative stress, apoptotic cell death, senescence, or tissue inflammation and connects them in unproven generalized causal relations with general objectives of well-being.

Those messages are clearly not addressed to patients, but to consumers. They tell us that we are in control to improve our lives by buying this product. Never mind the biological complexities – science has taken care of that. The huge complexity of metabolic cell processes is reduced to a single proposition: “Buy this pill and you will live better”. This is magic dressed in science language. The product is sold at specific price points, which makes them desirable and affordable, no matter the efficacy or the dose. NAD boosting supplements are not designed to treat a medical condition, but to compete for a slot in consumers' budgets.

An evaluation

Now let's try to evaluate all this. The key question is, if we should believe the marketing stories of NAD⁺ booster suppliers and buy their products in order to slow down aging. To make it short, there is certainly

a lot of hype around NMN, NR, and NAD+ at the moment. There is clear evidence, that these molecules are in effect involved in cellular processes of aging. But will scientists be able to manipulate these processes and counter age-related diseases? That is not clear at all. Safety of NMN and NR has been established, but only for short-term and dose specific application. We know absolutely nothing about what will happen, if those supplements were taken long-term – which in real life situation would almost certainly be required to be effective. While some animal organisms have shown that NMN and NR reliably convert to NAD+ in cells (the so-called bioavailability), human trials have not established yet the same bioavailability in all tissue cells. Pathways of how NMN and NR are converted to NAD+ in which tissue cells are messy and need many more trials (Sinclair 2019). With regards to efficacy in humans, results are just not obvious yet at all. This does not mean, that NMN or NR would be less effective in humans than in investigated animal organisms. But it is still early times. Human trials have just started, and more results are expected to be published in the coming few years.

An important point to keep in mind is that marketing claims from supplement suppliers are not really supported by the current status of science. They rather reflect the hope that science will ultimately deliver prove in the future. Good to know in this context is also that the ongoing research on NMN and NR is typically financed by supplement suppliers (note 1). A lack of public funds is possibly caused by the fact that aging has not been recognized as a disease yet by the FDA. As a result, private funding is essential here. This is not a bad thing in itself. We should just be aware that strong commercial and academic career interests stand behind research on NMN and NR as a possible treatment of aging. In fact, most publications about research results involving NMN and NR are directly or indirectly informed by commercial interests, as all players do rely on positive information to maintain funding support.

The problem of private funding is that it often depends on simplified representations of complex realities. Cell biology is highly complex, and the role of NAD+ is by far not as simple as it tends to be presented by scientists and businesses concentrating on its potential use as longevity treatment. Some gambling is certainly involved here. Again, that's not necessarily a bad thing. In the contrary, private funding reflects courage and provides hope. It's just good to know the wider field, when we gamble.

Last question

Now the last question: Should anyone take NR or NMN supplements? Well it depends. For safety and efficacy reasons it might make sense to wait a few years. On the other hand, trying something new might not be wrong, if someone is already suffering of an age-related condition, which might even get worse. In that case one would be able to carefully observe the short-term effects on an existing disease, something not possible in a purely preventive situation. An even better alternative might of course be to increase exercise and to eat less. But that is a different subject (note 2).

Notes

- (1) E.g. Elysium (Basis) and ChromaDex (Niagen)
- (2) This is my opinion as informed consumer. I am not a medical doctor!

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