

Spermidine: A Critical Nutraceutical for the Autophagy-NAD Axis

By Gene Bruno, MS, MHS, RH(AHG)
Chief Scientific Officer, Nutraland USA

Autophagy and NAD are vital regulators of metabolic balance required for the alleviation of cellular stress. Furthermore, both autophagy activity and NAD levels decline with age, and boosting either may help promote lifespan extension while promoting health and wellness¹—and the nutraceutical spermidine can play a critical role in this process. Before jumping into this, let's first review autophagy and NAD.

Autophagy

Autophagy (pronounced “ah-TAH-fah-gee”) is the body’s process of breaking down old and damaged cell parts. This allows cells to disassemble junk parts and repurpose the salvageable components into new, usable cell parts, while discarding the unusable or unneeded parts. In addition, autophagy works as cellular *quality control*. Essentially, an excess of junk components in a cell takes up space and can slow or prevent a cell from functioning correctly. Autophagy helps eliminate cellular clutter, optimizing cellular performance. Furthermore, autophagy also plays an important role when it comes to well aging. As a person ages, autophagy decreases, which can lead to a build-up of cellular junk parts and, in turn, cells that aren’t functioning at their best.²

NAD

NAD (nicotinamide adenine dinucleotide) is an important coenzyme in the body involved in energy metabolism, and multiple biochemical processes in the body. As with autophagy, NAD production decreases with age, which has been associated with hallmarks of aging and may underlie a wide range of age-related symptoms, while increasing NAD may slow aspects of aging.³

The autophagy-NAD axis

Over the past decade, research has revealed that NAD-consuming enzymes can directly regulate autophagy in cells, and autophagy deficiency induces fatal depletion of NAD which can be attenuated by NAD precursor supplementation. This suggests a role for autophagy in NAD maintenance. Therefore, NAD and autophagy form a bidirectional feedback relationship which may be linked to longevity and age-related health maintenance and could represent a target for therapeutic intervention.⁴ Support for the autophagy-NAD can be achieved through the use of nutraceuticals that promote autophagy, and with nutraceuticals that are precursors to NAD.

NAD precursor nutraceuticals

The two most widely promoted nutraceuticals that function as NAD precursors, increasing NAD production, are NMN (nicotinamide mononucleotide) and NR (nicotinamide riboside). The problem is that the FDA has indicated that NMN is not a dietary ingredient, and researchers have questioned the safety of NR. However, another NAD precursor is niacinamide, a readily available form of vitamin B3. Research has demonstrated that 200 mg of niacinamide has been shown to increase whole blood concentration of NAD by 30-fold after 30 minutes⁵—making it a viable and vastly less expensive NAD precursor.

Spermidine: an autophagy promoter

Spermidine is a polyamine, a group of organic compounds having two or more amino groups. Spermidine is one of the main polyamines that play important roles in cellular growth/health in mammalian cells (including humans) and plants. Spermidine can be found in a variety of different foods⁶. Nutraland USA offers Miricell[®], a natural, non-GMO, allergen-free, vegan friendly, rice-derived source of spermidine with other naturally occurring polyamines.

Research⁷ clearly demonstrates that spermidine induces autophagy by inhibiting a compound (acetyltransferase EP300) that would otherwise repress autophagy. But what does this mean from a practical standpoint?

Spermidine and cognitive function

To begin with, consider that memory function becomes less efficient with increasing age. In part, this is due to changes in the connections between nerve cells (neurons)—known as synaptic plasticity. Spermidine operates directly at synapses, allowing for an autophagy-dependent regulation of presynaptic specializations.⁸ The practical effects of this were shown in a multicentric double-blind preliminary study⁹ focusing on the effect of oral spermidine supplementation (1.9 mg or 3.3 mg, six days per week) on older adults' cognitive performance. Memory tests were carried out on 85 subjects aged between 60 and 96 years in 6 nursing homes. The results demonstrated a clear correlation between the intake of spermidine and the improvement in cognitive performance in the group treated with the higher spermidine dosage.

Spermidine and immune function

Failure to make adaptive immune responses, such as antibodies via B cell production, is a hallmark of aging. Reduced B cell function leads to poor vaccination efficacy and a high prevalence of infections in the elderly. Research^{10 11} has shown that reduced autophagy is a central molecular mechanism underlying immune senescence. Autophagy levels are specifically reduced in mature lymphocytes (immune cells), leading to compromised memory B cell responses in old individuals. As previously discussed, spermidine induces autophagy, and also rejuvenates memory B cell responses. Basically, supplementation helps restore a biochemical pathway and improve the responses of old human B cells. Likewise, research¹² has shown that spermidine increased autophagy and T-cell activation in a dose-dependent manner.

Spermidine and hair

Research¹³ on human scalp hair follicle has demonstrated that spermidine is a potent stimulator of human hair growth. More meaningfully, a randomized, double blind, placebo controlled, clinical study¹⁴ with 60 men and women (aged 18-60 years) with telogen effluvium (stress-related hair loss) demonstrated that spermidine alone (0.5 mg) or spermidine in association with other nutrients helped to reduce significantly the clinical symptoms and the instrumental values related to the presence of telogen effluvium. This included a reduction in hair loss, an increase in hair stem diameter, and an increase in the anagen phase (hair growth phase when the hair follicle forms a new hair shaft). Another randomized, double-blind, placebo-controlled trial¹⁵ in 100 healthy men and women found that the same combination of spermidine and other nutrients increased the number of anagen hair follicles after three months of treatment, accompanied by increased cellular proliferation—all significantly better when compared to the placebo group. The hair pull test showed no loss of hair after six months in all patients receiving the spermidine supplement, while 68% of the subjects in the placebo group had hair loss with the pull test.

Other spermidine research

In addition to the aforementioned studies, animal research suggests that spermidine elicits cardioprotective effects¹⁶, may offer benefits for eye health¹⁷, and may support circadian rhythms¹⁸—among other potential benefits. Perhaps most significant to the topic of this article, animal research¹⁹ has shown that spermidine can extend lifespan, and recent population studies²⁰ evidence suggests that increased uptake of spermidine with food may offer similar benefits in humans.

Conclusion

The Autophagy-NAD axis is a vital regulator of metabolic balance. Also, NAD and autophagy form a bidirectional feedback relationship which may be linked to longevity and age-related health maintenance. Since both autophagy activity and NAD levels decline with age, boosting either may help promote lifespan extension while promoting health and wellness.²¹ Miricell®, rice-derived source of spermidine, is an effective autophagy promoter, with demonstrated benefits for cognitive and immune function, as well as hair health. Other research suggests that spermidine may also have cardioprotective, eye health, circadian rhythm and life extension benefits.

Nutraland USA offers clean, plant-based and sustainable branded ingredients supported by science. Our nutraceuticals are good for you, and good for the planet. For more information about how you can use Miricell®, rice-derived source of spermidine, in your dietary supplements, contact gene.bruno@neutralandusa.com; 949-988-7615.

References

- ¹ Wilson N, Kataura T, Korsgen ME, Sun C, Sarkar S, Korolchuk VI. The autophagy-NAD axis in longevity and disease. *Trends Cell Biol.* 2023 Mar 4;S0962-8924(23)00023-5.
- ² Autophagy. Cleveland Clinic. Last reviewed by a Cleveland Clinic medical professional on 08/23/2022. Retrieved May 24, 2023 from <https://my.clevelandclinic.org/health/articles/24058-autophagy#:~:text=Autophagy%20allows%20your%20body%20to,potentially%20preventing%20and%20fighting%20disease.>
- ³ Aman Y, Qiu Y, Tao J, Fang EF. Therapeutic potential of boosting NAD+ in aging and age-related diseases. *Translational Medicine of Aging.* 2018; 2:30-37
- ⁴ Wilson N, Kataura T, Korsgen ME, Sun C, Sarkar S, Korolchuk VI. The autophagy-NAD axis in longevity and disease. *Trends Cell Biol.* 2023 Mar 4;S0962-8924(23)00023-5.
- ⁵ Ito TK, Sato T, Hakamata A, et al. A nonrandomized study of single oral supplementation within the daily tolerable upper level of nicotinamide affects blood nicotinamide and NAD+ levels in healthy subjects. *Translational Medicine of Aging.* 2020; 4:45-54.
- ⁶ Muñoz-Esparza NC, Latorre-Moratalla ML, Comas-Basté O, Toro-Funes N, Veciana-Nogués MT, Vidal-Carou MC. Polyamines in Food. *Front Nutr.* 2019 Jul 11;6:108.
- ⁷ Pietrocola F, Lachkar S, Enot DP, Niso-Santano M, Bravo-San Pedro JM, Sica V, Izzo V, Maiuri MC, Madeo F, Mariño G, Kroemer G. Spermidine induces autophagy by inhibiting the acetyltransferase EP300. *Cell Death Differ.* 2015 Mar;22(3):509-16.
- ⁸ Bhukel A, Madeo F, Sigrist SJ. Spermidine boosts autophagy to protect from synapse aging. *Autophagy.* 2017 Feb;13(2):444-445.
- ⁹ Pekar T, Bruckner K, Pauschenwein-Frantsich S, Gschaidner A, Oppliger M, Willesberger J, Ungersbäck P, Wendzel A, Kremer A, Flak W, Wantke F, Jarisch R. The positive effect of spermidine in older adults suffering from dementia : First results of a 3-month trial. *Wien Klin Wochenschr.* 2021 May;133(9-10):484-491.
- ¹⁰ Zhang H, Alsaleh G, Feltham J, Sun Y, Napolitano G, Riffelmacher T, Charles P, Frau L, Hublitz P, Yu Z, Mohammed S, Ballabio A, Balabanov S, Mellor J, Simon AK. Polyamines Control eIF5A Hypusination, TFEB Translation, and Autophagy to Reverse B Cell Senescence. *Mol Cell.* 2019 Oct 3;76(1):110-125.e9.
- ¹¹ Metur SP, Klionsky DJ. The curious case of polyamines: spermidine drives reversal of B cell senescence. *Autophagy.* 2020 Mar;16(3):389-390.

-
- ¹² Fischer M, Ruhnau J, Schulze J, Obst D, Flöel A, Vogelgesang A. Spermine and spermidine modulate T-cell function in older adults with and without cognitive decline ex vivo. *Aging (Albany NY)*. 2020 Jun 30;12(13):13716-13739.
- ¹³ Ramot Y, Tiede S, Bíró T, Abu Bakar MH, Sugawara K, Philpott MP, Harrison W, Pietilä M, Paus R. Spermidine promotes human hair growth and is a novel modulator of human epithelial stem cell functions. *PLoS One*. 2011;6(7):e22564.
- ¹⁴ Rinaldi F, Sorbellini E, Bezzola P, Marchioretto DI. Biogenina® based food supplement: hair growth enhancer. *NutraFood*. 2003;2:1-7.
- ¹⁵ Rinaldi F, Marzani B, Pinto D, Ramot Y. A spermidine-based nutritional supplement prolongs the anagen phase of hair follicles in humans: a randomized, placebo-controlled, double-blind study. *Dermatol Pract Concept*. 2017 Oct 31;7(4):17-21.
- ¹⁶ Eisenberg T, Abdellatif M, Zimmermann A, Schroeder S, Pendl T, Harger A, Stekovic S, Schipke J, Magnes C, Schmidt A, Ruckenstein C, Dammbroeck C, Gross AS, Herbst V, Carmona-Gutierrez D, Pietrocola F, Pieber TR, Sigrist SJ, Linke WA, Mühlfeld C, Sadoshima J, Dengjel J, Kiechl S, Kroemer G, Sedej S, Madeo F. Dietary spermidine for lowering high blood pressure. *Autophagy*. 2017 Apr 3;13(4):767-769.
- ¹⁷ Han W, Li H, Chen B. Research Progress and Potential Applications of Spermidine in Ocular Diseases. *Pharmaceutics*. 2022 Jul 19;14(7):1500.
- ¹⁸ Zwihaft Z, Aviram R, Shalev M, Rousso-Noori L, Kraut-Cohen J, Golik M, Brandis A, Reinke H, Aharoni A, Kahana C, Asher G. Circadian Clock Control by Polyamine Levels through a Mechanism that Declines with Age. *Cell Metab*. 2015 Nov 3;22(5):874-85.
- ¹⁹ Madeo F, Carmona-Gutierrez D, Kepp O, Kroemer G. Spermidine delays aging in humans. *Aging (Albany NY)*. 2018 Aug 6;10(8):2209-2211.
- ²⁰ Kiechl S, Pechlaner R, Willeit P, Notdurfter M, Paulweber B, Willeit K, Werner P, Ruckenstein C, Iglseder B, Weger S, Mairhofer B, Gartner M, Kedenko L, Chmelikova M, Stekovic S, Stuppner H, Oberhollenzer F, Kroemer G, Mayr M, Eisenberg T, Tilg H, Madeo F, Willeit J. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018 Aug 1;108(2):371-380.
- ²¹ Wilson N, Kataura T, Korsgen ME, Sun C, Sarkar S, Korolchuk VI. The autophagy-NAD axis in longevity and disease. *Trends Cell Biol*. 2023 Mar 4:S0962-8924(23)00023-5.