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Spermidine Promotes Cardioprotective Autophagy

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Summary

A recent study published in *Nature Medicine* reports that dietary supplementation with spermidine, a natural polyamine, extends life span and reverses aging-associated cardiac dysfunction in mice through induction of autophagy. Similar protective effects of spermidine on human cardiovascular health were also suggested by epidemiological studies.[1]

Background

Our population is aging -- shifting in distribution towards older age -- at an unprecedented pace. Based on US population reports, the percentage of people older than 65 years is estimated to increase from 13.4% in 2012 to 19.3% in 2030. And as aging is the greatest risk factor for major life-threatening disorders, including cardiovascular and neurodegenerative diseases, metabolic syndromes, and cancer, these demographic shifts are of great significance.[2] Further, the simple extension of longevity falls short of the over-riding objective of extending *healthy* life (“square-waving life”). Therefore, there is great interest in interventions that target the aging process *per se*, as they could potentially provide novel preventive and/or therapeutic approaches for a wide range of age-associated diseases.

In the past two decades, studies have identified multiple genetic and pharmacological interventions that extend the lifespan of model organisms, including yeast, worms, flies, and mammals. Caloric restriction (CR), and pharmacological agents that mimic the effects of CR, including rapamycin, metformin, resveratrol, and spermidine, promote longevity in model organisms.[3] Interestingly, most interventions converge on a limited number of common cellular processes, including nutrient signaling (insulin and mTOR pathways), mitochondrial efficiency, and autophagy. Both CR and inhibition of nutrient signaling induce autophagy, an evolutionarily conserved mechanism that targets damaged or long-lived proteins and organelles for degradation. Autophagy is down-regulated over the course of aging, and inhibition of autophagy abolishes the longevity-promoting effects of many manipulations, indicating a strong connection between autophagy and aging.[4]

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Cardioprotective effects of spermidine

Spermidine is a naturally occurring polyamine found in abundance in certain foods, such as rice bran, soybeans, aged cheese, mushrooms and broccoli.[5] Eisenberg and colleagues have previously reported that spermidine supplementation prolongs lifespan in yeast, flies and worms in an autophagy-dependent fashion.[6,7] In this most recent paper, these authors extended this observation to mammals, reporting that life-long dietary spermidine supplementation led to significant increases in median lifespan in laboratory mice. A similar beneficial response was observed when spermidine was administered later in life.[1] (Figure)

Polyamines such as spermidine are involved in a wide range of cellular processes, including protein and nucleic acid synthesis and autophagic protein quality control, culminating in effects on cell proliferation, differentiation, and death.[7] In the present study, necropsy analysis revealed that spermidine treatment did not impact the incidence of cancer, a major life-limiting condition in mice, indicating that the beneficial effect of spermidine was not due to suppression of carcinogenesis, as is the case with another CR mimetic, rapamycin.[8] In contrast, mice fed spermidine showed significant improvement in key features associated with cardiac aging, including left ventricular (LV) hypertrophy, diastolic dysfunction, and increased LV stiffness.[9] Notably, this effect was independent of impact on blood pressure, lipid profile, insulin sensitivity, and body composition, suggesting that spermidine directly affected the heart. Myocardial tissue from aged mice fed spermidine manifested a “rejuvenated” molecular pattern on transcriptome and proteome analyses in terms of preservation of the contractile apparatus, improved mitochondrial function, and suppression of inflammation. In addition, spermidine also increased phosphorylation of titin2B, an event which is linked with reduced passive stiffness of cardiomyocytes.

Similar to what was previously observed in other model organisms, the beneficial effects of spermidine in mice were autophagy-dependent. Dietary spermidine increased cardiomyocyte autophagic flux and mitophagic activity. Intriguingly, the cardioprotective effects of spermidine were abolished when Atg5, an essential autophagy-related protein, was deleted specifically in cardiomyocytes.

To assess whether spermidine has similar protective effects in a model of disease, the investigators turned to Dahl salt-sensitive rats fed a high salt diet, a model of hypertension-induced cardiac remodeling and heart failure. They found that spermidine-fed rats manifested delayed onset of hypertension, attenuated cardiac hypertrophy, and improved diastolic function. In addition to effects on the heart, hypertension-associated renal injury was attenuated in spermidine treated animals.

Finally, the investigators extended their findings to test for evidence of benefit in epidemiological studies. They report a correlation between survey-reported consumption of spermidine-rich foods and lower incidence of cardiovascular diseases in humans.

Significance and future directions

This study enhances our understanding of the role of autophagy in cardiac aging. Spermidine, as shown in this paper, induced autophagy and mitophagy in the heart, and

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autophagy is required for the cardioprotective benefit of spermidine. This lends additional credence to the strong link between autophagy and cardiac aging, and suggests that restoration/potentiation of autophagy by spermidine might be an effective way to combat aging-associated pathologies. Previous work using human and yeast cells suggested that spermidine promotes autophagy independent of SIRT1 or mTOR, but rather by inhibiting histone acetyltransferase.[10] It would be interesting to test whether similar mechanisms pertain here and how changes within the acetylproteome impact the aging process.

Second, this study sheds important new light on the biology of aging, especially cardiac aging. Studies have shown that rapamycin extends the lifespan of rodents mainly by inhibiting carcinogenesis, whereas resveratrol only extends the longevity of mice fed a high calorie diet, likely through effects on metabolism.[2,8] In the present study, the authors ruled out the impact of spermidine on carcinogenesis, blood pressure and metabolic profile in aging mice. This allows the intrinsic cardiac changes of aging to be investigated absent these confounding factors. The investigators went on to present evidence that spermidine treatment attenuated key features of cardiac aging, likely through improving mitochondrial function, inhibiting chronic inflammation, and modifying phosphorylation of certain key proteins, such as titin. Therefore, spermidine might be a useful tool to investigate the aging process.

Like other excellent studies, this paper raises questions that warrant further investigation. Is the longevity extension benefit of spermidine solely due to its cardioprotective effects? How is it that regularizing cardiomyocyte autophagy has a seemingly profound effect to prolong lifespan? Is “cardiac aging” a limiting process in organismal aging? What is the impact of spermidine on aging phenotypes in other organ systems? What is the mechanism whereby spermidine actually increases LV hypertrophy in Atg knockout mice? Here, it will be critical to measure blood pressure in these animals. Furthermore, the fact that spermidine treatment also reduced LV mass and enhanced LV compliance in young (3–4 months old) wild-type mice suggests that spermidine likely has additional effects beyond its impact on aging.

In this study, spermidine conveyed cardioprotective effects in a salt-induced hypertension rat model. However, it is difficult to parse whether this benefit is due to direct cardioprotection or secondary to its blood pressure lowering effects. Although the authors proposed that the antihypertensive effect of spermidine is likely due to improvements in nitric oxide (NO) production and bioavailability, why is this only seen in hypertensive rats? Further studies to test the effect of spermidine on endothelial cells, and in other disease models, such as other models of hypertension, diabetic cardiomyopathy, etc, will provide critical insights into the cardioprotective effects of spermidine, as well as how the heart ages under both physiological and pathological conditions.

Conclusions drawn from the epidemiological studies must be interpreted with caution. First, dietary survey questionnaires are notoriously inaccurate. Second, individuals who consumer polyamine-rich foods may well harbor other important differences in lifestyle, socioeconomic status, and more.

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In the end, the authors are to be congratulated on a study which unveils novel mechanism and points to immediately translatable events in cardiovascular biology. It is known that circulating levels of spermidine decrease with aging and those levels can be restored via dietary supplementation in both model organisms and humans.[7] Given its naturally occurring presence in common foods, spermidine likely has a better safety profile compared with other CR mimetics. Furthermore, evidence presented here points to potential benefits even if spermidine consumption commences later in life. Therefore, it is tempting to speculate that a diet rich in spermidine, either via supplement consumption or dietary modifications, might have beneficial effects on aging and aging-associated diseases. Of course, the safety and effectiveness of spermidine supplementation will need to be tested in other species and ultimately by carefully designed, large cohort clinical trials, in humans.

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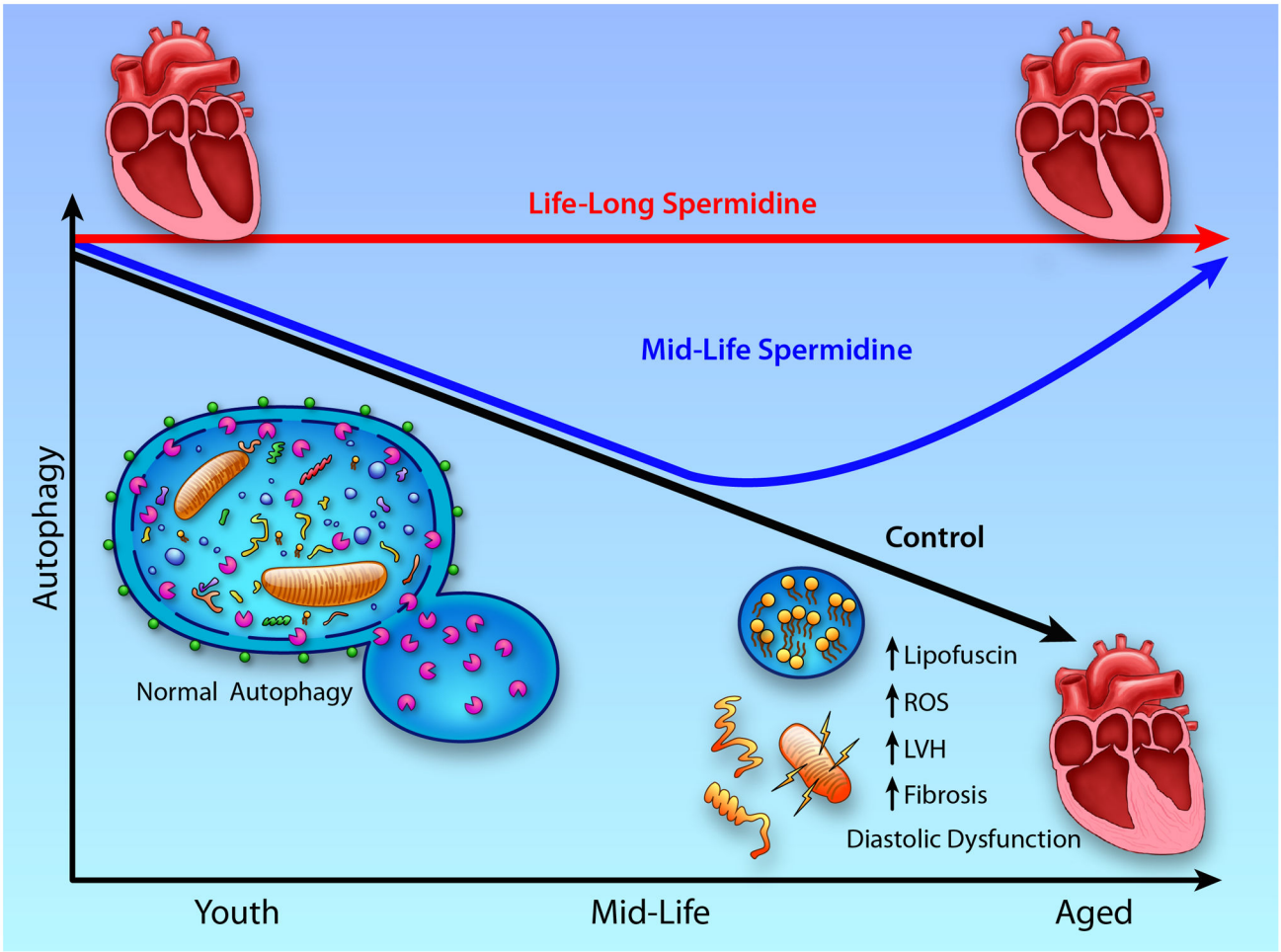

Figure.