

Regulation of different nutrient-sensing pathways by Yogic diet and practice – A descriptive study

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ABSTRACT

Overeating and eating unsuitable or unseasonable food reduces healthspan due to the gathering of toxins like Reactive oxygen species (ROS) in the body, which are the cause of various diseases. This article shows how Fasting and Yogic diet/ mitahara can extend healthspan and longevity through regulating different nutrient-sensing ways: mTOR, AMPK, P53, and SIRTUINS, Boosting NAD+ level. From ancient times in various Yogic and Ayurvedic texts, there has been an emphasis on nutrition and diet, that a wholesome diet is essential for maintaining a healthy lifespan which provides a long life full of bodily and mental strength, with no illness or disease.

Keywords: Diet, Nutrient-sensing, Aging, Health span, Longevity

DIFFERENT NUTRIENT- SENSINGWAYS: mTOR, AMPK, P53, and SIRTUINS

1. mTOR (Mammalian target of rapamycin)

This particular enzyme encoded the mTOR gene. Rapamycin targets a specific enzyme in mammalian tissue it has immunosuppressive and anti-cancer activity. mTOR, Insulin, and IGF-1, SIRT, and AMPK pathways control the cell's metabolism. mTOR system is to synchronize cell activities to energy and oxygen availability by endorsing or suppressing catabolic and anabolic different

pathways in response to stimuli such as nutrient sensing and growth factors (Laplanche & Sabatini, 2012). This pathway senses the abundance of nutrition and activates the mechanism required for the growth and repair of the cell. It also regulates proliferation, motility and survival of the cell, transcription, autophagy processes to maintain protein homeostasis (Harrison et al., 2009). mTOR pathways have beneficial as well as harmful effects. mTOR pathway increases energy production and metabolism but also produces junk products in the process (Yang et al., 2012). Autophagy recycles cellular material breakdown junk products and recycles them. But the autophagy pathway is only

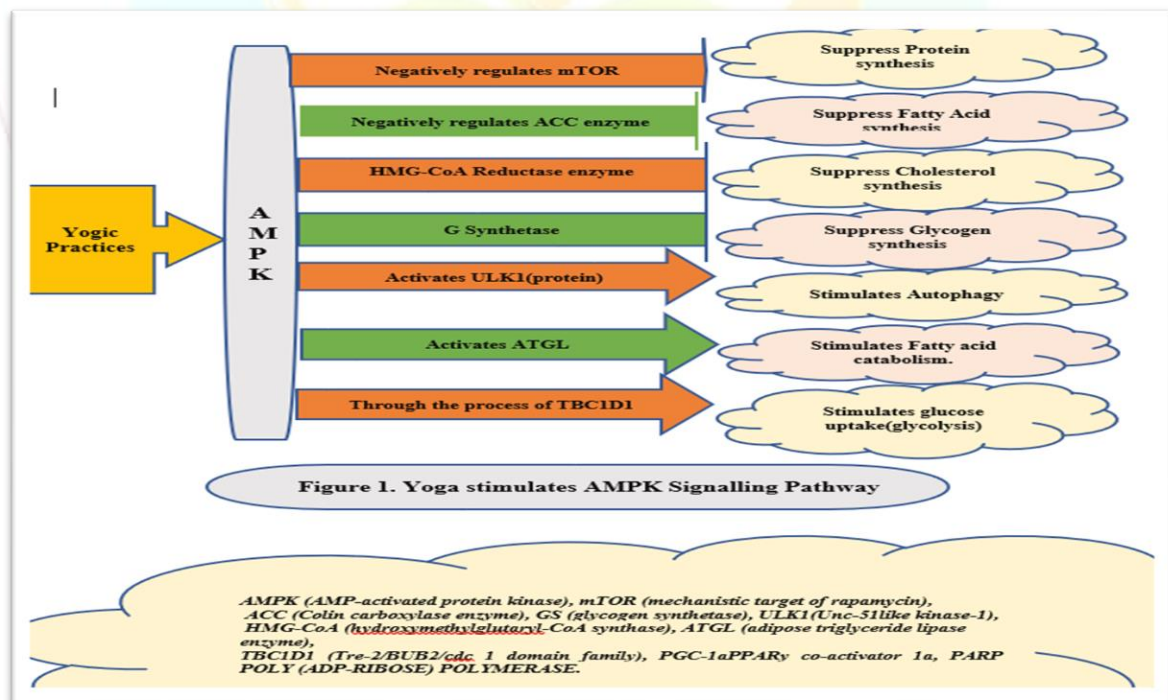
functional when the mTOR pathway is inhibited. So too much mTOR pathway activation can also contribute to many chronic ailments like tumor, metabolic syndrome and neurodegeneration (Dormond, 2019),(Wilkinson et al., 2012). Inhibition of the mTOR pathway improves insulin sensitivity and promotes autophagy.

Another enzyme, AMPK, is also a kinase activation of AMPK that stimulates autophagy. Both AMPK and mTOR pathways can't be activated simultaneously. As AMPK shuts the mTOR pathway and stimulate autophagy (Alers et al., 2012). mTOR pathway is activated by the abundance of nutrients chiefly proteins and can be inhibited by rapamycin and methionine. The AMPK pathway is activated by fasting or exercise and inhibits the mTOR pathway. So overeating and non-veg food can over-activate the mTOR pathway. A balanced diet, fasting, and calorie restriction activate the AMPK and autophagy

pathway instead mTOR pathway which recycles and repairs cells of the body.

2. AMPK

AMPK is 5 adenosine monophosphate-activated protein kinase that have various anti-aging properties which regulates through different cellular Pathways (Viollet et al., 2009). AMPK is controlled by AMP:ATP ratio, Adenosine monophosphate and adenosine triphosphate respectively during energy diminution. When this ratio increases AMPK get stimulated and is considered as an energy sensor and master regulator of energy metabolism for the cell. Most of the study supports that AMPK is an anti-aging strategy as in response to muscle contraction and nutrient exhaustion it can be naturally stimulated. *Metformin* is used to activate the AMPK pathway to delay age-associated ailments such as cardiovascular diseases, metabolic syndrome, malignancy, cognitive decline, and death.



Summary of AMPK Signalling pathway

↑Increases glucose uptake and utilization

↑Increases fatty acid oxidation

↑Increases autophagy

↓Decreases glycogen synthesis

A balanced diet, fasting, and calorie restriction activate the AMPK and autophagy pathway which recycles and repairs cells of the body. AMPK inhibits the signalling of the Nuclear factor kappa B (NFkB) pathway results reduces chronic inflammation, promoting the release of energy, and renewal of cellular components eliminating damaged DNA inducing mitochondrial biogenesis, and stimulating the production of Sirtuin 1(SIRT-1) enzyme which repairs DNA. AMPK leads to an uptake of nutrients in catabolism, not in anabolism. This increased catabolism and decreased anabolism means decreased energy expenditure and increases energy production by utilizing nutrients (Carapeto & Aguayo-Mazzucato, 2021).

3. Sirtuins

Sirtuins are a group of seven different proteins that show a critical role in regulating healthspan and extend lifespan also known as longevity genes, because it regulates many functions that

influence the aging process. It regulates mitochondrial biogenesis, apoptosis, and autophagy, repair damaged DNA, stimulate signaling to improves intercellular communication between the nucleus and mitochondria, and on a systemic level between the hypothalamus and fat tissue. Sirtuin can function in the existence of NAD (Nicotinamide adenine dinucleotide) which is a derivative of nicotinic acid also known as niacin or B6. Sirtuin is also used by DNA repairing molecules called POLY (ADP-RIBOSE) POLYMERASE (PARPS), and PARPS consumes NAD as like Sirtuin but PARPS and SIRTUIN too much activation can exhaust NAD supply and can cause cell death. SIRT1 can regulate PGC-1 α (Rodgers et al., 2005). PPAR γ co-activator 1 α (PGC-1 α) a compound that improves anti-oxidant status, fatty acid oxidation and mitochondriogenesis (Fernandez-Marcos & Auwerx, 2011), (Jäer et al., 2007).

4. P53

Another protein called P53 this protein is responsible for the lamination of carcinogenic cells. Too much activation of P53 protein can destroy too many cells and can accelerate the aging process. Activation of the PARP enzyme can induce overexpression of P53 (**Jones et al., 2005**).

As we age NAD level declines and Sirtuin and PARP become less functional. As NAD level declines energy transfer decreases slowing mitochondrial function and increasing oxidative stress. This will cause chronic inflammation, and cognitive dysfunction and increases free radicals which damage DNA. NAD precursors maintain a level of NAD such as but these are much more expensive so another one is niacin (B6) but taking niacin has effects related to skin and liver, and the use of Trimethylglycine (TMG), Resveratrol, Pterostilbene but as a supplement these have side effects as well as expensive or suppress one pathway to activate another one which may suppress the immune system.

REGULATION OF DIFFERENT NUTRIENT-SENSING PATHWAYS

FASTING STIMULATES

- Decrease in insulin signaling
- Liver glycogen converts into Glucose.
- Gluconeogenesis (proteins into glucose)
- Glucose Metabolism shifts to Fat metabolism
- Human growth hormone (HGH) levels rise.

Balancing MTOR AND AMPK

mTOR and AMPK are antagonistic to one another as AMPK pathway activation shuts the mTOR pathway and both pathways have benefits as both are crucial for long and healthy life. One aspect of aging that correlates with diminishing health span like fragility, and sarcopenia, and the best way to avoid this is through exercise and Yogic practices to activate the mTOR pathway. But it needs to balance activating the AMPK pathway through fasting or caloric restriction. Anabolic/mTOR (this is the period building up muscles tissue but also fat tissue) through nutrition and exercise/ yogic practices and Catabolic/AMPK (is the period tearing down fat tissue with muscle tissue also and cellular repair) through caloric restriction/ yogic diet/extended fasting/intermittent fasting/yogic practices.

Fasting is not all about breaking down Proteins into amino acids it is also about recycling amino acids into new proteins/new tissues. The whole process is the profound fact in maintaining health span and longevity. Lack of nutrients stimulates the AMPK pathway which in turn shut down the mTOR, insulin and IGF-1 pathway, with the activation of AMPK which activates autophagy.

BENEFITS OF FASTING

- Improves metabolism
- Reduce the risk of neurodegenerative diseases.
- Remove microbes, viruses, and toxins.
- Prevent the onset of cancer.
- Improve cardiovascular health.

NAD⁺ Boosters and Aging

Nicotinamide adenine dinucleotide (NAD⁺) is a molecule that is a derivative of vitamin B3 also known as nicotinamide and niacin. It is the amplest molecule in the human body it regulates numerous metabolic reactions to cell survival. It is essential for over five hundred metabolic reactions and plays crucial roles in increasing cell life, DNA repair, gene expression, and various other biological processes. Importantly it is used in the activation of various crucial pathways (**Imai & Guarente, 2014**), (**Imai & Johnson, 2018**), (**Chini et al., 2017**). One of them is the Sirtuin pathway, Sirtuin genes are also called longevity genes, it has been reported that in humans Sirtuins metabolize nicotinamide (**Frye, 1999**). Sirtuins class of enzymes uses NAD⁺ to regulate metabolism, and maintain chromosomes and DNA integrity, But

as DNA damage and chromosome instability increase with age, Sirtuin consumes more NAD⁺ and decreases NAD⁺ level. NAD⁺ level declines with increased old age resulting in abnormal metabolism linked with bigger disease vulnerability (**Ansari & Raghava, 2010**). NAD⁺ plays an important role in regulating mitochondrial biogenesis, apoptosis, and intercellular communication. Another pathway activated by NAD⁺ is a family protein called

PARP and these proteins are intricate in various cellular reactions such as DNA restoration, programmed cell decease, and genomic steadiness, (**Jokinen et al., 2017**). Both of these Pathways are crucial to many other repair processes and NAD⁺ fuels these processes, without NAD⁺ these processes do not occur and the continued accumulation

of damaged components within the cells causes the death of the cell and accelerates biological aging.

NAD⁺ is involved in the oxidation and reduction processes. NAD⁺ molecule accepts electrons to become NADH, and NADH gives up electrons to become NAD⁺. Most of the NAD⁺ in our body comes from the recycling of NADH. As NAD⁺ level drops in the body with age many of the processes slow down including repairing which accelerates aging.

Cause of declining NAD⁺

The primary cause of declined NAD⁺ with age is the CD-38 enzyme, as CD38 increases with mitochondrial and DNA functions decay with increased old age (**Chini et al., 2020**). As the CD38 level goes up NAD⁺ level goes down with age. Another cause of declined NAD⁺ is damaged DNA which activates PARPs which consume NAD⁺ to repair damaged DNA. This depletion of NAD⁺ during aging contributes to various diseases. Enzymes in our immune system also consume NAD⁺ enzyme which increases with aging (**Cantó et al., 2009**). The FOXO transcription factor may reduce protein imbalance and toxicity which helps in lifespan extension (**Vilchez et al., 2012**).

Boosting NAD⁺ level

The use of flavonoids particularly known as APIGENIN decreases CD38 and increases NAD⁺ level but it is highly unstable and expensive as a supplement.

The next strategy for boosting the NAD⁺ level Involved the Salvage pathway. When NAD⁺ Level is depleted, a molecule called nicotinamide or NAM is created. Nicotinamide is converted into NAD⁺ by an enzyme called NAMPT. The best indicator of NAMPT level is VO₂ Max and this can be improved through yogic practices without any side effects.

Another way to improve your NAMPT is calorie restriction /Mitahara (**yogic concept of diet**). And a small molecule called SBI-797812 is shown to activate NAMPT. Through taking NAD⁺ Booster precursor such as niacin supplement. But niacin supplements can be hepatotoxic and cause skin irritation(**Rajman et al., 2018**).

CONCLUSION

Over time with aging, toxins accumulate in the body, due to which whole body become toxic and lethargic. Fasting and Yogic diet/ mitahara can extends healthspan and longevity through regulating different nutrient-sensing ways: mTOR, AMPK, P53, and SIRTUINS, Boosting NAD⁺ level. A Yogic balanced diet (mitahara), fasting, and other traditional practises of yoga all support health, disease prevention, immunity boosting, healing, and longevity. According to ancient yogic writings, by engaging in certain yoga practises, a practitioner might delay the onset of old age, get rid of wrinkles, whitening hair, and tremors, and resemble a youthful man.

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