Deficiencies of Aging

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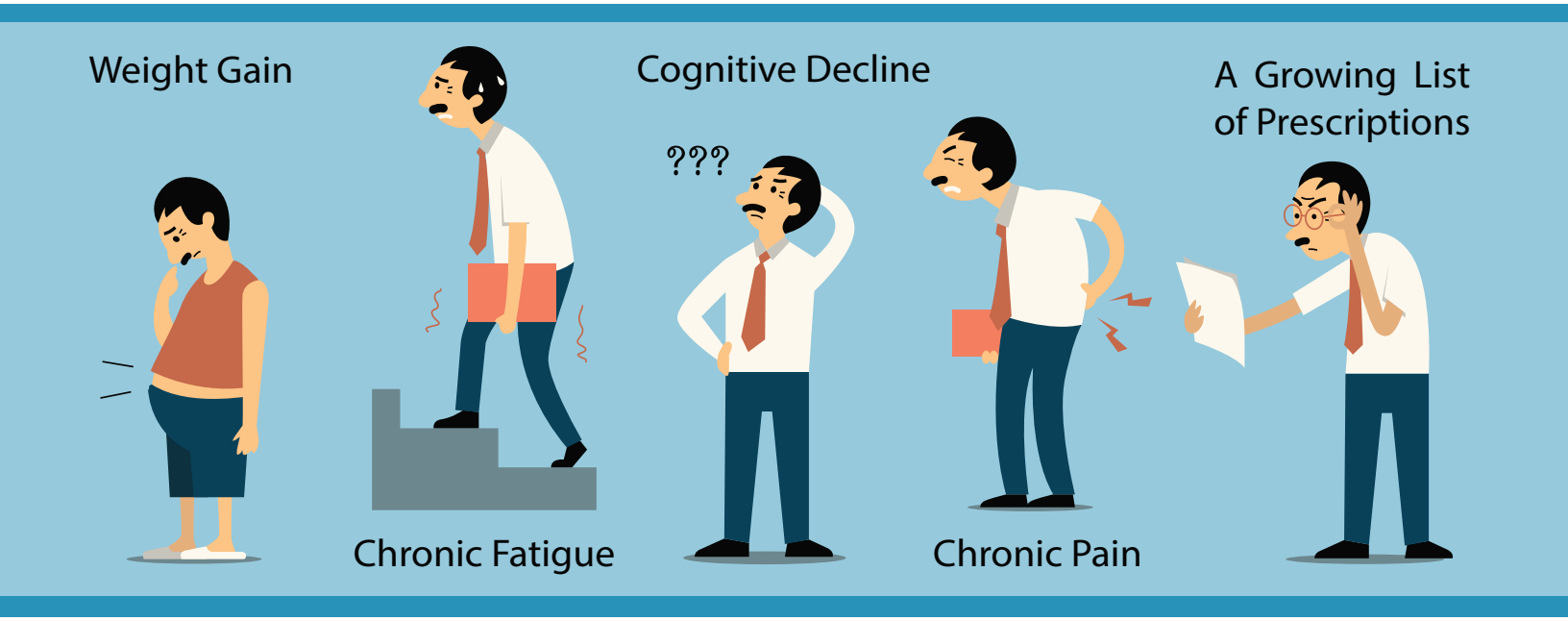
What is "Normal" Aging, Anyway?

There are many conditions we tend to accept as "normal" consequences of aging:



As we learn more about the human body and how these conditions develop, we can identify methods to suppress the symptoms of aging and improve quality of life. The symptoms of aging are not simply the result of passing time, but rather they are the result of youthful levels of key metabolic components dwindling down. This reveals new targets for combating the conditions of aging.

GLUTATHIONE - peptide which protects cells from oxidative damage

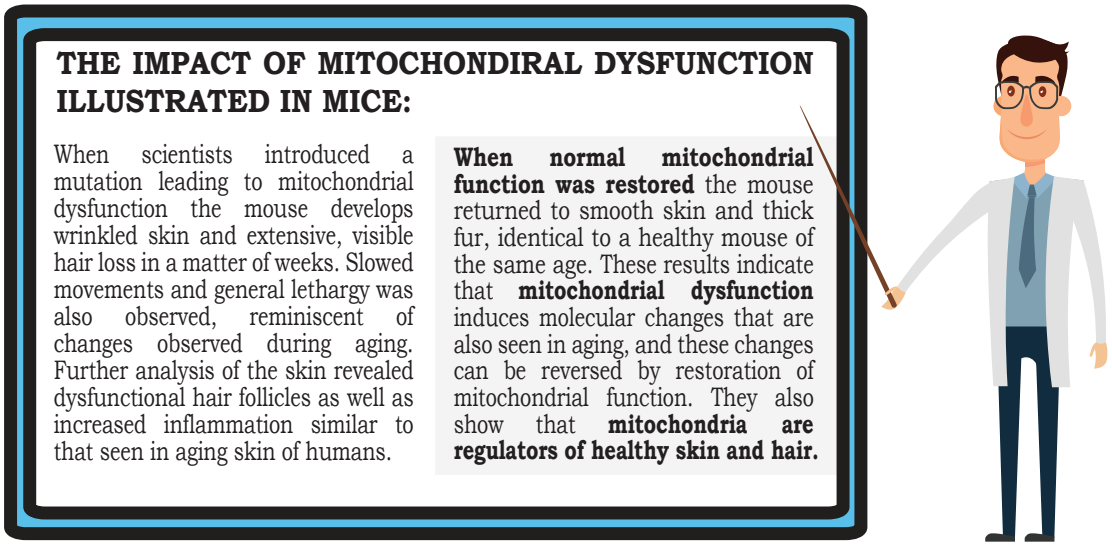
NAD+ - coenzyme found in all living cells

AMPK - enzyme which manages energy homeostasis

Studies have confirmed that supplements which increase these levels trigger favorable changes in metabolism, inflammation, insulin sensitivity, and lifespan.

Mitochondrial Dysfunction

Mitochondria are crucial for optimal health and longevity. Mitochondria are found in every cell of the human body except red blood cells, and convert the energy from food into ATP, which powers most cell functions. Mitochondria truly are *the powerhouse of the cell* but the body's ability to manufacture new mitochondria decreases with age. Aging and diseases such as cardiovascular disease and diabetes contribute to a decline in mitochondrial function. The diverse roles of mitochondria and the ATP they generate means that mitochondrial function plays an important role in metabolic and cellular health. Accumulating evidence suggests a strong link between mitochondrial dysfunction, aging, and aging-related diseases.



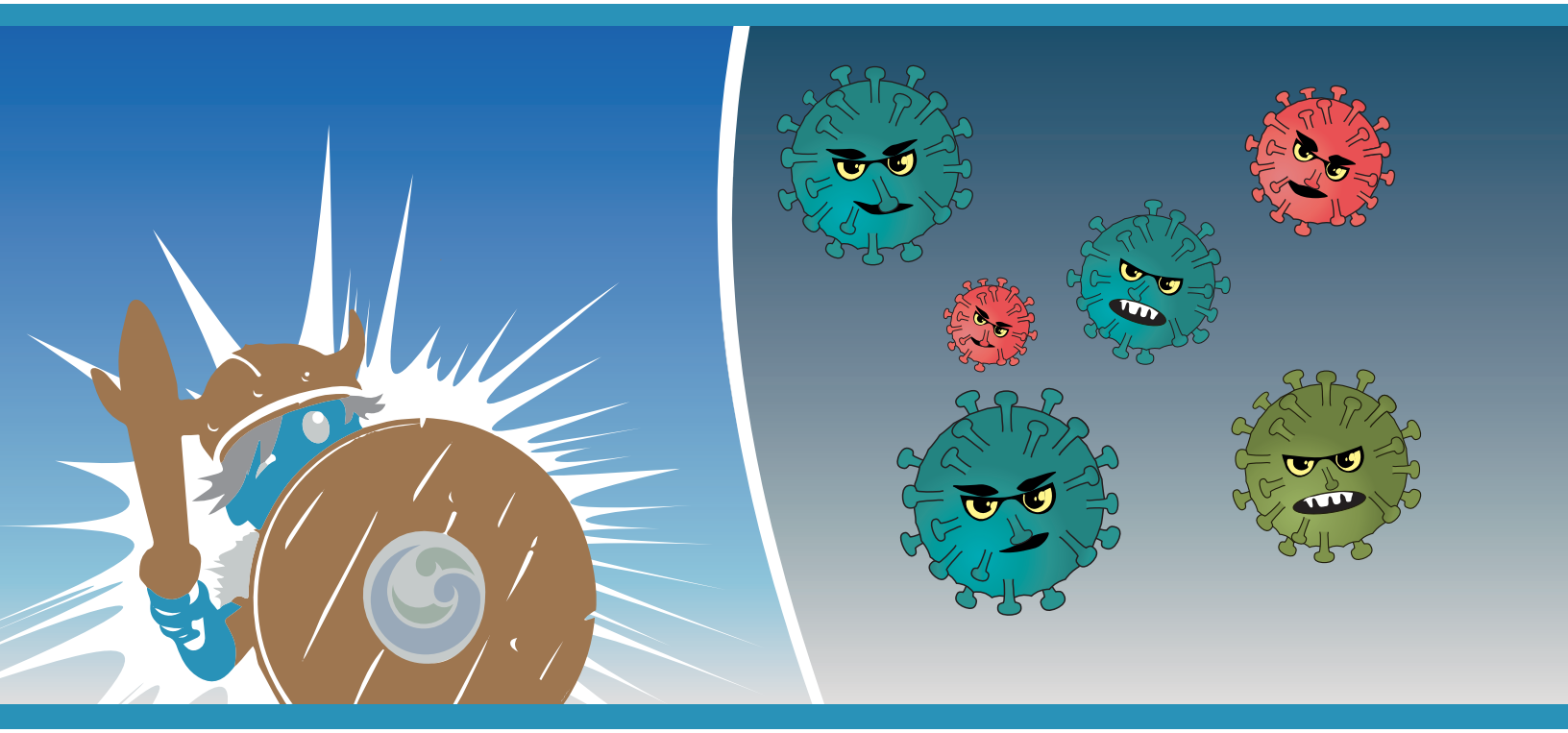
NAD+, Glutathione, and AMPK each play important roles in protecting cells and keeping mitochondria functioning properly.

Researchers have discovered specific pathways which the body uses to protect itself from mitochondrial damage, which can ultimately lead to DNA damage and cell death. However, as these mechanisms become less effective with age, supplementing these pathways may help prevent, and even reverse, age-related mitochondrial dysfunction.

NAD+, Glutathione, and AMPK have each been linked to health and longevity because of their role in protecting mitochondria and preserving optimal function.

GLUTATHIONE

Glutathione is a powerful antioxidant that helps with the body's natural detoxification mechanisms for environmental stresses, air pollutants, heavy metals, and other toxins. As an antioxidant, Glutathione neutralizes free radicals and peroxides, preventing them from damaging cells and tissues. Glutathione also keeps other antioxidants, such as vitamins C and E, working at full efficiency.



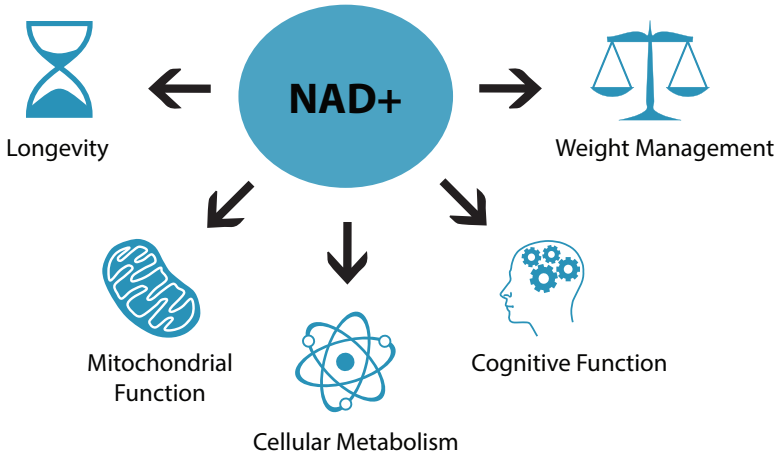
PROTECTION FROM OXIDATIVE DAMAGE

Without proper levels of antioxidants such as glutathione, oxidative stress causes cell damage that contributes to impaired energy production and development of degenerative diseases such as type 2 diabetes.

Glutathione depletes with age, leaving older cells much less well equipped to deal with stress & toxins. "The cells from older animals were quickly depleted of glutathione and died twice as fast when subjected to stress" compared to youthful cells.[3]

Studies have shown that glutathione concentrations can protect against the development of insulin resistance, which strongly suggests a link between increased oxidative stress, mitochondrial dysfunction and compromised metabolism in diabetic complications. "Supplementing diets to correct [Glutathione] deficiency and reduce oxidative stress provides significant metabolic benefits [...] by improving insulin sensitivity."[4]

NAD+



Nicotinamide adenine dinucleotide (NAD+) "is involved in more reactions than any other known vitamin-derived molecule"[1]. NAD+ serves as a cofactor in a number of metabolic processes including breaking down fats and sugar, and reducing fat synthesis.

NAD+ also plays an important role in ATP production and protects against the devastating effects of mitochondrial dysfunction which can lead to organ failure, cognitive deterioration, and even death.

NAD+ activates enzymes known as sirtuins (SIRT), which trigger favorable changes in metabolism, inflammation, insulin sensitivity, and lifespan. Sirtuins compete with the enzyme PARP1 for use of NAD+. PARP1 activity increases during aging and in response to high energy intake, reducing the pool of NAD+ available for sitruins, causing an energy deficit and increased oxidative stress.

BOOSTING NAD+ SLOWS AGING

NAD+ levels decline with age, resulting in degenerative disorders of the brain and heart, deteriorating quality of sleep, and impaired metabolism. A precursor to NAD+, nicotinamide, has been demonstrated to increase NAD+ and promote youthful cell function.

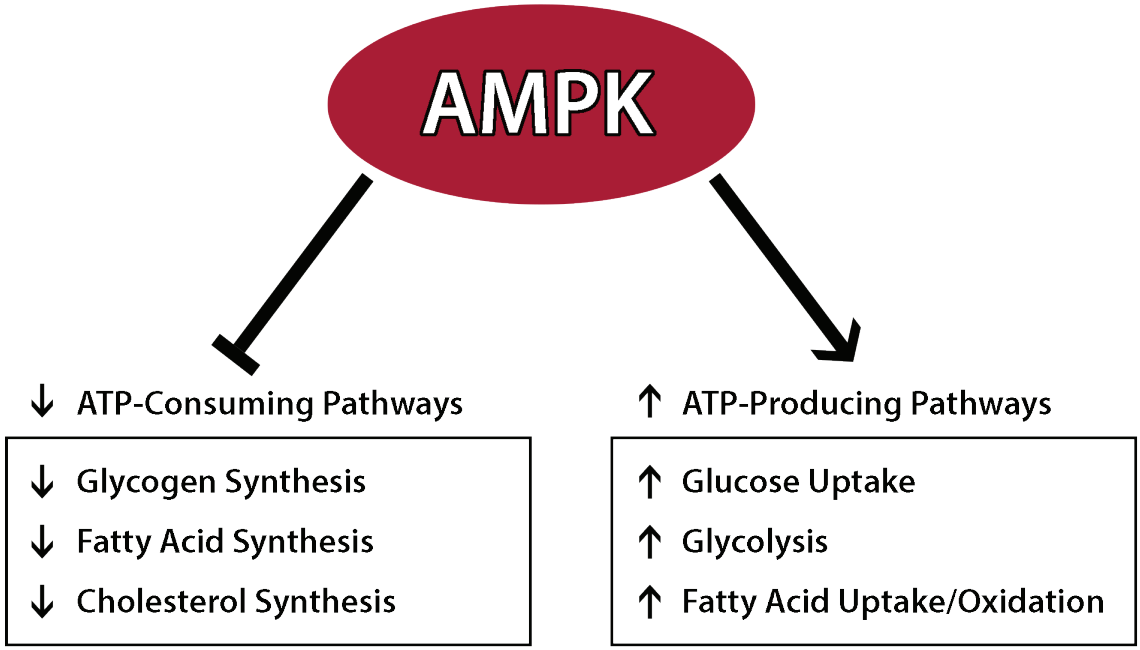
Various studies have demonstrated the importance of NAD+ metabolism and suggest that altered NAD+ metabolism could underlie symptoms associated with aging. Replenishing NAD levels by supplementing with nicotinamide may provide a novel therapeutic approach to age management.

Furthermore, NAD+ deficiency accelerates the depletion of glutathione, the paramount antioxidant for preventing cell damage from oxidative stress which tends to decrease with age.

AMPK

AMPK has been referred to as a metabolic 'master switch'. Activation of AMPK tells the cells to decrease ATP usage and increase ATP production by reducing fat storage, producing new mitochondria, and utilizing stored fat, effectively turning off many damaging effects of aging.

During youth, AMPK is activated at high levels. As we age, levels of activated AMPK sharply declines. As AMPK decreases, energy levels decrease and fat storage increases - many will increase caloric intake in an attempt to sustain energy levels which leads to further fat storage. As one gains weight and becomes obese, AMPK activation decreases even further.



AMPK PROMOTES LONGEVITY

AMP-activated protein kinase (AMPK) promotes longevity via multiple longevity pathways including maintaining mitochondrial efficiency and metabolic function.

As the name implies, AMPK is activated in the presence of AMP - when fruit flies were engineered to have high levels of AMP, AMPK activity increased significantly. AMPK activity was accompanied by a life-span one-third longer than the non-engineered controls. "These data establish AMP and AMPK as determinants of adult life span" (Stenesen, 2013).

Sources of Longevity

Supplementing with these nutrients can restore youthful levels of glutathione, NAD+, and AMPK.

GLUTATHIONE

Studies have found that oral consumption of glutathione can effectively increase cellular levels of glutathione. Further studies have found superior benefits from sublingual applications.

> Glutathione (GSH) levels in blood increased after 1, 3 and 6 months versus baseline at both doses. At 6 months, mean GSH levels increased 30-35 % in erythrocytes, plasma and lymphocytes and 260 % in buccal cells in the high-dose group ($P < 0.05$). GSH levels increased 17 and 29 % in blood and erythrocytes, respectively, in the low-dose group ($P < 0.05$). In most cases, the increases were dose and time dependent, and levels returned to baseline after a 1-month washout period. A reduction in oxidative stress in both GSH dose groups was indicated by decreases in the oxidized to reduced glutathione ratio in whole blood after 6 months. Natural killer cytotoxicity increased >twofold in the high-dose group versus placebo ($P < 0.05$) at 3 months. (Richie, 2015)

> The study was a three-week randomized crossover trial. 20 Volunteers with metabolic syndrome were enrolled. GSH levels and several oxidative stress markers were determined at different times during each 21-days period. Compared to oral GSH group, an increase of total and reduced GSH levels in plasma and a higher GSH/GSSG ratio ($p=0.003$) was observed in sublingual GSH group. After 3 weeks of administration, there was a significant increase of vitamin E level in plasma only in sublingual GSH group (0.83 µmol/g; $p=0.04$). Our results demonstrate the superiority of a new sublingual form. . . (Schmitt, 2015)

NICOTINAMIDE

Nicotinamide is a 'flush-free' form of niacin, or Vitamin B3, the essential dietary precursor for formation of NAD+. "Most tissues take up both forms of vitamins to synthesize NAD+ and NADP+ , although nicotinamide is the preferable substrate" (Surjana, 2010).

> Nicotinamide (50–500 µM) increased intracellular NAD + and enhanced the repair of DNA damage induced by N-methyl-N -nitro-N-nitrosoguanidine (MNNG) in cultured primary human mammary epithelial cells [23]. Preincubation with 74 µM nicotinamide prevented NAD+ depletion after dimethyl sulphate (DMS) exposure and increased strand break rejoining rate [89]. Increasing NAD+ status by the addition of nicotinamide thus improved the capacity of DNA repair. NAD+ is also an important determinant of skin cell survival following UV radiation. 0.1 and 33 µM nicotinamide added to UV-irradiated cultured human skin fibroblasts increased cell survival 7 days post irradiation in a dose-dependent manner [90]. Even in the absence of genotoxic stress, NAD+ depletion increased spontaneous DNA damage in human HaCaT keratinocytes, which was reversible with the addition of nicotinamide [91]. (Surjana, 2010)

ADENOSINE MONOPHOSPHATE

AMPK, Adenosine Monophosphate-activated Protein Kinase, is activated when a cell has high concentrations of AMP. Studies have found that oral AMP is absorbed by the cells to activate AMPK.

> AMP effectively improved hypertension, plasma triglyceride, and HDL-cholesterol, glucose, kidney function parameters, hepatic lipid, enhances plasma nitric oxide, and plasma adiponectin accompanied by the up-regulation of mRNA expression levels of the hepatic adiponectin receptor 2. Single and chronic oral administration of AMP affected the hepatic mRNA expression levels of genes involved in β-oxidation, fatty acid synthesis, and AMP-activated protein kinase. Furthermore, a single oral dose of AMP (40 mg/kg body weight) improved hypertension and hyperglycemia in SHRSP. In conclusion, AMP displays a novel effect in ameliorating metabolic-related diseases in SHRSP. (Ardiansyah, 2011)

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