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Halalopathy: Role of Entropy in the Aging Process

Alzeer, Jawad

ABSTRACT

Many diseases, such as cancer and Alzheimer, are often referred as age-related diseases. The main causes of these diseases are remarkably similar to the causes that can lead to aging. Consequently, one would think that aging should be considered as a health problem rather than a natural process that needs to be monitored and cured. The literature indicates that there are many factors that are likely to cause aging, but efforts to reverse, stop, or slow aging may be completely misguided. Aging is a natural, spontaneous process that can be better understood by focusing on a natural, spontaneous process that occurs in a living system. Spontaneous processes, such as catabolic processes, are mainly driven by entropy, suggesting that entropy formation and accumulation may play a key role in understanding and controlling the aging process. Entropy is a dispersed or suppressed form of potential energy that tends to generate heat. The accumulation of heat creates very unbalanced conditions that can promote the development of diseases or accelerate the aging process. Entropy is inversely proportional to potential energy, and any enrichment of potential energy or reduction of entropy can contribute to healthy aging. Potential energy can be used to fight entropy. Activating anabolic processes, growth hormones, and maintaining an anabolic mindset can enrich potential energy. Resisting fear and grief, reducing food intake, minimizing stress, maintaining a balanced heat flow, and avoiding a catabolic mindset can reduce the formation and accumulation of entropy.

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Review Article

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Halalopathy: Role of Entropy in the Aging Process

Jawad Alzeer*

Department of Halalopathy, Swiss Scientific Society for Developing Countries, Switzerland

*Corresponding author: Jawad Alzeer, Department of Halalopathy, Swiss Scientific Society for Developing Countries, Zurich, Switzerland.

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Abstract

Many diseases, such as cancer and Alzheimer, are often referred as age-related diseases. The main causes of these diseases are remarkably similar to the causes that can lead to aging. Consequently, one would think that aging should be considered as a health problem rather than a natural process that needs to be monitored and cured. The literature indicates that there are many factors that are likely to cause aging, but efforts to reverse, stop, or slow aging may be completely misguided. Aging is a natural, spontaneous process that can be better understood by focusing on a natural, spontaneous process that occurs in a living system.

Spontaneous processes, such as catabolic processes, are mainly driven by entropy, suggesting that entropy formation and accumulation may play a key role in understanding and controlling the aging process. Entropy is a dispersed or suppressed form of potential energy that tends to generate heat. The accumulation of heat creates very unbalanced conditions that can promote the development of diseases or accelerate the aging process. Entropy is inversely proportional to potential energy, and any enrichment of potential energy or reduction of entropy can contribute to healthy aging. Potential energy can be used to fight entropy. Activating anabolic processes, growth hormones, and maintaining an anabolic mindset can enrich potential energy. Resisting fear and grief, reducing food intake, minimizing stress, maintaining a balanced heat flow, and avoiding a catabolic mindset can reduce the formation and accumulation of entropy.

Keywords: Aging; Potential Energy; Entropy; Heat Flow; Epigenetics

Introduction

The human body is the most incredible and diverse system of organs and tissues with about 60 trillion cells. The body possesses a natural mechanism for restoring cells to their proper state and function, however, the processes associated with repair or alignment will never result in perfect restoration and proper repair of all the cells that make up the body. Consequently, a certain degree of unavoidable imperfections will always remain. These imperfections initially pass undetected at the microscopic level; however, over time, more cells will fail to restore their native state and function. As a result, these errors gradually accumulate until

the critical amount of errors is reached and the entire system collapses [1].

Senescence or biological aging involves a gradual deterioration of biological processes in living organisms [2]. Human lifespan depends on environment, genetic makeup, lifestyle, diet, and mental state [3]. Biological systems, to function effectively, must be programmed to receive and exchange information throughout the system. Genetics and epigenetics are a storehouse of information, and any change in gene sequence can result in the loss of information that can affect the control of biological processes,



the organization of biostructures, and the response to stimuli [4]. Genetic information is translated into proteins, that are responsible for almost all biological processes in the human body.

The effectiveness of a protein's function is preserved as long as it is enriched with information, and classically the native information is preserved in the protein's native structure. The structure of proteins is affected by heat, which in turn affects the hydrogen bonds, hydrophobic effect, and self-assembling structure [5]. Denaturation of the protein structure leads to a complete loss of information, rendering the proteins non-functional [6]. Depending on the role of these proteins, they influence either an anabolic or a catabolic process and thus affect energy production and distribution. The aging process is always accompanied by the formation of many denatured and non-functional proteins [7].

Halalopathy offers a new perspective for the prevention and recovery of diseases. In this context, halalopathy introduced entropy as the main cause of disorder and potential energy as the main source of order in the body. To maintain homeostasis in the body, a balance must be established between potential energy, which acts as a driving force for anabolic and growth-promoting processes, and entropy, which promotes spontaneous processes for energy production. Spontaneous processes, such as catabolic processes, usually lead to the degradation of highly ordered macromolecules and ultimately generate highly disordered micromolecules. In this article, we would like to discuss the factors that can potentially lead to protein denaturation in the human body and explain the role of catabolic and anabolic metabolic pathways in the aging process from the perspective of halalopathy.

Aging Process

Aging is a progressive deterioration of physiological function and is characterized by a declining ability to respond to stress, increasing homeostatic imbalance, and risk of age-related diseases such as cancer and heart disease [8]. Despite all the major breakthroughs in molecular biology and genomics, the mechanism of aging is still largely unknown. There are several theories of aging, and their number is increasing. It is now agreed that aging is multifactorial and complex process, thereby it is difficult to come up with a single theory or cause for the aging process. From the literature, there are many factors that are likely to cause aging, such as radicals [9], shortening of telomeres [10], accumulation of epigenetics [11], mutation [12], fusion of chromosomes [13], DNA breakage [14], continuous stress [15], reversal of epigenetics [16], mitochondrial dysfunction [17], metabolic rate [18], cellular senescence [19], unhealthy diet [20], and poor-quality exercise [21].

Aging is a natural process of life, but efforts to stop or slow aging can be completely misguided. The aging process can occur at different levels: molecular, cellular and tissue [22]. However, there is an interesting debate as to whether tissue aging is always the result of cellular or molecular aging. As we wait for effective solutions, there are some simple changes that can be incorporated into daily life that can help reverse or slow the aging process by improving health and reducing the risk of early death from common but preventable diseases. It is generally accepted that a healthy lifestyle with plenty of exercise, a healthy diet and sufficient sleep can help improve performance and maintain overall health even at old age [23].

Reverse Aging

Evidence from some scientific experiments with human cells and simple organs has shown that it is possible to reverse the aging process [24]. But it is not yet possible to reverse the aging process in humans, despite hopes for young blood transfusions in Silicon Valley [25]. The technology to reverse aging still has a long way to go, although clinical trials of regenerative stem cell therapies for diseases such as heart failure are underway [26]. However, there are concerns that reversing cell aging could lead to uncontrolled proliferation of cells and thus could eventually provoke the development of cancer. Every day, the cells in the body perform numerous metabolic reactions. Although they are essential for life, they produce toxic metabolites that accumulate until they eventually contribute to disease and death.

A connection between the aging process and the loss of information in the cells remains an unanswered question. The brain is an information-processing organ, and information is stored in the form of genetic and epigenetic information. As long as the structure and sequence of DNA and epigenetics are preserved, the information is stored well, but with time, many DNA breaks and mutations occur. Normally, errors such as mutations and double-strand breaks are repaired in the cell, but following many repairs, the proteins involved in the repair do not return to the desired location, as in the case of the longevity proteins. If information is the key to the aging process and if information is lost, is it possible to recover it.

The information theory of aging predicts that the loss is epigenetic rather than genetic information that occurs in the form of mutations [27]. At the epigenetic level, the reverse of information seems to be possible. Changes in the epigenome that occur with age due to methylation changes, often related to an individual's exposure to environmental factors. Epigenomic drift and noise can be a major factor in aging process [28]. Damage to DNA, particularly

DNA breaks, is a driving force for this process. Changes in the number and positions of DNA methylation tags on DNA can be used to predict life expectancy based on marking time from birth. In epigenomic reprogramming or cloning of an organism, methyl tags are removed, thereby could potentially reverse the age of the cell. This is called the DNA methylation clock [29]. Infecting mice with the reprogramming genes Oct4, Sox2, and Klf4 reverses the age of the cells through the TET enzymes, removing just the right methyl tags on the DNA, turning back the clock on aging, and allowing the cells to survive and grow like newborns. How the enzymes manage to know which tags are the young ones is still a mystery. However, reprogramming virus, which contains three Yamanaka factors, has restored vision in mice, but has yet to be tested in humans [30].

It might be possible to reverse certain tissues in human body, but reverse aging in the whole body sounds very challenge. However, other studies suggest that these efforts to reverse the aging process are completely misguided and as a consequence, the reverse process is never observed in nature. Apparently, systems tend to evolve from a lower to a higher entropy, in plants, the leaves turn green, yellow and brown and fall off the trees. Currently, there is no way known to reverse the aging process and return the brown leaves into green before being detached and fallen down.

Key Factors in Aging Process

In aging, individual cells have one of two options: either they slow down the biological process and reduce cause-effect information, thus gradually losing their function, or they accelerate and proliferate uncontrollably and become cancerous. Therefore,

over time, our cells either become slow to respond or become active and develop into cancer. Although aging could potentially lead to cancer, to some extent cancer does not lead to a resumption of the normal aging process; cancer could represent rejuvenated cells that have high metabolic heat production (entropy) and maintain a high metabolic rate. On the other hand, the removal of cancer cells by chemotherapy, radiation or surgery does not slow down the aging process, on the contrary, the cells associated with aging will continue to accumulate and slowly degrade its function [31].

Aging systems, if left alone, spontaneously human evolve from young to old. As aging is a spontaneous process, thus it is likely the process is not driven by potential energy, but most likely entropy/heat driven. In the body, there is a similar process that occurs spontaneously and is not driven by potential energy but by entropy, namely the process of catabolism. The catabolic process is a breakdown process in which large molecules are broken down into smaller molecules, resulting in an increase in entropy due to the increase in the number of small molecules produced during the breakdown of macromolecules. This makes the catabolic process entropy driven and explains why the catabolic process is a spontaneous process. The anabolic process is a growth process in which complex molecules are formed from simpler molecules. Consequently, the anabolic process requires potential energy for the growth of macromolecules, while the catabolic process does not require potential energy to proceed; on the contrary, the catabolic process generates energy in the form of adenosine triphosphate (ATP) [32].

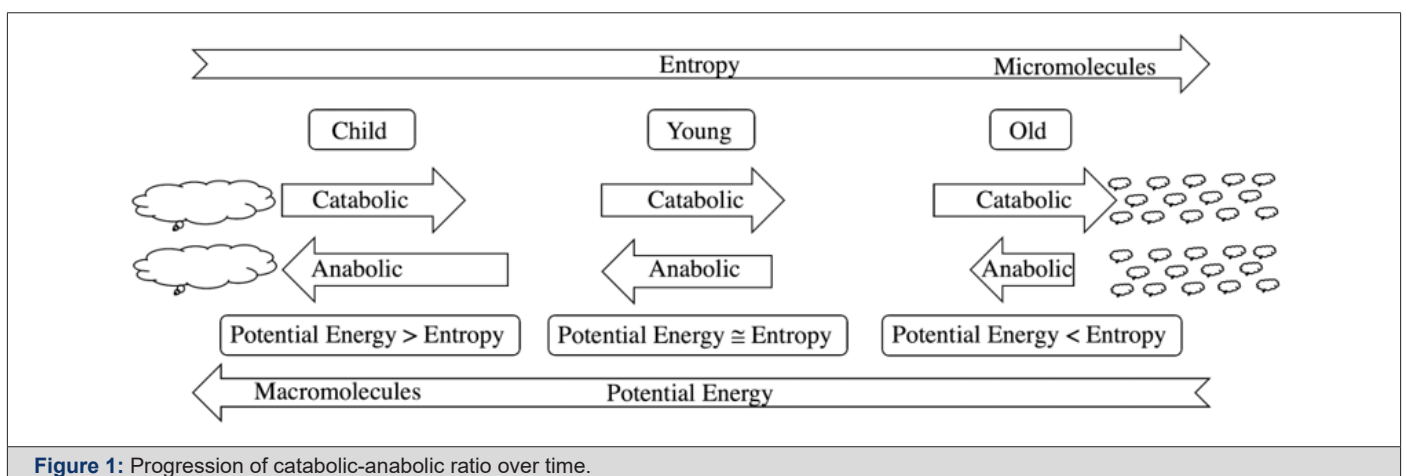


Figure 1: Progression of catabolic-anabolic ratio over time.

When we are young, the anabolic process is more dominant, consequently more potential energy is needed, coming mainly from food, to support the growth process (Figure 1). Meanwhile, the catabolic process is always active and supports the anabolic process in terms of energy supply by processing and breaking down food,

and this process will always be accompanied by the accumulation of entropy [33]. In the anabolic process, small molecules and building blocks are combined to form a high-potential macromolecule. As small molecules combined, the number of collisions between the small molecules is reduced, thus during anabolic process

entropy decreases. During the building process, ATP is converted into another form of potential energy, resulting in the formation of a highly complex, self-assembling, and highly functional macromolecule. According to the second law of thermodynamics, every change in the form of energy results in the release or loss of some energy in the form of entropy.

Thus, on the one hand, anabolic processes reduce entropy; on the other hand, a change in the form of energy causes entropy to be subsequently liberated. Evidently, the formation of entropy remains effective in both processes, although entropy is partially reduced during the anabolic process. As human growth is completed, the anabolic process is reduced, while the catabolic process remains active at all times. The accumulation of entropy reduces the efficiency of the anabolic process, allowing it to be activated on demand. Overall, entropy continues to increase, leading to a dispersion or suppression of potential energy and eventually to an increase in disorder in the system. These are favorable circumstances for the aging process, and the maximum entropy in the body leads to death, the final destination of the life process. Since the accumulation of entropy is inevitable and the conversion of entropy into potential energy is probably impossible, this means that reversing the aging process is most likely impossible but slow down the formation of entropy is possible, consequently healthy aging remains as the only possible option [34].

Reduction of Entropy for Healthy Aging

Heat Flow

The potential energy cannot bear to stay in the body, it will always flow around to perform a necessary activity. During this process certain amount of potential energy changes into lower quality form and becomes less available to do work, this energy is liberated in form of heat and called entropy. Heat production continues in the living system, causing an increase in entropy

accumulation. Once heat has accumulated in the body, it increases the disorder and cause more collisions between molecules, thus more heat is generated. Heat can be reduced by the flow or exchange of heat with the environment. In a warm atmosphere, the heat flow is usually very slow, while in a cold atmosphere it is fast.

The heat flow must remain in balance, neither too slow nor too fast, and the optimum temperature for optimal flow is around 20 °C. Ideally, the rate of heat generation and heat flow should be nearly equal. However, any reduction in the flow rate will cause heat accumulation, and any increase in the flow rate will accelerate the catabolic process to replace the rapid heat loss during cold and keep the body temperature constant at 37 °C. In both situations, disorder increases, and more entropy is created in the system (Figure 2). A balanced heat flux allows the body to live longer and perform more metabolic work, indicating that the entropy production rate is low; however, an increase in the entropy production rate appears to be associated with an increase in the rate of aging and the development of diseases. Patients with different kinds of diseases showed elevated rates of heat production.

If the heat flow is slow and the outside temperature is close to 37°C, drinking water can trigger a sweating response and accelerate the heat flow to the outside. Fortunately, water has the highest specific heat, allowing additional heat to be absorbed by water without significantly increasing the body temperature. If the heat cannot flow and is trapped in the body, the situation is similar to manure production or alcoholic fermentation, where the heat flow is blocked and accelerates the catabolic process in which large molecules break down into small molecules, resulting in spontaneous combustion and internal fires. Consequently, the blockage of heat flow leads to human death. Restoration and improvement of heat flow can be achieved through breathing techniques and meditation exercises [34].

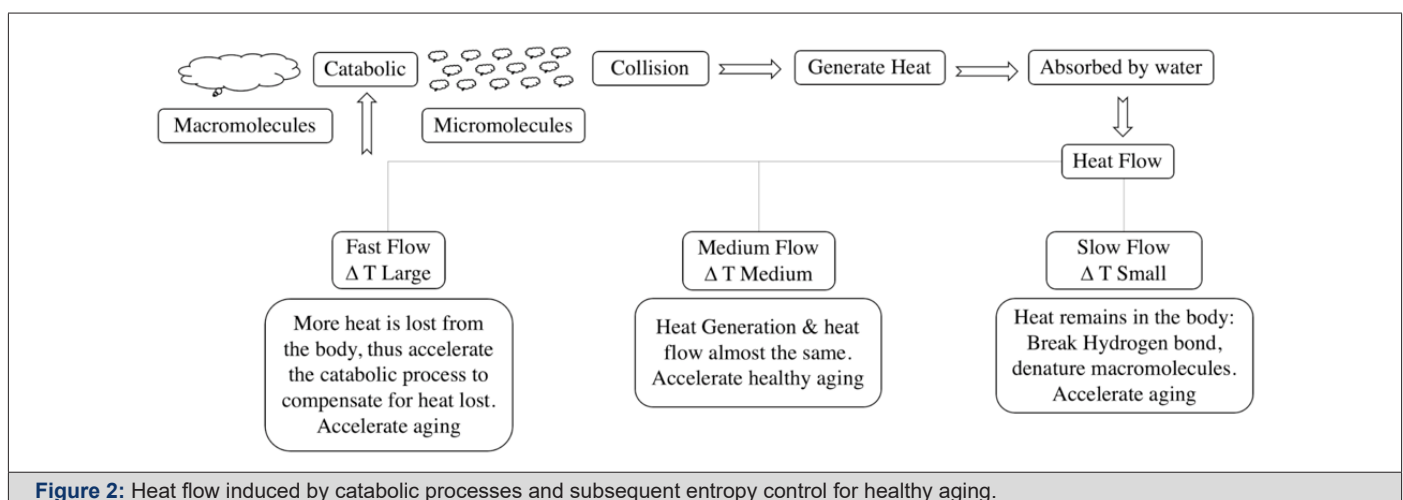


Figure 2: Heat flow induced by catabolic processes and subsequent entropy control for healthy aging.

Activate Anabolic Process

Human growth hormone stimulates growth, cell reproduction and cell regeneration in the human body. Growth hormone behaves more effectively during sleep, exercise, low sugar intake and fasting. Experts estimate that 75% of human growth hormone is released during sleep [35]. Elastic potential energy is enriched by effective exercises that cause the release of human growth hormone, stimulate the growth of new nerve and muscle cells, and in turn promote the anabolic process and healthy sleep [36]. Those who exercise regularly show no signs of age-related loss of muscle mass and strength, have no increase in cholesterol or body fat, and the production of T cells, a type of immune cell, remains high. Swimming is the most beneficial sport suitable for all ages. Apart from the positive effect achieved by the collective muscle movement, this sport is practiced in water and allows the entropy generated by the body in the form of heat to easily flow out and be absorbed by water.

Activate Anabolic Thinking

Thinking is a powerful way to produce ideas, yet having an idea is not enough, however, turning it into reality and making it useful for people is the most attractive trends in thinking. By default, every person is an idea generator, but not every person is an idea translator. Anabolic and constructive thinking is actually a way of generating green potential energy, almost no entropy. Using the power of the good and constructive word is useful to motivate and provide our body with enough energy to create a productive work [32]. A good and constructive word is indeed like a tree with roots, branches and fruits, it represents strength and potential, it has value and motivates individuals to be creative and productive, and most importantly, it accelerates to adapt anabolic thinking in life. The high quality, high interest and high value of the idea activate the excitatory neurotransmitters. The accumulation and amplification of excitatory neurotransmitters creates an action potential, a source of potential energy that could drive us to turn the potential into productive work [37].

Avoid Catabolic Thinking

Destructive and non-constructive thinking is harmful to the body and disperses the potential energy, therefore destructive words are like a tree without roots, branches and without fruits, they represent weakness, their presence only irritates and causes no added value. Destructive thinking, whether from us or from the surroundings, activates the inhibitory neurotransmitters, when they accumulate, they prevent the propagation of the action potential, thus whoever has no potential is unable to give anything [32].

Eat Biodegradable and Compatible Food

Biodegradable foods that can be broken down into smaller molecules in the soil by bacteria, fungi or microbes, ideally without contamination, are considered compatible to the human body. Biodegradable foods cause less stress and need less time and energy during metabolism compared to non-compatible or non-biodegradable foods. Lifestyles are diverse and can be classified as vegan, vegetarian, kosher, halal, lactose-free, gluten-free, or glucose-free [38]. Foods that are compatible with the individual lifestyle create a compatible system, reduce disorders and activate potentials.

Improving compatibility between mind and body (concept behavior) leads to greater selectivity and specificity, thereby improving concentration, reducing confusion, and emitting dispersed energy in the form of entropy. A compatible system improves the mind-reality connection and directs efforts to improve work and productivity, which in turn maximizes cause-effect information [39]. Non-compatible/non-biodegradable chemicals are considered foreign substances that need to be excreted, causing the body to make greater efforts to oxidize and/or conjugate these molecules to convert them into water-soluble and inactive metabolites that can be easily removed from the body.

Less Food Intake

Entropy increases when the number of cells and the total energy in the body increases. Thus, when the body grows beyond an optimal configuration, more disorder is created internally. The growth hormone is a fasting hormone that is mainly activated during sleep and/or reduced food intake [40]. Thus, a further effective measure that may contribute to maintaining the balance between anabolic and catabolic hormones, is a diet control by means of intermittent fasting [41]. During fasting, on the one hand, food intake is reduced, which ultimately decreases the breakdown of food, reduces the catabolic process, in turn reducing entropy. On the other hand, lack of glucose and lipid intermediates amplify growth hormone secretion, lower insulin level, thereby promote growth and increase potential energy in the body [42].

Reduction of Stress

Stress in general disperses or suppresses potential energy and leads to high entropy. Mental stress leads to anxiety or depression, while physical stress consumes a large amount of potential energy that is used to process the stress and remove it from the body. Physical stress usually occurs when our body is exposed to a large amount of food or medication. The elimination process is lengthy and consumes a large amount of potential energy. Anxiety, which arises from fear, disperses potential energy and activates the

fright mode, while depression, which arises from grief, suppresses potential energy and initiates the flight mode [32].

Fight entropy

Life is constantly a struggle to maintain low entropy. Daily we are exposed to constant attacks from pathogens, internal and external negativity, passive behavior, and catabolic thinking, all of which are sources of increasing entropy. Yet we are also determined to overcome challenges and achieve goals that make us valuable and productive, all of which are sources of increasing potential. If we allow entropy to take over, it will accumulate rapidly, and death is the destination [34]. Therefore, we must prepare for the worst and set our minds in fight mode, which in turn strengthens the immune system and keeps it alert to fight damages and restore functions. Fighting mode is the state in which defects can be corrected without being accumulated, it is a state in which it is possible to fight entropy in our body more effectively.

Another way to keep the fight mode active is to resist and fight fear and grief; this is yet another way to fight entropy and to activate potentials. Basically, we are constantly fighting entropy with potential energy, but as we age, our ability to maintain high potential decreases as entropy continues to increase. Disorder begins to accumulate until it reaches a critical state that severely limits our ability to fight entropy, this state is called death.

Discussion

Humans are driven by vital forces, namely instincts and organic needs, with the purpose of maintaining a well-defined configuration and a self-organized structure. Living organisms need to obtain energy to perform biological work and sustain their life. Potential energy is used to fulfil the demands of anabolic processes and stress response. Instincts and organic needs, to function effectively, must be programmed to receive and exchange information throughout the system. Information flow from genetic and epigenetic sources and then it is transcribed and translated to generate highly functional proteins. Any change at the genetic and epigenetic levels could result in a change or loss of information, similarly, the flow and transmission of information through many entities could potentially minimize cause-effect information.

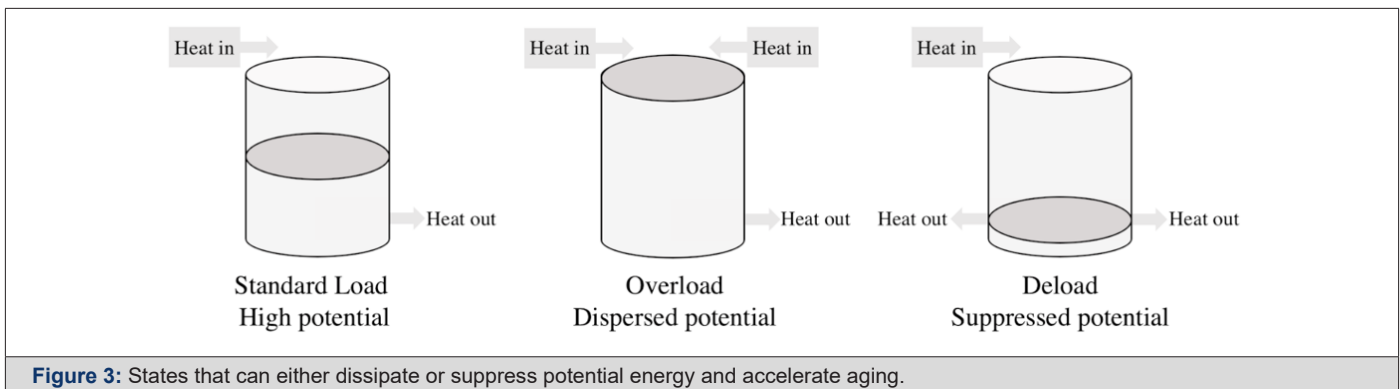
Entropy in biological systems is characterized as either a dispersed or a suppressed form of potential energy. Entropy and potential energy have been introduced by the medicine of Halalopathy as key elements for prevention and cure [43-45]. Entropy is a measure of disorder, a state in which molecules operate in an uncoordinated manner and increase continuously in a living system. Entropy significantly increases the probability of collisions between molecules and releases heat as a by-product. Therefore,

potential energy is actually used to generate work, while entropy is mainly involved in the generation of heat. When heat is generated, the body temperature does not increase significantly, but the extra heat is either absorbed by the water in the body or flows out of the body. The rate of flow depends on the external temperature, i.e. it flows slowly when the temperature is close to 37 °C and quickly when the temperature approaches zero.

The extra heat absorbed by the water in the body is still considered insufficient to do any significant work, but it mainly increases the random and disorder motions of the molecules and could eventually disrupt the weak inter- and intramolecular forces. Hydrogen bonds are sensitive to this type of heat, causing macromolecules such as proteins and nucleic acids to denature from their native structure. Both macromolecules in native form have high potential and are rich in information. Any heat accumulation leads to a faster rotation of the side chains, weakening the hydrophobic interaction and disrupting the self-assembly, resulting in a denaturation of the macromolecular structure and a reduction of the cause-effect information. As a result, the efficiency of cells, tissues and organs in the body decreases, causing the body to enter a threshold period where the catabolic process is faster than the anabolic process and as a result, the aging process dominates.

Sources of entropy arise mainly from spontaneous processes, such as catabolic process, and partly from changes in energy form, as described by second law of thermodynamic "whenever the energy form changes, some of that energy is lost in the form of entropy". As a result, entropy cannot be reversed, and consequently, aging is unlikely to be reversed, and hence the only option remains to promote healthy aging by slowing the build-up of entropy. Slow entropy formation and effective entropy flow play the main role in maintaining healthy aging. The reduction of entropy requires the acceleration of non-spontaneous processes, such as anabolic processes, which allow the assembly of highly potent macromolecules, anabolic process act as a reverse process to catabolism.

The activation of growth hormones is a suitable way to promote the anabolic process, which can be stimulated by fasting, adequate sleep and exercise; swimming is a suitable sport for this purpose. Water has one of the highest specific heat capacities and can therefore absorb heat very effectively. Consequently, water with a mild temperature accelerates the flow of heat out of the body, but at a steady rate, without causing internal stress. An extremely slow or fast heat flow is perceived as stress, which must be avoided (Figure 3). At lower temperatures, heat flow is rapid and heat loss must be compensated to maintain the balance between heat production and flow. This accelerates the catabolic process and generates more energy on the one hand and more entropy on the other.



The slowing of entropy formation can also be achieved by reduced food intake, which in turn reduces the catabolic process. Food represents mass and energy and is therefore a source of stressors and potential energy (ATP). In general, food must be metabolized, and the metabolic wastes must be eliminated. When food is metabolized, potential energy and heat are generated and used to maintain body temperature. Less food intake therefore slows down the catabolic process, which in turn generates less heat and thus less entropy. The fight against entropy is a constant challenge and can be defeated by increasing potential energy. Therefore, it is important to control stress factors that cause potential energy to be either dispersed or suppressed. Entropy is inversely proportional to potential energy, thus, resisting or fighting fear and grief plays a key role in the fight against entropy. Constant fear and worry create anxiety, while constant grief and regret create depression.

Anxiety disperses potential energy, while depression suppresses potential energy, consequently resisting anxiety and depression is an important element of fighting entropy. Another source of stressors that needs to be addressed is catabolic thinking, indeed, destructive, and negative thinking is a major source of a stressor that needs to be avoided. Anabolic thinking is essential to keep the anabolic process active, certainly constructive, and positive thinking must be strongly recommended as it provides green potential energy given that no entropy is generated in this process. It is important to keep the immune system in a healthy state (fight mode), a state in which errors can be corrected without being accumulated; this is an essential factor in preventing/fighting disease and consequently promoting healthy aging while producing entropy at a slow rate. Finally, every system tends to evolve from low to high entropy, i.e., green leaves with low entropy become yellow or brown, likewise spontaneous events move towards high entropy, spring with high potential comes before autumn and youth before aging, i.e. potential energy before entropy. These phenomena remain part of the laws of nature, which can only be changed or reversed by miraculous circumstances.

Conclusion

Halalopathy focuses on entropy and potential energy as key elements for disease prevention and recovery. Entropy is inversely proportional to potential energy. Slowing down entropy formation and accumulation is therefore important to maintain healthy aging. Entropy formation is accelerated when the balance is shifted in favour of the catabolic process over the anabolic process. Therefore, to slow down the shift in equilibrium, it is useful to enrich growth hormones and in turn accelerate the anabolic process. Growth hormones can be stimulated by reduced food intake, adequate sleep, and age-appropriate exercise. Reducing caloric intake through food choices is challenging, but intermittent fasting can be practiced.

Exercise, such as swimming, is beneficial as the body remains physically active in the water and the heat generated is absorbed by the water, keeping the heat flow constant without causing internal heat build-up. Exercise ensures a healthy sleep, improves performance and maintains overall healthy aging. Fear and grief are very important stressors that are programmed to stay in the body for a while. When either state lasts longer than expected, potential energy is dispersed and suppressed, thereby increasing entropy, generating more heat, and causing the immune system to remain either in flight or fright mode. Fighting fear and grief plays a key role in fighting entropy, therefore reduction of both states leads to activation of potential and restoration of function.

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Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

None.

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