THE EFFECTS OF CALORIE RESTRICTION ON EXTENDING HUMAN LIFESPAN

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Abstract

Aging is the time-dependent functional decline that affects most living organisms. A plethora of diseases have been shown to be directly linked to aging and the functional decline associated with it. Therefore, the postponement, prevention or reversal of aging may represent an important therapeutic target for the prevention of many diseases. One strategy proposed to tackle aging and therefore its associated diseases is calorie restriction. Epidemiological data has revealed a number of disparate areas around the world, termed 'blue zones', where people allegedly live far longer than the average life expectancy. Calorie restriction has been proposed as one of the key reasons for increased longevity in these populations.

Indeed, in both rodents and primates calorie restriction has been shown to extend lifespan, and therefore represents a possible therapeutic target to slow aging. Determining the mechanism through which calorie restriction exerts its effects on lifespan may allow us to target particular genes and emulate the effects of calorie restriction without having to employ calorie restriction itself. Therefore, the use of calorie restriction mimetic drugs thought to activate the mechanisms underlying the anti-aging effects of calorie restriction may be the most reasonable treatment to extend lifespan. The purpose of this review is to put forward evidence in the scientific literature relating to this hypothesis.

Introduction

At present, Ireland has the youngest population of any EU country. However, increasing life expectancy coupled with falling birth rates will result in an aging population. It is estimated that by 2041 there will be 2.4 million people aged over 60 on the island of Ireland, up from 1.1 million people in 2015 [1]. This is a trend that is also seen globally; by 2050, it is expected that there will be 2.1 billion people aged over 65, up from 1 billion in 2020 [2]. This will impose new challenges for many countries, as old age is a risk factor for many diseases and leads to an increased demand for healthcare [3]. In Ireland, costs of long-term healthcare are projected to triple by 2050,[4] while total healthcare costs are expected to increase from 8.3% to 13% of the Irish Gross National Income between 2019 and 2050 [4]. Therefore, given the projected increase in the elderly population and healthcare costs, it seems it would be medically prudent to introduce prophylactic interventions which aim to reduce the risk of succumbing to age-related diseases, or at the very least, mitigate their impact.

What is aging?

Aging is the time-dependent functional decline that affects most living organisms. In humans, aging is associated with a decline in a number of physiological metrics including muscle mass and strength, maximum heart rate, and VO_2 max (which measures the maximum rate of oxygen consumption during exercise and is a popular indicator of cardiorespiratory fitness) [5]. Indeed, aging is a potent risk factor for many of the deadliest diseases in developed countries, such as Cancer, Cardiovascular Disease and Neurodegenerative Disorders [6]. These ailments are often a function of aging. Therefore, the postponement, prevention or reversal of aging may represent an important target for the prevention of many diseases.

What mechanisms underlie aging?

Several mechanisms have been shown to manifest during normal aging. In addition, the experimental amplification of these mechanisms has been shown to accelerate aging, while their experimental silencing has been shown to slow aging [7]. Therefore, the following cellular and molecular mechanisms have been proposed to be the hallmarks of aging: Genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication (Figure 1).

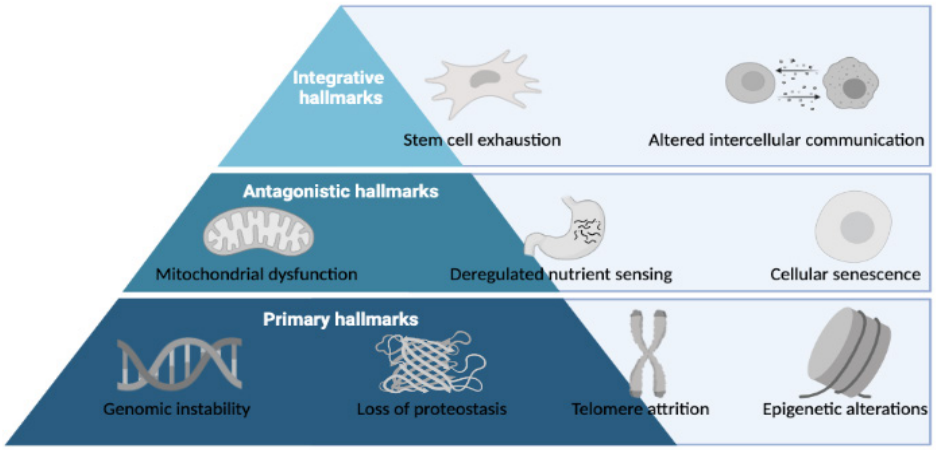

Figure 1. Proposed hierarchical relation between the hallmarks of aging hallmarks: the primary hallmarks underlie the antagonistic hallmarks, both of which underlie the integrative hallmarks.

There appears to be some degree of hierarchical relation between these hallmarks [7]. Genomic instability, telomere attrition, epigenetic alterations and loss of proteostasis are thought to be the primary hallmarks of aging and could be the initial triggers that lead to cumulative damage over time. In turn, this may cause the antagonistic hallmarks (deregulated nutrient-sensing, mitochondrial dysfunction and cellular senescence) to become progressively more damaging in response to the primary triggers. Finally, the integrative hallmarks (stem cell exhaustion and altered intercellular communication) arise when the damage caused by the primary and antagonistic hallmarks not be compensated [7]. Thus, if these proposed hallmarks and their hierarchical organization are accurate, an intervention to combat the primary hallmarks would be most effective.

Why does aging happen?

Longevity is a multifactorial trait, determined by a number of genes as well as environmental factors. A 1996 study by Herskind *et al.* into longevity in twins concluded that longevity is only approximately 20% determined by heritable traits [8]. However, later work has suggested that the true heritability of human longevity is below 10%, and that it had previously been overestimated due to the effects of assortative mating (a form of sexual selection in which individuals with similar phenotypes mate with one another more frequently than would be expected under a random mating pattern) [9]. Whatever the case may be, it is clear that a significant component of longevity is determined by environmental factors, which are modifiable. Improving longevity must therefore focus on modification of environmental factors with the goal of attenuating one or more of the hallmarks of aging [8,9].

The role of 'blue zones' in human longevity.

There are several areas where an unusual number of people regularly live longer than average and encounter less age-related morbidities [10]. These areas are known as 'blue zones', five such areas being Loma Linda (USA), Nicoya (Costa Rica), Sardinia (Italy), Ikaria (Greece) and Okinawa (Japan) [10]. In these areas, the proportion of people reaching 100 years of age is ten times greater than in the United States [10]. Epidemiological studies have investigated the lifestyle of the populations in these regions, in order to determine common environmental factors that are associated with increased lifespan. In these 'blue zones', the authors noted several traits they believe are associated with longevity; including calorie restriction, regular physical activity, moderate alcohol consumption, stress reduction and a plant-based diet [10].

However, the 'blue zones' are not without their criticisms. A 2020 paper by Newman [11] proposed that fraud and error play a primary role in generating remarkable human age records. Their data revealed that so-called remarkable age attainment is predicted by indicators of error and fraud, such as poverty, high crime rates, and the absence of birth certificates [11]. The author concluded that these findings raised serious questions about the validity of the research based on the remarkable reported ages of the studied populations and individuals. However, this study is yet to be peer-reviewed, and as of yet its findings remain allegations [11]. Despite this, any claim of extreme advanced age must hold up to rigorous scrutiny, especially after the prominent case of Japan's 230,000 phantom centenarians casting further doubt on the validity of such demographic data [12,13]. While the status of the 'blue zones' remains up for debate, some of the traits presented by the authors of the original study warrant further research for their purported role in extending the human lifespan [10].

Calorie restriction: an anti-aging strategy in humans?

Calorie restriction (CR) has been called the most reasonable anti-aging intervention and has been demonstrated in a number of model organisms [14]. CR typically involves a caloric intake of 60-70% of what an *ad libitum* animal would consume, while still maintaining proper nutrient intake. Research shows that CR and genetic manipulations are generally more effective than medications at extending the total lifespan in the models *C. elegans* and *Drosophila* across numerous studies [14]. Furthermore, analysis of genetic manipulations that extend lifespan suggested that many of these genes or pathways were associated with CR [14]. The effects of CR can also reliably increase both median and maximum lifespan in rodents [15]. Similarly, a study by Colman *et al.* reported that in a 20-year study of Rhesus macaques, CR of 30% lowered the incidence of aging-related deaths; at the time of the report, only 50% of control fed animals survived compared with 80% survival of CR animals [16]. In addition to this, CR delayed the onset of age-associated pathologies, such as Diabetes, Cancer, Cardiovascular Disease, and Brain Atrophy, suggesting that CR slows aging in a primate species [16].

However, the effects of CR on non-human primates are still up for debate. A similar study by Mattison *et al.* which also performed CR of 30% on Rhesus macaques over 23 years found that CR had no significant effects on longevity when compared to the control group [17]. However, a 2014 comparative review between these two studies found significant differences in body weight between control groups [18]. This suggested that when compared with the control animals from the original Colman *et al* study, the Mattison *et al* controls were calorie restricted, albeit to a lesser degree than the true calorie restricted groups [16-18]. Therefore, the researchers concluded that moderate rather than extreme calorie restriction is sufficient to produce the observed health and longevity benefits in Rhesus macaques [18].

The anti-aging effects of CR in a human population have been most notably assessed on the Japanese island of Okinawa. An epidemiological study by Willcox *et al.* spanning over 60 years observed that low-calorie intake coupled with high physical activity levels appeared to have contributed to a CR phenotype in older Okinawans [19]. This phenotype results in reduced mortality from age-associated diseases, and extended lifespan [19]. While the conclusions were tentative, an adaptive response to early and mid-life energy restriction in the older cohort of Okinawans may be implicated in their low morbidity rates and exceptionally long survival [19]. This is consistent with the well-known literature that supports a beneficial effect of CR on lifespan in several animal models. However, the young people of Okinawa are increasingly abandoning the traditional Okinawan diet [20]. The effects of the increasing Westernisation of the dietary habits of Okinawans are yet to be seen but present an opportunity for further research into CR if this new cohort were to be used as a control against proponents of the traditional Okinawan diet.

The mechanism for the anti-aging effects of CR demonstrated in primates and rodents remains unclear. However, it has been proposed that CR increases lifespan by reducing oxidative damage in cells as CR attenuates the production of reactive oxygen species while simultaneously increasing the production and activity

of endogenous antioxidant enzymes [21]. In addition, CR has been shown to improve lifespan in rats by reducing 'inflammaging' (a phenomenon of chronic low-grade inflammation present in aged populations) via blockade of the TLR4/NF-kB signalling pathway [22]. Thus, CR is hypothesized to act on several of the proposed hallmarks of aging: genomic instability, mitochondrial dysfunction and altered intracellular signalling [7].

Calorie restriction mimetics.

Following on from the experimental success of CR in the extension of the lifespan of both rodents and primates, research has begun into calorie restriction mimetics (CRMs), which aim to mimic the anti-aging effects that CR has on several model organisms. One drug which is proposed to be a CRM is Metformin. Most commonly used in the treatment of Diabetes, a 2017 review by Campbell *et al*. found that diabetics on Metformin had lower rates of Cancer, Cardiovascular Disease and lower all-cause mortality when compared with both non-diabetics and diabetics who were not treated with Metformin [23]. The authors stated that Metformin appears to extend health and lifespan independently of its effect on Diabetes and concluded that Metformin may be able to extend lifespan in the general population. In addition to this, mice treated with low doses of Metformin have higher insulin sensitivity, reduction of low density lipoproteins and cholesterol levels in plasma, increased antioxidant protection and reduction of chronic inflammation; effects similar to those found with CR [16,21,24].

In line with these findings, the mice treated with low doses of Metformin lived 5.83% longer, which was a statistically significant increase in mean lifespan when compared to the control group [24]. Metformin caused altered gene expression similar to that observed in calorie restriction. Researchers observed increased expression of several genes involved in mitochondrial energetics and antioxidant production, thus suggesting that metformin prevents oxidative damage [24]. There was also significant downregulation of the gene encoding the proinflammatory transcription factor NF-κB, thus inhibiting chronic inflammation [24]. The overall interpretation of these results is that Metformin causes altered gene expression which is similar to that observed in CR mice, which causes increased longevity.

Conclusion

In developed countries such as Ireland, falling birth rates coupled with extended lifespan has resulted in aging populations. However, efforts to counteract aging will enable us to ameliorate the observed age-related decline in function, thus decreasing the number of dependent, aged individuals in the population, undoubtedly a favourable outcome on both the individual and national level. There are a number of disparate areas around the world, termed 'blue zones', where people allegedly live far longer than the average life expectancy. Several common factors between these populations have been proposed as the reason for the increased longevity of these populations, such as calorie restriction. In rodents and primates, calorie restriction has been shown to extend lifespan, and therefore may represent a prophylactic measure that can ameliorate aging. However, the nature of calorie restriction makes it a difficult strategy to implement across the level of the entire population, as the acceptability of and adherence to prolonged calorie restriction may be low in many patients when compared to a pharmacological intervention [25,26]. Determining the mechanisms through which calorie restriction exerts its effects on lifespan may allow us to target particular genes and emulate the effects of calorie restriction without having to undergo calorie restriction itself. Therefore, the use of CR mimetic treatments such as Metformin that are thought to mimic the mechanisms of calorie restriction may be the most reasonable treatment to extend lifespan.

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