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Caloric restriction, longevity and aging: Recent contributions from human and non-human primate studies

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ABSTRACT

The health benefits of chronic caloric restriction (CR) resulting in lifespan extension are well established in many species and has been recently demonstrated also in non-human primates, but its effects in humans remain to be proven on a long-term basis. CR might be a very efficient anti-aging strategy but its definition and limits must be well understood before envisaging to apply it to human. In this review, we first report and compare the recently issued CR studies in non-human primates and humans and then try to understand what an optimal caloric intake is. In a last part, we will discuss the pertinence of using CR as an anti-aging strategy with respect to the risks of frailty and obesity.

1. Calorie restriction, an efficient strategy to increase longevity

Caloric restriction (CR), consists in reducing calorie availability by up to 50%. It is one of the rare non genetic strategies that extends lifespan.While CR might be a very efficient anti-aging strategy, its definition and limits must be well understood before envisaging to apply it to human. In this review, we first report and compare the recently issued CR studies in non-human primates (focusing on longevity studies) and humans and then try to understand what an optimal caloric intake is. One of the goal of the present mini-review is to address the pertinence of using CR as an anti-aging strategy with respect to the risks of frailty and obesity, what we discuss in a last part.

In short-lived species such as rodents, CR can increase maximal lifespan up to 50% (McCay et al., 1935) while improving general health and decreasing aging-associated diseases (Fontana et al., 2010). CR reduces the onset of several diseases, among which atherosclerosis, cancers, diabetes, renal, neurodegenerative and respiratory diseases (for review see (Fontana et al., 2010; Chung et al., 2013; Fontana et al., 2018)). Beneficial effects of CR on age-related diseases have also been reported for long-lived species including rhesus monkeys (*Macaca mulatta*) at the Wisconsin National Primate Research Center (Colman et al., 2009; Colman et al., 2014) and at the National Institute on Aging (Mattison et al., 2012). Increased survival was however only reported in the Wisconsin National Primate Research Center study (Colman et al., 2009; Colman et al., 2014; Mattison et al., 2017) while the National Institute on Aging study detected no significant survival effect. Direct comparison of data from both studies suggested that differences in outcomes of the two studies may have been due to study design differences including the age of CR onset, feeding regimen, diet composition, and genetics (Mattison et al., 2017; Vaughan et al., 2018). Alternatively to studies in macaques, the effects of CR were recently demonstrated on the health and lifespan of the grey mouse lemur (*Microcebus murinus)*, a small lemurid primate originating from Madagascar. With a median survival in captivity of 5.7 years for males and maximum lifespan of 12 years (Languille et al., 2012), mouse lemurs represent an emerging promising model for human aging (Bons et al., 2006; Austad and Fischer, 2011; Ezran et al., 2017). They display age-related alterations of their sensorial system, motor functions, biological rhythms, immune and endocrine systems (Languille et al., 2012). In this species, aging leads to increased prevalence of diseases such as neoplasia or sarcopenia (Hämäläinen et al., 2015) and glucoregulatory function alterations (Djelti et al., 2016) that also increase with aging in humans. Finally, their cerebral aging profile is similar to that of humans as they display age-related cognitive alterations associated to cerebral atrophy (Picq et al., 2012a) as well as Alzheimer's disease-like amyloid lesions (Mestre-Francs et al., 2000). Like humans and other non-human primates they are genetically heterogeneous providing a natural diversity of aging profiles. Because of their reduced life span (as compared to macaque), cohorts of CR-animals can be easily created to evaluate mechanisms leading to CR-related changes.

In 2006, a CR study was initiated on captive adult (~3 y.o.) male mouse lemurs receiving chronically 30% less calories (CR, $n = 19$) compared to a control cohort (CTL, $n = 15$) (for detailed protocol see (Dal-Pan et al., 2011b; Pifferi et al., 2018)). Their longevity, age-related

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pathologies, cognitive abilities, motor skills, and cerebral atrophy were then followed until their natural death. As expected, CR animals consistently exhibited lower body mass than the CTL animals. Consistently with studies in smaller species and one cohort of macaques, CR had a strong positive effect on mouse lemur lifespan. When all the CTL animals had died (15/15), 26% of the CR animals were still alive (5/19). Median survival was 6.4 and 9.6 years for CTL and CR animals, respectively, which corresponds to a 50% increase in median lifespan. Also, 7 CR animals reached 13 years of age which is far beyond the maximal life span of 12 years reported in the entire breeding colony (Languille et al., 2012) and of 11.3 years reported in the CTL animals. The maximal lifespan of CR animals finally reached 13.8 years (Pifferi et al., 2019). The increased lifespan of CR individuals was accompanied by a lower incidence of age-related pathologies such as cancer and chronic nephritis. Also, the mortality rate associated to age-related diseases was 60% lower in CR (0.44 deaths/year) compared to CTL animals (1.1 deaths/year). Although CR has been reported to protect against many aspects of brain aging in mammals (Martin et al., 2006), deleterious effects of CR on cognitive performance have been reported for rats (Yanai et al., 2004) and for cerebral and emotional functions in humans (Dirks and Leeuwenburgh, 2006; Redman and Ravussin, 2011). In the mouse lemur study, cognitive performances were assessed and were not different between CTL and CR animals. Motor performances, which are important for physical independence and healthy aging in humans (Collino et al., 2013), were also assessed. CR animals exhibited similar endurance abilities (Pifferi et al., 2018) and even better motor performances measured in a high jump task. In this task, CR animals were able to jump 5.6 cm higher than CTL animals when taking into account all the jump sessions in which animals effectively jumped over the 10 years of the study (mixed-effects model, $p = .02$; $F(1,32) = 5.98$). More interestingly, after 5 years of treatment, among 13 sessions of jump task for CTL animals, only 6 sessions led to a jump (other animals did not jump at all) with a mean height of 27 cm, while among the 23 sessions of the CR animals, 22 sessions led to a jump with a mean height of 29.5 cm, *unpublished data*). This last result illustrates well how much CR animals were in better physical condition compared to CTL.

In humans and non-human primates, including mouse lemurs, aging induces a cerebral atrophy that is associated with cognitive impairments (Chetelat et al., 2003; Picq et al., 2012b; Shamy et al., 2011). However, in the two studies that addressed this question in the context of CR in primates, results are contradictory. In the macaques study, data demonstrate that brain atrophy was rescued by CR in some brain regions in rhesus monkeys for both grey and white matter (Colman et al., 2009; Bendlin et al., 2011). Concerning white matter in particular, and according to the authors, the results were regionally specific and also suggested that CR is not salutary across all white matter29. Comparable analysis of serial MRI of mouse lemur brains were performed and revealed contradictory results, mainly about grey matter atrophy. In that last study, a stronger reduction of grey matter volume with age in the CR group as compared to CTL animals was reported. Regarding white matter, a lower rate of atrophy was observed in the CR group compared to the CTL group. These results corroborate previous studies in rhesus monkeys (Bendlin et al., 2011) and mice (Guo et al., 2015) reporting a beneficial effect of CR in preserving white matter.

The lemur study supports the hypothesis that CR has important beneficial effects on healthspan and lifespan in primates, as it does in many animals with a shorter lifespan. However, CR also accelerated atrophy of grey matter in old mouse lemurs, although no alteration of cognitive performances was detected in CR animals. This latter result provides a cautionary note for using CR strategies to extend lifespan in older primates including Man (Martin et al., 2016).

Concomitantly to the publication of the study in mouse lemurs (Pifferi et al., 2018), a conclusive study on the effects of chronic moderate calorie restriction in humans was issued (Redman et al., 2018). In this study, voluntary subjects were submitted for 2 years to a 15% caloric restriction without modifying meals composition. The study found a mean weight loss of 9 kg in the test subjects, while control subjects (who did not modify their dietary habits) gained 1.8 kg. Caloric restriction in humans induced a slowing in metabolism and decreased production of free radicals. According to the “Rate-of-living Theory of Aging”, metabolic activity is inversely correlated to longevity in mammals (Redman et al., 2018). The “Free Radical Theory of Aging” posits that free radicals production is responsible for the multiplication of cellular lesions leading to aging symptoms (Redman et al., 2018). Thus, according to these two theories, the changes induced by caloric restriction in humans could slow down aging processes and may have visible benefits on clinical outcomes but it remains to be proven by long-term longitudinal studies.

2. Better defining the optimal caloric intake?

So far, most of CR studies, from yeasts to non-human primates, come to the same conclusion: CR is an efficient strategy to increase healthspan and lifespan. However, a fundamental question is still not answered: what is the nutritional status of CTL animals compared to CR animals? Are control animals receiving optimal caloric intake or are they generally overfed and thus metabolically morbid, as proposed by Martin and colleagues (Martin et al., 2010)? The question deserves to be addressed. Determining the optimal caloric intake for a given species is difficult, mainly because it depends mainly on the level of locomotor activity. In this context, it is possible to compare the body weight of laboratory bred animals to wild conspecifics. In the case of mouse lemurs, the mean body weight of the CTL group was between 90 and 110 g, while those under CR were comprised between 60 and 80 g[19] (both measures concern summer-acclimated animals, mouse lemur exhibiting physiologic seasonal body weight variations). In comparison, wild animals during the same season weigh around 60 g according to field studies (Schmid and Speakman, 2000; Schmid and Speakman, 2009). Even if longevity of wild animals is much shorter than animals bred in captivity, they are supposed to receive the correct amount of food, corresponding to their needs and the environment in which they evolved and are thus adapted for. In addition, field animals are very active in comparison to laboratory animals (the home range of a wild male is comprised between 1 and 2.5 ha) (Radespiel, 2000). Taking into account that CR lemurs perform 25% more spontaneous locomotor activity (Dal-Pan et al., 2011a) (a phenomenon called food-anticipatory behavior (Caba and Mendoza, 2018; Challet, 2013)), CR animals are much closer to wild animals in term of body weight and activity than CTL. CTL animals could thus be considered overfed (and also probably sedentary), both conditions being deleterious for their longevity. From that point of view, mouse lemurs bred in captivity can be considered as a good model of modern human. Data from Redman and colleagues, (the 2 years CR human study (Redman et al., 2018)), tell us that before CR, both experimental groups exhibited a body mass index (BMI) over 25. Such BMI corresponds to an overweight status according to the World Health Organization (WHO, 2018) definition. As expected, after 2 years, CR resulted in an average 8.7 kg weight loss, whereas control individuals gained 1.8 kg. After 2 years of treatment, BMI of the CR group decreased to 22.5 while it reached 26 in the CTL group. Body mass variations were mainly due to fat mass changes according to the authors (Redman et al., 2018). It confirms that even in human studies the definition of a CTL group is not evident. If control should not be considered as receiving high-calorie diet, they are probably in an intermediary situation between an optimal caloric intake and high-calorie diet. Thus, it is necessary to clearly define, for a given species, and for a given level of activity, what is an adequate control in order to fully endorse the beneficial effects of CR.

3. Caloric restriction and aging: juggling with the risk of frailty and obesity

The vast majority of studies on CR in humans describe beneficial health effects (recently summarized in a review by Most and colleagues (Most et al., 2017)). However, CR is also worrying gerontologists. It is true that it can be risky to simply declare that CR is good for all, and Lebourg and Redman perfectly highlighted the risks of simple translation of animals data to humans (Le Bourg and Redman, 2018). Caloric intake should depend on a long list of parameters on top of which are activity level, physical condition and age. The frailty of a given individual should thus be taken into account. The concept of frailty can be defined as "*a reduced physiological reserve with aging, leading to a lower resistance to stressors, frail elderly being at higher risk for adverse health events, disability and death*" (Féart, 2018). Since unintentional weight loss is part of Fried's items criteria (a scale defining the frailty status), CR can lead to increased risk for frailty. According to Fried and colleagues (Fried et al., 2001), the unintentional weight loss is a marker of frailty susceptibility, thus nutritional status is an important criteria in defining frailty. As a consequence, malnutrition is commonly observed in frail people (Lorenzo-López et al., 2017). Even if frailty and malnutrition are clearly distinct phenomenon, 90% of older people in situation of malnutrition are considered frail (Féart, 2018). In the general population of older adults (> 65 y.o.), prevalence of frailty is about 10% (Collard et al., 2012). In this specific population, it is obvious that CR should not be considered as a potential intervention. In addition, to our knowledge, there are no studies supporting a beneficial impact of long-term CR in aged animals or individuals.

This said, the risk of frailty must be considered at the light of the prevalence of obesity and obesity-related mortality. Excess weight is clearly a worldwide growing public health concern (including in undeveloped countries) (, n.d.-c). The prevalence of obesity in the adult population in 2017 was over 35% in the U.S. and 15% in France (Collard et al., 2012) and it keeps increasing (NCD Risk Factor Collaboration (NCD-RisC), 2016). A huge number of studies have found an excess risk of death of obese individuals compared to normal-weight adults, obesity being associated with diseases of the circulatory system, diabetes, kidney diseases, and respiratory infections, as well as with cancers of several sites (see (Jura and Kozak, 2016; Avram et al., 2005) for review). Both obesity and aging are conditions leading to increased risk for disease and death. Aging is associated with an increase in abdominal obesity, a major contributor to insulin resistance and metabolic syndrome. Obesity in the elderly is thus also a serious concern and impairs life quality and expectancy. In a study conducted in four European countries (Stenholm et al., 2017), in people aged between 50 and 75 years, the proportion of life spent in good perceived health was 81% in normal weight people *vs* 53% in the BMI > 35 category. The proportion of life without chronic diseases was around 65% in normal weight people and 35% in the BMI > 35 category. It corresponds to an average of 9 and 7 more years without chronic diseases in normal weight men and women respectively, compared to BMI > 35 obese men and women (Stenholm et al., 2017). Thus, there is a clear life-quality and longevity benefit to lower BMI before (maybe even during) the onset of aging. Interestingly, in a recent analysis of the Wisconsin National Primate Research Center CR study (Yamada et al., 2018), the authors report that weakness, poor endurance, slowness, and low physical activity level were significantly higher in control compared to CR macaques as was total incidence of frailty. CR clearly reduced the incidence of frailty and increased healthy lifespan in macaques. Comparable observations were made in lemurs, CR animals being in better physical conditions (revealed by motor and endurance tasks) despite, or thanks to, their lower body weight. It suggests that, for people not at risk of unintentional weight loss, CR, instead of leading to a risk of frailty is able to limit its occurrence. More than age, it is the body condition and health status of an individual that should condition the opportunity of CR. It also suggests that, for better efficiency, CR, or optimization of caloric intake, should be envisaged before the onset of obesity-related pathologies.

Numerous additional studies will be mandatory to address the remaining questions about CR efficiency in primates. Among them, and keeping in mind that the optimal caloric intake remains to be defined for most species, the timing and duration of CR also remains to be elucidated. However, it seems obvious that implementing caloric restriction in human is unlikely. Worse, results in human demonstrate that diets often lead to weight gain on a long-term basis. In a study comparing dieting to non-dieting twins, Schur and colleagues demonstrated that those dieting gained more weight over a four-years follow-up than their non-dieting twins (Schur et al., 2010). Long-term weight loss maintenance is thus difficult to sustain (Anderson et al., 2001) and demonstrates the need for alternative strategies. From our point of view, the two main alternatives to CR are: 1) increasing activity levels and 2) developing drugs that mimic the cellular and molecular pathways of CR (making CR studies mandatory to understand the underlying mechanistic pathways). Ideally, a combination of nutritional, behavioral and therapeutic interventions could lead to strong synergic beneficial effects for a better healthspan and longer lifespan. It constitutes a promising direction for future research.

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