Chapter 2
Somatotropic Axis' Role in Ageing and Longevity Could Depend on Life-History Strategies of Species

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Abstract It is often argued that food restriction and modulation of the somatotropic axis could increase lifespan in all species, and particularly in human beings. However, this rationale does not take into account the life-history strategies of species and the way they adapt to environmental challenges, particularly to food restriction. It is argued that, for short-lived species of a small size, the best strategy to survive starvation is staying at the same place and increasing lifespan, because they cannot migrate to discover new food sources, because of a high predatory load and/or an inability to cross long distances. Emigration is an appropriate strategy for long-lived species of a large size less at risk of predation. Because humans tend to emigrate when facing unfavourable conditions rather than staying at home, food restriction is not expected to increase lifespan in humans. As an outcome, modulating the somatotropic axis would probably not increase human lifespan, because increased lifespan has not been selected as a strategy: how a genetic pathway could modulate lifespan in the absence of any selective pressure?

Keywords Lifespan · Ageing · Food restriction · Somatotropic axis · Human beings · Model organisms · Life-history strategies

2.1 Introduction

It has been said that "molecular, cellular, and developmental biologists ask "how" questions about mechanisms", while "evolutionary biologists ask "why" questions" (Masel and Promislow 2016). The role of the somatotropic axis in health, ageing and longevity cannot be considered only as a "how" question, i.e. wondering "how" the information needed to manage energy supply is best used by the organism, via hormones, cellular receptors, transcription factors and so on. This is also a "why"

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question linked to evolutionary biology, and this article wonders whether, depending on their life-history strategies, the somatotropic axis modulates the ageing process and the longevity of species. This chapter does not recapitulate the information provided in the second part of this book and some views could be at variance with those expressed elsewhere in this book.

On the one hand, it is often possible to increase lifespan in various species by relying on environmental means. For instance, decreasing the environmental temperature increases lifespan of *Drosophila melanogaster* flies (e.g. David 1988), food restriction increases lifespan of the nematode *Caenorhabditis elegans* (e.g. Johnson et al. 1984; Houthoofd et al. 2005) and various chemicals increase lifespan in these species (e.g. Frankowski et al. 2013; Brack et al. 1997). In mammals, Turkish hamsters *Mesocricetus brandti* kept at 22 °C and transferred 5.5 months a year at 5 °C lived longer if they hibernated for 12–33% of their life (Lyman et al. 1981). Food-restricted mice and rats often live longer than ad libitum-fed ones (Speakman et al. 2016, but see Liao et al. 2010 and Harper et al. 2006).

On the other hand, the search for long-lived mutants was disappointing up to the seminal article of Klass (1983) who isolated 8 long-lived mutants among 8000 *C. elegans* clones. Two of these mutants spontaneously entered the Dauer larval stage, as wild-type nematodes do when starved (Klass and Hirsh 1976), and the remaining 6 mutants had a reduced food intake. Later on, Friedman and Johnson (1988) or Kenyon et al. (1993) isolated other long-lived *C. elegans* mutants and mutations increasing lifespan were also discovered in *D. melanogaster* (e.g. Clancy et al. 2001) and mice (review in e.g. Bartke 2005). As emphasised by Klass (1983), "there were no mutants that specifically altered only life span", and these mutations in these species were all linked to the somatotropic axis (Bartke et al. 2013) and to the homologue of the insulin-like growth factor 1 (IGF-1) signalling pathway in invertebrates (Kenyon 2010). In other words, these mutations disturb the normal way of using energy like food restriction does.

Relying on results showing that lifespan can be increased either by mutating the somatotropic axis or by food restriction, some authors have concluded that similar results could be observed in human beings. For instance, Kenyon (2010) wrote that "it seems reasonable to think that mutations in our future evolution could give us longer lifespans and that, if they do, then drugs that mimic their effects should too". Similarly, Weindruch (2006) wrote that "it would be surprising if appropriately applied, chronic dietary restriction would not significantly increase the average lifespan of people".

Recently, Bartke (2016) summarised the whole idea: "both average and maximal longevity can be increased by various environmental factors as well as by dietary, genetic, and pharmacological interventions in species ranging from yeast and worms to insects and mammals. There is also increasing appreciation of the fact that many of the fundamental mechanisms of aging are evolutionarily conserved … and shared by most if not all living organisms … and that interventions that extend life in experimental animals can be expected to have similar effects in our own species." However, this rationale could be wrong because it does not take into account the contrasted life-history strategies of species and the way they adapt to environmental

challenges, particularly to food restriction, and thus it is not sure "that interventions that extend life in experimental animals can be expected to have similar effects in our own species".

In 1973, Theodosius Dobzhansky wrote his famous article "Nothing in biology makes sense except in the light of evolution". This title has become a motto, because it grasps in a single sentence a fundamental idea now common to nearly all biologists. Paraphrasing Dobzhansky (1973), and turning our eyes towards the biology of ageing, one could add that "nothing in biology of ageing makes sense except in the light of life-history strategies".

2.2 Short- and Long-Lived Species Have Different Life-History Strategies

Because all species do not face the same challenges, not all life-history strategies—the way to manage survival and reproduction—are probable to the same extent for each species. For instance, African elephants *Loxodonta africana* living for only 20 years could simply not exist as a species because they would not have a sufficient time to reproduce, because of a long time to maturity (ca 10 years), a 2-year gestation time (only one singleton), a 4–5-year inter-birth interval, and a long parental care. Thus, elephants *must* live long to survive as a species and one can easily understand why the various life-history traits of species (fecundity, lifespan, gestation time, and so on) are highly correlated. A low fecundity is correlated with a long lifespan because species giving birth to only one offspring at a time must repeat reproductive episodes, which often implies to wait for the next year or more, and thus to live long. By contrast, mice reproducing quickly and giving birth to many offspring in a single reproductive season can afford to live only for a few months in the wild (Phelan and Austad 1989).

This comparison of elephants and mice shows that different species have different life-history strategies (Pianka 1970). In mammals, there is a continuum (Stearns 1983). Short-lived species with a small body size mature quickly after a short gestation time and give birth at short intervals to many offspring, as mice and rats do. These species are opposed to large ones that live long and need long gestation time and parental care to reach adulthood, and give birth to a few offspring during successive years, like elephants or primates do. It is however not to say that all mammals perfectly fit to these life-history because some of them can be as small as mice and live much longer (e.g. bats, Austad and Fischer 1991).

In the wild, because of a high predatory load, short-lived species of a small body size may reproduce only once or, if they are lucky, several times in a single season. By contrast, larger and longer-lived species are more spared from predation because of their size that makes them not so easy prey. Indeed, hunting a mice or an elephant is not the same challenge. However, because of the contrasting life-history

strategies of elephants and mice, hunting adult elephants makes them soon an endangered species but mousetraps do not bear such a risk for mice.

Because of their life-history strategies, some species can quickly exploit a new environment if resources are plentiful and produce many offspring to do so ("opportunistic species": Demetrius 2005), while other ones are usually unable to so quickly thrive in a favourable environment ("equilibrium species"). In mammals, opportunistic species are short-lived and of a small body size, and equilibrium species are usually large and long-lived ones.

Could these contrasting life-history strategies imply that means to cope with ecological constraints in the wild, and particularly food shortage, vary among species?

2.3 Different Life-History Strategies Imply Different Means to Cope with Food Shortage

There are mainly two strategies to cope with food shortage: looking for food elsewhere, i.e. emigration, and waiting at the same place for better times, which can imply to increase lifespan. At a first sight, one could argue that emigration is the best strategy, because it can be implemented immediately and one can bet there is a higher chance to eat soon if trying to discover food, rather than staying at the same place. To make an analogy with human behaviour, if the supermarket is closed, it seems better to shop in another one than waiting for the next opening hours. However, emigration is not possible for all species.

2.3.1 Short-Lived Species

Nematode worms *C. elegans* live for less than 2 days in the soil (Van Voorhies et al. 2005) and ca 3 weeks in the laboratory. If food is lacking, they enter the Dauer larval stage for up to 2 months before resuming the normal life cycle, which thus increases longevity (Klass and Hirsh 1976). This strategy—waiting at the same place for better times and increasing lifespan—is surely better than emigration, which seems simply impossible for a worm living in soil for a very few days.

The same could be said regarding the spider *Frontinella pyramitela*. These sedentary spiders live for ca one week in the wild and several weeks in the laboratory. In the laboratory, their lifespan increases and their fecundity decreases when food supply decreases (1, 3 or 5 *D. melanogaster* flies per week, Austad 1989): in the wild, this strategy would be more optimal than emigration, because spiders catch prey on the web.

Small rodents could attempt to emigrate when facing famine, but as body size is positively correlated with the maximal distance covered by mammal species

(r^2 = 0.50 to ca 0.70: ca one km in the meadow vole *Microtus pennsylvanicus* and 300 km in the wolf *Canis lupus*, see Bowman et al. 2002), they would have a low chance to discover a better environment. In addition, as small rodents are subjected to a high predatory load, emigration is a very risky decision. Taking into account the low covered distance and the high predation risk, it is not so surprising that food-restricted mice often live longer than ad libitum-fed ones, possibly up to the next reproductive season, i.e. to the next year, before resuming reproduction (see Holliday 1989; de Grey 2005), because it is maybe the only possible strategy available to them.

Therefore, it can be concluded that, for some species, increasing lifespan in the event of starvation has been selected as an appropriate response, and thus that some species have a very plastic lifespan. In other words, species unable to emigrate are expected to live longer when food-restricted.

2.3.2 *Long-Lived Species*

Large and long-lived species reproduce in successive years and have a lower predation risk than small species. In such conditions, migration seems to be a wise strategy in the event of a too low food supply, and this is observed every year in migratory birds. However, migratory species can become resident ones if migration is no longer needed. For instance, the long-lived white storks *Ciconia ciconia* (39–48 years: Wasser and Sherman 2010) are now becoming resident birds, because landfills in Portugal provide them with food along the year, and thus they do not longer need to winter in sub-Saharan Africa (Gilbert et al. 2016). Humans is another example of a species well able to emigrate in the event of famine (or of other disasters): the history of mankind is replete with people walking across countries or even continents to find a better place to live. The difference between migration of various species and emigration of humans is that the latter is not linked to the season and is often a one-way process.

Unfortunately, only a very few studies on the effect of food restriction on lifespan have been carried out in these long-lived species, even if many species are known to migrate (ungulates, elephants, and so on). However, the effect of food restriction on lifespan of Rhesus macaques *Macaca mulatta* has been studied and is still in progress.

On the one hand, Colman et al. (2009, 2014) have reported that "age-related mortality", not linked to mere accidents, and overall mortality of animals food-restricted from the age of 7–14 years were lower than those of control ones and that food-restricted animals were less affected by diseases (Colman et al. 2009). On the other hand, no decreased age-related and overall mortalities were observed in animals food-restricted from the ages of 16–23 or 1–14 years (Mattison et al. 2012, see Le Bourg 2016 for other details).

In both studies, food-restricted monkeys weighed ca 25% less than control ones, but animals had a lower weight in Mattison et al. (2012). In Colman et al. (2009, 2014),

monkeys were fed with a "typical Western modern diet rich in refined and processed foods" (Cava and Fontana 2013) and control monkeys were ad libitum fed. Animals in Mattison et al. (2012) ate a diet "more similar to the traditional Mediterranean or Japanese diet" (Cava and Fontana 2013), the food of control monkeys being portioned to prevent obesity, and thus control monkeys were not really ad libitum-fed. Thus, control monkeys of Colman et al. (2009, 2014) ate ad libitum a diet known to be detrimental while those of Mattison et al. (2012) had a better diet in conditions preventing obesity. Could it explain that, both sexes pooled, control monkeys lived for ca 26 years and food-restricted ones for 29 years in Colman et al. (2014), while females and males lived longer, respectively ca 28 and 35 years, in Mattison et al. (2012)? If it were the case, showing that restricting a "typical Western modern diet" can increase longevity would not mean that food restriction increases longevity, but more probably that this diet is hazardous. For the time being, one can conclude that food restriction does not increase lifespan in *M. mulatta*, provided the control group is not offered a bad diet.

Food-restricted dogs of the labrador breed were reported to live longer than control ones (median lifespans of 13 vs. 11 years, Kealy et al. 2002) but, as the authors made use of a breed prone to severe obesity (fat mass was 40% of weight in control dogs at 12 years of age and 23% in food-restricted ones: 13 vs. 6 kg, lean weight being ca 20 kg for both groups), it is probable that food-restriction simply lowered the deleterious effect of obesity on lifespan (other details on this study in Le Bourg 2010). However, because the domestic dog *C. lupus familiaris* is a very peculiar sub-species of *C. lupus*, it is necessary to wonder what could happen in food-restricted dogs.

Dogs are long-lived and probably well able to migrate, like the wolf *C. lupus* or the coyote *C. latrans* (Bowman et al. 2002) and, at first sight, they should be an equilibrium species, but this is probably no longer the case. The wolf *C. lupus* has a seasonal reproduction (with the same father among seasons), a rather small litter size (around 6 pups), a long parental care with an active social life in the pack, and offspring do not reproduce before the third year of life (Mech 1974): all these features do not favour an explosive reproduction. Thus, *C. lupus* can be considered as an equilibrium species (Demetrius 2005). In sharp contrast, dogs have more pups, reproduce twice a year and at any time (with different fathers) as soon as at 6 months of age, parental care is short, and pups are soon independent because there is no pack. In such conditions, dogs cannot be considered as an equilibrium sub-species but rather as an opportunistic one (Demetrius 2005) able to quickly thrive in a favourable environment. Thus, the original species *C. lupus* and one of its sub-species, *C. lupus familiaris*, display highly different life-history strategies. The domestication process can explain the evolution of a different strategy in dogs (Lord et al. 2013). Dogs live with or near humans and have no need to hunt for food, which is provided by owners or, e.g., in landfills for free dogs. In such conditions, fecundity can be not seasonal and more important than in wolves but, as emphasised by Lord et al. (2013) "the increase in fecundity has the consequence of an increased juvenile mortality when population levels reach carrying capacity", exactly as it happens in opportunistic species. However, because dogs were

originally an equilibrium species and food restriction is not a threat for most of the dogs for millennia, one can hypothesise that food restriction would not increase lifespan in this sub-species, contrarily to what happens in opportunistic species such as mice, because there is no selective pressure for an increased lifespan in starvation conditions. Thus, it seems probable that, if food restriction would be a threat, dogs would emigrate, like the original species does, rather than staying at the same place and living longer like mice do.

2.3.3 Conclusions

Strategies of species in case of food restriction are dependent on their life-history strategies. Obviously, a species like the nematode cannot leave its environment, i.e. the soil. For mice, emigrating under the sight of predators is probably a suicidal strategy and they cannot cover a long distance (Bowman et al. 2002). As an outcome, for these species, the best strategy is maybe to wait at the same place until the threat is over: short-lived species reproducing in a single season have a better chance to survive if staying at the same place and increasing their lifespan, because they cannot rely on migration.

Long-lived species, which reproduce in successive years and can thus delay reproduction to the next year or even later, can afford to migrate because they are less exposed to predation and can cover long distances (Bowman et al. 2002). There is maybe no selective pressure for a genetic pathway favouring increased lifespan when food is scarce in these long-lived species. Therefore, one could expect that food restriction does not increase lifespan in these species. It seems that, for the time being, no data contradict this conclusion.

Most et al. (2016) argued that "a forced 20% CR (calorie restriction) without malnutrition" during World War II made human mortality to decrease in Norway. "Circulatory diseases" strongly decreased in a strict parallel with consumption of fat, before both rose again in post-war times (Fig. 4 in Strøm and Jensen 1951). However, as tobacco consumption of men was cut by half at the same time (Lund et al. 2009), one may bet that this decrease explains a part of the mortality fall. Indeed, while the positive effect of food restriction on human lifespan is a hypothesis, the deleterious effect of tobacco is not.

2.4 Can a Genetic Pathway Modulate Lifespan in the Absence of Any Selective Pressure?

On the one hand, it thus seems that, depending on their life-history strategies, food restriction either increases lifespan of species or has no effect. On the other hand, because the somatotropic axis is evolutionary conserved, it has been argued by

many authors that its modulation (e.g. by mutations) could make lifespan to increase, including in human beings (e.g. Milman et al. 2016). These two previous conclusions seem to be at variance: if the somatotropic axis regulates the use of nutrients by increasing lifespan when they are scarce, how explaining that food restriction does not increase lifespan in some species? This contradiction can be overcome by postulating that the size of the effect of the somatotropic axis on lifespan is similar to that of food restriction: if food restriction makes lifespan to strongly increase in a given species, one could expect that some mutations of the somatotropic axis in this species could strongly increase lifespan; if food restriction does not increase lifespan in another species, no mutation of this axis is expected to increase lifespan in this species.

This rationale could be falsified (Popper 1935) if there were a strong discrepancy between the effect of food restriction and that of the modulation of the somatotropic axis in a species. Let us examine what happens in *C. elegans*, *D. melanogaster,* mice, and humans.

Food restriction strongly increases lifespan in *C. elegans* (e.g. Johnson et al. 1984) like do mutations of IGF-1 (e.g. Fontana et al. 2010), as expected.

Mutations of IGF-1 also increase lifespan in *D. melanogaster* (e.g. Clancy et al. 2001; Martins et al. 2016). However, the effect of food restriction on lifespan has been debated, some authors claiming to observe such an effect while other ones did not report a positive effect (review in Le Bourg 2010). As flies can fly, it could be hypothesised that, in sharp contrast with nematodes, they could emigrate, and thus that increasing lifespan when facing starvation is not mandatory. It could also be argued as well that they cannot cover long distances and that an increased lifespan could be a valuable strategy. However, food restriction did not increase lifespan in other fly species (*Ceratitis capitata*, *Musca domestica*, *Anastrepha ludens*, *Bactrocera tryoni*, review in Le Bourg 2010). Therefore, it is not clear whether results of the effect of food restriction and of mutations of IGF-1 in *D. melanogaster* are in accordance in this species.

Food restriction increases lifespan in mice (but see Harper et al. 2006; Liao et al. 2010) and most of the results on the positive effect of the genetic modulation of the somatotropic axis have been obtained in mice (Bartke 2016). Therefore, results on the effect of food restriction and on this modulation seem to point in the same direction.

There is no result showing that food restriction can increase lifespan in human beings (reviews in Le Bourg 2010, 2012, 2016) and genetic modulation of the somatotropic axis does not seem to strongly modulate human lifespan. The few dwarf human mutants do not seem to live longer than their contemporaries (review in Le Bourg 2016) and, even if some studies have reported that lifespan can be linked to the *FOXO3A* gene polymorphism in some cohorts (e.g. Flachsbart et al. 2009), other ones have shown that the results could be dependent on the studied birth cohort (Nygaard et al. 2014). A high plasmatic IGF-1 level has been linked to a low remaining lifespan in nonagenarian women with a history of cancer, but not in all men and in women without a history of cancer (Milman et al. 2014). By contrast, a high growth hormone (GH) level at fasting was linked with a high

all-cause mortality in ca 50-year-old men at baseline followed for ca 15–20 years (Maison et al. 1998; Hallengren et al. 2014), but not in women whose plasmatic GH level is nevertheless 10-fold higher than that of men (Hallengren et al. 2014).

On the whole, it has not been shown that food restriction can increase human lifespan, and results on a link between IGF-1 and GH, on one hand, and lifespan on the other hand can be opposite in men and women, when such links do exist (Kaplan et al. 2012). Obviously, studies of the effect of, e.g., IGF-1 on lifespan and ageing of very old people, such as nonagenarians (e.g. Van der Spoel et al. 2015), do not explain ageing and lifespan of the numerous people dying before this very old age. Milman et al. (2016) reviewed the results on the links between the somatotropic axis and human ageing and lifespan. They reported either positive, negative, or no effects of e.g. IGF-1 level and concluded that "much of the knowledge about the effects of the GH/IGF-1 axis on age-associated diseases and aging in humans remains inconsistent".

For the time being, it seems possible to conclude that no mutation (or allelic variants) of the somatotropic axis can increase human lifespan and that food restriction does not increase human lifespan: because humans can emigrate in the event of food starvation, there is probably no need to rely on the somatotropic pathway to increase lifespan in starved humans.

On the whole, it thus seems possible to strongly increase lifespan by modulating the signalling pathway regulating energy use in species whose lifespan increases when facing starvation, but not in species whose lifespan does not increase. However, it is maybe not an all-or-none answer and one could imagine a more graduated response. Food restriction and the modulation of IGF-1 could have no effect on lifespan in some species at one extremum, while huge effects could be observed at the other extremum, say 100% lifespan increase, with some species showing less important effects, say 10 or 20% increases.

2.5 Conclusions

Model organisms used in the laboratory to study ageing are usually opportunistic species (Demetrius 2005) with a short lifespan, such as the nematode *C. elegans* (ca 3 weeks at 20 °C), the fly *D. melanogaster* (ca 2 months at 25 °C), or the mouse (ca 2–3 years), and it is possible to increase their lifespan in the laboratory by modulating their environment, and particularly the availability of nutrients (but see the debate above on the effect in flies).

It is often accepted that these results could be extended to equilibrium species (Demetrius 2005) such as humans (e.g. Bartke 2016), but one can argue that experiments showing lifespan increases in short-lived model organisms will be never replicated in long-lived species such as humans, because life-history strategies of these species strongly differ. In contrast to opportunistic species, equilibrium species do not rely on lifespan increase to survive environmental threats in the wild: human beings facing famine and staying at the same place die while people

emigrating get a chance to survive. Because a lifespan increase has not been selected as a strategy during evolution, there is no ground to expect that food restriction could increase human lifespan, as argued for instance by Yu (2006).

If food restriction does not increase human lifespan there is no reason to expect that modulating the human somatotropic axis could increase it. One can thus hypothesise that the modulation of e.g. IGF-1 and GH levels (e.g. by food restriction mimetics, see de Cabo et al. 2014) or food restriction would have no beneficial effect on ageing and lifespan in people without any pathology linked to this axis. Obviously, this conclusion does not apply to people suffering from acromegaly, obesity and other ailments linked to the somatotropic axis. To give a clear example, young men with a body mass index (BMI) of 21 kg/m^2 and eating a well-balanced diet, such as the Mediterranean one, without calories excess, should not expect to live longer if restricting their food. By contrast, overweight (BMI $\geq$ 25), obese (BMI $\geq$ 30), and severely obese people (BMI $\geq$ 35) eating a too caloric junk food, like in the 2004 movie *Super Size me*, could maybe live longer if choosing a more appropriate food. This result would be more probably due to the avoidance of life-shortening diseases rather than to a true life-extending effect of food restriction.

One could argue that there is a caveat in the fact that some favourable effects of food restriction on health indicators have been observed in the USA (e.g. Omodei and Fontana 2011). However, 30% of US people are expected to be overweight in 2020, 45% of them being obese (Stewart et al. 2009). Because the percentage of proteins in the US diet has regularly decreased in favour of fat and carbohydrates from at least 1971 to 2004, before a slight increase and a plateau from 2005 to 2010 (Ford and Dietz 2013), or since 1960 according to Simpson and Raubenheimer (2005), having a well-balanced diet for life is a daily challenge, if not an unreachable goal. At the same time, and maybe as a consequence of a decreased proportion of proteins in the diet (Simpson and Raubenheimer 2005), the mean food intake strongly increased in the USA (Ford and Dietz 2013). In such conditions, one can bet that adopting a better diet and decreasing the caloric intake would have favourable effects in most of US subjects, even if they are not (still) overweight. One can bet, too, that such a result would be less observed in European countries less affected by the obesity epidemics than the USA.

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