Energy Metabolism and Ageing in the Mouse: A Mini-Review

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Keywords

Energy metabolism · Laboratory mice · Ageing · Comparative biology · Growth hormone signalling · Insulin · Insulin-like growth factor-1 · Longevity pathways · Caloric restriction · Genetic mouse models of extended lifespan

Abstract

The mouse has rapidly become the mammalian model organism of choice in ageing research due to its relatively short lifespan, the proximity of its genome and physiology to humans, and most importantly due to its genetic pliability and the availability of mutant strains. Mouse models have provided great insights into the ageing process, which in its broadest sense is the progressive decline of body functions over time. In this mini-review, we briefly cover the historical views on the link between ageing and metabolic rate, highlight genetically modified transgenic mouse models of extended lifespan, discuss endocrine pathways linked to senescence and ageing, and then examine pathways by which caloric restriction is postulated to result in longevity.

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Introduction

Ageing and senescence encompass declining functional changes and increased mortality risk observed in individuals with increasing adult age [1]. This decline is characterised by progressive changes in biochemistry, energy metabolism, and physiological capacity or even storage of fat, which was recently highlighted as a prominent predictor of murine lifespan [2].

Clearly, using humans in ageing research is mechanistically difficult and ethically complex. The mouse has been extensively used since the 1970s and became the mammalian model organism of choice in ageing research in part due to its ability to be easily reared in the laboratory, its short lifespan, the relative proximity of its genome and physiology to humans, and most importantly due to its genetic pliability and the availability of mutant strains that have produced “healthily aged mice.” We believe that in ageing research, it is important to focus on mouse models that represent healthy ageing, and not solely mice with inbred pathological changes that result in reduced lifespan.

Contrary to the common belief that animals die from disease, animals often die from starvation and predation before they get a chance to experience senescence in the

Fig. 1. Characteristic physiological and metabolic changes of senescent mice. For metabolic phenotyping of ageing in mice, see Houtkooper et al. [11]. * The dynamic changes in body fat during ageing are described in the text and in Mitchell et al. [2].

wild [3]. In the wild, mice of the genus *Mus musculus* were reported to have median longevity of 3–4 months only, with 90% of the population being dead by about 6 months of age [4]. In contrast, laboratory mice are reported to have mean lifespans of 2–3 years under unperturbed and well-protected conditions, i.e., when housed securely, cleanly, and with good care [5]. Despite their clear advantages, questions were raised regarding the appropriateness of the use of inbred laboratory mice for modern ageing research [6–8]. Laboratory mice are genetically identical (isogenic) and homozygous at essentially all loci [6], with potential loss of naturally developing alleles that may delay the ageing process. Wild-derived mouse stocks maintained in the laboratory might provide a more diversified genetic stock for research, but they also come with real-life problems such as infectious diseases and genetic imprinting dependent on maternal nutrition [6–8]. In 2 studies on lifespan, one showed an increased lifespan of wildtype mice, whilst the other showed no difference [6–8].

In this mini-review, we will touch upon energy usage and metabolic pathways in ageing mice, the development of healthy aged mouse models, and interventions such as caloric restriction (CR), which affect rodent lifespan.

Changes in Physiology during Ageing

It is worth emphasising that ageing is an intrinsic, deleterious, and cumulative process that with time reduces an organism's ability to withstand external stressors (such as infection and starvation) and increases its mortality risk [9].

Aged mice from several strains have a lower food consumption, lower voluntary running and energy ex-

penditure, as well as physiological changes such as decreased olfactory and auditory senses, and pathological changes such as increased cancer risk [10]. Body fat mass shows different dynamics: while fat stores increase until 1–2 years of individual age, mice lose fat with older age, although this is highly strain-dependent [2]. In a comprehensive study, Houtkooper et al. [11] integrated in vivo phenotyping with gene expression, biochemical analysis, and metabolomics, to describe a metabolic footprint of ageing in C57BL/6J mice. Aged mice exhibited altered nutrient handling (glucose intolerance, insulin resistance, reduced fatty acid oxidation, reduced ketogenesis), decreased mitochondrial biogenesis and oxidative phosphorylation, decreased expression of stress defence genes, and decreased apoptosis regulation. Some of these changes may be prevented by CR at varying extents and protocols summarised in the paper by Speakman and Mitchell [12]. CR has proved the most consistent non-genetic manipulation, which extends lifespan in mice, and will be discussed further throughout this article.

In an extensive study, Bronikowski et al. [13] observed that genetically heterogeneous mice selectively bred for high voluntary exercise had retarded cardiac ageing, an increased mean (but not maximum) lifespan, and fewer changes in gene expression with increasing age. In another study, restricting exercise led to higher body weights, lower metabolism, and an earlier time of death [14]. Similarly, Holloszy [15] found that in rats average longevity was increased in exercised individuals.

A common feature of ageing-related disease is metabolic and organellar dysfunction leading to physiological decline. Figure 1 summarises some of the physiological and metabolic changes that occur in ageing mice.

Metabolic Rate and Longevity

Metabolic rate has long been associated with ageing. Over a century ago, early comparative studies in 5 species showed that body mass correlated with lifespan [16]. Rubner's calculations that smaller animals have higher resting metabolic rates gave rise to the "rate of living hypothesis," which posited that exhausting a finite number of metabolic events leads to death [17–19]. Using the "rate of living hypothesis" and Metchnikoff's earlier suggestion that ageing and death are consequences of toxic by-products of metabolism [20], the "free-radical theory of ageing" was put forward [21]. It suggested that increased metabolic rate per unit mass in smaller animals results in higher free radical production, increased macromolecular oxidative damage, and cellular senescence [21].

Over time, various findings have debunked the "rate of living hypothesis." For example, birds have a metabolic rate up to twice as high as similarly-sized mammals, yet they live on average about 3 times as long as body mass-matched mammals [22]. Furthermore CR, which is a commonly used intervention known to extend lifespan, does so with still unresolved effects on metabolic rate [12]. In an outbred strain of laboratory mice, the MF1 strain, daily energy expenditure (DEE) and lifespan were positively correlated [23]. Thus, individual mice with higher DEE lived longer, and there was no effect of body mass on longevity in this cohort [23]. Of course, higher DEE can reflect higher cellular ATP consumption or higher uncoupling rates (where the proton motive force is dissipated as heat rather than ATP, akin to heat from a light bulb). Some data suggest that mice with higher metabolic rates have greater uncoupled mitochondrial respiration mediated by adenine nucleotide translocase and uncoupling protein 3 (UCP3) [22], leading to adoption of the "uncoupling to survive" hypothesis [24]. Here, it is postulated that mitochondrial uncoupling results in lower reactive oxygen species production and longer lifespan. There is some evidence that increased mitochondrial uncoupling results in lowering of reactive oxygen species production [25], although there is no direct evidence for uncoupling affecting lifespan. Interestingly, Rose et al. [26] analysed the genetic variability of human UCPs in 598 subjects ranging between 64 and 105 years of age and found that the genetic variability of the *UCP2*, *UCP3*, and *UCP4* genes affects the individual's chances of surviving to old age. As previously acknowledged, it is important to note that higher DEE does not necessarily equate to greater uncoupling, and the mechanistic link between DEE and lifespan remains tenuous.

Tissue Fatty Acid Composition and Ageing

Observing a relationship between fatty acid composition and mitochondrial efficiency and ageing in different species, Hulbert [27] and others have suggested that energy production and utilisation within the cell, i.e., mitochondrial oxidative phosphorylation, proton motive force, and metabolic efficiency, are likely regulated by membrane fatty acid composition. The "membrane pacemaker hypothesis of ageing" predicts that long-living species will have more peroxidation-resistant membrane lipids than shorter-lived species [27]. Polyunsaturated fatty acids, particularly those from the n-3 class, are highly susceptible to peroxidation and are key suspects for the propagation of cellular oxidative stress [27]. Yet, the highly unsaturated and long-chain docosahexaenoic acid (C22:6, n-3), largely present in all membranes and especially in neuronal tissues, showed no correlation with lifespan [28]. Furthermore, C57BL/6 mice whose tissues were enriched in n-3 fatty acids through dietary intervention did not live shorter lives [29]. In a cross-species comparative study, a low n-3:n-6 ratio (rather than absolute amounts) appeared to correlate with long-lived mammals [28], and this was recapitulated in the longer-lived Ames dwarf mice compared to their shorter-lived heterozygous siblings [29]. Ames dwarf mice possess tissues with less n-3 polyunsaturated fatty acids throughout all examined organs at concomitantly higher levels of n-6 polyunsaturated fatty acids [29]. Interestingly, we also observed that in heterozygous control mice, and to a lesser extent in the Ames dwarf mice, the heart, liver, skeletal muscle, and brain membranes from 1-, 2-, and 6-month-old animals differed in n-3 polyunsaturated fatty acids, with higher levels in the 6-month-old individuals [29]. Other than these studies, there is little in the way of further investigation of the n-3:n-6 fatty acid ratio in the context of longevity, and the links remain correlative rather than causative. The wide variety of cellular pathways with which fatty acids are associated (membrane formation in the endoplasmic reticulum, mitochondria, and other organelles, as well as intra- and extracellular signalling) makes it difficult to speculate how this tissue composition might play a role in ageing. Future research in this area, reinforced by the methodological approaches of modern lipidomics, might shed light on possible causal relationships.

Fig. 2. Long-lived Ames dwarf mouse (left) and heterozygous (short-lived) sibling (right).

Genetic Mouse Models of Extended Lifespan

Major progress in ageing research has been made by observing the consequences of genetic modifications on the lifespan of mice on top of nutritional or dietary manipulations such as CR or some life-extending food additives such as metformin, rapamycin, and resveratrol [30, 31].

One outstandingly long-lived genetic model is the homozygous Ames dwarf mouse (Fig. 2), which carries a recessive loss of function mutation in the *prophet of pituitary factor-1* (*Prop-1*) gene that results in failure of somatotroph differentiation in the pituitary [32]. Ames dwarf mice can live up to 50% longer than heterozygous siblings when additionally challenged with scarce food supply [33, 34]. They were reported to exhibit low n-3 polyunsaturated fatty acids [29], low circulating insulin-like growth factor-1 (IGF-1) levels, suppressed insulin and glucose, and increased insulin sensitivity [34]. Due to the mutation in *Prop-1*, their pituitary secretion of thyroid-stimulating hormone, growth hormone (GH), and prolactin is abolished, while the other pituitary hormones appear to be unaffected [34]. Snell, Laron (GHR-KO) and Little (Ghrhr-/-) mice (Table 1) also share deficient somatotrophic signalling, reduced body size (Fig. 2), increased resistance to various kinds of external cellular stressors in vivo, and increased adiponectin (produced in white adipose tissue) which promotes insulin sensitivity and exerts anti-inflammatory and anti-atherogenic effects [35]. These mice have lower body temperature (despite a higher mass of brown adipose tissue) [36, 37], altered mitochondrial function, reduced respiratory quotient favouring fat over carbohydrate metabolism [37],

and increased energy intake and metabolic rate [37]. Contrary to non-genetic mouse models that show characteristic declines in metabolic traits (outlined in Fig. 1) during ageing, long-lived dwarf mouse models maintain a youthful phenotype, immune system, and metabolism until late life [32–34].

Similar to the long-lived dwarf mice, “normal-sized” genetic mouse models of extended lifespan reveal specific mutations in the IGF-1 and insulin receptor substrate (IRS) pathways [38]. These mouse models together provide sound evidence that somatotrophic and insulin signalling (GH-releasing hormone, GH, IGF-1, IRS-1, IRS-2) coupled with mild hypothyroidism [35] can impact “healthy” or “attenuated” ageing, and have informed primary targets for manipulating health during ageing [38] (Table 1). Critically, the long-lived mutants in this context not only live longer lives, but also show lower levels of several age-sensitive markers and finally maintain a young and healthy phenotype for longer than their wild-type conspecifics [39]. The fact that these effects have remained robust over the last decade underlines their evolutionary importance in context with energy balance in old age. They have also been bolstered by data indicating that GH levels are inversely correlated with longevity in mice, and that overexpression of these pathways results in murine lifespan reduction [40]. Identifying polymorphisms in the genes involved in these pathways is therefore appealing in ageing research, although the impact of similar endocrine states on human lifespan still remains unclear [40].

Interestingly, these signalling pathways control key biological pathways involved in ageing, including autophagy, stress response, genome maintenance, mitochondrial biogenesis, and energy homeostasis as well as inflammation and infection control. These pathways are simplified in Figure 3 and will be discussed further in the subsequent section [41].

It is perhaps interesting to consider why these pathways are important in ageing, and the evolutionary theories on ageing may provide some insight (see Information Box).

Pharmacological Strategies for Lifespan Extension

Caloric Restriction

CR is defined as a reduction in caloric intake (typically by up to 50% of ad libitum consumption) without malnutrition. Weindruch et al.’s important work from the mid 1980s showed uniformly that dietary restriction

Table 1. Long-lived mouse mutant models, genes affected, mechanisms, phenotype, and their reported lifespan with relevance in the field (as of Scopus® search of April 22, 2016)

Mouse name	Mutation	Gene	Proposed mechanism of lifespan extension	Dwarfism	Reported lifespan, days	Number of publications	Most cited publication
Ames	Prop1 ^{df/df}	<i>Prop-1</i>	pituitary GH deficiency	x	1,206 ± 32 females 1,076 ± 56 males	221	547
Snell	Pit1 ^{dw/dw}	<i>Pit-1</i>	GH and PRL deficiency	x	1,148 ± 39 females 1,037 ± 53 males	275	496
Laron GHR-KO	GH receptor knockout	<i>Ghr/bp</i>	GH receptor deficiency	x	1,031 ± 41 females 975 ± 106 males	55	207
Little Ghrhr(–/–)	GH-releasing hormone receptor	<i>Ghrhr</i>	GH-related genes	x	1,070 ± 123 females 1,093 ± 186 males	154	496
FIRKO	fat-specific insulin receptor knockout	<i>Ir</i>	insulin signalling		887	14	796
Irs 1(–/–)	insulin receptor substrate-1	<i>Irs-1</i>	insulin signalling		1,141 ± 34 females 911 ± 11 males	287	1,454
Irs 2(+/-)	insulin receptor substrate-2	<i>Irs-2</i>	insulin signalling		958 ± 16 females 945 ± 11 males	235	1,128
Igf1r(+/-)	insulin-like growth factor-1	<i>Igfr</i>	insulin signalling		756 ± 46	212	182
S6K1(–/–)	protein kinase S6 kinase 1 KO	<i>S6 k</i>	mTOR signalling, GH/IGF-1		1,201 ± 31 females 1,095 ± 13 males	379	937
MIF-KO	macrophage migration inhibitory factor KO	<i>Mif</i>	inflammation, carcinogenesis		774	230	569
MCAT	mitochondrial targeting of catalase overexpression	<i>Mcat</i>	antioxidant pathways			852	934
p66 shc KO	P66 shc protein KO	<i>p66 shc</i>	stress apoptotic response		973 ± 37	210	554

Note that while the column “Number of publications” refers to the absolute number of contributions containing the name of the mouse, the column “most cited publication” indicates the amount of citations one of the total publications from the previous column reached until April 22, 2016. GH, growth hormone; IGF-1, insulin-like growth factor-1; PRL, prolactin.

increases the lifespan in rodents [42]. Criticisms both on the applicability and on the generalisations of CR have been put forward [6, 8]. CR was originally reported to lower the metabolic rate and body temperature of mice [42, 43]. Today we know that CR results in changes in the transcriptome, metabolome, and proteome, especially in the mammalian nutrient sensing systems such as insulin signalling and even adiponectin [41] (Fig. 3). It also reduces endocrine hormone signalling pathways, e.g., thyroid, reproductive, and growth/insulin hormones [12, 44]. See Figure 3 for the widespread effects of CR.

Since CR affects such a large number of pathways, attempts to genetically isolate the responsible factors have proven difficult. For example, IGF-1 levels are inversely correlated with lifespan in mice and humans, but certain populations with IGF receptor mutations did not have a higher death risk [45]. Similarly for SIRT, the jury appears

to be out: CR has been shown to increase its levels in some tissues while reducing them in others [45].

Consistently, however, mice exposed to CR show suppressed GH and IGF-1, lowered body temperature and transiently lower metabolism, lower thyroid hormones, and lower glucose and insulin [36], together all pointing to the importance of the GH/IGF-1 pathway as the longevity pathway par excellence [32, 46].

Notably, CR in GH-deficient Ames dwarf mice results in an additional lifespan extension, whereas it barely does so in GH-resistant GH receptor knockout Laron (GHR-KO) mice [40], suggesting pleiotropic mechanisms rather than simple GH and GH receptor interactions. Although sharing the endocrine phenotype of absent or lower GH, suppressed GH and IGF-1, the life-extending effects of CR seem to involve more than one longevity pathway alone. Collectively, CR is likely to be complex, affecting

Fig. 3. Metabolic pathways involved in regulating mammalian longevity. Lifespan has been verifiably modulated by genetic, pharmacological, and dietary interventions in model systems. CR is the most robust intervention in extending mean and median lifespan by acting on the adiponectin, GH, and cytokine pathways, thus modulating the AMPK, SIRT, mTOR, and PI3k/Akt pathways. This results in better stress response, mitochondrial biogenesis, better cellular and genome maintenance, as well as reduced inflammation. Lifespan extension might be achieved with pharmacological agents such as rapamycin which inhibits mTOR, metfor-

min which stimulates AMPK, and possibly with resveratrol which activates SIRT, although there is lack of robust findings. CR, caloric restriction; Foxo, forkhead box; GH, growth hormone; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; IRS, insulin receptor substrate; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; PI3k, phosphatidylinositol 3 kinase; PKB, protein kinase B; SIRT, sirtuin; TNFα, tumour necrosis factor-α.

autophagy, mitochondrial biogenesis (controlled by peroxisome proliferator-activated receptor gamma coactivator 1 alpha), stress response, and inflammatory pathways that all affect longevity [41]. This is summarised in Figure 3. The relationship between CR and energy metabolism is extensively reviewed in the paper by Speakman and Mitchell [12]. Briefly, increased mitochondrial function is key to the life-extending effect of CR, and increased mitochondrial respiratory rates are associated with extended lifespan [47, 48]. Postponed senescence due to altered cellular metabolism during CR was also reported from various stem cells, including hematopoietic stem

cells where the signalling activity of mammalian target of rapamycin (mTOR) and other growth factor pathways was reduced [48] and stem cell maintenance was improved [47, 48].

Drugs That Mimic CR

There is some evidence that drugs such as metformin, rapamycin, and resveratrol mimic the beneficial effects of CR in preventing ageing [30, 49, 50] although metabolically likely being associated with different processes [31, 51, 52]. Resveratrol is a plant-derived polyphenol which was reported to increase lifespan in high-fat-fed mice,

Table 2. Comparative life history traits in mice and humans [modified and extended from 1, 8, reviewed in 1], complemented with the AnAge database (<http://genomics.senescence.info/species>)

	<i>Mus musculus</i> (mouse)	<i>Homo sapiens</i> (human)

Clade/taxon	Rodentia	Primates
Average body mass, kg	0.03	70
Maximum lifespan, years	4	122 (90) ^a
Predicted maximum lifespan ^b	5.5	23.6
Longevity quotient ^b	0.7	5.1
Mortality rate doubling time, years	0.3	8
Initial mortality rate per year	0.01	0.0002
Basal metabolic rate, W	0.2710	82,780
Lifetime energy expenditure, kcal/g	240	800
Maximum longevity residual, %	51	463
Litter size (average species specific)	4–8	1
Reproductive span, years	2	35

Note that the information detailed in the table does not refer to predictors of lifespan. Rather, it highlights the big differences in ecology and biology of these species when it comes to ageing. ^a Here we refer to the absolute maximum lifespan of *Homo sapiens* although it was reached by only one individual (Jeanne Calment). It has been suggested to use 90 years for comparative purposes. ^b For nonflying eutherian mammals, $y = 10.67 M_{kg}^{0.189}$ based on equations compiled by Austad and Fischer [64].

which had better mitochondrial function, insulin sensitivity, and survival [50]. Similar metabolic benefits were described in a non-obese mouse model, but lifespan extension was not observed [53]. It is postulated that resveratrol exerts its effects by activating SIRT1, a molecule that is involved in controlling insulin action, glucose metabolism, fat storage, and inflammation. However, caution must be exercised as SIRT levels have never been shown to be correlated with lifespan, and it may be that resveratrol acts pleiotropically. Furthermore, other studies do not support a role for resveratrol in lifespan extension in mice [51, 52], and overall, there is insufficient evidence to support either camp [53].

The antidiabetic drug metformin is believed to be a strong activator of AMPK, and while metformin alone does not appear to extend lifespan in rats [41] and mice [31], it robustly extended mouse lifespan only when combined with rapamycin, as reported recently in an extensive study of the National Institute on Aging Interventions Testing Program [31, 51]. There has been considerable interest in finding AMPK agonists since it is upregulated by exercise and CR, both of which are associated with healthfulness, although the evidence for the effect of exercise on ageing is weak. In sedentary mice, 4 weeks of treatment with the AMPK agonist AICAR substantially enhanced running endurance [54], but this has

yet to be tested in other organisms. In humans, metformin monotherapy was reported as improving the survival of patients with type 2 diabetes compared with matched non-diabetic patients [55], but there was notable confounding from other agents such as antihypertensives as well as anticholesterol and antiplatelet agents, which were used twice as frequently in the first group compared to the second.

The mTOR pathway is a conserved energy and growth factor signalling pathway (Fig. 3) whose aberrant activation has been linked to age-related diseases such as cardiovascular disease and type 2 diabetes mellitus [56]. Inhibition of this pathway leads to lifespan extension in worms and insects, and protects against diet-induced obesity and enhances insulin resistance in mice [56]. However, the story is not so simple in humans. Rapamycin, an inhibitor of mTOR, has numerous side effects, including hyperglycaemia, dyslipidaemia, immunosuppression, vasospasm, renal failure, and in males testicular atrophy. Therefore, it is suggested that mTOR inhibition may require tissue-specific fine-tuning to realise its beneficial effects. In summary, the data on drug interventions for decreasing ageing and increasing lifespan in mice and humans appears to be heterogeneous, although they continue to hint at metabolic pathways playing a role in these fundamental processes (Fig. 3).

Information Box: Some Evolutionary Perspectives in Ageing

Why has ageing evolved? Consider that the rate at which an organism dies from external causes (predation, starvation, infection) plays an important role in shaping an animal's "life history." An organism with a higher mortality rate at a young age is likely to evolve to reproduce early, whereas organisms with a lower mortality rate could theoretically devote more resources towards growth prior to reproduction, which would reflect a different trade-off between early-age benefits and late-age costs. These simplified predictions gave rise to the "life history theory," in which an organism's biology, behaviour, and ultimately lifespan would be shaped by natural selection. Although mice are among the most dominant model systems to study human ageing, their life history is very different from that of humans (as summarised in Table 2). To explain why humans age much more slowly than mice, Demetrius [1] put forward the discrepancy in metabolic stability between mice and humans correlating positively with the maximum lifespan potential (Table 2). Metabolic stability in turn defines physiological properties (outlined in the chapters above), pathogenesis, and cancer incidence/susceptibility, and finally on a population level, life history properties that include age-specific fecundities and mortalities of individuals in a population [1] (Table 2).

Interestingly, Kirkwood and Shanley [57] postulated that given a limitation in resources (e.g., food), animals must allocate these resources either to fecundity/reproduction or to other bodily functions (soma) and to extension of lifespan. Kirkwood and Shanley essentially said that the evolutionary value of "additional" life declines steadily following reproductive age. Johnston et al. [58] tested this concept by placing mice on calorie-restricted or high-fat diets and found that calorically restricted female mice were "having it all" – both greater fecundity and longer lifespan. Interestingly, CR in male mice appears to reduce major urinary proteins [59] and thus investment into reproduction, which may confer reproductive success by driving scent marking and thus possibly pointing to decreasing fecundity [59].

In contrast, George Williams took a slightly different view regarding the role of natural selection on ageing. He postulated that senescence would arise if late-acting deleterious genes were actually favoured by selection due to their early-acting beneficial effects [reviewed in 60]. This "antagonistic pleiotropy" refers to evolutionary advantages earlier in life, but implies a detrimental phenotype later [40]. Genes involved in GH signalling partly fit this concept [32, 40]. For example, the evolutionary advantage of high GH signalling early in life (i.e., somatic growth, enhanced muscle formation, sexual maturation, fertility) prevents elimination of the detrimental phenotype (i.e., insulin resistance, ageing, cancer) during postreproductive survival by natural selection [32, 40]. Of course we are not suggesting that GH is universally detrimental in the older population (for example, GH replacement therapy in rats is effective in preventing age-related sarcopenia [61]), but merely providing an evolutionary perspective on its heterogeneous effects in childhood versus adulthood.

Conclusions

We have provided a historical perspective on how metabolism has long been associated with modulation of longevity. Research in rodent models such as mice is facilitated by their experimental accessibility and the fact that they share genetic, metabolic, and physiological similarity with ageing humans. We feel it is important to focus research on healthy ageing and rates of ageing and not solely on lifespan [62] as has been done previously. Studying cellular properties of long-lived healthily aged mice and transferring this knowledge into shorter-lived ones by trying to extend their lifespan is a major achievement and ongoing task of modern gerontological research. Not surprisingly, over 20 long-lived mouse models have been reported [63], many of which have aberrations in their GH/IGF-1 pathways. These genetic studies, alongside metabolomic and transcriptomic analyses, have confirmed GH/IGF-1 pathways as key players in the modulation of the ageing process. Elucidating these pathways should help uncover potential therapeutic targets to delay ageing-related diseases and potentially mitigate the burden of ageing in humans.

Acknowledgements

We would like to thank Prof. Georg Wick, Editor-in-Chief of *Gerontology*, for inviting us to compile this mini-review, and Christine Süss for assistance during the process. Further, we are very grateful to Prof. John R. Speakman and Dr. L. Kennard for critical reading of the manuscript and providing ideas in the context. For their artwork presented in Figure 3 we thank Karolin and Sarah Ohrnberger as well as Sarah Postner. For very thoughtful revisions on our mini-review we are grateful to 2 anonymous reviewers.

Statement of Ethics

Ethical approval is not applicable to this mini-review.

Disclosure Statement

The authors declare no conflict of interest.

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