Mechanisms of Ageing and Development 131 (2010) 591–598

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Plasma IGF-1 is negatively correlated with body mass in a comparison of 36 mammalian species

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ARTICLE INFO

Article history:
Received 21 May 2010
Received in revised form 8 July 2010
Accepted 14 August 2010
Available online 21 August 2010

Keywords:
Insulin-like growth factor-1
IGF-1
Lifespan
Body mass
Longevity
Aging

ABSTRACT

In mammals, insulin-like growth factor-1 (IGF-1) is positively correlated with adult body mass, in comparisons made within a given species. In mice, IGF-1 deficiency is associated with dwarfism, whereas IGF-1 overproduction in transgenic animals causes gigantism. Surprisingly, the opposite is true in an inter-species context. We collected published plasma total IGF-1 data for adults of 36 mammalian species and analyzed it with respect to body mass. In contrast to the intra-species observation, this analysis revealed a significant negative correlation of plasma IGF-1 with body mass. Interestingly, IGF-1 is negatively correlated with longevity, and suppression of IGF-1 signalling in worms, flies and mice increases lifespan. Smaller mouse strains, for example, tend to have lower plasma IGF-1 levels and to be longer-lived. However, when plasma total IGF-1 was analyzed relative to the maximum lifespans of the 36 species examined here, there was no statistically significant correlation. Low plasma IGF-1 levels in larger mammalian species may be physiologically significant, considering the roles of this hormone in metabolism, tissue regeneration, and cancer incidence.

1. Introduction

In mammals, insulin-like growth factor (IGF-1) is produced in many tissues, and has endocrine, paracrine and autocrine functions during development and in the physiology of adults. Plasma IGF-1, however, is thought to originate primarily from the liver (see Stratikopoulos et al., 2008 and references therein). Both local and plasma IGF-1 contribute approximately equally to organismal growth and adult body mass of mice (Stratikopoulos et al., 2008). Intra-specific comparisons of plasma IGF-1 and adult body mass within dogs (Spichiger et al., 2006) or primates (Bernstein et al., 2007) illustrate significant positive correlations between the two variables in both species. Within a species, deficiencies in plasma IGF-1 are associated with dwarfism, and elevated IGF-1 with gigantism (Yakar et al., 2002). Thus, plasma IGF-1 is an important positive regulator of growth and development in mammals.

Plasma IGF-1 (Yuan et al., 2009) and growth *per se* (Rollo, 2002) are, however, also negatively correlated with longevity in mice and other animals (Kenyon, 2010). In a study of 31 laboratory strains, adult mice showed a significant negative correlation between plasma IGF-1 and median lifespan (Yuan et al., 2009). Presumably, this is related to the known physiological activities of this hormone. While its mitogenic properties stimulate growth and regenerative tissue repair (e.g. Philippou et al., 2007), higher IGF-1 levels are also permissive for cancer growth (Longo and Fontana, 2010). Indeed, much of the lifespan extension arising from reduced plasma IGF-1 in rodents may be due to the concomitantly reduced susceptibility to cancer (see Sonntag et al., 2006 and references therein). Reduced IGF-1 signalling is also associated with increased organismal and cellular stress resistance via the activation of FOXO transcription factors under these conditions (summarized in Robb et al., 2009). For example, mice deficient in IGF-1 signalling due to hemizygosity for the IGF-1 receptor are stress resistant (Holzenberger et al., 2003). In contrast, in a murine stroke model high plasma IGF-1 is associated with greater brain damage, while reduced IGF-1 ameliorates brain damage (Endres et al., 2007).

Although intra-specific data is relatively robust in indicating associations between plasma IGF-1, body mass and longevity, there is no similar insight into the possible role(s) of IGF-1 in an inter-specific context. Mammalian species' body masses and maximum lifespans (MLSPs) range over six and two orders of magnitude, respectively, which lends itself to such an analysis. In addition, inter-species comparisons are facilitated by the fact that the IGF-1 amino acid sequence is highly conserved amongst mammals. For example, the sequence is 100% conserved between humans, pigs, dogs, cows, rabbits, and guinea pigs and 95% conserved between humans and rats, mice and hamsters. Here, we have analyzed published values for plasma total IGF-1 levels from young adults of 36 mammalian species with respect to body mass and MLSP. This analysis reveals a strong negative correlation

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doi:10.1016/j.mad.2010.08.005

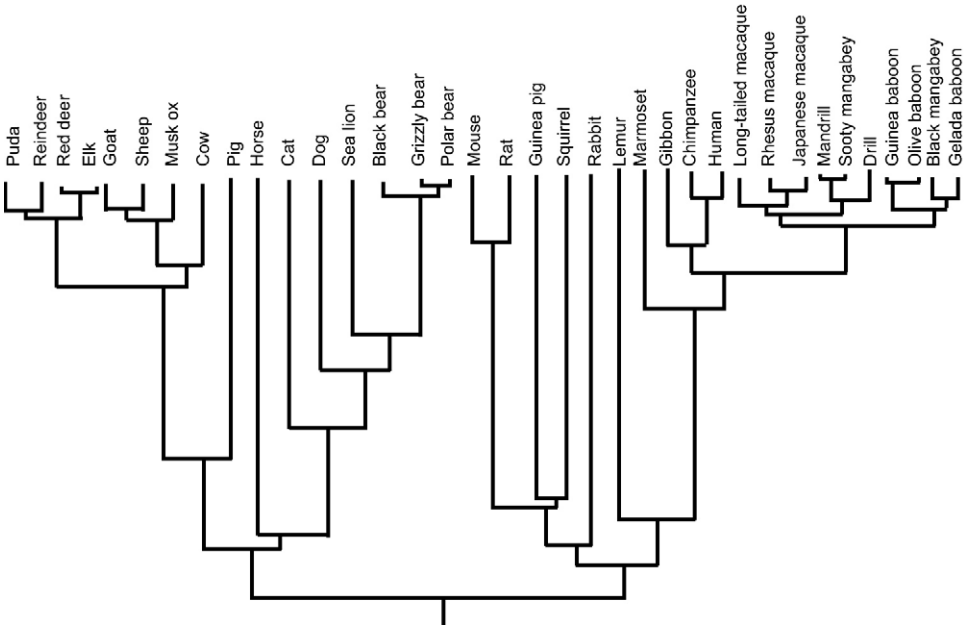

Fig. 1. Phylogeny of 36 mammalian species included in the data set. Common names shown; see Table 1 for species names.

between body mass and plasma IGF-1, which is opposite that observed within a species. We find no correlation between MLSP and IGF-1 across species, which also differs from observations made within-species.

2. Results

Plasma total IGF-1 values from 36 mammalian species (Fig. 1) were obtained from published studies (Table 1). As IGF-1 tends to increase markedly during adolescence and then decrease in old age, we used data from physically mature young adults, unless otherwise indicated. In some species, there are significant differences in plasma IGF-1 between the sexes. We therefore used, wherever possible, data from both males and females of a given species, calculating a species mean for the pooled data. Plasma IGF-1 is also affected by nutritional status, so we avoided using data obtained from calorie restricted or starving animals. In the case of wild animals, wherever possible we used data from publications sampling what appeared based on descriptions to be well-nourished individuals. Pregnancy and lactation also influence IGF-1, and so data from pregnant and lactating individuals were avoided as well, though in a few instances this was not possible (as indicated in Table 1).

The data in Table 1 represent either the best estimates from the literature, or the only available data for all mammalian species for which data could be found. For any given species, the number of publications reporting plasma IGF-1 is proportional to the human relevance of that species. Laboratory models (e.g. mice, rats, rabbits), livestock (e.g. cows, pigs, sheep) and primates (e.g. humans, macaques) are all over-represented in the literature. In the case of many of these species, the range of reported plasma IGF-1 data was occasionally rather large and seemed to reflect inter-laboratory variability in addition to 'normal' trait variance. In these instances we attempted to establish the normal range for a particular species and excluded data that were deemed to be outlying. Table 1 contains data from selected studies deemed to be generally representative.

Table 2 contains summary data for all 36 species for which plasma total IGF-1 data could be obtained. Where multiple plasma IGF-1 values were reported for a given species, a single value was estimated from these values. In other cases only a single published value could be found for a particular species, so this value was transferred directly to Table 2. Adult body masses are either means from the cited studies or, in instances where they were not provided in the cited studies, taken from other sources, including AnAge (de Magalhães et al., 2005) as indicated. Species' MLSP values in Table 2 were taken from AnAge (de Magalhães et al., 2005) or, in the case of several primate species absent from this database, from Rowe (1996). Species in Table 2 include representatives of seven mammalian orders (Artiodactyla, Carnivora, Lagomorpha, Pinnipedia, Perissodactyla, Rodentia, and Primates). The correlational analyses were performed on data in Table 2.

In the 36 mammalian species examined, the correlation of plasma IGF-1 with adult body mass was highly significant ($P < 0.0005$) and negative ($r = -0.62$, Fig. 2), indicating that lower plasma IGF-1 are actually associated with increasing species body mass. However, because the correlational analysis used data from multiple species, with shared phylogenetic history, it was necessary to evaluate the phylogenetic signal contained within the data. We used Felsenstein's phylogenetically independent contrasts (FIC; Garland et al., 2005; Speakman, 2005) to re-evaluate the relationship between IGF-1 and body mass using an estimated phylogeny of all 36 species. This analysis generally weakened the strength of the correlation and the outcome was dependent upon how the analysis was performed. FIC analysis of raw (not Ln-transformed) data using the estimates of relative branch lengths depicted in Fig. 1 (based on published phylogenies), gave a weaker correlation between plasma IGF-1 and body mass ($r = -0.42$, Fig. 3a) that nonetheless remained statistically significant ($P < 0.01$). The analysis was repeated using Ln-transformed data and branch lengths equal to one, as in the speciation model of character change (Martins and Garland, 1991; Price, 1997), and the correlation was weakened ($r = -0.27$, $P < 0.1$, Fig. 3b). Thus, phylogenetic history appears to contribute to the correlation between plasma IGF-1 and body mass. However, there is nonetheless an effect of body mass *per se*, with larger species generally having lower plasma IGF-1.

As IGF-1 signalling is strongly implicated in longevity (reviewed in Kenyon, 2010), we sought to determine whether there was a relationship between plasma IGF-1 and MLSP. An initial analysis revealed no evidence for correlation of these traits (Fig. 4a). However, for the 36 species included in this analysis, MLSP and

Table 1
Plasma IGF-1 values used in this analysis.

Common, strain and species name	Data source	Body mass (g)	[IGF-1] (ng/ml)	Reference
Male C57BL/6 mice (*Mus musculus*)	4 months old, laboratory reared, fed ad libitum, overnight fast prior to blood sampling	27	600	Hempenstall et al. (2010)
Male DBA/2 mice (*Mus musculus*)	4 months old, laboratory reared, fed ad libitum, overnight fast prior to blood sampling	27	600	Hempenstall et al. (2010)
Female wild/laboratory hybrid mice (*Mus musculus*)	14 months old, 6 genetic lines of cross-bred mice, laboratory reared	17–35	350–650	Harper et al. (2006)
Wild-derived mice (*Mus musculus*)	6 months old, laboratory reared	17–20	300–460	Miller et al. (2002)
Gray mouse lemur (*Microcebus murinus*)	Mean age 2.3 years, laboratory reared	80	592	Terrien et al. (2008)
Golden-mantled ground squirrel (*Spermophilus lateralis*)	Adult, wild-caught and maintained in laboratory, male and female	150	650	Schmidt and Kelley (2001)
Wistar rats (*Rattus Norvegicus*)	Adult, laboratory reared, fed ad libitum	210	900	Osorio et al. (1998)
Sprague–Dawley rats (*Rattus Norvegicus*)	14 weeks old, laboratory reared, fed ad libitum	250	960	Garcia et al. (2008)
Sprague–Dawley rats (*Rattus Norvegicus*)	>6 months old, laboratory reared	450	1400	Lian et al. (2004)
Sprague–Dawley rats (*Rattus Norvegicus*)	Adult, laboratory reared	490	730	Tarasiuk and Segev (2005)
Marmoset monkeys (*Callithrix jacchus*)	Adult, laboratory reared	350	500	Tomas et al. (1997)
Guinea pigs (Cavia *porcellus*)	Sham surgery	430	440	Conlon and Kita (2001)
Male rabbits (*Oryctolagus cuniculus*)	Adult, laboratory reared	4200	222	Carter et al. (1997)
New Zealand white rabbits (*Oryctolagus cuniculus*)	Females, 3.5 months old, laboratory reared	3000*	450	Sirotkin et al. (2009)
Long-tailed macaque (*Macaca fascicularis*)	Females, 8–20 years old, laboratory reared	3300	670	Shively et al. (2005)
Agile gibbons (*Hylobates agilis*)	3–4 years old, laboratory reared	4250	500	Suzuki et al. (2003)
Domestic cats (*Felis cattus*)	2–5 years old, laboratory reared	5500*	200	Campbell et al. (2004)
Domestic cats (*Felis cattus*)	Male and female, 4.5 years old, neutered	4830	440	Leray et al. (2006)
Sooty mangabey (*Cercocebus torquatus atys*)	Male and female, adult, laboratory reared	8600	692	Bernstein et al. (2007)
Japanese macaques (*Macaca fuscata*)	Male and female, free-ranging	9800	500	Suzuki and Ishida (2001)
Japanese macaques (*Macaca fuscata*)	Male and female, 3 years old, laboratory reared	9000	1000	Suzuki etal. (2000)
Rhesus macaques (*Macaca mulatta*)	Male and female, zoo populations	9900	355	Bernstein et al. (2007)
Black mangabey (*Lophocebus aterrimus*)	Male and female, zoo populations	9000	166	Bernstein et al. (2007)
Pudu deer (*Pudu puda*)	Male, 2–5 years old, kept in pens	12000*	225	Bartoš et al. (1998)
Domestic dogs (*Canis lupus familiaris*)	Male beagles, 1 year old	11000	210	Dubreuil et al. (1996)
Domestic dogs (*Canis lupus familiaris*)	Many varieties and ages	25000	300	Spichiger et al. (2006)
Gelada (*Theropithecus gelada*)	Male and female, zoo populations, 9–36 years old	15500	417	Bernstein et al. (2007)
Drill (*Mandrillus leucophaeus*)	Male and female, zoo populations, 10–28 years old	16500	380	Bernstein et al. (2007)
Guinea baboon (*Papio hamadryas papio*)	Male and female, zoo population, 8–22 years old	19000	269	Bernstein et al. (2007)
Olive baboon (*Papio hamadryas anubis*)	Male and female, adults, laboratory reared	19500	138	Bernstein et al. (2007)
Mandrill (*Mandrillus sphinx*)	Male and female, zoo populations, 9–34 years old	31600	589	Bernstein et al. (2007)
Sheep (*Ovis aries*)	Male Soay, adult, castrated, housed in pens	35000	300	Rhinda et al. (2000)
Sheep (*Ovis aries*)	Male Soay, adult rams, housed in pens	39000	920	Lincoln et al. (2001)
Sheep (*Ovis aries*)	Female Finn and Cambridge, 9 months old	36000	200	Spicer et al. (1993)
Goats (*Capra hircus*)	Adult females, lactating	45000	55	Nielsen et al. (1990)
Chimpanzees (*Pan troglodytes*)	Adult males, laboratory raised, 11–16 years old	62000	519	Videan et al. (2009)
Humans (*Homo sapiens*)	Adult males and females	75000	190	Fontana et al. (2008)
Humans (*Homo sapiens*)	Healthy males 20–40 years old	75000	210	Leifke et al. (2000)
Reindeer (*Rangifer tarandus*)	Adult males and females, paddock reared	80000*	350	Bubenik et al. (1998)
Black bear (*Ursus americanus*)	Females 2–20 years old, held in pens	90000*	390	Donahue et al. (2006)
Pigs (*Sus scrofa*)	Adult males and females, reared in pens	105000	130	Suzuki et al. (2004)
Pigs (*Sus scrofa*)	Males and females, 11 months old	160000	95	Hilleson-Gayne and Clapper (2005)
Stellar sea lion (*Eumetopias jubatus*)	Females, 2.5–6 years old, held in captivity	180000	225	du Dot (2007)
Grizzly bear (*Ursus arctos*)	Adult males and females, >3 years old, free-ranging	200000*	235	Gau and Case (2002)
Red deer (*Cervus elaphus*)	Adult males, 2–9 years old, paddock reared	200000*	300	Bartoš et al. (2009)
Elk (*Cervus canadensis*)	Females, 1.5–7 years old, paddock reared	200000*	50	Cook et al. (2001)
Polar bears (*Ursus maritimus*)	Females ~12 years old, free-ranging	300000*	50	Lennox and Goodship (2008)
Muskoxen (*Ovibos moschatus*)	Adult females, free-ranging	300000*	30	Adamczewski et al. (1998)
Horses (*Equus caballus*)	Females, 6–23 years old	530000	160	Heidler et al. (2003)
Horses (*Equus caballus*)	Female Haflinger, 7–15 years old	460000	150	Deichsel et al. (2005)
Horses (*Equus caballus*)	Male and Female, ages 8–12 years	500000*	240	Noble et al. (2007)
Cows (*Bos Taurus*)	Adults, lactating	450000*	80	Castigliego et al. (2009)
Cows (*Bos Taurus*)	Holstein Fresian	575000	90	Roberts et al. (2005)
Bulls (*Bos Taurus*)	Angus-cross steers	262000	185	Waggoner et al. (2009)

* Not reported in cited studies, so these body masses represent average values for adults of a given species taken from AnAge (de Magalhães et al., 2005).

Table 2
Adult body mass, maximum lifespan (MLSP) and mean plasma total IGF-1 in the 36 mammalian species analyzed in this study.

Species (common name)	Adult body mass (g)	MLSP (years)	Mean [IGF-1] (ng/ml plasma)[a]
Mouse	23	4	450 (100)
Gray mouse lemur	80	18	592 (6)
Ground squirrel	150	10	650 (13)
Rat	350	5	975 (30)
Marmoset monkey	350	12[b]	500 (6)
Guinea pig	430	12	440 (6)
Rabbit	3600[c]	9	340 (25)
Long-tailed macaque	3300	39	670 (12)
Agile gibbon	4250	49	500 (2)
Domestic cat	5200[c]	30	320 (16)
Japanese macaque	9500	38.5	750 (194)
Rhesus macaque	9900	40	355 (5)
Black mangabey	9000	33[b]	166 (3)
Sooty mangabey	8600	18[b]	692 (203)
Pudu deer	12000[c]	18	225 (6)
Domestic dog	18000	24	255 (48)
Gelada baboon	15500	36	417 (15)
Drill	16500	39	380 (10)
Guinea baboon	19000	40[b]	269 (73)
Olive baboon	19500	45[b]	138 (199)
Mandrill	31600	40	589 (26)
Sheep	37000	23	400 (36)
Goat	45000	21	55 (40)
Chimpanzee	62000	60	519 (10)
Human	75000	122	200 (618)
Reindeer	80000[c]	22	350 (9)
Black bear	90000[c]	34	390 (5)
Pig	135000	27	115 (220)
Stellar sea lion	180000	33	225 (8)
Grizzly bear	200000[c]	40	235 (23)
Red deer	200000[c]	32	300 (8)
Elk	200000[c]	22	50 (43)
Polar bear	300000[c]	44	50 (12)
Muskoxen	300000[c]	28	30 (18)
Horse	500000	57	190 (21)
Cow	500000	20	110 (29)

[a] Numbers in parentheses indicate sample size for IGF-1 measurements.
[b] Data from Rowe (1996). All other MLSP data from AnAge.
[c] Not reported in cited studies, so these body masses represent average values for adults of that species taken from AnAge (de Magalhães et al., 2005).

body mass are highly correlated ($r = 0.65$, $P < 0.001$, Fig. 4b). Therefore, the residuals of the MLSP versus body mass plot were correlated with the residuals of MLSP versus plasma IGF-1, to remove the effect of body mass, and then subjected to FIC analysis (Fig. 4c). This analysis also indicated no correlation between MLSP and plasma IGF-1 ($r = 0.1$). Therefore body mass, but not MLSP, is correlated with plasma IGF-1 in mammalian species.

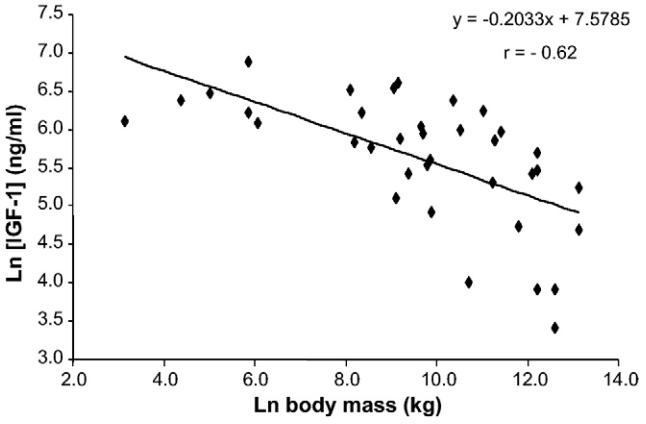

Fig. 2. Plasma total IGF-1 concentrations are negatively correlated with species' adult body mass. Each data point represents a single mean value for a species. Correlation is significant ($P < 0.001$).

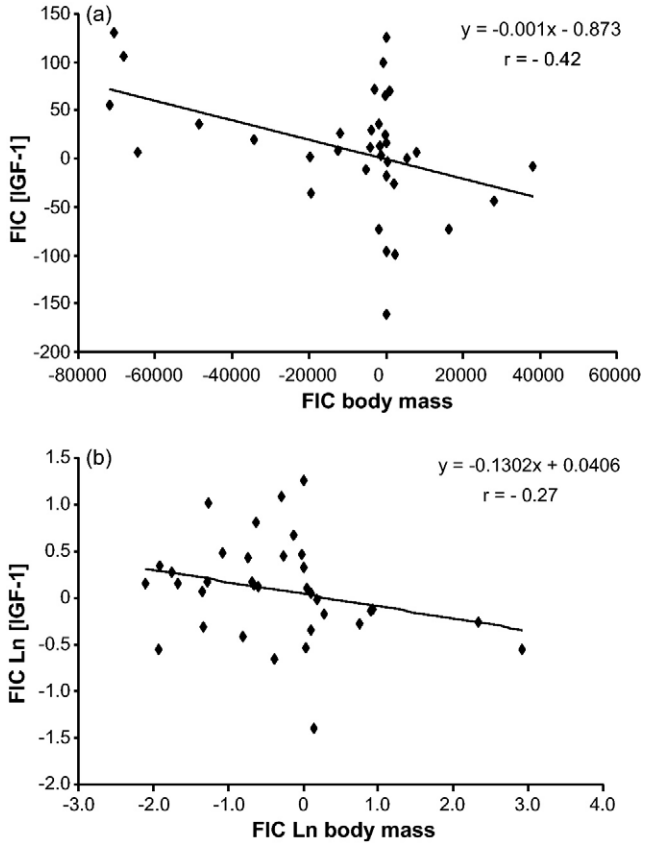

Fig. 3. Re-analysis of data set using Felsenstein's phylogenetically independent contrasts (FIC) using (a) estimated branch lengths from Fig. 1, or (b) all branch lengths equal to 1. Both correlations are statistically significant, at $P < 0.01$ and $P < 0.05$, respectively.

The data set is particularly rich in primate species, with 15 individual species varying in average adult mass from 80 to 75000 g. This permits an analysis of IGF-1 correlations exclusively within this clade. Within primates, plasma total IGF-1 appeared to be negatively correlated with species body mass ($r = -0.36$) and also with species MLSP ($r = -0.40$) (results not shown). Neither correlation was statistically significant at the $P < 0.05$ level, though both were at the $P < 0.1$ level. However, both correlations were highly dependent upon the human data point. Exclusion of human data lowered correlation coefficients to $r = -0.27$ and -0.25, respectively, and rendered $P > 0.1$.

3. Discussion

It is clear that there is substantial inter-laboratory variability in measurements of plasma free IGF-1 even for highly inbred strains of a particular species. For example, IGF-1 levels for 6–7-month-old Sprague–Dawley rats of similar body mass have been reported as 730 ng/ml (Tarasiuk and Segev, 2005) and 1400 ng/ml (Lian et al., 2004). Such substantial differences, which are observed within multiple individual species and strains, are unlikely to reflect primarily the use of recombinant IGF-1 standards originating from a species other than that being measured. Amino acid sequence is highly conserved amongst mammals (100% in most species included in this study), and recombinant rat, human and bovine IGF-1 standards are commercially available and used routinely. Instead, the inter-laboratory variability probably reflects more general differences in analytical methods. A standardized protocol for IGF-1 measurement would be useful in overcoming this problem in the future. However, by using multiple reported

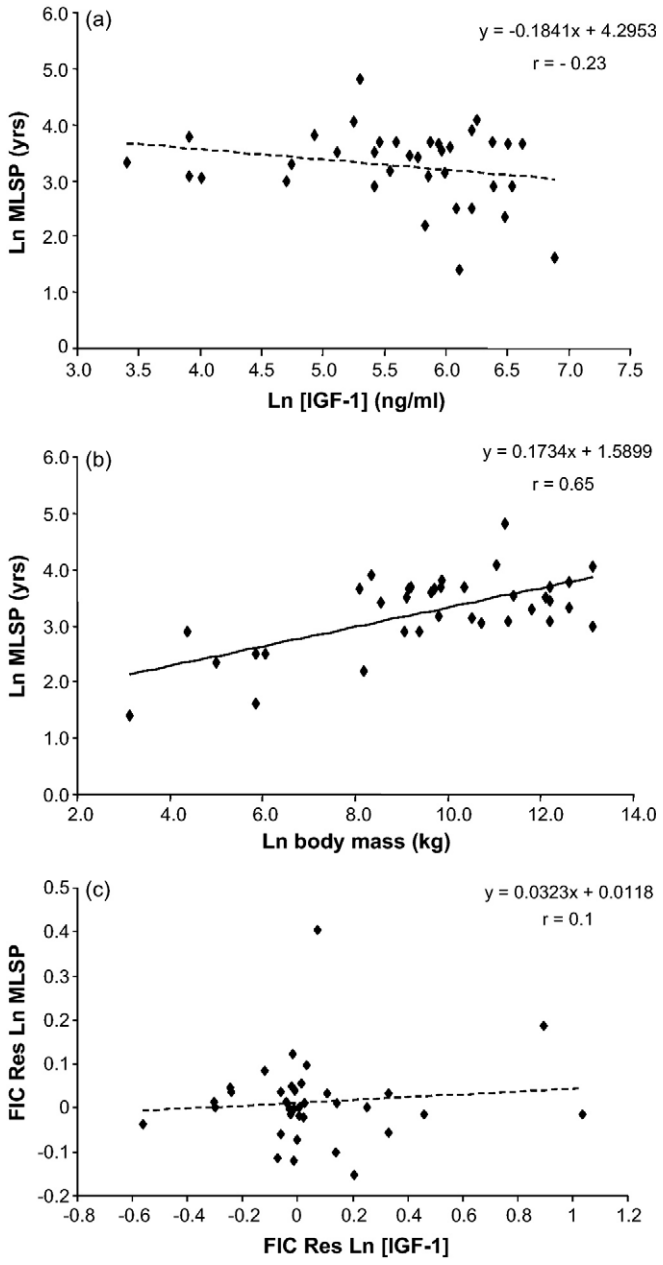

Fig. 4. Correlation of MLSP with plasma total IGF-1 concentration: (a) correlation of Ln-transformed data is not significant ($P > 0.05$), (b) MLSP and body mass are significantly correlated in the data set ($P < 0.05$), so (c) data was re-analyzed using residual analysis and FIC to account for independent effects of body mass and phylogeny, respectively. This correlation was also not significant ($P > 0.05$).

measurements of IGF-1 for individual species (where possible) we were able to minimize the effects of this 'noise' so that underlying trends were not completely obscured, and the significant negative correlation between body mass and plasma IGF-1 was detectable.

Within a species, increased IGF-1 signalling and/or expression of specific IGF-1 variants play(s) significant roles in determining adult body mass. Inbred strains of mice (Yuan et al., 2009) and dogs (Spichiger et al., 2006) with reduced plasma IGF-1 show concomitantly reduced body masses. Presumably this reflects IGF-1's mitogenic capacity to stimulate the generation of cells and tissue. Similarly, reduced plasma IGF-1 in aged animals has been linked to reduced tissue regenerative potential (Scicchitano et al., 2009; Kooijman et al., 2009). From this perspective, it is counter-intuitive that very large mammalian species maintaining substantial masses of body tissue would have relatively lower circulating IGF-1 levels.

Circulating IGF-1 originates primarily in the liver, an organ that is proportionately smaller and less metabolically active in larger mammalian species (see Porter, 2001 and references therein). So, while liver tissue constitutes approximately 5.5% of body mass in the smallest species included here (mice), it is only about 0.5% of body mass in the largest species (e.g. horses or cows). In addition, the rate of oxygen consumption by an individual horse or cow hepatocyte is only about one-tenth that of a mouse hepatocyte (Porter, 2001). Therefore, the product of these two values should be almost 100 times lower in a horse than in a mouse. If the rate of IGF-1 production and secretion in hepatocytes is roughly proportional to their overall metabolic activity, this would predict significantly reduced circulating levels of the hormone.

It should be noted, however, that plasma levels of other metabolically important hormones (e.g. thyroxine; Hulbert and Else, 2004) do not scale with body mass. In addition, we have no information regarding the levels of IGF-1 binding proteins (IGFBP) in plasma as they relate to species' body masses. As IGFBPs affect the half-life of plasma IGF-1 (Lee and Gorospe, 2010), differences in IGFBP abundance could contribute ultimately to lower steady-state IGF-1 levels. Similarly, we do not know growth hormone (GH) levels, which strongly regulate IGF-1 secretion, for all of the species included in this study. Given the pulsatile nature of GH secretion from the pituitary (Sherlock and Toogood, 2007), and differences in the timing and amplitude of the GH secretion cycle in nocturnal or crepuscular species (e.g. many rodents) versus diurnal species, this information may be difficult to acquire reliably. Like liver though, pituitary mass as a proportion of body mass is indirectly correlated with species body mass (Stahl, 1965), so larger species will have proportionately smaller pituitary glands. This could result in a reduced rate of GH secretion in larger species. In summary, while we can robustly conclude that plasma IGF-1 levels are indirectly correlated with species body mass, we do not know mechanistically why this is so.

The lower circulating IGF-1 levels in larger mammalian species could also contribute to their reduced mass-specific metabolic rates (Rolfe and Brown, 1997). In a rat model of adult onset IGF-1 deficiency, a reduction of plasma IGF-1 by about 35% was associated with 20–40% lower rates of glucose utilization, and lower ATP levels, in various brain regions (Sonntag et al., 2006). Brain tissue accounts for up to 20% of whole body metabolic rate in rats and humans (Rolfe and Brown, 1997). Therefore, this could make an appreciable contribution to the observed differences in mass-specific metabolic rates, particularly if other tissues are similarly affected.

IGF-1 is also a powerful mitogen, with roles in regulating growth of various tissues, including muscle and brain. In adults, IGF-1 is implicated in the regeneration of damaged tissue (e.g. see Ten Broek et al., 2010), and remodelling of existing tissue as in neural plasticity (Sonntag et al., 2005). In adult mammals, reduced circulating IGF-1 levels associated with advanced age have been implicated in the reduced capacities for tissue regenerative repair and remodelling (Ten Broek et al., 2010). Thus, the lower levels of circulating IGF-1 in larger mammalian species might be expected to contribute to slower rates of proliferative growth. While this would be expected to slow the rate of wound healing and tissue repair, it may equally be important in avoiding the permissive environment for cancer growth created by high IGF-1 levels (e.g. Dunn et al., 1997; Wu et al., 2002). Plasma IGF-1 is reduced typically about 40% in CR rodents, and this corresponds to reduce incidences of a variety of tumours (see Sonntag et al., 2006 and references therein). This effect can be reversed by direct injection of IGF-1 in CR animals (Ramsey et al., 2002). Epidemiological studies of humans also indicate a correlation between circulating IGF-1 levels and cancer growth and metastasis (Khandwala et al., 2000). Thus, lower plasma IGF-1 levels in larger species may contribute to the cancer resistance that is associated

with longevity. Seluanov et al. (2007) demonstrated a negative correlation between telomerase activity and body mass in rodents, which presumably is protective against unregulated cell division. There is evidence that IGF-1 stimulates telomerase activity in some cell types (e.g. Wetterau et al., 2003; Movérare-Skrtic et al., 2009). It is possible the lower IGF-1 levels of larger species contribute to these observed reductions in telomerase activity.

Reduced IGF-1 signalling is also strongly associated with increased stress resistance in invertebrates and mammals, mediated at least in part via interactions with FOXO transcription factors (Kenyon, 2010). Most mutant mouse strains with increased longevity show concomitantly enhanced stress resistance at whole animal and cellular levels (Robb et al., 2009). Kapahi et al. (1999) demonstrated a robust direct correlation between stress resistance of skin fibroblasts and MLSP in mammalian species. The reduced plasma IGF-1 of larger species may play a role in mediating these differences in cellular stress resistance. Investigation of elements of the IGF-1 intracellular signalling pathway in the inter-species context will provide further insight into this possibility.

The contribution of IGF-1 to the physiological regulation of body mass is achieved by both local (paracrine) and systemic (endocrine) effects. Delineating the relative contributions of paracrine and endocrine IGF-1 signalling has been contentious. Whereas Yakar et al. (1999) provided evidence that IGF-1 actions in mice are entirely paracrine, more recently Stratikopoulos et al. (2008) have shown approximately equal contributions of systemic and local IGF-1 to body mass determination. In rats, systemic injection of IGF-1 is capable of rescuing the effects of congenital GH/IGF-1 deficiency during development (Sonntag et al., 2005), which also indicates the importance of endocrine IGF-1 signalling. We are unable here to determine whether tissue IGF-1 levels scale similarly to plasma IGF-1, due to a lack of published data across a broad range of species. However, it would be interesting to make such measurements in the future.

It is interesting that the correlation between plasma IGF-1 and species body mass may be detectable within primates alone. Though this correlation was not statistically significant, this may be due to the relatively low statistical power associated with our dataset of only 15 primate species. Bernstein et al. (2007) similarly found evidence for a weak ($r = -0.20$, not statistically significant) negative correlation between plasma IGF-1 and body mass in females of eight papionin primate species. Application of a standardized IGF-1 measurement protocol to primate plasma samples may reveal real relationships between IGF-1 and body mass or MLSP.

In summary, while intra-species comparisons have revealed a positive correlation between plasma total IGF-1 and body mass, we have shown the opposite trend in an inter-species context. This negative correlation between circulating IGF-1 levels and species body mass is interesting because of the significant roles of IGF-1 in metabolism, cancer, cellular stress resistance, and longevity. Larger mammalian species are generally also longer-lived, and it is tempting to speculate that reductions of plasma IGF-1 contribute to important aspects of the large mammal phenotype. The reductions in plasma IGF-1 in larger mammals may promote a hormonal environment conducive to longevity.

4. Experimental procedures

PubMed and Web of Science database searches were performed to find published values for plasma total IGF-1 in as many species and orders of the vertebrate class Mammalia as could be found.

A phylogeny for the 36 species used in this study (Fig. 1) was estimated by amalgamating mammalian phylogenies from Chatterjee et al. (2009), Delisle and Strobeck (2005), Lindqvist et al. (2009), Matthee and Davies (2001), Pitra et al. (2004), Springer and Murphy (2007) and Yang and Yoder (2003).

Correlational analyses were performed essentially as described in Page et al. (2010). *P*-Values for correlational analyses were determined using one-tailed tests. To distinguish between possible effects of MLSP versus those of body mass, residual analysis was employed. To account for phylogenetic relationships, PDAP (Garland et al., 2005) was used to perform FIC (Felsenstein, 1985). FIC analysis employed the branch length estimates from the phylogenetic tree (Fig. 1), or all branch lengths set to one, as in the speciation model of character change (Martins and Garland, 1991; Price, 1997).

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