Insulin-like growth factor 1 of wild vertebrates in a life-history context

Jaanis Lodjak\textsuperscript{a,b,*}, Simon Verhulst\textsuperscript{b}

\textsuperscript{a} Department of Zoology, Institute of Ecology and Earth Sciences, University of Tartu, 46 Vanemuise Street, Tartu, 51014, Estonia
\textsuperscript{b} Groningen Institute for Evolutionary Life Sciences, University of Groningen, Nijenborgh 7, 9747 AG, Groningen, Netherlands

\textbf{A R T I C L E  I N F O}

Keywords: Adaptation Fitness Hormone Somatic maintenance Trade-off

\textbf{A B S T R A C T}

Broad variation in intra- and interspecific life-history traits is largely shaped by resource limitation and the ensuing allocation trade-offs that animals are forced to make. Insulin-like growth factor 1 (IGF-1), a growth-hormone-dependent peptide, may be a key player in the regulation of allocation processes. In laboratory animals, the effects of IGF-1 on growth- and development (positive), reproduction (positive), and longevity (negative) are well established. We here review the evidence on these effects in wild vertebrates, where animals are more likely to face resource limitation and other challenges. We point out the similarities and dissimilarities in patterns of IGF-1 functions obtained in these two different study settings and discuss the knowledge we need to develop a comprehensive picture of the role of IGF-1 in mediating life-history variation of wild vertebrates.

1. Introduction

Life history of animals consists of a complex combination of traits, which coevolve to maximize Darwinian fitness. The lifelong race to maximize fitness takes place on multiple levels. First, young animals have to grow to their adult body size, then they have to reproduce successfully as sexually mature individuals, and, above all, they have to survive through these costly challenges. Broad variation in intra- and interspecific life history traits is thought to be largely shaped by resource allocation trade-offs, since there is a limit on the resources that animals can consume (Flatt and Heyland, 2011; Stearns, 1976, 1992). Natural communities often live in unpredictable environmental conditions, with stochastic changes in food supply, which can cause substantial variation in the growth rates of young vertebrates, with cascading effects on their reproductive performances as mature individuals and age-specific survival during their lifetime (Flatt and Heyland, 2011; Martin, 1987; Van De Pol et al., 2006). As food supply or energetic demand of an animal changes, optimal resource allocation is also likely to change (Schubert et al., 2009). When allocating resources, an individual faces trade-offs due to simultaneous selective investment into different physiological mechanisms (Zera and Harshman, 2001), enhancing fitness in different ways. Characterising these trade-offs is a challenge for evolutionary ecologists, because the link between individual variation in physiology and individual variation in life history traits is seldom straight-forward. In this respect, hormones are thought to be important modulators underlying fitness correlates among free-living vertebrates (Bonier et al., 2009; Dantzer and Swanson, 2012; Hau et al., 2010).

In this review, we focus on the insulin-like growth factor 1 (IGF-1) of wild animals in a life-history context. IGF-1 is a growth hormone (GH)-dependent peptide, which is secreted into the circulatory system by the liver (Yakar et al., 2001). In laboratory conditions the growth- and development-promoting effects (e.g. Lupu et al., 2001), reproduction-enhancing effects (e.g. Liu et al., 2000), and longevity-reducing effects (e.g. Holzenberger et al., 2003) of IGF-1 in animals are well recognized. However, in wild animals, we are only really just beginning to explore the variety of patterns regarding how IGF-1 is associated with life history of wild vertebrates (Table 1). Laboratory animals live protected lives when compared with wild animals, and natural challenges can have strong effects on fitness consequences of molecular and/or physiological variation (Briga and Verhulst, 2015), complicating extrapolation of laboratory-based studies to wild animals. This review will give an overview of our knowledge on IGF-1 in wild vertebrates and discuss avenues for future research.

2. IGF-1 synthesis

Combinations of cues from the environment and the internal physiological state of vertebrates initiate and modulate the release of growth hormone releasing hormone (GHRH) and somatostatin from the hypothalamus (Juntilla et al., 2013). These two peptides respectively stimulate and inhibit the release of growth hormone (GH) from the pituitary

\textsuperscript{*} Corresponding author. Department of Zoology, Institute of Ecology and Earth Sciences, University of Tartu, 46 Vanemuise Street, Tartu, 51014, Estonia.
E-mail address: jaanis.lodjak@ut.ee (J. Lodjak).

https://doi.org/10.1016/j.mce.2020.110978
Received 15 January 2019; Received in revised form 3 August 2020; Accepted 3 August 2020
Available online 14 August 2020
0303-7207/© 2020 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
characterized in mammals and fish, and appears evolutionarily conserved among vertebrates (Hwa et al., 1999; Nakae et al., 2001). It is further important to note that while every receptor in the system has its own distinct role, their functions can overlap; for example, IGF-1 also binds to insulin receptors, although with lower affinity (Nakae et al., 2001).

As the most notable of IGFBP’s physiological functions, the ability to transport (e.g. IGFBP3) IGF-1 (and IGF-2) to target tissues is characterized (Allard and Duan, 2018; Butler and Le Roith, 2001). In humans, free IGF-1 (i.e. free from binding proteins) levels are shown to be only a small fraction (~1%) of the total IGF-1 concentrations (Allard and Duan, 2018; Juul et al., 1997). For example, IGFBP3 has been described as a compound that is involved in DNA damage repair on the one hand, and a compound that regulates apoptotic processes on the other hand (Baxter, 2013). IGFBP4 appears to be unique, in that it seems to be the only IGFBP that functions mostly like a traditional binding protein, and apparently without having clear IGF-independent functions (Mazebourg et al., 2004). Its physiological effects are not fully understood, since IGFBP4 is inhibiting IGFs functions, but IGFBP4−/− mice show rather retarded than increased body growth (Mazebourg et al., 2004).

IGFBP7, when secreted into the circulatory system, has a low affinity to IGFs, but uniquely is able to bind to IGF-1 receptor (IGF1r) in humans and thereby block the activation by IGF signalling (Evdokimova et al., 2012). To what extent the findings described above also apply to animals exposed to natural environments is not yet known.

Evolutionary studies provided some important insights in how different IGFBP genes have evolved in different vertebrate classes. For example, in teleost fish IGFBP genes underwent a duplication resulting in multiple copies of various IGFBP genes with different functionality, while birds have lost functional IGFBP6 (Bassas et al., 1988; Daza et al., 2011). In physiological studies of free-living populations, the focus of hormonal effects has mostly been on hormonal levels alone, and integrating this information with the action of the IGFBP system may considerably increase our understanding of how experiments can have diverse effects on IGF functioning in different species.

IGF signalling is mediated through three receptors – IGF1r, IGF-2 receptor (IGF2r) and the insulin receptor (Ir) (Nakae et al., 2001). These three receptors are attached to insulin receptor substrates (IRS1–IRS4) which are docking molecules from which numerous different pathways (including phosphatidylinositol 3-kinase and mitogen-activated protein kinase) will begin (Hanke and Mann, 2009; Shaw, 2011). The IGF receptor system varies between different vertebrate taxa. For example, functional IGF2r appear to be absent from fish and birds (Wood et al., 2005), where IGF-1 and IGF-2 exert their effects through IGF1r and Ir. In humans and other mammals in which this was studied, IGF1r mediates IGF-1 and IGF-2 actions on prenatal somatic growth while postnatal growth is primarily modulated through IGF-1 (Nakae et al., 2001). The insulin receptor is increasingly recognized as an important mediator of IGFs effects on growth (Boucher et al., 2016; Nakae et al., 2001; Plum et al., 2005). For example, studying prenatal development in IGF1r/−/IGF2 knockout mice, Louvi et al. (1997) showed that Ir is able to take over IGF signalling if the primary IGF-2 pathway is inactive. Similar patterns of overlapping signalling between three ligands and their receptors of the insulin/insulin-like signalling (IIS) can be expected also for reproduction, neural tissue maintenance, and longevity (Barthe, 2008; Bluher et al., 2003; Bonkowski et al., 2009; Bröning et al., 2006; Plum et al., 2005). Given that the IIS system can flexibly compensate for different parts of IIS, at least in laboratory mammals, it would be interesting to know whether wild vertebrates that compete for resources are similarly flexible.

Total plasma IGF-1 levels of vertebrates tend to be relatively stable in the short-term (compared to e.g. glucocorticoids and prolactin) and change according to the prevailing environmental conditions with relatively high individual repeatability (Beckman, 2011; Hwa et al., 1999; Lewin et al., 2017; Nakae et al., 2001; Wheatcroft and Kearney, 2009; Wilkinson et al., 2006). Physiological effects of IGF-1 are modulated by levels of fluctuating densities of receptors and their substrate proteins, and IGFBP levels. This kind of complex and likely flexible
signalling dynamics of IGF-1 enables vertebrates to respond readily to the changing environment (e.g. nutritional conditions) to maximize their Darwinian fitness.

3. IGF-1 and somatic postnatal growth

3.1. Growth-enhancing effects of IGF-1

IGF-1 has an important role in regulating embryonic and post-natal growth across vertebrate classes (Baker et al., 1993; Beccavin et al., 2001; Liu et al., 1993; Lupu et al., 2001; Schlüeter et al., 2007), and IGF-1 functions in a similar fashion in most tissue types (e.g. muscles, bones, brain; O’Kusky et al., 2000; Otto and Patel, 2010; Yakar et al., 2002). Among the central signalling cascades regulating the somatic growth of animals is the intracellular phosphatidylinositol 3-kinase/protein kinase B/target of rapamycin (PI3K/Akt/TOR) and mitogen-activated protein kinase (Ras-Raf-MAPK) pathway (Richardson et al., 2004), of which IGF-1 is one of the main mediators. Two above-mentioned pathways modulate a wide array of functions, such as cell proliferation, cell differentiation and protein synthesis (Sjögren et al., 2001).

Embryos that have genetically impaired IGF-signalling pathway have shown either developmental arrest or somatic growth retardation. These effects have been shown both on the levels of IGF-1 and its receptor. GH on the other hand seems to have no apparent role in prenatal growth (at least in mammals), despite the presence of its functional receptor (García-Aragón et al., 1992; Pantaleon et al., 1997). Absence of GH actions due to targeted mutations or experimental ablation of the pituitary had no effect on prenatal growth (Lupu et al., 2001). For example, GH-deficient mice had normal birthweights, suggesting that IGF-1 could be synthesised independently of GH during prenatal development (Agrogiannis et al., 2014). Human studies found that (placental) GH in conjunction with IGF-1 may still have a substantial role in the prenatal growth and development (Velegakis et al., 2017). In contrast to GH, IGF-1 nullzygous (−/−) mice have a birth weight of ca. 60% of control mice and the difference with control mice increased even more with parallel loss of IGF2 functions (Liu et al., 1993). In humans, Woods et al. (1997) described even more severe effects of partial IGF-1 gene deletion in exons 4 and 5. The condition caused a patient to have increased GH levels, normal IGFBP3 levels, but undetectable serum IGF-1 levels that resulted in substantial intrauterine growth failure and abnormal central nervous system development. Embryos of mice and zebrafish (Danio rerio) that lacked a functional IGF-1 receptor (IGF1r−/−) had even more reduced embryonic growth than IGF-1 knockout models, and embryos suffer from developmental arrest and died during the early stages of the postnatal period (Liu et al., 1993; Schlüeter et al., 2007). In mice, IGF1r−/− animals that survived until birth exhibited a profound growth deficiency while being only 45% of normal size when born, and died shortly after birth. During postnatal periods, effects of IGF-1 signalling inhibition on body size tend to be consistent with the prenatally observed patterns described above. In addition to GH more strongly affecting the variation of growth, IGF-1 heterozygous knockout mice attained a body weight of up to only 1/3 the weight of controls (Lupu et al., 2001; Stratikopoulos et al., 2008). Further support comes from studies of chickens. In a chicken strain selected for high postnatal growth rates, attaining faster growth relied on increased plasma IGF-1 levels (Beccavin et al., 2001). Secondly, when eggs were injected with human recombinant IGF-1, early post-hatch body mass growth rates were increased alongside with their feeding efficiency (Kocamis et al., 1998). This indicates that proportionally more of the consumed energy and nutrients may have been directed into the build-up of their body.

Correlational evidence from animal studies has mostly focused on postnatal periods and has shown that a link between IGF-1 levels and growth/body size in natural populations agree with the experimental work on (captive) model species. Lodjak et al. (2014) studied passerine birds and showed that plasma levels of IGF-1 were higher in the pre-fledging phase in free-living broods of nesting great tits (Parus major) where some nestlings had been experimentally removed, which displayed increased growth rate compared with those in control and enlarged broods. Consistent nutrition-induced increases in IGF-1 followed by increased somatic growth rate has been well described in teleost fish in fisheries. For example, juvenile rockfish (Sebastes serra-noidea) that were on high feed level had a 60% increase in body mass growth rate and 22% increase in the growth rate in length compared to rockfish that were on low feed level (Hick et al., 2018). Furthermore, plasma IGF-1 levels were higher in high feed level fish, and IGF-1 levels and hepatic IGF-1 mRNA levels correlated positively with somatic growth rates. Additionally, in the rainbow-trout (Oncorhynchus mykiss) it has been shown that nutrition following a fasting-induced zero growth rate caused a significant increase of IGF-1 and IGF-1 mRNA levels locally in the muscles (Bower et al., 2008). In mammals, positive associations between circulating IGF-1 levels and body size and antler size have been shown in several deer (Cervidae) species, either in captivity or free-ranging conditions (red deer Cervus elaphus; Sattie et al., 1985; roe deer Capreolus capreolus; Schamann et al., 1992) white-tailed deer Odocoileus virginianus, (Ditchkoff et al., 2001). Also juvenile levels of IGF-1 were positively associated with body mass in free-living spotted hyenas (Crocuta crocuta) (Lewin et al., 2017). However, Sparkman et al. (2009) found that in free-ranging garter snakes (Thamnophis elegans) the presence of a positive association between IGF-1 levels and adult body size was dependent on habitat type. One of the main reasons behind the possibility of IGF-1 being associated with the body mass in various ways in wild animals could be variation in food availability between populations at the time of study, while such variation is absent from standard laboratory environments. This possibility is supported by human studies, where nutrition-dependent deviations from the positive association between IGF-1 levels and body size have been described (Fall et al., 1995). In wild birds there is some experimental evidence of effects of IGF-1 on growth, Lodjak et al. (2017) found that injections of IGF-1 lead to overall larger body size and the accelerated somatic growth rate in pied flycatcher (Ficedula hypoleuca) nestlings. These data collectively illustrate that IGF-1 is intimately involved with the normal growth trajectory of a young animal.

IGF-1 may affect different organs differently during development. The administration of IGF-1 increased proportionally more heart, spleen, kidney, and thymus in hypophysectomised rats, but decreased the size of fat tissue (Guler et al., 1988; Ohlsson et al., 2009). Knocking out the IGF-1 gene has been shown to increase liver size via reduced GH feedback and increased pituitary GH release in mice (Ohlsson et al., 2009). In wild nesting birds, Lodjak and Mägi (2018) conducted an IGF-1 administration experiment and showed a stronger trade-off between growth of linear size and mass in control nestlings than in IGF-1 injected nestlings, suggesting that IGF-1 injection partially released nesting from the constraint that generated this trade-off. It has also been shown that mRNA levels of IGF-1 increased in the pectoralis muscle of migratory Gambel’s white-crowned sparrows (Zonotrichia leucophrys gambelii), but decreased in the gastrocnemius muscle, at pre-departure stage to facilitate somatic growth of muscles for flight (Pradhan et al., 2019). Selective investment via IGF-1 signalling into different tissues is not fully understood. This is partly because the response to different manipulations of the IGF-1 signalling pathway often varies. It has been shown that GH has also differential effects on overall body growth and growth of different organ sizes that are presumably independent of GH (Guler et al., 1988; Lupu et al., 2001; Guler et al., 2008; Kamenický et al., 2014; Lupu et al., 2001). Also different organs vary in their responsiveness to locally produced IGF-1 in studies where systemic IGF-1 synthesis was manipulated (Kamenický et al., 2014). However, it is important to note that local production of IGF-1 is not sufficient in most cases to replace the liver-derived segment of the hormone production (Ohlsson et al., 2009).

Finally, growing older successfully relies on maintaining the integrity of tissues. During the more energy demanding phases of life,
physiological mediators such as glucocorticoids are released to mobilise energy from carbohydrates, fats, and proteins (Jimeno et al., 2018). When energy stores diminish, tissues atrophy due to the protein breakdown by the ubiquitin-proteasome system and autophagy lysosome system (Braun and Marks, 2015). IGF-1 signalling is shown to counteract or at least mitigate tissue atrophy as well as tissue damage from physical activity on several levels, such as in increased protein synthesis through the activity of TOR pathway, enhances rate of cell division, as well as modulating peripheral activity of glucocorticoids. This has well been described in the case of muscle and bone tissues in humans and rodents during both pre- and postnatal periods (Fournier et al., 2003; Gupta and Gupta, 2013; Locatelli and Bianchi, 2014; Shangguan et al., 2018; Song et al., 2005; Yin et al., 2009). To this day, we do not have much information on effects of IGF-1 on tissue maintenance from free-living animals throughout their ontogeny, which would be integral part of understanding fitness prospects of animals in their natural habitats.

3.2. Nutrition dependency of IGF-1

Nutritional condition of a vertebrate animal is strongly associated with the IGF-1 levels (protein and mRNA) in the bloodstream and in tissues as well as plasma IGFBP levels (Estivariz and Ziegler, 1997; Underwood, 1996). IGF-1 levels decrease as animals are fasting and increase following food consumption. This pattern is consistently found in studies across vertebrate classes and even in invertebrates that have insulin-like peptides (ILPs) instead of IGFs (Estivariz and Ziegler, 1997; Platt and Heyland, 2011; Regan et al., 2019). Systemically produced IGF-1 (mainly) in the liver and the locally synthesised protein are both regulated robustly in a similar way by the consumed food (Bro¨ning et al., 2000; Estivariz and Ziegler, 1997). This nutrition-mediated hormonal effect likely arises through multiple physiological mechanisms (Fig. 1), including levels of adipocyte-derived leptin (anorexigenic hormone), liver-derived ghrelin (orexigenic hormone), and pancreas-derived insulin, which are all sensitive to the nutritional state of the organism and modulate synthetic pathways for glucocorticoids (see section 3.4) and IGF-1 via the hypothalamus (Cassy et al., 2003; Inui, 2001; Laron, 2001). In addition, under food-limited conditions, an increased level of ghrelin, which induces an increase in the food intake, has a direct stimulatory effect on the secretion of GH (Kaiya et al., 2013; Takaya et al., 2000).

Activation of IGF-1 and IGFBP synthesis as well as IGF-1-initiated growth promoting PI3K/AKT/TOR signalling pathway is dependent on additional signals from nutritional compounds (e.g. amino acids, glucose, free fatty acids micronutrients and vitamins; Fig. 1), and is

Fig. 1. Synthesis of insulin-like growth factor 1 (IGF-1). IGFBP denotes insulin-like growth factor binding proteins, IGF1r denotes IGF-1 receptors, GC denotes glucocorticoids, IGF-2 denotes insulin-like growth factor 2. Dashed lines emphasize the fact that a collective signal regarding the nutritional state of an organism is needed for the normal synthetic cascade to function.
consequently inhibited when food is a limiting factor (Fingar and Blenis, 2004; Ross and Buchanan, 1996; Scacchi et al., 2003).

Firstly, we focus on the effects of micronutrients, such as zinc (Zn), selenium (Se), and magnesium (Mg). In the case of Zn deficiency, IGF-1 and IGFBP3 levels are significantly lower and oral supplementation of Zn is able to increase IGF-1 levels in humans (children and adults) and rodents (Cesur et al., 2009; Estivariz and Ziegler, 1997; Hamza et al., 2012). For example, continuously infusing rats with GH did not cause significant changes in serum IGF-1 or liver mRNA levels in individuals with Zn deficiency (Estivariz and Ziegler, 1997; Rocha et al., 2015). In addition to the described mode of action, Zn positively impacts IIS on the level of hypothalamus, pituitary, liver, and target tissue, as well as interact (positively or negatively) with insulin, vitamin D, testosterone, oestrogen, and thyroid hormones (Rocha et al., 2015). The latter effects are beyond the scope of this study, but illustrate the physiological complexity involved. In cases of Mg and Se the positive effects shown on IGF-1 synthesis and activity are relatively similar with the effects of Zn, but with even bigger effect sizes (Estivariz and Ziegler, 1997). New born rats ceased to grow after 3 weeks on Mg-deficient food with a serum IGF-1 level drop of 60% (Dorup et al., 2007). When fed Se-deficient food, the drop in IGF-1 levels and growth rate was even more pronounced. In both cases, growth and IGF-1 levels recovered with 2–3 weeks with a diet without these deficiencies, but body size remained smaller (Dorup et al., 2007). Mineral deficiencies of Mg and Se may also trigger a chronic inflammation and released cytokines can indirectly act as inhibitors of IGF-1 signalling and its regulatory role of immune system (Maggio et al., 2013; O’Connor et al., 2008).

Secondly, impacts of protein consumption on IGF-1 levels have been especially well studied in teleost fish, poultry, and stock animals due to economic impacts as well as in laboratory rodents (Dukes et al., 2015; Pérez-Sánchez et al., 1995; Rosebrough and McMurtry, 2007; Wan et al., 2017). Studies have demonstrated roughly the same pattern, with increasing IGF-1 levels with increasing protein consumption, with a levelling off or decrease towards the higher protein consumption. For example, a decline up to 4% in crude protein levels reduced serum IGF-1 levels as well as liver IGF-1 expression in piglets, with associated effects on somatic growth (Wan et al., 2017). Similar changes in IGF-1 levels in response to protein consumption have been shown in humans (Fontana et al., 2008; Giovannucci et al., 2003; Levine et al., 2014), with an interesting nuance. As IGF-1 levels decline with age, plasma IGF-1 levels reduced in response to protein deficiency only in individuals younger than 65, but this effect was not observed in elderly people (Fontana et al., 2008). A search of more specific compounds has revealed amino acids such as methionine and tryptophan to have strong effects on the upregulation of IGF-1, especially when acting through peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear receptor and a transcription factor (Dukes et al., 2015; Wan et al., 2017). These effects have been thoroughly reviewed elsewhere (Auwerx et al., 2003).

Finally, if food availability is high, increases in the production of metabolic compounds have mixed or suppressive effects on GH secretion, but up-regulating effects on the synthesis of IGF-1 (Ho et al., 1988; Mohan and Kesavan, 2012; Ross and Buchanan, 1996). On the other hand, when individuals are energy restricted, the production of metabolic compounds is limited, GH synthesis tends to increase, and IGF-1 levels decrease (Breier, 1999; Morón and Castillo-Cortazar, 2012; Noguerà et al., 2015). Therefore, another dimension to IGF-1 nutrition-dependency can be observed on the level of GH (Breier, 1999; Ross and Buchanan, 1996; Scacchi et al., 2005; see section 2).

There are not many studies on nutrition dependence of IGF-1 levels in wild animals. In 3-month-old brown house snakes (Lampropeltis fuliginosa), feeding rate correlated positively with their plasma IGF-1 levels, however the association was absent in 6-month-old snakes (Sparkman et al., 2010). In captive and castrated male red deer, the plasma IGF-1 levels followed the pattern of food intake throughout the year and when the animals were food-restricted their IGF-1 levels decreased and seasonality disappeared (Rhind et al., 1998).

Experimental data concerning nutrition-dependency of IGF-1 levels are even scarcer. Some evidence comes from brood size manipulations with passerine birds. Several studies on great tits have shown that brood size manipulation affects the per capita provisioning rate resulting in reduced growth rate in those chicks that grew with an increased number of siblings (Neuenschwander et al., 2003; Pettifor et al., 2001; Smith et al., 1988; Tinbergen, 1987). Lodjak et al. (2014) showed that chicks in enlarged broods had also lower IGF-1 levels compared to those whose broods were reduced.

Collectively, the studies discussed above indicate that IGF signalling during early post-natal period and throughout adulthood is flexible in response to variation in food abundance and its nutritional quality. There is also some evidence that the regulation is broadly similar across vertebrate classes. Since wild animals are likely to be more variable compared to captive animals in their ability to tolerate competition, choose optimal foraging sites, and choose their primary feeding items, their ways of responding to nutritional restrictions via IGF-1 may also differ to a greater extent. In that regard, we are only at the beginning of investigating the link between IGF signalling and its role in solving the trade-offs wild animals face throughout their lives.

### 3.3. Changing of IGF-1 levels with age

How IGF-1 levels in the blood stream change with age seems to be dependent on life-history phase, but knowledge of the effects of age on circulating IGF-1 levels is almost exclusively based on studies of humans and laboratory rodents. Serum IGF-1 levels in humans increase during early phases of childhood, followed by the steeper increase during puberty (Juul et al., 1994), and the peak in serum IGF-1 levels is achieved at 12–14 years of ages. IGF-1 levels in girls tend to peak around 2 years earlier than in boys, in line with the difference in sex-specific growth pattern (Alberti et al., 2011; Ashpole et al., 2017; Gupta et al., 2015; Kanbur-Oksuz et al., 2004). A similarly sharp rise in IGF-1 levels during early phases of postnatal life has been shown in rodents (Ashpole et al., 2017). In birds, plasma IGF-1 levels were found to increase gradually with age during early postnatal development of precocial chickens (Beccavin et al., 2001; Giachetto et al., 2004). In contrast, in great tits and pied-flycatchers, both altricial bird species, IGF-1 levels decreased from the middle towards the end of the nestling period (Lodjak et al., 2014, 2017). The age-related changes in IGF-1 levels appear to coincide with the rate of somatic growth (see section 3.1) in all abovementioned studies.

Humans and rodent species have significantly different life-histories, but in both cases the peak and the early decline in circulating IGF-1 levels have been associated with individuals attaining sexual maturity. For example, mice strains with lower circulating IGF-1 levels have significantly delayed sexual maturation (Yuan et al., 2012). Interestingly, delayed sexual maturation was associated with extended lifespan, indicating possible IGF-1 regulation of a trade-off between the life-history traits (Yuan et al., 2012). In humans, circulating IGF-1 levels have also shown to peak higher in cases of adenarche (Baquedano et al., 2005). However, when IGF-1 levels are suppressed by disorders (e.g. nodding syndrome), the growth rate is reduced and sexual maturity is delayed (Piloya-Were et al., 2014). Whether the same pattern is present in other vertebrate classes remains to be established.

As humans and rodents age after sexual maturity, circulating and neural IGF-1 levels decrease (Ashpole et al., 2017; Wrigley et al., 2017). This is thought to increase resistance to cancer as it results in lower rates of cell division. However, this decrease may also entail a cost in old age, through a decreasing effect on insulin sensitivity and neuroprotective abilities (Vitale et al., 2019; Wrigley et al., 2017), which are both associated with aging (Ferramini et al., 1996; Wrigley et al., 2017). Higher IGF-1 bioavailability, as characterized by increased ratio of IGF-1/IGFBP3, is associated with better insulin resistance in centenarians (Paolizzo et al., 1997), and humans who have higher circulating IGF-1 levels had increased cognitive abilities at old age (Rollero et al., 2017).
Glucocorticoids such as cortisol and corticosterone are steroid hormones that are released into the circulatory system by the adrenal glands as part of the hypothalamic–pituitary–adrenal (HPA) axis. Glucocorticoids interact with IGF-1 and modulate its synthesis and effects, ranging from effects on IGF-1 levels to its carrier protein levels (e.g. IGFBPs 1 and 3) and receptor densities (IGF1r) (e.g. Conover et al., 1996; Jux et al., 1998; Li et al., 1997; Mazzotti and Giustina, 2013; Okazaki et al., 1994). Conversely, IGF-1 signalling has effects on glucocorticoid downstream signalling (Pansters et al., 2013; Paulsen et al., 2006). This complex bidirectional interaction is important for fitness components and correlates based on the overall section.

During prenatal and early postnatal development, and at low concentrations (during periods of lower energetic requirements in relatively stable environment), glucocorticoids promote the maturation and functionality of systems such as brain, gastrointestinal tract and skeletal muscle, together with the GH/IGF axis (Chiesa et al., 2008; Majumdar and Nielsen, 1985; Robson et al., 2002; Sapolsky et al., 2000; Welberg and Seckl, 2001). However, there is a timeframe specific to particular organs, during which the enhancing effects of glucocorticoids outweigh the possible inhibitory (e.g. atrophy) costs (Miller et al., 2012; Newham and Moss, 2001; Qian, 2012). During later stages of prenatal development, the synthetic activity and proliferation of pituitary GH cells coincides with the rise in glucocorticoid levels in the circulation (Qian, 2012). Glucocorticoid effects on GH synthetic activity persist in postnatal life, where they change the pituitary sensitivity to growth hormone releasing hormone and modulate the negative feedback loop of IGF-1 rather than acting directly on the GH pool (Mazzotti and Giustina, 2013). Glucocorticoids are also able to induce global (in liver) and organ-specific (especially in kidneys, lungs, adrenals, gut) increases in glucocorticoid levels and IGF-1 expression and serum IGF-1 levels (Thakur et al., 2000). Abovementioned studies described the interactions between glucocorticoids and GH/IGF-1 in humans and other mammalian species (e.g. rodents, rabbits), but it has been also described in the chicken (Bossis and Porter, 2003; Zheng et al., 2008). Similar effects could be noted in wild animals. Lodjak et al. (2016) studied wild great tits reared in experimentally manipulated broods. They showed that in high-quality nestlings (high growth rate and better physiological condition) were living in good nutritional conditions, IGF-1 was positively correlated with glucocorticoid levels. This suggests that in good growth conditions there is no profound physiological trade-off between the organism’s energy management (mediated by glucocorticoids) and somatic growth (mediated by IGF-1). This is consistent with the idea that intra-individual variation in glucocorticoid levels is positively related to the metabolic demand of an individual (Jimeno et al., 2018). Interestingly, this is the universal pattern in various life-history trade-offs, with trade-offs only appearing when nutrients are limited (reviewed in Zera and Harshman, 2001). Therefore, in conditions where the energy demand of young animals is either lower or higher, but the needs of an animals are fulfilled, glucocorticoid levels likely facilitate growth and energy allocation, as well as stimulating the release of IGF-1.

In more challenging environments, increasing glucocorticoid levels inhibit energetically costly functions to maintain the energy-balance. Elevated glucocorticoid levels for extended periods during pre- and postnatal development also inhibit GH/IGF-1 axis activity. For example, when rats are prenatally stressed, they show reduced hippocampus and frontal cortex IGF-1 levels reduced IGF-1r phosphorylation levels, and reduced postnatal IRS1 phosphorylation (Basta-Kaim et al., 2014). In chickens and humans under nutrient-limited conditions, persistent high levels of glucocorticoids inhibit the global synthesis of GH and IGF-1 (Bossis and Porter, 2003; Mazzotti and Giustina, 2013; Zheng et al., 2008) and the expression of their receptors across tissues (Jux et al., 1998; Klaus et al., 2000). In adult tilapia (Oreochromis mossambicus), that were reared in fresh water tanks, administration of exogenous cortisol (the main glucocorticoid in fish) induced a decrease of plasma IGF-1 levels and IGF-1 mRNA expression in the liver (Kajimura et al., 2003), suggesting that a decrease in plasma IGF-1 levels is mediated through the attenuation of IGF-1 gene expression. This change can also be mediated by glucocorticoid-induced inhibition of growth hormone or synthesis of its receptor as shown in humans and rats (McCarthy et al., 1990; Unterman et al., 1993). In wild animals, Lodjak et al. (2016) showed that the association between levels of glucocorticoid and IGF-1 was negative in nestlings. These nestlings were still growing but poor nutritional restrictions forced nestlings to selectively allocate resources between physiological functions, such as maintenance activities and somatic growth.

Interestingly, GH, through downstream IGF-1 signalling, can modulate the physiological effects of glucocorticoids, mainly through peripheral metabolism on the levels of 11β-hydroxysteroid dehydrogenases (11βHSDs). 11βHSDs are regulators of glucocorticoid action before their binding to receptors and are abundantly expressed in the adipose tissue, liver, and kidneys (Agba and Monson, 2007; Vitku et al., 2016). There are two types of 11βHSD: 11βHSD1 predominantly converts inactive glucocorticoids to their active forms (e.g. cortisone to cortisol in humans) and 11βHSD2 irreversibly acts the opposite way (Sapolsky et al., 2000). GH/IGF-1 signalling activity inhibits the expression of 11βHSD1 and enhances the expression of 11βHSD2 (Agba and Monson, 2007; Paulsen et al., 2006; Sapolsky et al., 2000; Sigurjonsdottir et al., 2006). This means that the local conversion of glucocorticoids to their active form is decreased and clearance rate of the hormone from the bloodstream is increased when GH/IGF-1 signalling activity increases. However, effects of GH/IGF-1 on different components of peripheral glucocorticoid conversion is time dependent. In human obesity studies, 11βHSD1 was relatively quick to respond to GH treatment with a decrease already after 6 weeks, while 11βHSD2 activity increased after 9 months of treatment (Sigurjoensdottir et al., 2006). Hence, the peripheral interaction between the GH/IGF-1 and glucocorticoid signalling is likely to be regulated to act independently in response to short-term and long-term environmental stochasticity.

Collectively, the interaction between levels of IGF-1 and glucocorticoids is part of a highly flexible physiological mechanism for animals to respond to energy requirement changes in their environments. Both hormones are dependent on the nutritional conditions, and they most likely interact at the levels of synthesis and functioning also in wild animals, and are thereby part of an adaptive mechanism maintaining homeostasis.
Evidence for IGF-1 involvement in telomere dynamics is provided by medical studies on acromegaly and *in vitro* studies with human cells. Patients with acromegaly have excess of GH and IGF-1 which is associated with reduced telomere lengths compared to healthy controls (Matsumoto et al., 2015). Moreover, in subjects with acromegaly, average telomere length correlated negatively with the duration that patients had the illness, suggesting that the duration of elevated levels of GH and IGF-1 was directly related to telomere shortening (Matsumoto et al., 2015). *In vitro* studies with human fibroblasts have shown that IGF-1, but not GH, accelerated the rate of telomere attrition (Matsumoto et al., 2015; Matsumoto and Takahashi, 2016). In contrast, a cross-sectional and correlational study reported a positive association between IGF-1 levels and leukocyte telomere length in the human population of Southern Italy (Campagna region) that was independent of age (Barbieri et al., 2009). Authors noted that in an unpublished parallel study no association between two traits was found in Flemish and Danish cohorts. Interestingly (Kaplan et al., 2009), did report a similar positive relationship between human leukocyte telomere length and IGF-1 levels in a cross-sectional cohort of Americans 65 years and older. Overall, studies seem to indicate that IGF-1 could be a predictor of telomere lengths compared to healthy controls (Matsumoto et al., 2003; Flatt and Heyland, 2011). The IIS pathway in vertebrates may pay these costs both during the early growth period and towards vertebrate life-history evolution.

On the level of telomerase, which lengthens telomeres at early developmental stages and in the male germ line, the interaction between the enzyme and IGF-1 gets even more complex. Firstly, mice without telomerase (Terc−/− knockout) have lower serum IGF-1 and IGFBP3 (main carrier of IGF-1 in the bloodstream) levels and lower tissue expression of IGF-1, IGF-2, IGFBP-5, and IGFBP6 genes compared to wildtype controls (Saged et al., 2015). The absence of functional telomerase impaired self-renewal in several tissues in mice, such as bones, muscles, skin, and intestines, resulting in a smaller body size (Sacco et al., 2010; Saged et al., 2015; Tomas-Loba et al., 2008). In line with these findings, overexpression of telomerase resulted in mice having higher serum IGF-1 levels (Tomas-Loba et al., 2008). Secondly, IGF-1 can directly affect telomere attrition by increasing telomerase activity, making the interaction between IGF-1 and telomerase bi-directional. This was demonstrated by adding IGF-1 to cultured prostate cancer cells, which have active telomerase, which increased telomerase activity, both on the level of mRNA expression and protein synthesis (Wetereau et al., 2003). Similar results have been described for a multiple myeloma cell line (Akiyama et al., 2002). Additionally, when human dermal fibroblasts, where transformed to pluripotent stem cells, addition of IGF-1 increased telomerase activity consistently with findings in cancer cells (Li et al., 2011). Overall, abovementioned studies reach to similar conclusion, whatever the exact mechanism is, the activity of PI3-kinase/Akt signalling – a central cell division pathway (see section 3) – seems to be central in observed IGF-1 effects on telomere dynamics. This could provide us an avenue for studies beyond cell cultures and towards vertebrate life-history evolution.

3.5.2. Effects of IGF-1 on antioxidant enzymes

As animals invest for the benefit of immediate fitness gains in the face of various environmental challenges, for example to survive such challenges, they are bound to endure fitness costs that are paid later (Stearns, 1976). The level of oxidative stress is one way via which animals may pay these costs both during the early growth period and through life (e.g. Alonso-Alvarez et al., 2007). There is evidence from laboratory rodents, e.g. mice and hamsters, that exposure to IGF-1 may modulate the ways in which vertebrates defend themselves against oxidative damage, by regulating the activity of enzymatic antioxidants (Espinoza-Diez et al., 2015; Loboda et al., 2016), possibly through activation of the nuclear factor erythroid 2-related factor (Nrf2)/antioxidant response element (ARE) pathway (Morón and Cal- lifia-Cortázar, 2012).

Higashi et al. (2013) showed that IGF-1 administration reduced low-density lipoprotein induced reactive oxygen species (ROS) production and hydrogen peroxide induced premature cell senescence in human aortic endothelial cells, which was accompanied with increased glutathione peroxidase (Gpx) activity, and unchanged catalase (CAT, degrades hydrogen peroxide) and superoxide dismutase (SOD, catalyses the removal of superoxides O₂⁻) activity. Similar patterns have been shown in rat and human chondrocytes, with IGF-1 inducing a decrease in cellular ROS levels in chondrocytes of humans as well as mature and aged rats but not in chondrocytes of young rats (Jalali et al., 2007). In their experiment, IGF-1 induced a rise in the activity of Gpx, but not in SOD and CAT. Additionally, an in vivo study induced diabetes in rats with streptozotocin, which caused sharp decrease in serum IGF-1 levels, increase in liver damage, spiked liver malondialdehyde levels, which was accompanied with a correlated reduction of Gpx activity (Aksu et al., 2013). With regards to wild vertebrates, Lodjak and Mägi (2017) conducted an IGF-1 injection experiment to accelerate investment into growth and observed elevated Gpx activity in nesting pied flycatchers. Collectively the studies indicate that IGF-1 upregulates Gpx activity, increasing antioxidant defence capacity of an organism, but Gpx is also important for normal cellular growth and proliferation as well as apoptotic and inflammatory processes (Lubos et al., 2011).

Effects of IGF-1 on CAT and SOD activity seem to be more complex than effects on Gpx activity and are important for blood cell formation. It has been shown that increased IGF-1 levels inhibited C2-ceramidase-induced HL-60 cell apoptosis by the inhibition of oxidative damage (Kondo et al., 2002). Through a series of experiments, they noted that antioxidant effects of IGF-1 on HL-60 were mediated primarily by CAT through caspase-3 protein using PI-3 kinase signalling. Interestingly, Tan et al. (2008) revealed that transcription factor Foxo3a (Fisherk family transcription factor) is a compound that can modulate human cardiomyocyte hypertrophy by respectively transcriptionally down-regulating or upregulating catalase activity through modulation of myocardin activity. Myocardin thus has an important role in conveying the hypertrophic signal of IGF-1 (and insulin) on cardiomyocytes (Tan et al., 2008). It is noteworthy that regulating effects of IGF-1 on SOD have been shown to depend on Foxo3a also, but the resulting effect could vary. Adding IGF-1 to rat vascular smooth muscle cells has been shown to increase SOD activity (Li et al., 2006). On the other hand, Yamamoto et al. (2005) showed in vitro and in vivo in mice that klotho protein activated the Foxo3a, among other forkhead transcription factors, that was dependent on klotho protein ability to inhibit IGF-1 signalling. Authors showed that klotho protein binds to its respective cell-surface receptor, which results with the nuclear Foxo transcription factor binding to the SOD promoter and up-regulating SOD expression. Collectively, IGF-1 signalling is an important regulator of enzymatic antioxidant defence response to environmental challenges and notably the physiological interaction uses PI-3 kinase/Foxo pathway, which may partly be the reason why it has risen to the focus of the physiological studies of aging and lifespan across different vertebrate taxa.

4. IGF-1 and longevity

Adaptive physiological modulation of metabolic cascades is one mechanism underlying variation in longevity and the rate of ageing (Barbieri et al., 2003; Flatt and Heyland, 2011). The IIS pathway in particular is a metabolic cascade that is evolutionary well conserved, having been demonstrated in a wide range of vertebrates and invertebrates (Flatt and Heyland, 2011; Holzenberger et al., 2003; Seo et al., 2013). For example, knocking out the GH receptor in mice, making them insensitive to GH and binding protein gene (ghr−/−), which in return substantially decreases circulating IGF-1 levels, increased female lifespan on average 21% and male lifespan 40% (Coschigano et al., 2003). However, it should be kept in mind that the magnitude of the lifespan increase in rodents depends on genetic background. Being insensitive to GH causes Laron syndrome, which has also been described in humans Guevara-Aguirre et al. (2011). Mean lifespan of an Ecuadorian population of Laron dwarfs did not differ from a control group;
however, Laron dwarfs had less diabetes, atherosclerosis, and cancer-related illnesses, but increased mortality due to accidents and alcoholism. Furthermore, Holzenberger et al. (2003) found that heterozygous IGF-1 receptor knockout (igf1r−/−) mice live on average 26% longer than their wild-type siblings and this difference was stronger in females. Results consistent with these examples have been reported on the level of receptor substrates. Deletion of functional IRS1 protein (irs1−/−) extended female mice lifespan by 32%, with no significant change in male mice (Selman et al., 2008). However, deletion of functional IRS2 protein (irs2−/−) decreased the lifespan of mice from both sexes, with the effect size being more profound in males (84%) than females (26%) (Selman et al., 2008). The list of study systems for the link between IIS and longevity is far more extensive than summarised above (Junnila et al., 2013), but point in the same direction. Downregulating the activity of IIS at any particular step appears to extend longevity in mammals, but differently in the sexes. While we do not have any experimental support of lifespan-extending of reduced IIS on reptiles and birds, molecular data indicate that IIS could function in a similar fashion as described in mammals (Hoekstra et al., 2020; McGaugh et al., 2015).

How IGF-1 affects lifespan exactly is not well understood. IGF-1 affects numerous transcription factors (e.g. forkhead box O (FOXO), c-Jun N-terminal kinase (JNK), and heat shock factor 1 (HSF-1)), that link rate of ageing and lifespan to multiple physiological pathways (Greer and Brunet, 2005; Kloe and Burginger, 2011; Seo et al., 2013; Steinkraus et al., 2008). Inhibition of IIS in most of these physiological pathways ends with a similar, if not the same, result – decreased energetic investment into growth and reproduction and an increase of lifespan. Reduced IIS causes cells to become more resistant to different sources of stress (e.g. oxidative damage, proteotoxicity) by causing animals to invest more into self-sustainability to survive unfavourable conditions until the environment improves (Flatt and Heyland, 2011). Studies on the naked mole-rats (Heterocephalus glaber) – longest living rodent with negligible senescence – have shown that reduction of IIS needs to happen on several levels for lifespan to be extended (Brohuis et al., 2015). These involve IGF-1 levels, IGFBP levels, respective receptor densities, and activities of IGFBP proteases. However, it is not clear if the observed increase in longevity is due to slowing down of the entire ontogenetic period or if animals extend or postpone the period of senescence.

Interestingly, GH transgenic rainbow trout have short lifespans outside controlled environments, especially in habitats with fluctuating food availability (Devlin et al., 2001). This raises questions about the possible role of IIS downregulation in the evolution of vertebrate lifespan under natural conditions. In this respect there are considerable caps in our knowledge, since we are not aware of any experimental studies on wild animals that have tested the causality between lifespan and IGFI. There are however two comparative studies of mammals (Swanson and Dantzer, 2014) and passerine bird species (Lodjak et al., 2018) that used plasma IGF-1 levels as a proxy for IIS activity. These studies showed very similar patterns in birds and mammals, with fast life-histories being associated with high IGF-1 plasma concentrations, consistent with the results discussed above from laboratory studies.

Therefore, it could be expected that how IIS is associated with lifespan or aging in free-living vertebrates is much more variable than shown in laboratory conditions. This is so, because free-living vertebrates have adapted to wide range of highly variable habitats, where they constantly have to compete for food and other resources. However, to this day we have so little information available in that regard.

5. IGF-1 and reproduction

In the beginning of the breeding season, somatic growth of reproductive organs is needed to produce gametes and hormones, and this process is IGF-1-dependent in both sexes, at least in mammals (Pitetti et al., 2013; Schams et al., 1999). Looking more closely, gonadotropin-releasing hormone (GnRH) is released in pulses from the median eminence, and each GnRH pulse initiates a release of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Subsequently, gonadotropins stimulate the release of sex steroids by the gonads. Stimulatory effects of IGF-1 are required at each of those steps to enable reproductive function, and this process has been characterized well in mammals (Daftary and Gore, 2003, 2005; Giudice, 1992). For example, Baker et al. (1996) showed that female and male mice with a homozygous IGF-1 gene knockout mutation are infertile. Interestingly, the effects of IGF-1 on different components of hypothalamic–pituitary–gonadal (HPG) axis change with age (see also section 3.3), in particular whether an individual has just achieved sexual maturity or is more mature (Daftary and Gore, 2003, 2005; Luckenbach et al., 2010). We have less information on this process in fish (Lin and Ge, 2009; Luckenbach et al., 2010; Weber and Sullivan, 2000), amphibians (David et al., 2000) and birds (Chabrolle et al., 2007; Tosca et al., 2000). There is correlative evidence that IGF-1 levels are elevated throughout gravidity and are positively associated with the total litter weight in reptiles (Guillette et al., 1996; Sparkman et al., 2009). Also, different variants of IGF-1 genes, as well as variation in IGF-1 levels, have been shown to affect egg production in poultry, or variation in the average quality of the eggs, in terms of weight and shell thickness (Hocking et al., 1994; Hui-fang et al., 2008; Nagaraja et al., 2000). In the longitudinal study of free-living spotted hyenas females, higher juvenile levels of IGF-1 were associated with earlier ages at first parturition, and IGF-1 predicted age at first parturition better than did juvenile mass, suggesting that reproduction may be more tightly regulated by internal metabolic signals than by body size (Lewin et al., 2017).

The relation between IGF-1 and reproduction in wild animals has also been studied using a comparative approach (mammals: Swanson and Dantzer, 2014); birds (Lodjak et al., 2018)). Results generally indicate positive associations between IGF-1 levels and reproductive traits, with differences between species in the details. Mammalian species with higher IGF-1 levels had reproduction strategies characterized by more rapid offspring development, smaller offspring average body size, the production of smaller offspring as well as reduced prenatal and postnatal parental investment (Swanson and Dantzer, 2014). Among passerine bird species (Passeriformes), IGF-1 levels were not correlated with clutch size or egg size across all species, but positively with egg size in large species and negatively in small species (Lodjak et al., 2018).

Collectively it can be said that IGF-1 signalling is an important part of physiological regulation of reproduction. Above, we elaborated on that on a mechanistic level and on a broader life-history scale. It should be emphasised however, that the exact mechanisms are still far from being understood. IGF-1 is shown to interact with the hypothalamic–pituitary–gonadal (HPG) axis and modulates each of its three levels. It would be interesting to know if the variation in IGF-1 effects is more intimately tied to the activin-inhibin-follistatin system, which modulate the time-specific maturation and selection process of follicles and ovulation of oocytes (Daftary and Gore, 2005; Findlay, 1993) or to nutritional (see paragraph 3.2) and stress response cascades (see paragraphs 3.5 and 4) to shape the reproductive phenotype of an animal. However, experimental evidence across life-history contexts is needed to develop a clearer view on how and to what degree IGF-1 mediates reproductive investment of individual animals.

6. Conclusion

Summarising the available evidence, it seems plausible that IGF-1 represents a physiological link underlying life-history variation associated with growth patterns, body sizes, and reproductive schedules. We have to emphasize however that other components of IIS, such as IGF-2, insulin, and IGFBPs, are intimately associated with the described effects of IGF-1. Generally, available studies indicate that at the inter- and intraspecific levels, IGF-1 seems to be associated with an increased investment into building up the body and reproduction across a range of
life-history strategies. However, we seem to know more about the variation of IGF-1 between species than we know about the variation within species in the wild. Interestingly, IGF-1 seems to increase an individual’s investment into reproduction and growth likely at the expense of survival. Such a robust model seems to hold in the case of wild vertebrates and laboratory systems. However, laboratory studies have vividly shown how complex IGF-1 signalling truly is and in this regard future studies should aim to experimentally describe these fascinating phenomena in the context of evolutionary ecology.

Acknowledgements

We thank three anonymous referees for their invaluable suggestions to improve the manuscript. J.L. was financially supported by the Estonian Research Council (PUT17 700), and the Estonian Ministry of Education and Research (IUT 34–8).

References

Agha, A., Monpon, J.P., 2007. Modulation of glucocorticoid metabolism by the growth hormone – IGF-1 axis. Clin. Endocrinol. 66, 459–465. https://doi.org/10.1111/j.1365-2222.2007.02763.x.

Aguzamho, G.D., Sifakis, M., Courcios, E.S., Konstantinidou, A.E., 2014. Insulin-like growth factors in embryonic and fetal growth and skeletal development (Review). Mol. Med. Rep. 10, 579–584. https://doi.org/10.3892/mmr.2014.2258.

Akiyama, M., Hidemasa, T., Hayashi, T., Taisi, Y.T., Minita, C.S., Minita, N., Chaban, D., Richner, P.N., McNicholas, K.C., 2002. Cytokine modulate telomerase activity in a human myeloma cell line. Canc. Res. 62, 3876–3882.

Akou, I., Baykara, B., Kiray, M., Guppar, T., Sisman, A.R., Ekerbicer, N., Tas, A., Sokolmen-Yazar, D., Uysal, N., 2013. Serum IGF-1 levels correlate negatively to liver damage in diabetic rats. Biotech. Histochem. 88, 194–201. https://doi.org/10.3109/13123860903392831.

Allard, J.B., Duan, C., 2018. IGF-binding proteins: why do they exist and why are there so many? Front. Endocrinol. 9 https://doi.org/10.3389/fendo.2018.00117.

Amorim e Costa, A., Bertrand, F., Faivre, B., Soric, G., 2007. Increased susceptibility to oxidative damage as a cost of accelerated somatic growth in zebra finches. Funct. Ecol. 21, 873–879. https://doi.org/10.1111/j.1365-2435.2007.01300.x.

Anwer, S., Kock, A.T., Knoll, C., 2003. PPARα: a thristry transcription factor. Nucl. Recept. Signal. 1, 10.2337/db16-0212.

Baker, J., Hardy, M.P., Zhou, J., Bondy, C., Lupu, F., Bellve, A.R., Briga, M., Verhulst, S., 2015. What can long-lived mutants tell us about mechanisms causing aging and lifespan variation in natural environments? Exp. Gerontol. 71, 20133287. https://doi.org/10.1016/j.exger.2015.09.002.

Beckman, B.R., 2011. Perspectives on concordant and discordant relations between insulin-like growth factor 1 (IGF-I) and growth in fishes. Gen. Comp. Endocrinol. 170, 233–252. https://doi.org/10.1016/j.ygcend.2010.08.002.

Bergan-Roller, H.E., Sheridan, M.A., 2018. The growth hormone signaling system: insights into coordinating the anabolic and catabolic actions of growth hormone. Gen. Comp. Endocrinol. 258, 119–133. https://doi.org/10.1016/j.ygcend.2017.07.028.

Blackburn, E.H., 1991. Structure and function of telomeres. Nature 350, 569–573.

Blüher, M., Kahn, B.B., Kahn, C.R., 2003. Extended longevity in mice lacking the insulin receptor in adipose tissue. Science 299, 572–574. https://doi.org/10.1126/science.1087221.

Bondy, C.A., Cheng, C.M., 2004. Signaling by insulin-like growth factor 1 in brain. Eur. J. Pharmacol. 490, 25–31. https://doi.org/10.1016/j.ejphar.2004.02.042.

Bouyer, P., Martin, P.R., Moore, I.T., Wingfield, J.C., 2009. Do baseline glucocorticoids predict fitness? Trends Ecol. Evol. 24, 634–642. https://doi.org/10.1016/j.tree.2009.04.013.

Bonkowski, M.S., Dominici, F.P., Arru, O., Rocha, J.S., Al Regaiey, K.A., Westbrook, R., Spone, G., Panici, J., Materasak, M.M., Kopchick, J.J., Barke, A., 2009. Disruption of growth hormone receptor prevents calorie restriction from improving insulin action and longevity. PLoS One 4, e5467. https://doi.org/10.1371/journal.pone.0005467.

Booij, J.J., Mulder, G.A., Salomons, H.M., Dijkstra, C., Verhulst, S., 2014. Nestling telomerene shortening, but not telomere length, reflects developmental stress and predicts survival in wild birds. Proc. R. Soc. Biol. Sci. B 281 (20133287). https://doi.org/10.1098/rspb.2013.3287.

Bossuyt, W.M., Porter, T.E., 2003. Evaluation of glucocorticoid-induced growth hormone gene expression in chicken embryonic pituitary cells using a novel in situ mRNA quantitation method. Mol. Cell. Endocrinol. 211, 1–23. https://doi.org/10.1016/j.ygcend.2003.06.009.

Boucher, J., Sefcic, S., El Ouazzami, A., Krumphoc, M.T., Kleinrieder, A., Kulkarni, R.N., O’Neill, B.T., Kahn, C.R., 2016. Differential roles of insulin and IGF-1 receptors in adipose tissue development and function. Diabetes 65, 2201–2213. https://doi.org/10.2337/db15-0968.

Bower, N.I., Li, X., Taylor, R., Johnston, I.A., 2008. Switching to fast growth: the insulin-like growth factor (IGF) system in skeletal muscle of Atlantic salmon. J. Exp. Biol. 211, 3859–3870. https://doi.org/10.1242/jeb.021417.

Bra, T.P., Marks, D.L., 2015. The regulation of muscle mass by endogenous glucocorticoids. Front. Physiol. 6, 573. https://doi.org/10.3389/fphys.2015.00512.

Breier, B.H., 1999. Regulation of protein and energy metabolism by the somatotropic axis. Domest. Anim. Endocrinol. 17, 209–218. https://doi.org/10.1016/S0739-7240(99)00038-7.

Brim, I., Matus, I., Koir, A., 2013. Longevity and growth hormone and the insulin-like growth hormone receptors have related and independent roles. Annu. Rev. Physiol. 63, 141–164. https://doi.org/10.1146/annurev.physiol.63.114111.100526.

Briga, M., Verhulst, S., 2015. What can long-lived mutants tell us about mechanisms causing aging and lifespan variation in natural environments? Exp. Gerontol. 71, 21–26. https://doi.org/10.1016/j.exger.2015.09.002.

Butler, A.A., Le Roith, D., 2001. Control of growth by the somatotropic axis: growth hormone and somatomedins. Endocrine Rev. 22, 1137–145. https://doi.org/10.1210/er.22.9.1137.

Chan, S.W.L., Blackburn, E.H., 2002. New ways not to make ends meet: telomerase, DNA repair, and aging. Cell 110, 571–573. https://doi.org/10.1016/S0092-8674(02)01167-7.

Chesnokov, A., Martin, P.R., Moore, I.T., Wingfield, J.C., 2009. Do baseline glucocorticoids predict fitness? Trends Ecol. Evol. 24, 634–642. https://doi.org/10.1016/j.tree.2009.04.013.

Chiesa, C., Osborn, J.F., Haass, C., Natale, F., Spinelli, M., Scapigliati, E., Spinelli, A., Pacifiels, L., 2008. Ghrelin, leptin, IGF-I, IGFBP-3, and insulin concentrations in bears: is there a relationship between growth and stress in hibernating bears? Clin. Chem. 54, 550–558. https://doi.org/10.1373/clinchem.2007.095299.

Conover, C.A., Lee, P.D., Rigs, B.L., Powell, D.R., 1996. Insulin-like growth factor-binding protein-1 expression in cultured human bone cells: regulation by insulin and glucocorticoid. Endocrinology 137, 3295–3301. https://doi.org/10.1210/endo.137.7.83295.
Dmitriew, C.M., 2011. The evolution of growth trajectories: what limits growth rate?

Espinosa-Diez, C., Miguel, V., Mennerich, D., Kietzmann, T., Estívariz, C.F., Ziegler, T.R., 1997. Nutrition and the insulin-like growth factor system.

David, I., Bosshard, R., Kloas, W., Reinecke, M., 2000. Insulin-like growth factor I in the breeding season. Comp. Biochem. Physiol. Mol. Integr. Physiol. 129, 887-895.

David, I., Bang, P., Hertel, N.T., Main, K., Dalgaard, P., Jorgensen, K., Muller, J., Hall, K., Juul, A., Holm, K., Kastrup, K.W., Pedersen, S.A., Michaelsen, K.F., Scheike, T., 2007. Modulation of the insulin-like growth factor-1 axis in ageing and longevity. Nat. Rev. Endocrinol. 9, 366. https://doi.org/10.1038/nrendo.2013.176.

Espinoza-Diez, C., Miguel, V., Mennerich, D., Kietzmann, T., Sanchez-Perez, P., Cadena, S., Lamas, S., 2015. Antioxidant responses and cellular adjustments to oxidative stress. Redox Biol. 6, 183–197. https://doi.org/10.1016/j.redox.2015.07.008.

Estivarell, C.F., Ziegler, T.R., 1997. Nutrition and the insulin-like growth factor system. Endocrine 7, 65–71.

Hack, N.L., Strobel, J.S., Journey, M.L., Beckman, B.R., Lema, S.C., 2018. Response of the insulin-like growth factor-1 (IGF-1) system to nutritional status and growth rate variation in olive rockfish (Sebastes planeus). Comp. Biochem. Physiol. Mol. Integr. Physiol. 224, 42–52. https://doi.org/10.1016/j.cbpa.2018.05.025.

Hamza, R.T., Hamed, A.I., Sallam, M.T., 2012. Effect of zinc supplementation on growth hormone-insulin growth factor axis in short Egyptian children with zinc deficiency. J. Endocrinol. Investig. 35, 699–705. https://doi.org/10.1007/s40618-012-0031-9.

Hanke, S., Mann, M., 2009. The phosphotyrosine interactome of the insulin receptor family and its substrates IRS-1 and IRS-2. Mol. Cell. Proteomics. 8, 519–534. https://doi.org/10.1074/mcp.M800040-MCP200.

Haus, M., Rickles, B.E., Wikel, M., Lee, K.A., Brawn, J.D., 2010. Corticosterone, testosterone and life-history strategies of birds. Proc. Roy. Soc. Biol. Sci. B 277, 2303–2312. https://doi.org/10.1098/rspb.2010.0673.

Higashi, Y., Pandey, A., Goodwin, B., Delafontaine, P., 2013. Insulin-like growth factor-1 regulates glutathione peroxidase expression and activity in vascular endothelial cells: implications for atheroprotective actions of insulin-like growth factor-1. Biochim. Biophys. Acta 1823, 391–399. https://doi.org/10.1016/j.bbadis.2012.12.005.

Ho, K.Y., Veldhuis, J.D., Johnson, M.L., Furlanetto, R., Evans, W.S., Alberti, K.G.M.M., Thorner, M.O., 1988. Fasting enhances growth hormone secretion and amplifies the complex rhythms of growth hormone secretion in man. J. Clin. Invest. 81, 968–975. https://doi.org/10.1172/jci113150.

Hocking, P., Bernard, R., Wilkie, R., Goddard, C., 1994. Plasma growth hormone and insulin-like growth factor-I (IGF-I) concentrations at the onset of lay in ad libitum and restricted broiler breeder fowl. Br. Poultry Sci. 35, 299–308. https://doi.org/10.1080/00071669408417694.

Hoeijkstra, L.A., Schwartz, T.S., Sparkman, A.M., Miller, D.A.W., Bronskowski, A.M., 2020. The untapped potential of reptile biodiversity for understanding how and why animals age. Funct. Ecol. 34, 38–54. https://doi.org/10.1111/1365-2435.13450.

Holzaepfel, M., Lenewe, J., Dupont, J.-L., Sampedro, G., Bolzman, A., Ewen, P.C., Cervera, P., Le Bour, Y., 2003. IGF-I receptor regulates lifespan and resistance to oxidative stress in mice. Nature 421, 182–187. https://doi.org/10.1038/nature01298.

Hui, J., Chen, S., Wang, C., Huang, S., 2008. Associations between GHR and IGF-1 gene polymorphisms, and reproductive traits in wenchang chickens. Turk. J. Vet. Anim. Sci. 32, 281–285. https://doi.org/10.3906/vet-0712-40.

Hvass, M.K.H., Nielsen, P., Christensen, J., Hjort, N., Christensen, L.J., 2010. Glucocorticoid-induced myopathy: pathophysiology, diagnosis, and treatment. Indian J. Endocrinol. Metab 17, 913–916. https://doi.org/10.4103/2220-8216.117215.

Juul, A., Bang, P., Hertel, N.T., Main, K., Dalgaard, P., Jorgensen, K., Muller, J., Hall, K., Juul, A., Holm, K., Kastrup, K.W., Pedersen, S.A., Michaelsen, K.F., Scheike, T., 2007. Modulation of the insulin-like growth factor-1 axis in ageing and longevity. Nat. Rev. Endocrinol. 9, 366. https://doi.org/10.1038/nrendo.2013.176.
suspected of growth hormone deficiency. J. Clin. Endocrinol. Metab. 82, 2497–2502. https://doi.org/10.1210/jcem.82.8.4127.

Juc, C., Leiber, K., Hügel, U., Blum, W., Oldston, C., Klaus, G., Mehlis, O., 1998. Dexamethasone impairs growth hormone (GH)-stimulated growth by suppression of local insulin-like growth factor (IGF-I) production and expression of GH- and IGF-I-receptor in cultured rat chondrocytes. Endocrinology 139, 3296–3305. https://doi.org/10.1210/endo.139.6.3296.

Kaiya, H., Kangawa, K., Miyazato, M., 2013. What is the general action of ghrelin for vertebrates? – comparisons of ghrelin’s effects across vertebrates. Gen. Comp. Endocrinol. 181, 187–194. https://doi.org/10.1016/j.gene.2012.10.015.

Kajimura, S., Hirano, T., Visitacion, N., Moriyama, S., Aida, K., Grau, E., 2013. What is the general action of ghrelin for vertebrates? – comparisons of ghrelin’s effects across vertebrates. Gen. Comp. Endocrinol. 181, 187–194.

Kanbur-Oksuz, N., Derman, O., Kinik, E., 2004. Correlation of sex steroids with IGF-1 and IGFBP-3 during different pubertal stages. Turk. J. Pediatr. 46, 315–321. https://doi.org/10.3906/geri-0309-5.

Kaplan, R.C., Fitzpatrick, A.L., Pollak, M.N., Gardner, J.P., Jenny, N.S., McGinn, A.P., 2004. Exposure of growth plate chondrocytes to corticosteroids. Pediatr. Res. 55, 105–110. https://doi.org/10.1203/01.bpr.0000008858.80421.8f.

Klaus, G., Jux, C., Fernandez, P., Rodriguez, J., Himmele, R., Mehls, O., 2000. Regulation of pituitary GnRH receptor in cultured rat chondrocytes. Endocrinology 141, 2350–2358. https://doi.org/10.1210/endo.141.4.692.

Kajimura, S., Hirano, T., Visitacion, N., Moriyama, S., Aida, K., Grau, E., 2013. What is the general action of ghrelin for vertebrates? – comparisons of ghrelin’s effects across vertebrates. Gen. Comp. Endocrinol. 181, 187–194.

Kanbur-Oksuz, N., Derman, O., Kinik, E., 2004. Correlation of sex steroids with IGF-1 and IGFBP-3 during different pubertal stages. Turk. J. Pediatr. 46, 315–321. https://doi.org/10.3906/geri-0309-5.

Kaplan, R.C., Fitzpatrick, A.L., Pollak, M.N., Gardner, J.P., Jenny, N.S., McGinn, A.P., 2004. Exposure of growth plate chondrocytes to corticosteroids. Pediatr. Res. 55, 105–110. https://doi.org/10.1203/01.bpr.0000008858.80421.8f.

Klaus, G., Jux, C., Fernandez, P., Rodriguez, J., Himmele, R., Mehls, O., 2000. Regulation of pituitary GnRH receptor in cultured rat chondrocytes. Endocrinology 141, 2350–2358. https://doi.org/10.1210/endo.141.4.692.

Kajimura, S., Hirano, T., Visitacion, N., Moriyama, S., Aida, K., Grau, E., 2013. What is the general action of ghrelin for vertebrates? – comparisons of ghrelin’s effects across vertebrates. Gen. Comp. Endocrinol. 181, 187–194.

Kanbur-Oksuz, N., Derman, O., Kinik, E., 2004. Correlation of sex steroids with IGF-1 and IGFBP-3 during different pubertal stages. Turk. J. Pediatr. 46, 315–321. https://doi.org/10.3906/geri-0309-5.

Kaplan, R.C., Fitzpatrick, A.L., Pollak, M.N., Gardner, J.P., Jenny, N.S., McGinn, A.P., 2004. Exposure of growth plate chondrocytes to corticosteroids. Pediatr. Res. 55, 105–110. https://doi.org/10.1203/01.bpr.0000008858.80421.8f.

Klaus, G., Jux, C., Fernandez, P., Rodriguez, J., Himmele, R., Mehls, O., 2000. Regulation of pituitary GnRH receptor in cultured rat chondrocytes. Endocrinology 141, 2350–2358. https://doi.org/10.1210/endo.141.4.692.

Kajimura, S., Hirano, T., Visitacion, N., Moriyama, S., Aida, K., Grau, E., 2013. What is the general action of ghrelin for vertebrates? – comparisons of ghrelin’s effects across vertebrates. Gen. Comp. Endocrinol. 181, 187–194.
Ross, R.J., Buchanan, C.R., 1990. Growth hormone secretion: its regulation and the influence of nutritional factors. Nutr. Res. 3, 143–162. https://doi.org/10.1210/jcem.50.7.1539.

Sacco, A., Mourniokitis, F., Tran, R., Choi, J., Llewellyn, M., Kraft, P., Shkrelli, M., Delp, S., Pomerantz, J.H., Artandi, S.E., Blau, H.M., 2010. Short telomeres and stem cell exhaustion model Duchenne muscular dystrophy in mdx/ntr mice. Cell 143, 226–239. https://doi.org/10.1016/j.cell.2010.09.011.

Saeed, H., Qiu, W., Li, C., Flybjerg, A., Abdallah, B.M., Kassem, M., 2015. Telomerase activity promotes osteoblast differentiation by modulating bitglf-signaling pathway. Biogerontology 16, 733–745. https://doi.org/10.1007/s10522-015-9562-2.

Sapolsky, R.M., Romero, L.M., Munch, A.U., 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, and stimulatory actions. Endocrinol. Rev. 21, 55–89. https://doi.org/10.1210/edrv.21.1.0389.

Scacchi, F., Finch, A.J., Cavagnaro, F., 2006. Functional growth hormone (GH) receptors and GH are expressed by preimplantation mouse embryos: a role for GH in early embryogenesis? Proc. Natl. Acad. Sci. U. S. A. 94, 5125–5130.

Polleri, A., 1998. Relationship between cognitive function, growth hormone and thyroxine in young adult females. J. Endocrinol. 159, 137–144. https://doi.org/10.1677/joe.0.159.137.

Polleri, A., 2000. Insulin-like growth factor-I promotes myogenesis by glucocorticoid and IGF-I signaling. J. Appl. Physiol. 114, 1329–1336. https://doi.org/10.1152/jappl.00363.2000.

Ponser, N.A., Langen, R.C., Wouters, E.F., Scholz, A.M., 2013. Synergistic stimulation of myogenesis by glucocorticoid and IGF-I-signaling. J. Appl. Physiol. 115, 1239–1247. https://doi.org/10.1152/japplphysiol.00373.2013.

Ponser, N.A., Langen, R.C., Wouters, E.F., Scholz, A.M., 2013. The role of insulin-like growth factor-I. Endocrinol. Rev. 34, 3059–3066. https://doi.org/10.1210/edrv.2014-0009.

Poulsen, S.K., Pedersen, S.B., Jørgensen, J.O.L., Fisker, S., Christiansen, J.S., Flyvbjerg, A., Richelsen, B., 2006. Growth hormone (GH) substitution in GH-depleted patients with GH-hypothalamic deficiency: relationship to ghrelin and plasma insulin-like growth factor-I, glucocorticoids, and thyroid hormones during skeletal growth. Pediatr. Res. 52, 158–165. https://doi.org/10.1210/endo.2003.12.023.

Poulsen, S.K., Pedersen, S.B., Jørgensen, J.O.L., Fisker, S., Christiansen, J.S., Flyvbjerg, A., Richelsen, B., 2006. Growth hormone (GH) substitution in GH-depleted patients with GH-hypothalamic deficiency: relationship to ghrelin and plasma insulin-like growth factor-I, glucocorticoids, and thyroid hormones during skeletal growth. Pediatr. Res. 52, 158–165. https://doi.org/10.1210/endo.2003.12.023.

Poulsen, S.K., Pedersen, S.B., Jørgensen, J.O.L., Fisker, S., Christiansen, J.S., Flyvbjerg, A., Richelsen, B., 2006. Growth hormone (GH) substitution in GH-depleted patients with GH-hypothalamic deficiency: relationship to ghrelin and plasma insulin-like growth factor-I, glucocorticoids, and thyroid hormones during skeletal growth. Pediatr. Res. 52, 158–165. https://doi.org/10.1210/endo.2003.12.023.

Poulsen, S.K., Pedersen, S.B., Jørgensen, J.O.L., Fisker, S., Christiansen, J.S., Flyvbjerg, A., Richelsen, B., 2006. Growth hormone (GH) substitution in GH-depleted patients with GH-hypothalamic deficiency: relationship to ghrelin and plasma insulin-like growth factor-I, glucocorticoids, and thyroid hormones during skeletal growth. Pediatr. Res. 52, 158–165. https://doi.org/10.1210/endo.2003.12.023.

Poulsen, S.K., Pedersen, S.B., Jørgensen, J.O.L., Fisker, S., Christiansen, J.S., Flyvbjerg, A., Richelsen, B., 2006. Growth hormone (GH) substitution in GH-depleted patients with GH-hypothalamic deficiency: relationship to ghrelin and plasma insulin-like growth factor-I, glucocorticoids, and thyroid hormones during skeletal growth. Pediatr. Res. 52, 158–165. https://doi.org/10.1210/endo.2003.12.023.

Poulsen, S.K., Pedersen, S.B., Jørgensen, J.O.L., Fisker, S., Christiansen, J.S., Flyvbjerg, A., Richelsen, B., 2006. Growth hormone (GH) substitution in GH-depleted patients with GH-hypothalamic deficiency: relationship to ghrelin and plasma insulin-like growth factor-I, glucocorticoids, and thyroid hormones during skeletal growth. Pediatr. Res. 52, 158–165. https://doi.org/10.1210/endo.2003.12.023.

Poulsen, S.K., Pedersen, S.B., Jørgensen, J.O.L., Fisker, S., Christiansen, J.S., Flyvbjerg, A., Richelsen, B., 2006. Growth hormone (GH) substitution in GH-depleted patients with GH-hypothalamic deficiency: relationship to ghrelin and plasma insulin-like growth factor-I, glucocorticoids, and thyroid hormones during skeletal growth. Pediatr. Res. 52, 158–165. https://doi.org/10.1210/endo.2003.12.023.
Weber, G.M., Sullivan, C.V., 2000. Effects of insulin-like growth factor-I on in vitro final oocyte maturation and ovarian steroidogenesis in striped bass, Morone saxatilis. Biol. Reprod. 63, 1049–1057. https://doi.org/10.1095/biolreprod63.4.1049.

Weber, G.M., Sullivan, C.V., 2000. Effects of insulin-like growth factor-I on in vitro final oocyte maturation and ovarian steroidogenesis in striped bass, Morone saxatilis. Biol. Reprod. 63, 1049–1057. https://doi.org/10.1095/biolreprod63.4.1049.

Welberg, L.A.M., Seckl, J.R., 2001. Prenatal stress, glucocorticoids and the programming of the brain. J. Neuroendocrinol. 13, 113–128. https://doi.org/10.1111/j.1365- 2620.2001.00601.x.

Wetterau, L.A., Francis, M.J., Ma, L., Cohen, P., 2003. Insulin-like growth factor I stimulates telomerase activity in prostate cancer cells. J. Clin. Endocrinol. Metab. 88, 3354–3359. https://doi.org/10.1210/jc.2002-021326.

Wheatcroft, S.B., Kearney, M.T., 2009. IGf-dependent and IGf-independent actions of IGF-binding protein-1 and -2: implications for metabolic homeostasis. Trends Endocrinol. Metab 20, 153–162. https://doi.org/10.1016/j.tem.2009.01.002.

Wilkinson, R.J., Porter, M., Woolcott, H., Longland, R., Carragher, J.F., 2006. Effects of aquaculture related stressors and nutritional restriction on circulating growth factors (GH, IGF-I and IGF-II) in Atlantic salmon and rainbow trout. Comp. Biochem. Physiol. Mol. Integr. Physiol. 145, 214–224. https://doi.org/10.1016/j.cbpa.2006.06.010.

Wood, A.W., Duan, C., Bern, H.A., 2009. IGF-dependent and IGF-independent actions of insulin-like growth factor I gene deletion causing intrauterine growth retardation and severe short stature. Acta Paediatr. 86, 39–45. https://doi.org/10.1111/j.1651-2227.1997. tb18367.x.

Wrigley, S., Arafah, D., Tropea, D., 2017. Insulin-like growth factor I: at the crossroads of brain development and aging. Front. Cell. Neurosci. 11 https://doi.org/10.3389/fncel.2017.00014.

Yakar, S., Liu, J.-L., Fernandez, A.M., Wu, Y., Schally, A.V., Frystyk, J., Chernausek, S.D., Mejia, W., Le Roith, D., 2001. Liver-specific igf-1 gene deletion leads to muscle insulin insensitivity. Diabetes 50, 1110–1118. https://doi.org/10.2337/ diabetes.50.5.1110.

Yakar, S., Rosen, C.J., Beamer, W.G., Ackert-Bicknell, C.L., Wu, Y., Liu, J.-L., Ooi, G.T., Seters, J., Frystyk, J., Boitot, P.K., LeRoith, D., 2002. Circulating levels of IGF-I directly regulate bone growth and density. J. Clin. Invest. 110, 771–781. https://doi.org/10.1172/JCI00215463.

Yamamoto, M., Clark, J.D., Pastor, J.V., Gurnani, P., Nandi, A., Kurosu, H., Miyoshi, M., Ogawa, Y., Castrillon, D.H., Rosenblatt, K.P., Kuro-o, M., 2005. Regulation of oxidative stress by the anti-aging hormone Klotho. J. Biol. Chem. 280, 38829–38834. https://doi.org/10.1074/jbc.M509039200.

Yin, H.N., Chai, J.K., Yu, Y.M., Shen, C.A., Wu, Y.Q., Yao, Y.M., Liu, H., Liang, L.M., Tompkins, R.G., Sheng, Z.Y., 2009. Regulation of signaling pathways downstream of IGF-I/insulin by androgen in skeletal muscle of glucocorticoid-treated rats. J. Trauma 66, 1083–1090. https://doi.org/10.1097/TJR.0b013e31817e7420.

Yuan, R., Meng, Q., Nautiyal, J., Flurkey, K., Tsaih, S.-W., Krier, R., Parker, M.G., Harrison, D.E., Paigen, B., 2012. Genetic coregulation of age of female sexual maturity and lifespan through circulating IGF1 among inbred mouse strains. Proc. Natl. Acad. Sci. USA 109, 8224–8229. https://doi.org/10.1073/pnas.1121113109.

Zera, A.J., Harshman, L.G., 2001. The physiology of life history trade-offs in animals. Annu. Rev. Ecol. Syst. 32, 95–126. https://doi.org/10.1146/annurev.ecolsys.32.111800.114406.

Zheng, J., Takagi, H., Tsutsui, C., Adachi, A., Sakai, T., 2008. Hypophyseal corticosteroids stimulate somatotrope differentiation in the embryonic chicken pituitary gland. Histochem. Cell Biol. 129, 357–365. https://doi.org/10.1007/s00418-007-0364-9.