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

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ABSTRACT

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 key 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 (Junnila et al., 2013). These two peptides respectively stimulate and inhibit the release of growth hormone (GH) from the pituitary

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Table 1

Estimated levels of knowledge that exists in IGF-1 effects on three major life-history components: growth, reproduction and longevity. Level of knowledge has been estimated for mammals, birds, reptiles, amphibians and fish separately in laboratory/captivity and wild systems. Estimations have been done in the scale of 'absent', 'low', 'medium', and 'high' and should be read as ball-park estimates to give a general impression of the state of knowledge. Level 'absent' denotes that there is no experimental or correlational information. Level 'high' denotes that there is relatively strong support for IGF-1 effects, but does not imply that the mechanism mediating the IGF-1 effect is well understood.

	Life-history trait	Study system	Level of knowledge
Mammals	Growth	Lab/captivity	High
		Wild	Low
	Reproduction	Lab/captivity	High
		Wild	Low
	Longevity	Lab/captivity	High
		Wild	Low
Birds	Growth	Lab/captivity	Medium
		Wild	Low
	Reproduction	Lab/captivity	Low
		Wild	Low
	Longevity	Lab/captivity	Absent
		Wild	Low
Reptiles	Growth	Lab/captivity	Medium
		Wild	Low
	Reproduction	Lab/captivity	Low
		Wild	Low
	Longevity	Lab/captivity	Absent
		Wild	Absent
Amphibians	Growth	Lab/captivity	Low
		Wild	Absent
	Reproduction	Lab/captivity	Low
		Wild	Absent
	Longevity	Lab/captivity	Absent
		Wild	Absent
Fish	Growth	Lab/captivity	Medium
		Wild	Low
	Reproduction	Lab/captivity	Low
		Wild	Low
	Longevity	Lab/captivity	Low
		Wild	Absent

(Junnila et al., 2013). Increased GH levels promote RNA and protein synthesis for physiological processes ranging from metabolism to development (Bergan-Roller and Sheridan, 2018). Furthermore, when secreted into the blood circulation, GH induces and modulates IGF-1 release by the liver (Yakar et al., 2001). In return, IGF-1 mediates much of the growth effect attributed to GH's growth promoting functions (reviewed in section 3). However, even IGF-1's influences on growth are also modifiable by other hormones including ghrelin, leptin, and insulin, which levels vary with nutritional state to modulate the physiological functions induced by IGF-1 (Cassy et al., 2003; Inui, 2001; Laron, 2001). IGF-1 has also been associated with variety of longevity-regulating (see section 4) and reproduction-modulating effects (see section 5). In addition to IGF-1 released by the liver, IGF-1 can also be synthesised locally (autocrine/paracrine factor) in most tissues, and its functions are believed to be very similar (Bondy and Cheng, 2004; Lupu et al., 2001; Stratikopoulos et al., 2008). For example, locally produced IGF-1 levels drop after birth in humans, but remain physiologically significant in several functions including neurogenesis, where they can act in combination with circulating IGF-1 that is able to cross blood-brain barrier (Fernandez and Torres-Alemán, 2012).

The signalling pathway and regulation of IGF-1 is relatively well characterized in mammals and fish, and appears evolutionarily conserved among vertebrates (Hwa et al., 1999; Nakae et al., 2001; Rajaram et al., 1997; Wood et al., 2005). IGF signalling is primarily a three-ligand system, including IGF-1, IGF-2, and insulin. IGFs are transported to cells and their availability to receptors is modulated by IGF-binding proteins (IGFBP). Physiological effects of IGF-1 are mediated by ligand specific cell surface receptors (Daza et al., 2011; 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 (Mazerbourg 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 (Mazerbourg 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/Ir/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 (Bartke, 2008; Blüher et al., 2003; Bonkowski et al., 2009; Brüning et al., 2000; 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; Schlueter 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 (Garcia-Aragon 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 (Velegrakis et al., 2017). In contrast to GH, IGF-1 nullizygous (−/−) 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; Schlueter 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 be 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 nestling 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 serranoides*) 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 (Hack 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,* (Suttie et al., 1985); roe deer *Capreolus capreolus*, (Schams 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 nestling 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 nestling 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 IGF-1 (Guler et al., 1988; Lupu et al., 2001) (Guler et al., 1988; 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 break down 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 (Estívariz 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 (Estívariz and Ziegler, 1997; Flatt 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 (Brüning et al., 2000; Estívariz 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
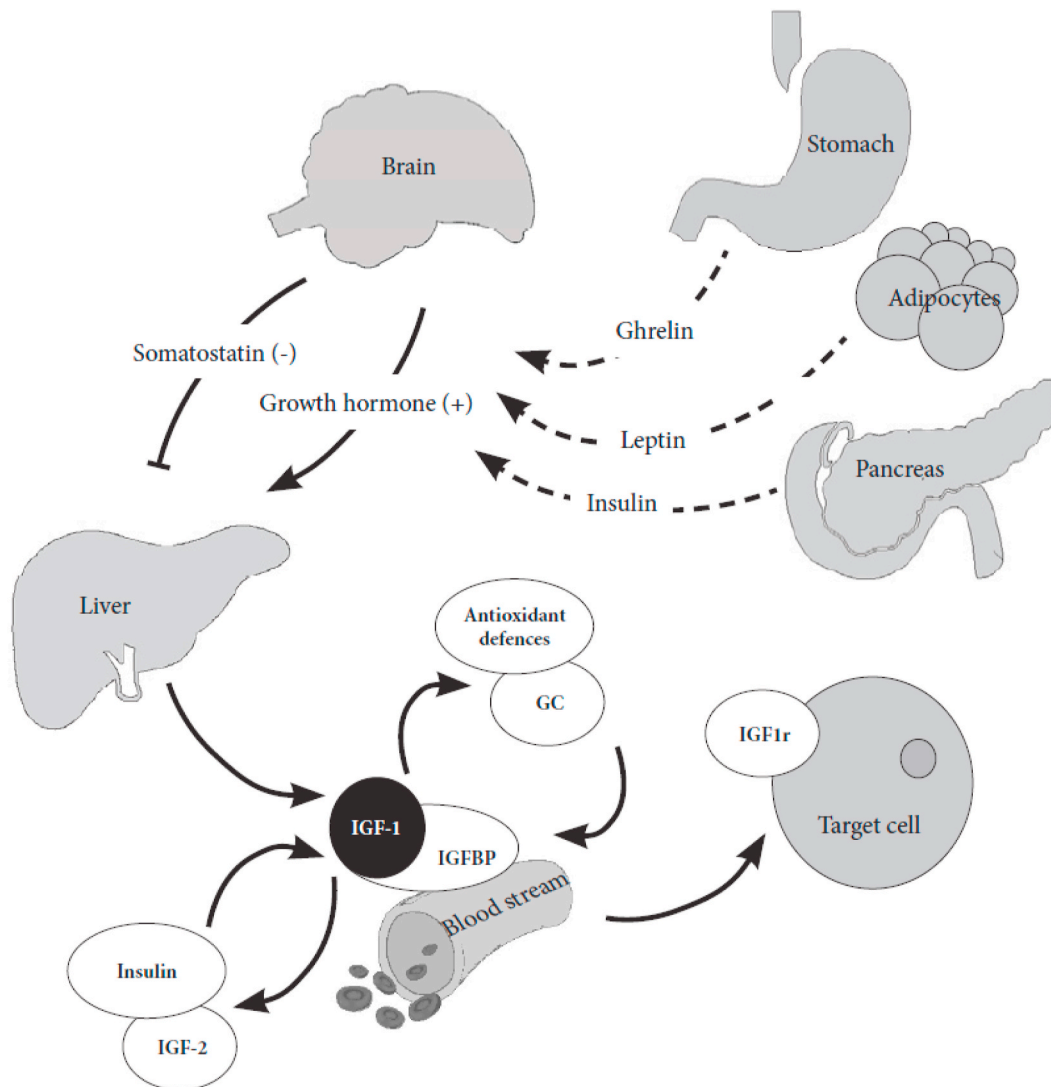

Fig. 1. Synthesis of insulin-like growth factor 1 (IGF-1). IGFBP denotes insulin-like growth factor binding proteins, IGF1r denotes IGF-1 receptors, GC denotes glucocorticoids, IGF-2 denotes insulin-like growth factor 2. Dashed lines emphasize the fact that a collective signal regarding the nutritional 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, 1990; 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; Estívariz and Ziegler, 1997; Hamza et al., 2012). For example, continuously infusing rats with GH did not cause significant changes in serum IGF1 or liver mRNA levels in individuals with Zn deficiency (Estívariz 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 (Estívariz 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% (Dørup 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 (Dørup 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, 1990). 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 Castilla-Cortázar, 2012; Noguera et al., 2015). Therefore, another dimension to IGF-1 nutrition-dependency can be observed on the level of GH (Breier, 1999; Ross and Buchanan, 1990; Scacchi et al., 2003; 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 (*Lamprophis fuliginosus*), 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 about 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 peaking 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 adrenarche (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 (Ferrannini 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 (Paolisso et al., 1997), and humans that have higher circulating IGF-1 levels had increased cognitive abilities at old age (Rollero et al.,

1998). However, numerous contradicting studies can be found on this topic and IGF-1 functions during aging are not well understood (Wrigley et al., 2017).

3.4. Physiological interactions of IGF-1 with glucocorticoids

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; Mazziotti 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 with its impact on fitness components and correlates is the subject of this 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 skeleton, 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; Newnham 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 (Mazziotti and Giustina, 2013). Glucocorticoids are also able to induce global (in liver) and organ-specific (especially in kidneys, lungs, adrenals, gut) increases in IGF-1 expression and serum IGF-1 levels (Thakur et al., 2000). Abovementioned studies describe 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; Mazziotti 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 nestling great tits living in poor nutritional conditions (lower growth rate and worse physiological condition). 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 level 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 (Agha and Monson, 2007; Vitku et al., 2016). There are two types of 11βHSDs: 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 (Agha and Monson, 2007; Paulsen et al., 2006; Sapolsky et al., 2000; Sigurjónsdóttir 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 (Sigurjónsdóttir 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.

3.5. IGF-1 and the mediation of a trade-off between growth and somatic maintenance

3.5.1. Effects of IGF-1 on telomere attrition

Offspring that achieve optimal body size faster often have a selective advantage to survive and reproduce better later in life. However, if this were generally true it is difficult to understand why so much genetic variation in growth rates persists in natural populations (Dmitriew, 2011). A potential explanation for this paradox is that high growth rate also entails a cost, for example through a negative effect on lifespan (Metcalfe and Monaghan, 2001). Indications that such a trade-off may occur are that IGF-1 (IIS activity in general) levels are shown to be negatively affecting lifespan (see section 4). However, costs could be paid also through modified or accelerated senescence. Telomeres – repeated DNA-protein complexes at ends of linear chromosomes (Blackburn, 1991; Chan and Blackburn, 2002) – have been suggested to link growth rate to senescence and lifespan (Boonekamp et al., 2014; Metcalfe and Monaghan, 2003), and we here discuss links between IGF-1 and telomeres.

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 lengths in the human population of Southern Italy (Campania 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 dynamics but there is insufficient evidence to paint a clear picture of the interaction between the two measures.

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, IGFBP5, and IGFBP6 genes compared to wildtype controls (Saeed 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; Saeed 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 (Wetterau 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 pluropotent 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 studies, mostly obtained using cell cultures, that indicate that IGF-1 can modulate the ways in which vertebrates defend themselves against oxidative damage, by regulating the activity of enzymatic antioxidants (Espinosa-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 Castilla-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 O_2^-) 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 (Jallali 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 nestling 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-ceramide-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 (Forkhead 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; Kloet and Burgering, 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 (Brohus 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 IGF1. There are however two comparative studies of mammals (Swanson and Dantzer, 2014) and passerine birds (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., 2008). 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

References

Agha, A., Monson, 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.1365-2265.2007.02763.x.

Agrogiannis, G.D., Sifakis, S., Patsouris, 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., Hideshima, T., Hayashi, T., Tai, Y.-T., Mitsiades, C.S., Mitsiades, N., Chauhan, D., Richardson, P., Munshi, N.C., Anderson, K.C., 2002. Cytokines modulate telomerase activity in a human multiple myeloma cell line. Canc. Res. 62, 3876–3882.

Aksu, I., Baykara, B., Kiray, M., Gurpinar, T., Sisman, A.R., Ekerbicer, N., Tas, A., Gokdemir-Yazar, O., Uysal, N., 2013. Serum IGF-1 levels correlate negatively to liver damage in diabetic rats. Biotech. Histochem. 88, 194–201. https://doi.org/10.3109/10520295.2012.758311.

Alberti, C., Chevenne, D., Mercat, I., Josserand, E., Armoogum-Boizeau, P., Tichet, J., Léger, J., 2011. Serum concentrations of insulin-like growth factor (IGF)-1 and IGF binding protein-3 (IGFBP-3), IGF-1/IGFBP-3 ratio, and markers of bone turnover: reference values for French children and adolescents and Z-score comparability with other references. Clin. Chem. 57, 1424. https://doi.org/10.1373/clinchem.2011.169466.

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.

Alonso-Alvarez, C., Bertrand, S., Faivre, B., Sorci, 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.

Ashpole, N.M., Logan, S., Yabluchanskiy, A., Mitschelen, M.C., Yan, H., Farley, J.A., Hodges, E.L., Ungvari, Z., Csiszar, A., Chen, S., Georgescu, C., Hubbard, G.B., Ikeno, Y., Sonntag, W.E., 2017. IGF-1 has sexually dimorphic, pleiotropic, and time-dependent effects on healthspan, pathology, and lifespan. Geroscience 39, 129–145. https://doi.org/10.1007/s11357-017-9971-0.

Auwerx, J., Cock, T.A., Knouff, C., 2003. PPAR-γ: a thrifty transcription factor. Nucl. Recept. Signal. https://doi.org/10.1621/nrs.01006, 1, nrs.01006.

Baker, J., Liu, J.-P., Robertson, E.J., Efstratiadis, A., 1993. Role of insulin-like growth factors in embryonic and postnatal growth. Cell 75, 73–82. https://doi.org/10.1016/S0092-8674(05)80085-6.

Baker, J., Hardy, M.P., Zhou, J., Bondy, C., Lupu, F., Bellvé, A.R., Efstratiadis, A., 1996. Effects of an Igf1 gene null mutation on mouse reproduction. Mol. Endocrinol. 10, 903–918. https://doi.org/10.1210/me.10.7.903.

Baquedano, M.S., Berensztein, E., Saraco, N., Dorn, G.V., de Davila, M.T., Rivarola, M.A., Belgorosky, A., 2005. Expression of the IGF system in human adrenal tissues from early infancy to late puberty: implications for the development of adrenarche. Pediatr. Res. 58, 451–458. https://doi.org/10.1203/01.PDR.0000179392.59060.93.

Barbieri, M., Bonafè, M., Franceschi, C., Paolisso, G., 2003. Insulin/IGF-I-signaling pathway: an evolutionarily conserved mechanism of longevity from yeast to humans. Am. J. Physiol. Endocrinol. Metab 285, E1064–E1071. https://doi.org/10.1152/ajpendo.00296.2003.

Barbieri, M., Paolisso, G., Kimura, M., Gardner, J.P., Boccardi, V., Papa, M., Hjelmborg, J.V., Christensen, K., Brimacombe, M., Nawrot, T.S., Staessen, J.A., Pollak, M.N., Aviv, A., 2009. Higher circulating levels of IGF-1 are associated with longer leukocyte telomere length in healthy subjects. Mech. Ageing Dev. 130, 771–776. https://doi.org/10.1016/j.mad.2009.10.002.

Bartke, A., 2008. Insulin and aging. Cell Cycle 7, 3338–3343.

Bassas, L., Lesniak, M.A., Serrano, J., Roth, J., De Pablo, F., 1988. Developmental regulation of insulin and type I insulin-like growth factor receptors and absence of type II receptors in chicken embryo tissues. Diabetes 37, 637–644. https://doi.org/10.2337/diab.37.5.637.

Basta-Kaim, A., Szczesny, E., Glombik, K., Stachowicz, K., Slusarczyk, J., Nalepa, I., Zelek- Molik, A., Rafa- Zablocka, K., Budziszewska, B., Kubera, M., Leskiewicz, M., Lason, W., 2014. Prenatal stress affects insulin-like growth factor-1 (IGF-1) level and IGF-1 receptor phosphorylation in the brain of adult rats. Eur.

Neuropsychopharmacol 24, 1546–1556. https://doi.org/10.1016/j.euroneuro.2014.07.002.

Baxter, R.C., 2013. Insulin-like growth factor binding protein-3 (IGFBP-3): novel ligands mediate unexpected functions. J. Cell Commun. Signal 7, 179–189. https://doi.org/10.1007/s12079-013-0203-9.

Beccavin, C., Chevalier, B., Cogburn, L., Simon, J., Duclos, M., 2001. Insulin-like growth factors and body growth in chickens divergently selected for high or low growth rate. J. Endocrinol. 168, 297–306. https://doi.org/10.1677/joe.0.1680297.

Beckman, B.R., 2011. Perspectives on concordant and discordant relations between insulin-like growth factor 1 (IGF1) and growth in fishes. Gen. Comp. Endocrinol. 170, 233–252. https://doi.org/10.1016/j.ygcen.2010.08.009.

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.ygcen.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.1078223.

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.

Bonier, F., 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., Arum, O., Rocha, J.S., Al Regaiey, K.A., Westbrook, R., Spong, A., Panici, J., Masternak, M.M., Kopchick, J.J., Bartke, A., 2009. Disruption of growth hormone receptor prevents calorie restriction from improving insulin action and longevity. PloS One 4, e4567. https://doi.org/10.1371/journal.pone.0004567.

Boonekamp, J.J., Mulder, G.A., Salomons, H.M., Dijkstra, C., Verhulst, S., 2014. Nestling telomere 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.

Bossis, I., 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. 201, 13–23. https://doi.org/10.1016/S0303-7207(03)00006-6.

Boucher, J., Softic, S., El Ouaamari, A., Krumpoch, M.T., Kleinridders, 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/db16-0212.

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.024117.

Braun, T.P., Marks, D.L., 2015. The regulation of muscle mass by endogenous glucocorticoids. Front. Physiol. 6 https://doi.org/10.3389/fphys.2015.00012.

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.

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.

Brohus, M., Gorbunova, V., Faulkes, C.G., Overgaard, M.T., Conover, C.A., 2015. The insulin-like growth factor system in the long-lived naked mole-rat. PloS One 10, e0145587. https://doi.org/10.1371/journal.pone.0145587.

Brüning, J.C., Gautam, D., Burks, D.J., Gillette, J., Schubert, M., Orban, P.C., Klein, R., Krone, W., Müller-Wieland, D., Kahn, C.R., 2000. Role of brain insulin receptor in control of body weight and reproduction. Science 289, 2122–2125. https://doi.org/10.1126/science.289.5487.2122.

Butler, A.A., Le Roith, D., 2001. Control of growth by the somatotropic axis: growth hormone and the insulin-like growth factors have related and independent roles. Annu. Rev. Physiol. 63, 141–164. https://doi.org/10.1146/annurev.physiol.63.1.141.

Cassy, S., Derouet, M., Crochet, S., Dridi, S., Taouis, M., 2003. Leptin and insulin downregulate leptin receptor gene expression in chicken-derived leghorn male hepatoma cells. Poultry Sci. 82, 1573–1579. https://doi.org/10.1093/ps/82.10.1573.

Cesur, Y., Yordaman, N., Dogan, M., 2009. Serum insulin-like growth factor-I and insulin-like growth factor binding protein-3 levels in children with zinc deficiency and the effect of zinc supplementation on these parameters. J. Pediatr. Endocrinol. Metab. 22, 1137–1143. https://doi.org/10.1515/jpem.2009.22.12.1137.

Chabrolle, C., Tosca, L., Crochet, S., Tesseraud, S., Dupont, J., 2007. Expression of adiponectin and its receptors (AdipoR1 and AdipoR2) in chicken ovary: potential role in ovarian steroidogenesis. Domest. Anim. Endocrinol. 33, 480–487. https://doi.org/10.1016/j.domaniend.2006.08.002.

Chan, S.W.L., Blackburn, E.H., 2002. New ways not to make ends meet: telomerase, DNA damage proteins and heterochromatin. Oncogene 21, 553–563. https://doi.org/10.1038/sj.onc.1205082.

Chiesa, C., Osborn, J.F., Haass, C., Natale, F., Spinelli, M., Scapillati, E., Spinelli, A., Pacifico, L., 2008. Ghrelin, leptin, IGF-1, IGFBP-3, and insulin concentrations at birth: is there a relationship with fetal growth and neonatal anthropometry? Clin. Chem. 54, 550–558. https://doi.org/10.1373/clinchem.2007.095299.

Conover, C.A., Lee, P.D., Riggs, 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/en.137.8.3295.

Coschigano, K.T., Holland, A.N., Riders, M.E., List, E.O., Flyvbjerg, A., Kopchick, J.J., 2003. Deletion, but not antagonism, of the mouse growth hormone receptor results in severely decreased body weights, insulin, and insulin-like growth factor I levels and increased life span. Endocrinology 144, 3799–3810. https://doi.org/10.1210/en.2003-0374.

Daftary, S.S., Gore, A.C., 2003. Developmental changes in hypothalamic insulin-like growth factor-1: relationship to gonadotropin-releasing hormone neurons. Endocrinology 144, 2034–2045. https://doi.org/10.1210/en.2002-221025.

Daftary, S.S., Gore, A.C., 2005. IGF-1 in the brain as a regulator of reproductive neuroendocrine function. Exp. Biol. Med. 230, 292–306. https://doi.org/10.1177/153537020523000503.

Dantzer, B., Swanson, E.M., 2012. Mediation of vertebrate life histories via insulin-like growth factor-1. Biol. Rev. 87, 414–429. https://doi.org/10.1111/j.1469-185X.2011.00204.x.

David, I., Bosshard, R., Kloas, W., Reinecke, M., 2000. Insulin-like growth factor I in the anterior pituitary of the clawed frog *Xenopus laevis*: immunocytochemical and autoradiographic indication for a paracrine action and corelease with prolactin. J. Neuroendocrinol. 12, 415–420. https://doi.org/10.1046/j.1365-2826.2000.00464.x.

Daza, D.O., Sundstrom, G., Bergqvist, C.A., Duan, C., Larhammar, D., 2011. Evolution of the insulin-like growth factor binding protein (IGFBP) family. Endocrinology 152, 2278–2289. https://doi.org/10.1210/en.2011-0047.

Devlin, R.H., Biagi, C.A., Yesaki, T.Y., Smailus, D.E., Byatt, J.C., 2001. Growth of domesticated transgenic fish. Nature 409, 781–782. https://doi.org/10.1038/35057314.

Ditchkoff, S.S., Spicer, L.J., Masters, R.E., Lochmiller, R.L., 2001. Concentrations of insulin-like growth factor-I in adult male white-tailed deer (*Odocoileus virginianus*): associations with serum testosterone, morphometrics and age during and after the breeding season. Comp. Biochem. Physiol. Mol. Integr. Physiol. 129, 887–895. https://doi.org/10.1016/S1095-6433(01)00351-8.

Dmitriew, C.M., 2011. The evolution of growth trajectories: what limits growth rate? Biol. Rev. 86, 97–116. https://doi.org/10.1111/j.1469-185X.2010.00136.x.

Dørup, I., Flyvbjerg, A., Everts, M.E., Clausen, T., 2007. Role of insulin-like growth factor-1 and growth hormone in growth inhibition induced by magnesium and zinc deficiencies. Br. J. Nutr. 66, 505–521. https://doi.org/10.1079/BJN19910051.

Dukes, A., Davis, C., El Refaey, M., Upadhyay, S., Mork, S., Arounleut, P., Johnson, M.H., Hill, W.D., Isales, C.M., Hamrick, M.W., 2015. The aromatic amino acid tryptophan stimulates skeletal muscle IGF1/p70s6k/mTor signaling in vivo and the expression of myogenic genes in vitro. Nutrition 31, 1018–1024. https://doi.org/10.1016/j.nut.2015.02.011.

Espinosa-Diez, C., Miguel, V., Mennerich, D., Kietzmann, T., Sánchez-Pérez, P., Cadenas, 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.

Estívariz, C.F., Ziegler, T.R., 1997. Nutrition and the insulin-like growth factor system. Endocrine 7, 65–71. https://doi.org/10.1007/BF02778066.

Evdokimova, V., Tognon, C.E., Benatar, T., Yang, W., Krutikov, K., Pollak, M., Sorensen, P.H.B., Seth, A., 2012. IGFBP7 binds to the IGF-1 receptor and blocks its activation by insulin-like growth factors. Sci. Signal. 5 https://doi.org/10.1126/scisignal.2003184 ra92.

Fall, C.H., Pandit, A.N., Law, C.M., Yajnik, C.S., Clark, P.M., Breier, B., Osmond, C., Shiell, A.W., Gluckman, P.D., Barker, D.J., 1995. Size at birth and plasma insulin-like growth factor-1 concentrations. Arch. Dis. Child. 73, 287–293. https://doi.org/10.1136/adc.73.4.287.

Fernandez, A.M., Torres-Alemán, I., 2012. The many faces of insulin-like peptide signalling in the brain. Nat. Rev. Neurosci. 13, 225–239. https://doi.org/10.1038/nrn3209.

Ferrannini, E., Vichi, S., Beck-Nielsen, H., Laakso, M., Paolisso, L., Smith, G., 1996. Insulin action and age: European group for the study of insulin resistance (EGIR). Diabetes 45 (947). https://doi.org/10.2337/diab.45.7.947.

Findlay, J.K., 1993. An update on the roles of inhibin, activin, and follistatin as local regulators of folliculogenesis. Biol. Reprod. 48, 15–23. https://doi.org/10.1095/biolreprod48.1.15.

Fingar, D.C., Blenis, J., 2004. Target of rapamycin (TOR): an integrator of nutrient and growth factor signals and coordinator of cell growth and cell cycle progression. Oncogene 23, 3151–3171.

Flatt, T., Heyland, A., 2011. Mechanisms of Life History Evolution: the Genetics and Physiology of Life History Traits and Trade-Offs. Oxford University Press, New York, USA.

Fontana, L., Weiss, E.P., Villareal, D.T., Klein, S., Holloszy, J.O., 2008. Long-term effects of calorie or protein restriction on serum IGF-1 and IGFBP-3 concentration in humans. Aging Cell 7, 681–687. https://doi.org/10.1111/j.1474-9726.2008.00417.x.

Fournier, M., Huang, Z.-S., Li, H., Da, X., Cercek, B., Lewis, M.I., 2003. Insulin-like growth factor I prevents corticosteroid-induced diaphragm muscle atrophy in emphysematous hamsters. Am. J. Physiol. Regul. Integr. Comp. Physiol. 285, R34–R43. https://doi.org/10.1152/ajpregu.00177.2002.

!"count(.//sb:host[1]/child::*//sb:date)">Garcia-Aragon, J., Lobie, P.E., Muscat, G.E., Gobius, K.S., Norstedt, G., Waters, M.J., . Prenatal expression of the growth hormone (GH) receptor/binding protein in the rat: a role for GH in embryonic and fetal development? Development 114, 869–876.

Giachetto, P.F., Riedel, E.C., Gabriel, J.E., Ferro, M.I.T., Di Mauro, S.M.Z., Macari, M., Ferro, J.A., 2004. Hepatic mRNA expression and plasma levels of insulin-like growth factor-I (IGF-I) in broiler chickens selected for different growth rates. Genet. Mol. Biol. 27, 39–44. https://doi.org/10.1590/S1415-47572004000100007.

Giovannucci, E., Pollak, M., Liu, Y., Platz, E.A., Majeed, N., Rimm, E.B., Willett, W.C., 2003. Nutritional predictors of insulin-like growth factor I and their relationships to cancer in men. Cancer epidemiol. Biomarkers Prev 12, 84–89.

Giudice, L.C., 1992. Insulin-like growth factors and ovarian follicular development. Endocr. Rev. 13, 641–669. https://doi.org/10.1210/edrv-13-4-641.

Greer, E.L., Brunet, A., 2005. FOXO transcription factors at the interface between longevity and tumor suppression. Oncogene 24, 7410–7425. https://doi.org/10.1038/sj.onc.1209086.

Guevara-Aguirre, J., Balasubramanian, P., Guevara-Aguirre, M., Wei, M., Madia, F., Cheng, C.-W., Hwang, D., Martin-Montalvo, A., Saavedra, J., Ingles, S., de Cabo, R., Cohen, P., Longo, V.D., 2011. Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. Sci. Transl. Med. 3 https://doi.org/10.1126/scitranslmed.3001845, 70ra13.

Guillette, J.L.J., Cox, M.C., Crain, D.A., 1996. Plasma insulin-like growth factor-I concentration during the reproductive cycle of the American Alligator (*Alligator mississippiensis*). Gen. Comp. Endocrinol. 104, 116–122. https://doi.org/10.1006/gcen.1996.0147.

Guler, H.P., Zapf, J., Scheiwiller, E., Froesch, E.R., 1988. Recombinant human insulin-like growth factor I stimulates growth and has distinct effects on organ size in hypophysectomized rats. Proc. Natl. Acad. Sci. U.S.A. 85, 4889–4893. https://doi.org/10.1073/pnas.85.13.4889.

Gupta, A., Gupta, Y., 2013. Glucocorticoid-induced myopathy: pathophysiology, diagnosis, and treatment. Indian J. Endocrinol. Metab 17, 913–916. https://doi.org/10.4103/2230-8210.117215.

Gupta, S., Deoskar, A., Gupta, P., Jain, S., 2015. Serum insulin-like growth factor-1 levels in females and males in different cervical vertebral maturation stages. Dental Press J. Orthod 20, 68–75. https://doi.org/10.1590/2176-9451.20.2.068-075.oar.

Hack, N.L., Strobel, J.S., Journey, M.L., Beckman, B.R., Lema, S.C., 2018. Response of the insulin-like growth factor-1 (Igf1) system to nutritional status and growth rate variation in olive rockfish (*Sebastes serranoides*). 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. Ital. J. Pediatr. 38, 21. https://doi.org/10.1186/1824-7288-38-21.

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.M800407-MCP200.

Hau, M., Ricklefs, R.E., Wikelski, M., Lee, K.A., Brawn, J.D., 2010. Corticosterone, testosterone and life-history strategies of birds. Proc. R. Soc. Biol. Sci. B 277, 3203–3212. 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 1832, 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/JCI113450.

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.

Hoekstra, L.A., Schwartz, T.S., Sparkman, A.M., Miller, D.A.W., Bronikowski, 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.

Holzenberger, M., Dupont, J., Ducos, B., Leneuve, P., Geloen, A., Even, P.C., Cervera, P., Le Bouc, Y., 2003. IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. Nature 421, 182–187. https://doi.org/10.1038/nature01298.

Hui-fang, L., Wen-qi, Z., Kuan-wei, C., Xu, W., Qing-ping, T., Yu-shi, G., 2008. Associations between GHR and IGF-1 gene polymorphisms, and reproductive traits in wenchang chickens. Turk. J. Vet. Anim. Sci. 32, 281–285.

Hwa, V., Oh, Y., Rosenfeld, R.G., 1999. The insulin-like growth factor-binding protein (IGFBP) superfamily. Endocr. Rev. 20, 761–787. https://doi.org/10.1210/er.20.6.761.

Inui, A., 2001. Ghrelin: an orexigenic and somatotrophic signal from the stomach. Nat. Rev. Neurosci. 2, 551–560. https://doi.org/10.1038/35086018.

Jallali, N., Ridha, H., Thrasivoulou, C., Butler, P., Cowen, T., 2007. Modulation of intracellular reactive oxygen species level in chondrocytes by IGF-1, FGF, and TGF-β1. Connect. Tissue Res. 48, 149–158. https://doi.org/10.1080/03008200701331516.

Jimeno, B., Hau, M., Verhulst, S., 2018. Corticosterone levels reflect variation in metabolic rate, independent of 'stress'. Sci. Rep. 8, 13020. https://doi.org/10.1038/s41598-018-31258-z.

Junnila, R.K., List, E.O., Berryman, D.E., Murrey, J.W., Kopchick, J.J., 2013. The GH/IGF-1 axis in ageing and longevity. Nat. Rev. Endocrinol. 9, 366. https://doi.org/10.1038/nrendo.2013.67.

Juul, A., Bang, P., Hertel, N.T., Main, K., Dalgaard, P., Jorgensen, K., Muller, J., Hall, K., Skakkebaek, N.E., 1994. Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. J. Clin. Endocrinol. Metab. 78, 744–752. https://doi.org/10.1210/jcem.78.3.8126152.

Juul, A., Holm, K., Kastrup, K.W., Pedersen, S.A., Michaelsen, K.F., Scheike, T., Rasmussen, S., Muller, J., Skakkebaek, N.E., 1997. Free insulin-like growth factor I serum levels in 1430 healthy children and adults, and its diagnostic value in patients

suspected of growth hormone deficiency. J. Clin. Endocrinol. Metab. 82, 2497–2502. https://doi.org/10.1210/jcem.82.8.4137.

Jux, C., Leiber, K., Hügel, U., Blum, W., Ohlsson, C., Klaus, G., Mehls, 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.139.7.6099.

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, 187–191. https://doi.org/10.1016/j.ygcen.2012.10.015.

Kajimura, S., Hirano, T., Visitacion, N., Moriyama, S., Aida, K., Grau, E., 2003. Dual mode of cortisol action on GH/IGF-I/IGF binding proteins in the tilapia, *Oreochromis mossambicus*. J. Endocrinol. 178, 91–99. https://doi.org/10.1677/joe.0.1780091.

Kamenický, P., Mazziotti, G., Lombès, M., Giustina, A., Chanson, P., 2014. Growth hormone, insulin-like growth factor-1, and the kidney: pathophysiological and clinical implications. Endocr. Rev. 35, 234–281. https://doi.org/10.1210/er.2013-1071.

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.

Kaplan, R.C., Fitzpatrick, A.L., Pollak, M.N., Gardner, J.P., Jenny, N.S., McGinn, A.P., Kuller, L.H., Strickler, H.D., Kimura, M., Psaty, B.M., Aviv, A., 2009. Insulin-like growth factors and leukocyte telomere length: the cardiovascular health study. J. Gerontol. A Biol. Sci. Med. Sci. 64A, 1103–1106. https://doi.org/10.1093/gerona/glp036.

Klaus, G., Jux, C., Fernandez, P., Rodriguez, J., Himmele, R., Mehls, O., 2000. Suppression of growth plate chondrocyte proliferation by corticosteroids. Pediatr. Nephrol. 14, 612–615. https://doi.org/10.1007/s004670000344.

Kloet, D.E.A., Burgering, B.M.T., 2011. The PKB/FOXO switch in aging and cancer. Biochim. Biophys. Acta 1813, 1926–1937. https://doi.org/10.1016/j.bbamcr.2011.04.003.

Kocamis, H., Kirkpatrick-Keller, D.C., Klandorf, H., Killefer, J., 1998. In ovo administration of recombinant human insulin-like growth factor-I alters postnatal growth and development of the broiler chicken. Poultry Sci. 77, 1913–1919. https://doi.org/10.1093/ps/77.12.1913.

Kondo, T., Kitano, T., Iwai, K., Watanabe, M., Taguchi, Y., Yabu, T., Umehara, H., Domae, N., Uchiyama, T., Okazaki, T., 2002. Control of ceramide-induced apoptosis by IGF-1: involvement of PI-3 kinase, caspase-3 and catalase. Cell Death Differ. 9, 682–692. https://doi.org/10.1038/sj.cdd.4401019.

Laron, Z., 2001. Insulin-like growth factor 1 (IGF-1): a growth hormone. Mol. Pathol. 54, 311–316. https://doi.org/10.1136/mp.54.5.311.

Levine, M.E., Suarez, J.A., Brandhorst, S., Balasubramanian, P., Cheng, C.-W., Madia, F., Fontana, L., Mirisola, M.G., Guevara-Aguirre, J., Wan, J., Passarino, G., Kennedy, B. K., Wei, M., Cohen, P., Crimmins, E.M., Longo, V.D., 2014. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. Cell Metabol. 19, 407–417. https://doi.org/10.1016/j.cmet.2014.02.006.

Lewin, N., Swanson, E.M., Williams, B.L., Holekamp, K.E., 2017. Juvenile concentrations of IGF-1 predict life-history trade-offs in a wild mammal. Funct. Ecol. 31, 894–902. https://doi.org/10.1111/1365-2435.12808.

Li, Y.H., Fan, J., Lang, C.H., 1997. Differential role of glucocorticoids in mediating endotoxin-induced changes in IGF-I and IGFBP-1. Am. J. Physiol. Regul. Integr. Comp. Physiol 272, R1990–R1997. https://doi.org/10.1152/ajpregu.1997.272.6.R1990.

Li, M., Chiu, J.-F., Mossman, B.T., Fukagawa, N.K., 2006. Down-regulation of manganese-superoxide dismutase through phosphorylation of FOXO3a by akt in explanted vascular smooth muscle cells from old rats. J. Biol. Chem. 281, 40429–40439. https://doi.org/10.1074/jbc.M606596200.

Li, Y., Shelat, H., Gao, S., Madjid, M., Zhu, M., Ge, X., Geng, Y.-J., 2011. Insulin growth factor-1 enhances telomerase activity and prevents mitochondrial dysfunction via the p53/PGC network in human induced pluripotent stem cells. Circulation 124, A12940.

Lin, S.-W., Ge, W., 2009. Differential regulation of gonadotropins (FSH and LH) and growth hormone (GH) by neuroendocrine, endocrine, and paracrine factors in the zebrafish—an in vitro approach. Gen. Comp. Endocrinol. 160, 183–193. https://doi.org/10.1016/j.ygcen.2008.11.020.

Liu, J.P., Baker, J., Perkins, A.S., Robertson, E.J., Efstratiadis, A., 1993. Mice carrying null mutations of the genes encoding insulin-like growth factor-i (igf-1) and type-1 igf receptor (igf1r). Cell 75, 59–72. https://doi.org/10.1016/s0092-8674(05)80084-4.

Liu, J.L., Yakar, S., Leroith, D., 2000. Conditional knockout of mouse insulin-like growth factor-1 gene using the Cre/loxP system. Proc. Soc. Exp. Biol. Med 223, 344–351. https://doi.org/10.1177/153537020022300403.

Loboda, A., Damulewicz, M., Pyza, E., Jozkowicz, A., Dulak, J., 2016. Role of Nrf2/HO-1 system in development, oxidative stress response and diseases: an evolutionary conserved mechanism. Cell. Mol. Life Sci. 73, 3221–3247. https://doi.org/10.1007/s00018-016-2223-0.

Locatelli, V., Bianchi, V.E., 2014. Effect of GH/IGF-1 on bone metabolism and osteoporosis. Internet J. Endocrinol. 2014 (25) https://doi.org/10.1155/2014/235060.

Lodjak, J., Mägi, M., 2017. Crosstalk between growth and somatic maintenance in young animals. J. Avian Biol. 48, 1360–1363. https://doi.org/10.1111/jav.01519.

Lodjak, J., Mägi, M., 2018. Insulin-like growth factor 1 relieves the constraints on the growth of young wild passerines. Ibis 160, 688–692. https://doi.org/10.1111/ibi.12608.

Lodjak, J., Mägi, M., Tilgar, V., 2014. Insulin-like growth factor 1 and growth rate in nestlings of a wild passerine bird. Funct. Ecol. 28, 159–166. https://doi.org/10.1111/1365-2435.12164.

Lodjak, J., Tilgar, V., Mägi, M., 2016. Does the interaction between glucocorticoids and insulin-like growth factor 1 predict nestling fitness in a wild passerine? Gen. Comp. Endocrinol. 225, 149–154. https://doi.org/10.1016/j.ygcen.2015.10.016.

Lodjak, J., Mägi, M., Sild, E., Mänd, R., 2017. Causal link between insulin-like growth factor 1 and growth in nestlings of a wild passerine bird. Funct. Ecol. 31, 184–191. https://doi.org/10.1111/1365-2435.12679.

Lodjak, J., Mänd, R., Mägi, M., 2018. Insulin-like growth factor 1 and life-history evolution of passerine birds. Funct. Ecol. 32, 313–323. https://doi.org/10.1111/1365-2435.12993.

Louvi, A., Accili, D., Efstratiadis, A., 1997. Growth-promoting interaction of IGF-II with the insulin receptor during mouse embryonic development. Dev. Biol. 189, 33–48. https://doi.org/10.1006/dbio.1997.8666.

Lubos, E., Loscalzo, J., Handy, D.E., 2011. Glutathione peroxidase-1 in health and disease: from molecular mechanisms to therapeutic opportunities. Antioxid. Redox Signal 15, 1957–1997. https://doi.org/10.1089/ars.2010.3586.

Luckenbach, J.A., Dickey, J.T., Swanson, P., 2010. Regulation of pituitary GnRH receptor and gonadotropin subunits by IGF1 and GnRH in prepubertal male coho salmon. Gen. Comp. Endocrinol. 167, 387–396. https://doi.org/10.1016/j.ygcen.2009.09.010.

Lupu, F., Terwilliger, J.D., Lee, K., Segre, G.V., Efstratiadis, A., 2001. Roles of growth hormone and insulin-like growth factor 1 in mouse postnatal growth. Dev. Biol. 229, 141–162. https://doi.org/10.1006/dbio.2000.9975.

Maggio, M., De Vita, F., Lauretani, F., Buttò, V., Bondi, G., Cattabiani, C., Nouvenne, A., Meschi, T., Dall'Aglio, E., Ceda, G.P., 2013. IGF-1, the cross road of the nutritional, inflammatory and hormonal pathways to frailty. Nutrients 5, 4184–4205. https://doi.org/10.3390/nu5104184.

Majumdar, A.P.N., Nielsen, H., 1985. Influence of glucocorticoids on prenatal development of the gut and pancreas in rats. Scand. J. Gastroenterol. 20, 65–71. https://doi.org/10.3109/00365528509089634.

Martin, T.E., 1987. Food as a limit on breeding birds: a life-history perspective. Annu. Rev. Ecol. Syst. 453–487. https://doi.org/10.1146/annurev.es.18.110187.002321.

Matsumoto, R., Takahashi, Y., 2016. Telomeres and cellular senescence in metabolic and endocrine diseases. In: Larramendi, M.L. (Ed.), Telomere: A Complex End of a Chromosome. InTech Publisher, Rijeka, Croatia, p. 143.

Matsumoto, R., Fukuoka, H., Iguchi, G., Odake, Y., Yoshida, K., Bando, H., Suda, K., Nishizawa, H., Takahashi, M., Yamada, S., Ogawa, W., Takahashi, Y., 2015. Accelerated Telomere Shortening in Acromegaly; IGF-I Induces Telomere Shortening and Cellular Senescence. PLoS ONE. 10, e0140189. https://doi.org/10.1371/journal.pone.0140189.

Mazerbourg, S., Callebaut, I., Zapf, J., Mohan, S., Overgaard, M., Monget, P., 2004. Up date on IGFBP-4: regulation of IGFBP-4 levels and functions, in vitro and in vivo. Growth Horm. IGF Res. 14, 71–84. https://doi.org/10.1016/j.ghir.2003.10.002.

Mazziotti, G., Giustina, A., 2013. Glucocorticoids and the regulation of growth hormone secretion. Nat. Rev. Endocrinol. 9, 265–276. https://doi.org/10.1038/nrendo.2013.5.

McCarthy, T., Centrella, M., Canalis, E., 1990. Cortisol inhibits the synthesis of insulin-like growth factor-I in skeletal cells. Endocrinology 126, 1569–1575. https://doi.org/10.1210/endo-126-3-1569.

McGaugh, S.E., Bronikowski, A.M., Kuo, C.-H., Reding, D.M., Addis, E.A., Flagel, L.E., Janzen, F.J., Schwartz, T.S., 2015. Rapid molecular evolution across amniotes of the IIS/TOR network. Proc. Natl. Acad. Sci. USA 112 (7055). https://doi.org/10.1073/pnas.1419659112.

Metcalfe, N.B., Monaghan, P., 2001. Compensation for a bad start: grow now, pay later? Trends Ecol. Evol. 16, 254–260. https://doi.org/10.1016/S0169-5347(01)02124-3.

Metcalfe, N.B., Monaghan, P., 2003. Growth versus lifespan: perspectives from evolutionary ecology. Exp. Gerontol. 38, 935–940. https://doi.org/10.1016/S0531-5565(03)00159-1.

Miller, S.L., Sutherland, A.E., Supramaniam, V.G., Walker, D.W., Jenkin, G., Wallace, E. M., 2012. Antenatal glucocorticoids reduce growth in appropriately grown and growth-restricted ovine fetuses in a sex-specific manner. Reprod. Fertil. Dev. 24, 753–758. https://doi.org/10.1071/RD11143.

Mohan, S., Kesavan, C., 2012. Role of insulin-like growth factor-1 in the regulation of skeletal growth. Curr. Osteoporos. Rep. 10, 178–186. https://doi.org/10.1007/s11914-012-0100-9.

Morón, Ú.M., Castilla-Cortázar, I., 2012. Protection against oxidative stress and "IGF-I deficiency conditions". In: El-Missiry, M.A. (Ed.), Antioxidant Enzyme. InTech, Croatia 89–117.

Nagaraja, S., Aggrey, S., Yao, J., Zadworny, D., Fairfull, R., Kuhnlein, U., 2000. Brief communication. Trait association of a genetic marker near the IFG-I gene in egg-laying chickens. J. Hered. 91, 150–156. https://doi.org/10.1093/jhered/91.2.150.

Nakae, J., Kido, Y., Accili, D., 2001. Distinct and overlapping functions of insulin and IGF-I receptors. Endocr. Rev. 22, 818–835. https://doi.org/10.1210/er.22.6.818.

Neuenschwander, S., Brinkhof, M.W.G., Kölliker, M., Richner, H., 2003. Brood size, sibling competition, and the cost of begging in great tits (*Parus major*). Behav. Ecol. 14, 457–462. https://doi.org/10.1093/beheco/arg025.

Newnham, J.P., Moss, T.J., 2001. Antenatal glucocorticoids and growth: single versus multiple doses in animal and human studies. Semin. Neonatol. 6, 285–292. https://doi.org/10.1053/siny.2001.0064.

Noguera, J.C., Monaghan, P., Metcalfe, N.B., 2015. Interactive effects of early and later nutritional conditions on the adult antioxidant defence system in zebra finches. J. Exp. Biol. 218, 2211–2217. https://doi.org/10.1242/jeb.120956.

O'Connor, J.C., McCusker, R.H., Strle, K., Johnson, R.W., Dantzer, R., Kelley, K.W., 2008. Regulation of IGF-I function by proinflammatory cytokines: at the interface of

immunology and endocrinology. Cell. Immunol. 252, 91–110. https://doi.org/10.1016/j.cellimm.2007.09.010.

O'Kusky, J.R., Ye, P., D'Ercole, A.J., 2000. Insulin-like growth factor-I promotes neurogenesis and synaptogenesis in the hippocampal dentate gyrus during postnatal development. J. Neurosci. 20, 8435–8442. https://doi.org/10.1523/JNEUROSCI.20-22-08435.2000.

Ohlsson, C., Mohan, S., Sjögren, K., Tivesten, A., Isgaard, J., Isaksson, O., Jansson, J.-O., Svensson, J., 2009. The role of liver-derived insulin-like growth factor-I. Endocr. Rev. 30, 494–535. https://doi.org/10.1210/er.2009-0010.

Okazaki, R., Riggs, B.L., Conover, C.A., 1994. Glucocorticoid regulation of insulin-like growth factor-binding protein expression in normal human osteoblast-like cells. Endocrinology 134, 126–132. https://doi.org/10.1210/endo.134.1.7506203.

Otto, A., Patel, K., 2010. Signalling and the control of skeletal muscle size. Exp. Cell Res. 316, 3059–3066. https://doi.org/10.1016/j.yexcr.2010.04.009.

Pansters, N.A., Langen, R.C., Wouters, E.F., Schols, A.M., 2013. Synergistic stimulation of myogenesis by glucocorticoid and IGF-I signaling. J. Appl. Physiol. 114, 1329–1339. https://doi.org/10.1152/japplphysiol.00503.2012.

Pantaleon, M., Whiteside, E., Harvey, M., Barnard, R., Waters, M., Kaye, P., 1997. Functional growth hormone (GH) receptors and GH are expressed by preimplantation mouse embryos: a role for GH in early embryogenesis? Proc. Natl. Acad. Sci. USA 94, 5125–5130.

Paolisso, G., Ammendola, S., Del Buono, A., Gambardella, A., Riondino, M., Tagliamonte, M.R., Rizzo, M.R., Carella, C., Varricchio, M., 1997. Serum levels of insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 in healthy centenarians: relationship with plasma leptin and lipid concentrations, insulin action, and cognitive function. J. Clin. Endocrinol. Metab. 82, 2204–2209. https://doi.org/10.1210/jcem.82.7.4087.

Paulsen, 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-deficient patients inhibits 11β-hydroxysteroid dehydrogenase type 1 messenger ribonucleic acid expression in adipose tissue. J. Clin. Endocrinol. Metab. 91, 1093–1098. https://doi.org/10.1210/jc.2005-1694.

Pérez-Sánchez, J., Martí-Palanca, H., Kaushik, S.J., 1995. Ration size and protein intake affect circulating growth hormone concentration, hepatic growth hormone binding and plasma insulin-like growth factor-I immunoreactivity in a marine teleost, the gilthead sea bream (*Sparus aurata*). J. Nutr. 125, 546–552. https://doi.org/10.1093/jn/125.3.546.

Pettifor, R.A., Perrins, C.M., McCleery, R.H., 2001. The individual optimization of fitness: variation in reproductive output, including clutch size, mean nestling mass and offspring recruitment, in manipulated broods of great tits *Parus major*. J. Anim. Ecol. 70, 62–79. https://doi.org/10.1111/j.1365-2656.2001.00465.x.

Piloya-Were, T., Odongkara-Mpora, B., Namusoke, H., Idro, R., 2014. Physical growth, puberty and hormones in adolescents with Nodding Syndrome; a pilot study. BMC Res. Notes 7, 858. https://doi.org/10.1186/1756-0500-7-858.

Pitetti, J.-L., Calvel, P., Zimmermann, C., Conne, B., Papaioannou, M.D., Aubry, F., Cederroth, C.R., Urner, F., Fumel, B., Crausaz, M., Docquier, M., Herrera, P.L., Pralong, F., Germond, M., Guillou, F., Jégou, B., Nef, S., 2013. An essential role for insulin and IGF1 receptors in regulating sertoli cell proliferation, testis size, and FSH action in mice. Mol. Endocrinol 27, 814–827. https://doi.org/10.1210/me.2012-1258.

Plum, L., Schubert, M., Brüning, J.C., 2005. The role of insulin receptor signaling in the brain. Trends Endocrinol. Metab 16, 59–65. https://doi.org/10.1016/j.tem.2005.01.008.

Pradhan, D.S., Ma, C., Schlinger, B.A., Soma, K.K., Ramenofsky, M., 2019. Preparing to migrate: expression of androgen signaling molecules and insulin-like growth factor-1 in skeletal muscles of Gambel's white-crowned sparrows. J. Comp. Physiol. A Neuroethol. Sens. Neural. Behav. Physiol 205, 113–123. https://doi.org/10.1007/s00359-018-1308-7.

Qian, X., 2012. Glucocorticoids: New Recognition of Our Familiar Friend, InTech.

Rajaram, S., Baylink, D.J., Mohan, S., 1997. Insulin-like growth factor-binding proteins in serum and other biological fluids: regulation and functions. Endocr. Rev. 18, 801–831. https://doi.org/10.1210/er.18.6.801.

Regan, J.C., Froy, H., Walling, C.A., Moatt, J.P., Nussey, D.H., 2019. Dietary restriction and insulin-like signalling pathways as adaptive plasticity: a synthesis and re-evaluation. Funct. Ecol. 34, 107–128. https://doi.org/10.1111/1365-2435.13418.

Rhind, S.M., McMillen, S.R., Duff, E., Hirst, D., Wright, S., 1998. Seasonality of meal patterns and hormonal correlates in red deer. Physiol. Behav. 65, 295–302. https://doi.org/10.1016/s0031-9384(98)00164-4.

Richardson, C.J., Schalm, S.S., Blenis, J., 2004. PI3-kinase and TOR: PIKTORing cell growth. Semin. Cell Dev. Biol. 15, 147–159. https://doi.org/10.1016/j.semcdb.2003.12.023.

Robson, H., Siebler, T., Shalet, S.M., Williams, G.R., 2002. Interactions between GH, IGF-I, glucocorticoids, and thyroid hormones during skeletal growth. Pediatr. Res. 52, 137–147. https://doi.org/10.1203/00006450-200208000-00003.

Rocha, E.D., de Brito, N.J., Dantas, M.M., Silva Ade, A., Almeida, M., Brandao-Neto, J., 2015. Effect of zinc supplementation on GH, IGF1, IGFBP3, OCN, and ALP in non-zinc-deficient children. J. Am. Coll. Nutr. 34, 290–299. https://doi.org/10.1080/07315724.2014.929511.

Rollero, A., Murialdo, G., Fonzi, S., Garrone, S., Gianelli, M.V., Gazzerro, E., Barreca, A., Polleri, A., 1998. Relationship between cognitive function, growth hormone and insulin-like growth factor I plasma levels in aged subjects. Neuropsychobiology 38, 73–79. https://doi.org/10.1159/000026520.

Rosebrough, R.W., McMurtry, J.P., 2007. Protein and energy relationships in the broiler chicken: 11. Effects of protein quantity and quality on metabolism. Br. J. Nutr. 70, 667–678. https://doi.org/10.1079/BJN19930162.

Ross, R.J., Buchanan, C.R., 1990. Growth hormone secretion: its regulation and the influence of nutritional factors. Nutr. Res. Rev. 3, 143–162. https://doi.org/10.1079/nrr19900010.

Sacco, A., Mourkioti, F., Tran, R., Choi, J., Llewellyn, M., Kraft, P., Shkreli, 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/mTR mice. Cell 143, 1059–1071. https://doi.org/10.1016/j.cell.2010.11.039.

Saeed, H., Qiu, W., Li, C., Flyvbjerg, A., Abdallah, B.M., Kassem, M., 2015. Telomerase activity promotes osteoblast differentiation by modulating httIGF-signaling pathway. Biogerontology 16, 733–745. https://doi.org/10.1007/s10522-015-9596-6.

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

Scacchi, M., Pincelli, A.I., Cavagnini, F., 2003. Nutritional status in the neuroendocrine control of growth hormone secretion: the model of anorexia nervosa. Front. Neuroendocrinology 24, 200–224. https://doi.org/10.1016/S0091-3022(03)00014-1.

Schams, D., Barth, D., Heinze-Mutz, E.-M., Pflaum, G., Karg, H., 1992. Antler Growth in Roe Deer: Effects of Casting and Correlations with Growth Hormone and Insulin like Growth Factor I. In: Brown, R.D. (Ed.), The Biology of Deer. Springer, New York, USA, pp. 505–510.

Schams, D., Berisha, B., Kosmann, M., Einspanier, R., Amselgruber, W.M., 1999. Possible role of growth hormone, IGFs, and IGF-binding proteins in the regulation of ovarian function in large farm animals. Domest. Anim. Endocrinol. 17, 279–285. https://doi.org/10.1016/S0739-7240(99)00044-2.

Schlueter, P.J., Peng, G., Westerfield, M., Duan, C., 2007. Insulin-like growth factor signaling regulates zebrafish embryonic growth and development by promoting cell survival and cell cycle progression. Cell Death Differ. 14, 1095–1105. https://doi.org/10.1038/sj.cdd.4402109.

Schubert, Kristin A., de Vries, G., Vaanholt, Lobke M., Meijer, Harro A.J., Daan, S., Verhulst, S., 2009. Maternal energy allocation to offspring increases with environmental quality in house mice. Am. Nat. 173, 831–840. https://doi.org/10.1086/598495.

Selman, C., Lingard, S., Choudhury, A.I., Batterham, R.L., Claret, M., Clements, M., Ramadani, F., Okkenhaug, K., Schuster, E., Blanc, E., Piper, M.D., Al-Qassab, H., Speakman, J.R., Carmignac, D., Robinson, I.C.A., Thornton, J.M., Gems, D., Partridge, L., Withers, D.J., 2008. Evidence for lifespan extension and delayed age-related biomarkers in insulin receptor substrate 1 null mice. FASEB 22, 807–818. https://doi.org/10.1096/fj.07-9261com.

Seo, K., Choi, E., Lee, D., Jeong, D.-E., Jang, S.K., Lee, S.-J., 2013. Heat shock factor 1 mediates the longevity conferred by inhibition of TOR and insulin/IGF-1 signaling pathways in *C. elegans*. Aging Cell 12, 1073–1081. https://doi.org/10.1111/acel.12140.

Shangguan, Y., Wen, Y., Tan, Y., Qin, J., Jiang, H., Magdalou, J., Chen, L., Wang, H., 2018. Intrauterine programming of glucocorticoid-insulin-like growth factor-1 axis-mediated developmental origin of osteoporosis susceptibility in female offspring rats with prenatal caffeine exposure. Am. J. Pathol. 188, 2863–2876. https://doi.org/10.1016/j.ajpath.2018.08.008.

Shaw, L.M., 2011. The insulin receptor substrate (IRS) proteins: at the intersection of metabolism and cancer. Cell Cycle 10, 1750–1756. https://doi.org/10.4161/cc.10.11.15824.

Sigurjónsdóttir, H.A., Josef, K., Magnus, A., Bengt-Åke, B., Gudmundur, J., 2006. GH effect on enzyme activity of 11βHSD in abdominal obesity is dependent on treatment duration. Eur. J. Endocrinol. 154, 69–74. https://doi.org/10.1530/eje.1.02061.

Sjögren, K., Wallenius, K., Liu, J.-L., Bohlooly-Y, M., Pacini, G., Svensson, L., Törnell, J., Isaksson, O.G.P., Ahrén, B., Jansson, J.-O., Ohlsson, C., 2001. Liver-derived IGF-I is of importance for normal carbohydrate and lipid metabolism. Diabetes 50, 1539–1545. https://doi.org/10.2337/diabetes.50.7.1539.

Smith, H.G., Källander, H., Fontell, K., Ljungström, M., 1988. Feeding frequency and parental division of labour in the double-brooded great tit *Parus major*: effects of manipulating brood size. Behav. Ecol. Sociobiol. 22, 447–453. https://doi.org/10.2307/4600175.

Song, Y.-H., Li, Y., Du, J., Mitch, W.E., Rosenthal, N., Delafontaine, P., 2005. Muscle-specific expression of IGF-1 blocks angiotensin II–induced skeletal muscle wasting. J. Clin. Invest. 115, 451–458. https://doi.org/10.1172/JCI22324.

Sparkman, A.M., Vleck, C.M., Bronikowski, A.M., 2009. Evolutionary ecology of endocrine-mediated life-history variation in the garter snake *Thamnophis elegans*. Ecology 90, 720–728. https://doi.org/10.1890/08-0850.1.

Sparkman, A.M., Byars, D., Ford, N.B., Bronikowski, A.M., 2010. The role of insulin-like growth factor-1 (IGF-1) in growth and reproduction in female brown house snakes (*Lamprophis fuliginosus*). Gen. Comp. Endocrinol 168, 408–414. https://doi.org/10.1016/j.ygcen.2010.05.006.

Stearns, S.C., 1976. Life-history tactics: a review of the ideas. Q. Rev. Biol. 51, 3–47.

Stearns, S.C., 1992. The Evolution of Life Histories. Oxford University Press, Oxford, UK.

Steinkraus, K.A., Smith, E.D., Davis, C., Carr, D., Pendergrass, W.R., Sutphin, G.L., Kennedy, B.K., Kaeberlein, M., 2008. Dietary restriction suppresses proteotoxicity and enhances longevity by an hsf-1-dependent mechanism in *Caenorhabditis elegans*. Aging Cell 7, 394–404. https://doi.org/10.1111/j.1474-9726.2008.00385.x.

Stratikopoulos, E., Szabolcs, M., Dragatsis, I., Klinakis, A., Efstratiadis, A., 2008. The hormonal action of IGF1 in postnatal mouse growth. Proc. Natl. Acad. Sci. USA 105, 19378–19383. https://doi.org/10.1073/pnas.0809223105.

Suttie, J.M., Gluckman, P.D., Butler, J.H., Fennessy, P.F., Corson, I.D., Laas, F.J., 1985. Insulin-like growth factor 1 (Igf-1) antler-stimulating hormone? Endocrinology 116, 846–848. https://doi.org/10.1210/endo-116-2-846.

Swanson, E.M., Dantzer, B., 2014. Insulin-like growth factor-1 is associated with life-history variation across Mammalia. Proc. R. Soc. Biol. Sci. B 281, 20132458. https://doi.org/10.1098/rspb.2013.2458.

Takaya, K., Ariyasu, H., Kanamoto, N., Iwakura, H., Yoshimoto, A., Harada, M., Mori, K., Komatsu, Y., Usui, T., Shimatsu, A., Ogawa, Y., Hosoda, K., Akamizu, T., Kojima, M., Kangawa, K., Nakao, K., 2000. Ghrelin strongly stimulates growth hormone release in humans. J. Clin. Endocrinol. Metab. 85, 4908–4911. https://doi.org/10.1210/jcem.85.12.7167.

Tan, W.Q., Wang, K., Lv, D.Y., Li, P.F., 2008. Foxo3a inhibits cardiomyocyte hypertrophy through transactivating catalase. J. Biol. Chem. 283, 29730–29739. https://doi.org/10.1074/jbc.M805514200.

Thakur, A., Sase, M., Lee, J.J., Thakur, V., Buchmiller, T.L., 2000. Effect of dexamethasone on insulin-like growth factor 1 expression in a rabbit model of growth retardation. J. Pediatr. Surg. 35, 898–905. https://doi.org/10.1053/jpsu.2000.6914.

Tinbergen, J.M., 1987. Costs of reproduction in the great tit - intraseasonal costs associated with brood size. Ardea 75, 111–122.

Tomas-Loba, A., Flores, I., Fernandez-Marcos, P.J., Cayuela, M.L., Maraver, A., Tejera, A., Borras, C., Matheu, A., Klatt, P., Flores, J.M., Vina, J., Serrano, M., Blasco, M.A., 2008. Telomerase reverse transcriptase delays aging in cancer-resistant mice. Cell 135, 609–622. https://doi.org/10.1016/j.cell.2008.09.034.

Tosca, L., Chabrolle, C., Crochet, S., Tesseraud, S., Dupont, J., 2008. IGF-1 receptor signaling pathways and effects of AMPK activation on IGF-1-induced progesterone secretion in hen granulosa cells. Domest. Anim. Endocrinol. 34, 204–216. https://doi.org/10.1016/j.domaniend.2007.03.001.

Underwood, L.E., 1996. Nutritional regulation of IGF-I and IGFBPs. J. Pediatr. Endocrinol. Metab 3 (9 Suppl. l), 303–312.

Unterman, T.G., Jentel, J.J., Oehler, D.T., Lacson, R.G., Hofert, J.F., 1993. Effects of glucocorticoids on circulating levels and hepatic expression of insulin-like growth factor (IGF)-binding proteins and IGF-I in the adrenalectomized streptozotocin-diabetic rat. Endocrinology 133, 2531–2539. https://doi.org/10.1210/endo.133.6.7694841.

Van De Pol, M., Bruinzeel, L.W., Heg, D.I.K., Van Der Jeugd, H.P., Verhulst, S., 2006. A silver spoon for a golden future: long-term effects of natal origin on fitness prospects of oystercatchers (Haematopus ostralegus). J. Anim. Ecol. 75, 616–626. https://doi.org/10.1111/j.1365-2656.2006.01079.x.

Velegrakis, A., Sfakiotaki, M., Sifakis, S., 2017. Human placental growth hormone in normal and abnormal fetal growth. Biomed. Rep 7, 115–122. https://doi.org/10.3892/br.2017.930.

Vitale, G., Pellegrino, G., Vollery, M., Hofland, L.J., 2019. ROLE of IGF-1 system in the modulation of longevity: controversies and new insights from a centenarians' perspective. Front. Endocrinol 10. https://doi.org/10.3389/fendo.2019.00027, 27–27.

Vitku, J., Starka, L., Bicikova, M., Hill, M., Heracek, J., Sosvorova, L., Hampl, R., 2016. Endocrine disruptors and other inhibitors of 11β-hydroxysteroid dehydrogenase 1 and 2: tissue-specific consequences of enzyme inhibition. J. Steroid Biochem. Mol. Biol. 155, 207–216. https://doi.org/10.1016/j.jsbmb.2014.07.007.

Wan, X., Wang, S., Xu, J., Zhuang, L., Xing, K., Zhang, M., Zhu, X., Wang, L., Gao, P., Xi, Q., Sun, J., Zhang, Y., Li, T., Shu, G., Jiang, Q., 2017. Dietary protein-induced hepatic IGF-1 secretion mediated by PPARgamma activation. PLoS ONE 12, e0173174. https://doi.org/10.1371/journal.pone.0173174.

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.1365-2826.2001.00601.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., 2005. Insulin-like growth factor signaling in fish. Int. Rev. Cytol. 243, 215–285. https://doi.org/10.1016/S0074-7696(05)43004-1.

Woods, K., Camacho-Hübner, C., Barter, D., Clark, A., Savage, M., 1997. 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., Arafa, D., Tropea, D., 2017. Insulin-like growth factor 1: 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., Setser, J., Frystyk, J., Boisclair, Y.R., LeRoith, D., 2002. Circulating levels of IGF-1 directly regulate bone growth and density. J. Clin. Invest. 110, 771–781. https://doi.org/10.1172/JCI200215463.

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, 38029–38034. 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/TA.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 maturation 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. Off. Syst. 32, 95–126. https://doi.org/10.1146/annurev.ecolsys.32.081501.114006.

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.