Mediation of vertebrate life histories via insulin-like growth factor-1

Ben Dantzer*† and Eli M. Swanson†

Department of Zoology, Michigan State University, East Lansing, MI, 48824, USA

ABSTRACT

Life-history traits describe parameters associated with growth, size, survival, and reproduction. Life-history variation is a hallmark of biological diversity, yet researchers commonly observe that one of the major axes of life-history variation after controlling for body size involves trade-offs among growth, reproduction, and longevity. This persistent pattern of covariation among these specific traits has engendered a search for shared mechanisms that could constrain or facilitate production of variation in life-history strategies. Endocrine traits are one candidate mechanism that may underlie the integration of life history and other phenotypic traits. However, the vast majority of this research has been on the effects of steroid hormones such as glucocorticoids and androgens on life-history trade-offs. Here we propose an expansion of the focus on glucocorticoids and gonadal hormones and review the potential role of insulin-like growth factor-1 (IGF-1) in shaping the adaptive integration of multiple life-history traits. IGF-1 is a polypeptide metabolic hormone largely produced by the liver. We summarize a vast array of research demonstrating that IGF-1 levels are susceptible to environmental variation and that IGF-1 can have potent stimulatory effects on somatic growth and reproduction but decrease lifespan. We review the few studies in natural populations that have measured plasma IGF-1 concentrations and its associations with life-history traits or other characteristics of the organism or its environment. We focus on two case studies that found support for the hypothesis that IGF-1 mediates adaptive divergence in suites of life-history traits in response to varying ecological conditions or artificial selection. We also examine what we view as potentially fruitful avenues of research on this topic, which until now has been rarely investigated by evolutionary ecologists. We discuss how IGF-1 may facilitate adaptive plasticity in life-history strategies in response to early environmental conditions and also how selection on loci controlling IGF-1 signaling may mediate population divergence and eventual speciation. After consideration of the interactions among androgens, glucocorticoids, and IGF-1 we suggest that IGF-1 be considered a suitable candidate mechanism for mediating life-history traits. Finally, we discuss what we can learn about IGF-1 from studies in free-ranging animals. The voluminous literature in laboratory and domesticated animals documenting relationships among IGF-1, growth, reproduction, and lifespan demonstrates the potential for a number of new research questions to be asked in free-ranging animals. Examining how IGF-1 mediates life-history traits in free-ranging animals could lead to great insight into the mechanisms that influence life-history variation.

Key words: constraint, modularity, glucocorticoids, hormones, life history, phenotypic integration, plasticity, somatotrophic axis, insulin-like growth factor-1, testosterone.

CONTENTS

I. Introduction ........................................................................................................... 415
II. Introduction to insulin-like growth factor-1 ........................................................ 416
III. Relationships between IGF-1 and life-history traits in laboratory and domesticated animals .......................................................... 417
   (1) Overview ............................................................................................................. 417
   (2) Effects of IGF-1 on embryonic and postnatal growth and adult body size ........... 417
   (3) Role of IGF-1 in reproduction ........................................................................... 418
   (4) Effects of IGF-1 on aging and lifespan ................................................................. 418
IV. Pleiotropic effects of IGF-1 on life history traits .................................................. 419

* Address for correspondence (Tel: 517-432-5555; E-mail: bendantzer@gmail.com).
† Authors contributed equally.
I. INTRODUCTION

Life-history traits describe parameters of an organism that are associated with growth, reproduction, and survival (Roff, 1992; Stearns, 1992). Although life-history variation is a hallmark of biological diversity, most empirical studies have found a persistent pattern of covariation among life-history traits and that some combinations of life-history traits simply do not exist in nature (Charnov, 1993; Dunham & Miles, 1985; Harvey & Zammuto, 1985; Promislow & Harvey, 1990; Shine & Charnov, 1992). Understanding why patterns of life-history variation exist is of eminent importance in evolutionary biology given their intrinsic associations with individual fitness and population growth (Roff, 1992; Stearns, 1992).

Correlations among life-history traits can represent life-history strategies. Perhaps the best-studied suite of life-history traits involves positive and negative correlations among traits associated with growth, age at maturity, fecundity, and longevity. Specifically, high growth rates, early age at maturity, and high reproductive rates tend to be associated with shortened lifespan, both in evolutionary life-history theory (Charnov, 2004, 2005; Stearns, 1992; Williams, 1966) and in empirical studies (Cox & Caldebeek, 2010; Gasser et al., 2000; Mertz, 1975; Reznick, 1985; Reznick, Nunney & Tessier, 2000; Sinervo & DeNardo, 1996; Snell & King, 1977; Stearns, 1983). A similar suite of life-history traits, generally excluding somatic growth rate, but including the closely related ‘age at sexual maturity’ has also been described as a ‘fast-slow’ continuum of life-history variation in comparative studies of some taxa, with animals that grow quickly, reproduce early and often, but die more quickly at the ‘fast’ end (Bielby et al., 2007; Careau et al., 2010; Dobson & Oli, 2007; Oli, 2004).

Correlations among life-history traits such as growth, reproduction, and lifespan can reflect past or current selection acting to produce beneficial combinations of life-history traits (Roff, 1992, 2007; Sinervo & Svensson, 2002; Stearns, 1992). Much of the research to date on life-history variation has explored the evolutionary reasons to expect these trade-offs, and we have developed a fairly good understanding of the predictions for life-history evolution under different environmental conditions (Charnov, 1993; Shine & Charnov, 1992; Stearns, 1992; Vasi, Travisano & Lenski, 1994).

Such combinations of life-history traits such as reproduction, growth and lifespan may in fact be beneficial as a result of physiological trade-offs due to allocation of limited resources (Reznick et al., 2000; Ricklefs & Wikelski, 2002; Sinervo & Svensson, 1998; Stearns, 1989, 1992; Van Noordwijk & De Jong, 1986; Zera & Harshman, 2001). Here, shared physiological mechanisms can have opposing or concerted effects on different life-history traits. If there is genetic variation underlying these physiological mechanisms, such a simplified system in which a physiological mechanism has pleiotropic effects on multiple life-history traits could enable a coordinated, rapid, and adaptive response to selection (Finch & Rose, 1995; McGlothlin & Ketterson, 2008; Stearns, 1989, 1992). Therefore, we might expect the presence of proximate mechanisms with pleiotropic effects on life-history traits that produce beneficial combinations of life-history traits.

Hormones are intrinsically linked to energy allocation and affect multiple physiological, morphological, and behavioural characteristics. Accordingly, hormones may underlie the integration of multiple phenotypic and life-history traits and they are thought to mediate life-history trade-offs (Ketterson & Nolan, 1992; Ricklefs & Wikelski, 2002; Sinervo & Svensson, 1998; Zera & Harshman, 2001; Zera, Harshman & Williams, 2007). For example, testosterone is a metabolic hormone that can positively affect growth and investment in reproduction but decrease survival (Hau, 2007). Thus, selection acting on one life-history trait could produce a correlated and beneficial response due to the pleiotropic effects of testosterone (Ketterson, Atwell & McGlothlin, 2009; McGlothlin & Ketterson, 2008). Although these and similar studies on other steroid hormones have proven invaluable in demonstrating that shared hormonal mechanisms may underlie life-history trade-offs (Boonstra, 2005; Hau, 2007;
Ketterson *et al*., 2009; Ketterson & Nolan, 1992; Ketterson, Nolan & Sandell, 2005; McGlothlin & Ketterson, 2008; Ricklefs & Wikelski, 2002; Romero, 2004; Sinervo & Svensson, 1998), other hormones that have received less attention from evolutionary ecologists may prove to be equally suitable candidate mechanisms. Here we review the relevant literature to propose that insulin-like growth factor-1 (IGF-1) might play a central role in life-history trade-offs in free-ranging vertebrates. Although we refer to selection on IGF-1 signaling, we use this shortened terminology to mean selection on life-history traits whose expression is affected by IGF-1 signaling.

IGF-1 is a polypeptide metabolic hormone that has been shown to influence the key life-history traits involved in a major life-history trade-off among growth, reproduction, and lifespan. Here, we review the wealth of information from previous studies in laboratory and agricultural animals that shows that IGF-1 is a potent stimulator of growth and reproduction but decreases lifespan. We then review the empirical work in natural populations, and suggest what we view as potentially fruitful avenues of research. Although we largely focus on the effects of IGF-1 signaling in free-ranging vertebrate species and especially mammalian species, the functions of IGF-1 and its homologues are highly conserved, and thus similar questions and future avenues of research proposed below remain valid for other vertebrate and invertebrate species as well (Zera *et al*., 2007).

II. INTRODUCTION TO INSULIN-LIKE GROWTH FACTOR-1

The insulin and insulin-like ligand signaling pathways have been well characterized in a number of species and there is strong evolutionary conservation of molecular mechanisms and function among vertebrate species (Carter, Ramsey & Sonntag, 2002; Narasimhan, Yen & Tissenbaum, 2009; Pertseva & Shpakov, 2002). Invertebrates have several insulin-like ligands with similar functions (Brogiolo *et al*., 2001; Leevers, 2001), whereas many vertebrate species studied to date have three: insulin, insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-2 (IGF-2; Butler & LeRoith, 2001; Jones & Clemmons, 1995; McMurtry, Francis & Upton, 1997).

Previously known as sulfation factors (Salmon & Daughaday, 1957) or somatomedin C (Clemmons & Underwood, 1991; Daughaday *et al*., 1972), IGF-1 has a molecular structure similar to that of insulin (Clemmons & Underwood, 1991; Klapper, Svoboda & Van Wyk, 1983; Rinderknecht & Humbel, 1978; Ullrich *et al*., 1986). Production and release of growth hormone (GH) from the anterior pituitary is regulated via release of GH-releasing hormone and somatostatin from the hypothalamus (Fig. 1; Brazeau *et al*., 1973; Jones & Clemmons, 1995; López-Fernández *et al*., 1996). The release of GH increases cellular production of IGF-1 in the liver and this endocrine IGF-1 has a major influence on various traits that we discuss below.

*Fig. 1.* Production of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in response to environmental stimuli and its effects on somatic growth in vertebrates. The figure represents a hypothetical relationship in which environmental information causes an increase in production of somatostatin (growth-hormone-inhibiting hormone) or growth-hormone-releasing hormone (GHRH) in the hypothalamus, which then causes a decrease or increase, respectively, in the release of GH in the anterior pituitary. An increase in GH levels causes an increase in hepatic production of IGF-1, which can then cause negative feedback on IGF-1 production at the level of the hypothalamus and pituitary. The release of GH in the anterior pituitary can directly increase growth of skeletal and smooth muscle but most of the anabolic effects of GH are mediated through IGF-1. The potential for local production (autocrine or paracrine) of IGF-1 in muscle tissues (dotted line) is also indicated. Solid lines indicate positive relationships while dashed lines indicate negative relationships. IGF-1R represents the receptor for unbound IGF-1. The multiple binding proteins that are often bound to and inactivate IGF-1 are not shown here.

(Stratikopoulos *et al*., 2008). However, local production also occurs in other tissues (Butler & LeRoith, 2001; Clemmons & Underwood, 1991; Sjogren *et al*., 1999; Yakar *et al*., 1999). Increased circulation of IGF-1 in the plasma reduces GH production through negative feedback at the level of the hypothalamus and pituitary (Fig. 1; Berelowitz *et al*., 1981; Tannenbaum, Guyda & Posner, 1983).

Invertebrates appear to have a single receptor for all insulin-like ligands (Barbieri et al., 2003), but vertebrates appear to have separate but homologous insulin and IGF-1 receptors, which modulate distinct processes (Morgan et al., 1997; Narasimhan et al., 2009; Rinderknecht & Humbel, 1978; Ullrich et al., 1986). Most circulating IGF-1 is bound to one of six of its binding proteins (IGFBP; Hwa, Oh & Rosenfeld, 1999; Rajaram, Baylink & Mohan, 1997), but unbound IGF-1 can bind to both insulin-specific and IGF-1-specific (IGF-1R) receptors (Butler & LeRoith, 2001; LeRoith et al., 1995; Nakae, Kido & Accili, 2001). However, IGF-1 binds to IGF-1R with a much greater affinity than to insulin-specific receptors (Clemmons & Underwood, 1991; LeRoith et al., 1995; Nakae et al., 2001). IGF-1Rs are transmembrane tyrosine kinase receptors; binding by IGF-1 causes a conformational change and autophosphorylation of IGF-1R, which allows these receptors to modulate intracellular processes via phosphorylation of specific proteins (Butler et al., 1998; Kadowaki et al., 1987; LeRoith et al., 1995; Nakae et al., 2001; Schlessinger, 2000). Collectively, in vertebrates, this system of GH, IGF-1, IGF-II as well as their binding proteins and receptors is generally referred to as the somatotrophic axis.

III. RELATIONSHIPS BETWEEN IGF-1 AND LIFE-HISTORY TRAITS IN LABORATORY AND DOMESTICATED ANIMALS

(1) Overview

Historically, the role of IGF-1 was viewed as only mediating the effects of growth hormone (GH), but now IGF-1 is thought to have its own distinct role (Butler & LeRoith, 2001; Carter et al., 2002; Jones & Clemmons, 1995). In vertebrates, insulin primarily regulates metabolism, whereas IGF-1 is thought to influence cell growth, differentiation, and survival (Jones & Clemmons, 1995; Kenyon, 2010; LeRoith et al., 1995). Although the exact mechanisms are far from clear, numerous studies in laboratory and domesticated animals have permitted some generalizations about the effects of IGF-1. Specifically, IGF-1 is a necessary factor for embryonic and postnatal growth, and for normal functioning of the reproductive system in both sexes, in addition to having an influence on lifespan. Heightened activity of IGF-1R caused by high levels of plasma IGF-1 is associated with increased postnatal growth (Baker et al., 1993; Jones, 1995; Scanes, 2009) and reproductive output (Baker et al., 1996; Hiney et al., 1996), but decreased lifespan (Bartke, 2005; Fontana, Partridge & Longo, 2010; Kenyon, 2010). Below we review the evidence for associations between IGF-1 signaling and life-history traits in laboratory and domesticated animals.

(2) Effects of IGF-1 on embryonic and postnatal growth and adult body size

The “somatomedin hypothesis” was first proposed (Salmon & Daughaday, 1957) to explain how somatic growth was regulated by a then unknown intermediary substance whose production was controlled by pituitary growth hormone (Butler & LeRoith, 2001; LeRoith et al., 2001). This hypothesis proposed that pituitary growth hormone (GH) encouraged hepatic secretion of what we now know as IGF-1, which then circulated throughout the body, stimulating growth in connective tissue and bones, and exerted negative feedback on pituitary GH production (Butler & LeRoith, 2001; LeRoith et al., 2001). More recent studies have corroborated most of this hypothesis, but have also shown that IGF-1 is produced in other cells throughout the body during embryonic and postnatal life, which can have powerful autocrine and paracrine effects on somatic growth (Butler & LeRoith, 2001; Sjogren et al., 1999; Yakar et al., 1999). However, the effects of IGF-1 on postnatal growth, as well as other traits, may be due in part to endocrine processes (Stratikopoulos et al., 2008), which bodes well for studies that correlate plasma IGF-1 concentrations with life-history traits.

While the original somatomedin hypothesis has been refined, the overall conclusion that IGF-1 is an essential and potent driver of embryonic and postnatal growth has been widely supported in most vertebrate species. IGF-1 appears to influence postnatal growth through its positive effects on cell growth, proliferation, and survival, which can occur through autocrine, paracrine, or endocrine processes (Sjogren et al., 1999; Stratikopoulos et al., 2008; Yakar et al., 1999). Most cell types have IGF-1Rs and the activation of IGF-1Rs stimulates growth and/or proliferation in a variety of cell types including adipocytes, fibroblasts, lymphocytes, chondrocytes, osteoblasts, epithelial cells, and smooth and skeletal muscle cells (Baserga, Prisco & Hongo, 1999; Baxter & Twigg, 2009; Butler & LeRoith, 2001; Duan, Ren & Gao, 2010; Froesch et al., 1985; Kawai & Rosen, 2010; Leach & Twal, 1994).

IGF-1 and IGF-1R knockout (KO) mouse models and transgenic mice in which IGF-1 has been overexpressed have provided some of the clearest evidence of the importance of IGF-1 for postnatal growth. For example, in IGF-1 KO mice, birth mass and adult body size are reduced to 60% and 30%, respectively, compared to littermate controls (Baker et al., 1993; Romero et al., 2010). Local or global overexpression of IGF-1 in transgenic mice can increase the rate of skeletal muscle proliferation and differentiation, as well as the growth of brain, connective, and adipose tissue (D’Ercole, 1999; Stratikopoulos et al., 2008).

The effects of IGF-1 signaling on somatic growth have been increasingly exploited in agricultural and fisheries research to manipulate the growth and skeletal muscle characteristics of animals grown for human consumption. For example, domesticated sheep that have been artificially selected for increased plasma IGF-1 concentrations exhibit higher postnatal growth rates until weaning than unselected sheep (Kenyon et al., 2009; Kenyon et al., 2007). Although the relationship between postnatal growth and IGF-1 in avian species is generally more ambiguous than in mammals (McMurtry, 1998; Scanes, 2009), domesticated chickens that have been artificially selected for high postnatal growth
rates have higher plasma IGF-1 concentrations than those selected for low postnatal growth rates (Beccavin et al., 2001; see also Tomas et al., 1998). Injections of IGF-1 can be used to increase skeletal muscle mass in domesticated pigs, and transgenic pigs expressing increased IGF-1 in skeletal muscle have been developed to increase overall muscle development (Huí et al., 2001). Lastly, transgenic salmonid fishes with up-regulated GH expression grow significantly faster than their age-matched counterparts (Devlin et al., 1994).

These studies and others have shown that the growth-promoting effects of IGF-1 result in accelerated embryonic or postnatal growth, which may or may not result in increased adult body size in animals with determinate growth, as well. While the most detailed studies have been performed in select laboratory and domesticated animals, they clearly demonstrate the importance of IGF-1 signaling in postnatal growth in vertebrates. Lastly, recent studies in non-traditional captive animals such as seals (Richmond, Norris & Zinn, 2010) and snakes (Sparkman et al., 2010) have supported the view that plasma IGF-1 concentrations are positively correlated with overall growth rates.

(3) Role of IGF-1 in reproduction

In addition to its role in directing somatic growth, IGF-1 is necessary for proper functioning of the male and female reproductive systems, and therefore has important consequences for life-history traits. IGF-1 augments the rate of steriodogenesis of reproductive hormones as well as the cellular growth of specific reproductive structures. For example, activation of IGF-1Rs stimulates ovarian production of estradiol and progesterone (Demeestere et al., 2004; Giudice, 1999; Onagbesan & Peddie, 1995; Wilson, 1998) and testicular production of testosterone (Wang & Hardy, 2004; Weinzimer & Cohen, 1999). In mammals and birds, the increased production of these reproductive steroid hormones is thought to be through the mitogenic effects of IGF-1 on ovarian granulosa, granulosa-luteal, and theca cells (Giudice, 1999; McMurtry et al., 1997; Onagbesan et al., 1999), as well as Leydig cells in the testes (Côlon et al., 2007; Wang & Hardy, 2004; Weinzimer & Cohen, 1999).

IGF-1 and IGF-1R KO mice have again provided some of the most convincing evidence of the importance of IGF-1 in reproduction, as IGF-1 KO mice are effectively infertile. Compared to normal mice, IGF-1 KO mice have highly reduced testis, ovary, and uterus sizes and their circulating testosterone and estradiol concentrations are significantly lower (Baker et al., 1996; D’Ercole, 1999; Wang & Hardy, 2004). Female IGF-1 KO mice do not have corpora lutea and do not ovulate spontaneously or in response to gonadotropin-releasing hormone (GnRH; Baker et al., 1996; D’Ercole, 1999). Although male IGF-1 KO mice possess viable sperm, spermatogenesis is highly reduced compared to normal mice, and IGF-1 KO males do not exhibit mounting behaviour when paired with females (Baker et al., 1996; D’Ercole, 1999). The effects of IGF-1 signaling on fertility appear independent of GH and IGF-2, as growth hormone receptor (GH-R) and IGF-2 KO mice are fertile but IGF-1 KO mice are not (Butler & LeRoith, 2001; Danilovich et al., 1999; Dechiara, Efstratiadis & Robertson, 1990; Zhou et al., 1997).

Laboratory studies with various vertebrate species have demonstrated that variation in plasma IGF-1 concentrations may influence life-history traits such as age at first reproduction and litter size. In many vertebrates, sexual maturation is associated with rising plasma IGF-1 concentrations (Chandrashekaran, Zaczek & Bartke, 2004; Daftary & Gore, 2005). In laboratory and agricultural animals, heightened plasma IGF-1 concentrations are associated with younger age of first ovulation (Moyes et al., 2004; Velazquez, Spicer & Wathes, 2008; Wilson, 1998) and experimental supplementation of IGF-1 advances the age of puberty (Danilovich et al., 1999; Groaz et al., 1997; Hiney et al., 1996; Wilson, 1998). This association between IGF-1 signaling and age at sexual maturity may be due to the stimulatory effects of IGF-1 on rates of ovarian follicular and oocyte maturation and/or the hypothalamic-pituitary-gonadal axis. For example, IGF-1 influences the production of gonadal steroid hormones through a variety of mechanisms around the period of sexual maturation (Daftary & Gore, 2005; Hiney et al., 1996, 2009; Pine et al., 2006; Todd et al., 2010). Additionally, in vitro studies have demonstrated that IGF-1 can accelerate the rate of maturation of ovarian follicles and human oocytes (Adashi et al., 1985; Demeestere et al., 2004; Gomez, Tarin & Pellicer, 1993; Nelson & Van Der Kraak, 2010). As such, IGF-1 has a stimulatory role in reproduction and this could potentially influence the inter-birth interval in multiparous species. Variation in IGF-1 signaling may also influence litter size independent of maternal body size. For example, litter size was reduced in mice in which IGFBP-1 was overexpressed (Gay et al., 1997). These examples demonstrate a potentially important source of variation in life-history traits that could easily be quantified in free-ranging vertebrate species.

(4) Effects of IGF-1 on aging and lifespan

Perhaps the most widely studied and intriguing effect of IGF-1 and its homologues in invertebrates (insulin-like ligands) is on the rate of aging and lifespan. Such effects have received various levels of support in yeast, worms, flies, mice, dogs, and humans (Barbieri et al., 2003; Bartke, 2005; Fontana et al., 2010; Kenyon, 2010; Narasimhan et al., 2009). The insulin/IGF-1 signaling pathway is perhaps the best-characterized mechanism that affects longevity among several others that have also been described (Fontana et al., 2010; Kenyon, 2010). Although this review focuses on vertebrate species, the most striking and well-documented examples of lifespan extension through reduced insulin/IGF-1 pathway signaling come from invertebrate model animals. For example, targeted disruption of the insulin-signaling pathway that decreases the levels of the insulin/IGF-1 receptor homologues daf-2 in Caenorhabditis elegans and insulin-like receptor in Drosophila can increase lifespan up to 250% (Arantes-Oliveira, Berman & Kenyon, 2010).
In vertebrates, the relationship between IGF-1 signaling and lifespan was first observed in Ames and Snell mice that exhibit hereditary dwarfism due to a lack of GH production and a major reduction in plasma IGF-1 concentrations (Berryman et al., 2003; Liang et al., 2003). Compared to wild-type controls, the Ames and Snell dwarf mice exhibit reduced signs of aging (e.g. increased resistance to oxidative and cellular stress, no age-related decline in locomotor activity) and their lifespan is extended up to 68% and 76%, respectively (Bartke, 2005; Berryman et al., 2008; Liang et al., 2003). More causal evidence comes from mice in which the IGF-1R gene (Igf1r) is inactivated using gene knockout techniques (Holzenberger et al., 2003). IGF-1R densities were approximately halved in otherwise normal heterozygous Igf1r KO mice (Holzenberger et al., 2003). Heterozygous Igf1r KO females lived 33% longer than wild-type littermates, whereas lifespan was not significantly extended in males. Homozygous knockout mice with complete inactivation of Igf1r died at birth. More recently, mice with partially inactivated brain IGF-1Rs were generated using brain-specific Igf1r knockout mice (Kappeler et al., 2008). Both male and female mice with half the brain IGF-1Rs of wild-type mice lived significantly longer than wild-type control littermates (Kappeler et al., 2008).

Observational studies in domesticated dogs and in humans have also indirectly demonstrated a relationship between IGF-1R activity and lifespan. Small dogs live longer than large dogs and some of the size and lifespan differences may be due to a single-nucleotide polymorphism at the IGF-1 gene (IGF1) in small dogs that also have lowered plasma IGF-1 concentrations (Sutter et al., 2007). Additionally, long-lived humans show overrepresentation of mutations or variant alleles in the IGFIIR gene that are associated with reduced activity of IGF-1R (Suh et al., 2008) or low levels of plasma IGF-1 concentrations (Bonań et al., 2003; Guevara-Aguirre et al., 2011).

Although the link between insulin-signaling pathways and lifespan is pervasive and highly conserved across taxa, the downstream mechanisms driving this avenue of lifespan extension in invertebrates and vertebrates are varied and currently under investigation (Fontana et al., 2010; Kenyon, 2010). However, in both invertebrates and vertebrates, one major link between IGF-1 and its homologues and lifespan appears to be mediated by the downstream effects of these hormones on the activity of Forkhead box transcription factors. These relationships have been explored in detail in invertebrate models and are being examined indirectly in vertebrates. In C. elegans and Drosophila, the lifespan-extending effects of reduced insulin-signaling are dependent upon decreased phosphorylation of the Forkhead box transcription factors daf-16 (Kenyon et al., 1993; Lin et al., 1997; Ogg et al., 1997) and dFOXO (Giannakou & Partridge, 2007; Giannakou et al., 2004; Hwangbo et al., 2004), respectively. Observational studies in humans have also supported a relationship between FOXO activity and lifespan. For example, polymorphisms in the Forkhead box O3A (FOXO3A) gene in humans, which is homologous to daf-16 in C. elegans, is associated with longevity in independent populations of long-lived humans (Flachsbart et al., 2009; Kuningas et al., 2007; Wilcox et al., 2008).

The Forkhead box transcription factors affected by IGF-1 or its homologues are thought to upregulate or downregulate a variety of genes associated with cellular stress responses, antimicrobial activity, and resistance to oxidative stress or xenobiotics, which consequently lengthens the lifespan (Fontana et al., 2010; Kenyon, 2010; Murphy et al., 2003). In vertebrates, one major hypothesized mechanism behind lifespan extension under reduced insulin/IGF-1 signaling in several taxa is increased resistance to oxidative stress, but the evidence supporting this hypothesis is equivocal. For example, mice with fewer IGF-1Rs in several tissues showed increased resistance to oxidative stress and lived longer than their control littermates (Holzenberger et al., 2003). However, in a separate experiment, mice with fewer brain IGF-1Rs lived longer than their control littermates but did not have a higher probability of survival following heightened oxidative stress (Kappeler et al., 2008).

The downstream mechanisms that foster an extended lifespan and buffer individuals with reduced IGF-1 signaling from aging represent an active area of research in vertebrate model animals. Nonetheless, there is convincing evidence demonstrating a clear and conserved link between IGF-1 or its homologues and lifespan. However, there is still much to be learned about how IGF-1 signaling affects lifespan in vertebrate laboratory animals, such as understanding how the timing of reduced IGF-1 signaling prior to or during adulthood affects lifespan (Dillin, Crawford & Kenyon, 2002) and elucidating the apparently separate but interactive effects of dietary restriction and IGF-1 signaling on lifespan (Grandison, Piper & Partridge, 2009; Kenyon, 2010).

IV. PLEIOTROPIC EFFECTS OF IGF-1 ON LIFE HISTORY TRAITS

Circulating IGF-1 is positively associated with growth rates and reproductive activity, and negatively associated with lifespan. This specific relationship, where growth rate and reproductive activity are positively correlated with each other, and both negatively correlated with lifespan, is predicted generally to be beneficial by life-history theory, assuming physiological costs to growth and reproduction (Sears, 1992). This suggests that IGF-1 could act as an adaptive shared mechanism driving these beneficial combinations, as the mechanism underlying the physiological cost, or as both. A mechanism that pleiotropically influences multiple traits simultaneously in directions that should be adaptive with respect to each other would be predicted generally to facilitate evolution (McGlothlin & Ketterson, 2008). However, such pleiotropic mechanisms may also constrain the rate of evolution, if specific ecological conditions...
lead to a situation where an atypical combination of life-history traits is adaptive. Such atypical combinations can sometimes be optimal, because subtle or extrinsic differences in ecology can lead to different predictions. For example, although both predation and nutrient limitation represent sources of juvenile mortality in fish, size-specific selection on juvenile fish generally selects for fast growth (Urban, 2007), while nutrient limitation will often select for slow growth (see Blanckenhorn, 2000). Thus, predictions concerning the direction of the resulting evolution of growth rates are dependent upon not only the direction of change in juvenile mortality, but the actual source of mortality, and thus on the specific ecology of a species. For some traits such ambiguity may be common. As a result, for life-history traits, we should expect shared mechanisms to be the norm, yet the ability to break away from the shared mechanism should be maintained, or maladaptive combinations could occur. Certainly, genetic correlations can be broken fairly quickly for morphological traits (Agrawal, Conner & Rasmann, 2010; Conner, 2003; Frankino et al., 2005) and colour polymorphisms (Beldade, Koops & Brakefield, 2002).

One possibility is that the ability to select against perhaps the most important axis of life-history variation is maintained through second-order selection for evolvability (e.g. Woods et al., 2011). The second possibility potentially maintaining the ability to break this genetic correlation and avoid strong constraints on the rate of evolution is simply that it may be difficult to completely deplete genetic variation along the axes of lesser variation, and as long as variation is present it can be selected upon (Agrawal et al., 2010). This remaining variation may represent the action of other hormones, variation in temporal or locational specificity of IGF-1 expression or binding, or some alternative mechanism. While laboratory and agricultural studies provide us with a solid background on the effects of IGF-1, studies in natural populations are necessary to understand the importance of the role that IGF-1 plays in natural systems. Data from natural systems are especially needed to understand better the relationship between traits influenced by IGF-1 and fitness, as well as how these traits respond to selection.

V. EFFECTS OF VARIATION IN PLASMA IGF-1 CONCENTRATIONS IN FREE-RANGING ANIMALS

(1) Overview

Although they remain less common, there have been several observational studies documenting plasma IGF-1 concentrations in vertebrate species that are not commonly used in laboratory or domestic animal research. Many of these studies have measured plasma IGF-1 concentrations in captive- or hatchery-reared animals (Beckman, 2011), and although such studies are valuable, the relationship between IGF-1 signaling, life-history traits, and fitness can only be documented fully in free-ranging animals. Thus, we instead focus on studies in natural populations that have measured associations between IGF-1 signaling (plasma IGF-1 concentrations), the environment, and/or life-history traits or other traits potentially affecting fitness (Table 1). All studies on IGF-1 concentrations in truly free-ranging species that we are aware of are included in Table 1.

(2) Summary of observational studies

Several observational studies in natural populations have corroborated a relationship between plasma IGF-1 concentrations and postnatal growth rate. However, obtaining repeated measures of mass or structural size in free-ranging animals is difficult and therefore no study that we are aware of has measured the relationship between IGF-1 and growth. However, several studies in free-ranging animals have at least found a relationship between plasma IGF-1 concentrations and adult body size. For example, plasma IGF-1 concentrations measured in adults are positively associated with adult body size in free-ranging loggerhead turtles (Caretta caretta; Crain et al., 1995), white-tailed deer (Odocoileus virginianus; Ditchkoff et al., 2001), and garter snakes (Thamnophis elegans; Sparkman, Vleck & Bronikowski, 2009). One caveat here is that positive associations between IGF-1 and body size can potentially reflect different metabolic rates, different rates of food intake, or different growth rates. These studies are strictly observational but future studies in natural populations that examine the effects of experimental manipulation of prenatal exposure to androgens (e.g. testosterone: Groothuis et al., 2005) and glucocorticoids (GCs: Meylan & Clobert, 2005) on postnatal growth rates might also examine how these hormonal manipulations affect plasma IGF-1 concentrations or perhaps even directly manipulate IGF-1 levels.

A few studies in natural populations have documented a positive relationship between plasma IGF-1 concentrations and traits potentially associated with fitness (e.g. antler size and social dominance rank). For example, a positive relationship between plasma IGF-1 concentrations and antler size in white-tailed deer (Ditchkoff et al., 2001) may imply a functional role of IGF-1 affecting fitness-related traits in this polygynous species. Secondly, Sapolsky & Spencer (1997) demonstrated that low-ranking male savannah baboons (Papio anubis) exhibited suppressed plasma IGF-1 concentrations, which were presumed to be due to their low rank after ruling out age, stress, and nutrition as factors driving suppression. Because lower ranking males have less access to estrous females (Bulger, 1993), IGF-1 concentrations corrected for age, stress, and nutrition may directly predict reproductive success in this species.

(3) Case study of relationships between IGF-1 and life-history traits in garter snakes

Currently the most comprehensive example that combines measurements of both IGF-1 signaling and life-history traits in free-ranging animals comes from two different ecotypes of garter snakes in California that have recently evolved
Table 1. Summary of all known studies measuring associations between concentrations of plasma insulin-like growth factor-1 (IGF-1) and life-history traits or other characteristics in free-ranging vertebrates. We only include studies in which the animals were demonstrably free-ranging and not captive, fed, or otherwise subject to hatchery or captive conditions at any point in their lives. Traits or other features that were significantly associated with plasma IGF-1 concentrations are indicated in bold.

<table>
<thead>
<tr>
<th>Taxa</th>
<th>Species</th>
<th>Association with life-history traits</th>
<th>Other associations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reptiles</td>
<td>Loggerhead turtles</td>
<td>Body size ↑</td>
<td>Sex, season</td>
<td>Crain et al. (1995)</td>
</tr>
<tr>
<td></td>
<td>(Caretta caretta)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>American alligator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Alligator mississippiensis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Garter snake</td>
<td>Body size↑ or ↓, reproductive output↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Thamnophis elegans)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammals</td>
<td>Rhesus macaque</td>
<td>Body size ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Macaca mulatta)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Savannah baboon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Papio anubis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muskoxen (Ovibos moschatus)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>White-tailed deer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Odocoileus virginianus)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Japanese macaque</td>
<td>Body size ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Macaca fuscata)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grizzly bear (Ursus arctos)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yellowstone elk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Cervus canadensis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polar bear (Ursus maritimus)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aDirection of relationship between IGF-1 and body size depends upon snake ecotype.
bRelationship between IGF-1 and reproductive output only for female snakes.
cPlasma IGF-1 concentrations decreased with age in males.
dPlasma IGF-1 concentrations increased with age until sexual maturity in males and females.

from a common ancestor (Bronikowski & Arnold, 1999; Manier & Arnold, 2005). In this population of garter snakes, the “meadow” ecotype lives in mountain meadows with variable food abundance while the “lakeshore” ecotype lives near lakeshores with more plentiful and consistent food availability (Bronikowski & Arnold, 1999). These two ecotypes have divergent life histories, with the meadow ecotype having lower growth rates, later sexual maturation, but lower mortality compared to the lakeshore ecotype (Bronikowski & Arnold, 1999).

A recent study examining the physiological basis of these divergent life-history traits found that snakes of the slow-growth meadow ecotype with lower reproduction and lower mortality than the fast-growth ecotype also had lower plasma IGF-1 concentrations (Sparkman et al., 2009). However, these relationships were somewhat more complex as they depended on reproductive status and season. For example, in one year of the three years of study, males and nongravid females of the meadow ecotype actually had significantly higher IGF-1 concentrations than the lakeshore ecotype. Body size and plasma IGF-1 concentrations were either positively (lakeshore ecotype), negatively (meadow ecotype), or not (meadow ecotype) associated depending upon the year in which they were measured. In both meadow and lakeshore ecotypes, IGF-1 concentrations were positively associated with reproductive output (total litter mass). While this example comes from an observational study, it highlights the potential role for IGF-1 in mediating life-history trade-offs among growth, reproduction, and longevity in free-ranging animals and should stimulate further research examining relationships between IGF-1 signaling and life-history traits. This example also illustrates that if selection acts upon life-history traits that are affected by IGF-1 signaling, it could produce correlated responses in other life-history traits that are predicted to be beneficial based upon life-history theory.

VI. FUTURE AVENUES OF IGF-1 RESEARCH IN FREE-RANGING ANIMALS

1) Can changes in IGF-1 signaling enable adaptive plasticity in life-history strategies?

A central feature of IGF-1 signaling is its plasticity and responsiveness to environmental variation in resource availability. Plasma IGF-1 concentrations vary in response to nutrition (Clemmons & Underwood, 1991; McGuire et al., 1992; Straus, 1994) to the degree that they could be used as indicators of nutritional status or overall condition (Richmond et al., 2010; Ross et al., 1991). Food restriction is generally associated with decreased plasma IGF-1 concentrations, which may be due to GH resistance rather than a direct effect of nutritional information on IGF-1 production (Clemmons & Underwood, 1991).

Pre- and postnatal food restriction can have interesting and lifelong programming effects on IGF-1 production.
and consequently offspring growth trajectories and adult body size (McMillen & Robinson, 2005; Woodall et al., 1996). For example, juvenile laboratory mice exposed to short periods of nutritional restriction prior to weaning (0–16 days post-parturition) had significantly lower plasma IGF-1 concentrations and somatotrophic activity in general than control or overfed mice during and after the period of food restriction (up to 20–90 days post-parturition: Kappeler et al., 2008, 2009). Mice that were exposed to nutrition restriction were also significantly smaller both in length and weight during and after the period of nutritional restriction (Kappeler et al., 2008, 2009). Here, nutrition restriction prior to weaning that caused a reduction in plasma IGF-1 concentrations actually simulated the same negative effects on growth and body size as mice with partially inactivated brain IGF-1Rs (Kappeler et al., 2008).

The responsiveness of IGF-1 to external resource levels may enable adaptive adjustment of postnatal growth, body size, and other characteristics that match the predicted resource levels (i.e. adaptive developmental plasticity or predicted adaptive response). Periods of prenatal or postnatal nutritional restriction are commonly associated with persistent consequences on postnatal growth, body mass, insulin sensitivity, as well as a constellation of other chronic health effects that are generally viewed as disruptive in humans (Bateson et al., 2004; Gluckman & Hanson, 2004; Godfrey, Gluckman & Hanson, 2010; McMillen & Robinson, 2005). When viewed from the point of view of free-ranging animals, the plastic response to nutritional availability and consequent lifelong phenotypic consequences mediated by changes in IGF-1 signaling may have evolved due to selection to maximize offspring or maternal fitness. For example, these lifelong phenotypic changes mediated by IGF-1 may maximize offspring fitness by matching offspring phenotype to the predicted environment that they will encounter as adults (Gluckman & Hanson, 2004; Gluckman, Hanson & Beedle, 2007). However, there may be sex differences in the persistence of early environmental experiences such as intrauterine or postnatal nutrition restriction (Wilkin & Sheldon, 2009). Therefore, male and female offspring may differ in their sensitivity or response to variation in the early nutritional environment (Gatford et al., 1998). On the other hand, the plastic phenotypic response to early nutrition mediated by IGF-1 may have evolved to maximize maternal fitness by matching offspring phenotype to the maternal environment (Love & Williams, 2008; Marshall & Uller, 2007). Of course there may be maternal-offspring conflict or agreement in these strategies, which could decrease or increase offspring sensitivity to these maternal cues about their predicted resource environment (Uller, 2008).

Studies in natural populations are complicated by the difficulty of decoupling the plastic response of IGF-1 to nutrition from genetic variation in IGF-1 production. For example, the observed differences in plasma IGF-1 concentrations between the meadow and lakeshore ecotypes of the garter snake described above might be due to genetic differences in IGF-1 production due to past divergent selection for life-history traits in the two habitats. On the other hand, these differences between the ecotypes might be due to plastic responses in IGF-1 due to seasonal or variable food availability (Sparkman et al., 2009). The latter is illustrated by the finding that in one year of study, plasma IGF-1 concentrations in snakes from the meadow habitat significantly declined over time (May–June) while those from the lakeshore habitat did not. In this year, the authors noted that food availability in the meadow habitat was restricted whereas it was not in the lakeshore habitat. Therefore, these differences between the two ecotypes could be due to plastic responses to the environment such as consistent differences in food abundance between the lakeshore and meadow habitats (Sparkman et al., 2009).

The plasticity of IGF-1 signaling in response to variation in the maternal or external resource environment and its persistent consequences for growth could enable plastic modification of life-history decisions in response to nutrition or other environmental information (Gluckman et al., 2007; McMillen & Robinson, 2005). Under poor conditions, this plasticity would allow organisms to slow reproduction and growth, waiting for favourable conditions, or taking advantage of such conditions when they arrive to grow quickly and reproduce rapidly. Understanding when relationships between IGF-1 and life-history traits in individual species are due to genetic variation in IGF-1 production or plastic responses to variation in food availability will require careful experimentation (e.g. common garden experiments) or long-term monitoring in natural populations. In particular, these relationships can be elucidated by obtaining repeated measures of plasma IGF-1 concentrations, growth, and reproduction across the lifespan of individually marked animals that are monitored from birth until death. In study systems in which a multigenerational pedigree is available, these studies can also examine the importance of interindividual genetic variation in IGF-1 production versus the plastic response of IGF-1 to the environment.

(2) Can changes in IGF-1 signaling drive rapid divergence and speciation?

(a) Overview

The potential role of IGF-1 in speciation is one of the most interesting and important roles IGF-1 may play in terms of pleiotropic control of correlated suites of life-history traits. Adaptive single-gene changes with major pleiotropic effects are predicted to result in more rapid speciation than small gene changes during the early stages of reproductive isolation (Orr, 1998), and there is some evidence that quantitative trait loci (QTLs) with large phenotypic effects can play a major role in speciation events (Schwamb & Bradshaw, 1999). We discuss the potential role of evolutionary responses in IGF-1 signaling for selection on life-history traits driving population divergence and eventual speciation by expanding upon two specific examples: domesticated dogs (Canis lupus

The observable phenotypic divergence in dogs is to a large extent a result of artificial selection by humans whereas in T. elegans phenotypic divergence appears to have resulted from adaptation to local environmental conditions (Sparkman et al., 2009).

(b) Divergence in domesticated dog breeds due to artificial selection on IGF-1

Major changes in the size of dog breeds resulted from artificial selection on body size that has acted strongly on a single locus controlling IGF-1 production (Sutter et al., 2007). Although large dogs do exhibit a longer period of postnatal growth than small dogs (Wayne, 1986a), large dogs also have higher absolute postnatal growth rates (Favier et al., 2001; Trangerud et al., 2007; Tryfonidou et al., 2003). Body size is commonly associated with plasma IGF-1 concentrations in domestic dogs (Eigenmann, Patterson & Froesch, 1984; Maxwell et al., 1998; Reynaud et al., 2010; Sutter et al., 2007), suggesting an association between IGF-1 and growth rates, although this has not been demonstrated directly. These size changes are associated with differences in longevity, with small dogs living longer than large dogs (Greer, Canterberry & Murphy, 2007; Patronek, Waters & Glickman, 1997), as would be expected if lifespan and growth rate were correlated due to strong selection on a correlated trait coupled with a shared mechanism.

Increased plasma IGF-1 concentrations in dogs are also associated with stimulatory effects on the reproductive system. Specifically, increases in plasma IGF-1 concentrations are associated with increases in both the number and diameter of pre-ovular follicles (Reynaud et al., 2010). In addition, IGF-1 is indirectly associated with reproductive output in dogs as litter size increases with maternal mass (Kirkwood, 1985; Robinson, 1973, 1982). Finally, artificial selection that influenced the level of IGF-1 signaling may have produced correlated responses such as paedomorphic cranial morphology (Wayne, 1986b) or behavioural (personality) and energetic attributes (Careau et al., 2010). There is no evidence that artificial selection has acted directly on folliculogenesis or lifespan in domestic dogs, suggesting that these changes have been indirect, through selection on size or personality (Careau et al., 2010). These differences in life history so strikingly characterize breed divergence among domestic dogs despite less than 15,000 years of artificial selection, that they could represent steps towards reproductive isolation among some breeds. This example in domesticated dogs demonstrates that selection on a single nucleotide polymorphism controlling IGF-1 production that strongly influences body size could lead to relatively rapid and major changes in life-history traits as well as other morphological and behavioural traits.

(c) Divergence in garter snakes due to potential natural selection on IGF-1

In the garter snake example illustrated in Section V in which life-history variation is associated with differences in plasma IGF-1 concentrations, population divergence associated with differences in IGF-1 signaling most likely occurs in response to differences in predation and food availability between the two habitats (Bronikowski, 2000; Sparkman et al., 2009). Perhaps the most interesting aspect of this system is that the fast-growing lakeshore ecotype has arisen a number of times from the ancestral meadow population (Manier & Arnold, 2005), implying that these major phenotypic differences in body size, reproductive output, and lifespan arise quite readily in response to ecological pressures. Although the apparent ease of these changes may suggest adaptive plasticity, there does appear to be a genetic basis for at least some of the variation in growth rates (Bronikowski, 2000), suggesting that genetic divergence plays a role in the observed differences in life-history traits. Demonstrating genetic divergence in this example is important because, if genetic change at loci related to IGF-1 signaling is implicated in some of the phenotypic differences between these two ecotypes, this would suggest that IGF-1 may play an important role in ecological speciation whenever selection regimes on life-history traits differ consistently between environments.

(d) Can evolution of the IGF-1 system cause rapid speciation?

The two examples given above for domesticated dogs and garter snakes demonstrate that a single mutation influencing IGF-1 or IGF-1R might lead to coordinated changes in important life-history traits in response to artificial selection or natural selection brought on by fluctuations in ecological pressures. In free-ranging animals such as in the garter snake example, natural selection acting on loci controlling IGF-1 signaling might produce a coordinated response of beneficial combinations of life-history traits in regard to the new environmental conditions (Hau, 2007; Ketterson et al., 2009; McGlothlin & Ketterson, 2008; Sinervo & Svensson, 1998). These pleiotropic changes in life-history traits should be in directions that are adaptive with respect to one another (Fig. 2). If the phenotypic changes are adaptive in a new environment, then the allele should fix in the population. In addition, because traits such as reproductive output and lifespan that are influenced by IGF-1 are so closely tied to fitness, fairly minor gene changes could create a situation where hybrid fitness is decreased relative to either ancestor in their respective environments. Such decreased hybrid fitness could drive population divergence, reproductive isolation and eventual speciation (Coyne & Orr, 2004).

The examples illustrated above demonstrate that artificial or natural selection that targets alleles associated with IGF-1 signaling can produce pleiotropic changes in life-history traits that generally follow life-history theory (Fig. 2). Investigation of IGF-1-mediated population divergence and putative speciation in other natural systems, especially where growth, mortality or related life-history changes are involved would greatly improve our understanding of how pleiotropic control mechanisms, and IGF-1 in particular, can function in speciation.
(3) Is IGF-1 a suitable candidate mechanism for mediating life-history trade-offs?

Most studies that have examined the proximate basis of life-history trade-offs have focused on relationships between a few life-history traits (e.g., reproduction versus longevity) and androgens or GCs (Boonstra, 2005; Hau, 2007; Ketterson et al., 2005, 2009; Ketterson & Nolan, 1992; McGlothlin & Ketterson, 2008; Ricklefs & Wikelski, 2002; Romero, 2004; Sinervo & Svensson, 1998). However, the effects of androgens and GCs on life-history traits that have been documented previously may actually be mediated in part through the effects of IGF-1 signaling on growth, reproduction, and lifespan. For example, a variety of studies have found that prenatal exposure to androgens (Groothuis et al., 2005; Manikkam et al., 2004) and GCs (Lordi et al., 1997; McCormick, 2006) can increase and decrease postnatal growth rates or body size, respectively. However, these changes in growth rates may actually be due to changes in IGF-1 signaling because circulating plasma concentrations of androgens (Colak et al., 2011; Crespi et al., 2006; Hobbs et al., 1993) and GCs (Luo, Reid & Murphy, 1990; Unterman et al., 1993) may upregulate and downregulate IGF-1 production and/or availability, respectively. These studies, and the abundant laboratory studies documenting that IGF-1 signaling affects growth, reproduction, and lifespan suggest that IGF-1 signaling may prove to be an equally suitable candidate mechanism as androgens and GCs for mediation of life-history trade-offs and production of a coordinated phenotypic response to environmental variation. Future studies measuring associations between life-history traits and plasma androgen or GC concentrations should also investigate relationships between these steroid hormone levels and IGF-1.

VII. WHAT CAN WE LEARN ABOUT IGF-1 FROM STUDIES IN FREE-RANGING ANIMALS?

A stronger understanding of the function and role of IGF-1 requires future research in natural populations regarding the associations between IGF-1 and life-history traits. Laboratory and agricultural studies are extremely valuable in understanding the mechanisms mediating effects of IGF-1 on growth, reproduction, and lifespan, but we can only understand fully the value of these studies by examining the degree of support for associations between IGF-1 signaling and life-history traits in natural populations. In particular, common laboratory environments can lead to a reduction in phenotypic variance caused by shared conditions and/or ad libitum feeding (Falconer & Mackay, 1996). As a result, we may not have a grasp of the full scope of variation in IGF-1 signaling unless we measure these traits in natural populations. Secondly, no study of which we are aware has documented a direct association between IGF-1 signaling and lifespan in free-ranging animals. The lifespan of animals living in nature likely never reaches the upper limit that can be achieved in controlled laboratory environments. As a result, IGF-1 signaling may affect lifespan in laboratory environments when lifespan is artificially enhanced, but may have little or no influence on lifespan in nature where lifespan is affected by ecological pressures such as nutrition or predation. Therefore, studies in natural populations documenting IGF-1 signaling and life-history traits are critical to understand how and why IGF-1 influences lifespan.

VIII. CONCLUSIONS

(1) A large body of literature demonstrates that IGF-1 signaling plays a crucial role in mediating trade-offs along a major axis of life-history variation involving growth, reproduction, and lifespan. In many laboratory or domesticated animals, increased IGF-1 signaling or specifically IGF-1R activity is associated with increased postnatal growth, decreased age of first reproduction, increased reproductive output, and decreased lifespan. The vast array of clinical and laboratory research on the effects of IGF-1 on growth, reproduction, and lifespan represents...
a critical resource for evolutionary ecologists interested in natural systems.

(2) In stark contrast, there are very few studies in free-ranging animals examining relationships between IGF-1 signaling and life-history traits. The few studies that have been conducted are promising and have shown that plasma IGF-1 concentrations are influenced by the environment and also are associated with body size, reproduction, and other traits potentially associated with fitness.

(3) Previous studies performed on laboratory and domesticated animals should spur evolutionary ecologists to generate hypotheses to test in natural populations concerning how IGF-1 may mediate the evolution of suites of life-history traits in free-living animals. In particular, IGF-1 may mediate adaptive developmental plasticity in response to variation in nutrition, and selection on loci that control IGF-1 signaling can potentially lead to adaptive variation in a number of critical life-history traits in response to ecological pressures driven by changing environments. Such major phenotypic changes in response to local environmental conditions and controlled by a very few loci could easily lead to population divergence and potentially eventual speciation.

(4) The effects of androgens and GCs on life-history trade-offs that have been documented previously may actually be mediated in part through the effects of IGF-1 on growth, reproduction, and lifespan. Future studies measuring androgens and GCs in free-ranging animals should consider monitoring IGF-1 as well.

(5) Future research in free-ranging animals is critical for us to have a comprehensive view of phenotypic variation in IGF-1 signaling as well as its effects on lifespan. Evolutionary ecologists can discover new avenues of research by examining the body of literature regarding the associations between IGF-1 and life-history traits, but those interested in biomedical applications can also gain new insights from studying IGF-1 in free-ranging animals.

IX. ACKNOWLEDGMENTS

We thank Kay Holekamp, Andrew McAdam, Alex Stringfield and two anonymous reviewers for comments on a previous version of this manuscript. E.M.S. was supported by a predoctoral fellowship from the National Science Foundation.

X. REFERENCES


Crespi, Duan, Dobson, Danilovich, Coyne, Ditchkoff, Dillin, Clemmons, Charnov, Conner, Biologically Reviews 426


