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The Big and Small of It: How Body Size Evolves

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ABSTRACT Body size is a biological variable of fundamental importance and plays a central role in analyses of life history, sexual dimorphism, allometry, and natural and sexual selection. Yet, there remains a sizeable gulf in our understanding that lies between what we hypothesize influences change in size, from the point of view of ultimate causation, and what we know about how shifts in body size are regulated from a proximate perspective. I seek here to tie these two perspectives together, and specifically to argue that an understanding of the hormonal regulation of body size is necessary for constructing hypotheses regarding how body size evolves. Recent work using model organisms points to the insulin/insulin-like growth factor pathway as playing a key role in the regulation of growth, size, reproduction, and senescence. I review the role of various components of this pathway in regulating growth and size and illustrate the evidence for different ways in which these might work to generate differences in size in various organisms. Of particular interest are the tradeoffs between size and other life history traits produced by experimental alterations in this pathway. Recent work emphasizing the ways in which body size can be altered based on extrinsic factors provides the opportunity to link advances in uncovering the proximate bases of growth and size and offers an opportunity to frame new hypotheses regarding how variation in size evolves. Yrbk Phys Anthropol 53:46–62, 2010.

"Well, I'll eat it," said Alice, "and if it makes me grow larger, I can reach the key; and if it makes me grow smaller, I can creep under the door: so either way I'll get into the garden, and I don't care which happens!" - Lewis Carroll, *Alice's Adventures in Wonderland*

Alice's Machiavellian take on the dilemma presented to her after her initial tumble down the rabbit's hole sums up the view that most organisms must have regarding their size: they don't care how they get there. As evolutionary biologists, however, we care to know how living things get to be as big or small as they are. Traditionally, we approach this issue by asking "why." Thinking from this perspective of ultimate causation, scholars have identified a great number of reasons why changes in size happen. Almost always, these reasons center on some fitness advantage that is conferred by the change in size. One can also approach the issue of size change from a proximate perspective; that is, "how" does an animal get bigger or smaller? These mechanistic explanations tend to focus on the organism as a self-contained system, and often do not explicitly consider the adaptive nature of changes in development. In this article, my aim was to review what we know about one of the most important mechanistic pathways through which changes in size (and other important traits) may be generated, and to situate this information in a broader adaptive context. I begin with a brief review of some of the "ultimate" explanations for body size variation, and then discuss key components of the growth hormone (GH)/insulin-like growth factor (IGF) axis and how they affect size throughout the course of ontogeny. I follow this with examples of how these components covary with growth and size in dogs, nonhuman primates, flies, and humans, and touch on how this pathway is implicated in prenatal programming and transgenerational effects on size. Finally, I close with a discussion of how these various areas of study can provide fruitful ground for the construction and testing of hypotheses regarding the evolution of body size.

BODY SIZE AND THE "BIG PICTURE"

Body size in nonhuman primate and human evolution

Living mammals span an impressive range of body size, as do living primates (Smith and Jungers, 1997). The range of body size encompassed by fossil primate taxa is even greater than that among extant groups. Debate regarding the body size of the ancestral primate is ongoing. One group of scholars argues that based on the available fossil evidence and the adaptations that would have occurred before the early Eocene radiations, the ancestral primate would have been very small, perhaps less than 50 g (e.g., Gebo, 2004). Another group suggests that an increase to 1 kg or more in the primate stem lineage led to the reduction of claws to nails (e.g., Soligo and Martin, 2006). There seems to be a consensus that the earliest anthropoids were small-bodied, with supporting evidence from some very small stem anthropoid fossils (e.g., Ross, 2000; Williams et al., 2010). Multiple primate radiations have clearly been characterized by extremes in size (e.g., platyrrhines, Ford and Davis, 1992; lemurs, Godfrey et al., 1990; cercopithecines, Delson et al., 2000). Sexual dimorphism in body size is common among anthropoids (Plavcan, 2001), and intraspecific variation in body size among primate species has

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been attributed to a wide range of influences, including competition, female body weight, diet, substrate use, and phylogeny (e.g., Plavcan and van Schaik, 1997). Life history profiles of primates are likely to have evolved both through grade shifts that were body mass dependent and shifts that took place independently of changes in mass (Kelley and Smith, 2003; Marroig and Cheverud, 2005).

In human evolution, three notable shifts in body size have occurred (Ruff, 2002). First, a shift to markedly larger body size and more modern-human like body form in early *Homo erectus/ergaster* provides evidence that this was the first hominin to "strategize" in a manner similar to *H. sapiens* (e.g., food acquisition and reproduction) (Wood and Collard, 1999). Aiello and Key (2002) examine, in detail, the costs of each reproductive event for female *H. erectus* and conclude that to successfully navigate the costs of reproduction as a large-bodied hominin with infants likely larger in brain and body size than australopithecines, a major transformation of the way in which female *H. erectus* acquired and used energy would have been necessary. The pressures associated with reproduction at larger sizes may have resulted in adaptations involving reduced energy investment in offspring prenatal development, which when combined with high diet quality, permits the growth of a relatively fat baby with a large brain (Ulijaszek, 2002a). Body composition at birth is thought to play a very important role in protecting energy reserves to the rapidly developing human brain, and in modifying mortality risk during early growth (Kuzawa, 1998).

After the enlargement in body size with *H. erectus/ergaster*, the next major shift occurred around 500,000 years ago. Another increase in average body size is thought to have emerged as hominins occupied higher latitudes, and clinal distribution of body size follows what is seen in modern humans (Katzmaryk and Leonard, 1998). The following shifts in size occurred first starting around 50,000 years ago, with a decline in average mass, and, most recently over the past few hundred years, a positive secular trend in size has been seen in some populations (Stinson, 1985).

Drivers of body size evolution

Body size in mammals, in general, and primates in particular, is related to a great number of physiological, environmental, and behavioral variables, including but not limited to diet, locomotor style, habitat, seasonality, competition and predation risk, energetic requirements, and body size distributions within organismal communities (e.g., Leonard and Roberston, 1994). It also corresponds with a number of fitness characters, including age at first reproduction, offspring number and size, and life span (Klingenberg and Spence, 1997).

It has often been argued that the main forces that exert pressure for the evolution of larger size are fecundity selection (for females) and sexual selection (for males), and that these forces are at some point balanced by viability selection, because of the fitness costs of large size (Blanckenhorn, 2000). Generally speaking, the interaction of organisms with their environment and pressures exerted by ecological processes limit the range of possible body size via a mixed bag of factors, including energy availability (for growth and maintenance) (Cumming and Havlicek, 2002). There seem to be clear size distributions evident in primate evolution that relate to specific ecological and behavioral adaptations (e.g., Fleagle, 1985).

The rules. There are a number of general evolutionary trends observable in body size throughout various organismal forms. These include Cope's rule (e.g., phyletic size increase), which states that taxa tend to evolve larger body sizes over evolutionary time, because of the advantages conferred by large size, including the ability to better withstand short-term fluctuations in the environment and the capability to exploit a broader range of low-quality resources (Maurer et al., 1992). This has been explained by some as representing not true evolutionary trends in size, but rather differential preservation in the fossil record, biased toward larger forms. Stanley's rule explains Cope's rule as a statistical generalization and also states that clades tend to originate at small body sizes, thereby giving rise to a pattern of size increase during radiation (Gillman, 2007). It has been suggested that although plesiadapiforms (variably attributed as either the extinct sister group or precursor of primates) followed an overall trend of increasing body size with evolutionary time and, therefore, conformed to Cope's rule, primates as a whole did not, whether considered as an order or as individual radiations (Soligo and Martin, 2006).

Rensch's rule holds that sexual size dimorphism (SSD) is more pronounced in larger species; further refinements of this rule state that SSD increases with increasing size when males are the larger sex, and decreases with increasing size when females are the larger sex (e.g., Szekely et al., 2004). The link between male and female body size within a species is usually explained as being the result of genetic correlations between the sexes; therefore, any change in size of one sex usually results in some change in size in the other sex. There seems to be some support for Rensch's rule in haplorhine primates (e.g., Clutton-Brock et al., 1977), although the best-known examples (of changes in both male- and female-biased SSD) are found in arthropods, reptiles, fish, and birds (e.g., Andersson, 1994). Interestingly, some meta-analyses suggest that manifestations of Rensch's rule are influenced by latitude (e.g., Blanckenhorn et al., 2006).

Bergmann's rule describes the trend of body mass increasing in concert with latitude. This is based on the idea that larger animals will tend to produce relatively more heat and lose relatively less, providing an advantage in cooler climates (Meiri and Dayan, 2003). However, this idea can be modified further by Allen's rule, which carries specific predictions for surface area and body shape: regardless of overall size, a decrease in surface area will lead to more efficient heat retention, and an increase in surface area will lead to more efficient cooling (Ray, 2005). Studies in primates have found support for Bergmann's rule, after controlling for phylogeny (Harcourt and Schrier, 2009). Limited resource availability at higher latitudes likely explain the presence of this effect within the primate distribution (Meiri et al., 2005).

The "island rule" dictates that when isolated on islands away from mainland groups, small-bodied taxa will increase body size (with a tendency toward gigantism), and large-bodied taxa will decrease body size (with a tendency toward dwarfing). Evolution of body size on islands has been proposed to occur at a faster rate than in mainland counterparts (Millien, 2004). Evidence to support the island rule has mainly come from

mammals, and it has been suggested that primates add to this support (Bromham and Cardillo, 2007), although other studies of the relationship of variation in morphology to island distribution find no such support (Schillaci et al., 2009). This is likely influenced by factors such as predation, resource availability, island area and age, and distance to mainland (Boback, 2003). Overall, though, the shifts in body size seen in insular species are directed toward an optimal size when taking into account ecological strategies and body plan (Lomolino, 2005).

Getting there: Development and size. Several studies have carefully documented that the differential extension of common patterns of relative growth, or ontogenetic scaling, is pervasive throughout the primate order and can explain much of the morphological diversity seen within and among species. Specifically, many craniofacial and postcranial features may vary as correlates of selection for larger or smaller body size. For example, much of the intra- and interspecific variation in craniofacial traits in great apes (Shea, 1983; Schaefer et al., 2004), interspecific variation in cranial and postcranial form in cercopithecine monkeys (Shea, 1992b; Ravosa and Profant, 2000), interspecific variation in craniofacial and postcranial proportions in living and fossil strepsirrhines (Ravosa, 1992, 1998, 2007; Ravosa et al., 1993; Ravosa and Daniel, 2010), variation in cranial form within and among papionin species (Leigh and Cheverud, 1991; Leigh, 2006), and interspecific cranial proportions among howler monkeys (Ravosa and Ross, 1994) can be explained as the result of ontogenetic scaling.

An advantage imparted by studies of allometry and heterochrony is that they show how morphological transformations can result from alterations in the regulation of development (e.g., Klingenberg, 1998). In analyses of size and shape change, the features of organisms that are relatively easy to quantify are often considered to be the major targets of selection. This presents a problem because traits that may be much more closely related to the organism's fitness than those that are being measured are overlooked (Ryan and Semlitsch, 1998). Therefore, a potential pitfall inherent in interpretations of changes in observed patterns of development based strictly on morphology is that this approach may ignore other factors driving the evolution of developmental patterns. When trying to interpret adult size variation, developmental information not only of morphology but of underlying developmental systems can provide valuable insight because natural and sexual selection act not only on final adult form, but also throughout ontogeny (Shea, 1992a). Growth rates and age at maturation are important life history variables that shape adult size, and differences in the rate of growth or in the duration of growth periods can drastically affect adult size outcome (Shea, 1983).

Charnov's model (Charnov and Berrigan, 1993) explains the relationship between body size, developmental time, mortality risk, and longevity. Specifically, it holds that large body size is related to a delayed age at maturation, implying a longer period of development, which is "allowed" in an environment of low adult mortality. Development along this course is also associated with increased longevity. This is thought to be advantageous because a larger mother is potentially able to invest more energy in offspring, as long as she can balance these costs with those incurred by growing and maintaining her own large body.

Primate life histories are often characterized as "slow" because a number of life history traits seem to clump at that end of the continuum (e.g., low growth rates, long subadult periods, long lifespans, and low fertility rates). There is actually a fair amount of variation in the relative "speed" of the components of the subadult period in primates (Leigh, 2001). It is important to note that allometric relationships between body size and life history variables do not, in and of themselves, explain the adaptive value of the variables themselves. When considering the relationship between body size and such variables, it is possible to orient analyses with a few different points of view (Millar and Hickling, 1991). For one, it could be that body size alone has been the target of selection and that life history traits are dragged along with changes in size. Alternatively, life history traits may be considered to be the target of selection themselves, with changes in body size resulting in correlated fashion. Finally, it is possible that the evolution of body size and of adaptive groups of life history traits proceed independently. Correlation analyses cannot tease apart these alternatives; instead, the causal nature of the relationship between body size and patterns of life history must be determined: is there evidence, from a regulatory standpoint, of one influencing the other? To do this, one must be able to assess what the "signature" looks like for body size increase or decrease, and what proximate causes underlie shifts in life history patterns.

HORMONES AND THE EVOLUTION OF BODY SIZE

A developmental perspective is particularly important for understanding variation in body size because ontogenetic studies focusing on humans and nonhuman primates reveal that adult morphologies can be produced through different developmental processes (Leigh and Shea, 1995). These processes generally involve differences in the rate or timing of somatic growth. Consequently, different processes of somatic growth may lead to similar patterns of body sizes. Despite the importance of hormones in these processes, their role in the regulation of rate and timing differences has remained difficult to assess, leaving major gaps in our understanding of how patterns of growth and development, and body size, evolve (Shea, 1992a). Life history traits, such as age-specific patterns of growth, body size, sexual maturity, and longevity are precisely those features that are known to be tightly controlled by hormones (Finch and Rose, 1995).

Hormones not only regulate most of the major components of ontogeny and life history, but they also each tend to affect a number of phenotypic traits. "Hormonal pleiotropy" has, therefore, been proposed as a likely candidate underlying the genetic correlations that are ultimately largely responsible for the evolution of constraints, tradeoffs, and life histories more generally (Zera et al., 2007). Hormones are secreted into the circulatory system, travel unbound or bound to a carrier protein, and activated in various tissues. Activation occurs either through interaction with outer cell membranes, beginning signaling cascades within the cell, or through entry into the cell's nucleus to directly affect gene transcription. Hormones interact in complex feedback loops, which are regulated by different stimuli and operate at

varying thresholds throughout life. Because of this, it remains a formidable challenge to discern how hormones are regulated to produce a given trait. Because of the relative ease of sample collection and measurement, circulating hormone levels have been used most often as indicators of endocrine status. Measurement of target tissue receptor density or location and identification of all components of various intracellular signaling cascades are approaches that are likely to yield more meaningful information regarding the relationship between hormones and phenotype; but, these kinds of studies are much more difficult to conduct.

Hormone levels have been hypothesized to affect trait evolution in two ways (Cox et al., 2009). The "evolutionary constraint hypothesis" posits that it is mainly through alterations in circulating levels of hormone levels that traits evolve. The "evolutionary potential hypothesis" suggests instead that tissue responsiveness is the target of selection, allowing a wide range of variation in trait expression to evolve with similar circulating hormone levels. These hypotheses predict different scenarios in relationship to the role of hormones in body size evolution. If the evolutionary constraint hypothesis is accurate, then we should see clear differences in circulating hormone levels during growth among animals of different body sizes. If the evolutionary potential hypothesis is correct, then circulating hormone levels may or may not show any difference among animals of different size; instead, variation in target-tissue level receptor density or distribution, or local hormone production and utilization via autocrine or paracrine mechanisms will correlate with variation in body size. It is important to note that these hypotheses are not mutually exclusive.

Shea (1992a) proposed that investigation of the genetic and hormonal control of development would yield a greater understanding of size change and allometric patterning and drew particular attention to the GH/IGF axis as playing a central role in these processes. Earlier experimental work with giant transgenic mice revealed that an increase in circulating GH and IGF-I led to increased overall growth in skull, postcranial, and organ sizes, some of which was characterized as an extension of common growth allometries in the control group (Shea et al., 1987, 1990). Alterations in components of this axis had also been linked to size differences in pygmy populations and dog breeds characterized by "giant" or "dwarfed" size (reviewed below).

The GH/IGF system

Normal growth involves the action of a number of hormones, working singly or with others in an integrated fashion, with specific effects on bone, cartilage, muscle, and organs. During the life course of an organism, certain hormones are more influential at certain stages in development than others. The traditional focus among endocrinologists has been on models prioritizing the somatotropic axis (GH and IGF-I) (Fig. 1). The models have undergone modification with time, beginning with theories explaining the function of GH as promoting growth through endocrine effects of IGF-I (Daughaday et al., 1987). Later, theoretical views shifted to GH and IGF-I having growth-promoting properties directly on target tissue via paracrine and autocrine pathways (Murphy et al., 1987). More recently, gene knockout techniques have enabled evaluation of these models with mice by manipulating the levels of circulating IGF-I through targeted deletion of the hepatic production of IGF-I (Yakar et al., 1999). The knockout mice grow to normal size despite drastic reductions in circulating levels of IGF-I, leading researchers to conclude that paracrine and autocrine IGF-I, rather than endocrine IGF-I, is most important for postnatal growth (Butler and LeRoith, 2001). Still, experimental findings such as those that demonstrate significant growth responses after subcutaneous IGF-I therapy in individuals with either IGF-I gene deletion or GH receptor (GHR) dysfunction suggest that endocrine IGF-I plays an important role in human growth (e.g., Camacho-Hübner et al., 1999). Therefore, the relative importance of systemic versus local actions of IGF-I is still unclear (D'Ercole and Calikoglu, 2001). Further, despite the tremendous value of a knockout model, such an approach does not document naturally occurring variation across species in these systems, limiting an application of their results to evolutionary explanations for diversity in size.

Growth hormone. GH secretion occurs in the somatotroph cells of the anterior pituitary gland, release is stimulated by GH releasing hormone from the hypothalamus, and inhibited by somatostatin. Circulating levels of IGF-I exert regulatory control on GH release through these hypothalamic mechanisms, and a number of other factors are believed to affect GH release. GH acts through binding to the GHR, which stimulates growth of muscle, bone, and cartilage (Angetsinger and Carter-Su, 1996). A high-affinity binding protein, GH binding protein (GHBP) (Baumann et al., 1986), has been identified as the product of either alternative splicing or proteolysis of the GHR (Dastot et al., 1996). Humans with GHR deficiency are short in stature and have very low or absent levels of GHBP (Fontoura, 1991). A study by Martini et al. (1997) found evidence to show that GHBP can be produced by both proteolysis and alternative splicing in the liver of rhesus macaques (*Macaca mulatta*). However, these researchers did not find evidence of a splice variant of the GHR in rhesus tissue, similar to that found in the human, which is potentially responsible for the circulating high amounts of GHBP in humans (Ross et al., 1997). GH itself seems to have little effect on prenatal growth, and its effects on postnatal growth are largely mediated through IGF-I, IGF binding protein (IGFBP)-3, and the acid-labile subunit (ALS), which travels in a ternary complex with IGF-I and IGFBP-3. In addition to growth-promoting properties, GH acts in regulating lipid and carbohydrate metabolism (Rosenfeld and Hwa, 2009).

Insulin-like growth factor-I. The IGF "family" of growth factors includes insulin, IGF-I, and IGF-II. The IGFs share a large amount of sequence homology, and the structure of the IGFs and proinsulin are similar in structure, supporting the idea that the IGFs and insulin diverged from a common ancestral molecule. The structure of IGF-I is highly conserved, demonstrated by cross-reactions generated by the serum of all mammals in a radioimmunoassay established for human IGF-I (Zangger et al., 1987). IGF-I is produced in many tissues, including the liver, ovary, uterus, bone, and skeletal muscle. During pregnancy, IGFs are synthesized in the placenta, as well, and these may also have autocrine or paracrine roles in the regulation of fetal growth (Rutherford, 2009). The regulation of IGF-I involves many factors, including GH, estradiol, glucocorticoids, prolactin, parathyroid hormone, cyclic AMP, transforming growth

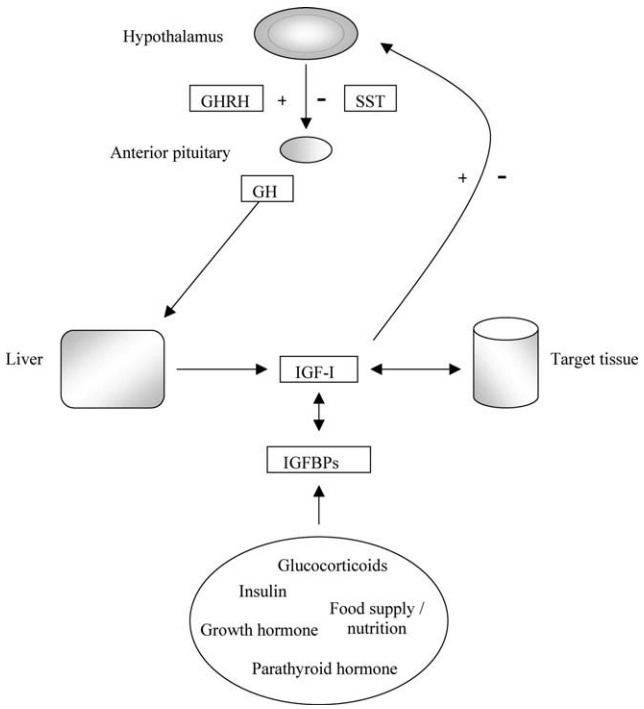

Fig. 1. The main components and pathways of the somatotropic (GH/IGF-I) axis. GHRH, growth hormone releasing hormone; SST, somatostatin; GH, growth hormone; IGF-I, insulin-like growth factor-I; IGFBPs, insulin-like growth factor binding proteins.

factor-β, nutritional state, and insulin. Most circulating IGF is complexed with binding proteins (IGFBPs), which modulate ligand–receptor interaction on target cells. Depending on the particular protein (there are at least six IGFBPs), actions range from physical transportation and inactivation of IGFs to interaction with target cells and facilitation of the delivery of IGFs to their receptors. The majority of circulating IGF-I is complexed with IGFBP-3 and the ALS, to form a 150-kDa complex. This complex prolongs the half-life of serum IGF-I.

The functions of IGFs are many and vary over the course of an organism's life span. Generally, they are involved in mechanisms that control the proliferation and differentiation of many types of cells. IGF-I is more GH-dependent and mitogenic than IGF-II, which is more insulin-like in its actions in postnatal life and present in circulation three times higher than IGF-I (Froesch et al., 1985). The IGFs are also involved in the control of gametogenesis and reproductive functions in both sexes. IGF-I also plays a physiological role in glucose homeostasis and potentiates the action of other hormones.

A number of studies have documented IGF-I gene polymorphisms, which are associated with constitutionally short stature, altered serum IGF-I levels, and variation in birth weight and head circumference in children small for gestational age (SGA) (Schneid et al., 1990; Arends et al., 2002; Kim et al., 2002; Vaessen et al., 2002). Twin studies of circulating IGF-I levels demonstrate that this measure has a genetic component; levels of IGF-I in cord or childhood serum are better correlated in monozygotic than dizygotic twins; other studies estimate the additive genetic influence on circulating IGF-I levels to be 38–63% in adults (Hong et al., 1996).

IGF-I has been shown to have a positive effect on growth rates, organ weight, appendicular skeleton length, stature, and body mass (e.g., Liu and LeRoith, 1999). A brief review of the secretion and function of IGF-I during the human lifespan follows. In summary, IGF-I relates to size and growth rates both in fetal and postnatal life and plays an important role in the pubertal growth spurt in conjunction with sex steroids.

IGF-I throughout the lifespan. IGF-II is the primary factor involved in embryonic growth, whereas IGF-I is the dominant regulator in later gestation. Human fetal serum IGF-I significantly increases between 18 and 40 weeks (Zhou et al., 2001). In fetal life, IGF-I and IGF-II regulate the placental transport of amino acids and substrates necessary for intrauterine growth. Fetal IGF-I also plays an important role in the regulation of fetal growth, as demonstrated by gene knockout studies on mice (e.g., Powell-Braxton et al., 1993). Mice with the *IGF1* gene knocked out generally die after being born at a very small size; if they survive, they show limited growth and are infertile; *IGF2* knockouts do not demonstrate the high mortality rates of *IGF1* knockouts, and, although they are small at birth, they grow at normal rates postnatally (Liu et al., 1998). In most studies of growth-retarded fetuses, fetal IGF-I levels are significantly lowered (e.g., Ostlund et al., 1997).

The main regulator of IGF-I levels in the fetus is not GH, but fetal insulin, under the regulation of fetal glucose availability. This pattern of fetal nutritional regulation of IGF-I is thought to persist until approximately 6 months postnatally (Yeung and Smyth, 2003). The fetal system is sensitive to maternal nutrition. Studies in sheep have shown that maternal nutrition can affect fetal and placental growth through IGF-I and IGFBP-3 expression (Osgerby et al., 2003). Experimental studies with rats suggest that maternal IGF-I affects fetal growth through the promotion of amino acid transfer through the placenta (Thongsong et al., 2002). Pregnant food-restricted rats have lower IGF-I levels associated with reduced weight gain and smaller fetal and placental sizes than those without food restriction (Monaco and Donovan, 1997).

At birth, cord serum levels of IGF-I show positive correlations with birth weight, placental weight, and gestational age at birth regardless of the fact that female infants generally have higher levels of IGF-I than male infants (Geary et al., 2003). Premature infants show lower levels of IGF-I, IGFBP-3, and ALS in umbilical cord blood compared with infants born at term, and infants from preeclamptic pregnancies with low birth weight have associated low levels of IGF-I and IGFBP-3 (Diaz et al., 2002). Infants born large for gestational age have significantly higher IGF-I serum levels than infants average for gestational age (Christou et al., 2001). Similarly, infants SGA have significantly lower IGF-I levels than average for gestational age infants (Giuduce et al., 1995). In infancy, IGF-I levels decrease from birth up to 6 months of age and then rise again in later infancy. Recent research has uncovered a positive association between immediate postnatal growth velocity and IGF-I levels (Skalkidou et al., 2003).

In humans, IGF-I levels are generally highest in colostrum produced during the first few days postpartum, after which IGF-II is the IGF in highest concentrations in milk. Milk IGFs affect the developing gastrointestinal tract of the neonate and can also be transported at very

low levels into the neonate's circulation (Donovan and Odle, 1994). Studies in humans and nonhumans have suggested relationships between maternal IGF-I levels, levels of IGF-I in colostrum and breast milk, IGF-I levels in infant circulation, and infant growth rates and size (e.g., White et al., 1999). Dietary fat supplementation of lactating pigs resulted in increased levels of milk fat and IGF-I, which, in turn, was associated with enhanced suckling piglet growth rate (Averette et al., 1999). Supplementation of pregnant rhesus macaques with GH from the second trimester through 7 weeks postpartum was correlated with a significant increase in milk fat, which was, in turn, associated with greater increase in neonatal weight (Wilson et al., 1991).

IGF-I levels increase slowly throughout childhood, and levels in 1 year may be used to predict height velocity the following year (Juul et al., 1994). GH begins to exert significant effects on growth with the onset of the childhood phase of growth. In children with earlier onsets of this phase of growth, higher IGF-I levels are found as a result of the earlier increases in GH. In children who were born at low birthweight, increases in IGF-I are associated with the period of "catch-up growth" (e.g., Leger et al., 1996). IGF-I levels are positively correlated with many different growth-related parameters in prepubertal children, including thigh muscle mass, oxygen uptake, and bone mass (e.g., Olney, 2003). The GH-IGF-I axis undergoes activation at the onset of puberty: the pulse amplitude of nocturnally secreted GH increases, and concentrations rise concurrent with onset of height velocity acceleration. Once peak height velocity is reached, GH decreases gradually to prepubertal levels. Unlike GH, IGF-I levels (which also parallel increases in height velocity through peak velocity) remain elevated for a time after peak height velocity, despite a decrease in height velocity.

IGF binding proteins. Only a minor percentage (<5%) of total circulating IGF-I is free, or not bound to IGFBPs. The half-life of bound IGF-I is longer than that of the free form. There are six described IGFBPs, produced in a variety of biological tissues and with varying functions and actions to modulate IGF–receptor interaction, as well as independent functions (reviewed in Kelley et al., 1996). All of the IGFBPs form binary complexes with the IGFs, but only IGFBP-3 (and to some extent, IGFBP-5) forms a high-molecular-weight complex with IGFs and an ALS (Baxter and Martin, 1989). This ternary complex is where more than 75% of IGF-I circulates. All six binding proteins are highly conserved; within species, 50% of their overall protein sequence is homologous, and, in corresponding, binding proteins between species share up to 80% nucleotide sequence homology (Lamson et al., 1991).

IGFBP-I binds only a small fraction of circulating IGF-I, and because its production is related to insulin levels, it is believed to regulate *in vivo* IGF-I bioavailability in relation to food supply. IGFBP-2 binds IGF-II with higher affinity than IGF-I and is found in significant amounts in cerebrospinal fluid and serum; its regulation is dependent on nutritional factors and GH (Jones and Clemmons, 1995). IGFBP-4 binds both IGF-I and IGF-II with equal affinity. Regulated by parathyroid hormone among other mechanisms, it is involved in the regulation of bone turnover (Zhai et al., 2003). IGFBP-5 has a higher binding affinity for IGF-II, and levels of this protein are regulated principally by glucocorticoids. Like IGFBP-4, it seems to be involved in bone physiology (Nicolas et al., 1995). IGFBP-6 also has higher binding affinity for IGF-II, but little is known about its regulation (Bach, 1999).

Levels of IGFBP-3, unlike GH, exhibit only minor diurnal variation, and because of this, IGFBP-3 measurements may provide a suitable substitute for GH profiles (Blum et al., 1993). The bond between ALS and IGFBP-3 is relatively weak, and dissociation readily occurs at cell surfaces, facilitating IGF transport to target tissues. When rats are administered equimolar concentrations of IGF-I and IGFBP-3, stimulation of growth and an increase in bone mineral density results (Maor et al., 1999). In Snell dwarf mice administered a molar excess of IGFBP-3 with IGF-I, an inhibition of the IGF-I stimulated growth response is observed (Pete et al., 1999). It has been suggested that IGFBP-3 acts locally to potentiate the effects of IGF-I by inhibiting apoptosis (Clemmons, 1997).

Proteolysis of IGFBP-3 acts as a mechanism to increase IGF bioavailability, with protease activity detectable in individuals with malnutrition (e.g., Stoving et al., 1999), Type 1 or 2 diabetes (e.g., Bereket et al., 1995), and those undergoing major surgery (e.g., Skjaerbaek et al., 1998). During pregnancy, IGFBP-3 proteolysis is induced in the third trimester, when the majority of the size growth of the fetus takes place. IGFBP-3 proteolysis seems to be increased in multiple fetus pregnancies (Langford et al., 1995). Pregnancy-related proteolysis of IGFBP-3 seems to be limited to humans among primates, although extensive comparative data is lacking (Giudice et al., 1993).

In postnatal life, IGFBP-3 levels change in a similar fashion but to a lesser degree than IGF-I. During puberty, researchers have noted an increase in the molar ratio of IGF-I:IGFBP-3 and suggested that this may reflect an increase in free, biologically active IGF-I (Juul et al., 1995). Increased GH secretion, and possibly an increased sensitivity to GH, is thought to be mainly responsible for the pubertal increases in IGF-I, IGFBP-3, and ALS during this time. The increased mass and amplitude of GH secretion in puberty is stimulated mainly by estrogens and aromatized androgens (e.g., Metzger and Kerrigan, 1994). These also have direct effects on IGF-I secretion. It is believed that there must be some other estrogen-dependent hypothalamopituitary mechanisms operating to sustain amplified GH secretion with concurrently elevated IGF-I levels in normal male and female puberty. At any other time, elevated IGF-I levels would feed back to suppress further GH release (Veldhuis, 1996).

GH/IGF axis in regulation of size: Nonhumans

Domestic dogs. Domestic dogs provide an excellent "natural experiment" for researchers interested in how variation in body size is regulated, from a mechanistic perspective. Early research, comparing circulating levels of growth factors among genetic subgroups of different body sizes within a single breed, found that IGF-I levels were positively correlated with size (Eigenmann et al., 1984a). The same research group also noted that GH levels did not reflect difference in body size (Eigenmann et al., 1984b). However, both of these studies quantified hormone levels in adult dogs and were, therefore, not particularly informative with regard to how hormone levels during growth might relate to final size. Further studies remedied this deficiency by measuring IGF-I and

GH levels in prepubertal Great Danes and miniature poodles, finding support for IGF-I relating positively to size (Nap et al., 1993). Investigation of GH levels during development revealed that there was an initial increase in basal GH during early development that declined with age, whereas, in miniature poodles, basal GH levels began and stayed low (Nap et al., 1992). After this, Favier et al. (2001) measured GH, IGF-I, and IGFII in Great Danes and beagles throughout development and found that, although both breeds had relatively elevated GH levels at very young ages, which then declined with age, the absolute levels were higher and sustained for a longer period of time in Great Danes. However, no difference in circulating IGF-I or IGF-II was found between the two breeds. Recent genetic research in domestic dogs has identified a single nucleotide polymorphism of the *IGF1* gene that is ubiquitous to all small breeds and absent from giant breeds (Sutter et al., 2007). This is strong evidence indicating that this gene and its products play a major role in determining body size in small domestic dogs; furthermore, the authors note that the sequence variants likely predate the estimated time of domestication, allowing for extremely rapid diversity in size when breeds were established. Taken together, this body of research suggests that in an environment of strong selection pressures (in this case, artificial selection—whether directly on size or on some other behavioral or morphological phenotype that causes a correlated change in size), where diversity in both size and shape has occurred very rapidly, there may be a number of different hormonal "pathways" for reaching larger or smaller sizes.

Nonhuman primates: Single-species studies. Considerable detail concerning the hormonal regulation of growth and size in rhesus macaques (*M. mulatta*) has been established through a series of experiments involving administration of IGF-I and estradiol to female rhesus macaques. Some of the earliest work in this area establishes that gonadal status (intact vs. not intact) influences changes in body weight in association with IGF-I (Wilson et al., 1984). Estradiol was shown to have a direct effect on IGF-I secretion independent of GH (Wilson, 1986). A comparison of the tempo of hormonal and skeletal maturation among groups of female rhesus housed indoors and outdoors demonstrates that those individuals housed outdoors show a distinct seasonal rhythm in secretion of GH and IGF-I, in contrast to those housed indoors (Wilson et al., 1988). As a consequence of this, together with delayed reproductive maturation in females housed outdoors, skeletal maturity of females housed indoors is significantly advanced. Other experiments show that administration of IGF-I inhibits further GH release but still stimulates growth in crown-rump length (Wilson, 1997). These experiments are important and have generated a large amount of information regarding the operation of mechanisms that regulate puberty and growth in *M. mulatta*. However, the experimental context within which most of this information was obtained makes it difficult to apply to evolutionary explanations of variation in growth and size. Specifically, it is unclear whether the responses shown by an animal's physiology to administration of exogenous hormones are similar to what would result from endogenous rises in hormone levels. Such techniques can, through this type of manipulation, define the boundaries for age-related effects of hormones, but cannot explain why these patterns may vary in a natural population.

Several other studies of mostly cercopithecine primates in a laboratory context have confirmed the central role of IGF-I and IGFBP-3 (and interaction of these with steroids) in postnatal growth and attainment of adult size. An analysis of IGF-I levels in cross-sectional and longitudinal samples of *M. mulatta*, in relation to body growth, shows that levels are increased in pregnant females, and that an adolescent rise in IGF-I is significantly correlated with weight velocity (Styne, 1991). A longitudinal study on the effects of stress on hormones and development in rhesus macaques considered the effect of IGF-I, GH, and cortisol and showed that dominant animals have lower cortisol levels, higher IGF-I levels, larger body sizes, and accelerated skeletal development relative to subordinate animals, which have higher cortisol levels, lower IGF-I levels, and retarded skeletal development (Ochoa, 1995).

One of the earliest studies on the hormonal correlates of puberty in baboons uses analyses of IGF-I levels (Copeland et al., 1982). This research demonstrates an increase in IGF-I levels at puberty in *Papio cynocephalus*. Further, Copeland et al. found that males have higher IGF-I levels than females, and that these levels are associated with increased testes size and body mass. No correlations with morphological changes are reported in females. The samples used in this study were cross-sectional and represent animals younger than 4 years and older than 10 years. This was purposefully done to describe prepubertal, pubertal, and adult concentrations of IGF-I. An obvious drawback to this approach is the predetermination of what puberty is before characterizing the hormones associated with this phenomenon, resulting in a gap in the sampling of 6 years.

Crawford et al. (1997) reported on the analysis of mixed longitudinal samples of IGF-I, IGFBP-3, testosterone, and DHEAS along with body measurements in a captive colony of *P. hamadryas*. The results include the finding of a spurt in mass and length gain in male, but not female, baboons, although the authors recognize that their cross-sectional data collection methods might have precluded finding one in females. They found that there are no sex differences in levels of IGF-I, IGFBP-3, or DHEAS, but that there are differences in the patterns of IGF-I and IGFBP-3 secretion, with males having peaks later than females for both.

In a study of wild *P. anubis*, the influence of rank is shown to affect levels of IGF-I (Sapolsky and Spencer, 1997). The authors demonstrate that social subordinance is associated with suppressed IGF-I concentrations in wild baboons. Because the animals in this study have completed growth ($N = 37$), it is difficult to determine whether this pattern is persistent and, in any way, affected the growth of subordinate individuals. Instead, they suggest that the suppressed IGF-I levels might reflect some other aspects of these animal's physiology, including immunocompetence, gonadotropin production, or metabolism.

Nonhuman primates: Comparative studies. Following on the groundwork laid by the studies described above, a recent article explored the relationship between adult size and levels of IGF-I, IGFBP-3, and GHBP in 11 papionin species (Bernstein et al., 2007). In particular, the goal of this research was to assess whether larger-bodied papionins have higher levels of growth-related

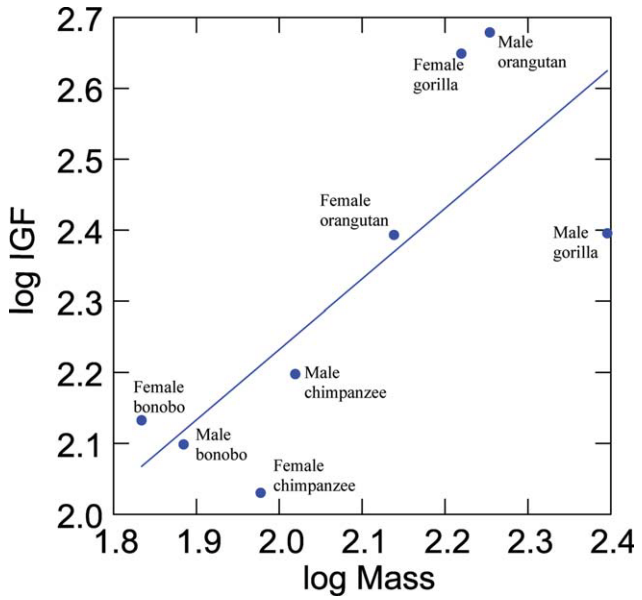

Fig. 2. IGF-I and mass in great apes. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

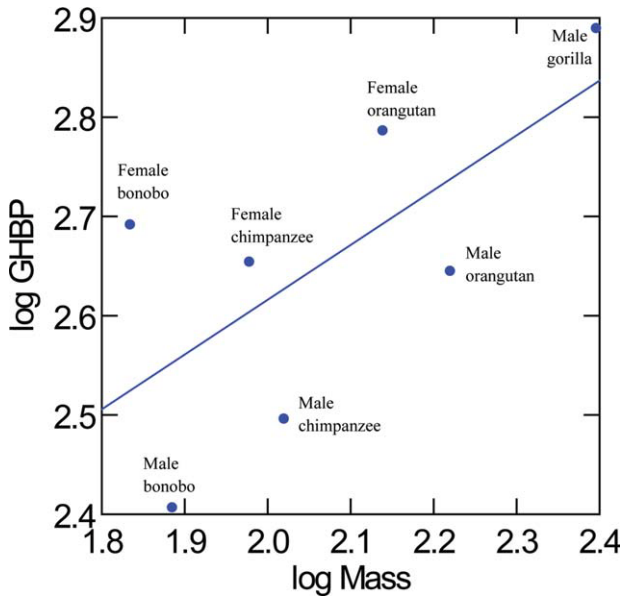

Fig. 3. Growth hormone binding protein and mass in great apes. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

hormones than smaller-bodied papionins. Results of this study showed that although hormone levels increased in a predictable manner during ontogeny, and peaking with a spurt in mass, absolute hormone levels do not co-vary with size either during growth or in adulthood. Specifically, some smaller-bodied species (e.g., *Cercocebus*) have higher absolute hormone levels than larger-bodied species (e.g., *Papio*). Differences in some hormone levels seem to track the papionin molecular phylogeny more than body size. For example, *Mandrillus* and *Cercocebus* both share high levels of IGF-I, and *Papio*, *Theropithecus*, and *Lophocebus* share lower levels.

Another comparative study focusing on papionin hormones, growth, and size investigated the relationship between serum hormone levels and morphometrics during ontogeny in *P. anubis* and *Cercocebus atys* (Bernstein et al., 2008). Using a mixed longitudinal sample, this study compared change in 18 different measurements, which reflect overall size growth as well as growth in length and circumference, with levels of six growth-related hormones and binding proteins. Results suggested that levels of these endocrine factors can be used to predict local and overall growth during ontogeny, and that integration between multiple hormone axes (e.g., somatotropic and gonadotropic) is indicated. Ontogenetic changes in hormone and binding protein levels are more tightly correlated with changes in morphometric measurements in baboons than mangabeys.

Ontogenetic scaling, or the differential extension of a common growth trajectory to different size/shape space, has been argued to be responsible for many of the form differences seen among extant African apes (Shea, 1983). Therefore, a comparative study was undertaken to investigate the relationship between size, IGF-I, and GHBP levels in the great apes (Bernstein, 2005). Using over 100 serum samples collected from animals in zoological institutions, this study calculated species mean hormone levels and compared them with body mass. Both IGF-I and GHBP are significantly positively correlated with mass (Figs. 2 and 3). Although further study is needed to investigate the significance of differences in male and female values, these results suggest that differences in these hormone levels may relate to the scaling of size and shape seen in the African great apes.

Insects and insulin/IGF signaling. Variation in body size can be broadly understood as generated through alterations in rate and/or duration of growth. In model systems such as *Drosophila*, it has become clear that these two processes are regulated through specific genetic and endocrine pathways. The insulin/IGF-signaling (IIS) pathway in *Drosophila* regulates the rate of local and systemic growth, and the release of hormones initiated by the activity of the insulin-signaling pathway determine the duration of phases of growth in this holometabolous insect (Shingleton, 2005). Of the evolutionarily conserved metazoan pathways, the insulin-signaling pathway is the major pathway influencing cell size, cell number, and organismal size (Oldham and Hafen, 2003). This pathway is centrally involved in the regulation of metabolism, growth, reproduction, and longevity (Géminard et al., 2006). Insects possess a single insulin/IGF system, which corresponds to the dual systems seen in vertebrates. Activity of the IIS pathway promotes glucose import and nutrient storage, as does the homeostatic function of vertebrate insulins (e.g., Rulifson et al., 2002). They both affect feeding behavior, lifespan, and reproduction. IIS also regulates cell growth during development, as do the mammalian IGFs (Efstradiatis, 1998).

The rate of cell growth, nutrient use, cell size, and body size in both flies and mammals is dependent on IIS (Edgar, 2006). Further, aspects of these systems that play a role in senescence may be evolutionarily conserved from yeast to mammals (Barbieri et al., 2003). Rather than an insulin-secreting pancreas, insects such as *Drosophila* have clusters of cells located in the brain that produce insulin-like peptides (DILPs); these substances exert the effects of the vertebrate insulin and IGFs (Okamoto et al., 2009). Adult individuals with impaired insulin/IGF signaling often manifest reduced

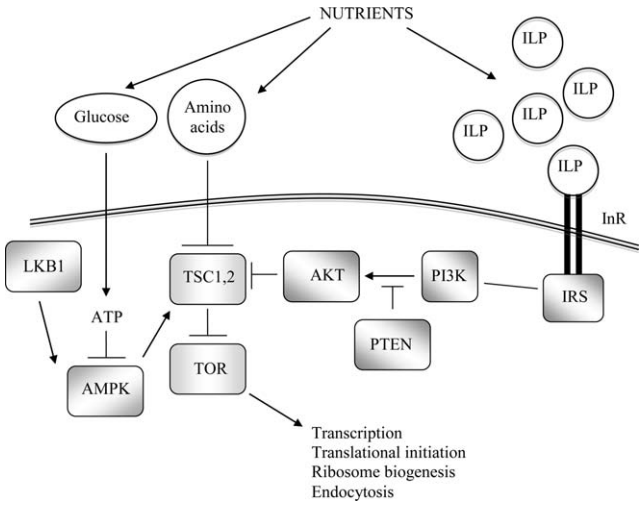

Fig. 4. Model of insulin/IGF and TOR signaling in *Drosophila melanogaster* (modified from de Jong and Bochdanovits, 2003). ILP, insulin-like peptides; INR, insulin receptor; IRS, insulin receptor substrate; PI3K, phosphoinositide 3-kinase; PDK, phosphoinositide-dependent kinase; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PKB, protein kinase B; PTEN, phosphatase and tensin homolog; S6K, S6 kinase; TOR, target of rapamycin; TSC, tuberous sclerosis complex.

reproduction, increased stress resistance, and longer life span (Tatar et al., 2003). Studies have shown that, in many cases, individual long-lived humans possess an efficient insulin response and lowered circulating IGF-I levels (e.g., Paolisso et al., 2001). Other centenarian human populations show mutations in the IGF-I receptor gene that confers reduced activity of the IGF-I receptor despite high serum IGF-I levels (Suh et al., 2008). The interaction between nutritional status and intracellular signaling suggests that the longevity benefits of caloric restriction might be mediated through this pathway. As has been documented in several mammalian species with regard to the IGF pathway, mutations in components of the insulin signaling pathway of *Drosophila* that decrease DILP production cause reductions in size, whereas overexpression of the DILPs causes coordinated increase in body, organ, and cell size (Oldham et al., 2002).

Many of the overlapping effects of insulin and the IGFs are likely because of multiple interactions with the insulin receptor. The DILPs bind to the insulin receptor and initiate a signal transduction cascade that regulates the rate of cell growth and division. This pathway in *Drosophila* is highly homologous to the insulin and IGF pathways in humans (Fig. 4) and is particularly important for coordinating growth with nutritional conditions. In *Drosophila*, amino acids in food are required for signaling to progress beyond the PI 3-kinase, whereas, in mammalian cells, target of rapamycin kinase acts in a similar "nutrient checkpoint" (Wullschleger et al., 2006). This means that the nutritional status of the fly and mammal is directly linked to intracellular metabolism.

Worldwide latitudinal clines in size exist for *D. melanogaster*, with larger body size found in cooler temperatures and smaller flies in warmer climates (de Jong and Bochdanovits, 2003). Flies in temperate areas show faster rates of development, increased growth efficiency, and preferential allocation of stored resources toward growth. In tropical populations, flies grow at a relatively slow rate, use resources less efficiently, and allocate reserves toward survival functions rather than growth to large size. A number of associated life history differences also sort between the populations: temperate populations experience higher larval survival rates, greater fecundity (as measured by ovariole number), and greater adult longevity. It is hypothesized that variation along the insulin signaling pathway underlies the clinal variation in body size in *D. melanogaster*, and that more "cold-adapted" populations have stronger signaling activity along this pathway (de Jong and Bochdanovits, 2003). These hypotheses are based on the fact that experimental manipulation of genes along the insulin-signaling pathway causes alterations in body size and associated traits listed above (Brogiolo et al., 2001; Britton et al., 2002). The insulin/IGF signaling pathway, therefore, presents an obvious candidate for investigation into where variation in signal strength originates—and would speak not only to how body size, rate, and duration of growth vary across generations of naturally occurring ectothermic or laboratory-reared experimental organisms, but also to how these traits might evolve.

GH/IGF axis in regulation of size: Human pygmies

The existence of human pygmy populations in multiple areas across the world suggests that this phenotype has evolved in parallel multiple times and perhaps in response to similar ecogeographical environmental conditions. Several hypotheses have been proposed to account for the evolution of human pygmy populations, by explaining their morphology in terms of adaptation to tropical rainforest environments (e.g., Cavalli-Sforza, 1986; Diamond, 1991). These include predictions regarding thermoregulation, mobility, and limited food availability (reviewed in Perry and Dominy, 2009). The growth of these populations in relationship to such factors has not been studied in great detail. A flurry of articles in the 1980s and 1990s produced evidence (at times conflicting) of modifications to the GH/IGF axis in pygmy populations across the world.

A detailed study on the growth allometry of Efe pygmies found that size differences both between male and female pygmies, and among pygmies and nonpygmies, could largely be explained by ontogenetic scaling (Shea and Bailey, 1996). The authors evaluated various adaptive scenarios to account for the small body size of the Efe and proposed that shifts in circulating hormone levels, as suggested by most studies quantifying IGF-I and GHBP in pygmy populations, could account for the overall "scaled-down" phenotype of the pygmies.

Earlier investigations into the physiological underpinnings of pygmy body size have touched both on circulating hormone levels and in cell responsiveness to growth-related hormones. Testing the response of pygmy IGF-I secretion to exogenous GH administration demonstrated that the failure to elicit a normal increase in IGF-I in the majority of individuals tested was most similar to what occurs in people with a dwarfed, low-IGF-I phenotype (Merimee et al., 1982). Measuring serum levels of IGF-I in Efe pygmies, Merimee et al. (1987) found that levels were blunted mainly during adolescence, and that the adolescent growth spurt was similarly depressed. No significant differences in IGF-I levels were found before puberty, and no differences in IGF-II or testosterone were

found across any age groups. In the same year, an article was published that detailed the endocrine status of the Mountain Ok people of Papua New Guinea; IGF-I, IGF-II, and GH levels were all within normal range (Schwartz et al., 1987). Further research using pygmy T-cell lines quantified the *in vitro* response to IGF-I, GH, insulin, and assessed receptor binding (Geffner et al., 1993). This study showed that pygmy cells demonstrated no clonal responsiveness to IGF-I or GH, although they did respond normally to insulin. This suggested a clear, very specific deficit in the IGF-I receptor, with resistance to GH as a secondary effect. After this, additional research investigated the cell surface expression of IGF-I receptors and discovered that gene transcription and signaling of these receptors was significantly decreased (Hattori et al., 1996). Other studies of circulating hormone levels in other pygmy populations showed evidence for decreased IGF-I, IGFBP-3, and GHBP, as well as compromised nutritional status (Ati: Clavano-Harding et al., 1999 and Aeta and Mamanwa: Dávila et al., 2002).

More recently, a study of Baka pygmies, compared with Bantu, showed a highly significant decrease (eightfold) in GHR gene expression that was not associated with any sequence variation of the GHR gene (Bozzola et al., 2009). As in most other studies of circulating hormone levels in pygmies, serum hormone levels were reduced in the Baka compared with the Bantu (GHBP more so than IGF-I, however). One of the major drawbacks of several of these studies is that, given their opportunistic nature, sampling often centers on adults or individuals in the latter part of adolescence.

Recent work links the pygmy growth pattern to a life history strategy that maximizes reproductive fitness in a high-mortality environment. Researchers looking into the cause of small stature in human pygmy populations have suggested that a relatively early onset of reproductive maturation is the key to understanding this phenotype (Migliano et al., 2007). Specifically, the shift to earlier female fitness peaks relative to those in nonpygmy populations is explained by high mortality rates and limited resource availability (e.g., Charnov and Berrigan, 1993). Importantly, the authors emphasize that short stature is a by-product of selection for earlier maturation, rather than being the target of selection itself. In this case, one would not necessarily expect that levels of growth-related hormones during ontogeny would differ between pygmy populations and nonpygmy populations; rather, one might see modifications of the temporal expression of the GH/IGF axis as a secondary effect of earlier activation of the hypothalamic–pituitary–gonadal axis.

Walker et al. (2006) found that variation in growth rates among groups was related to energetic constraints, with better nutritional conditions correlating with faster growth and slower growth resulting from the likelihood of poorer conditions. Faster growth, however, was also associated with higher mortality risks. Specifically, accelerated childhood and juvenile growth rates, coupled with a depressed adolescent growth spurt, were found in pygmy populations and suggested to reflect adaptations in the hormonal regulation of growth, especially in GH/IGF-I resistance, that allow less plasticity in ontogenetic trajectories. Taking these findings to the next level, and incorporating ideas from earlier work on the presence and function of the adolescent growth spurt (cf. Leigh, 1996), the authors propose that slow childhood and juvenile growth, coupled with rapid adolescent growth spurts, is a cost-saving strategy that allows parents to optimize energy to multiple dependent offspring.

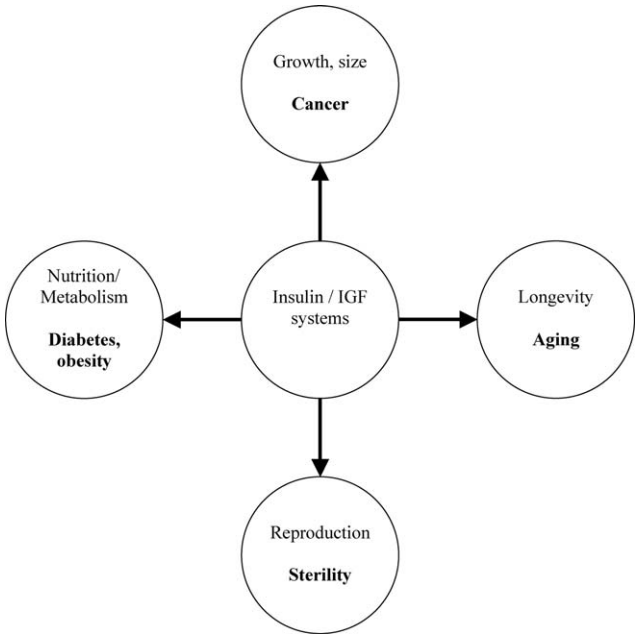

Fig. 5. The myriad functions of the insulin/IGF systems. Pleiotropic effects are noted in outside circles, with outcomes of dysregulation or senescent effects bolded. Modified from Nijhout (2003).

Developmental programming and transgenerational epigenetic effects

Stearns (1992) defines tradeoffs as fitness costs that occur when a beneficial change in one trait is linked to a detrimental change in another and as linkages between traits that constrain the simultaneous evolution of two or more traits. Hormones initiate the transfer of resources from somatic functions to reproductive functions when they mobilize an organism for reproduction and are, therefore, key mediators of resource tradeoffs between growth, maintenance, and reproduction. Hartfelder (2000) suggests that researchers look at hormones with a number of different effects ("hormonal pleiotropy") in a comparative perspective to elucidate how different species have dealt with coordinating life histories in variable environmental conditions over evolutionary time. The GH/IGF system lies at the crossroads of growth, metabolism, and nutrition and is, therefore, an ideal candidate for investigation of apparent tradeoffs in modern human populations that have affected body size (e.g. Migliano et al., 2007). The evolution of correlated suites of traits, such as size, age at maturation, and longevity, could be linked to alterations in this system (Fig. 5). Recent literature describing the programming of human metabolic parameters in early life suggests a mechanism by which this might occur.

Developmental programming occurs when environmental conditions affect permanent changes in tissue structure and function (Fowden and Forhead, 2009). Epigenetic effects include changes in the pattern of gene expression without modification of the gene sequence and involve DNA methylation and histone modifications (Patisaul and Adewale, 2009). Transmission of these

effects to subsequent generations can occur in the presence or absence of modifications to the germ line. In intrauterine life, hormones affect phenotype in a variety of ways, including effects on placental morphology, structure and modification of synthesis and metabolism of hormones, and direct effects on tissues. In these roles, they shape intrauterine development in response to environmental conditions; in effect, they produce an epigenome representative of conditions during development (Fowden and Forhead, 2009, p 619).

Studies in humans show that birthweight, weight during growth, bone mass, and disease (e.g., diabetes and cardiovascular) are correlated with one another. These correlations can be explained, at least in part, by a programming of homeostatic set points of hormone axes (e.g., GH/IGF-I) that occurs during intrauterine development and early postnatal life. Evidence is accumulating that suggests that these set points are influenced *in utero* by factors such as maternal diet, physical activity, and obesity. Postnatally, they seem to be influenced by birth weight (and specifically whether catch-up growth occurs after low birth weight), breastfeeding/formula feeding, and dietary quality during childhood growth. In cases of intrauterine growth restriction associated with lowered levels of IGFs, later life metabolic consequences are suspected, including insulin resistance and hypertension (Setia and Sridhar, 2009). In newborns either born preterm or SGA, decreased levels of IGF-I and IGFBP-3 are associated with inadequate stores of adipose tissue, by impaired glucose metabolism (Martos-Moreno et al., 2009). Clearly, the effects of early postnatal nutrition, modified through the developmental control of the GH/IGF axis, resonate through postnatal life (Kappeler et al., 2009).

The transition between infancy and childhood growth patterns, which represents a shift from rapid deceleration of growth velocity to a growth rate plateau and stabilization, is thought to be linked to environmental cues signaling energy supply. In this view, the plasticity of the human subadult growth period provides an advantage. If energy crises are present because of disease or undernutrition, the infant-to-childhood (IC) transition is delayed, with permanent growth deficits as an effect (Hochberg and Albertsson-Wikland, 2008). During and after the IC transition, growth is mainly under control of the GH/IGF-I axis. The IC transition does not occur in GH-deficient children, and levels of IGF-I and IGFBP-3, both influenced by GH, rise in parallel with normal or late-onset IC transition (Low et al., 2001). These authors propose that energy crises around and during the time of the IC transition result in epigenetic programming that can affect the growth and size of future generations. In fact, one study on the effect of grandparental nutrition during prepubertal growth points to possible effects on growth, disease, and mortality in grandchildren (Kaati et al., 2007).

The Dutch Hunger Winter Families Study tracks the later-life effects of an adverse *in utero* environment in offspring of mothers who experienced nutritional stresses during gestation (Lumey et al., 2007). During the winter of 1944, the German occupation blocked the delivery of food supplies to the Western areas of the Netherlands, and rations dwindled to around 500 kcal/day close to the time of liberation. The careful recording of birth and medical records has allowed researchers to follow the offspring of women pregnant during the famine, and in more recent years, to follow their grand-offspring. Because maternal undernutrition during pregnancy has been associated with restricted fetal growth, small size at birth, and an increased risk of poor health in adulthood, this population has provided an important resource for the investigation into the effects of early life insults to growth on later life disease and morbidity. Researchers have found, for example, that famine exposure during early gestation is associated with increased risk of cancer and diabetes (e.g., Roseboom et al., 2006) and a dyslipidemic pattern seen in female, but not male, offspring (Lumey et al., 2009). Transgenerational effects associated with famine exposure include increased adiposity and decreased length in grand-offspring (Painter et al., 2008). Experimental work with mice describes a hormonal mechanism by which transgenerational epigenetic effects of nutrition on size may operate (Dunn and Bale, 2009). Offspring of mothers fed a high-fat diet showed significantly longer bodies than mothers fed normal diets, an effect which persisted through to the following generation. The researchers suggest that reduced insulin sensitivity was at work and pointed to modifications of the GH/IGF axis as underlying this epigenetic effect. Changes to maternal diet, specifically including increased caloric (and protein) availability, may offer a way for length to increase rapidly across generations.

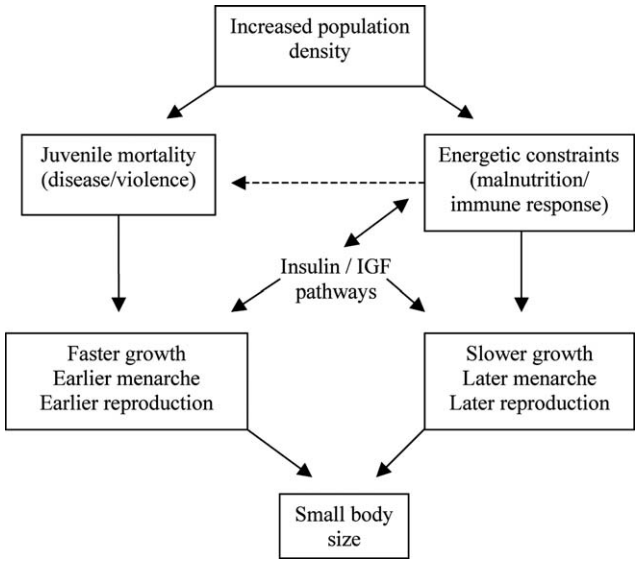

Fig. 6. Illustration of pathways through which population density can affect body size. Modified from Walker and Hamilton (2008).

Walker and Hamilton (2008), in illustrating how high population densities can affect body size, tie together nutritional constraints with (specifically juvenile) mortality risk as driving a reaction norm between age at reproductive maturity and adult body size. In their view, small body size, or the ability to get small, represents both a plastic response to inadequate nutrition and high disease loads, both more likely in higher population density scenarios, and a consequence of size-specific mortality. Given the preceding discussion on the prenatal (through placental/maternal hormone levels) and early life epigenetic effects (via dietarily influenced endogenous hormone production and sensitivity) on metabolism and growth, it seems fitting to add the insulin/IGF pathways as a mechanistic link between the manifestations of growth and size variation in response to environmental influences (Fig. 6).

Endocrine pathology in the fossil record?

There is a long history of invoking pathologies, and abnormal hormonal states in particular, to explain morphological variation seen in the fossil record. For example, acromegaly, a condition involving excessive secretion of GH and IGF-I in adults that leads to marked and stereotypical alterations in facial features and extremities, was drawn into discussions of Neanderthal skull morphology in the early 20th Century (Keith, 1911). These ideas persisted for several decades, growing to include hormonal shifts in timing and intensity of steroid secretion (Brothwell, 1975), and altered or abnormal endocrine states were further proposed to explain the hypertrophic postcranial morphology in both late *H. erectus* and Neanderthals (Ivanhoe and Trinkaus, 1985). Although some alterations in patterns of hormone secretion (and likely in receptor sensitivity and distribution) during ontogeny surely played a role in modifying the phenotypes of various hominin lineages, marked hormonal shifts are not satisfactory explanations for anatomical variation in the fossil record (e.g., Churchill, 1998).

The pathological perspective on hominin morphology has experienced a revival within the past 6 years. When the very recent remains of a hominin assigned to a new species, *H. floresiensis*, were reported (Brown et al., 2004), a flurry of articles followed, which sought to interpret the short stature and unusual anatomical proportions (especially relative brain size) (e.g., Argue et al., 2006). One group argued that the best explanation for the small body size and cranial capacity seen in this hominid was that it was actually a pathological *H. sapiens* specimen, most likely a microcephalic (e.g., Martin et al., 2006). A proposal that the individuals discovered on Flores belonged to a population of myxoedematous cretins offered a list of traits shared among modern humans born without a functioning thyroid and the *H. floresiensis* remains, including an enlarged pituitary fossa and dental anomalies (Obendorf et al., 2008). Another report attempted to invoke Laron syndrome, a suite of traits united in origin with insensitivity of the GHR and associated decreased IGF-I levels, to explain the morphology of *H. floresiensis* (Hershkovitz et al., 2007). The majority of analyses conducted to date suggest that *H. floresiensis* is a valid taxon rather than being a group of abnormal or pathological humans (e.g., Falk et al., 2009; Kaifu et al., 2009; Morwood and Jungers, 2009; Weston and Lister, 2009). Similarly, an understanding of the way in which hormone regulatory pathways can change over evolutionary time should make it clear that potentially any number of nonpathological modifications to the GH/IGF axis could have occurred during the evolution of the *H. floresiensis* phenotype. There is no need to infer endocrine dysregulation to explain it.

SUMMARY AND CONCLUSIONS

This review has focused on some components of one of the more important hormonal networks involved in determining adult size. The GH/IGF system plays a key role in growth, metabolism, reproduction, and senescence, from nematodes to humans. According to the evolutionary constraint and evolutionary potential hypotheses of hormone action, hormones can affect trait evolution through modification of circulating hormone levels or through alteration in tissue responsiveness. The small portion of the literature dealing with the GH/IGF system and size reviewed here clearly show that both are important. Specifically, circulating levels of IGF-I vary with size across a number of taxa, and receptor sensitivity also affects size.

However, the fact that not all human populations with short stature have lowered IGF-I levels, or that differences in body size among domestic dogs are not always explained by correlated differences in IGF-I levels, illustrates that size evolution is not constrained to a single mode or pathway. Instead, there are multiple aspects of the system that can be modified to generate similar sizes. What this means is that we can envision any number of tinkerings of the GH–IGF axis, and that there is no need to search for pathological explanations when proposing a mechanistic cause of dramatic shifts in size in the (sub)fossil record. Currently, we have only a very limited understanding of the hormonal variation that might relate to size and associated shape variation in modern human populations; we have an even more restricted understanding of how hormones might regulate size and shape differences in primates more generally. The preliminary research describing patterns of IGF-I and GHBP with size in African apes (Bernstein, 2005) may provide some support for Shea's proposal that systemic alterations in circulating levels of hormones relates to ontogenetic scaling in these primates. The finding that body size does not seem to be positively correlated with circulating IGF-I levels among papionins suggests that, in these animals, modifications to tissue responsiveness to circulating hormone levels might instead be more important for explaining how size variation evolved (Bernstein et al., 2007).

Although this review focused on particular aspects of one hormonal system, it is of course true that size differences are not generated by modifications to the GH/IGF axis alone. There are myriad other hormones involved in the processes of growth, maturation, and attainment of final adult size. Glucocorticoids and sex steroids, in particular, exert potent effects on size both prenatally and postnatally. Sex steroids play a critical role during fetal and early neonatal development in the determination of specific gender-related patterns of spontaneous GH profiles. In particular, linear skeletal growth, body weight, and organ size exhibit a strong dependence on either a pulsatile or continuous ("male" or "female") temporal mode of GH release, which are, in turn, related to higher and lower somatic growth rates, respectively. These differential temporal patterns of GH delivery to target tissues can markedly influence tissue responses at the level of specific gene expression and protein production. In the generation of size variation, estrogens are particularly important because they act to promote closure of long bone epiphyses and, therefore, place limits on overall measures of length or stature.

Because the GH/IGF axis (and insulin/IGF system in insects) is centrally involved in mediating the effects of the environment by, in essence, signaling context-appropriate growth and metabolic strategies to the organism, it probably plays an important role in mediating life history tradeoffs. Specifically, it seems that correlated suites of life history traits (including developmental rate, fecundity, and longevity) and their relationship to overall size are strongly influenced by metabolic parameters that are regulated by various components of these signaling pathways (e.g., de Jong and Bochdanovits, 2003). Given the apparent sensitivity of the rate and timing of

growth and maturation in various human populations to extrinsic factors (e.g., Walker et al., 2006), it is likely that the risk of adopting a strategy of taking a long time to grow up in a high mortality environment must be communicated to offspring. Evidence from developmental programming studies suggests that maternal nutrition, among other factors, directly affects offspring metabolism, size, and longevity, through the GH/IGF axis. To successfully adapt to varying conditions, the responsiveness in altering the course of both prenatal and postnatal development based on cues experienced *in utero* as well as in early postnatal life would seem to impart a significant advantage (e.g., Kuzawa, 2007). This agrees with the idea that there is not, perhaps, a universal "human growth pattern," but rather that the ability to maximize chances of success within a given environment is itself an adaptation. In this perspective, the evolution of size as a consequence, or a part, of a multifaceted cascade that extends back to prenatal life (and beyond, in the case of transgenerational epigenetic effects) presents a compelling area for further research.

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