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Endocrinology, Energetics, and Human Life History: A Synthetic Model

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Abstract

Human life histories are shaped by the allocation of metabolic energy to competing physiological domains. A model framework of the pathways of energy allocation is described and hormonal regulators of allocation along the pathways of the framework are discussed in the light of evidence from field studies of the endocrinology of human energetics. The framework is then used to generate simple models of two important life history transitions in humans, puberty and the postpartum return to full fecundity in females. The results of the models correspond very closely to observations made in the field.

Introduction

The essence of life can be defined as "metabolism in the service of reproduction." Organisms capture energy from the environment and turn it into more organisms. Natural selection has favored those variations that perform this task more reliably and more efficiently than their competitors. But the route from energy capture to reproduction can be complex. Even in the simplest organisms some captured energy must be devoted to growth and maintenance of the organism as well as to reproduction. Reproduction without growth would rapidly lead to smaller and smaller organisms until the size limits of viability were reached. Investment in maintenance leads to increased survivorship and opportunities to continue reproducing. The partitioning of available energy among these non-overlapping categories gives rise to the patterning of life histories -- variation in age-specific probabilities of mortality and fertility, trajectories of growth, rates of senescence, and other aspects of phenotype that are only manifest in a diachronic view, in the way an organism's life unfolds rather than in its state at any given time.

Life history theory emphasizes trade-offs and how optimal energy allocation varies with age and environmental circumstances. But this body of theory often leaves unspecified the physiological mechanisms that govern and regulate those trade-offs. The field of human reproductive ecology has emerged out of an effort to understand those mechanisms as they relate to the regulation of reproductive effort in particular

(Ellison, 2003a, 2009). More recent efforts to illuminate the mechanisms governing trade-offs of investment in growth and immune function are helping to further advance an integration of the physiological mechanisms of energy allocation decisions with the conceptual framework of life history theory (Flatt and Heyland, 2011). The focus of this paper will be a consideration of the ways the endocrine system helps to regulate metabolic energy allocation to generate the structure of human life history.

The endocrine system is one of the three major systems of integration of vertebrate physiology based on molecular communication, the other two being the nervous system and the immune system. The power of the endocrine system as a physiological integrator lies in two properties: (i) the diffuse nature of its communication, reaching all cells of the organism, and (ii) its ability to regulate both cellular activity and gene expression. Together these properties position the endocrine system to regulate energy allocation in ways that integrate with developmental and life history changes.

There are, however, two frequent biases in endocrinology that we should be particularly aware of in considering the regulation of metabolic energy allocation: the "top down bias" and the "newcomer bias." The top down bias is manifest in a predilection for assuming that the brain is in charge of the body. In many areas this is true, but it is not an absolute hierarchy of regulation. Elsewhere (Ellison, 2009) I have noted that molecular communication can be classified by the channels through which it flows into (a) central-nervous-system (CNS)-to-soma, (b) soma-to-CNS, (c) soma-to-

soma, and, (d) CNS-to-CNS. Behavioral endocrinology is dominated by soma-to-CNS communication, coordinating behavior with the physiological state of the organism, particularly as regards the regulation of reproductive effort. The most potent messengers along this pathway are those that easily cross the blood-brain barrier, especially steroids, as well as peptides that gain access to the basal hypothalamus. CNS-to-soma communication primarily flows through the hypothalamic-pituitary "transducer", integrating sensory and other information from basal ganglia and higher cortical areas in the regulation of peripheral organs and endocrine glands. Larger protein molecules are typical messengers along this pathway. Both the soma-to-CNS and CNS-to-soma channels can have important effects on the allocation of metabolic energy. But the primary conduit for messages regulating energy allocation is the soma-to-soma channel. This pathway includes messengers of all chemical types, including steroids (both gonadal and adrenal), thyroid hormones, proteins (including pancreatic hormones), and peptides (including gut hormones and adipokines). In large part, as will be described, the action of messages flowing through the CNS-to-soma pathway on energy allocation is achieved by modifying the action of messages in the soma-to-soma pathway.

The newcomer bias is manifested in a natural fascination with newly discovered or described messenger molecules and the desire to see them as particularly important in their effects. This can often be the case, but should not cause us to neglect the central roles that are often played by those messengers who have long featured in our

understanding of endocrine physiology. Many of these, such as steroids, thyroid hormones, pancreatic and gut hormones, also feature prominently in the soma-to-soma channel.

Keeping these biases in mind, we can consider the major features of the endocrine regulation of energy allocation decisions and their impact on human life history. The framework described here will necessarily be an over-simplification, like all models. Yet hopefully it will capture enough of the important features of the system to be heuristic, in organizing and synthesizing information, in illuminating complex interactions and processes, and in generating hypotheses. Where possible, we will pay attention to evidence from and applications to field studies of human physiology.

The endocrine framework of human energetics

The basic framework of human energetics, the flow of energy through the organism, is represented by the diagram in Figure 1 where the pathways indicated by specific arrows are associated with the hormonal regulators shown in Figure 2. As a model, not all the pathways of physiological integration and regulation that affect energetics are included, nor all the potential endocrine signals involved. Those that are included are considered to be major pathways and regulators which account for major aspects of energy allocation and its life history effects.

At the center of the framework is “available metabolic energy,” available for immediate allocation to any one of a number of non-overlapping categories. Inputs to available metabolic energy come either from direct intake, or from stores, filtered by the regulation of ATP production. The major allocation categories for available metabolic energy are identified as storage, activity, anabolism, and maintenance. Anabolic sub-categories include growth and reproduction. The parts of this framework will be considered in turn.

Regulation of energy balance

Energy balance refers to the difference between energy intake through nutrition and energy expenditure through all metabolic pathways. Of the various pathways of energy expenditure, physical activity can be separated out as distinct from those that contribute to resting metabolic rate. The net of energy intake and expenditure in activity can be considered as the contribution to available metabolic energy from the environment.

Energy intake is not tightly regulated by the endocrine system, since it depends greatly on environmental factors. Appetite regulation, however, is strongly affected by endocrine signals (Badman and Flier, 2005; Blundell et al., 2015a; Blundell et al., 2015b; Crespo et al., 2014; Meier and Gressner, 2004; Schwartz, 2000; Schwartz et al.,

2000; Webber et al., 2015). Two signaling molecules that will be considered in this model are leptin and ghrelin. Both are peptides, principally produced in the soma but capable of some penetration of the blood-brain barrier. Leptin is primarily produced by adipocytes, ghrelin by the gut. Both carry information to the hypothalamus that can affect appetite. Leptin, a tonic hormone reflecting the mass of adipocytes, is associated with reduced hunger when circulating levels are high and increased hunger when levels are low (Schwartz et al., 2000). Ghrelin, an episodic hormone which reflects short-term status of gut contents, with high levels occurring when the gut is relatively empty for an extended period, stimulates hunger when its levels are high (Pinkney, 2014). These orexigenic effects are mediated by and coordinated with other neural signaling, primarily in the ventromedial hypothalamus (Webber et al., 2015).

Energy expenditure in activity is not under tight hormonal control in humans, but in rodent models, lowered leptin levels were early observed to correlate with increased levels of physical activity, perhaps reflecting a stimulation of the motivation to forage for food (Pelleymounter et al., 1995; Wolf, 1996). In many rodents, food foraging exposes the animal to significant predation risk. Appetite regulation may serve to help regulate foraging effort in a way that balances risks versus benefits. There is no evidence at this time that foraging effort in human hunter-gatherer societies (the evolutionarily salient human subsistence pattern) or any other ecological context is related to hormonal appetite regulation. However, there is clinical evidence that exercise may affect appetite through the mediation of appetite regulating hormones (Blundell et al., 2015b).

Studies of human leptin and ghrelin levels in the field have produced some notable results, particularly highlighting population variation in average levels (Bribiescas, 2001, 2005; Bribiescas and Hickey, 2006; Kuzawa et al., 2007; Miller et al., 2006; Munch-Andersen et al., 2013; Sharrock et al., 2008; Tanaka et al., 2005). In general, subjects in non-western populations and populations engaged in subsistence economies have significantly lower levels of both appetite regulating hormones than in western, developed societies. This is true for leptin even after correcting for fat mass. At the least this suggests that caution needs to be exercised in interpreting the significance of absolute levels of these hormones. It is likely that the set-points for appetite regulation may be influenced by developmental factors (Sharrock et al., 2008) and may reflect population differences in overall energy budgets.

Regulation of energy availability

a. Release of oxidizable substrates

Oxidizable substrates (principally carbohydrates and fatty acids) are released from stores into the blood stream under the regulation of several different hormones. Among the most important regulators of energy substrate release in humans are cortisol, epinephrine, and glucagon. Epinephrine and glucagon are relatively short-term

177 regulators, involved in defending blood sugar homeostasis against the vagaries of
178 intake and expenditure on a time scale of minutes to hours. Because of their short-term
179 effects, these hormones are often involved in behavioral responses, including “fight or
180 flight” scenarios. However, they are not directly implicated in the longer term regulation
181 of energy substrate release that is typically involved in life history strategies and
182 transitions.
183
184 Cortisol, on the other hand, is involved in longer term regulation of energy
185 substrate availability. Cortisol has been associated with responses to psychosocial
186 stress, to the extent that it is frequently referred to as a “stress” hormone. However, it
187 can be misleading to label cortisol in this way, since psychosocial stress is only one
188 potential trigger for its release. Other than categorizing cortisol by one of the multiple
189 factors the can cause its release, it would be better to categorize it by its downstream
190 effects as a “metabolic” hormone. Cortisol’s principal actions involve the stimulation of
191 lipolysis to release fatty acids from adipose stores and the antagonism of
192 gluconeogenesis, resulting in an increase in available oxidizable substrates (Widmaier
193 et al., 2013). Although cortisol is elevated as a consequence of short-term stresses, it
194 rapidly returns to baseline when those stresses are removed. Chronic energy
195 demands, as can occur with infection and undernutrition (or, in other animals, migration
196 and hibernation), can result in chronically elevated cortisol and a shift toward greater
197 reliance on stored energy reserves. Shifts in chronic cortisol release also occur with

198 reproductive state in human females, being elevated during pregnancy to mobilize
199 maternal fat reserves to support fetal growth (Widmaier et al., 2013).
200
201 It should be noted that while cortisol promotes the release of free fatty acids via
202 lipolysis, it does not stimulate the beta oxidation pathway by which fatty acids gain entry
203 to the tricarboxylic acid cycle (Widmaier et al., 2013) Pathological elevation of cortisol
204 without increased energy expenditure, as in Cushing's syndrome, can result in
205 excessive fat accumulation in adipose depots and ectopic locations less sensitive to
206 cortisol action and thus be associated with redistribution of fat rather than loss of fat
207 (Despres and Lemieux, 2006).
208
209 In part because cortisol is readily measured in saliva and urine, as well as in
210 blood, there are numerous field studies of human cortisol. Many studies focus on short-
211 term cortisol dynamics in relation to psycho-social stress. Field studies of longer term
212 effects have focused on immune function, pregnancy, and lactation (Cohen et al., 2012;
213 Janicki-Deverts et al., 2016; Nepomnaschy et al., 2006; Oaks et al., 2016; Valeggia and
214 Ellison, 2004; Valeggia and Ellison, 2003).
215
216 *b. Efficiency of ATP production*
217
218 At the cellular level the utilization of oxidizable substrates is auto-regulated by the
219 accumulation of downstream products, and thus ultimately driven by energy

expenditure. However, basal metabolic rate, the baseline turnover of energy substrates in the body, is itself subject to hormonal regulation. Among the most potent regulators of basal metabolism are the thyroid hormones, especially thyroxine (T4). Under conditions of chronic energetic stress, such as fasting and starvation, T4 is lowered, resulting in a lower baseline rate of energy consumption by the body (McAninch and Bianco, 2014).

Up-regulation of T4 production can be part of an adaptive response to cold stress (Leonard et al., 2005; Leppaluoto et al., 2005). The efficiency of ATP production by the mitochondrial electron transport chain in some tissues, particularly brown fat, is regulated by T4 through the up-regulation of uncoupling protein (UCP) (Busiello et al., 2015; Leppaluoto et al., 2005). UCP decouples the return flow of hydrogen ions across the mitochondrial inner membrane from ATP production, resulting in an increased production of heat. UCP is particularly abundant in brown adipose tissue which can assist in the regulation of core body temperature, particularly in infants. Field studies of high latitude populations have also demonstrated seasonal shifts in T4 production and basal metabolism in adults associated with recurrent cold stress, a response that appears to be greater in populations native to high latitudes than to more recent migrants (Leonard et al., 2014; Levy et al., 2013; Tkachev et al., 1991).

Insulin-independent maintenance effort

Energy allocation is organized hierarchically. Wade and Jones (Wade and Jones, 2004) schematically represent this hierarchy in three levels: functions that must be maintained at or near normal levels at all times; functions that can be down-regulated at need, but cannot easily be interrupted for long periods; and functions that can be interrupted at need for extended periods. The top priority functions include the maintenance of brain function via the constant maintenance of membrane depolarization as well as indispensable vegetal activities such as heart and respiratory function, and some aspects of kidney and liver function. Mid-level priority functions include physical activity, immune function, and protein anabolism. Dispensable or interruptible functions include growth and reproduction, although these are also subject to mid-level down-regulation as well as interruption.

Reproductive state can reorganize this hierarchy somewhat in females. During pregnancy and lactation fetal growth and infant nutrition assume relatively high priorities, at or near the top level. The interruption of female fecundity by pregnancy and early lactation can be viewed as evidence of the priority of the fetus and infant over lower level maternal priorities. The down-regulation of maternal basal metabolism that can occur during pregnancy and lactation when energy availability is limited, noted above, can be seen as evidence of the higher metabolic priority assigned to the fetus and infant than mid-level priorities of the mother.

Top-level metabolic priorities are largely insulin-independent (Fernandez-Real and Ricart, 2003). The brain and fetus are particularly clear examples of insulin-independent substrate uptake. Energy flow to these priorities is regulated only by the availability of oxidizable substrates in the blood. The role of cortisol, glucagon, and epinephrine can be best understood as buffering energy flow to top-level functions. That is, when energy demands increase at lower levels, such as those precipitated by "fight or flight" scenarios, these hormones increase the levels of oxidizable substrates in the blood so that the new demands can be met without compromising top-level functions. Down-regulation of competing demands for oxidizable substrates can also increase their availability for top level functions. Physiological responses to fasting and starvation, for example, include down-regulation of mid-level and low-level functions to free up energy for the top priority functions (Keys et al., 1950).

Energy allocation to storage and anabolic effort

In textbooks the role of insulin at the organismic level is most often presented in terms of glucose homeostasis, its function being to stimulate the clearance of excess circulating glucose (Widmaier et al., 2013). But this is a poor and incomplete characterization of its function. Insulin does not simply facilitate removal of glucose from the blood, a function also performed by the kidney. It stimulates the uptake of glucose by target tissues especially for storage in adipose tissue and to support protein anabolism. Insulin also stimulates mitotic activity in many target tissues which, in

conjunction with its anabolic effects, can promote cellular proliferation and tissue growth (Sandow, 2009).

Viewed in these terms, the key role of insulin is to promote energy allocation to medium and low priority metabolic functions on a facultative basis, not simply the regulation of circulating glucose levels. When metabolic energy is available in excess of high and mid-level category requirements, insulin promotes the diversion of the excess either to storage or to anabolism. Similarly, the "counter-regulatory hormones" cortisol, glucagon, and epinephrine, do not simply counter-balance the effects of insulin on blood glucose, but buffer the flow of energy to top-level metabolic functions from fluctuations in intake and lower level demands independently of insulin. The balance of these hormones results in the hierarchical regulation of energy flow within the body, not simply in the avoidance of the pathological consequences of hyperglycemia.

Insulin was one of the first protein hormones to be isolated, characterized, and used therapeutically, due to its clinical importance in the pathogenesis and treatment of diabetes mellitus (Sanger and Tuppy, 1951a, b). In this context, a great deal is known about short-term insulin dynamics in relation to changes in blood glucose. But recently a new approach, based on measurement of C-peptide of insulin in urine, has been utilized to study longer-term changes in baseline insulin levels under field conditions and not in the context of disease (Sherry and Ellison, 2007). C-peptide of insulin is a section of the pro-insulin molecule that is cleaved in the production of active insulin. It is

produced in a 1:1 ratio to active insulin and is cleared intact into the urine. Thus measurement of urinary C-peptide, indexed by time, creatinine, or specific gravity, can be used as a proxy measurement of insulin production. Urinary C-peptide measured in samples collected in the field has been used to study longitudinal and cross-sectional variation in energy balance in Samoa (Sherry and Ellison, 2007; Sherry et al., 2014), Argentina (Ellison and Valeggia, 2003; Valeggia and Ellison, 2001, 2004; Valeggia and Ellison, 2003), and The Gambia (Reiches et al., 2013; Reiches et al., 2014), among other settings.

Biasing of energy allocation towards growth effort

Insulin controls energy allocation to lower priority metabolic categories, including energy storage, and the anabolic categories growth and reproduction. The triage of energy allocation among these competing categories, however, is largely under the control of a trio of phylogenetically related protein hormones: growth hormone (GH), prolactin (PRL), and human placental lactogen (hPL). The genes for growth hormone and human placental lactogen are both located on chromosome 17 and display ~96% sequence homology, indicating common ancestry through a gene duplication event. PRL is more distantly related, located on chromosome 6 and displaying ~ 85% sequence homology with GH. GH and PRL are both synthesized and secreted by acidophilic cells of the anterior pituitary, while the hPL gene is expressed in the

placenta. All three hormones have suppressive effects on whole body insulin sensitivity, primarily through an inhibition of glucose uptake by somatic adipose tissue. At the same time, however, all three synergize with insulin in promoting anabolic processes in target tissues: accumulation of skeletal and lean body mass in the case of GH, mammary gland glucose uptake and milk synthesis in the case of PRL, and fetal glucose transfer and fetal growth in the case of hPL (Forsyth and Wallis, 2002; Goffin et al., 1996; Wallis et al., 2005).

The secretion of these hormones varies with maturational and reproductive status, resulting in the differential allocation of available metabolic energy among these anabolic categories. GH follows a steep decline following birth as the high rate of infant growth declines to low levels in mid-childhood, but it undergoes an endogenous rise in puberty, serving to promote skeletal and lean body growth (Bona et al., 1999; Rose et al., 1991). At the same time, by increasing insulin resistance in adipose tissue it limits energy allocation to storage and causes a transient rise in basal insulin levels (Guercio et al., 2002). hPL by the placenta increases through pregnancy, elevating insulin resistance in the mother and increasing the flow of metabolic energy to the fetus (Braunstein, 2003; Mesiano and Jaffe, 2004). PRL production during lactation is stimulated by infant nursing demand and acts to promote the uptake of glucose and fatty acids by the mammary gland and the production of milk. At the same time it increases insulin resistance in maternal adipose tissue, resulting in a diversion of metabolic energy to milk production (Molitch, 2004).

There is a long history of measuring prolactin in field studies of lactation (see (Ellison, 1995) and growth hormone in studies of human growth (see Bogin, 1999). Studies of hPL are confined to clinical settings.

Energy allocation to reproductive effort

Energy allocation to reproductive effort is primarily reflected and governed by gonadal steroids (Ellison, 2003b). In females, ovarian steroids directly modulate fecundity, influence sexual attractiveness to males as well as receptive and proceptive sexual behavior, and promote energy storage in adipose tissue (an important form of somatic reproductive effort in females). In males, testosterone maintains sperm production, stimulates libido and mating effort and may also support increased social confidence and assertiveness, and promotes increases in muscle mass (an important form of somatic reproductive effort in males).

The production and release of gonadal steroids is governed by the gonadotropin hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH) secreted by the anterior pituitary. However, the effectiveness of this gonadotropin stimulation depends strongly on insulin, so strongly that insulin is sometimes characterized as a co-gonadotropin (Poretsky et al., 1999; Poretsky and Kalin, 1987). This effect has been

mostly clearly demonstrated in *in vitro* studies of steroid production by cultured ovarian granulose cells, where insulin receptor has been identified as the mediator of the effect, increasing the rate of steroid production per cell.

Gonadal steroids, in their turn, synergize with insulin in promoting somatic reproductive effort in both sexes, promoting increases in muscle mass in males (androgens) and increases in adipose mass in females (estrogens) (Grumbach and Styne, 2003). The mutual synergies between insulin and gonadal steroids constitute a positive feedback loop that can dramatically up-regulate the flow of metabolic energy to reproductive effort to take advantage of conditions of positive energy balance and the availability of metabolic energy in excess of the needs of high priority categories.

The advent of practical methods for assaying gonadal steroids in saliva (Ellison, 1988; Lipson and Ellison, 1989), in addition to blood and urine, led to a rapid increase in the number of field studies of gonadal steroids in human populations. Many examples are provided elsewhere in this issue.

Hormonal gating of energy allocation

The hormonal framework described above governs the allocation of available metabolic energy to competing domains in a hierarchical way. Top priority metabolic categories, including brain and vegetal physiology, as well as fetal growth and infant

nutrition during pregnancy and lactation, receive energy in direct proportion to its availability. That availability is determined by the hormones that mobilize oxidizable substrates and those that govern the rate and efficiency of ATP production as well as by the competing demands of physical activity.

Insulin controls the gate for allocation of energy to lower level, “dispensable” categories such as energy storage, growth, and reproduction. Cortisol opposes this allocation, increasing the availability of metabolic energy to mid-level categories such as immune function as well as buffering top level allocations. Allocation of metabolic energy among potentially competing lower level categories is governed by GH, PRL, hPL, and gonadal steroids interacting with and modifying the action of insulin.

The dynamic interaction of the key hormones governing energy allocation helps to organize key life history transitions. Puberty and postpartum resumption of ovarian function are two particularly clear examples and will be considered here in some detail.

The pubertal transition

Puberty involves a transition in energy allocation from growth to adult reproductive potential during which the body is modified, sexual dimorphism is elaborated, and reproductive potential is established (Ellison et al., 2012). Although not as dramatic as the metamorphosis of holometabolous insects or most amphibians, it is

the human equivalent, changing juvenile morphology to a distinctively adult pattern and elaborating immature, nonfunctional reproductive organs into mature, functioning ones. Puberty involves the close coordination of primary reproductive maturation with the rapid growth and transformation of the body. Reproductive maturation involves the appearance (or, more properly, reappearance) of pulsatile release of gonadotropin releasing-hormone (GnRH) by the median eminence of the hypothalamus, which in turn stimulates increased production of FSH and LH (Grumbach and Styne, 2003). The factors that determine this change in GnRH production are still incompletely understood, but the change begins quite early, well before internal or external manifestations of increasing gonadal activity. The skeletal growth spurt that is typical of puberty is primarily caused by an endogenous increase in GH and its downstream consequences (Grumbach and Styne, 2003). Again, the causes of the increase in GH secretion are incompletely understood, but its timing is roughly synchronous with the first appearance of pulsatile gonadotropin secretion, suggesting a linkage between the two events (Suter, 2004; Gahete et al., 2016). The elaboration of somatic sexual dimorphism results from the interaction of pubertal growth with rising titers of gonadal steroids. Differential growth between the sexes resulting in adult sexual dimorphism is mediated by gonadal steroids, both androgens and estrogens (Ellison et al., 2012).

The hormonal management of energy allocation during the pubertal transition can be sketched out in terms of the framework described above. We assume that the process is set in train when pulsatile GnRH reappears and GH begins to rise, even if the

direct causes of those two events remain to be fully understood. Rising levels of GH stimulate growth and divert energy away from storage. The elevated GH also results in increasing insulin resistance in adipose tissue, causing basal levels of insulin to rise. Rising insulin would synergize with the increasing gonadotropin titers resulting from increasingly stable GnRH pulses to promote gonadal steroid production and release. As they approach mature levels, gonadal steroids in turn will potentiate the peripheral effects of insulin, leading to a shift back toward lower insulin levels and increased energy allocation to fat storage (in females) and muscle mass (in males), now as sexually dimorphic forms of somatic reproductive effort. Even as they shift the direction of energy allocation, gonadal steroids cause the closure of epiphyseal growth plates and the cessation of skeletal growth as well as causing the remodeling of the female pelvis.

In this way the pubertal transition unfolds as an endogenous process governed by the interaction of the endocrine framework of energy allocation and its integration with the growth and maturational processes involved. Energy allocation is first diverted away from storage to support somatic growth and transformation and then returned to storage as well as sexually dimorphic somatic forms of reproductive effort. A characteristic and transient period of hyperinsulinemia is a central part of the process, helping to accelerate gonadal steroid production to its mature levels. The mature steroid levels in turn resolve the transient insulin resistance.

462 This schema is consistent with observations of shifting energy allocation priorities
463 in female Gambian adolescents (Reiches et al., 2014). In the midst of the pubertal
464 transition, when skeletal growth is still underway, Gambian girls will respond to periods
465 of energetic stress by defending lean body mass at the expense of fat mass, but later in
466 the process as skeletal growth comes to a halt the same periods of energetic stress are
467 associated with a defense of fat mass at the expense of lean body mass. The
468 metabolic priority given to growth early gives way to a metabolic priority of somatic
469 reproductive effort late (Figure 3).
470
471 *A mathematical model of the pubertal transition*
472
473 The smooth, autonomous nature of the transition can also be demonstrated in a
474 quantitative model of female puberty. The specifics of the model are provided in
475 Supplementary Materials. The point of the model is to demonstrate that the interactions
476 between the principal hormonal regulators reviewed above act like interlocking gears,
477 so that changes in one component drive changes in the system as a whole. The shape
478 of the changes that ensue is a function of the feedback links within the system. The
479 central set of interactions are those between insulin directing energy to anabolic effort,
480 the pituitary proteins (prolactin, growth hormone, placental lactogen) biasing energy to
481 growth effort and feeding back on insulin through their effects on somatic insulin
482 resistance, and the gonadal steroids (estradiol, progesterone, and testosterone) biasing
483 energy to reproductive effort and feeding back negatively on the pituitary proteins

484 regulating growth effort. Because the interactions of these hormones are interlocking,
485 the system as a whole can be changed by changes in any one of the components. But
486 the nature of the interactions causes the system to “switch” from a bias toward growth
487 effort to a bias toward reproductive effort, a switch that reflects the essential nature of a
488 life history transition as defined in this paper. Both the transition from growth to
489 reproduction at puberty (described here) and the resumption of ovarian function
490 postpartum (described below) can be modeled by the same system of interactions.
491
492 The assumptions and parameter settings of the quantitative models are meant to
493 be as simple as possible. In the model of the pubertal transition, GH is assumed to be
494 the independent driving factor, with all other variables dependent on it. In fact, the
495 initiation of the GH rise remains something of a mystery. There is mounting evidence
496 suggesting that the rise in GH may be tied to the same neural mechanisms, including
497 kisspeptin signaling to the pituitary, that disinhibit GnRH pulsatility in the hypothalamus
498 (Gahete et al., 2016). This would suggest that the initiation of the GH rise and the
499 nocturnal, sleep-associated appearance of pulsatile LH may be more or less coincident
500 (Apter, 1997, Suter 2004). In any event, increases in GH ordinarily precede detectable
501 increases in gonadal steroids (Rogol, 2010). So in this model the assumption is made
502 that a rise in GH starts the transition.
503
504 GH is assumed to fall steeply with age prior to puberty in parallel with growth
505 velocity (Bona et al., 1999; Rose et al., 1991; Chemaitilly et al., 2003), according to a

506 rational function (a simple mathematical expression for a pattern of smooth, asymptotic
507 decline (Otto and Day, 2007), with an endogenous, normally shaped rise and fall
508 beginning at about age 8 years and centered on age 12.5 years. These ages are
509 arbitrary, but are chosen to reflect contemporary observations of adolescent growth for
510 females in the US and other developed nations where high quality longitudinal data are
511 available (Kuczmarski et al., 2002). For males, the age parameters can be set
512 approximately two years later. The normal shape of the GH rise during puberty is an
513 arbitrary assumption that generally reflects the observed pattern (Albertsson-Wikland et
514 al., 1994). The exact shape of the trajectory isn't important to the model; what is
515 important is that GH undergoes a rise at puberty before falling to adult levels.
516
517 Insulin, *independent of the effect of GH,* is assumed to follow a slow logistic rise
518 from childhood to adult levels (Ballerini et al., 2016). However, the effect of GH on
519 insulin resistance, assumed to be proportional to the level of GH, results in a transient
520 increase in insulin. Estradiol*, in the absence of insulin,* is assumed to follow a slow
521 logistic rise to adult levels, becoming noticeable (about 10% of adult levels) at about the
522 same time as the start of the GH rise, driven by gonadotropin levels that are themselves
523 responding to the resumption of pulsatile GnRH release. The logistic form of the
524 estradiol trajectory is arbitrary but is a simple mathematical form that can be used to
525 model sigmoid patterns (Otto and Day, 2007). A dummy factor ("lag") is introduced to
526 center the inflection point of the estradiol at about 12.5 years (around the time of
527 menarche) and an asymptotic approach to adult levels at around 20 years. This pattern

reflects empirical observations indicating continued increases in ovarian function for a number of years after menarche until at least the late teens/early twenties (Lipson and Ellison 1992, Ellison 1996). Under the stimulating influence of insulin, assumed to be proportional to insulin level, the rise in estradiol becomes steeper and overshoots final adult levels slightly before converging on them in the late teens. Growth rate is assumed to be proportional to GH levels, minus a braking effect assumed to be proportional to estradiol levels, resulting from the action of estradiol in accelerating the closure of the epiphyses of the long bones. The breaking effect of estradiol results in a more rapid deceleration of growth that reaches its steepest decline at about the time of menarche. The resulting pattern is represented in Figure 4. As noted above, the parameters have been arbitrarily set to reflect the timing of puberty similar to that in the US and other industrialized populations. Delay in the initial rise in GH would shift the entire pattern to the right, typical of later puberty. Substitution of testosterone for estradiol, together with a later onset of the GH rise, would generate a model typical of males. Note that testosterone conversion to estradiol in the growth plates results in the same breaking effect on linear growth as in females. Note also that the model does not specify exact hormone levels, but only relative levels, with 1.0 representing typical adult values.

The postpartum resumption of ovarian function

A second example of the hormonal orchestration of a life history transition is the postpartum resumption of ovarian function. In this case, a transition occurs between energetic allocation to milk and energetic investment in fecund reproductive capacity. The transition unfolds in a manner very reminiscent of the pubertal transition, with PRL taking on the role played by GH during puberty. In a lactating mother early in the postpartum period milk production assumes a high priority. It is driven by PRL secretion which is responsive to infant demand but also reflective of maternal energy availability (Ellison, 1995). When infants are exclusively breastfed by mothers facing energetic constraints, PRL levels will be high and insulin levels low. PRL directs energy toward milk production by increasing the insulin resistance of peripheral maternal adipose tissue (though there is also evidence that PRL increases insulin sensitivity in mammary adipose tissue). Gonadal activity is extremely low, though FSH levels are near normal (McNeilly et al., 1994), suggesting ovarian resistance to gonadotropin stimulation.

Later in the postpartum period PRL levels begin to decline. This occurs most often as a consequence of the introduction of supplementary foods into the infant's diet (McNeilly et al., 1994), reducing the demand for milk. Reduced energy demand for milk production results in increased energy availability to the mother and rising levels of basal insulin. Energy allocation to storage rises as a consequence, but PRL levels remain sufficient to cause elevated insulin resistance. As a result, insulin levels rise above the typical level for the mother, manifesting a brief, transient period of hyperinsulinemia. This transient period of hyperinsulinemia, although briefer in

duration, is very reminiscent of the transient period of elevated insulin in puberty. The elevated insulin synergize with FSH levels to stimulate ovarian steroid production toward normal mature levels. The rising titers of estradiol that result in turn potentiate energy storage in adipose tissue, increasing adipose insulin sensitivity and returning insulin levels to normal.

As with the pubertal transition, the resumption of postpartum ovarian function is governed endogenously by the endocrine architecture of energy allocation. Insulin once again plays a central role, modified by the actions of PRL and gonadal steroids. The unfolding sequence is clearly displayed by Toba mothers in Argentina (Ellison and Valeggia, 2003; Valeggia and Ellison, 2001, 2004; Valeggia and Ellison, 2003) (Figure 5), and a comparable pattern has even been observed in wild chimpanzees in Uganda (Emery Thompson et al., 2012).

A mathematical model of the postpartum resumption of ovarian function

As with the pubertal transition, the smooth, endogenous nature of the resumption of ovarian function postpartum can be represented in a qualitative model (details in Supplementary Materials). This model includes analogous hormonal interactions to those presented in the puberty model above. In this case, PRL level is assumed to be the independent driving factor with other variables being dependent on it. Prolactin is assumed to decline following a logistic function (a simple expression for a sigmoid

pattern, Otto and Day, 2007) and to represent the energy demand for milk production. In the version of the model presented here the decline in PRL is parameterized to return to baseline by 40 months with a maximal rate of decline at 18-20 months. This is an arbitrary parameterization designed to reflect patterns observed in the Toba (Valeggia and Ellison, 2004). Different values for the parameters of the logistic could be chosen to reflect earlier or later weaning or other factors affecting energy availability. Energy availability for lower level priorities than milk production is assumed to be proportional to the complement of PRL (where peak PRL is set at 1.0 as a reference). Insulin is expected to be proportional to energy availability, but modified by the insulin resistance caused by prolactin. If insulin sensitivity were constant, insulin levels would rise proportionally to energy availability. However, due to the declining effect of prolactin on insulin resistance, insulin rises more steeply and overshoots typical "post lactation" levels (set at 1.0). Estradiol levels rise proportionally to insulin with a slight, arbitrary lag time, while postpartum weight gain is proportional to the product of energy availability and insulin. The resulting pattern is represented in Figure 6 with parameters adjusted to be roughly equivalent to observations made on the Toba. Once again, variable values are relative with 1.0 representing adult, non-lactating values of all variables except PRL, where 1.0 represents peak values early in lactation.

The heuristic value of the mathematical model is to make explicit the fact that the mutual interactions of a core set of hormones regulating energy allocation, interactions that are well-established in the literature, are sufficient to generate the rather complex

615 trajectories of hormones and anabolic variables (e.g., growth rate, milk production,
616 weight gain) that are observed during two important life history transitions, puberty and
617 the post-partum resumption of ovarian function. It is not necessary to assume any
618 special set of interactions or drivers to generate these patterns. Rather the "switch"
619 from growth effort to reproductive effort is latently embedded in the effect these
620 important regulators have on each other. Natural selection has been able to leverage
621 the same endocrine architecture to orchestrate two different life history transitions by
622 making use of two different, but phylogenetically related, modifiers of anabolic energy
623 allocation, GH and PRL. Although beyond the scope of this paper, it can be argued that
624 this architecture has analogues in other vertebrates (Chandrashekar and Bartke, 2003,
625 Kawashima et al., 2007, Flatt and Heyland, 2011).
626
627
628 *Concluding comments*
629
630 The model framework presented here is just that: a model that represents only a
631 few of the major features of a complex network or interacting signals that govern human
632 energetic allocation. Its heuristic value is illustrated in its ability to capture the major
633 signals and interactions in sufficient detail to illuminate the dynamic aspects of the
634 control of energy allocation during major life history transitions. In doing so, it helps to
635 connect our knowledge of the mechanisms that govern energy allocation with the
636 predictions and tradeoffs that feature in life history theory. As a major branch of

637 evolutionary theory, life history theory has proven very powerful in predicting and
638 explaining major features of life history diversity, and in doing so it leans very heavily on
639 generalized concepts of energetic tradeoffs. But less effort has been made to integrate
640 life history theory with proximate mechanisms until recently (Flatt and Heyland, 2011).
641
642 The model presented here also underscores the central role of insulin, not as a
643 gluco-regulatory hormone, but as the major gatekeeper of energy allocation to mid- and
644 lower level physiological priorities. Insulin does not simple clear glucose from the
645 circulation to guard against negative effects of hyperglycemia, it directs energy toward
646 growth and reproductive effort, synchronizing investment in those physiological
647 categories with the availability of metabolic energy over and above the requirements of
648 higher priority categories. This centrality of insulin in the modulation of energy
649 allocation helps to make sense of the phylogenetically highly conserved relationship
650 between insulin and insulin-like signaling and lifespan variation (Barbieri et al., 2003;
651 Singleton, 2011; Tatar et al., 2003). Insulin is one of the best known and longest
652 studied human hormones. It may not have the cachet of more recently identified
653 neuropeptides and cytokines, nor does it represent control of the soma by the CNS. Yet
654 its role in life history energetics is crucial.
655
656 Finally, although developed in the context of human physiology, there is reason
657 to suspect that the framework presented here may have more general application,
658 either directly or as a template to modify and build on. The comparability of the

659 trajectory of C-peptide of insulin in relation to the postpartum resumption of ovarian
660 function in humans and chimpanzees is one example that supports this notion. The
661 framework developed and presented here may serve as an impetus for comparative
662 studies of the hormonal architecture of energy allocation in non-human primates and
663 mammals generally.
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Figure Captions

Figure 1: The basic framework of energy flow underlying human life history energetics. Numbers associated with the arrows refer to the groups of hormonal regulators specified in Figure 2. The parenthetical number associated with energy flow from available metabolic energy to activity indicates potentially weak or indirect hormonal regulation.

Figure 2: Categories of hormonal regulators associated with the pathways of energy flow specified in Figure 1. Examples of major hormonal regulators in each category are given and further elaborated upon in the text.

Figure 3: Body composition changes (means ± SE) in adolescent females in The Gambia during periods of relative energy abundance (harvest season) and energy constraint (hungry season) subdivided by growth rate. Details provided in Reiches et al. 2014.

Figure 4: Trajectories of growth hormone, growth rate, estradiol, and insulin during puberty generated by a simple model of the basic framework of human life history energetics presented in this paper and illustrated in Figure 1. The Y-axis units are expressed in proportion to adult values for each variable. Details of the model are provided in Supplementary Materials.

Figure 5: Plots of first morning urinary C-peptide of insulin levels expressed as a proportion of individual, post-resumption average levels for each individual during the postpartum lactation period as observed among Toba women compared with the trajectories of (A) BMI and (B) urinary estrone conjugates (urinary metabolite of estradiol). Compare these trajectories with those generated by the model depicted in Figure 5. Data from Ellison and Valeggia 2003, Valeggia and Ellison 2001, 2003, 2004.

Figure 6: Trajectories of insulin, estradiol, postpartum weight gain, energy availability, and prolactin during the postpartum lactating period generated by a simple model of the basic framework of human life history energetics presented in this paper and illustrated in Figure 1. The Y-axis units are expressed in proportion to adult values for each variable. Details of the model are provided in Supplementary Materials.

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