The Effects of Exercise on Growth

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The Effects of Exercise on Growth

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Contents

Summary

The way in which exercise influences statural, hypertrophic and reparative growth is examined from the perspective of the human lifespan.

Statural growth depends on a neuroendocrine programme which channels nutrient energy towards increments in lean body mass. Exercise can facilitate statural growth and is a necessary stimulus for reparative growth through its stimulatory effects on secretion of growth hormone (GH) and other anabolic hormones. An exercise-associated increase in GH secretion is a response to acute or prolonged exercise-induced fuel shortage that directs metabolism towards utilisation of lipids and promotes growth. Exercise can transiently block the expression of statural growth by competitively removing the necessary nutritional support for growth. Statural growth retardation can be corrected by catch-up growth, but stunting may also be permanent (depending on the timing and magnitude of the energy drain).

Hypertrophic growth is less dependent on hormonal and nutritional support than statural growth, and exercise provides the necessary mechanical stresses for growth and remodelling of the musculoskeletal system. Excessive mechanical strain may suppress hypertrophic growth. The intermittent nature of exercise provides temporal organisation that is necessary for the normal operation of cellular growth processes.

Exercise by pregnant women does not appear to influence fetal growth. Evaluation of the effect of exercise on growth of children and adolescents is complicated by nonrandom selection of individuals for participation in organised sports, and by lack of information on the magnitude of exercise-induced energy drain.

Exercise is essential for regulation of body composition in adulthood. It provides mechanical and metabolic stimuli that are necessary for hypertrophy of the musculoskeletal system and increased GH secretion for reparative growth.

Growth is generally defined as an increase in size of the body or its parts by addition of material through assimilation into the living organism. However, in this review discussion of the term 'growth' will be limited to lean body mass. Thus, the concept of growth includes: (i) *statural or incremental growth,* by which human body mass increases in size from conception until some time after puberty; and (ii) *hypertrophic growth,* by which parts of the lean adult body mass enlarge in response to increased functional demands. It is less evident that growth processes also operate in repair and structural maintenance of the body. This (iii) *reparative growth* becomes most apparent as it declines with advancing age.

Physical activity influences all three manifestations of growth in at least three different ways. First, as muscle contractions generate mechanical stresses on the musculoskeletal system, the tissues most actively engaged in generation of movement experience strains which are necessary for hypertrophic response. Mechanical stresses also shape early morphogenetic stages of incremental growth, and permit the maintenance of musculoskeletal mass in adulthood. Hypertrophic growth does not require extensive nutritional and hormonal support, and contributes importantly to the maintenance of the musculoskeletal system in adulthood.

Secondly, exercise produces increased metabolic energy demands. These are met through neuroendocrine and autonomic adjustments in the supply and utilisation of energy. This metabolic need engages hormones which have metabolic as well as anabolic actions. The metabolic actions provide an immediate solution to the metabolic fuel need. The anabolic actions provide structural growth for the body, in general, and for organs engaged in the supply of oxygen and oxidative utilisation of lipids, in particular. This growth contributes importantly to maintenance of fat-free body mass and regulation of body composition in adulthood, and its expression depends on abundant nutrient supply.

Finally, the majority of physical activities involve intermittent muscle contractions, and the intermittent presentation of mechanical and metabolic stimuli is a necessary condition for expression of statural and hypertrophic growth.

Evidence for a direct influence of exercise on growth is fragmentary because of several complicating factors. Firstly, depending on its type, volume and intensity, physical activity can provide predominantly *mechanical* stimulation necessary for hypertrophic growth, or predominantly *metabolic* stimulation necessary for whole-body growth. In most instances both stimuli are present, making the study of their individual contributions difficult.

Secondly, depending on its intensity and volume, exercise can either stimulate or curtail growth, and our understanding of the minimal effective thresholds and dose-response ranges conducive or inhibitory to growth is particularly limited.

Thirdly, exercise effects are hard to distinguish from manifestations of endogenous growth. It is particularly difficult to evaluate exercise effects on growth in growing children and adolescents who participate in organised sports where they are often selected for some inherited, desirable physical and functional attributes. Growth comparisons with population norms or with sedentary control groups are often not valid, as appropriate matching of individuals for genetic attributes or the stage of skeletal development is lacking.

Finally, growth processes are influenced by the timing of physical activities, nutrient intake, and endocrine secretion and action. Our incomplete understanding of these periodicities or failure to control for them also hampers the study and interpretation of the effects of exercise on growth.

The present review first describes how exercise can affect incremental, hypertrophic and reparative growth at different stages of human life, and then examines the available evidence as to whether it does so.

1. Factors Controlling Growth

1.1 Neuroendocrine Control of Statural and Reparative Growth

Statural and reparative growth both affect the entire lean body mass. They depend on the availability of abundant nutrient energy and on guidance by growth hormone (GH) and other anabolic hormones. The operation of this growth process during fetal development is poorly understood. Early fetal growth is largely under genetic, nutritional and local growth factor control.[1,2] Later fetal growth is controlled by a GH variant expressed in the placenta (but not in the pituitary gland),[3,4] by growth factors, insulin and by the supply of nutrients arriving through placental circulation. The contribution of fetal pituitary and maternal GHs to fetal growth is also not well understood.

Towards the end of the first year after birth, pituitary GH assumes primary control over the rate of statural growth.[5] The rate of early growth is determined by the volume and rate of GH secretion.[6,7] High plasma GH levels in early infancy decline through childhood in parallel with the height-velocity curve;[6,7] thyroid hormones amplify the anabolic actions of GH.[8,9]

The anabolic actions of GH are dependent on the temporal pattern of its secretion and on actions of (and interactions with) other hormones. In rodents, the linear growth rate is highest when GH secretory bursts are separated by about 3 hours of very low GH levels,[10-12] as is the case in the male rat, and is reduced when GH levels show small deviations around a relatively high baseline, as is the case in the female rat.[13,14] Thus, a gender-related difference in the pattern of GH secretion[13,14] is responsible for the difference in the rate of growth and adult body size in male and female rats[15] and this can be simulated by experimental manipulation of the GH pulse frequency.[10] Thyroid hormones increase transcription of pituitary GH genes in rats but not in humans,[16] and synergistically increase the anabolic actions of GH.[8,9]

GH controls statural and reparative growth from the end of the first year after birth.[5] High GH volumes[6,7] and the intermittent pulsatile delivery of GH[10-12] are required, along with an abundance of nutrient energy for stimulation of statural and reparative growth. A neuroendocrine programme assures this pattern of GH secretion early in development, and endurance exercise restores high pulsatile GH secretion[71,81,84] after it has started to spontaneously decline. In circulation, GH is bound to a protein which is structurally nearly identical to its membrane receptor[17,18] and which may remain bound to the hormone when it attaches to the membrane receptor.[19] The signal transduction through which GH produces its postreceptor effects is not well understood. It may involve phosphorylation of a receptor-associated tyrosine kinase, a non-receptor tyrosine kinase,[20] activation of a G protein, and production of diacyl glycerol and phosphokinase C.[19]

Anabolic effects of GH at the tissue level (fig. 1) involve both differentiating and proliferative actions. A dual effector hypothesis of GH action[21] attempts to explain the differentiating and proliferative postreceptor events. GH action includes up-regulation of its receptor and binding protein,[22,23] increases in cell responsiveness to growth factors, and initiation of transcription of growth factor genes and their binding proteins.[24-26] This differentiating action is followed in the bone growth plate by proliferation of differentiated chondrocytes[27] in response to both GH and growth factor action. Dual action consists of the proliferative and differentiating response of chondrocytes to growth factors that were induced by earlier GH action. These growth factors are released by chondrocytes to bind to their own and adjacent cell membrane receptors, and thus act in autocrine or paracrine fashion.

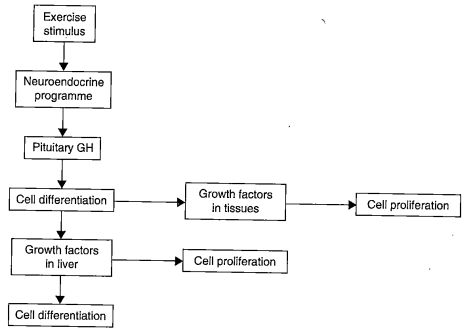

Fig. 1. Neuroendocrine control of statural and reparative growth by growth hormone (GH). High GH volumes[6,7] and the intermittent pulsatile delivery of GH[10-12] are required, along with an abundance of nutrient energy for stimulation of statural and reparative growth. A neuroendocrine programme assures this pattern of GH secretion early in development, and endurance exercise restores increased GH secretion[71,81,84] after it has started to spontaneously decline. The anabolic action of GH is dual:[21] it directly induces differentiation and proliferation of cells throughout the lean body mass. Growth factors that have been induced by GH then continue to have differentiating and proliferating action.

GH induces the expression of growth factors and their binding proteins in the liver; these are released into circulation and act in endocrine fashion. Circulating growth factors extend the differentiating and proliferative action of GH. The best studied of the GH-induced growth factors is insulin-like growth factor one (IGF-I) [somatomedin-I]. This was originally thought to be the sole mediator of the anabolic actions of GH;[28] however, recently the somatomedin hypothesis of GH action has been expanded to include the already mentioned direct anabolic actions of GH in target tissues.[11,29,30]

Quantitative control of GH secretion driving statural growth during childhood and puberty resides in a genetically determined neuroendocrine programme. This neuroendocrine mechanism includes the stimulatory actions of GH releasing hormone (GHRH) neurons located in the arcuate region of the hypothalamus and the inhibitory actions of somatostatin neurons located in the preoptic and periventricular hypothalamus. Both sets of neurons have pituitary somatotrophs as their target.[31] The reciprocal inhibition of these 2 neuropeptides and their alternating pattern of release into the hypophyseal portal circulation control transcription, expression and release of pituitary GH.[32]

Stimulatory action of gonadal steroids over GH secretion[33-44] and their joint actions on IGF-I release are the endocrine trigger of pubertal growth spurt. Increased secretion of gonadal steroids occurs in response to changes in the pattern and the amount of pituitary gonadotrophin secretion;[34,40,42,43] gonadotrophins in turn react to pubertal changes in the control of hypothalamic gonadotrophin releasing hormone. Gonadal steroids stimulate basal GH secretion and initiate pubertal growth spurt, its magnitude supported in equal measure by actions of estradiol[45-47] or androgens[36,41,44,48] and GH.[33]

Gonadal hormones also enhance the magnitude of exercise-induced GH release during puberty.[49] The stimulatory action of gonadal steroids consists of increases in amplitude of individual GH pulses

rather than in the number of pulses or the rate of GH clearance.[37-39]

Initiation of puberty depends on attainment of a critical body mass, stature and skeletal maturity;[35,50-54] nutrient availability can thus advance or postpone its onset. Overabundance of food during early development in humans and animals enhances the rate of incremental growth, increases adult stature and advances the onset of puberty.[55-59] Energy shortage and the depletion of storage fat reduce growth rate, retard skeletal maturity[60-62] and statural growth, and delay onset of puberty[50,51] and of the associated growth spurt. These conditions can be produced through nutrient restriction,[50-54,60-62] oxygen shortage,[63,64] or a large volume and intensity of exercise.[65,66] Delayed onset of puberty will take place after the energy restriction and other restraints have been removed and compensatory catch-up growth[67-70] has taken place. There appears to be some kind of feedback which delays the onset of the pubertal growth spurt and the conversion of neural growth controls into a mechanism for regulation of body composition until sufficient lean body mass or skeletal growth has been attained.

Statural growth stops some time after puberty, in part due to involutional influence of gonadal and adrenal steroids on the epiphyseal growth plates.[33] More importantly, growth stops due to a modification of the brain mechanism responsible for the release of high volumes of GH and for opportunistic channelling of available nutrients towards growth. Basal GH secretion is now suppressed, energy expenditure in the form of spontaneous physical activity has increased, and energy balance is achieved through matching of energy intake to energy expenditure.[71-73] Basal GH secretion and its anabolic actions display a progressive decline over the rest of human lifespan.[74-77] The endogenously driven high levels of GH secretion are now superseded by GH secretion that is contingent on stimuli signalling shortage of metabolic energy.

Elicitation of GH surges by high-resistance exercise,[78] or other circumstances creating acute energy needs,[16,79,80] and stimulation of basal pulsatile GH secretion by endurance exercise[81-84] or other circumstances of prolonged energy need,[85] provide the necessary hormonal conditions for acceleration of growth once its rate has started to decline. Acceleration of statural growth by exercise takes place if the epiphyseal growth plates remain open.[86,87] Lean body mass[88-90] is maintained or increased when statural growth is no longer possible. In either case, abundant nutrient energy is necessary for the expression of such growth.

The central role of exercise in stimulation of GH release and growth is clearly seen in exercising adult hamsters. These animals experience a sustained increase in metabolic energy need as a consequence of large volumes of habitual voluntary running that in scale approximates human marathon distances.[91] Rodents retain the capacity for incremental skeletal growth throughout much of their adult lifespan,[92,93] but a neuroendocrine mechanism[71,72] brings about a maturational decline in GH secretion and incremental growth. Voluntary running accelerates growth in sexually mature hamsters only after their exponential growth rate has started to decline and the growth-inhibiting brain mechanism has begun to operate.[94] Such habitual endurance activity leads to increased basal pulsatile GH[81,82] and glucocorticoid secretion,[95] skeletal elongation,[87] permanent increases in body mass[86,96] and reduction in body fat level.[97] As the expression of growth[86,87,96] and reduction in body fat[97] in exercising hamsters depends on the presence of intact pituitaries,[98] both growth and increased utilisation of storage lipids appear to be related to GH oversecretion. Increased secretion of GH and of glucocorticoid hormones[95] enhances mobilisation and oxidation of lipids, and the anabolic byproduct of increased GH action is acceleration of somatic and skeletal growth.[87,96]

As found with exercising hamsters, endurance training in 30-year-old women stimulates an increase in basal pulsatile GH secretion.[83,84] In the absence of capacity for linear growth, increased GH action is applied towards maintenance of, or

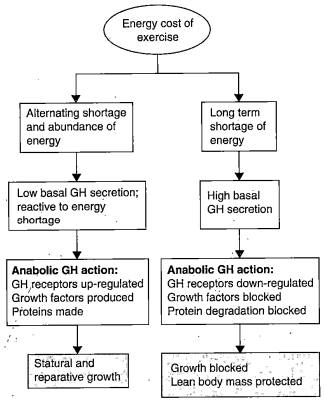

Fig. 2. Nutritional control of the expression of growth. *Abbreviation:* GH = growth hormone.

an increase in, the lean body mass, and towards utilisation of storage lipids for energy.[88-90]

1.2 Nutritional Control of Statural and Reparative Growth

The timing of nutritional manipulations with respect to the rate and stage of incremental growth determines the extent to which nutrition will accelerate or retard the rate of growth and affect adult stature. During early childhood and adolescence, overabundance of nutrient energy accelerates growth of fat-free body mass and (even more so) of body fat depot and produces greater than average adult stature.[55-59] Obese children expend less energy and eat greater than average quantities of food.[99-101] Growth deficits incurred during the early phase of rapid growth are not fully corrected by subsequent *ad libitum* realimentation, in contrast to those that take place at later stages of development.[102]

Exercise can block the expression of statural growth when it competes for limited nutrient energy. Substantial energy expenditure in very young rats, in the form of compulsory swimming[103] or running,[104] reduces their rate of accretion of lean body mass as well as body fat, with the latter affected more than the former. Termination of exercise is followed by catch-up growth resulting in partial compensatory increase in the lean body mass;[104] however, stunting of growth by substantial, compulsory early exercise depends on the timing and magnitude of energy drain and is not fully corrected.[103,104] In freely running adult hamsters, expression of exercise-induced growth is blocked during nutrient shortage, and is then carried out as delayed, but intense, catch-up growth after the reinstatement of unlimited supplies of food.[96,105] Exercise was reported to produce higher rates of catch-up growth and greater adult stature when it was made available during *ad libitum* realimentation in animals and children.[106]

When nutrient energy is abundant, increased GH secretion (induced by either developmental neuroendocrine programs or exercise) stimulates statural or reparative growth (fig. 2). When nutrient energy is not limiting, increased GH secretion exerts anabolic action by upregulating GH receptors[107,108] and stimulating production of growth factors[113] in target tissues and in the liver. When nutrient energy is limiting, the basal rate of GH secretion increases,[85,109-111] but the number of GH receptors[107,112] and tissue and plasma levels of growth factors decline,[112-118] and tissues become resistant to the anabolic action of GH.[107-111,116-123]

Nutritional blockade of statural and reparative growth (fig. 2) occurs through changes in secretion and action of anabolic hormones, their metabolic actions and secretion of other metabolic hormones. When energy shortage is severe, a decline in plasma insulin levels leads to a reduction in cellular uptake of carbohydrates and amino acids, in biosynthesis of proteins, glycogen and triglycerides, and in transcription and synthesis of hepatic IGF-I[112-115] and GH receptor[112] genes. Plasma IGF-I levels decline during energy shortage.[115-118]

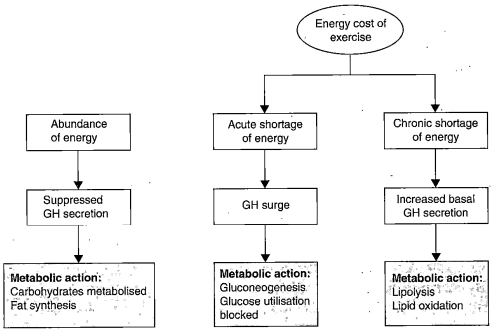

Fig. 3. Control by growth hormone (GH) of fuel metabolism.

A fasting-induced increase in plasma glucocorticoid hormones[80] facilitates catabolism of proteins to provide amino acids for gluconeogenesis, and inhibits GH gene transcription in the anterior pituitary.[120,121] Thyroid hormone synthesis is redirected from tri-iodothyronine (T_3) to reverse T_3 production when nutrient energy is restricted,[9] thus reducing T_3-GH synergism. Food restriction reduces the number of GH receptors and the level of GH binding protein in circulation,[107,108,122] thus attenuating GH action at the receptor site. Acute signals of energy shortage, such as an episode of hypoglycaemia,[16,79,80] or a bout of intense exercise[78] elicit a GH surge, while energy deficits lasting for an extended period of time increase the basal pulsatile secretory pattern of the hormone through an increase in the number of GH pulses and in the mass of hormone secreted in each pulse.[85,109-111]

Although there is a significant increase in the basal pulsatile GH secretion at times of energy shortage, the liver[113,123] and other target tissues[118] become resistant to GH action. In contrast to a decrease in circulating IGF-I levels, fasting has little impact on the plasma levels of IGFBP-3, the GH-dependent binding protein (BP) that serves as a reservoir for circulating IGF-I[118] but increases the level of IGFBP-1,[118,124-126] the binding protein that is negatively regulated by insulin.[127] Thus, during energy shortage, besides a decline in the number of GH receptors,[107,108,112,122] a resistance to GH action develops at the postreceptor site.[123] The cumulative effect of all of these endocrine changes is an inhibition of protein synthesis and growth when nutrient availability is inadequate.

Through its metabolic actions, GH increases the availability of metabolic fuels in circulation and influences which nutrients will be metabolised. During energy shortage, the actions of GH are predominantly metabolic. In addition to acting in a homeostatic fashion to increase the availability of blood glucose and free fatty acids when circulating levels of these fuels decline,[16,128-131] GH also influences the type of metabolic fuels used. GH promotes utilisation of lipids and inhibits cellular uptake and utilisation of carbohydrates[129-132] (fig. 3).

When there is an overabundance of circulating metabolic fuels, GH secretion and actions are blunted,[140,141] and high plasma insulin level promotes carbohydrate metabolism and synthesis of

lipids. Acute fuel shortage elicits GH surges which help to increase plasma levels of glucose and free fatty acids.[16,128-131] GH directs energy metabolism towards utilisation of lipids, first by suppressing utilisation of carbohydrates and fat synthesis, and secondly by promoting lipolysis and oxidative metabolism of lipids.[128,129]

Unlike the short-lived catecholamine action,[133,134] GH promotes lipolysis after a delay of 1 hour and produces sustained rather than dose-response lipolytic effects.[135-138] This sustained lipolytic GH action is further enhanced by increased basal glucocorticoid secretion that is a consequence of intense endurance training in animals and man.[95,139] By reducing carbohydrate utilisation and concomitantly increasing fat oxidation, GH helps to draw energy for metabolism out of storage lipids, preventing loss of lean body mass.

When nutrient energy does not have a limiting effect, exercise generates brief episodes of heightened metabolic need which trigger secretion of GH and other counter-regulatory hormones. These provide immediate release and use of stored energy, and are followed by increased food consumption to restore energy balance and replenish energy stores. Increases in basal GH[81-83] and glucocorticoid[95,139] secretion represent a neuroendocrine adaptation to recurring episodes of energy need which, in conjunction with increased food consumption, provide necessary conditions for incremental[86,96] and reparative growth.[88-90]

Finally, when overnutrition and inactivity result in obesity, GH action is diminished due to decreased basal GH secretion,[140,141] blunted GH release to a variety of stimuli[141-143] and increased basal insulin level.[145-150] As obese individuals have a greater than average amount of lean body mass,[151] diminished GH secretion in obese humans can thus be seen as a response to the overexpansion of the adult lean body mass.

1.3 Growth Hormone–Eliciting Features of Exercise

Several physiological effects of exercise act as effective stimuli for GH secretion in humans (fig. 4). First, GH is released in response to increased need for metabolic fuels during exercise.[78] Suppression of GH secretion by high plasma glucose[152] and free fatty acid levels[152,153] illustrates the important role of GH in fuel homeostasis. Increased oxygen need during exercise is a second, effective stimulus for GH release.[154-158] Acute GH surges occur when exercise intensity exceeds the anaerobic threshold;[155,156] an increase in plasma lactate level is by itself a sufficient stimulus for GH secretion.[158] Furthermore, basal pulsatile GH secretion increases only when, during endurance training, the rate of oxygen utilisation exceeds the rate of oxygen supply.[83]

A third exercise-associated stimulus for GH secretion is a rise in core temperature resulting from elevated exercise metabolism.[159-162] An acute exercise-induced GH surge can be blocked by preventing exercise-associated rises in core temperature.[159,160] GH-deficient individuals thermoregulate poorly while exercising in hot environments.[163]

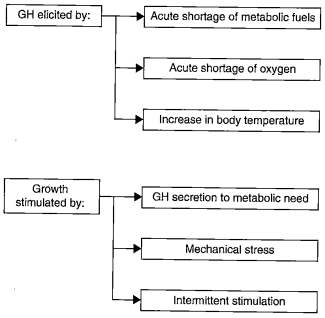

Fig. 4. Growth hormone (GH) and growth eliciting features of exercise. Three physiological effects of exercise are potent growth hormone secretagogues: acute shortage of metabolic fuels,[78] acute shortage of oxygen,[154-158] and increase in core temperature.[159-163] Besides its capacity to elicit GH secretion, other growth eliciting features of exercise are mechanical stress[180] and intermittent presentation of metabolic and mechanical stimuli.[176-183]

GH secretory response to several different physiological effects of exercise suggests that a functional relationship between exercise and GH secretion may have evolved as a bioenergetic solution to immediate metabolic needs and as a means of producing structural adaptations to meet long term metabolic needs. Extended increases in GH secretion protect structural proteins against being used for metabolism, and promote synthesis of lean body tissues, particularly those essential for oxidative metabolism. In conjunction with thyroid hormones, GH helps increase mitochondrial mass and membrane lipids,[164] mitochondrial enzymes involved in fatty acid oxidation,[165,166] and left ventricular size and ejection fraction[167-170] – all well-known adaptations to habitual endurance exercise. Thyroid hormones, on the other hand, initiate transcription of mitochondrial[171] and of muscle myosin genes.[172]

1.4 The Importance of Timing in the Control of Growth

Another feature of physical activity that provides a necessary stimulus for somatic growth is its intermittent temporal organisation. Many types of exercise involve intermittent muscle contractions. The intermittent loading pattern characterised as a repetition maximum (RM) of 10 is a more effective stimulus for GH elicitation than is the single maximal load applied as RM1.[173] The intermittent stimulus of locomotion in rats[174,175] induces widening of the epiphyseal growth zones and elongation of the foot bones. Intermittent[176-180] rather than static[176,179] loading is a necessary condition for appositional bone growth in skeletal modelling and remodelling.

In addition to the acute rhythmic nature of most physical activities, their occurrence is also organised in an episodic fashion over time. Diurnal humans and nocturnal rodents distribute physical activity and rest during distinct phases of the photoperiod. The growth process is episodic and discontinuous, whether measured during a period of one day[181-186] or over longer spans of time.[187] Enzymes responsible for longitudinal bone growth show peak activities during the quiescent portion of the nyctohemeral cycle, while the enzymes responsible for appositional growth are most active during periods of increased physical activity.[188-190] Thus, the nyctohemeral alternation of rest and activity appears to be a necessary prerequisite for both longitudinal and appositional growth, and disruption of such rhythms by immobilisation[191-193] or removal of photoperiodic entrainment (for example during space flights[194-196]) may contribute to musculoskeletal atrophy and to the breakdown of reparative growth processes.

1.5 Mechanical Control of Hypertrophic Growth

Early embryonic development is largely under genetic, hormonal and nutritional control, but a gravitational field and a mechanical substrate against which cells can attach, move and organise are a necessary condition of early morphogenesis.[197,198] Stresses on the body structure generated by contracting muscles and by gravity provide the mechanical stimulus for normal incremental growth, for the maintenance of structural body components, and for the hypertrophic or atrophic structural adjustments to changes in mechanical load-bearing.

When nerve damage or immobilisation impedes the movement of parts of the body, the lack of mechanical loading results in muscle atrophy.[191-193] When the mechanical component of movement is cancelled in the zero-gravity environment of outer space, there is significant loss of muscle mass and bone mineral content.[194-196] Conversely, a changed pattern, or an increase in magnitude of loading of the musculoskeletal system, leads to skeletal remodelling,[176-180,199,200] increases in bone density[201-204] and increases in muscle mass and contractile strength.[205-210]

In contrast to the mechanism of statural growth, the distinguishing feature of hypertrophic growth in muscle[211-213] and bone[214] is that mechanical activation of the genes for growth factors and

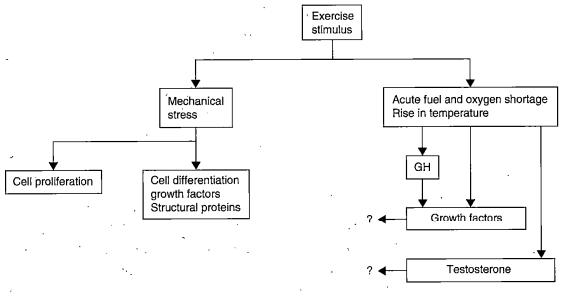

Fig. 5. Control by mechanical stress of hypertrophic growth. Distinguishing features of mechanical stress as a stimulus for hypertrophic growth are that it can directly induce cellular differentiation[211-214] in overloaded musculoskeletal tissue without dependence on hormonal[211,215,216] or abundant nutritional support.[217-219] It is not certain to what extent hormones[237-240] and growth factors[241-245] that are released in response to high-resistance exercise contribute to the expression of hypertrophic growth. *Abbreviation:* GH = growth hormone.

structural proteins in challenged tissues can proceed without hormonal guidance or abundant nutrient energy (fig. 5). Hypertrophic response produces the same relative increases in muscle mass in the absence of GH[215,216] or insulin action and during energy deprivation[217-219] as it does in hormonally intact and well nourished animals. Transcription of IGF-I and IGF-II genes proceeds in the overloaded muscles in the presence as well as in the absence of GH action.[211] This implies that overloading of the muscle can produce hypertrophy in individuals who are GH–deficient, diabetic, food restricted, obese or aged.

Hypertrophic cellular growth is specific to the tissues exposed to mechanical stress, and thus will take place only in those muscles and bones which are overloaded. In bone, growth factors are incorporated into the matrix during modelling, and are released to exert their differentiating and anabolic effects during the resorption phase of the bone remodelling.[220]

Hypertrophic growth has the capacity to change not only the absolute size but also the functional properties of mechanically loaded muscle and bone. In bone, with its crystalline hydroxyapatite structure, mechanical strains generate a piezoelectric effect. The electrical charges at the compressed surface stimulate the osteoblasts to deposit new bone matrix,[221-225] while the opposite charges at the stretched surface induce bone resorption via osteoclasts. In muscle, high-resistance exercise can alter the biochemical and functional characteristics of muscle fibre types. Mechanical loading alters the genetic expression of components of actin, myosin and other structural muscle proteins, and facilitates their interconversion between slow and fast isoforms.[207,208,226]

Hypertrophic and cellular growth response to increased mechanical loading is linear in the lower range of stresses, and declines or becomes negative when acting forces exceed the limit of adaptive biological response. Some examples of this biphasic growth response to loading of bones[174,175] are seen in growing animals and children (see section 2.2).

While extensive endocrine support is not needed for the expression of hypertrophic growth, it is possible that hormones and growth factors acutely released in response to high-resistance exercise may play a modulating role in this growth.

High-resistance exercise elicits GH release; the magnitude of GH surge is proportional to the magnitude of overload.[78] GH facilitates the synthesis of the mineralising enzyme alkaline phosphatase *in vitro*,[227,228] and induces osteoblasts to deposit mineral.[229-231] However, administration of exogenous GH was not found to augment the hypertrophic muscle growth induced by weight-bearing exercise in humans, but rather increased nitrogen retention throughout the lean body mass.[232-234]

GH surges during exercise are occasionally but not consistently accompanied by increased plasma IGF-I levels.[235-239] Increases in plasma testosterone levels are substantially greater in males than in females during high-resistance exercise,[173,237,239,240] and androgens are known to enhance GH secretion and trigger the pubertal growth spurt.[36-44,48]

A number of other growth factors are reportedly released in response to exercise, such as nerve growth factor,[241] epidermal growth factor,[242,243] bone morphogenetic protein Gla[244] and the fibroblast growth factor;[245] but their possible anabolic significance has not been unequivocally established.

The fact that increased mechanical loading produces hypertrophic muscle growth was known to the Ancient Greeks; its present-day applications are widespread in bodybuilding[205] and orthodontics,[246] and in efforts on the part of health professionals to counteract age-associated or pathological declines in bone density and bone and muscle strength.[247]

2. Growth and Different Stages of Human Life

2.1 Exercise and Fetal Growth

Three issues are of interest in the discussion of maternal exercise on maternal and fetal growth: the impact of the energy cost of maternal exercise; the effect of the oxygen need generated in the fetus by reduced placental and uterine blood supply; and the influence of pregnancy on maternal pituitary GH secretion and reparative growth.

Whether maternal exercise can stimulate fetal growth or produce enough of an energy drain to compromise it[248-251] is still uncertain because the available studies have limitations. A number of studies are retrospective with nonrandom assignment of participants to exercising and sedentary conditions; information about activity levels was gathered through interviews and questionnaires; and demographic, physiological and medical variables were not fully controlled.[250] In some studies showing a positive relationship between heavy physical work and low infant birth weight, the confounding variable of occupational stress has not been eliminated.[252]

In addition, most studies provide no quantitative measures of the energy cost of exercise involved.[250] If these are estimated from tables of energy expenditure for different physical activities and sports,[253] then the following three conclusions can be made. When the weekly exercise energy expenditure of pregnant women is below 1000 kcal (4180kJ),[254-256] physical activity has no effect on infant birth weight, and at best causes a modest reduction in maternal weight gain.[257] In at least 2 studies where the energy cost of exercise was estimated at about 750 kcal/week (3135 kJ/week)[258] and 1750 kcal/week (7315 kJ/week),[259] there was a positive correlation between the amount of maternal exercise and infant birth weight. In both cases, there could have been a selection bias in that study participants determined both the intensity of the exercise and the level of compliance; the fetal growth may have been a consequence of these uncontrolled confounding variables.

Energy expenditure in the form of exercise consuming about 2000 kcal/week (8360 kJ/week) throughout pregnancy in trained and very lean runners and dancers [i.e. those with maximal oxygen uptake (VO_{2max}) values above 50 ml/kg/min and body fat levels of below 17%] reduced maternal weight gain by 2.9kg and infant birth weight by 300 to 400g.[260-262] 70% of the infant weight shortfall was attributable to fat loss; no change was seen in infant length or head circumference.[261]

In women who subsisted on 1500 to 1600 kcal/day (359 to 383 kJ/day), daily energy intakes that are 30% below the World Health Organization and Food and Agriculture Organization standards, heavy physical work reduced pregnancy weight gain by 2.6kg and infant birth weight by about 200g.[263,264] Most of the deficit was in the nonfetal fraction of pregnancy weight gain.

Thus, there is no firm evidence that maternal exercise facilitates growth in the fetus. In addition, human fetal growth appears to be well protected from the energy drain of maternal exercise consuming as much as 2000 kcal/week (8360 kJ/week) and from dietary intake as low as 70% of basic energy requirements.

Animal studies employing compulsory exercise protocols also seldom provide quantitative information about the energy cost of exercise. When moderate training intensities were employed, exercise had no effect on fetal mass at birth, although in some instances maternal weight gain was reduced.[265-268] Reduced fetal mass[269,270] or a reduced number of live young born[271,272] are reported in some studies, and retarded bone ossification in fetal limbs accompanied reduced birth weight in others.[273,274]

In addition, intermittent reduction in placental and uterine blood flow may present either a stimulus for fetal lung growth or a reduction in the energy supply to the fetus. Experiments with pregnant ewes suggest that the fetus and the uteroplacental tissue extract a constant amount of oxygen despite the variable rates of blood flow.[275] Placental weight either did not change[261] or increased[276] even when exercise in women was extensive enough to result in reduced infant birth weight. In pregnant animals subjected to compulsory exercise, infant lung size either was not affected[277] or was reduced,[267,270,278] while the placentas were smaller[270,271] and fetoplacental diffusing capacity was reduced.[270]

Thus, maternal exercise does not appear to stimulate faster or greater growth and development of human fetal lung, although it may affect growth of fetoplacental tissue. In humans, there is evidence for stimulation by maternal exercise of placental size, while high levels of compulsory exercise may inhibit placental growth in pregnant animals and retard fetal lung growth and maturation.

The last issue concerns the capacity of a pregnant woman to maintain lean body mass in view of the endocrine changes from pregnancy. Of particular interest is the role of the placental GH variant[3,4] expressed and secreted during pregnancy, providing the negative feedback sufficient to shut down maternal pituitary GH secretion.[279,280] It is not yet known whether exercise can elicit GH secretion in an exercising pregnant woman, or how the reduced pituitary GH secretion affects the maintenance of her lean body mass. In hamsters, pregnancy does not suppress the release of pituitary GH but does reduce maternal linear growth. This effect is compounded by the added energy cost of voluntary exercise and food restriction.[281]

2.2 Exercise and Growth During Childhood

Exercise provides mechanical and metabolic stimuli that can either facilitate or curtail growth in children and young animals. This conflicting outcome accounts for our limited understanding of the relationship between these 2 variables at this stage of human development. Incremental growth in children and during early postnatal growth in animals is guided by anabolic hormones and depends on the plane of nutrition.

Exercise in children may provide conflicting stimuli in that its energy costs can reduce the nutrients available for growth. At the same time, its stimulation of GH secretion can augment the endogenous hormonal stimulus for growth, and is used by paediatricians to evaluate the adequacy of GH release in childhood.[282-284]

Physical activity in children provides mechanical stress that is a necessary condition for incremental as well as hypertrophic growth. This is illustrated by musculoskeletal atrophy consequent to immobilisation,[285] and in the rodent animal model by changes in the rate of cellular proliferation in the epiphyseal growth zones of the rat foot in accordance with the magnitude of the mechanical

stress during locomotion.[174,175] Excessive mechanical loading of bone joints in young children can damage the epiphyseal growth plates, and ultimately curtail the incremental growth of injured limbs.[286-289]

Metabolic demand for increased oxygen supply during exercise provides a stimulus for the hypertrophic growth of lungs during early rodent growth.[290] Increased respiratory vital capacity is a well documented adaptation to endurance physical activities in humans.[291] The very strong correlation between maximal oxygen consumption capacity and lean body mass[292-295] or body length[296-298] in childhood argues for a functional relationship between metabolic oxygen demands and the magnitude of whole body growth response.

Tests of this hypothesis are hampered by the difficulty of controlling the exercise variable in children over periods of years, and in equalising groups of active and inactive children by their genetic growth potential, starting skeletal age and confounding nutritional and social variables. In most of the available studies, rates of growth of children engaged in organised sports are compared with growth norms available for the more sedentary general population.[299,300] A strong confounding variable in such studies is the obvious selection of phenotypically and genetically different children for individual sports. Significantly different body mass, body length and skeletal maturity, or combinations of these, attest to selection of nonrandom populations of children for sports such as gymnastics,[301-304] ballet,[305] basketball,[300,306] ice hockey,[307] swimming[308] and others.

Reports of advanced skeletal maturity of children in sports where participants appear to be selected for large body size[309-311] indicate either a selection bias for children that are developmentally advanced for their chronological age at the outset, or a stimulatory influence of these sports over the rate of the children's growth and development.

Similar difficulties are found in those sports for which small or slender children are favoured. Gymnastics[301-304,312-316] and ballet[65,66,305] are associated with reduced growth rates and delayed skeletal maturity of the participants relative to their chronological age. Other developmental markers such as the onset of puberty are also delayed in gymnasts and ballet dancers,[65,66] indicating that the energy cost of their physical activity, along with their dietary practices for the maintenance of desired weights, combine to retard the rate of growth and skeletal maturation.

Even when the skeletal age information is available, it usually is not used as a basis for comparison of growth rates between exercising and less active children, so that the effect of exercise on growth can not be properly evaluated. Correction of the growth curves of child participants in organised sports for the reported advance in the skeletal age[310] indicates that the growth rates of exercising children are superior to those of their more sedentary counterparts.[300]

A valid assessment of the effects of exercise on growth should include an understanding of the magnitude of the energy cost of the particular physical training programme relative to the total energy balance of the child. Measurements of energy expenditure, energy intake and level of stored energy, complemented by information on plasma insulin, GH, and IGF-I levels, can reveal whether the energy cost of exercise training is creating a temporary restraint over the expression of growth. If so, a full evaluation of the stimulatory effects of exercise requires an allowance for statural catch-up growth after the discontinuation of training or removal of dietary restraints.

2.3 Exercise and the Pubertal Growth Spurt

Since adolescents engaging in organised sports often start these physical activities before puberty, the same problems in experimental design and analysis that were discussed for exercise during childhood prevail. Thus, phenotypically and genetically different populations are usually selected for participation in specific sports.[301-308] Skeletal maturities of such adolescents are usually different from the reference group either at the outset or at the time of final assessment.[309-311,317]

The comparisons of growth rates of adolescents participating in sports and the more sedentary reference population generally fail to reveal any stimulatory effect of exercise,[300,317,318] and show instead an inhibition of growth and development in gymnasts[300-316] and ballet dancers.[65,66,300] However, a correction for the reported difference in skeletal age in a longitudinal study[317] of the effects of training on growth reveals that physically active peripubertal boys appear to be larger, heavier, and to have larger upper arm and calf circumferences than their sedentary counterparts. Similarly, a correction for the reported advance in the skeletal maturity of adolescent participants in organised sports[310] yields evidence of faster statural growth rates in youths engaged in a number of sports.[300,318]

As is the case with children, the effect of exercise on the growth of adolescents has been confounded by selection of adolescents of different physiques or skeletal developmental ages, or by variable involvement of nutritional restraint. A physiological marker of an adolescent's energy and growth status in the form of plasma levels of IGF-I would be necessary to determine whether a temporary growth arrest is being imposed by the energy cost of exercise. Where there is evidence of nutritional suppression of growth, a sufficiently long period of reduced energy expenditure or of unrestrained caloric intake should be provided to allow for delayed expression of the stimulatory effects of exercise in the form of catch-up growth.

2.4 Exercise and Regulation of Adult Body Composition

While the adult stage of development is considered as the time when regulation of body energy and body composition is fully operational, the largely sedentary populations in Western developed countries deviate from the expected pattern. From their mid-30s, adults in these countries gradually lose lean body mass at a rate of about 15oz (425g) per year[319-322] and bone mineral content at a rate of about 1% per year (the latter is accelerated in women upon the onset of menopause).[323-325] At the same time there is progressive accumulation of excess storage fat at a rate of about 1 pound (454g) per year.[319-322] These changes are in part associated with a secular increase in energy intake[326] and a reduction in physical work of both the high-resistance and endurance types.[327,328] These anthropometric and lifestyle changes are accompanied by a large decline in the rate of basal and stimulated GH secretion[74-77,140,141] and by increases in basal insulin level and resistance to insulin action.[145-149] The predominantly intra-abdominal distribution of excess fat is associated with insulin resistance,[148-150,329-331] hypertension and increased risk of coronary heart disease.[330]

High-resistance physical activities induce muscle hypertrophy in young adults as well as in elderly individuals.[331-334] High-resistance exercise induces increases in the mineral content and density of bones,[335-337] an effect which is augmented by the presence of adequate titres of gonadal hormones.[338-340]

Habitual endurance exercise is associated with reduced storage levels of fat in individuals ranging from young adults[88-89] to the elderly,[341] and with greater than average sizes of the lean body mass.[88-90,341] Other training effects include a change in the muscle fibre type from predominantly white and insulin-resistant in overweight men and women to oxidative glycolytic red fibres displaying greater insulin sensitivity.[342,343] Increased insulin sensitivity and reduced basal and stimulated insulin secretion accompany endurance training even when the training is not associated with a reduction in the mass of the fat depot.[150,344] Trained adults secrete more GH both in response to an acute exercise stimulus[345] as well as in the form of basal pulsatile release at rest.[83] Improved regulation of the relative sizes of the lean and fat body masses in exercise-trained adults is in part a consequence of the anabolic and lipolytic action that accompanies increased GH secretion. Support for the hypothesis that GH contributes to regulation of adult body composition comes from studies demonstrating significant anabolic and lipolytic effects of exogenous GH administered to elderly men.[346,347]

The prevalence of a sedentary lifestyle and the attendant reduction in energy expenditure is believed to contribute more to age-associated increases in body fat than do quantitative and qualitative aspects of dietary intake. A case can be made that a sedentary lifestyle contributes importantly to the age-associated decline in GH secretion and in lean body mass, and to the increased health risks associated with obesity.

3. Conclusions

Exercise can be seen to have a pervasive and important role both in the control of growth and in maintenance of human lean body mass at all stages of extra-uterine life. Exercise generates stresses necessary for normal statural and hypertrophic growth. The metabolic demands of exercise call for neuroendocrine adaptations promoting incremental and reparative growth and hypertrophy of organs associated with oxidative energy use. The stimuli of exercise are provided in intermittent fashion, a form of presentation that is most effective for stimulation of hypertrophic, incremental and reparative growth. Physical effort also provides an essential behavioural component for the regulation of lean body mass in adulthood that is greatly affected by the choice of a sedentary lifestyle.

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