Published in final edited form as:
World Rev Nutr Diet. 2013 ; 106: 100–104. doi:10.1159/000342535.

Catch-up Growth: Cellular and Molecular Mechanisms

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Abstract

In mammals, after a period of growth inhibition, body growth often does not just return to a normal rate but actually exceeds the normal rate, resulting in catch-up growth. Recent evidence suggests that catch-up growth occurs because growth-inhibiting conditions delay progression of the physiological mechanisms that normally cause body growth to slow and cease with age. As a result, following the period of growth inhibition, tissues retain a greater proliferative capacity than normal, and therefore grow more rapidly than normal for age. There is evidence that this mechanism contributes both to catch-up growth in terms of body length, which involves proliferation in the growth plate, and to catch-up growth in terms of organ mass, which involves proliferation in multiple non-skeletal tissues.

Introduction

Growth impairment can result from many systemic disorders, including endocrine, nutritional, gastrointestinal, cardiac, pulmonary, and renal disease. If these conditions resolve, growth velocity often does not just return to normal but actually exceeds the normal rate for age, causing the child's body size to re-approach the pre-illness growth trajectory (1). This tendency to rapid linear growth that occurs after a period of growth inhibition is termed *catch-up growth*. Clinically, this phenomenon has been observed in a variety of circumstances including hypothyroidism, malnutrition (celiac disease, anorexia nervosa) and glucocorticoid excess (2). It occurs both in terms of height, implying rapid growth at the growth plates, and in terms of organ size, implying rapid growth in multiple other tissues.

Catch-up in the growth plate

Bone elongation is the result of chondrocyte proliferation and further differentiation in the growth plates. Growth plates are found in tubular bones and vertebrae but not in the intramembranous bones of the face and skull. The growth plate is composed of three principal layers, the resting zone, the proliferative zone, and the hypertrophic zone (3). Resting zone chondrocytes act as progenitor cells, capable of producing clones of proliferative chondrocytes (4). These proliferative cells, which are aligned in columns parallel to the long axis of the bone, replicate repeatedly but then undergo terminal differentiation and enlarge to form the hypertrophic zone. This hyperplasia and hypertrophy of chondrocytes, combined with cartilage matrix synthesis contributes to generation of new

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cartilage. The newly formed cartilage is then invaded by blood vessels and bone cells and thus remodeled into bone tissue. The net effect is bone elongation. The regulation of skeletal growth at the growth plate is complex and involves systemic and local mechanisms, including hormones, genetic and growth factors, environment and nutrition (5).

Catch up growth occurs at the growth plate. Transient impairment of longitudinal bone growth is followed by accelerated bone elongation. Because bone length determines overall body length, this accelerated growth at the growth plate is responsible for catch-up growth in terms of body stature. Catch-up growth in children's height following illness or malnutrition was described more than 50 years ago (6;7).

Professor Tanner, one of the pioneers in the field of childhood growth, hypothesized that catch-up growth involves a central nervous system mechanism that compares actual body size to an age-appropriate set point (8). According to this "sizostat" hypothesis, a circulating factor is produced by growing tissues in a concentration that reflects the size of the child. A central nervous system "sizostat" compares this concentration to an age-appropriate set point and then modulates the growth rate to bring the actual body size closer to its set point. Thus, if a child is too small for age, the mechanism senses this abnormality and initiates catch-up growth.

However, subsequent data suggest that catch-up growth at the growth plate is due to a local, rather than a systemic mechanism. In rabbits, growth inhibition in a single growth plate, induced by local dexamethasone infusion, is followed by local catch-up growth in the affected growth plate (9). This local catch-up growth is not readily explained by a systemic mechanism involving the central nervous system and circulating factors but instead suggests a mechanism intrinsic to the growth plate itself.

Recent work suggests that catch-up growth in the growth plate is related to the developmental process of growth plate senescence (10;11). This term refers to the physiologic loss of function combined with structural involution that the growth plate undergoes during juvenile life. With increasing age, there is a progressive decline in both chondrocyte proliferation and in the overall height of the growth plate, associated with a decreased number of proliferative and hypertrophic chondrocytes per column. As the proliferative rate declines, the rate of longitudinal bone growth decreases (12;13).

The developmental program of growth plate senescence appears to be driven, not by time per se, but rather by growth. Growth-inhibiting conditions, such as glucocorticoid excess in rabbits (14) or hypothyroidism in rats (10), or tryptophan deficiency in rats (11), slow the process of growth plate senescence. This slowing involves structural changes in the growth plate, such as the decline in the number of chondrocytes in each zone, functional changes, such as the decline in proliferation rate, and molecular changes, such as the decline in *Igf2* mRNA expression (10). These findings imply that, when growth-inhibiting conditions resolve, the growth plates are less senescent than normal and therefore proliferate at a rate that is greater than normal for age, resulting in catch-up growth.

Indirect evidence suggests that linear catch-up growth in humans, as well as laboratory animals, is related to delayed growth plate senescence. In one study, when children with growth impairment due to celiac disease were placed on a gluten-free diet, the children's linear growth rate exceeded the normal for chronological age, indicating catch-up growth (15). However, the growth pattern was normal for a child of younger age. Specifically, the subsequent growth rate matched the normal pattern of growth expected based on the initial bone age or height age. Because linear growth reflects longitudinal bone growth at the growth plate, the data imply that the growth plate function was appropriate for a younger child, consistent with the delayed senescence hypothesis.

In conclusion, catch-up growth at the growth plate appears to be due primarily to a local mechanism intrinsic to the growth plate rather than a systemic mechanism and can be explained, at least in part, by a delay in growth plate senescence.

Catch up growth in multiple organs

Catch-up growth occurs not only in bone length but also in the mass of non-skeletal organs and the overall body mass (16;17). The catch-up growth in non-skeletal organs occurs also in terms of DNA content, indicating that accelerated cell proliferation makes an important contribution (16). The mechanisms responsible for catch-up growth in non-skeletal organs appear to be analogous to the mechanisms in the growth plate, involving a delay in the loss of proliferative capacity.

In fetal and early postnatal mammalian life, cell proliferation is rapid, not only in the growth plate, but also in many non-skeletal organs. This rapid proliferation slows with age, primarily because of a decrease in the growth fraction (fraction of cells remaining in the cell-cycle) (18). In both the growth plate and in non-skeletal organs, this decline in proliferation appears to be due to local, rather than systemic, mechanisms as evidenced by transplantation experiments between animals of different ages. When juvenile organs, including the growth plate (19;20), intestine (21;22), kidney (23), and heart (24) are transplanted into older recipients, these organs continue to grow rapidly, suggesting that growth deceleration is an intrinsic property of the organ.

Recent evidence suggests that cell proliferation is suppressed with age because of a complex growth-limiting genetic program that occurs during juvenile life in multiple tissues (25;26). This common program involves the downregulation with age of a large set of growth-promoting genes, including transcription factors like Plagl1, Ezh2, and Mycn, and extracellular growth factors like Mdk, Ptn, and Igf2 (25;26).

Importantly, this juvenile multi-organ genetic program appears to be driven, not by time, but by growth. Thus, growth-inhibiting conditions slow the progression of the genetic program, and thereby conserve future growth potential (25). This concept is supported by studies in rats, using a tryptophan deficient diet or hypothyroidism to slow growth. After the period of growth inhibition, mRNA analysis indicated that the growth-limiting genetic program was delayed (26). The period of growth inhibition due to tryptophan deficiency also appeared to delay the decline in proliferation rate in kidney and lung. Thus, after the animals had been returned to a normal diet, the proliferation rate in liver, kidney, and lung was greater than in control animals. Taken together these data suggest that growth inhibition slows progression of the growth-limiting genetic program and thus delays the loss of proliferative capacity, allowing for subsequent catch-up growth.

Conclusions

After a period of growth inhibition, catch-up growth occurs, both in terms of body length, which reflects growth plate chondrocyte proliferation, and in terms of organ mass, which reflects proliferation in various non-skeletal tissues. Recent evidence suggests that catch-up growth in both the growth plate and in non-skeletal tissues occurs, at least in part, because growth-inhibiting conditions slow the physiological mechanisms that normally cause body growth to decelerate with age and cease. Therefore, if the growth inhibiting condition resolves, the normal growth-limiting mechanisms are less advanced than normal, allowing for more rapid and more prolonged subsequent growth.

Acknowledgments

This work was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH.

Our work was supported by NIH intramural project HD000640-16 PDEG

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