

**ENDOCRINE CONTROL OF GROWTH: A WHOLE-FISH
PERSPECTIVE AND EVOLUTIONARY CONSIDERATIONS**

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EXTENDED ABSTRACT ONLY - DO NOT CITE

The major endocrine axis controlling growth in vertebrates consists of pituitary growth hormone (GH), insulin-like growth factor-I (IGF-I) and IGF binding proteins (IGFBPs). Most reviews of this system depict a hierarchical organization (figure 1), in which GH released by the pituitary stimulates hepatic production of IGF-I. IGF-I circulates in the blood bound to the IGFBPs with approximately 1% or less of the IGF-I in the free form (not bound to IGFBPs). IGF-I is a potent mitogenic factor and also maintains cell number by reducing apoptosis. Comprehensive reviews of this axis in fish are available (Duan, 1997; Moriyama, 2000, Kelly et al. 2000). The conventional depiction of the GH-IGF axis (figure 1) gives the impression that there is a top-down hierarchy of events for endocrine control of growth; GH stimulates IGF and then they both enhance growth. Although this depiction of the GH-IGF axis has heuristic value, it does not give an accurate impression of the operation of the axis and may lead to an overemphasis of the role of GH production in controlling growth. The aim of this review is to present different perspectives of the GH-IGF axis and speculate on the importance of its constituents in controlling growth.

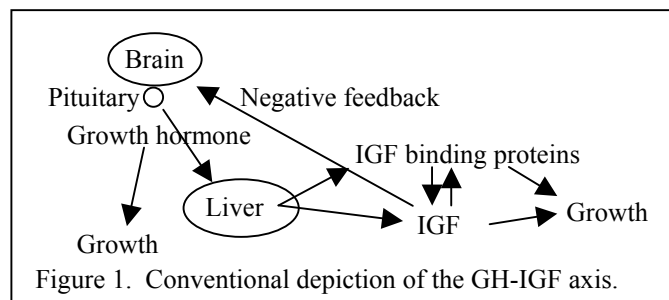
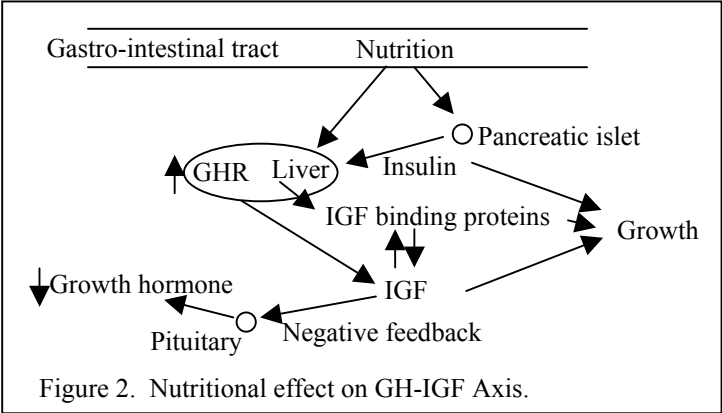


Figure 1. Conventional depiction of the GH-IGF axis.

A whole-fish perspective

It is well established that the primary determinants of fish growth are nutrition (ration and energy content) and temperature. Secondary influences on growth include photoperiod in temperate fishes, stress, and reproductive status, among others. For nutritional effects, experiments on fish involving either feeding and fasting or nutritional modification by changing ration or dietary protein level reveal generally consistent effects on the GH-IGF axis. Fasting causes a decline in plasma IGF level and an increase in plasma GH. Dietary modification shows similar effects, for example, Perez-Sanchez et al. (1995; see reviews cited for refs) showed that feeding gilthead seabream isocaloric diets with varying protein content (35, 45 and 55% protein) resulted in graded increases in plasma IGF and graded decreases in plasma GH. The decrease in plasma GH in fasting or dietary protein restriction seems paradoxical, since it may be expected that plasma growth hormone should increase in nutritional states of enhanced growth. However, the enhanced IGF production (plasma IGF levels) during enhanced growth is due, at least in part, to an increase in GHR in the liver. Dietary protein increases plasma amino acids, which enhance hepatic GHR. The increased hepatic GHR makes the liver more sensitive to the stimulatory effects of GH despite decreased total plasma GH. High plasma IGF reduces pituitary release of GH by negative feedback to the brain hypothalamus and pituitary. The decline in plasma GH in response to fasting has been seen almost universally in vertebrates (except in some rodents). The results suggest that GH production may be reduced in high nutritional state. The influence of nutrition on the GH-IGF axis is shown in Figure 2.



What are the relative roles of GH and IGF in controlling growth?

Often cited evidence for the importance of GH in growth is from experiments with hypophysectomy and hormone replacement, in which replacement with GH has been found to be more effective than replacement with IGF alone. Additional evidence comes from GH transgenics, which show substantially enhanced growth. Although these experiments are informative, hypophysectomized and transgenic animals are extreme manipulations. Recent studies of hormone and hormone receptor knock-outs in mice, although still artificial, may be more informative of how the axis works, at least in mice. Lupu et al., (2001) have made GHR, IGF-I and double mutant knock-outs and compared resultant growth inhibition. They estimated that the GH-IGF axis accounts for 83% of total body growth, with IGF alone accounting for 35%; GH and IGF together accounting for 34%, and GH alone accounting for 14%. In hamsters, which are insensitive to GH, the contribution of GH to total body growth is zero. The IGF-independent contribution of GH to growth of fish is not known. However, GH clearly has a role in regulation of seasonal growth. In salmonids, it is well-established that increasing photoperiod enhances GH release. In addition, GH or GHR deficiencies would be excellent candidates for a role in dwarf forms of fishes, which is a largely unexplored endocrine topic in fish.

Evolutionary considerations

A better understanding of the evolution of the GH-IGF axis may shed light on its functional aspects. The evolution of IGF-I as a separate entity from insulin appears to have occurred in tunicates (McRory and Sherwood, 1997). Since there is no evidence for GH in the suggested pituitary precursor, *Hatchek's pit* of *Branchiostoma*, then pituitary control of IGF may have first occurred in the vertebrate agnathans. The IGFBPs may have first occurred in agnathans, as well, although the earlier evolution of IGFBPs is attractive in view of their association with Hox genes, which began proliferating in cephalochordates. It could be speculated that there may have been a need for control of axial skeletal growth apart from softer tissue growth for the insulin-IGF dichotomy. Alternatively, separation of tissue hypertrophy (insulin) from hyperplasia (IGF) could also have been adaptive. The evolution of IGF-II presumably from IGF gene duplication appears to have occurred in elasmobranchs, which coincides with the appearance of vertebrate viviparity. This last step may have allowed separate control of embryonic and fetal growth.

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