

Expression and Regulation of IGF-1 in Cartilage and Skeletal Muscle

Isgaard presents a mini-review of this topic of great importance. The major questions to be answered relate to the roles that growth hormone (GH) and insulin-like growth factor 1 (IGF-1) play individually and collaboratively on the acute and long-term growth of cartilage and skeletal muscle.

Because of the length and complexity of the review, only the introduction and concluding remarks are reproduced here, along with a brief editorial comment. Those who are interested, and there should be many, will wish to obtain and read the entire article.

INTRODUCTION

A number of studies have demonstrated that both GH and IGF-1 have important roles for skeletal growth. Although IGF-1 was originally considered to be produced mainly in the liver, it is now generally recognized that IGF-1 is synthesized in numerous organs and tissues of many animal species. It appears that IGF-1 synthesis in most tissues is regulated by GH, and autocrine and paracrine functions of IGF-1 have been suggested as important components of GH action. Moreover, several studies have revealed enhanced expression of IGF-1, both on the messenger and protein level, during tissue regeneration and repair. The present review is mainly focused on recent studies of IGF-1 and their relevance to possible *in vivo* effects during growth and regeneration of skeletal tissues.

CONCLUDING REMARKS

Accumulating evidence indicates an important role of IGF-1 in the promotion of tissue growth and repair. However, the relative importance of autocrine/paracrine versus endocrine actions remains to be fully clarified and matters of opinion differ. It has been suggested that the autocrine/paracrine actions of IGF-1 play a minor role compared to endocrine effects, which would account for approximately 80% of the total accumulated GH-IGF-1 dependent postnatal height in humans. These investigators base their assumption on the fact that local administration of GH into the growth plate or via the arterial blood supply of one hindlimb of hypophysectomized rats produces only 12% to 22% of the maximal growth that can be achieved with systemic administration of GH. However, it is improbable that the conditions during these experiments are comparable to those when GH is administered systemically. Therefore, it is highly unlikely that local administration of GH

could produce effects of the same order of magnitude as systemically administered GH. It would also be reasonable to assume that locally produced IGF-1 is of importance during tissue hypertrophy and repair, when high levels of IGF-1 mRNA are expressed without a concomitant rise in circulating IGF-1. Moreover, the stimulatory effect of locally administered GH on the growth plate of hypophysectomized rats was completely abolished if antibodies to IGF-1 were coinjected with GH. This observation argues for the fact that locally produced IGF-1 is essential for the growth-promoting effect of GH *in vivo*.

The role of GH in the regulation of IGF-1 expression in peripheral tissues other than the growth plate is less clear. IGF-1 synthesis appears to be regulated by GH in most tissues, since the levels of both IGF-1 and IGF-1 mRNA decrease in a large number of tissues after hypophysectomy. On the other hand, during tissue regeneration following injury, increased expression of IGF-1 has been demonstrated in the regenerating tissue, both in intact and hypophysectomized animals. It is conceivable that GH regulates the synthesis of IGF-1 in tissues during normal growth and development, in contrast to emergency situations such as tissue injury or loss of tissue, during which this GH dependence may be uncoupled. Precisely which are the factors that regulate the synthesis of IGF-1 during tissue repair have yet to be clarified.

Isgaard, J. *Growth Regulation* 1992;2:16-22.

Editor's comment: *This paper reviews the data known on the role of IGF-1 in cartilaginous and muscular growth and repair. In vitro, as well as in vivo, studies show that it is an important factor. However, the respective effects of endocrine GH-dependent and local paracrine/autocrine IGF-1 are not yet clarified, and the regulation of local IGF-1 by GH is still controversial. Some experiments quoted in this review, based on the expression of IGF-1 and the measurement of its mRNA in cartilage and muscle under influence of GH, suggest that the endocrine and/or GH-dependent effects are predominant under normal conditions. It can thus be speculated by Isgaard that GH regulates the synthesis of IGF-1 in tissues during normal development, in contrast to emergency situations, during which this dependence to GH may be uncoupled.*

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