STUDIES OF THE REGULATION OF THE SOMATOTROPHIC AXIS, WITH PARTICULAR REFERENCE TO THE GROWTH HORMONE RECEPTOR

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ABSTRACT

The somatotrophic axis plays a vital role in the hormonal regulation of growth and intermediary metabolism. It encompasses the regulation of pituitary growth hormone (GH) secretion from the pituitary gland, the actions of GH on peripheral tissues via interactions with specific growth hormone receptors (GHR) and subsequent endocrine, paracrine and autocrine events, many of which are mediated via the insulin-like growth factor (IGF) system and its regulators. There are multiple effectors and points of regulation within the axis, including feedback loops, functioning to maintain homeostasis of the organism in physiological and pathophysiological situations. This thesis focuses on a number of studies of GH action and the GH receptor and its regulation, and subsequent processes mediated via the IGF system. Specific aims include further understanding the role of GH and the GHR in fetal and early life, exploring the interaction of other hormones (particularly placental lactogen and somatostatin) with the somatotrophic axis and examining the somatotrophic axis in a rapidly growing tissue (the antler) which does not appear to express the GHR.

The ontogenic and GH regulation of the hepatic GHR (as reflected by hepatic bovine GH (bGH) specific binding) and serum GH binding protein (GHBP) were studied in the pig. Marked age-related increases were seen in serum GHBP and hepatic bGH binding, and both were increased by recombinant porcine GH treatment in infant and pubertal animals. Serum IGF-I correlated significantly with serum GHBP and hepatic bGH specific binding. Serum GHBP levels reflected major changes in the hepatic GHR, but not closely in pubertal animals, suggesting some differential regulation. Also, the low levels of hepatic GHR in the infant pig were inducible by GH, suggesting GH responsiveness and a role for GH in early life. In further exploring the role of GH in early life, GH (but not IGF-I) administration to neonatal dwarf rats was found to have small but significant somatogenic effects on growth, serum IGF-I and body composition, with an associated decrease in hepatic bGH specific binding. These studies support a role for GH and GH responsiveness in the neonatal rat. This concept was able to be explored indirectly in the human by studying birth weight and early growth in GH-deficient infants. These infants were short at birth with relative adiposity, and had impaired longitudinal growth in the first year of life, suggesting some GH-dependence of growth in fetal life and early infancy. In investigating the perinatal changes in the GHR and serum IGF-I levels, post-mature fetuses were found to have much lower hepatic bGH specific binding than neonatal lambs of the same post-conceptional age, suggesting that these increases relate

to events at parturition, and not to post-conceptional age or intrinsic timing. Thus, while evidence is emerging for a significant role of GH and the GHR in fetal life, major induction of these somatotrophic axis components appears to be inhibited until after birth.

Since placental lactogen (PL) has been suggested as having an important role in fetal growth and metabolism, the binding properties and somatogenic properties of ovine PL (oPL) were explored. Studies in dwarf rats demonstrated somatogenic effects of oPL which were in some instances greater than those of bGH. Receptor binding studies in rat and sheep livers consistently showed greater potency of oPL, although with detailed displacement studies in sheep showing parallel changes in oPL and bGH binding over a range of developmental stages. This and other supporting evidence suggest that oPL may interact with the GHR or a closely related receptor, although the possibility of a distinct oPL receptor cannot be conclusively discounted.

While the GHR is clearly of major importance in the regulation of growth in many tissues, no GHRs were demonstrated in deer antler by autoradiography or radioreceptor assays. Specific binding sites were identified for IGF-I and IGF-II, with properties suggestive of the type 1 and type 2 IGF receptors. Thus, endocrine IGF-I is proposed to have a prominent role in antler growth, although local IGF production and action is also likely to be important.

Finally, in exploring other potential regulators of the GHR, the possibility of direct effects of somatostatin on the GHR was examined, since somatostatin has been suggested to influence the peripheral somatotrophic axis by reducing GH-induced IGF-I expression. Octreotide administration was associated with decreased IGF-I expression, yet with increases in hepatic GHR expression, suggesting that the suppressive effects of octreotide on IGF-I metabolism are not mediated via downregulation of GHR expression, but more likely by direct effects on IGF-I expression.

The studies in this thesis have furthered the understanding of some aspects of the role and regulation of GH and the GHR in the somatotrophic axis. Many questions remain to be answered on the complicated role played by these systems in the regulation of growth and metabolism.

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PUBLICATIONS IN THE COURSE OF THIS THESIS

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ABBREVIATIONS

aa	amino acid (s)
bGH	bovine growth hormone
bp	base pairs
BSA	bovine serum albumin
cAMP	cyclic adenine monophosphate
cDNA	complementary deoxyribonucleic acid
CGHD	congenital growth hormone deficiency
CSF	cerebrospinal fluid
dCTP	deoxycytosine triphosphate
DNA	deoxyribonucleic acid
EPO	erythropoietin
FBN	fibronectin
g	grams
G-CSF	granulocyte-colony stimulating factor
GH	growth hormone
GH	growth hormone
GHBP	growth hormone binding protein
GHR	growth hormone receptor
GHRH	growth hormone releasing hormone
GM-CSF	granulocyte macrophage-colony stimulating factor
gp	glycoprotein
h	hours
hGH	human growth hormone
IGF-I	insulin-like growth factor-I
IGF-II	insulin-like growth factor-II
IGFBP	insulin-like growth factor binding protein
IL	interleukin
Ka	association constant
kb	kilobase
kD	kilodaltons
KIGS	Kabi Pharmacia International Growth Study
Lt_{sds}	length standard deviation score
M-6-P	mannose-6-phosphate
min	minutes
mRNA	messenger ribonucleic acid
MWt	molecular weight
N-A	nose-anus
N-T	nose-tail

nm	nanometer
oPL	ovine placental lactogen
PL	placental lactogen
PRL	prolactin
RNA	ribonucleic acid
rpGH	recombinant porcine growth hormone
RRA	radioreceptor assay
sc	subcutaneous
SDS	standard deviation score
Wt_{sds}	weight standard deviation score

Standard abbreviations used are those accepted by *Endocrinology*