Regulation of growth by the growth hormone axis.

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ABSTRACT

The somatotrophic axis has a major effect on lean growth in a number of species. GH, the main hormone of the somatotrophic axis, is controlled by growth hormone releasing hormone and somatostatin. GH can act directly on fat by increasing lipolysis, but its main anabolic effects are on muscle and bone via the Insulin like growth factor-I (IGF-I). IGF-I stimulates amino acid uptake into muscle *in vitro* but does not necessarily promote growth if given *in vivo*. The reason for this is that GH is now considered to control circulating IGF-I as well as local tissue production of IGF-I, the dual effector theory. This theory proposes that GH not only controls IGF-I production but controls differentiation of cells so that they can respond to the mitogenic effects of IGF-I. Insulin is another anabolic hormone which is affected by GH. Insulin, unlike GH, stimulates fat deposition, although it also increases protein accretion. The manipulation of the growth hormone axis by immunological procedures, selection or genetic engineering may provide an economic way for NZ farmers to increase the production of lean meat.

Keywords Growth; growth hormone; insulin-like growth factors; steroids; growth hormone releasing hormone; somatostatin

INTRODUCTION

The New Zealand meat industry could benefit by the introduction of the new techniques being developed in the biological sciences. The effective introduction of these new techniques will require a comprehensive understanding of the complex mechanisms that control growth and carcass composition of meat producing animals. One of the major systems controlling growth rate and carcass composition is the endocrine system. The endocrine system can be manipulated by altering the genome of an animal, controlling the endocrine system or by direct manipulation.

Somatotrophic axis

Growth hormone (GH), a large polypeptide of 190 amino acids, produced by the pituitary restores growth in many animals when administered to hypophysectomised animals (Tindal and Yokoyama, 1964). Numerous studies have demonstrated that when GH is given to normal growing animals, nitrogen retention, liveweight gain and lean content of the carcass are often increased. In sheep the effects of GH are mainly confined to decreasing carcass fat (Wagner and Veenhuizen, 1978). In general the actions of GH in many species are considered to be anabolic, anti-insulin and lipolytic. The identification of GH as a major controller of lean growth has led to interest in the actions and controls of GH so that the GH axis can be manipulated to increase lean efficient growth.

Neuropeptides controlling GH

GH secretion from the anterior pituitary is under the dual control of a stimulating growth hormone releasing hormone (GHRH) and a GH inhibiting peptide, somatostatin (Figure 1). These neurohormones are released from nerve endings in the median eminence into the hypophyseal - portal circulation and interact with the somatotrophs of the anterior pituitary.

Growth Hormone Releasing Hormone (GHRH)

GHRH has been isolated and sequenced; it occurs naturally with 40-44 AA and appears similar across species. The 1-29 sequence of GHRH is biologically active and this sequence is very highly conserved across species. GHRH studies in the rat showed that a pulsatile pattern of administration of GHRH gave optimal growth in rats (Clark and Robinson, 1985). In other species where GH pulsatility does not appear to be of physi-

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ological significance, a continuous infusion enhances growth hormone and growth (Fronk *et al.*, 1983). The 1-29 sequence of bovine GHRH stimulates GH release in a dose dependent fashion in sheep (Spencer *et al.*, 1990), when administered intravenously (IV). The same study found that the response of GH to intracerebrally (ICV) administered GHRH was reduced when compared with the same dose administered IV, and that ICV GHRH stimulated a rise in the GH inhibiting hormone SRIF in pituitary effluent blood. This indicates that GHRH and SRIF are in a self controlled equilibrium.

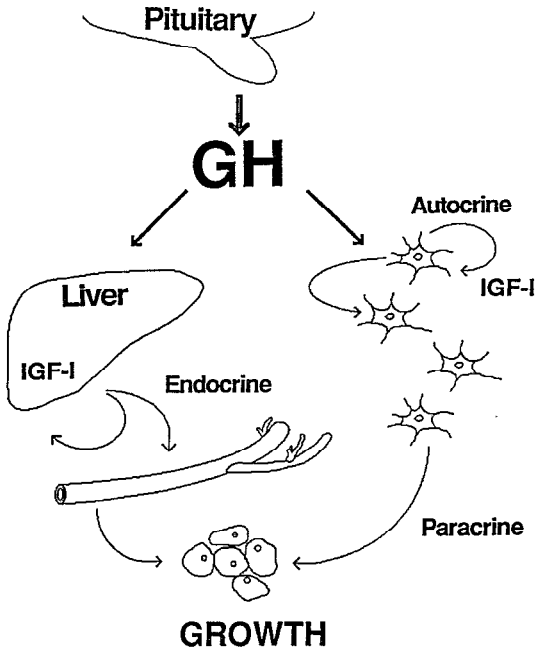

FIG 1 Growth hormone in the animal body.

Somatostatin (SRIF)

SRIF was originally isolated from the hypothalamus although it is also produced by the pancreas, gut and other cells throughout the body. Over 75% of total body SRIF is accounted for from extra-cerebral tissues. Therefore the levels of SRIF in the general circulation do not necessarily reflect the levels in the hypothalamus or hypophyseal portal circulation.

SRIF occurs naturally in two forms either with 14 (SRIF-14) or 28 (SRIF-28) amino acids. SRIF 1-14 is the predominant form but it has a shorter half life than the longer SRIF 1-28. SRIF has a wide range of inhibitory actions on endocrine systems and gastrointestinal and nervous functions (Bozikov, 1980). In monogastrics, SRIF administration inhibits growth hormone (GH), thyrotrophin (TSH), insulin and glucagon (Bozikov, 1980). In sheep the effects of SRIF have been found to be variable. Bryce and Hertelendy (1975) reported that SRIF did not affect basal plasma concentrations of glucose, insulin or glucagon in young sheep unless the hormones were artificially stimulated, whereas Sperling *et al.* (1977), in new-born lambs, and Brockman and Johnson (1977), in older sheep, found that SRIF depressed plasma concentrations of glucagon and glucose.

Varner *et al.* (1980) found that basal plasma concentrations of GH in sheep were increased by immunising against SRIF, whereas Spencer, Garssen and Hart (1983) found no basal response, although in both studies immunisation against SRIF increased plasma concentrations of GH after an infusion of arginine. Although SRIF immunisation failed to increase basal GH concentrations in all studies, it did increase plasma somatomedin concentrations in some studies (Spencer and Williamson, 1981; Spencer *et al.*, 1983; Bass *et al.*, 1987). Basal plasma concentrations of TSH were not affected by SRIF immunisation in sheep, whereas plasma concentrations of TSH increased in passively immunised rats (Arimura and Schally, 1986; Chihara *et al.*, 1979).The growth rate of sheep was increased after immunisation against SRIF in some studies,

(Spencer and Williamson, 1981; Bass *et al.*, 1987), whereas Varner *et al.* (1980) found that anti-SRIF titres and weight gain were negatively correlated. None of these studies found any changes in the percentage composition of the carcass, from dissected or chemical composition data, resulting from immunisation. The general conclusions that can be drawn from this work is that although hypothalamic SRIF is involved in GH control, changes in circulating levels of SRIF do not necessarily result in changes in GH.

GHRH and SRIF are regulated by neural activity, neuropeptides, hormones, blood-borne metabolites and also a direct interaction between GHRH and SRIF. GH infusions inhibit GHRH secretion and stimulate SRIF release, so inhibiting normal GH secretion (G.S.G. Spencer pers. comm.). Insulin-like growth

factor 1 (IGF-I) also inhibits GH secretion (Robinson and Clark, 1987), but this may not be an important inhibiting pathway as GH acts much more quickly on GH release than does IGF-1.

Growth Hormone

GH appears to only affect the post-natal growth of animals, as foetal hypophysectomy, ancephaly or decapitation in utero have only minor inhibitory effects on foetal growth. Post-natal growth is responsive to GH treatment in hypophysectomised, dwarf rats (Dobbie *et al.*, 1989) and many species of normal animals. The sheep shows a variable growth response to GH treatment whether it is hypophysectomised (Young *et al.*, 1989) or normal (Bass, *et al.*, 1989; Bass, *et al.*, 1988). However GH treatment of sheep has consistently been shown to reduce body fat (Johnsson, *et al.*, 1987). The lack of a consistent growth response in lambs to GH may be associated with:- a nutritional constraint as found in pigs (Newcomb, *et al.*, 1988); reduced tissue sensitivity to GH (Muir, *et al.*, 1983); or that bovine GH is not fully effective in the ovine. There is also the possibility that, as in the rat, GH needs to be administered in pulses to achieve maximum response, although the pattern of GH administration does not affect milk production in cattle (Fronk, *et al.*, 1983). It has been postulated GH may act directly on growth of tissues (Phillips, 1981) or indirectly through the insulin-like growth factors (Salmon and Daughaday, 1957).

The first step in GH action is the binding of a hormone to a cell membrane receptor. The cell surface binding sites for GH are heterogeneous with at least two affinity states for the somatogenic receptor (Breier, *et al.*, 1988), and the capacity of the higher affinity site has been shown to be correlated with growth rate in ruminants. The somatogenic receptor is absent in hepatic tissue in many species before birth which correlates with the lack of GH response in the foetus. The appearance of the receptor in the neonate and its regulation may vary in different tissues. GH control its own receptors, with chronic GH administration has been shown to increasing GH binding in the liver of domestic animal species. Nutrition also has a dominant influence on GH receptors (Breier *et al.*, 1986), with the number and affinity state of the GH receptors changing according to nutritional intake in ruminants. The high affinity receptor in the liver is not demonstrable at low nutritional levels but is present in sheep fed at high levels of nutrition. Oestradiol, which is a growth promotant for ruminants, has a major effect on the capacity of the GH receptor, but whether it is a direct effect of oestradiol or via increased GH is not known. The hepatic GH receptor is therefore under active endocrine and nutritional regulation and in the ruminant this regulation is a major determinant of the state of the somatotrophic axis.

Insulin-like growth factors

GH also acts indirectly through other hormones such as IGF-I and/or insulin. IGFI has been shown, *in vitro*, to have direct growth effects on muscle, adipose tissue and chondrocytes (Van Wyk and Underwood, 1978).

GH controls IGF-I secretion by the liver, which is considered the main source of circulating IGF-I, although IGF-I is also produced by a number of peripheral tissues (Isaksson, *et al.*, 1987). Green *et al.*, (1987) proposed that GH has two separate direct actions on tissue growth. GH causes cells to differentiate to a stage of maturation where they can produce and receive IGF-I and the locally produced IGF-I stimulates mitogenesis. Isaksson *et al.* (1987) showed, *in vivo*, that direct infusions of GH into cartilage growth plates of rats increased bone growth in the GH infused leg only, indicating that growth is not necessarily dependent on circulating IGF-I. The role of circulating IGF-I in growth is at present unclear. In certain dog breeds the circulating concentrations of IGF-I are highly correlated with their size. Selection of mice for high and low plasma IGF-I concentrations, results in changes in growth and composition (Baker *et al.*, 1989). Administration of recombinant IGF-I to hypophysectomised rats (Robinson and Clark, 1988) results in increased organ weights, but had little effect on overall proportional growth. Recently passive immunisation trials with IGF-I antibodies in guinea pigs (Kerr, *et al.*, 1990) and GH treated GH-deficient dwarf rats (G.S.G. Spencer; S.C. Hodgkinson; J.J. Bass, unpublished) had no effect on GH stimulated growth. However changes in IGF-I concentrations of cattle when nutrition and oestrogen levels are correlated with the growth rate of the animal (Bass *et al.*, 1987). The direct involvement of circulating IGF-I in the control of growth is therefore in

question. However circulating IGF-I is maintained at high concentrations by specific plasma binding proteins which decrease metabolic clearance (Hodgkinson *et al.*, 1988). Plasma bound IGF-I has been shown to be available to the tissues and so could act as a hormone, although the effect of the binding protein on the ability of the IGF-I to bind the receptors has not been fully established.

The sheep IGF-I binds in plasma to plasma binding proteins with molecular weights of 150kDa and 40-50kDa (Butler and Guckman, 1986), with several of the binding proteins co-eluting at 40-50kDa. The 150kDa bound IGF-I is sensitive to nutritional changes in the sheep (S.C. Hodgkinson, unpublished), but there was no corresponding changes in the 40-50kDa bound IGF-I. These observations strongly suggest that the IGF-I plasma binding proteins play a role in the control of the biological activity of IGF-I.

The biological activities of IGF-I, which stimulate the proliferation of many different cell types *in vitro*, are thought to be mediated by distinct high affinity tissue receptors (Alexandrides, *et al.*, 1989). Hormone responsiveness is thus determined by available hormone levels and tissue receptor availability. The IGF-I receptor capacity in muscle has been shown to change during development (Alexandrides *et al*, 1989) and specific binding of IGF-I increased in tissues from lungs, stomach, kidney and heart after fasting (Lowe *et al*, 1989). In sheep J. Oldham *(pers comm.)* found that the specific binding of IGF-I in muscle increases after fasting and that this change is associated with the muscle connective tissue and not muscle fibres in older sheep. The increase in specific IGF-I binding to connective tissue after fasting could be associated with an increase in receptor number or a decrease in receptor occupancy. In agreement with the first suggestion is that IGF-I receptor mRNA increases in fasting rats. This indicates that IGF-I tissue receptors increase when available IGF-I decreases.

Nutrition

In the ruminant the somatotrophic axis is very sensitive to changes in nutrition (Breier *et al.*, 1986). The neural centre which controls feeding and the GHRH producing neurons are situated in the arcuate hypothalamus, indicating a possible relationship between feeding behaviour and the somatotrophic axis. Circulating GH and IGF-1 levels respond to changes in nutritional status (Breier *et al.*, 1986), and so also do insulin, glucose and free fatty acids. An artificial fall in FFA in the blood has been shown to stimulate GH secretion (Redkopp *et al.*, 1980), as has an infusion of an amino acid, such as arginine. These changes in blood metabolites do not necessarily control GH secretion directly but may reflect other indirect mechanisms.

Insulin

GH treatment induces insulin resistance in adipose tissue (Vernon, 1982) and increases plasma insulin NEFA and glucose (Wallace and Bassett, 1966). GH has a wide spectrum of metabolic effects on different tissues. The overall metabolic action of GH is to increase the re-partitioning of energy to growing tissues. The most noticeable effect of GH is on fat, which has been associated with an increase in insulin resistance of adipose tissue, so reducing insulin induced lipogenesis (Lewis, 1988). This insulin resistance decreases lipogenesis and maintains or possibly increases lipolysis, so resulting in decreased fat deposition and a leaner animal. Insulin also stimulates growth because a lack of insulin stunts the growth of a number of species including pigs. In sheep, insulin has been shown to stimulate fat synthesis *in vivo* and *in vitro* (Lewis, 1988). Wolff *et al.* (1989) has shown, with a hind limb perfusion technique, that insulin has a significant anabolic effect on muscle in sheep. When lambs are selected on insulin status, as measured by glucose tolerance tests, the lambs with the highest time to clear half of the blood glucose (T-half) were heavier and had less carcass fat than the sheep with low T-half (Francis *et al.*, 1988). The differences in insulin status are probably due to differences in insulin receptors, particularly in muscles (Francis *et al.*, 1990).

Reproductive Hormones

The female (oestrogens) and male (androgens) sex hormones associated with growth are oestradiol and testosterone. These sex hormones, plus natural and synthetic compounds with oestrogenic or androgenic activity are the basis of many commercial growth promotants. Some or part of the sex hormone actions on

growth are via the somatotrophic axis.

Oestrogens

The action of oestradiol on growth is thought to be at least in part through the somatotrophic axis, although in sheep Muir *et al.*, (1983) failed to find an immediate GH response when growth was stimulated by a synthetic oestrogen, diethylstilboestrol. Oestradiol is thought to increase GH secretion (Davis *et al.*, 1977), but does not appear to change GH clearance rate (Gopinath and Kitts, 1984). The increased GH levels in oestradiol treated animals may be a result of increased hypothalamic GHRH or the modulation of the GHRH pituitary receptors (Trenkle, 1983). Oestradiol also increases the number of GH receptors in the livers of cattle (Breier *et al.*, 1986) and sheep (Bass *et al.*, 1989). The increase in receptors may be associated with the increase in GH. The increase in GH receptors has been associated with an increase in liver size as well as an increase in circulating IGF-I in cattle. As has already been reviewed IGF-I is considered to mediate the anabolic actions of GH. Oestrogen also directly binds to androgen and oestrogen muscle receptors, which indicates oestrogens may have a direct effect on muscle growth (Meyer and Rapp, 1985). After oestrogen treatment, possibly as a result of the increase in GH with its resulting diabetogenic effects (Trenkle, 1983), insulin also rises. This rise in insulin may contribute to an increase in lean growth if the anabolic effects of insulin are maintained with elevated GH which suppresses the lipogenic activity of insulin on fat depots.

Androgens

Androgens, unlike oestrogens, seem to stimulate growth by the direct action of testosterone on muscles (Wainman and Shipounoff, 1941) and not via the GH axis. *In vitro* studies have shown that testosterone can stimulate directly protein synthesis and that there are receptors for testosterone on muscle fibres. However male animals and testosterone treated castrates also have higher plasma IGF-I levels than castrates or females. This indicates that testosterone and possible other testicular factors also can stimulate the somatotrophic axis. The GH axis therefore probably plays some part in androgen stimulated growth.

Future Commercial Opportunities

Manipulation of the endocrine system for increased lean meat production is an area of considerable interest for the NZ farmer. The short term options that could be used within one season are the use of hormone therapy such as GH, GHRH and IGFs. However, the sex hormones are likely to remain the cheapest and most effective method of increasing lean growth in meat producing animals. The major drawback of the sex hormones is whether they remain acceptable to consumers in our major export markets.

The endocrine status of meat producing animals can also be manipulated via the immune system. Immunoneutralisation of growth inhibiting hormones, such as somatostatin (Bass *et al.*, 1987) and immunopotentiation of growth hormone with specific antibodies, enhance growth (Ashton *et al.*, 1986) and so have potential as future non-hormonal growth promotants.

The long term options available to farmers are traditional genetic selection including the possibility of making use of specific biochemical traits associated with growth, allowing early selection of animals with high genetic potential. Examples of this are the selection for glucose tolerance test (Francis *et al.*, 1990) and IGF-I plasma levels (Baker *et al.*, 1989).

Genetic engineering also offers opportunities for manipulating growth of farm animals. Genes for GH and GHRH have been expressed in transgenic mice, with dramatic increases in body size. Similar transgenic sheep have not displayed an increase in growth rate, despite high levels of GH in the blood. Unfortunately the lambs showed many adverse side effects which increased with age. It is obvious that simple gene insertion will not necessarily provide the meat producing animals of the future.

Our understanding of growth regulation of farm animals has made major advances in the last ten years but only now are we realising the intricate, interactive nature of the biological controls. To maximise the potential of the new biological techniques for the meat industry, our understanding of the mechanisms that control growth will have to be greatly improved.

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REFERENCES

Alexandrides T.; Moses A.C.; SmithR.J., 1989. Developmental expression of receptors for insulin, insulin-like growth factorI (IGF-I, and IGF-II in rat skeletal muscle. *Endocrinology 124*:1064-1076.

Arimura A.; Schally A.W., 1976. Increase in basal and thyrotropin-releasing hormone (TRH)-stimulated secretion of thyrotropin (TSH) by passive immunisation with antiserum to somatostatin in rats. *Endocrinology 98*:1069-1072.

Ashton R.; Holder A.T.; Preece M.A.; InvanyiJ., 1986. Potentiation of the somatogenic and lactogenic activity of human growth hormone with monoclonal antibodies. *Journal of Endocrinology 110*:381-388.

Baker R.L.; Bass J.J.; Peterson A.J.; Breier B.H.; GluckmanP.D., 1989. Divergent selection for insulin-like growth factor-1 or growth in mice. *Proceedings of the Endocrine Society of Australia and New Zealand Society of Endocrinology 32*:127.

Bass J.J.; Fowke P.; Breier B.H.; Gluckman P.D., 1987. Insulin-like growth factor-1 (IGF-I) response to bovine somatotrophin, oestradiol and nutritional status in ruminants. *Proceedings of the First European Congress of Endocrinology*, Copenhagen 21-589.

Bass J.J.; Fowke P.J.; Duganzich D.M.; Peterson A.J., 1989. Effect of different doses of 17b-oestradiol on growth and carcass composition of wether and ewe lambs. *Journal of Agricultural Science*, Cambridge *113*:103-187.

Bass J.; Fowke P.; Oldham J.; Carter W.; Hodgkinson S.; Gluckman P., 1988. Effect of growth hormone releasing hormones (GHRH), growth hormone (GH), and TRH on insulin-like growth factor-1 (IGF-I) in sheep. *Proceedings of 8th International Congress of Endocrinology*, Kyoto, Japan. Abs.*23*:19-089.

Bass J.J.; Gluckman P.D.; Fairclough R.J.; Peterson A.J.; Davis S.R.; CarterW.D., 1987. Effect of nutrition and immunizaton against somatostatin on growth and insulin-like growth factors in sheep. *Journal of Endocrinology 112*:27-31.

Bass J.J.; Oldham J.; Sauerwein H.; Hodgkinson S.C.; Breier B.H.; Gluckman P.D., 1989. The influence of nutritional status and growth hormone treatment on insulin-like growth factor-1, hepatic growth hormone receptors, growth and body composition. *Proceedings of the Endocrine Society of Australia and New Zealand Society of Endocrinology 32*:196.

Bozikov V., 1980. Somatostatin. *Diabetologia Croatica 1x1*:7-18.

Breier B.H.; Bass J.J.; Butler J.H.;Gluckman P.D., 1986. The somatotrophic axis in young steers: Influence of nutritional status on pulsatile release of growth hormone and circulating concentrations of insulin like growth factor 1. *Journal of Endocrinology 111*:209-215.

Breier B.H.; Gluckman P.D.; Bass J.J., 1988. The somatotrophic axis in young steers: Influence of nutritional and oestradiol-17ß on hepatic high and low affinity somatotrophic binding sites. *Journal of Endocrinology 116*:169-277.

Brockman R.P.; Johnson M.R., 1977. Evidence of a role for glucagon in regulating glucose and b-hydroxybutyrate metabolism in sheep. *Canadian Journal of Animal Science 57*:177-180.

Bryce D.A.; Hertelendy F., 1975. Studies with somatostatin, a hypothalamic hormone. *Texas Reports on Biology and Medicine 33*:561-565.

Butler J.H.; Gluckman P.D., 1986. Circulating insulin-like growth factor-binding proteins in foetal, neonatal and adult sheep. *Journal of Endocrinology 109*: 333-338.

Chihara K.; Arimura A.; Chihara M.; Schally A.V., 1979. Studies on the mechanism of growth hormone and thyrotropin responses to somatostatin antiserum in anaesthetized rats. *Endocrinology 103*:1916-1923.

Clark R.G.; Robinson I.C.A.F., 1985. Growth induced by pulsatile infusion of an amidated fragment of human growth hormone-releasing factor in normal and GHRF-deficient rats. *Nature 314*:281-283.

Davis S.L.; Ohlson D.L.; Klindt J.; Anfinson M.S., 1977. Episodic growth hormone secretory patterns in sheep: relationship to gonadal steroid hormones. *American Journal Physiology*; E519-E523.

Dobbie P.; Bass J.J.; Hodgkinson S.C.; Spencer S.; Clark R., 1989. Growth studies on a growth hormone-deficient dwarf rat and the effect of long term GH treatment. *Proceedings of the Endocrine Society of Australia and New Zealand Society of Endocrinology 32*:201.

Francis B.S.M.; Bickerstaff R.; O'Connell D.O., 1990. Genetic selection for leaness using a biochemical parameter. *Proceedings of Australian Association of Animal Breeding and Genetics*. (In press).

Francis S.M.; Bickerstaff R.; O'Connell D.O.; Munro J.M.; ParrattA.G., 1988. Using biochemical parameters for genetic selection of carcass quality in lambs. *Proceedings of the Nutrition Society of New Zealand 13*: 157.

Fronk T.J.; Peel C.J.; Bauman D.E.; Gorewit R.C., 1983. Comparison of different patterns of exogenous growth hormone administration on milk production in Holstein cows. *Journal of Animal Science 57*: 699-705.

Gopinath R; Kitts W.D., 1984. Growth hormone secretion and clearance rates in growing beef steers implanted with oestrogenic anabolic compounds. *Growth 48*:499-514.

Green H.; Zekulak K.; Djian P., 1987. On the action of growth hormone as revealed by the study of adipose conversion. In: *Growth Hormone - Basic and Clinical Aspects*: O.Isaksson, C.Binder, K.Hall, C.B.Hokfelt. (Eds.) 289-297. Elsevier, Amsterdam.

Hodgkinson S.C.; Moore L.; Napier J.R.; Davis S.R.; Bass J.J.; Gluckman P.D., 1988. Characteristics of insulin-like growth factor binding proteins in ovine tissue fluids. *Journal of Endocrinology 120*:429-438.

Isaksson O.G.P.; Lindahl A.; Nilsson A.; Isgaard J., 1987. Cellular mechanism(s) for the stimulating effect of growth hormone on longitudinal bone growth. In: *Growth Hormone, Basic and Clinical Aspects*. 1st Nordisk Insulin Symposium O.Isaksson, C.Binder, K.Hall, B.Hokfelt. Excerpta Medica, Amsterdam 307-319.

Johnsson I.D.; Hathorn D.J.; Wilde R.M, Treacher T.T.; Butler-Hogg B.W., 1987. The effects of dose and methods of administration of biosynthetic bovine somatotropin on live-weight gain, carcass composition and wool growth in young lambs. *Animal Production 44*: 405-414.

Kerr D.E.; Laarveld B.; Manns J.G., 1990. Effects of passive

immunisation of growing guinea pigs with an insulin-like growth factor-1 monoclonal antibody. *Journal of Endocrinology 124*:403-415.

Lewis K.J., 1988. Fat deposition in ovine fat. *Ph.D. Thesis*, University of Waikato.

Lowe Jr. W.L.; Adamo M.; Werner H.; Roberts Jr. C.T.; Le Roith, 1989. Regulation by fasting of rat insulin-like growth factor I and its receptor. Effects of gene expression and binding. *Journal of Clinical Investigations 84*: 619-626.

Meyer H.D.; Rapp M., 1985. Estrogen receptor in bovine skel*etal* muscle. *Journal of Animal Science 60*:294-297.

Muir L.A.; Wien S.; Duquette P.F.; RickesE.L.; CordesE.H., 1983. Effects of exogenous growth hormone and diethylstilbestrol on growth and carcass composition of growing lambs. *Journal of Animal Science 56*:1315-1323.

Newcomb M.P.; Grebner G.L.; Bechtel P.J.; McKeith F.K.; Novakofski J.; McLaren D.G.; Easter R.A.; Jones R.W., 1988. Response of 60-100 kg pigs treated with porcine somatotrophin to different levels of dietary crude protein. *Journal of Animal Science 66* (supple.1):281.

Phillips L.S., 1981. Nutrition, metabolism and growth. In: *Endocrine Control of Growth*. Ed. W.H. Daughday; N.Y., Elsevier:121-173.

Redkopp C.; Barrier L.D.; Livesey J.H.; Donald R.A., 1980. An *in vivo* model for testing somatostatin suppression of growth hormone release in sheep. *Journal of Endocrinology Investigation 3*:237-241.

Robinson I.C.A.F.; Clark R.G., 1987. The secretory pattern of GH and its significance for growth in the rat. In: *Growth Hormone - Basic and Clinical Aspects* O.Isaksson, C.Binder, K.Halland, B.Hokfelt Eds. 109-127. Elsevier, Amsterdam.

Robinson I.C.A.F.; Clark R.G., 1988. The growth promoting activity of IGF-I in the rat. *Acta. Ped. Scand.* In Press.

Salmon W.D.; Daughaday W.H., 1957. A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage *in vitro*. *Journal Laboratory Clinical Medicine 49*:825-836.

Spencer G.S.G.; Garssen G.J.; Hart I.E., 1983. A novel approach to growth promotion using auto-immunisation against somatostatin. 1. Effects on growth and hormone levels in lambs. *Livestock Production Science 10*:25-37.

Spencer G.S.G.; Williamson E.D., 1981. Increased growth in lambs following immunisation against somatostatin: preliminary observations. *Animal Production 32*:376.

Sperling M.A.; Grajwer L.; Leake R.D.; Fisher D.A., 1977. Effects of somatostatin (SRIF) infusion on glucose homeostasis in newborn lambs: evidence for a significant role of glucagon. *Pediatric Research 11*: 962-965.

Tindal J.S.; Yokoyama A., 1964. Studies on the growth of the goat kid after hypophysectomy. *Journal of Endocrinology 31*:45-5.

Trenkle A., 1983. Mechanisms of action for the use of anabolics in animals. *Anabolics in Animal Production*. Ofice International des Epizooties E.Meissonnier (Ed.), Seminar Feb 1987, 65-71.

van Wyk J.J.; Underwood L.E., 1978. The somatomedins and their actions. In: *Biochemical Actions of Hormones*, ed G.Litwack, Academic Press, N.Y. 5:101-148.

Varner M.A.; Davis S.L.; Reeves J.J., 1980. Temporal serum concentrations of growth hormone, thyrotropin, insulin and glucagon in sheep immunised against somatostatin. *Endocrinology 106*:1027-1032.

Vernon R.G., 1982. Effects of growth hormone on fatty acid synthesis in sheep adipose tissue. *International Journal of Biochemistry 14*:255-258.

Wagner J.F.; Veenhuizen E.L., 1978. Growth performance, carcass deposition and plasma hormone levels in wether lambs when treated with growth hormone and thyroprotein. *Journal of Animal Science 47* (Suppl.1):397-403.

Wainman P; Shipounoff G.C., 1941. The effects of castration and testosterone propionate on the striated perineal musculature in the rat. *Endocrinology 29*:975-979.

Wallace A.L.C.; Bassett J.M., 1966. Effect of sheep growth hormone on plasma insulin concentration in sheep. *Metabolism 15*:95-97.

Wolff J.E.; Petrie D.R., 1989. Growth responses of fat and muscle to insulin and somatotrophin. *12th Workshop on Overfatness and Lean Meat Production from Sheep NZ*: 36-37.

Young I.R.; Mesiano S.; Hintz R.; Caddy D.J.; Ralph M.M.; BrowneC.A.; ThorburnG.D., 1989. Growth hormone and testosterone can independently stimulate the growth of hypophysectomised prepubertal lambs without any alteration in circulating concentrations of insulin-like growth factors. *Journal of Endocrinology 121*:563-570.