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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.

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-
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 by 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, anencephaly 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 promonator 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. IGF-I 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 oestriadiol 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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