ENDOCRINOLOGY OF LEAN AND OBESE NON-RUMINANTS

by

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Introduction

The importance of regulating growth rate and composition of body gain has been emphasized frequently at these meetings (Hendrick, 1975; Allen et al., 1974; Kauffman, 1971). A calculation of the theoretical benefit from altering body composition of growing lambs is shown in Table 1. These calculations suggest that by diverting a portion of the energy (utilized for fat production) to protein synthesis, a significant increase in protein output could be achieved on the same dietary energy input. There is ample evidence that the composition of body gain is under endocrine control. The role of the endocrine system in regulating growth and body composition has been discussed at these meetings (Althen, 1975; Gerrits, 1968). More recent developments in this area are discussed in this presentation.

TABLE 1

Theoretical Efficiency Gain When Composition of Gain is Altered

1. Growing lambs deposit about 20 gm protein and 60 gm fat per day.[1]
2. If 1/3 of the energy used to store fat could be diverted to protein synthesis, the following could theoretically occur:
   a) 60 gm fat x 1/3 x 9 kcal/gm ÷ 72%[2] = 250 kcal spared,
   b) 250 kcal ÷ 5.7 kcal/gm x 84% = 37 gm protein formed.
3. Summary - By reducing lamb fat production from 60 gm per day to 40 gm per day, an approximate 2-fold increase in protein production could be achieved on the same energy intake.

[1]From Rattray et al., J. Anim. Sci. 38:378 (1974).

[2]From Baldwin, R. L. J. Dairy Sci. 51:104 (1968)

1. *Basic Approach*

In order to identify those endocrine factors which regulate body composition, genetic models of obesity are frequently used. The rationale is based on the concept that by examining animals that exhibit extremes in body growth, the regulatory mechanism(s) will be exaggerated and more easily identified. The usual variation found in commercial units is often insufficient to permit the researcher an opportunity to see significant changes in endocrine status and regulatory events. However, a number of animal models of obesity in pigs, rats, and mice serve the researcher with sufficient genetic variability to segregate endocrine factors which may be involved in regulating growth and body composition.

2. *Potential Control Through Endocrine Manipulation*

Previous studies of genetic obesities indicate a competition for available nutrients between muscle and adipose tissue when obese animals were pair-fed to lean controls (Table 2, from Deb et al., 1975; Martin, 1976). In effect, adipose cells are preferentially utilizing energy for fat synthesis over muscle tissue use for protein synthesis.

TABLE 2

Protein and Lipid Metabolism in Lean and Obese Rats

Parameter	Experimental Groups: Lean (Fa/fa)	Obese (fa/fa)
Protein Metabolism		
Protein intake (gm/4 wk)	94.0 ± 4.0[1a]	93.8 ± 4.1[a]
Protein gain (gm/ 4 wk)	21.9 ± 1.6[a]	8.0 ± 0.9[b]
Alanine conversion to fatty acid (nanomoles/hr/gm liver)	194 ± 45[a]	460 ± 69[b]
Alanine amino transferase (nanomoles/min/gm liver)	4.29 ± .48[a]	7.45 ± .76[b]
Lipid Metabolism		
Epididymal fat weight (gm)	5.3 ± .2[a]	15.3 ± .2[b]
Fat cell triglyceride synthesis (μmoles/hr/organ)	5.1 ± .4[a]	14.9 ± .5[b]
Fatty acid synthesis (Liver) (μmoles/min/organ)	0.52 ± .09[a]	1.99 ± .36[b]

[1]Mean ± SEM. Means with like superscripts are not significantly different (P <.05).

Some potential control mechanisms are presented in Figure 1. As adipose cell is enlarged (perhaps through the lipid anabolic actions of insulin and glucocorticoids), muscle cells may actually show a de-

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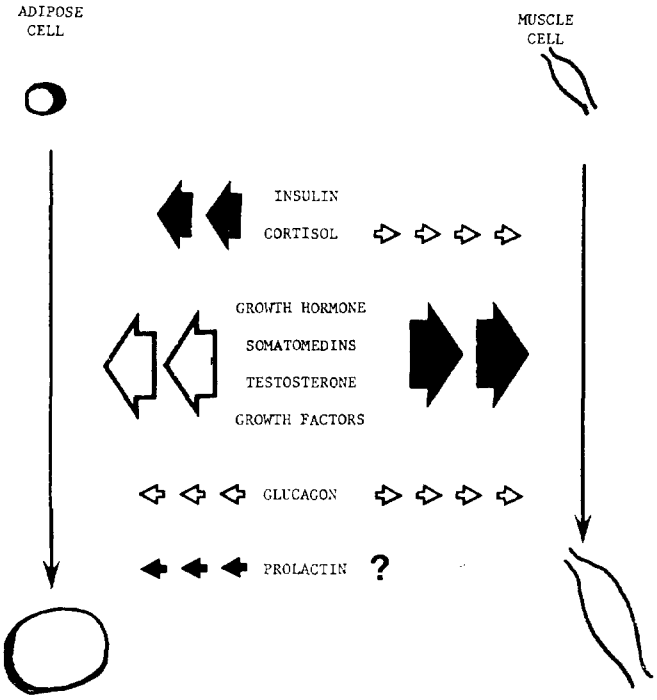

FIGURE 1

Potential endocrine changes which influence composition of gain. Open arrows indicate inhibition of development, and darkened arrows indicate stimulation of development.

crease in growth. Decreased muscle cell growth may be attributed to a decreased level of growth hormone, somatomedin, anabolic steroids and/or serum growth factors. In order to determine the role of the endocrine system in causing excessive lipid accumulation and decreased protein deposition, the hormone levels were examined in lean and obese animals. Data are summarized for two animal models, the Ossabaw pig (Martin et al., 1973) and the Zucker fatty rat (Zucker and Zucker, 1961).

3. *Genetic Models of Obesity*

A. Ossabaw Pig. Obesity in this model is characterized by shifts in adipose and liver tissue metabolism (Martin et al., 1973; Martin and Herbein, 1975; and Buhlinger et al., 1978). The hormonal changes seen in these pigs may explain the enhanced adipose cell lipogenesis and decreased muscle development. Plasma levels of growth hormone were significantly lower when measured during fasting or during a glucose tolerance test (Wangsness et al., 1977). More recently, it has been shown that when diurnal fluctuations of growth hormone levels were measured, a lower plasma growth hormone level was evident in the obese pig throughout a 24 hour cycle (Acker, 1978). Althen (1975) reported that growth hormone was not a primary cause of obesity in pigs genetically selected for backfat thickness. The lack of significant differences in growth hormone secretion rate may have been caused by the large variation seen in this parameter. Because of animal variation, a nearly twofold difference in growth hormone secretion rate was not statistically significant. In Ossabaw pigs, the depressed status of growth hormone may be responsible for their decreased muscle growth and development (Ezekewe and Martin, 1975).

Somatomedin has been identified as a group of peptide hormones having growth hormone action and being dependent on growth hormone for synthesis and release from the liver (Salmon, 1971; Daughday et al., 1975; Van Den Brande and Van Buul, 1978). When measured by bioassay, no detectable differences were observed in lean and obese pigs (Table 2). More specific assays for somatomedin (i.e., RIA) are required to determine for certain the somatomedin status of lean and obese pigs.

Obese pigs were not hyperinsulinemic but cleared glucose at a slower rate than lean controls (Wangsness et al., 1977). However, in the same study it was shown that provocative stimulation of insulin by arginine infusion produced a greater insulin response in obese pigs. Preliminary data suggest that obese pigs secrete more insulin in response to a meal than lean pigs (Aker, 1978).

Other hormones have been measured in lean and obese at birth (Table 3). Only triiodothyronine was found to be elevated at birth. Further characterization of hormone secretory response and diurnal patterns is needed before any suggestions can be made

TABLE 3

A summary of hormone studies in lean and obese pigs.

Hormone	Serum Levels		Reference
	Basal	Stimulated	
Growth Hormone[1]	Decreased	Decreased	Wangsness et al (1977)
Somatomedin[1]	NS[2]	---	Gahagan (1976)
Insulin[1]	NS	Increased	Wangsness et al (1977)
Cortisol[3]	NS	Decreased	Kasser et al (1979)
Thyroid Hormone[3]	NS	Decreased	Kasser et al (1978)
Thriiodothyromine[3]	Increased	NS	Kasser et al (1979)
Glucagon[3]	NS	---	Kasser et al (1979)

[1]These studies were performed in pigs approximately 6 months of age. Stimulation was achieved by either glucose infusion or arginine infusion.

[2]NS = None significantly different when compared to lean pigs.

[3]These studies were performed in newborn lean and obese pigs. Stimulated values are those observed after a 24 hour fast.

about their role in altering body composition of lean and obese pigs.

B. Zucker Fatty Rat. The spontaneously obese Zucker rat has been shown to have decreased protein deposition and increased lipid deposition even when food intake is restricted to that of lean littermates (Table 2). Alterations in tissue enzyme level and *in vitro* metabolite flux in the obese rat suggest a shift in metabolite utilization toward greater hepatic fatty acid synthesis and decreased muscle protein synthesis (Lemmonier et al., 1974; Taketomi et al., 1975; Martin, 1976; Martin et al., 1979). Endocrine involvement in metabolic lesions associated with spontaneous obesities has been proposed by several investigators (Hausberger and Hausberger, 1960; Mayer, 1960; Hellerstrom and Hellman, 1963). It is apparent from the data cited here that the integrated controls of tissue development and endocrine homeostasis are not functioning normally in the Zucker obese rate (Table 4).

Insulin has been shown to influence feeding behavior (Booth, 1970) and increase fatty acid synthesis. The early observation of elevated plasma insulin in obese Zucker rats suggested a role of this hormone in the etiology of the obese syndrome (Zucker and Antoniades, 1972; and Stern et al., 1972). However, by making both lean and obese rats diabetic and supplementing each with 3 units per day, the genetically obese-prone rat still gained excessive amounts of body fat (Stolz et al., 1977). It has also been shown that the biological properties and immunoreactivity of pancreatic insulin and glucagon were similar when lean and obese rats were compared (Laburthe et al., 1975).

TABLE 4

A summary of endocrine studies in lean and obese Zucker rats.

Endocrine Measurement	Serum Level	References
Insulin	Elevated	Zucker and Antonaides (1972)
Glucagon	Elevated	(Unpublished observations)
Growth Hormone	Decreased	Martin and Gahagan (1977)
Somatomedin	Decreased	Gahagan (1976)
TSH	CF[1]	York et al. (1972); Martin et al. (1978)
Thyroxine	Decreased	Martin et al. (1978)
Prolactin	Decreased	Martin and Gahagan (1977)
ACTH	NSD[2]	Yukimura et al (1978)
Corticosterone	Elevated	Martin et al (1978)
FSH and LH	NSD[2]	Bray et al (1973)

[1]Conflicting results. These studies indicate different conclusions.

[2]NSD = No Significant Difference.

Impaired protein deposition found in obese rats (Deb et al., 1976) may be caused by a decreased growth hormone status (Martin et al., 1978) and somatomedin activity (Gahagan, 1976). To test the hypothesis that the decreased levels of plasma growth hormone was a causal event in impaired protein deposition in obese rats, two types of experiments were performed. In the first, both lean and obese rats were hypophysectomized and injected with similar doses of porcine growth hormone (Stolz et al., 1977). When growth hormone status was equalized, the relative gain in body protein was the same in both lean and obese rats.

In a second series of experiments (Stolz et al., 1978), pituitary cells from lean and obese rats were implanted in hypophysectomized animals. Under these circumstances, no detectable differences were found in rate of gain or composition of gain in the recipient animals. Taken together, these studies support the following conclusions: 1) The differences in lean body growth seen in obese rats is caused by a reduction in plasma growth hormone levels; 2) The pituitary cells from lean and obese rats have similar capacities for stimulating growth; 3) No biological defect appears to be in either growth hormone or growth hormone receptors in obese rats.

Using a similar approach with older obese rats, Powley and Morton (1976) hypophysectomized both lean and obese rats and studied their maintenance of the obese condition. In these studies they concluded that the adiposity established before surgery was not eliminated by hypophysectomy. Body composition and lean body mass were not measured directly.

A proposed mechanism for decreased growth of lean body mass in obese rats is shown in Figure 2. The evidence of a hypothalamic defect is not direct.

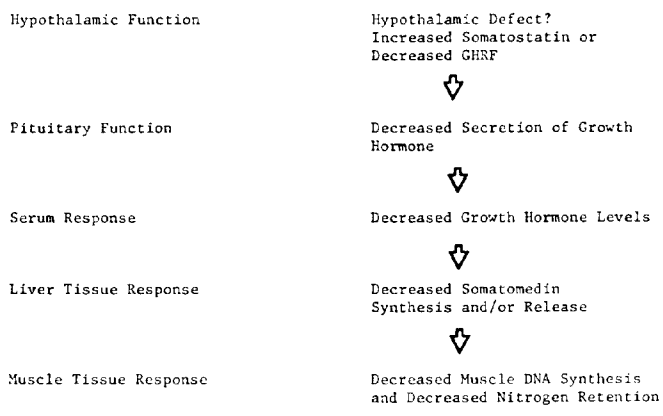

FIGURE 2

Proposed Mechanism for Decreased Growth of Lean Body Mass in Obese Rats.

For example, decreased tolerance to cold, impaired reproduction, decreased growth hormone status and hyperphagia can only be explained by a lesion in the central control of these events. More direct evidence of hypothalamic functions is necessary to identify a primary site for this genetic lesion.

A scheme for the regulation of adipose cell development in the Zucker rat is shown in Figure 3. This scheme was modified from Gruen et al. (1978). Changes in lipoprotein lipase activities in adipose tissue have been shown to correlate with the onset of adipose cell development (Gruen et al., 1978). Since this enzyme is inducible by insulin and insulin levels are elevated in obese rats, it is proposed that other factors which influence insulin secretion are causal events which lead to excessive lipid accumulation in this animal model.

4. *Bone Growth*

An important aspect of altering the potential for lean body growth and muscle development may be found in the regulation of bone growth. By increasing the skeletal length, the potential for muscle growth may be enhanced indirectly. It has been found that peak growth of muscle mass occurs just after peak growth in skeletal length (Tanner, 1968).

In obese rats (unpublished observation) and obese pigs (Martin et al., 1973), skeletal growth is impaired. It is proposed that the deficiency in growth hormone seen in both of the animal models of obesity, is influencing bone growth and thereby indirectly influencing muscle growth and protein depositions. More definitive studies on bone and muscle growth are needed to test this suggestion.

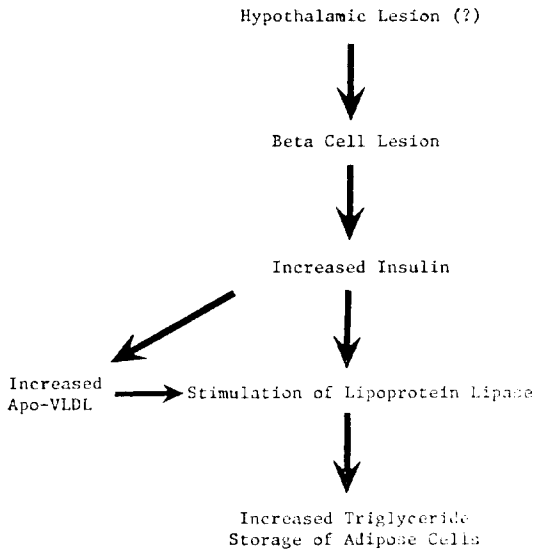

FIGURE 3

Beta Cell Lesion and Enhanced Lipoprotein Lipase.

Summary

Marked changes in endocrine status show that excessive deposition of body fat may be under hormonal control which, in turn, may be altered by genetic factors. The primary genetic lesions which lead to obesity in animal models have not been identified. Evidence is presented which suggests that decreased protein anabolic factors contribute to decreased protein deposition and enhanced lipid deposition in obese non-ruminants.

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