The partitioning of fat in farm animals

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Summary

This paper discusses aspects of metabolism in adipose tissue of pigs and ruminants. The major homeostatic and homeorhetic endocrine hormones responsible for the regulation of lipogenesis and lipolysis include insulin and the catecholamines. It is argued that a primary action of somatotropin (ST) in reducing body fat and increasing muscle gain is via reducing the actions of insulin. The increased effectiveness of ST in pigs compared to ruminants is related to an inherently lower sensitivity and responsiveness of ruminants to insulin. In contrast, the ß agonists produce a much greater response in ruminants and this is related to an increased sensitivity of adipose tissue to catecholamines. The pathways of fat metabolism are described with the aim of examining the possibility of regulating fat partitioning between depots in ruminants. The importance of acetate versus glucose+lactate differs between depots in the ruminant and it is proposed that this might allow for differential control of lipogenesis. In ruminants, diets promoting starch digestion in the small intestine clearly favour glucose as a lipogenic substrate and this may have an impact on the relative growth of different fat depots via the glucose/insulin axis. Chromium supplementation of ruminants consuming a diet low in chromium alters fat metabolism, probably via the glucose/insulin axis.

Introduction

Consumer preferences and the need to maximise profitability in the rural sector have resulted in an enormous research effort to maximise muscle and minimise fat in meat producing animals such as pigs, sheep and cattle. Leanness at all sites is not always desirable while some markets will pay a premium for beef meat containing extra levels of fat (marbling). In this review we outline the development of fat tissue during growth and how this relates to consumer preferences. The role of the main endocrine hormones which determine the partitioning between fat and protein is described. Endocrine sensitivity and responsiveness to insulin and catecholamines, and pathways of fat biosynthesis are then proposed as major reasons for differences in fat metabolism between the species and between fat depots. Finally the possibility for altering the distribution of fat between depots in ruminants is explored.

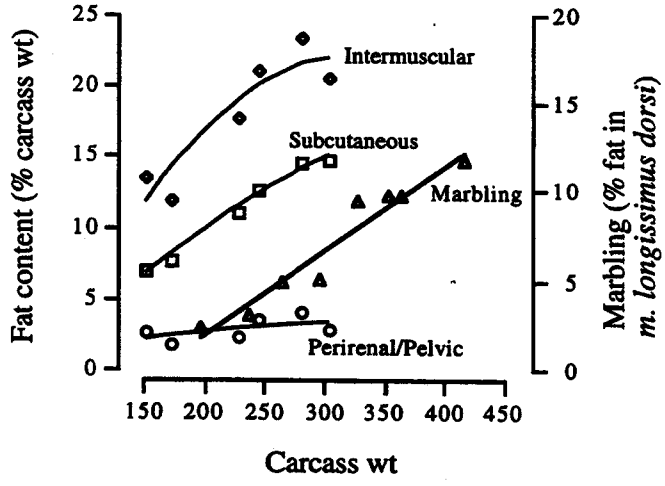
Growth of adipose tissue - practical aspects

Adipose tissue is deposited in specific depots which are similar for all mammals. The primary depots are within the abdominal cavity (perirenal, mesenteric and omental), intermuscular, subcutaneous and intramuscular. However the proportions differ between the species and are influenced by age. Thus the pig has more subcutaneous fat (70% of total body fat) and less abdominal fat then sheep and beef cattle (1).

Adipose tissue depots are thought to develop in the order of abdominal, intermuscular, subcutaneous and finally intramuscular (2). The progressive development of some fat depots in cattle is shown in Figure 1. The data suggest that abdominal fat changes largely in line with carcass (or body) weight while all other depots increase relative to carcass weight. Thompson et al (3) measured chemical fat content at all sites in mature Merino sheep and found intramuscular fat was 7% of total body fat. This compared with subcutaneous at 24%, intermuscular 20%, kidney fat 11%, omental fat 16% and mesenteric at 6%. Therefore the marbling depot is of moderate to small size.

Beef produced for the Australian domestic market originates from cattle yielding a carcass weight of about 200-220 kg and so this results in lean beef (Figure 1, muscle fat content of about 2.5 - 5%) since the subcutaneous and intermuscular fat can be trimmed leaving a low fat product. Alternatively some export markets are forced into producing excessive levels of subcutaneous and intermuscular fat to ensure the maximal development of marbling fat. Marbling is considered as a key factor in determining the organoliptic properties for the consumers in these markets and accordingly there is a pricing structure which pays on marbling score. On the domestic market there is little evidence that marbling plays an important role in palatability. When controlled studies are performed, the influence of marbling is relatively small when compared to the known effects of cold shortening and aging of meat (4,5).

Figure 1. The changes in fat depots during growth in beef steers (data is for Hereford, Angus and Hereford x Angus cross steers) (6,7)



Partitioning between muscle and fat - homeostasis and homeorhesis

The partitioning of nutrients between muscle and fat is regulated by a variety of hormones. Some of these have acute actions (eg insulin, catecholamines, glucagon) whereas others are more involved in the chronic regulation of metabolism (eg somatotropin, oestrogen, placental lactogen, prolactin). In 1929, Cannon (8) proposed the concept of homeostasis to describe the mechanisms which operate on an acute basis to maintain physiological equilibrium. The acute homeostatic regulation of metabolism by insulin, glucagon and the catecholamines is well documented.

However, the concept of homeostatic regulation is insufficient to describe the chronic regulation of partitioning between muscle, fat and other tissues as an animal moves from one physiological state to another. Bauman and Currie (9) introduced the concept of homeorhesis to describe the partitioning of nutrients in favour of a dominant physiological state. They postulated that homeorhetic mechanisms involve alterations in tissue response to homeostatic controls. The proposed mechanisms included: altered release and/or clearance of homeostatic hormones; altered blood flow and hence hormone and substrate supply to an organ; altered tissue sensitivity to a homeostatic hormone via altered receptor numbers and/or binding affinity; and altered tissue responsiveness to a homeostatic hormone through changes in post-receptor signal transduction. Many studies have now demonstrated that the major homeorhetic regulator of the partitioning of nutrients between fat and muscle, somatotropin (ST), exerts its effects through altering sensitivity and/or responsiveness to homeostatic hormones. A discussion of the metabolic actions of ST offers some insight as to how nutrients are partitioned during growth.

Effect of somatotropin on nutrient partitioning

Somatotropin increases lean tissue deposition and reduces fat deposition in both ruminants and pigs. Responses to ST appear to be greater in pigs than in ruminants and this may be related to the pig s reliance on glucose as a major energy source and an associated increased sensitivity and responsiveness to insulin. This will be examined below.

Insulin

Insulin has a number of metabolic actions in peripheral and hepatic tissues. Insulin stimulates lipogenesis and glucose oxidation and inhibits lipolysis in adipose tissue. Insulin also stimulates glucose uptake and utilization by skeletal muscle and inhibits gluconeogenesis and glucose output from the liver. There is now mounting evidence that at least some of the actions of ST on partitioning nutrients are mediated through altering sensitivity and responsiveness to insulin.

Reduced lipid deposition which occurs during ST treatment occurs through both increased lipolysis and decreased lipogenesis. Whether measured in vitro or in vivo, basal porcine adipose tissue lipogenesis is decreased by up to 90% due to ST treatment (10,11,12,13). Although effects are not as great, ST treatment also decreases lipogenesis in adipose tissue of ruminants (14,15,16). Consistent with changes in lipogenesis, the activity of key lipogenic and NADPH generating enzymes is similarly reduced in adipose tissue from pigs treated with pST (11,13). While pST (porcine somatotropin) may cause changes to lipogenic enzymes by allosteric and covalent mechanisms, the total activity and level of mRNA expression of acetylCoA carboxylase is reduced (17). In addition pST likely causes a reduced substrate availability within the adipocyte since glucose transport is reduced in adipose tissue from pST-treated pigs (11).

Both lipogenesis and lipolysis are regulated by insulin and the effects of somatotropin are due in part to alterations in insulin action. The ability of insulin to stimulate lipogenesis and glucose transport is reduced in adipose tissue obtained from ST-treated animals (18,10,11,12). Decreased stimulation of lipogenesis by insulin in the pig is due to both reduced responsiveness and sensitivity

Table 1. Effect of insulin and somatotropin on carbohydrate and lipid metabolism in the pig (12,22,23) and steer (24).

	STEER (250 kg)		PIG (80 kg)	
	Control	bST	Control	pST
Basal conditions				
Blood glucose (mmol/L)	4.28	4.59	4.20	5.21
Plasma insulin (mU/L)	22	56	17	72
Plasma NEFA (mol/L)	111	190	44	64
Glucose entry rate (mol/min/kg$^{0.75}$)	52	53	176	110
Hindlimb glucose uptake (mmol/min)	0.37	0.24	0.23	0.14
Hyperinsulinemia/Euglycaemia				
Blood glucose (mmol/L)	4.18	4.42	4.09	4.84
Insulin infusion (mU/min/kg$^{0.75}$)	20	20	18	18
Plasma insulin (mU/L)	621	652	337	322
Plasma insulin clearance (mL/min/kg$^{0.75}$)	33	33	54	60
Glucose entry rate (mol/min/kg$^{0.75}$)	134	119	328	341
Glucose infusion (mol/min/kg$^{0.75}$)	110	85	351	330
Adipose lipogenesis (g glucose/min/g fat)	ND	ND	24.4	8.2

to insulin (10). In vivo this insulin resistance is characterised by an increase in circulating levels of insulin and glucose (Table 1) and a reduced ability to clear glucose from the circulation in response to an insulin challenge (19,20) or glucose load (21) in ST-treated animals.

The data in Table 1 firstly highlight that pigs are more reliant on glucose as a substrate for intermediary metabolism. Thus the basal blood glucose and plasma insulin concentrations were very similar in the steer and pig despite a three-fold greater entry rate of glucose. Secondly they show that ST decreases insulin action since there is hyperglycemia and hyperinsulinemia yet a reduced uptake of glucose by muscle and adipose tissue, particularly in the pig. In addition plasma NEFA concentration was increased by ST treatment indicating a shift to lipolysis. Finally the effects of pST are greater in the pig than steer which can be seen in the dramatic effects on glucose turnover and feed intake in the pig. In the steer, basal feed intake and glucose entry rate were unchanged by ST treatment whereas for the pig there was a 35% decrease in both - this is thought to relate to a dramatic decrease in lipogenesis in pST treated pigs thus reducing the energy and glucose drain on the animal.

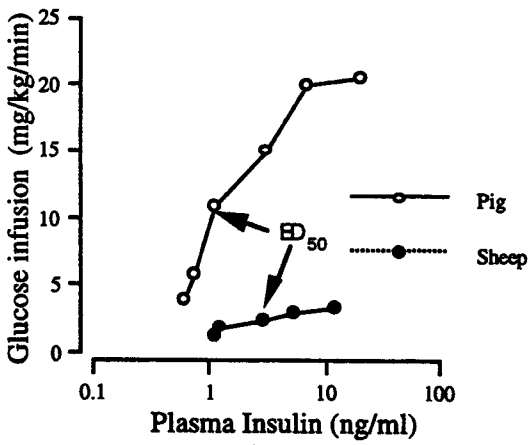


Fig 2(a) Glucose infusion required to maintain euglycemia in a hyperinsulinemic clamp (25,26).

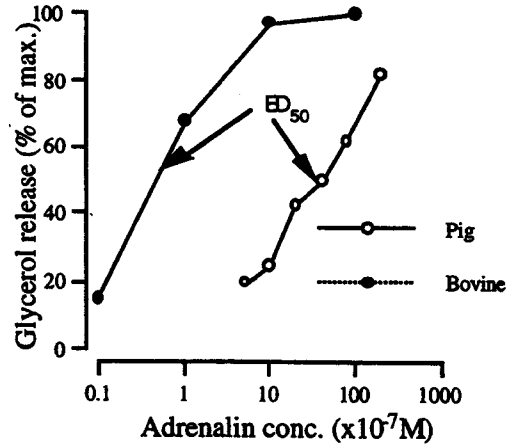


Fig 2(b) The effect of adrenalin on glycerol release from subcutaneous fat in vitro (27,28).

The hyperinsulinemic/euglycaemic clamp study (Table 1) shows that the ruminant is much less sensitive to insulin since glucose turnover was about three times higher in the pig despite half the plasma insulin concentration. This can be more clearly seen in Figure 2(a) where both the ED_{50} (concentration at half maximal response) for insulin and particularly the maximal response were lower in the ruminant (sheep) as compared to the pig. Plasma insulin clearance rates were also greater for pigs. These data demonstrate that ST decreases the response of tissues to insulin (sensitivity in muscle, sensitivity and responsiveness in adipose tissue) to partition glucose away from adipose tissue, especially in the pig.

Catecholamines

Somatotropin treatment also causes an increased lipolytic response to epinephrine in growing and lactating animals (19,29,20). Therefore, the elevated plasma NEFA and glycerol typically seen during ST treatment is likely due to increased responsiveness or sensitivity to endogenous catecholamines. It is not known whether ST treatment heightens sensitivity of other tissue ß-adrenergic receptors and whether this plays a role in increasing muscle deposition.

Effect of ß-agonists on nutrient partitioning

It has been known for some time that treatment of pigs with epinephrine increases growth and feed efficiency. More recently various ß-agonists (clenbuterol, cimaterol and ractopamine) have been developed specifically for use as potential growth promotants (30). However, unlike for ST, the repartitioning between fat and muscle appears to be greater for ruminants than for pigs (31). We

propose that this difference between species is related to their relative sensitivities to catecholamines.

Screening of ß-agonists for use as metabolic modifiers initially involved evaluation of their lipolytic activity since the proposed mechanism of action was decreased lipogenesis and increased lipolysis allowing more nutrients to be available for muscle growth. Certainly, treatment of ruminants with the ß-agonists cimaterol and clenbuterol decreases the rate of fat deposition and increases plasma NEFA concentrations (32,33,34). Also fasting plasma NEFA but not glycerol concentrations were elevated for up to 6 weeks after commencement of dietary cimaterol treatment (32,34). However, effects of ß-agonists on lipid metabolism in pigs are more equivocal. While carcass lipid and back fat are generally reduced by dietary ß-agonists such as ractopamine, this is not always been the case (30,35). When fed at levels which are efficacious for growth performance ractopamine has no effect on plasma NEFA concentrations (36,37).

Catecholamines

Evidence for a difference in sensitivity of adipose tissue to catecholamines between pigs and ruminants in shown in Figure 1(b) where the relative lipogenic responses of the heifer in late lactation (positive energy balance) and the pig are compared. There is a clear difference in the ED_{50} and further work examining NEFA response to intravenous catecholamines in the pig (38) and dairy cow (20) show a similar response. Since no significant differences in sensitivity have been observed between dairy cattle in different physiological states (27,20) it may be concluded that porcine adipose tissue is less sensitive to ß-agonists.

Lipid responses to ß-agonists are transient in nature, particularly in pigs. Thus the lipolytic response to intravenous catecholamine challenge after dietary ractopamine treatment decreases dramatically within 4 days and declines to about 30% of control after 10 days (37). The response returned to control values 7 d after withdrawal. This reduced response is due to a decrease in sensitivity (reduced ED_{50}) but not responsiveness during ractopamine treatment (38). In support of our findings in vivo, feeding ractopamine reduced adipose tissue adrenergic receptor density by 50% with differences being detectable as early as 1 d after feeding (39).

Catecholamines and insulin sensitivity

ß-agonists such as ractopamine, cimaterol, and isoproteronol antagonise the acute lipogenic and anti-lipolytic effects of insulin in porcine adipose tissue in vitro (40,41) possibly through reduced binding to adipocyte insulin receptors (42). Whether this phenomenon occurs in vivo is still unclear since ractopamine has been shown to lower circulating levels of insulin but have no effect upon the ability of insulin to depress blood glucose (36). Therefore, ractopamine appears to have little effect on the ability of insulin to stimulate glucose uptake by peripheral tissues in vivo. Also, while co-incubation of mouse adipocytes with ractopamine and clenbuterol also reduced insulin binding, adipocytes from mice treated with these ß-agonists in vivo actually had higher insulin binding than adipocytes from control mice (43). Therefore, it would seem that chronic administration of ß-agonists does not antagonise the actions of insulin in vivo.

Partitioning between adipose tissue sites

Despite the enormous research effort directed at partitioning fat versus protein, selective regulation of fat depots has been given little attention in farm animals. For example regulation of the economically important marbling depot is thought to be influenced by the genotype (heritability 0.37) (44) and age. The main production system is to lot feed cattle on a high energy diet for some 200-300 days resulting in high carcass weights (380-400kg) and elevated marbling scores. With such an expensive production system it is of interest to know whether fat deposition at the marbling site can be accelerated so as to reduce feeding time. The relatively small size of the marbling store suggests that small shifts in fat accretion to this depot would have a large impact on marbling score.

Pathways of de novo lipogenesis

Pigs and ruminants (45) synthesise fat de novo in adipose tissue rather than the liver and so regulation of lipogenesis within adipose tissue is central when considering fat accretion in the growing animal. Ruminants represent a special case with respect to de novo lipogenesis since most dietary carbohydrate is extensively fermented in the rumen, even when cereal grains such as wheat, barley and oats are fed (46). As a consequence acetate derived from fermentation in the rumen is thought to be the main source of carbon for fatty acid synthesis (2). However there is also evidence for some synthesis from glucose, especially via lactate (47,48).

Further work by Smith and Crouse (49) has shown that adipocytes associated with the marbling depot have a higher reliance on glucose and/or lactate as a substrate than acetate (Figure 3). Intramuscular adipocytes have lower rates of lipogenesis and associated smaller cell size than other depots (2) yet an increased absolute and relative contribution of glucose into fatty acids. Generally the marbling adipocytes were poorly responsive to increasing nutrition when parameters of fat synthesis were measured (ie ^{14}C incorporation of substrates, enzyme levels); however lipogenesis from glucose did respond to increasing energy intake at the intramuscular site but not in subcutaneous fat (49). These differences in the lipogenic pathways suggest the potential to manipulate fat depots since the pathways have different substrates and possibly hormonal sensitivity. In particular the role of the glucose/insulin axis should be critical and at least two questions seem obvious: (i) does upregulation of the glucose/insulin axis influence the pattern or absolute rate of lipogenesis and (ii) can the glucose/insulin axis be regulated by diet in ruminants?

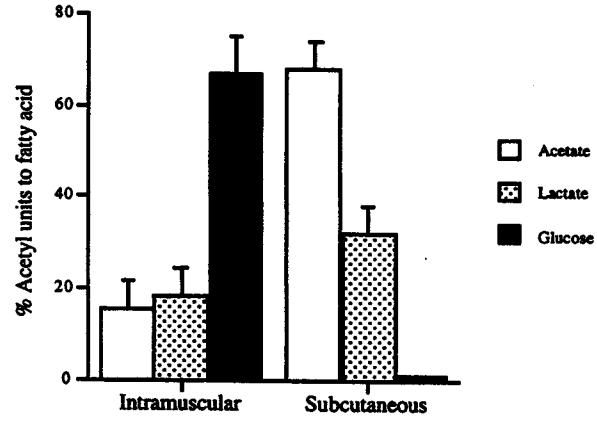


Figure 3. The relative contributions of carbon precursors to fatty acid synthesis in adipose tissue of 18 month old Angus steers (values are % SD) (49)

Effect of diet on pathways of de novo lipogenesis in ruminants

What practical scope is there to increase the effectiveness of the glucose/insulin axis in ruminants? In recent studies in our laboratory we have used ATP citrate lyase as a marker or exogenous glucose supply. ATP citrate lyase is a key, inducible enzyme of the citrate cleavage pathway which is necessary for fat synthesis from glucose. In addition it is assumed that the enzyme is a more general marker of the glucose/insulin axis since in the rat the main regulation of this enzyme is by modulation of transcription under the control of insulin (50). Initially we used glucose infusion similarly to Ballard et al (51) to show that the activity of ATP citrate lyase was positively sensitive to exogenous glucose supply (46). More recently we compared different dietary grains for their ability to induce ATP citrate lyase (52). Sheep were fed a diet of approximately 80% cereal grain fed at 1.8x maintenance (ie isoenergetic) for 6 weeks and samples of subcutaneous adipose tissue

taken at slaughter and the activity of ATP citrate lyase measured (Figure 4). The results are consistent with the digestion of starch in the small intestine regulating the expression of ATP citrate lyase. Lupin contains virtually no starch for digestion; the starch of oats is known to be extensively fermented in the rumen while some 30% of the starch from maize escapes fermentation. Much of the starch in sorghum can escape fermentation (~40%) however it is also resistant to digestion in the small intestine (53). To further investigate the sorghum response we repeated the experiment using steamed flaked sorghum as the dietary grain. Flaking the sorghum allowed for a similar expression of ATP citrate lyase as in maize suggesting that the starch escaping fermentation was now being more effectively digested in the small intestine.

The mechanism for this powerful regulation of enzyme activity by diet is not clear from this work; however it most likely involves the glucose/insulin axis. Most intriguing is the lack of enzyme response in the animals eating diets based on lupin and oats. The glucose entry rate in ruminants is

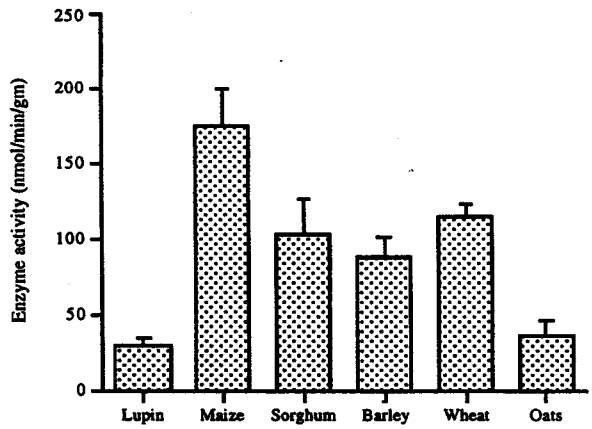


Figure 4. The effect of cereal grain type on the activity of ATP citrate lyase in subcutaneous adipose tissue of Merino sheep.

determined primarily by the intake of metabolisable energy rather than by diet composition and so all diets would have allowed for similar glucose entry rates (54). There seems to be something special about the digestion of starch in the small intestine and we might hypothesise differences in the effectiveness of the insulin axis. Thus diets with a low propensity to allow starch digestion in the small intestine mean the ruminant must rely on gluconeogenesis and so a low insulin level would be needed. Alternative and interacting regulatory candidates might be some of the hormonal or neural activities of the gut (55).

The extent to which changes in the glucose/insulin axis or different cereal grains influence body fat deposition has not been fully tested. However there is work to suggest that alterations in insulin action can cause significant partitioning between fat depots (56). Thus rams immunised against growth hormone releasing factor had increased abdominal and pelvic fat with no change in subcutaneous fat depth (measured at the ≅GR site) or body weight. As discussed early in this paper, reduced levels of growth hormone would increase insulin sensitivity, a result confirmed by Walkden-Brown (personal communication). Some work is available to suggest that body fatness and marbling is stimulated by diets promoting starch digestion in the small intestine. Thus Reddy et al (57) compared maize, triticale and wheat in feedlot rations given to cattle fed for 107 days and slaughtered at about 420 kg live weight. The level of intramuscular and subcutaneous fat was significantly increased on the maize ration.

We have recently used chromium supplementation (1 ppm addition of an amino chelate) to a basal diet low in chromium (0.05 ppm) to alter fat deposition in mature sheep (Figure 5). Chromium supplementation reduced subcutaneous fat depth ($P<0.05$) yet increased the activity of ATP citrate

lyase when expressed per g of tissue ($P<0.05$), indicating increased insulin sensitivity - the known main effect of chromium. The total capacity for fat synthesis as assessed by acetylCoA carboxylase was not altered and ATP citrate lyase still tended ($P=0.07$) to be elevated even when acetyl CoA carboxylase was used as a covariate. The age (2.5 years) and fat score (3-4) of the sheep would suggest little ability for partitioning the nutrients associated with reduced fat growth into muscle growth - a response more generally found in the growing pig after chromium supplementation (35). Relatively simple measures such as carcass weight and eye muscle area (*muscle longissimus dorsi*) supported this notion. Consequently it is tempting to suggest that fat was partitioned to more insulin sensitive fat depots, especially given the data of Walkden-Brown (56).

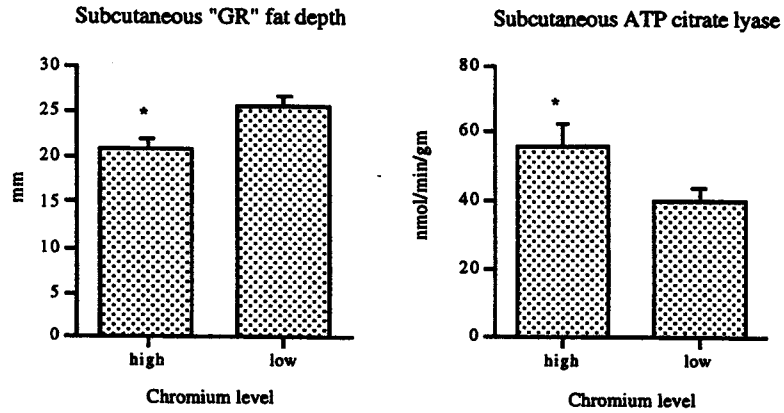


Figure 5. The effects of chromium supplementation on subcutaneous fat depth and ATP citrate lyase activity in subcutaneous fat of mature Merino sheep.

Conclusion

The challenge for the future is to determine the regulation of fat accretion between different depots in farm animals. Thus the glucose/insulin axis and catecholamines have been highlighted but these axes are modulated by several homeorhetic hormones. This modulation will differ between species and depot sites.

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