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Clenbuterol-Induced Insulin Resistance in Calves Measured by Hyperinsulinemic, Euglycemic Clamp Technique

By *K. Sternbauer*[1], *J. Luthman*[1], *A. Hänni*[2] and *SO. Jacobsson*[1]

[1]Department of Ruminant Medicine and Veterinary Epidemiology, Faculty of Veterinary Medicine, Swedish University of Agricultural Sciences and [2]Department of Geriatrics, Faculty of Medicine, Uppsala University, Sweden.

Sternbauer K, Luthman J, Hänni A, Jacobsson SO: Clenbuterol-induced insulin resistance in calves measured by hyperinsulinemic, euglycemic clamp technique. Acta vet. scand. 1998, 39, 281-289. – Hyperinsulinemic, euglycemic clamp tests were performed on calves before and after clenbuterol treatment. Clenbuterol was given as 2 intramuscular injections with an interval of about 12 h. The dose used was 1 μg/kg b.w. The treatment resulted in increased plasma levels of insulin and glucose. The results of the clamp tests showed that clenbuterol induced a transient decrease in insulin sensitivity. Both insulin mediated glucose disposal (M), expressed as μmol/kg live b.w./min. and the M/I-index (M divided by the average insulin concentration at steady state) were significantly reduced after treatment. The effect of clenbuterol on carbohydrate metabolism seemed to be rather short-lived, since significant changes occurred only in animals treated 5-6 h prior to the test. According to the literature, the metabolic effects of clenbuterol have been studied only after the high doses used for growth promoting purposes. The results from the present study showed that similar changes occur also after doses at the therapeutic level. The hyperinsulinemic, euglycemic clamp test was considered to be a valuable tool for the study of insulin sensitivity in cattle.

glucose.

Introduction

Insulin is a key hormone in the regulation of carbohydrate metabolism and its blood concentration varies under different physiological conditions. In dairy cows, basal insulin levels are lower during lactation than in the dry period (*Vasilatos & Vangsness* 1981, *Sartin et al.* 1988), and low milk yielders have been reported to show higher levels than high yielders (*Hart et al.* 1978, *Herbein et al,*1985). *Hove & Halse* (1978) found lower levels in ketotic than in normal cows, and further that the postprandial insulin response seemed to be impaired in ketotic cows.

Also the sensitivity to insulin and thus the uptake of glucose vary. Physical activities, the plane of nutrition and drugs are some of the factors which influence the sensitivity to insulin (*Campaigne & Gunnarsson* 1988, *Wallberg-Henriksson & Wahren* 1989, *Tappy et al.,* 1994).

The clamp technique is one of the methods used for the study of insulin secretion and tissue sensitivity to insulin. The clamp technique has been used in basic physiological studies and as a diagnostic tool in human medicine. The effect of insulin on glucose turnover in the lactating goat udder was e.g. studied by *Hove* (1978) using this technique. The hyperinsulinemic, eu-

glycemic clamp has become the standard method for the study of insulin sensitivity in man (*Alzaid & Rizza* 1993) and has also been successfully used in domestic animals by e.g. *Hay et al.* (1984), *Metcalf & Weekes* (1990) and *Sano et al.* (1991, 1993). Insulin and glucose are infused simultaneously and by adjusting the glucose infusion rate it thus becomes possible to clamp plasma glucose at a predetermined level in a state of hyperinsulinemia. The glucose infusion rate necessary to keep plasma glucose concentration constant is an indicator of the insulin mediated glucose uptake.

The primary aim of the study was to further evaluate the usefulness of the hyperinsulinemic euglycemic clamp technique under experimental conditions in cattle.

The acute metabolic effects of clenbuterol, a ß-agonist, have been intensely studied and there are indications that a transient insulin resistance develops shortly after clenbuterol administration (*Blum & Flückiger* 1988, *Zimmerli & Blum* 1990). By performing hyperinsulinemic, euglycemic clamp tests before and after clenbuterol it is thus possible to directly evaluate the effect of clenbuterol insulin sensitivity.

When clenbuterol is used as a broncho-dilatator in horses, cattle and dogs, the approved dose is 0.8 µg/kg b.w. (*Debuf* 1991), but clenbuterol has also had a widespread illegal use as a feed additive, especially to calves. When used as a feed additive, the daily dose is usually 10-20 µg/kg b.w. The beneficial effect of clenbuterol feeding, seen from an economical point of view, is a stimulation of muscular growth and a reduction of fat accretion.

Insulin infusion may induce hypokalemia and it has been a matter of discussion whether the hypokalemia shall be compensated by adding potassium to the infused solution. *Heinemann et al.* (1995) suggested that hypokalemia per se may influence the action of insulin.

A secondary aim of the study was therefore to study the relationship between hypokalemia and tissue sensitivity to insulin.

Materials and methods

Animals

Five bull calves of the Swedish Red and White breed were used. The animals were about 2 months old at the start of the experiment and weighed from 92 to 116 kg. At the second experiment, 2 months later, the weights had increased to 128 - 165 kg. All animals were kept indoors and were fed hay ad libitum and 0.5% concentrate per live kg bodyweight twice daily. The hay contained 9.1 MJ/kg t.s. and the concentrate contained 11.5 MJ/kg t.s. Each calf consumed approximately 2-3 kg hay daily.

Treatment

Two series of clamp tests were performed. In the first series, the calves were treated with 2 intramuscular injections of clenbuterol (Ventipulmin, 30 µg|ml, Boehringer Ingelheim, Malmö, Sweden) at a dose of 1 µg|kg b.w. The injections were given 25-26 and 16-17 h prior to the test.

The second series was performed with the same animals 2 months later. At that time clenbuterol, at the same dose, was injected 16-17 and 5-6 h prior to the clamp test.

Test performance

Hyperinsulinemic, euglycemic clamp tests were performed before and after clenbuterol treatment in calves. An interval of 2 weeks elapsed between the tests. Catheters were inserted in the jugular veins one day before the infusions. The animals were fed at 4 p.m. and remaining feed was taken away at 5 p.m. the day before experimental procedure. Feed was not allowed during the infusions.

The infusions were given by means of a 3-chan-

nel infusion pump (IVAC Medsystem 2860, IVAC Scandinavia AB, Täby, Sweden).

The tests were performed according to *DeFronzo et al.* (1979). Briefly, the priming dose of insulin was 148.3 mU/m^2, which corresponded to about 3 mU/kg live b.w. during the first minute. Thereafter the dose was decreased each min during the first 9 min at the rate recommended by *DeFronzo et al.* The recommendations were based on empirical data obtained in humans. From the 10th min insulin was infused at a constant rate of 56 mU/m^2/min, which corresponded to about 1 mU/kg live b.w. The total infusion time did not exceed 2 h. The mean levels of plasma insulin concentration and standard deviation during the last hour of the test are shown in table 3.

A stock solution containing 95.4 ml physiological saline, 0.6 ml insulin, a soluable monocomponent biosynthetic human insulin (Actrapid 100 IU/ml, Novo Nordisk, Pharma AB, Malmö, Sweden) with a rapid onset of effect, and 4 ml blood were prepared. The final solution for infusion was prepared by mixing 12 ml stock solution, 4 ml blood and 84 ml saline just before each test started.

Blood from the trial animal was added to the solution in order to avoid adherence of insulin to the walls of vessels and tubings. Anticoagulants was not added to any solution.

The glucose infusion started about 5 min after the insulin infusion. Glucose (Glucose 100 mg/ml, Kabi Pharmacia, Uppsala, Sweden) was infused at a varying rate. Blood samples for analysis of plasma glucose were collected every 5th min and the infusion rate was adjusted to maintain the predetermined plasma glucose level, 4.5 mmol/l, which was the mean of the calf group before entering the experiments.The infused volume of glucose was recorded every 20th min.

The insulin mediated glucose disposal (M), expressed as μmol/kg live b.w. and min during the period of stable plasma glucose concentration, 60-120 min was calculated for each calf by means of the amount of glucose infused and the body weight of the calf.

In human medicine the M/I index is used to describe the sensitivity to insulin. The M/I index is defined as the amount of glucose metabolized per unit plasma insulin. The index was used also in the present study and was calculated by dividing M with the mean insulin concentration during the period 60-120 min and multiplied with 100 (*Pollare et al.* 1990).

Analyses

Plasma glucose was analyzed in duplicate immediately after sampling using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, USA). A difference between duplicates exceeding 0.2 mmol/l was not accepted. In such cases the instrument was controlled and recalibrated if necessary and the sample was re-analyzed.

Potassium, calcium and magnesium ions were analyzed using a Kone Microlyte 6 Analyzer (Kone Instruments, Espoo, Finland).

Insulin analysis were performed by the Department of Clinical Chemistry, SLU, Uppsala. Pharmacia RIA 100 (Pharmacia Diagnostics, Uppsala, Sweden) was used to assay plasma concentrations of total insulin according to manufacturer's instructions. All samples were stored frozen (-18 °C) and analyzed when all clamp tests in each series had been performed. Serial dilutions of bovine plasma have been shown to produce displacement curves parallel to the standard curve. The intra-assay and inter-assay coefficients of variation were less than 10% and 8%, respectively and the sensitivity of the assay was 0.8 μU/ml.

Student's *t* test for paired values was used for statistical calculations.

All values given in text and figures are means and standard variations.

Table 1. Clenbuterol-induced changes in plasma insulin, glucose, and some mineral ions in calves. Mean ± SD.

	Before treatment	After treatment	
A. (n=5)			
Insulin μU/l	3.7 ± 1.5	4.5 ± 1.2	
Glucose mmol/l	4.3 ± 0.13	5.0 ± 0.4	$p < 0.01$
B. (n=5)			
Insulin, μU/l	6.0 ± 1.7	12.2 ± 3.5	$p < 0.01$
Glucose, mmol/l	5.1 ± 0.2	5.8 ± 0. 1	$p < 0.01$
Ca^{2+}, mmol/l	1.12 ± 0.12	1.33 ± 0.13	$p < 0.05$
Mg^{2+}, mmol/l	0.68 ± 0.10	0.60 ± 0.10	
Ca/Mg, mmol/l	1.68 ± 0.23	2.28 ± 0.28	$p < 0.02$
K^+, mmol/l	4.18 ± 0.13	4.15 ± 0.03	
Na^+, mmol/l	137.1 ± 1.13	137.9 ± 0.96	

A. Animals treated 25 - 26 and 16-17 h before sampling
B. Animals treated 16 - 17 and 5-6 h before sampling

Table 2. The concentrations (mmol/l) of some serum minerals in calves during hyperinsulinemic, euglycemic clamp test performed before and after clenbuterol treatment. n = 4, mean and SD.

	Minutes				
	0	30	60	90	120
Ca2+					
Before treatm.	1.14 ±0.13	1.26 ±0.14	1.31 ±0.09	1.25 ±0.01	1.31 ±0.12
After treatm.	1.36 ±0.13	1.37 ±0.04	1.39 ±0.08	1.35 ±0.02	1.32 ±0.23
Mg2+					
Before treatm.	0.70 ±0.10	0.70 ±0.09	0.72 ±0.03	0.69 ±0.10	0.67 ±0.09
After treatm.	0.56 ±0.07	0.67 ±0.06	0.75 ±0.08	0.64 ±0.04	0.68 ±0.04
K+					
Before treatm.	4.18 ±0.16	3.91 ±0.05	3.86 ±0.08	3.88 ±0.13	3.88 ±0.13
After treatm.	4.15 ±0.03	3.89 ±0.10	3.76 ±0.07	3.86 ±0.15	3.77 ±0.19

Results

The preinfusion levels of the studied parameters, e.g. the effect of clenbuterol, are shown in Table 1. Only glucose was significantly increased in the first series of experiment where the second clenbuterol injection was given 16-17 h prior to blood sampling.

In the second experiments where the last clenbuterol injection was given 5-6 h prior to blood sampling, the treatment increased the levels of both glucose and insulin significantly.

Minerals were analyzed only in the second series of experiments and as seen from Table 1 ionized calcium was significantly higher after clenbuterol treatment. Also the Ca/Mg ratio was significantly increased after treatment.

The infusions were well tolerated and no adverse reactions were observed. As shown in Table 2 serum potassium decreased during the clamp tests. The mean levels were significantly lower than the pre infusion levels at 120 min

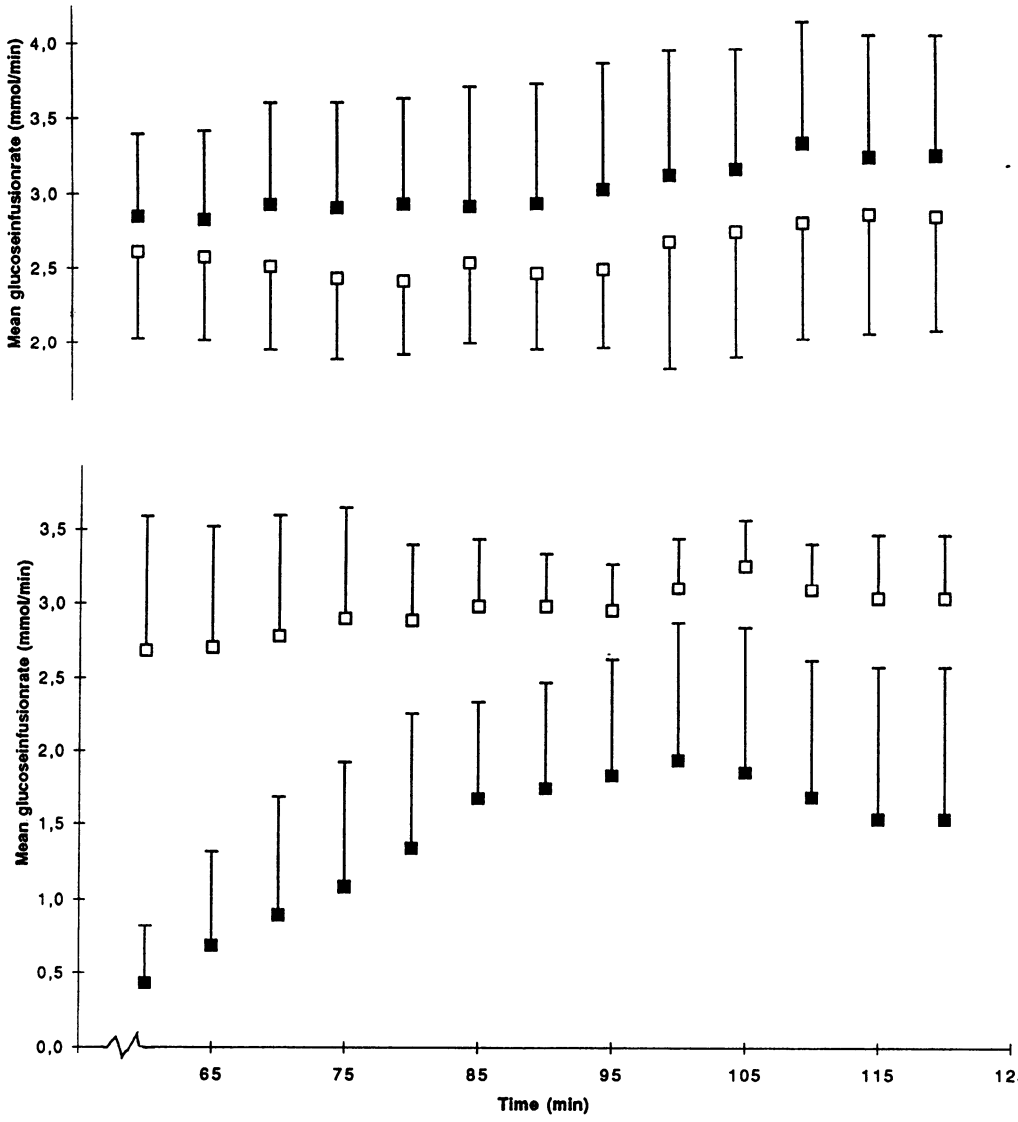

Figure 1. Glucose infusion rate during the last 60 min of the clamp test, before (□) and after (■) clenbuterol treatment. x ± SD.
Upper panel: Animals treated 25-26 and 16-17 h prior to the test. n = 5
Lower panel: Animals treated 16-17 and 5-6 h prior to the test. n = 4

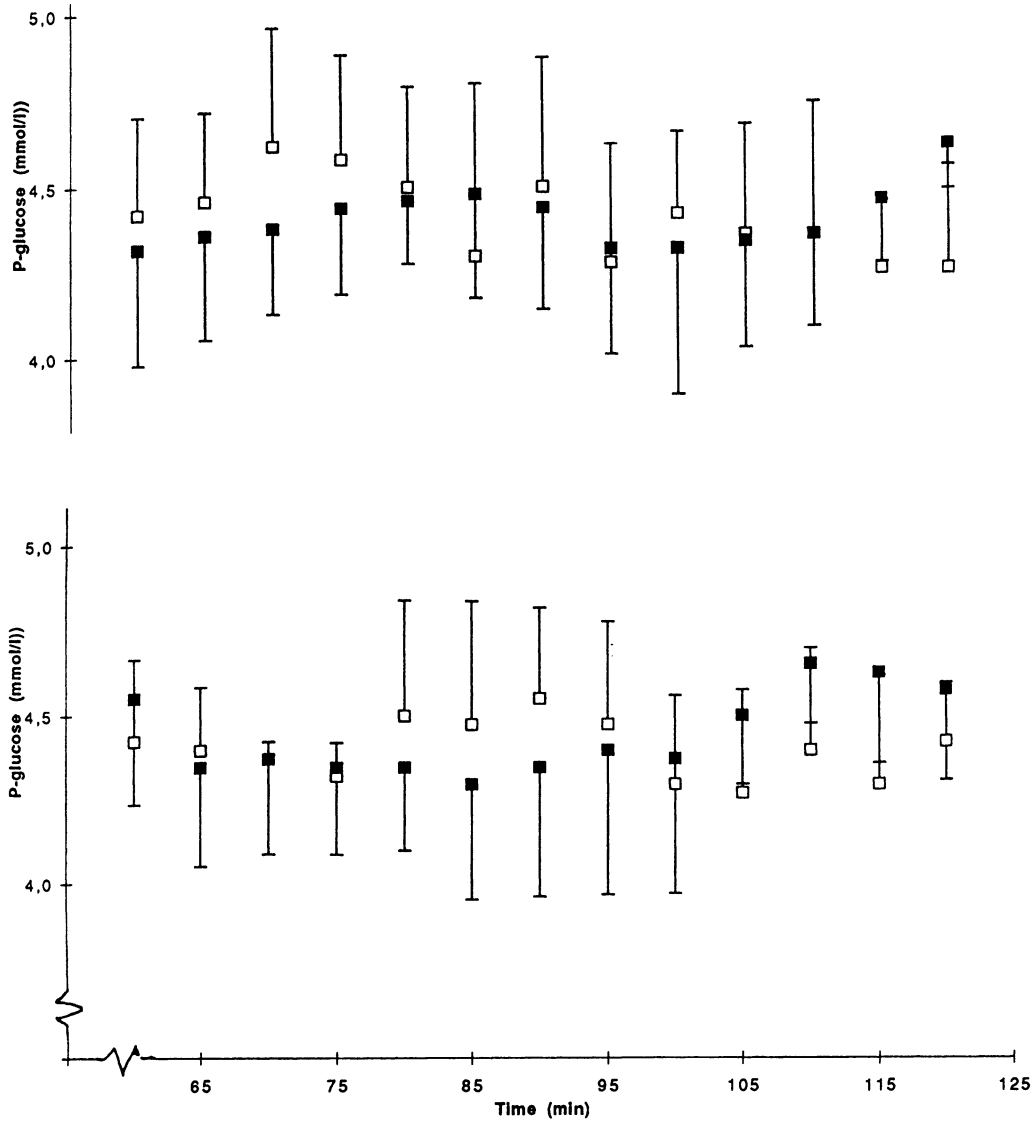

Figure 2. Plasma glucose during the last 60 min of the clamp test, before (□) and after (■) clenbuterol treatment. x ± SD.
Upper panel: Animals treated 25-26 and 16-17 h prior to treatment. n = 5
Lower panel: Animals treated 16-17 and 5-6 h prior to the test. n = 4

Table 3. Serum concentrations of insulin (mU/l) during the last hour of the clamp tests performed before and after clenbuterol treatment. Mean and SD

	Minutes		
	60	90	120
A. (n = 5)			
Before treatm.	69.1 ± 7,3	71.2 ± 6.4	70.8 ± 8.9
After treatm.	68.5 ± 7.5	68.3 ± 6.1	70.2 ± 4.0
B. (n = 4)			
Before treatm.	69.8 ± 6.2	66.2 ± 7.7	69.5 ± 8.7
After treatm.	73.4 ± 6.7	79.7 ± 15.8	74.7 ± 14.4

A. Animals treated 25-26 and 16-17 h prior to the test.
B. Animals treated 16-17 and 5 6 h prior to the test

($p<0.05$), both before and after clenbuterol treatment. The level of calcium ions increased when the test was performed before clenbuterol treatment.

The mean glucose infusion rates are shown in Fig.1 and Fig. 2. The infusion rate was significantly lower after clenbuterol treatment in the second series of experiments.

Stable plasma levels of glucose and insulin were in all cases reached after 60 min. The plasma levels during the last hour of the tests are shown in Fig. 1 and in Table 3.

Because of a technical error the results from one calf in the last clamp test in the second series of experiments had to be excluded from the evaluation.

M and the M/I index during steady state are shown in Table 4. Neither the insulin mediated glucose disposal (M) nor the insulin sensitivity index (M/I) was influenced by clenbuterol in the first series of tests, but was significantly changed in the second series, where both M and M/I were reduced by about 60%.

Table 4. Mean glucose disposal, M (μmol/kg and min-1) and insulin sensitivity index, M/I (I, mU/l) during steady state, before and after clenbuterol treatment. Mean ± SD

	Before treatment	After treatment	
A. (n = 5)			
M	25 ± 5	27 ± 5	
M/I	36 ± 8	39 ± 10	
B. (n = 4)			
M	21 ± 2	8 ± 3	$p < 0.01$
M/I	30 ± 6	12 ± 6	$p < 0.01$

A. Animals treated 25-26 and 16-17 h prior to the test
B. Animals treated 16-17 and 5-6 h prior to the test

Discussion

The metabolic effects of clenbuterol have usually been studied after the high doses used for growth promoting purposes. The results from the present study show that clenbuterol induces a remarkable but transient insulin resistance also after doses at the therapeutic level. Clenbuterol has been widely used for the treatment of chronic obstructive pulmonary disease in horses, but no adverse reactions which can be attributable to insulin resistance seem to have been reported.

It is obvious that the effects of clenbuterol on insulin and glucose were rather short-lived, since only glucose was significantly increased in the first series, while insulin levels probably had returned to the pre treatment level after 16-17 h. However, the levels of both insulin and glucose were significantly increased only in the second series where the animals were treated only 5-6 h prior to the test.

The mean glucose infusion rates necessary to maintain the predetermined glucose level in the 2 series of clamp tests are shown in Fig. 1 and 2. As seen from Fig. 1 significant changes in the infusion rate were not necessary after clenbuterol treatment in the second series.

Neither glucose disposal (M) nor the insulin sensitivity index (M/I) was influenced by clenbuterol in the first series of tests, but was significantly changed in the second series.

The doses of insulin used in the present study were according to the recommendations given by *Pollare et al.* (1990). The test was primarily developed for the use in humans and the dose recommendations are based on data obtained in humans, but the present results showed that the same doses can be used also in calves. *Sano et al.* (1991,1992) used a different infusion technique in their studies on insulin sensitivity in adult beef and dairy cows. No priming dose was given and insulin was administered at a constant rate of 6 mU/kg live b.w. and min^{-1}. However, the crucial point is to keep plasma glucose concentration constant in a state of hyperinsulinemia.

The results of the present study on the effects of clenbuterol on carbohydrate metabolism are supported by earlier published results. *Blum & Flückiger* (1988) found that calves treated with ß-agonists showed a decreased glucose clearance rate and an excessive insulin response to glucose, and it was later reported that treated calves showed a poor response to exogenous insulin (*Zimmerli & Blum* 1990). *Luthman & Jacobsson* (1993) found that treated calves showed exaggerated postprandial responses in glucose and insulin when compared with controls. The ß-agonist-induced insulin resistance is generally considered to be a consequence of a reduction of the number of insulin receptors (*Kirsch et al.* 1983, *Pessin et al.* 1983).The acute metabolic effects of ß-agonists are obviously not coupled to the growth promoting effects of ß-agonists, since *Zimmerli & Blum* (1990) reported that the metabolic effects e.g. increased levels of glucose, insulin and non-esterified fatty acids disappeared after continued medication. The diminishing response is probably due to a reduction of the number of ß-receptors (*Lindsay et al.* 1992).

The sensitivity to insulin can vary between different types of tissues. *Hove* (1978) found e.g. that insulin had no effect on the glucose turnover in the lactating goat udder. The hyperinsulinemic, euglycemic clamp test as performed in the present study, makes it possible to calculate the total tissue uptake of glucose, and thus the average sensitivity to insulin. Despite this limitation, the test must be considered as a valuable tool in the study of carbohydrate metabolism in various physiological and pathological conditions in cattle.

Potassium is usually added to the infusion solution as continuos infusion of insulin may cause hypokalemia (e.g. *Hostettler-Allen et al.* 1994). As shown in Table 2 there was only a slight decrease in plasma potassium, and addition of potassium does not seem to be necessary when the clamp test is performed under conditions similar to those in the present study. Similar conclusions can be made from results in humans published by *Pollare et al.* (1990). It is possible that plasma potassium decreases more profoundly, and that addition of potassium is necessary when longer infusion periods than 2 h are used. As the decrease in plasma potassium during the test was similar, both before and after clenbuterol treatment, it seems unlikely that the slight decrease in potassium had any influence on the tissue sensitivity to insulin.

Ionized calcium was significantly increased after clenbuterol treatment, while the magnesium level remained unchanged. As total calcium was not analyzed, it is not possible to conclude if the increase in ion concentration was due to an increase in total calcium or to a shift in the balance free ions/complex bound calcium. It was earlier shown that continuos infusion of the ß-agonist norepinephrine induced hypocalcemia, and that this kind of hypocalcemia was lipolysis-dependent (*Luthman & Holtenius* 1972).The repeated single dose regimen used in the present study may explain the difference in results.

As a consequence of the increase in ionized calcium, also the Ca/Mg ratio was significantly higher after clenbuterol treatment. This finding is interesting and deserves further study, since *Hänni et al.* (1997) found an inverse relationship between insulin sensitivity and the Ca/Mg ratio in man.

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Sammanfattning

Clenbuterolinducerad insulinresistens hos kalv studerad med hyperinsulinemisk, euglykemisk clamp teknik.

Hyperinsulinemisk, euglykemisk clamp test utfördes på kalvar före och efter behandling med clenbuterol. Två i.m. injektioner gavs med 12 timmars intervall. Den använda dosen var 1µg/kg kroppsvikt. Behandlingen resulterade i ökade plasmakoncentrationer av insulin och glykos. Resultaten av clamptesterna visade att clenbuterolbehandlingen resulterat i nedsatt insulinkänslighet. Det insulinmedierade vävnadsupptaget av glykos, M, uttryckt i µmol/kg kroppsvikt/min och insulinkänslighetsindex, M/I (M delat med medelinsulinkoncentrationen), var signifikant reducerade efter clenbuterolbehandling.

Effekten av clenbuterol var relativt kortlivad, insulinresistens påvisades endast hos de kalvar som behandlats 5-6 timmar innan testet.

Enligt tillgängliga litteraturuppgifter har tidigare effekter av clenbuterol endast studerats efter de höga doser som använts i tillväxtstimulerande syfte. Resultaten från denna studie visar att samma effekter kan induceras av terapeutiska doser.

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Reprints may be obtained from: K. Sternbauer, Department of Ruminant Medicine and Veterinary Epidemiology, Swedish University of Agricultural Sciences, P.O. Box 7019, S-750 07 Uppsala, Sweden. E-mail: Karin.Sternbauer@idmed.slu.se, tel: +46 18 67 17 72, fax: +46 18 67 35 45.