The effect of the α_2-adrenergic agonist, guanfacin, on the energy metabolism of steers fed on low-quality-roughage diets

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(*Received 18 March 1991 – Accepted 28 June 1991*)

The effect of the α_2-adrenergic agonist, guanfacin, on the energy metabolism, feed intake and live weight (LW) change of steers was studied in three experiments. In the first, the metabolic rate of twelve steers was measured after a 72 h fast. The next day, after a 96 h fast, six steers were injected intramuscularly with 15 mg guanfacin in sterile saline (9 g sodium chloride/l) and six with sterile saline alone, and metabolic rate was measured again. Treatment significantly ($P < 0.01$) lowered metabolic rate by approximately 20% (53·9 *v.* 66·8 kJ/kg per d). In the second experiment twelve steers were fed on long-chopped, low-quality roughage (Pangola grass (*Digitaria decumbens*) hay) *ad lib.* for 6 weeks. Six steers were continuously infused through a jugular catheter with 15 mg guanfacin/d (about 40 μg/kg LW) in sterile saline. The other six served as controls. There was no significant effect of treatment on feed intake (g dry matter (DM)/kg LW) or the rate of LW loss. Treatment significantly ($P < 0.05$) increased the retention time of fluid (17·9 *v.* 22·1 h) in the alimentary tract. In the final experiment twenty-three steers were divided into four treatment groups and fed on long-chopped, low-quality roughage (Pangola hay). Treated animals were continuously infused with guanfacin at the rate of 20, 40 or 80 μg/kg LW per d. Control steers were not infused. At the end of the 6-week feeding period metabolic rate was measured after a 72 h fast. Regardless of dose, guanfacin significantly ($P < 0.01$) lowered metabolic rate. Feed intake was not significantly affected by treatment but the rate of LW loss was significantly ($P < 0.05$) less in treated steers.

Guanfacin: α_2-Adrenergic agonist: Energy metabolism: Low-quality-roughage diets: Steers

Beef production in seasonally dry areas follows a pattern of weight gain during the wet season and weight loss during the dry, resulting in relatively small annual gains. Improvements in animal growth rates could be achieved if maintenance energy requirements were reduced without any concomitant reduction in feed intake and digestive and metabolic efficiency. Under such circumstances weight gains would be enhanced during the wet season and weight losses reduced during the dry.

It is possible that α_2-adrenergic agonists may be useful for chronic reduction in metabolic rate of cattle through their inhibitory effects on noradrenalin release. Noradrenalin-stimulated thermogenesis is an important component of total energy expenditure. Thompson *et al.* (1984) showed that the α_2-agonist clonidine decreased metabolic rate in humans by 8%.

The drug chosen for use in the experiments reported here was guanfacin, a novel antihypertensive agent which is about twelve times more selective for the α_2-receptor than clonidine (Scholtysik & Fetkovska, 1987). Its biological half-life is more than double that of clonidine which allows less frequent administration. It also has a less sedative effect than clonidine (Scholtysik *et al.* 1980). Guanfacin stimulates α_2-adrenoreceptors both in the central nervous system and in the periphery (Scholtysik & Fetkovska, 1987) and lowers plasma noradrenalin concentration by peripheral α_2-receptor stimulation in man (Brown &

Struthers, 1985). Scholtysik (1974) showed that it inhibited the release of noradrenalin during sympathetic nerve stimulation in skeletal muscle, an effect which was abolished by α_2-blockade (Pacha *et al.* 1975).

The present paper reports the effect of guanfacin on the fasting metabolic rate, feed intake and live weight (LW) change of cattle.

MATERIALS AND METHODS

Expt 1. The effect of acute administration of guanfacin on fasting metabolic rate of steers

Twelve Brahman (*Bos indicus*) steers, trained to experimental procedures, were fasted for 48 h and weighed. The mean (with SEM) fasted weight was 322 (4·6) kg. Before fasting they had been grazing good-quality pasture for 6 weeks. They were housed in individual pens in a roofed animal house and fed on a diet of long-chopped lucerne (*Medicago sativa*) hay, restricted to an intake of 15 g dry matter (DM)/kg fasted LW. The steers were treated with an anthelmintic to eliminate gastrointestinal helminths. They were divided into two groups of six steers of similar mean LW. After 2 weeks on the lucerne diet one steer from each group was fasted for 72 h and metabolic rate then measured in confinement-type respiration chambers, as described by Hunter & Vercoe (1987). The following day, after a 96 h fast, one of the steers was injected intramuscularly with 15 mg guanfacin in sterile saline (9 g sodium chloride/l). The other steer was sham-treated, receiving just saline. Metabolic rate was again measured commencing 1 h after the drug was given. As there were only two respiration chambers, this procedure was repeated with the other five pairs of steers.

Expt 2. The effect of guanfacin on feed intake and LW change of steers fed on a low-quality-roughage diet

The same twelve steers that were used in Expt 1 were housed in individual pens in the animal house; from 1 week before the experiment and for the experimental period of 6 weeks they were fed *ad lib.* on long-chopped Pangola grass (*Digitaria decumbens*) hay (5·5 g nitrogen/kg DM). Their mean (with SEM) initial weight was 390 (4·9) kg. The experiment commenced approximately 7 months after the completion of Expt 1. The steers were divided into two groups without regard to their treatment group in the first experiment. Each animal in one group was continuously infused via a jugular catheter with guanfacin in sterile saline at the rate of 15 mg/d for the duration of the experimental period. The infusate of 2·5 ml/d also contained EDTA (1 mg/ml) as an anticoagulant. The solution was delivered using a portable infusion pump (Infusa DSLT syringe pump; Medis, Medical Infusion Systems, Italy) mounted on a cradle which was carried on the animals' necks. Steers in the other group were not infused. The amount of feed offered each day was such that the residue was between 0·8 and 1·5 kg. Animals were weighed twice weekly just before the daily feed was offered. Feed intake (g DM/kg LW) was calculated on a weekly basis using the mean LW of each steer that week for each of the 6 weeks of the experiment. At one of the weighing times each week a sample of blood was collected by jugular venepuncture into heparinized tubes. Plasma was obtained by centrifugation and stored at −15°.

In the third week of the experiment steers were given oral drenches of solutions of the liquid-phase marker CrEDTA (0·5 g) and the solid-phase marker Yb $(NO_3)_3.4H_2O$ (6·0 g). Thereafter, a grab sample of faeces was collected each day for 8 d. The exact time of sampling in relation to marker administration was recorded so that the retention times of the markers in the gut could be determined. Retention time was calculated by dividing the time for half the dose of marker to appear in the faeces by 0·693.

Expt 3. The effect of three doses of guanfacin on feed intake, LW change and metabolic rate of steers

Twenty-three Brahman steers, initial weight 251 (SEM 2·9) kg, were housed in individual pens in the animal house and fed *ad lib.* on long-chopped Pangola hay (14·3 g N/kg DM) for 11 d before the experiment and for an experimental period of 6 weeks. Steers were divided into four treatment groups; five steers were continuously infused via a jugular catheter with guanfacin in sterile saline at 20 μg/kg LW per d, six steers were similarly infused at 40 μg/kg LW per d and six steers at 80 μg/kg LW per d. The other six steers were not infused. The infusion procedure was the same as in Expt 2. Because there were not enough infusion pumps to treat eighteen animals at the one time, the experiment was conducted in two periods, with three steers from each treatment group in period one and the remainder in period 2. Period 2 commenced immediately after the conclusion of period 1. At the end of six weeks, fasting (72 h) metabolic rate was measured. Infusion of guanfacin continued during fasting. Husbandry and experimental procedures were the same as for Expt 2.

After realimentation, the steers were again fed *ad lib.* on the experimental diet for 3 weeks without treatments being imposed. Daily intakes were recorded. Fasting (72 h) metabolic rate was measured at the end of the feeding period and the values were used in covariance analysis of the main effects. This course of action was not planned initially but was taken on completion of the infusion period because it was apparent that steers treated with guanfacin had lower intakes than those not treated, even though the difference was not statistically significant. It was assumed that since the half-life of guanfacin in the body is about 18 h (Scholtysik *et al.* 1980) the effects of the drug after 1 week of realimentation would be negligible.

Chemical analysis

The concentrations of DM in feed and faeces, and the concentrations of insulin, free 3,5,3′-triiodothyronine (T_3) and albumin in plasma were determined as described by Hunter & Vercoe (1987); the concentrations of chromium and ytterbium in faeces were measured as described by Hunter & Siebert (1986).

Statistical analysis

The significance of differences between treatment groups was determined by analysis of variance. Where some samples were collected at intervals throughout the experimental period, e.g. for feed intake and hormone concentration, temporal response curves were fitted to the values. Because the between-animal variances for free T_3 were not normally distributed, results were analysed after logarithmic$_{10}$ transformation. The SEM presented in the tables are based on the between-animal variation. The rate of LW change was derived from the regression of LW *v.* time, and a regression coefficient was calculated for each steer, after which the coefficients were tested by analysis of variance. If the regression coefficient was not significant, LW change was assigned a value of zero. Means were considered to be significantly different if $P < 0·05$.

RESULTS

Expt 1. The effect of acute administration of guanfacin on fasting metabolic rate of steers

Before treatment with an intramuscular injection of guanfacin there was no significant difference in metabolic rate between groups (Table 1). After treatment, those given guanfacin had significantly ($P < 0·01$) lower metabolic rates than the controls. When the results were analysed with covariance adjustment for metabolic rate before treatment, the probability that the difference was significant increased ($P = 0·004$). There was no obvious

Table 1. *Expt 1. The effect of an intramuscular injection of guanfacin on the metabolic rate of steers**

	72 h fast				96 h fast			
	Untreated (*n* 6)	Untreated† (*n* 6)	SEM	Comparison and test of statistical significance	Untreated (*n* 6)	Guanfacin (*n* 6)	SEM	Comparison and test of statistical significance
Fasted live wt (kg)	320	320	4·6	NS	315	316	4·8	NS
Fasting metabolism (MJ/d)	20·3	21·6	0·68	NS	20·7	17·0	0·33	$P < 0·01$
Fasting metabolic rate (kJ/kg per d)	62·7	67·0	3·08	NS	66·8	53·9	1·92	$P < 0·01$

* For details of procedures, see p. 338.
† This group contained the steers that were subsequently treated with guanfacin the next day before measurement after a 96 h fast.
NS, not significant.

sedation of treated steers. On return to their pens after measurement they immediately ate the feed offered.

Expt 2. The effect of guanfacin on feed intake and LW change of steers fed on a low-quality-roughage diet

Continuous infusion of 15 mg guanfacin/d did not affect significantly, the rate of LW loss (Table 2). There was a tendency for a reduction in feed intake associated with treatment ($P = 0·06$). The retention time of the liquid-phase digesta marker CrEDTA was significantly ($P < 0·05$) longer in treated steers, which indicated a slower passage of fluid and associated fine digesta particles through the alimentary tract. The retention time of the solid-phase digesta marker $Yb(NO_3)_3$ was not significantly different between treatments. Treatment had no effect on rectal temperature.

Expt 3. The effect of three doses of guanfacin on feed intake, LW change and metabolic rate of steers

Even at the highest dose there were no effects of the drug on visual appearance or behaviour of the animals. With one exception, there was no significant effect of period, nor was the treatment × period interaction significant. For free T_3 concentration in plasma there was a significant ($P < 0·01$) difference between periods, and the period × treatment interaction was significant ($P < 0·01$).

The *ad lib.* Pangola-hay diet provided around maintenance energy requirements. The rate of weight loss in steers given guanfacin was significantly ($P < 0·05$) less than that of the controls (Table 3). Regardless of dose, treatment with guanfacin did not significantly affect feed intake (g/kg LW) although there was a tendency for treated steers to have lower intakes. When the results were analysed with covariance adjustment for the individual intakes during the 3-week period following treatment when no drug was given, differences in intake associated with treatment became significant ($P < 0·01$). Feed intakes in the period when no treatments were imposed were 14·8, 14·5, 14·8 and 14·5 g DM/kg LW for the former control, low-, medium- and high-guanfacin groups respectively.

Treated steers had significantly lower metabolic rates ($P < 0·01$) than the controls, with a tendency for the depression to be greater at higher dose rates. As previous feed intake (kg/d) and LW affect metabolic rate, covariance adjustments were made. However, the

Table 2. *Expt 2. The effect of a continuous infusion of guanfacin on steers fed on a low-quality-roughage diet**

	Control (*n* 6)	Guanfacin (*n* 6)	SEM	Comparison and test of statistical significance
Initial wt (kg)	389	391	5·1	NS
Live-wt (LW) change (kg/d)	−0·28	−0·35	0·045	NS
Feed intake (g dry matter (DM)/kg LW)	11·9	10·1	0·92	NS
Feed conversion efficiency (feed DM/kg LW change)	−15·9	−13·0	1·86	NS
Retention time of chromium (h)	17·9	22·1	0·39	$P < 0·05$
Retention time of ytterbium (h)	38·0	42·0	1·92	NS
Rectal temperature (°)	37·9	37·9	0·05	NS
Plasma insulin (μunits/ml)	24	23	4·4	NS
Plasma albumin (g/l)	34	33	0·13	NS

NS, not significant.
* For details of procedures, see p. 338.

Table 3. *Expt 3. The effect of a continuous infusion of three doses of guanfacin on live weight (LW) change, feed intake and metabolic rate of steers fed on a low-quality-roughage (Pangola* (Digitaria decumbens) *hay) diet**

	Guanfacin (μg/kg LW per d)					
	Control (*n* 6)	20 (*n* 5)	40 (*n* 6)	80 (*n* 6)	SEM	Comparison and test of statistical significance
Initial wt (kg)	253	250	252	251	2·7	NS
LW change (kg/d)	−0·12	−0·04	−0·02	−0·02	0·013	$P < 0·05$
Feed intake (g dry matter (DM)/kg LW)	16·1	14·3	15·1	14·5	1·32	NS
Fasting metabolism (MJ/d)	19·1	17·3	15·4	15·5	0·42	$P < 0·05$
Fasting metabolism rate (kJ/kg per d)	86·0	73·7	65·3	67·4	1·94	$P < 0·01$
Plasma free T_3 (pg/ml)	2·4	2·0	2·3	2·3	1·07	NS
Plasma insulin (μunits/ml)	14	20	12	14	2·6	$P < 0·05$

NS, not significant; T_3, 3,5,3′-triiodothyronine.
* For details of procedures, see p. 338.

regressions of these measures with metabolic rate were not significant. Covariance adjustment was also made for metabolic rate in the absence of the drug. Again, the regression was not significant.

DISCUSSION

The dose of guanfacin normally recommended in human medicine for the treatment of hypertension varies between 0·5 and 3 mg/d (about 7–40 μg/kg per d; Sorkin & Heel, 1986). To maximize any effect of the drug on cattle the initial dose chosen for the first experiment was approximately the maximum scaled up on a LW basis. This dose, half of it and double it were then used in the final experiment without any visible sedation or behavioural changes in the steers.

The results of the study showed that guanfacin reduced fasting energy expenditure in steers by approximately 20%. However, the biological process by which this was achieved is unclear. That free T_3 concentrations in plasma were unaffected by treatment is evidence that changes in metabolic rate were not mediated via the thyroid hormone system. The available information on the pharmacokinetics and action of guanfacin concerns its antihypertensive properties in clinical medicine and not its energy-sparing effects. Further, it is not known at this stage whether the reduced metabolic rate was associated with the drug's α_2-adrenergic agonist properties or some other action. Although the former is more likely, there is evidence that in peripheral tissues guanfacin may bind with high affinity to a site other than α_2-receptors (Smith & Leslie, 1988), indicating that some other mechanism of action cannot be excluded. To account for the substantial reduction in metabolic rate recorded, the drug must have exerted an influence on metabolic rate outside the central nervous system, which itself accounts for only a minuscule proportion of an animal's energy requirements. Biochemical transactions in the liver and gut, mainly ion pumping and protein turnover, account for approximately half maintenance energy requirements in ruminants (Lindsay & Oddy, 1986). The other main consumer of energy is skeletal muscle which accounts for approximately 30% of total oxygen consumption (Oddy *et al.* 1985). It is possible that the drug was affecting the metabolism of these tissues, perhaps by inhibiting noradrenalin release. There is evidence that noradrenalin has an influence on energy metabolism of skeletal muscle as Shiota & Masumi (1988) showed that noradrenalin increased total O_2 consumption and ion pumping ($Na^+ - K^+$ ATPase (*EC* 3.6.1.3) activity) in perfused rat skeletal muscle. These responses were markedly decreased when α-blockers were perfused as well. There appears to be no relevant data on the effect of perturbation of normal catecholamine action on the energy transactions of the gut and liver.

For ruminants in the same environmental conditions, of the same genotype, age and physiological state, the principle factor controlling the voluntary feed intake of roughage diets is the rate of disappearance of organic matter from the rumen (see Weston, 1979). This is accomplished by fermentation in the rumen and passage of undigested residue from the rumen. The tendency for guanfacin treatment to depress feed intake was consistent with the longer transit time of fluid through the alimentary tract in treated steers. On roughage diets, relative retention times of solid- and liquid-phase markers, determined by faecal analysis, essentially reflect relative retention times in the rumen (Grovum & Williams, 1973). However, as control steers did not carry a cradle with the infusion pump, the effect of the drug on intake is confounded with infusion procedure. That there was almost no difference in intake between steers getting the high and low dose of guanfacin suggests that the intake depression may have been associated with the method of drug administration, rather than the drug itself. The similarity of intakes of the four groups in the period after treatment when the drug, cradles and infusion pumps were not used adds support to this suggestion, as does the result of a subsequent experiment at this laboratory in which guanfacin was administered to steers, fed on lucerne hay *ad lib.*, at the medium dose of the present study. Treated steers carrying the cradle and pump had similar intakes to control steers carrying the cradle with a block of wood of similar weight to the pump. In this experiment intake was measured for 2 weeks before the cradles and infusion pump or blocks of wood were attached. Treatments were then imposed for a further 5 weeks. The mean intakes of the treated and control steers, with covariance adjustment for previous intakes, were both 25·1 g DM/kg LW. It is also possible that the longer transit time of fluid digesta in treated steers was the result rather than the cause of the lower intakes (Weston & Hogan, 1967).

The results of the present study emphasize the different effects on energy metabolism of farm animals exerted by drugs that modify the catecholamine system. Whereas the β-

agonist, clenbuterol, has been shown to increase energy expenditure substantially (MacRae *et al.* 1988), the α_2-agonist, guanfacin, had the opposite effect. If such perturbations in energy metabolism can be duplicated by procedures suitable for use commercially, another possible avenue exists for increasing the biological efficiency of beef production.

This study was financed in part by the Australian Meat and Livestock Research and Development Corporation. Sandoz kindly donated the guanfacin. The technical assistance of Mr C. R. Holmes, Mrs C. G. Johnson, Mr T. Magner and Mr W. D. Sim is gratefully acknowledged.

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Printed in Great Britain