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SODIUM BUTYRATE IN GROWING AND FATTENING DIETS FOR EARLY-WEANED RABBITS

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Abstract: To study the effect of adding coated sodium butyrate (SB) to growing-fattening rabbit diets, 2 trials were conducted. In trial 1, 180 rabbits were housed in pairs and fattened from 23 (weaning) to 63 d of age to evaluate their zootechnical performance. Trial 2 involved 30 rabbits, from 23 to 37 d of age and housed individually in digestibility cages, to evaluate digestibility, caecal fermentative activity and morphology of the intestinal mucosa. In both trials rabbits were randomly divided into 2 groups, each receiving one of the following diets: control diet [CTR, 360 g neutral detergent fibre (NDF) and 170 g crude protein (CP)/kg dry matter (DM)] and SB diet. The SB diet, similar to CTR diet, included coated SB at 5 g/kg by replacement of an identical quantity of wheat. In trial 1, after the first 2 wk, the SB content was reduced from 5 to 3 g/kg. In trial 2, faeces were collected over the last 6 d (32-37 d of age), with rabbits being slaughtered at 37 d of age. Gastric and caecal pH were measured and fermentative activity was determined in caecal contents. Three sections of the small intestine were excised from 20 rabbits (10 per treatment) for microscopic examination of intestinal villi and crypts in the proximal region, central region and distal region. In the first 2 wk after weaning, SB rabbits grew 8% less than their counterparts (P=0.002), but had a better feed conversion ratio (1.58 *vs.* 1.61; P=0.036). During the whole trial 1 period, SB improved feed conversion (P=0.005) and decreased feed intake (104.1 CTR *vs.* 98.8 g/d SB; P=0.017). No difference was recorded in daily weight gain (42.7 *vs.* 42.9 g/d). In both diets, the digestibility of DM, organic matter, energy, CP and NDF were similar. In the 3 intestinal regions of rabbits fed SB diet, crypts were deeper ($P<0.05$). There were no significant differences in villus height and width between treatments. Pectinase activity was higher (P=0.054) with SB diet, but cellulase and xylanase activity remained unaffected by diet. In our experimental conditions, the addition of SB allowed an improvement in feed conversion.

Key Words: coated Na-butyrate, performance, small intestine morphology, caecal activity, digestibility, rabbit.

INTRODUCTION

Organic acids and their salts, as well as a limited number of inorganic acids (e.g., phosphoric acid), have a long history as food and feed preservatives. They also have a history of more than 2 decades as "acidifiers" in diets for piglets (Partanen and Mroz, 1999). The main use of these acidifiers is to control diarrhoea. More recently, there has been an upsurge of interest in these acids and salts, for either alone or in mixtures, as an alternative to antibiotic growth promoters – banned for use in Scandinavia and throughout the EU. Encouraging results have been obtained in several physiological stages and species, such as pigs (Partanen and Mroz, 1999), chickens (Hu and Guo, 2007) or calves (Gorka *et al.,* 2009). Positive growth results have typically been associated with gut changes (e.g., in gut morphology) and an increase in diet digestibility (Mroz, 2005).

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Data on the use of organic acids in rabbit diets are, as expected, much sparser than those obtained with the main production species, but the few available rabbit results suggest that organic acids may improve several production traits (Falcão-e-Cunha *et al.*, 2007; Romero *et al.*, 2011).

Although butyric acid occurs naturally in the digestive tract, supplementing diets with this acid has increased the secretion of digestive enzymes and the absorption capabilities of the gut, and improved the functioning of its cells in young calves (Guilloteau *et al.,* 2009). These effects may be related to a well-known action of butyric acid on the proliferation and differentiation of mucosal cells (Salminen *et al.,* 1998). These effects are likely to be stronger when the supplementation is started earlier (Guilloteau *et al.*, 2009). Coating the acid limits its absorption in the stomach, which occurs rapidly when the gastric pH is lower than the acid pKa (Partanen and Mroz, 1999) and thus allows for stronger intestinal effects and a wider effect.

The aim of this work was to study the supplementation of rabbit diets with organic acids, particularly with coated butyric acid in the post-weaning phase (when rabbits are especially prone to digestive upsets) and in the whole fattening period, as it had not been tested before.

MATERIALS AND METHODS

Experimental procedures

This study consisted of 2 trials. Trial 1 involved a total of 180 rabbits from 23 (weaning), with an average weight of 371 g, to 63 d of age (6 wk) split randomly into 2 groups of 90 with similar liveweights. Two rabbits were housed per commercial cage and rabbits and their faeces inspected every day. Mortality was registered when noticed. Feed intake per cage was measured twice per week and rabbits were weighed weekly.

Trial 2 involved a total of 30 rabbits, from 23 (weaning) with an average weight of 451 g, to 37 d of age (2 wk after weaning). Rabbits were divided into 2 groups of similar liveweight, and housed individually in digestibility cages since weaning day. During the last 6 d of the second week, faeces were collected for apparent faecal digestibility measurement and frozen and stored at –20°C. At 37 d of age all rabbits were slaughtered and the pH of the gastric and caecal contents was measured. Approximately 5-6 g of caecal contents, resuspended in 4 mL of a 0.03 M H_3PO_4 solution, were stored in bottles for later volatile fatty acids (VFA) analyses. Another 4 g of fresh caecal contents were bottled under a stream of CO_2, together with 10 mL of phosphate buffer, for fermentative activity measurements. Bottles were stored frozen at –80°C. In 10 rabbits from each treatment, 3 sections were taken from the small intestine: the first originated from the proximal region (40 cm from the pylorus), the second from the central region (halfway in the intestine), and the third from the distal region (40 cm from the ileocaecal valve). Tissues samples were fixed in 10% neutral buffered formalin and processed for mounting in paraffin embedding for microscopic examination of intestinal villi and crypts.

Diets

A control diet (CTR diet) was prepared according to the recommendations of de Blas and Mateos (1998). Coated sodium butyrate (n-butyric acid sodium salt 30%, in a fatty acid matrix) was added to this diet as replacement of an identical quantity of wheat (SB diet). The amount of coated sodium butyrate was 5 g/kg in the post-weaning phase (the first 2 wk of trial 1 and the whole period in trial 2) and 3 g/kg afterwards (the last 4 wk of trial 1) (Table 1). Diets and water were always available *ad libitum.*

Table 1: Ingredients (%) and chemical composition (% DM) of experimental diets [control, CTR; supplemented with Na-butyrate at 5 (SB 0.5) and 3 g/kg (SB 0.3)].

	CTR	SB 0.5	SB 0.3
Ingredients			
Wheat	25.7	25.2	25.4
Oat	15.0	15.0	15.0
Soya bean meal	20.0	20.0	20.0
Alfalfa	35.0	35.0	35.0
Vegetable oil	3.0	3.0	3.0
Vitamin/mineral premix[1]	0.2	0.2	0.2
Calcium carbonate	0.5	0.5	0.5
Calcium biphosphate	0.6	0.6	0.6
Na-Butyrate	0	0.5	0.3
Chemical composition			
Dry matter (DM)	90.5	90.2	90.5
Ash	6.7	6.9	6.6
Organic matter	93.3	93.1	93.4
Crude protein	16.8	17.2	17.0
Neutral detergent fibre	36.5	34.4	35.5
Acid detergent fibre	20.4	18.8	19.6
Gross energy (kcal/kg DM)	4590	4625	4612
Buffering capacity[2]	25.4	25.7	24.1

[1] Mineral and vitamin mixture (per kg diet): vitamin A, 4800 IU; vitamin D, 480 IU; vitamin E, 10 mg; vitamin B1, 0.8 mg; vitamin B2, 2 mg; nicotinic acid, 12 mg; pantothenic acid, 6 mg; vitamin B12, 0.006 mg; pyridoxine, 0.8 mg; biotin, 0.016 mg; choline, 0.3 g; Fe, 28 mg; Cu, 2.4 mg; Mn, 7.2 mg; Zn, 24 mg; I, 0.2 mg; Co, 0.04 mg; Se, 0.04 mg.

[2] Amount (mL) of 0.1 *N* HCl to lower 10 g of the diet to pH 4.0.

Chemical analyses

Feeds, and faeces after thawing, were dried at 70°C for 48 h then milled through a 1 mm screen. Dry matter (DM) was determined by oven drying at 104°C for 24 h and ash content by burning overnight at 550°C. Crude protein (CP) was measured by the Kjeldahl method (976.95; AOAC, 1995) and neutral detergent fibre (NDF, without sodium sulphite), acid detergent fibre (ADF) and acid detergent lignin (ADL), performed sequentially using the crucibles system, were expressed without residual ash; for feed samples, a thermo-stable α-amylase (Van Soest *et al.,* 1991) was used. Hemicellulose and cellulose were calculated as the differences NDF-ADF and ADF-ADL, respectively. The gross energy content of feeds and faeces was measured in a bomb calorimeter (Parr model 1261). The apparent digestibility of DM, organic matter (OM), CP, NDF, ADF, hemicellulose, cellulose and energy was calculated.

The pH values of gastric and caecal contents were measured with a glass electrode pH meter (Metrohm 744 meter). VFA levels in caecal contents were measured by gas chromatography, following the procedure of Jouany (1982). Bacterial fibre degrading activities –cellulolytic, xylanolytic and pectinolytic– in the caecal contents were measured as described in Falcão-e-Cunha *et al.* (2004). Microscopic examination and measurement of villi heights and crypt depths were performed in 7 µm thick tissue sections, stained with haematoxylin-eosin from 20 rabbits of trial 2 (10 from each treatment). An Olympus BX 511 microscope equipped with 4× and 10× lenses was used. Images were digitally captured with an Olympus DP 11 camera and the Olympus DP Soft software was used to measure the height and width of the villi and the depth of the crypts. Ten intact and correctly oriented villi and crypts were selected per intestinal region and animal.

The buffering capacity of the diets was measured according to Bünzen (2006). Briefly, 10 g of feed were added to 90 g of distilled water, the mixture was homogenised, then the pH was measured with a pH meter (Metrohm 744 meter) and the quantity of HCl 0.1 *N* needed to bring it down to pH 4 recorded.

Statistical analyses

Data concerning growing performance, apparent faecal apparent digestibility, fermentative activity parameters and intestinal morphology were subject to analysis of variance of one factor (the diet) by application of SAS System software (SAS, 1991). In trial 1, the experimental unit was the cage.

The mortality rate was compared by analysis of frequency using the chi-square test to evaluate the significance level of the difference (SAS, 1991).

RESULTS

Table 2 shows the growth performance of rabbits in trial 1. During the first 2 wk after weaning, SB rabbits (sodium butyrate included in the diet at 5 g/kg) grew 8% less than CTR rabbits group (*P*=0.002), but had a better feed conversion ratio (1.58 *vs.* 1.61; *P*=0.036). However, over the last 4 wk, rabbits fed with sodium butyrate diet (now at 3 g/kg) and control rabbits grew identically (45.2 *vs.* 44.2 g/d). Sodium butyrate rabbits again showed a better feed conversion ratio (*P*=0.008).

Looking at the whole 6 wk period of the trial, rabbits that received the diet containing sodium butyrate consumed less (98.8 *vs.* 104.1 g/d; *P*=0.017), but grew the same (42.7 *vs.* 42.9 g/d) and thus had a better FCR (2.35 *vs.* 2.43; *P*=0.005) than their control counterparts. Seven rabbits from the CTR group and 10 rabbits from the SB group died during trial 1 (*P*=0.58). Of these deaths, only 1 from the CTR group and 2 from the BS groups occurred in the first 2 wk after weaning (*P*=0.56). No rabbits died in trial 2.

Table 2: Effect of sodium butyrate on zootechnical performance of growing-fattening rabbits from 23 to 65 d of age (trial 1).

	Diets[1]			
	CTR	SB	RMSE[2]	*P*-value
No.	90	90		
Live weight (g)				
At 23 d of age	371.0	371.2	2.7	0.990
At 35 d of age	933.2	887.2	67.4	0.022
At 63 d of age	2077.9	2110.7	154.3	0.328
1st period (2 wk after weaning)				
Daily feed intake (g)	63.9	57.1	8.5	<0.001
Daily weight gain (g)	40.1	36.9	4.8	0.002
Feed conversion ratio	1.61	1.58	0.07	0.036
2nd period (37-63 d age)				
Daily feed intake (g)	116.6	113.5	13.7	0.298
Daily weight gain (g)	44.2	45.2	4.0	0.270
Feed conversion ratio	2.70	2.57	0.14	0.008
Whole period (23-63 d age)				
Daily feed intake (g)	104.1	98.8	9.9	0.017
Daily weight gain (g)	42.9	42.7	4.0	0.880
Feed conversion ratio	2.43	2.35	0.13	0.005

[1] SB diet identical to CTR diet, except in the diet SB 5 g/kg coated sodium butyrate replaced an identical quantity of wheat of the diet CTR during the first 2 wk and 3 g/kg afterwards. [2]RMSE: root mean square error.

Table 3: Effect of sodium butyrate on apparent faecal digestibility (trial 2).

	Diets[1]			
	CTR	SB	RMSE[2]	*P*-value
No.	15	15		
Performance during digestibility trial:				
Live weight (g): at 23 d	451.3	450.5	19.4	0.979
at 37 d	1070	1040	98	0.420
Daily feed intake (g DM/d)	65.8	58.0	10.6	0.059
Coefficients of total tract apparent digestibility (%)				
Dry matter (DM)	66.3	66.7	1.6	0.451
Organic matter	66.2	66.6	1.7	0.469
Crude protein	85.3	85.0	1.9	0.728
Neutral detergent fibre (NDF)	24.7	25.3	3.6	0.631
Acid detergent fibre (ADF)	13.3	14.2	4.3	0.567
Hemicelluloses NDF-ADF	38.8	38.9	3.4	0.939
Cellulose ADF-ADL	13.6	15.7	4.4	0.218
Gross energy	67.0	67.1	1.8	0.826

[1] SB diet identical to CTR diet, except in the diet SB 5 g/kg coated sodium butyrate replaced an identical quantity of wheat of the diet CTR. [2] RMSE: root mean square error. ADL: acid detergent lignin.

Sodium butyrate supplementation had no significant effect upon the apparent faecal digestibility of any of the analytical fractions that we considered (Table 3). Dry matter and OM digestibilities were similar (66 and 67%, respectively) and energy digestibility was around 67.0% in both groups. Crude protein digestibility was high, at 85%, and similar in CTR and BS treatments.

Table 4 shows the intestinal morphology data for rabbits in trial 2, slaughtered at 37 d of age. Irrespective of the region considered (proximal, medial or distal) there were no significant

Table 4: Effect of sodium butyrate on intestinal morphology of rabbits slaughtered at 37 d of age (trial 2).

	Diets[1]			
	CTR	SB	RMSE[2]	*P*-value
No.	10	10		
Small intestine-proximal[3]				
Villus height (µm)	486.2	529.2	128.2	0.463
Villus width (µm)	112.3	114.2	14.5	0.774
Crypt depth (µm)	87.2	113.1	12.3	<0.001
Villus height/crypt depth	5.5	4.7	1.2	0.139
Small intestine-mid[3]				
Villus height (µm)	417.7	364.8	101.6	0.260
Villus width (µm)	121.5	110.7	16.6	0.151
Crypt depth (µm)	91.6	130.1	13.3	<0.001
Villus height/crypt depth	4.7	2.7	0.9	<0.001
Small intestine-distal[3]				
Villus height (µm)	357.3	341.6	75.3	0.647
Villus width (µm)	109.5	101.9	26.2	0.526
Crypt depth (µm)	87.0	112.8	13.8	<0.001
Villus height/crypt depth	4.1	3.1	1.0	0.044

[1] SB diet identical to CTR diet, except in the diet SB 5 g/kg coated sodium butyrate replaced an identical quantity of wheat of the diet CTR. [2] RMSE: root mean square error. [3] Small intestine-proximal, from 40 cm from the pylorus; small intestine-mid, from the halfway in the intestine; small intestine-distal, from 40 cm from the ileocaecal valve.

Table 5: Effect of sodium butyrate on caecal fermentative activity in rabbits slaughtered at 37 d of age (trial 2).

	Diet[1]			
	CTR	SB	RMSE[2]	*P*-value
No.	15	15		
pH of content				
Stomach pH	2.28	2.04	0.04	0.338
Caecal pH	5.76	5.72	0.02	0.522
Dry matter of caecum content (%)	24.2	23.8	1.21	0.416
Enzymatic activity (mg sugar/h g DM caecum content)				
Pectinase	64.4	75.9	15.0	0.057
Xylanase	47.6	44.5	24.7	0.745
Cellulase	35.8	28.6	11.2	0.109
Total VFA (mmol/L)	83.9	96.9	32.6	0.313
Acetic acid (mmol/L)	64.4	75.2	25.8	0.287
Propionic acid (mmol/L)	6.9	8.1	2.2	0.154
Butyric acid (mmol/L)	12.7	13.5	6.1	0.715
VFA molar proportions				
Acetic acid (mol/100 mol)	76.3	77.5	3.2	0.348
Propionic acid (mol/100 mol)	8.6	8.8	2.1	0.799
Butyric acid (mol/100 mol)	15.1	13.7	3.3	0.288

[1] SB diet identical to CTR diet, except in the diet SB 5 g/kg coated sodium butyrate replaced an identical quantity of wheat of the diet CTR. [2]RMSE: root mean square error. VFA: volatile fatty acids. DM: dry matter.

differences in villus height and width between treatments. Crypts were always deeper, however, in the 3 regions of the rabbits fed with sodium butyrate diet ($P<0.001$). In consequence, the ratio villus height/crypt depth was always lower in the SB group, the difference being more significant in the medial (4.7 *vs.* 2.7; $P<0.001$) than in the distal (4.1 *vs.* 3.1; $P<0.044$) or proximal (5.5 *vs.* 4.7; NS) regions.

Gastric and caecal pH values (Table 5) were not different between CTR and SB treatments ($P>0.30$). Caecal fermentative activity, measured as total fatty acid concentration, was not different between treatments (Table 5). Pectinase activity was 18% higher in the SB group compared to CTR ($P=0.057$).

DISCUSSION

The inclusion of organic acids in the diets of monogastric species is usually accompanied by alterations in the microbial population of the upper gut (Tung and Pettigrew, 2006) and/or digestive enzyme activities (Guilloteau *et al.*, 2009). But the effects of organic acids vary with different factors, such as the chemical nature of the acid (or its salt), its rate of inclusion, the composition of the diet and the kind of animal stress (whatever its definition and measurement). Presumably, this complexity, together with gaps in our knowledge, is the reason that positive results are often obtained which are not statistically significant (Partanen and Mroz, 1999).

Although a negative effect on daily weight gain was recorded in the first weeks after weaning, our results bring out a positive effect of coated sodium butyrate on feed efficiency, either during the first 2 wk after weaning, or in the whole growing-fattening period, probably related to a potential higher ileal digestibility due to the lower intake, as there is no effect on faecal digestibility. We have no knowledge of previous studies performed with coated sodium butyrate as additive in rabbits' post weaning period. The few studies that include this organic acid or its salt as feed additive, such as those of Carraro *et al.* (2005) and Hullar *et al.* (1996), did not study this phase of rabbit life. Considering the entire period, Carraro *et al.* (2005) observed that diets supplemented with butyrate led to a greater increase in average daily weight gain and feed intake in comparison with the control diet. Hence, feed efficiency remained unaffected in their experiments. The inclusion rates used by these authors were 0.5, 1.0, and 2.0 g/kg. On the other hand, Hullar *et al.* (1996) obtained improvements in rabbits' performance after adding sodium butyrate to the diet for 4 wk. Dissenting results have also appeared with the addition of other acids: fumaric acid led to a improvement in the performance parameters of growing and fattening rabbits although not statistically significant (Scapinello *et al.,* 2001; Michelan *et al.,* 2002) and formic acid together with lactic acid improved the feed efficiency and average daily weight gain in 30-55 and 56-84 d old rabbits (Cesari *et al.,* 2008).

The improvement of feed efficiency recorded in our experiment did not result from an increase in the faecal digestibility of nutrients. In fact, the coefficients of apparent total tract digestibility of DM, OM, energy and CP remained unaffected by Na-butyrate addition. Previously, Hullar *et al.* (1996) showed an improvement of coefficients of apparent total tract digestibility in all analytical fractions evaluated except for CP. This study, however, was conducted in older rabbits (aged 10-12 wk). Carraro *et al.* (2005) observed a decrease in DM digestibility with butyrate addition, but their experimental diets had a lower digestibility than the diets fed in the present study. In other studies, no effect of dietary supplementation with acids was observed on digestibility coefficients (Michelan *et al.,* 2002; Abecia *et al.,* 2005). The characteristics and complexity of the diet and the nature of the raw materials may be influencing the magnitude of the effect achieved with the addition of organic acids. It is also possible that the dietary buffering capacity affected the results. In this work, diets had similar buffering capacities. The organic acid used in our diets was in the form of salt and coated, and this may partially be responsible for the lack of influence on the pH or the buffering capacity.

The original interest for the inclusion of organic acids in the weaning diets was the lowering of stomach content pH and the subsequent activation of proteolytic zymogens, which determines the digestibility of the nitrogen fraction (Partanen and Mroz, 1999). This was not observed in our study. No difference in the pH of the stomach contents and no effect on apparent protein digestibility were found. Some specificities of the digestive system of the rabbit (such as the low motility of the stomach and the long retention time of feed in this organ (3-4 h; Gidenne and Poncet, 1985) as well as the practice of caecotrophy, may sufficiently differentiate them from other animal species, even in their post-weaning period.

Again, the coating of the BS and the buffering capacity of the diet may also account for the absence of results. Some studies show that the dietary buffering capacity plays an important role on nutrient digestibility when acids are added to the diet (Blank *et al.*, 1999).

In this work, no effect of Na-butyrate was observed on villus height and width. However, the crypt depth increased in all regions of the small intestine, which indicates that coated BS reached the distal small intestine. The lack of significant effects on villus height and width indicates that there were no significant changes in the absorption area. An increased crypt depth has been associated with an increased production of crypt-cells (Pluske *et al.,* 1997) and/or an increased mucosa secretion (Kotunia *et al.*, 2004). These differences correspond to a larger energy expenditure. It might be related to the slight negative effect in weight gain during the first 2 wk after weaning in rabbits fed diets with Na-butyrate, probably because they were compensated by a higher feed efficiency.

The few studies on the effect of Na-butyrate on the morphology of rabbit small intestine were conducted in older animals. Presumably, this justifies the non-occurrence of remarkable effects with addition of BS (Carraro *et al.*, 2005).

Our results on the caecal fermentative activity show a trend to greater pectinase activity in rabbits given the SB diet compared to CTR rabbits, whereas total VFA was similar. These results might suggest that rabbits given the SB diet have no gastrointestinal disorder (Gidenne *et al.,* 2007), although no differences in mortality were reported between treatments. It is therefore possible that butyrate controlling the microbial population in the proximal part of the digestive tract consequently allows the development of beneficial bacteria in the distal part. In this sense, Hullar *et al.* (1996) observed a more desirable gut flora balance in 10 wk-old rabbits with the addition of 0.15% sodium butyrate.

CONCLUSIONS

Coated Na-butyrate improved feed conversion ratio for the entire length of the growing-fattening period by reducing feed intake, although in the post-weaning period it also reduced daily weight gain. Dietary supplementation with Na-butyrate affected the morphology of the intestinal mucosa leading to deeper crypts. This result, however, was not related to a better total tract apparent digestive utilisation of dietary nutrients.

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