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EFFECTS OF A SHORT-TERM FEED RESTRICTION ON GROWTH PERFORMANCE, BLOOD METABOLITES AND HEPATIC IGF-1 LEVELS IN GROWING RABBITS

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Abstract: A total of 144 weaned hybrid HYLA rabbits (40-day-old) were randomly divided into 4 groups, to investigate the effects of the intensity of one week's feed restriction on short- and medium-term growth performance, blood metabolites and hepatic IGF-1 in growing rabbits. Restricted groups were fed with 30% (Group L30), 50% (Group L50) 70% (Group L70) of *ad libitum* feeding for 1 wk and then fed *ad libitum* until the end of the experiment (75 d of age). The control group (Group AL) was fed *ad libitum* throughout the experiment. Total feed intake (–15.8%) and feed conversion ratio (–13.2%) were lower in the L50 than in the AL group ($P<0.05$), but no difference was found between the L30, L70 and AL groups ($P>0.05$) for these parameters. Total weight gain did not significantly differ among the 4 experimental groups (38.5 g/d; $P>0.05$). At the end of the feed restriction period, the total serum protein level ($P=0.01$) was higher in restricted rabbits than AL rabbits ($P<0.01$), while the hepatic IGF-1 level was lower in L30 and L50 groups than in the 2 other groups ($P<0.001$). However, no difference remained between groups at the end of the experiment. In contrast, calcium, triglycerides, alkaline phosphatase, urea nitrogen and total cholesterol levels were similar between groups ($P>0.05$) throughout the experiment. In conclusion, a short-term feed restriction improves feed conversion ratio in a lasting way, transiently alters serum protein and IFG-1 levels and leads to compensatory growth in growing rabbits.

Key Words: feed restriction, growth performance, blood metabolite, liver hormone, growing rabbits.

INTRODUCTION

Digestive disorders commonly occur in growing rabbits and cause most of the morbidity and mortality in commercial rabbit farms (Licois, 2004; Rosell *et al.,* 2010). The incidence of digestive disorders is reduced by feed restriction (Gidenne *et al.,* 2009b). When returning to *ad libitum* feeding, previously restricted animals can experience compensatory growth (Dalle Zotte *et al.,* 2005; De Oliveira *et al.,* 2012), increased nutrient digestibility (Di Meo *et al.,* 2007; Abdel-Wareth *et al.,* 2015) and increased feed conversion rate (Tůmová *et al.,* 2002). The level of compensatory growth depends on the duration, level and pattern of feed restriction (Di Meo *et al.,* 2007; Gidenne *et al.,* 2009b; Romero *et al.,* 2010; Abdel-Wareth *et al.,* 2015). Short-term feed restriction also alters the nutritional status of organisms and thus affects hormone secretion and blood metabolites concentrations (Renaville *et al.,* 2000; Cabaraux *et al.,* 2003; Guyton and Hall, 2006).

In animals, the growth hormone-insulin-like growth factor (GH-IGF) axis regulates growth. Circulating IGF-1 mainly originates from the liver (Sjogren *et al.,* 1999; Radcliff *et al.,* 2003). However, the relationship between liver IGF-1, blood biochemical parameters and feed restriction in growing rabbits has rarely been described. The aim of this study was to investigate the effects of the intensity of one week's feed restriction on short- and medium-term growth performance, blood metabolites and liver IGF-1 concentration in growing rabbits.

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MATERIALS AND METHODS

The experiment was carried out in accordance with the Animal Care and Use Guidelines of the College of Animal Science and Technology, Southwest University, Chongqing, China.

Animals, feeding and experimental conditions

A total of 144 weaned hybrid HYLA rabbits (35-day-old) were selected for this experiment. After 5 d of dietary adaptation (*ad libitum*), the rabbits were randomly divided into 4 groups at 40 d of age and each group contained 36 rabbits. The control rabbits were fed *ad libitum* throughout the experiment (AL group). Restricted groups were fed with 30% (L30 group), 50% (L50 group) and 70% (L70 group) of *ad libitum* feeding for 1 wk and then fed *ad libitum* until 75 d of age. The amount of feed administered daily during the restriction period based on preliminary curve of *ad libitum* feeding and was adjusted slightly by the actual feed intake measured in AL group. The ingredients and chemical composition of the experimental diet, offered in the form of pellets, was shown in Table 1. The rabbits were fed manually at 7:00 and 18:30 during the restriction period and the amount of feed administered was half the daily meal for each feeding. From the second week to the end of the experiment, the feed was administered at 7:00. Leftovers were removed and measured prior to the next administration during restricted period and every week during the *ad libitum* feeding period. The cages were composed of galvanised wire net and were cleaned and thoroughly disinfected by flame and disinfectants before putting the experimental rabbits. Each cage contained 2 rabbits (or one rabbit for the rest one) provided with a 0.1 m^2 space floor per rabbit. Animals were raised under natural lighting and automatic ventilation. Water was available *ad libitum* via nipple drinkers.

Experimental Measurements

Live weight was recorded weekly from 40 to 75 d of age. After the experiment was completed, feed intake, weight gain and feed conversion ratio were calculated for the restriction period (40-47 d of age), the *ad libitum* feeding period (47-75 d of age) and the total experimental period (40-75 d of age).

At 47 (the end of feed restriction) and 75 (the end of experiment) days of age, we choose 8 rabbits per group with weights close to the average weight in each group.

Blood (10 mL) was collected in 10 mL centrifuge tubes via cardiac puncture on non-fasting rabbits. After 1 h, blood was centrifuged in 4°C for 15 min at 3000 r/min to separate the serum and stored at –80°C in a refrigerator until subsequent analyses. Concentrations of alkaline phosphatase (ALP, 4-Nitrophenyl phosphate disodium salt), triglyceride (TG, colorimetric method), total cholesterol (TC, colorimetric method), total protein (TP, biuret colorimetric method), blood urea nitrogen (BUN, urease-glutamate dehydrogenase method) and calcium (Ca, Arsenazo III method)

Table 1: Ingredients and chemical composition of the experimental diet.

Ingredient (%)		Nutrient level (calculated)	
Maize	17.90	Digestible energy (MJ/kg)	10.46
Soybean meal	10.00	Crude protein (%)	15.08
Wheat bran	20.50	Crude fibre (%)	13.15
Alfalfa meal	21.01	Calcium (%)	0.63
Rice bran	6.00	Phosphorus (%)	0.45
Corn germ meal	15.00	Lysine (%)	0.70
Rice hulls	7.60	Methionine (%)	0.60
Dicalcium Phosphate	1.20	Neutral detergent fibre (%)	32.29
DL-methionine	0.09	Acid detergent fibre (%)	16.56
NaCl	0.50	Starch (%)	20.08
Premix[1]	0.20		

[1]Provided per kilogram of diet: 10000 IU of vitamin A; 1000 IU of vitamin D3; 30 mg of Vitamin E; 1 mg of vitamin K3; 1 mg of vitamin B1; 3.5 mg of Vitamin B2; 5 mg of Cu; 30 mg of Fe; 1 mg of I; 0.08 mg of Se; 30 mg of Zn; 15 mg of Mn.

were analysed in serum using commercial kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) and an automatic biochemistry analyser (Beckman DXC800, USA) in accordance with the manufacturer's instructions.

After blood collection, the rabbits were euthanised between 9:00-12:00 am using cervical dislocation. The livers were extracted, immediately placed in liquid nitrogen and transferred to a freezer set at –80°C until subsequent analyses. A 0.5 g thawed liver was homogenised at a ratio of 1:9 (g of liver/mL of buffer). The buffer consisted of PBS with pH of 7.2-7.4. Insulin-like growth factor-1 (IGF-1) levels in the liver were assayed in duplicate using ELISA kits (Shanghai Resun Biological Technology Co., Ltd., China) and following the manufacturer's instructions. Briefly, (1) diluent (40 µL) was added to samples (10 µL) in wells; (2) HRP-conjugate reagent (goat anti-rabbit IGF-1, 100 µL) was added before incubation for 1 h at 37°C; (3) each well was aspirated and washed using a wash solution (400 µL) and the process was repeated 4 times, resulting in a total of 5 washes; (4) chromogen solution A (0.5 ug/mL Carbamide peroxide, 50 µL) and chromogen solution B (0.4 ug/mL 3,3',5,5'-Tetramethylbenzidine, 50 µL) were added and the solution was mixed gently and incubated for 15 min at 37°C (free from light); (5) reaction was stopped using a stop solution (2 mol/L H_2SO_4, 50 µL). Optical density at 450 nm was read after 15 min. The measuring range is 2.5-150 ng/mL.

Data Processing

The 4 treatments were submitted to a one-way ANOVA and Tukey's range test in SPSS 19.0. Rabbits were blocked by body weight (BW). The statistical model used block as the random effect and feed restriction levels as fixed effect. Feed conversion from the 40th day to the 47th day of the experimental period was compared via Brown-Forsythe test of variances by considering the lack of homoscedasticity. An orthogonal contrast (L30+L50+L70 groups *vs.* AL group) was performed to compare the total feed intake and feed conversion ratio from 40 to 75 d of age and serum TC of rabbits at 47 d of age. Differences were considered significant at $P<0.05$.

RESULTS

Growth performance and health

Mortality during the experiment was similar in the 4 groups (8.3%; Table 2; not significant). The real feed restriction levels used in this study were 31% for L30, 52% for L50 and 70% for L70. Feed intake did not significantly vary

Table 2: Effect of feed restriction on growth performance of rabbits.

	days	L30	L50	L70	AL	SEM	*P*-value
Live weight (g)	40	833	839	824	831	11	0.928
	47	851^{a}	925^{ab}	990^{b}	1120^{c}	15	<0.001
	75	2150	2181	2187	2217	30	0.771
feed intake (g/rabbit/d)	40-47	26.3	44.7	60.2	85.4	2.79	NC
	47-75	136.8	127.4	129.8	143.1	4.87	0.150
	40-75	114.7^{ab}	110.9^{a}	115.9^{ab}	131.6^{b}	4.15	0.020
Live weight gain (g/rabbit/d)	40-47	2.6^{a}	12.3^{a}	23.8^{b}	41.3^{c}	2.38	<0.001
	47-75	46.4^{b}	44.8^{b}	42.7^{ab}	39.2^{a}	1.19	0.006
	40-75	37.3	38.3	38.9	39.6	1.22	0.701
Feed conversion ratio	40-47	46.06	3.82	2.56	2.10	16.43	0.212
	47-75	2.95^{a}	2.84^{a}	3.05^{a}	3.65^{b}	0.09	<0.001
	40-75	3.05^{ab}	2.89^{a}	2.98^{ab}	3.33^{b}	0.08	0.016
Mortality (% and n)	40-47	0 (0/36)	0 (0/36)	2.8 (1/36)	2.8 (1/36)	-	0.567
	47-75	7.1 (2/28)	10.7 (3/28)	7.1 (2/27)	11.1 (3/27)	-	0.931
	40-75	5.6 (2/36)	8.3 (3/36)	8.6 (3/36)	11.1 (4/36)	-	0.867

L30, L50, L70 group were fed at 30, 50 and 70% of normal daily feed intake for 1 wk and then fed *ad libitum* until the conclusion of the experiment; AL group was fed *ad libitum* during the experiment. SEM: Standard error of the means.
Means within a row with no common superscript differ at $P<0.05$.
NC: Not computable as the variability of the feed intake for the restricted groups is null.

(P>0.05) from days 47 to 75 (Table 2). For the whole experimental period, i.e. 40 to 75 d of age, the feed intake was significantly lower in the L50 group than in the AL group (P<0.05). Additionally, a contrast test showed that the total feed intake was lower in the 3 restricted groups than in the AL group (113.8 *vs.* 131.6 in L30+L50+L70 groups *vs.* AL group, respectively; P<0.05). The weight gain from days 40 to 47 was lower in L30, L50 and L70 groups than in the AL group (P<0.001). From days 47 to 75, the weight gain was 18.4% and 14.4% higher in the L30 and L50 groups than in the AL group, respectively (P<0.05), while no difference was found between 70% and AL groups. From days 40 to 75, weight gain was similar between the four groups (P=0.701). Live weight at 47 d of age was lower for rabbit having a restricted feeding but at 75 d of age, after 4 wk of *ad libitum* feeding live weight of rabbit was similar in the four groups. The feed conversion ratio of rabbit was similar between the 4 groups mainly due to a high variability in the L30 group. The feed conversion ratio from 47 to 75 d was lower in the 3 restricted groups than in the AL group (P<0.001). For the whole experimental period, the feed conversion ratio was significantly lower in the L50 group than in the AL group (P<0.05). Additionally, a contrast test showed that the feed conversion ratio between 40 and 75 d of age was better in the three restricted groups than in the AL group (2.97 *vs.* 3.33 in L30+L50+L70 groups *vs.* AL group, respectively; P<0.05).

Blood metabolites

On day 47, different feed restriction levels did not significantly influence the levels of ALP, Ca, BUN, TC and TG in the blood serum (P>0.05; Table 3) even if difference tended to be significant for BUN and TC (P<0.1). TP was higher in the restricted groups than in the AL group (P<0.05). A contrast test (L30+L50+L70 groups *vs.* AL) showed that TC level at 47 d was higher in restricted group than in higher group (P<0.05). At the end of the experiment (day 75), the ALP, TP, BUN, Ca, TC and TG blood levels were similar in the four groups (P>0.05).

Liver hormone

On day 47, hepatic IGF-1 level was the lowest in rabbits of the L30 group and the highest in rabbits of the L70 and AL group, the rabbits of the L50 group being intermediate (P<0.05, Table 3). However, there was no difference between the 70% restricted group and AL group (P >0.05). On day 75, the hepatic IGF-1 level was similar in the 4 groups (P>0.05).

DISCUSSION

Growth performance

On days 40-47, the loss of weight gain was not proportional to the degree of feed restriction. Compared to AL groups, reduction in weight gain in the L30, L50 and L70 groups (70%, 50%, 30% feed intake reduction) was approximately 94, 70 and 43%, respectively. In the same way, Díaz Arca *et al.* (1999) fed rabbits with 10, 40 and 60% of feed *ad libitum* for 15 d, observing reduction in weight gain of 163, 89 and 63% compared to rabbits on *ad libitum* feeding and measuring a negative energy balance (NEB) in the 10% and 40% groups. Severe NEB in lactating dairy cows significantly changed the gene transcription of hepatic IGF-I and some IGF-related members (Fenwick *et al.,* 2008). Romero *et al.* (2010) fed rabbits with 80% of AL feeding for 14 d, observed a loss of weight gain of 26%. These results were contrary to the findings of Boisot *et al.* (2003), Gidenne *et al.* (2009 b, c) and Martignon *et al.* 2010), which showed that weight gain reduction was lower than feed intake reduction in the post-weaning restriction period. This difference could be explained by the restriction duration in these experiments (Boisot et, 2003; Gidenne *et al.,* 2009b,c; Martignon *et al.,* 2010), which was longer (more than 21 d) than here. Martignon *et al.* (2010) observed a growth reduction of 24% during the whole restriction duration (days 28-53), while the feed intake reduction was 29%.

Weight gain in the L30 group on days 40-47 was very low (2.6 g/d). Some rabbits presented negative body weight gain and values fluctuated around zero. As a result, the feed conversion ratio was highly variable between rabbits in this group. When restricted rabbits were fed *ad libitum* again from 47 to 75 d of age, their feed intake was similar to that of non-restricted rabbits. This finding agrees with previous results (Taranto *et al.,* 2003; Gidenne *et al.,* 2009b, c; Di Meo et al, 2007) in rabbits. Gidenne and Feugier (2009) reported that restricted rabbits are unable to increase their

Table 3: Effect of feed restriction on blood metabolites and liver IGF-1 of rabbits (n=8/group).

	L30	L50	L70	AL	SEM	*P*-value
Observations at the end of feed restriction (rabbits age: 47 d old)						
Serum						
ALP (U/L)	208	198	213	205	13	0.856
TP (g/L)	46[b]	48[b]	52[b]	40[a]	2	0.007
BUN (mmol/L)	4.25	5.98	4.72	4.47	0.39	0.051
Ca (mmol/L)	3.61	3.47	3.71	3.50	0.07	0.144
TC (mmol/L)[1]	2.53	3.08	2.80	1.74	0.33	0.070
TG (mmol/L)	1.13	0.93	1.11	1.54	0.23	0.306
Liver						
IGF-1 (ng/mg protein)	0.61[a]	1.04[b]	1.32[c]	1.45[c]	0.05	<0.001
Observations at the end of the experiment (rabbits age: 75 d old)						
Serum						
ALP (U/L)	182	192	173	218	13	0.099
TP (g/L)	50	52	50	49	2	0.695
BUN (mmol/L)	7.14	7.73	7.81	7.49	0.72	0.879
Ca (mmol/L)	3.83	3.90	3.80	3.74	0.08	0.457
TC (mmol/L)	1.95	3.11	2.05	2.06	0.52	0.302
TG (mmol/L)	1.25	1.82	1.26	1.53	0.20	0.141
Liver						
IGF-1 (ng/mg protein)	1.38	1.31	1.28	1.26	0.06	0.507

L30, L50, L70 groups were fed at 30, 50 and 70% of normal daily feed intake for one week and then fed *ad libitum* until the end of the experiment; AL group was fed *ad libitum* throughout the experiment. SEM, Standard error of the means;
Means within a row with a common superscript differ at $P<0.05$. ALP: alkaline phosphatase; TP: total protein; BUN: blood urea nitrogen; Ca: calcium; TC: total cholesterol; TG: triglyceride; IGF-1: insulin-like growth factor-1.
[1]difference was found ($P<0.05$) by an orthogonal contrast ([L30+L50+L70] /3 *vs.* AL).

feed intake from 80 to 100% within 10 d. In the present study, the restricted rabbits were also unable to increase their feed intake to that observed in *ad libitum* group. This result was possibly related to the feeding habit of the rabbits. Rabbits eat 30-40 meals a day and their gastric volume accounts for about 30% of their entire digestive tract (Gidenne and Feugier, 2009).

When rabbits are allowed to return to their normal feeding habits after a feed restriction period, they can grow at a faster than optimal rate (Hector and Nakagawa, 2012; Hornick *et al.,* 2000). In this experiment, weight gains in L30 group were the highest during the re-feeding period, which showed that severe feed deprivation led to an increased growth rate after *ad libitum* feeding. In the present study, the final body weight in restricted groups was very close to that of rabbits in the AL group after 4 wk of re-feeding. Previous studies led to contradictory results on this point, depending on restriction duration and intensity as well as *ad libitum* feeding duration (Gidenne *et al.,* 2009a,b,c; Gidenne and Feugier, 2009; Boisot *et al.,* 2003). Effect of feed restriction on growth is more easily compensated if the restriction duration is short or mild.

Blood metabolites and liver hormone

Nir *et al.* (1996) reviewed the metabolic and hormonal changes in chickens as a consequence of feed restriction. In the present study, at the end of the feed restriction period, the TC levels in the feed restricted groups were higher than in the *ad libitum* group, in agreement with Ebeid *et al.* (2012). Previous results in cattle suggested that increased concentrations are caused by insufficient energy intake (Bruss, 1997) or adaptation of animals to an insufficiency in quality of grazing vegetation (Ndlovu *et al.,* 2009). By comparison, lower serum cholesterol concentrations are associated with a higher nutritional status in dairy cows (Kronfeld *et al.,* 1982). During fasting, the rate of lipolysis is higher than lipogenesis, which results in the net loss of fat cell triglycerides (Kersten, 2001). However, serum TG levels were not significantly different at the end of feed restriction in the present study. One possible reason lies in the

short duration of feed restriction. Rajman *et al.* (2006) observed in broiler chickens that TG levels did not differ in the early phases of severe or moderate feed restriction (from days 16 to 30 and 44), but significantly reduced on days 58 and 86. Similarly, Van Harten and Cardoso (2010) observed that a 30-day feed restriction in rabbits lowered TG.

The liver regulates the partitioning of nutrients. Blood IGF-1 is mainly derived from the liver (Sjogren *et al.,* 1999) and is involved in cell growth and metabolism. Our study revealed that feed restriction reduced the IGF-1 levels in the liver. Reduced IGF-1 may lead to a decrease in muscle production (van Harten and Cardoso 2010), eventually leading to weight diminution. But these levels returned to normal concentrations after the *ad libitum* feeding period. This finding is consistent with the changes in blood IGF-1 in previous studies (Renaville *et al.,* 2000; Fenwick *et al.,* 2008; van Harten and Cardoso 2010), which demonstrated that IGF-1 concentrations are markedly reduced by limited nutrition and are gradually increased to the IGF-1 concentrations in animals fed *ad libitum* in the compensatory period.

CONCLUSION

A feed restriction applied for one week during the post-weaning period induced a transitory reduction in growth, total serum protein and hepatic IGF-1 levels. However, the final live weight was not affected, thanks to compensatory growth following the *ad libitum* feeding period, and blood metabolite levels as well as hepatic IGF-1 were restored during the *ad libitum* feeding period.

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