Effects of Chronic Inflammation on Energy Metabolism and Growth Performance in Weanling Piglets*

H. K. Moon[1], In K. Han[2], J. L. Gentry[3], H. K. Parmentier[4] and J. W. Schrama[4]
[1] Sacheon Branch, National Livestock Research Institute, Sacheon 664-950, Korea
[2] Dept. of Animal Science & Technology, College of Agriculture & Life Sciences, Seoul National University, Korea
[4] Department of Animal Husbandry, Wageningen Agricultural University, 6700 AH Wageningen, The Netherlands

ABSTRACT : The effect of a chronic inflammation (cell-mediated immune response) on energy metabolism and growth performance was assessed in weanling piglets. Twenty four barrows of 4 wk of age were assigned to one of two immunization treatments : Control group [CON: immunized with Incomplete Freund's Adjuvant (IFA)] or Immunization group [IMMU: immunized with Complete Freund's Adjuvant (CFA)]. On d0, piglets were weaned and subcutaneously immunized at the medial side of the femur with 2 ml of IFA or CFA, respectively. Energy and nitrogen balances were measured per group during 13-d balance period, and total (HP_{tot}), activity-related (HP_{act}) and non-activity-related (HP_{cor}) heat production were determined every 9-min by indirect calorimetry. Ig total titers to *Mycobacterium butyricum*, which is present in CFA, were higher ($p<0.01$) in IMMU than in CON on d13 (2.5 vs 1.8) and d20 (2.9 vs 1.8) after immunization. There were no differences ($p>0.10$) between treatments in rectal temperature, performance, feed intake, and availability and partitioning of energy during the balance period. Average daily feed intake was numerically higher in IMMU than in CON (0.34 vs 0.32 kg/d), but there was no difference ($p>0.10$) in metabolizability of the dietary energy between treatments. HP_{act}/HP_{tot} was 16.24 and 16.89%, and retained energy was 251 and 268 kJ · $kg^{-0.75}$ · d^{-1} for CON and IMMU, respectively. Numerically, maintenance requirement of IMMU was even lower than that of CON (419 vs 427 kJ · $kg^{-0.75}$ · d^{-1}). The present study suggests that a chronic inflammation has no effect on energy metabolism and growth performance, in spite of the difference in systemic antibody responses. The reason was considered to be due to locally induced immune response, resulting from the possible encapsulation at the site of injection, and/or to a low systemic immune stress which is within a functionally acceptable physiological range for the piglets. (*Asian-Aus. J. Anim. Sci. 1999. Vol. 12, No. 2 : 174-179*)

Key Words : Chronic Inflammation, Energy Metabolism, Growth, Pig

INTRODUCTION

Animals raised under stressful environments, such as frequent exposure to microbial challenges, show poor growth rate and the alterations of nutrient partitioning, compared with those raised in less stressful environments due to continuous (or chronic) immune stimulation (immunologic stress) (Klasing et al., 1987; Klasing et al., 1991; Roura et al., 1992). Furthermore, weaning is considered to be a critical period in the life of piglets (Dividich and Herpin, 1994), therefore, they are very sensitive to stressors.

Generally, maintaining an immune response has been reported to be costly in terms of energy expenditure. On the other hand, there are some evidences that reallocation of energy expenditure occurs between maintenance processes in immunized piglets, and this was indicated by a reduction in energy spent on physical activity under systemic humoral immune responses to T-cell dependent antigens (Gentry et al., 1997), and subclinical atrophic rhinitis induced by Pasteurella multocida-toxin (van Diemen et al., 1995a).

We have hypothesized that energetic cost may be different according to the type of immune responses (humoral vs cellular). Cellular (or cell-mediated) immune response is known to be mediated by T_H1 cell activation of macrophages, and local inflammation and fever response are the most prominent characteristics, while humoral immune response being mediated by T_H2 cell activation of B cells (Mosmann and Sad, 1996). Thus, this study was designed to investigate the effect of a cell-mediated immune response (in the form of chronic inflammation) on the energy metabolism and growth performance in weanling piglets.

MATERIALS AND METHODS

Animals, housing and feeding

This study consisted of 4 trials with 2 immunization treatments: Control group [CON: immunized with Incomplete Freund's Adjuvant (IFA)] or Immunization group [IMMU: immunized with Complete Freund's Adjuvant (CFA)]. CFA (Cat No. 344289, CALBIOCHEM) used as immunogen consists of heat-killed *Mycobacterium butyricum* dry cells suspended in an emulsifying oil, which is known to induce cell-mediated immune response (chronic inflammation) (Tizard, 1982; Mosmann and Sad, 1996). IFA is identical with CFA except for the presence of *Mycobacterium butyricum* dry cells. In each trial three pairs of weanling barrows of approximately 4 weeks of age with average body weight of 7.7±0.144 kg were divided into two groups, based on litters and body weight, and assigned to one of two treatments (table 1). The group, therefore, was the experimental unit. The piglets were obtained from the Research Institute for Pig

[1] Address reprint request to H. K. Moon.
[3] Department of Animal Sciences, University of Kentucky, Lexington 40546-0215, USA.
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Husbandry in Rosmalen, The Netherlands. The piglets were originated from Dutch Landrace, Finnish Landrace, and Great Yorkshire rotational-bred sows and Great Yorkshire terminal boars.

Table 1. Arrangement of treatment within trials

Trial	Respiration chamber A	Respiration chamber B
1	Incomplete Freund's Adjuvant	Complete Freund's Adjuvant
2	Complete Freund's Adjuvant	Incomplete Freund's Adjuvant
3	Incomplete Freund's Adjuvant	Complete Freund's Adjuvant
4	Complete Freund's Adjuvant	Incomplete Freund's Adjuvant

Each balance trial lasted 13 days, which consisted of two consecutive periods with each 6 days and 7 days. On day 0 (the day of arrival), piglets were weaned, transported approximately 60 km to the respiration chambers and subcutaneously immunised at the medial side of the femur with 2 ml of CFA or IFA, respectively.

During the balance period of 13d, each group was housed in an open circuit indirect climatic respiration chamber which has inner dimensions of 1.0 m×0.8 m×0.97 m in length×width×height (Verstegen et al., 1987). In the chambers the temperature was kept within the thermoneutral zone (28, 27, 26, and 25℃ on d0 to d1, d2 to d5, d6 to d8, and d9 to d13, respectively) with the relative humidity of about 65-70%. Air velocity was <0.20 m/s. The piglets were exposed to 12 h of light and 12 h of darkness in chambers. The artificial light was on from 07:00 to 19:00. Piglets were allowed ad libitum access to feed, a commercial pelleted starter diet, and water. Determined gross energy (GE) and crude protein (CP) content were 17.6 kJ/g (1 cal = 4.184 J) and 19.5%, respectively.

Measurements

Body weight was measured I day prior to weaning for allotment to treatment groups, on arrival (d0), and at the end of each balance period (d6 and d13, respectively). Rectal temperature was measured twice a week at approximately 5 cm into the rectum. Blood samples were taken using coagulate blood tubes from the vena cava during (d0, 6, and 13) and after (d20, 27, and 34) the balance trial for measuring antibody titers. Total antibody titers to *Mycobacterium butyricum* were determined using ELISA (Enzyme Linked Immuno Sorbent Assay). Briefly, serial dilutions of sera from all animals, including a (pooled) standard positive control serum, were added to antigen-coated wells of a microtiterplate (2 μg/ml *Mycobacterium butyricum* as 200 μℓ coating buffer per well). After incubation for 1 h at 37℃ and subsequent washing, a one step conjugation was performed. Conjugation consisted of incubation for 1 h with a 1 : 8000 diluted peroxidase (PO) conjugated rabbit anti-swine IgG (H+L) (R∝Sw-IgG (H+L)/PO, Kpl, Gaithersburg MD, USA). After the wells were washed, tetramethylbenzidine (TMB, Sigma T2885) was added as a substrate. Colour development was stoped with 2.5 N sulphuric acid after 10 minutes. All absorbances were expressed relative to the absorbance curve of the standard positive control serum. The titer of antibodies to *M. butyricum* in a sample was the dilution that gave an extinction closest to the 50% of E_{max}, where E_{max} represents the highest mean extinction of a standard positive (pooled) serum.

Energy and nitrogen balances per group were measured during each balance period. Feed samples were randomly taken during these periods. Feces with urine production was measured quantitatively per group on the final day of each balance period (d6 and d13) and sampled for energy and nitrogen analysis. Gross energy (GE) values were determined by adiabatic bomb calorimetry and nitrogen contents by the Kjeldahl method (AOAC, 1990). Metabolizable energy (ME) intake per group was calculated from the energy contents of feed, feces and urine. The total heat production (HP_{tot}) per each group was determined every 9 minutes from the measurement of exchanges of oxygen and carbon dioxide as described by Verstegen et al. (1987). These gaseous exchanges were used to calculate HP_{tot} according to the formula of Brouwer (1965).

Heat production was measured throughout the balance period, excluding the days when the respiration chambers were opened for blood sampling and weighing the piglets.

Total energy retention (ER) was calculated by subtracting HP_{tot} from ME intake. Nitrogen retention was estimated from N in feed, feces, urine, aerial NH_3 and NH_4^+ of water that condensed on the heat exchanger. Energy retention as protein (ER_p) was derived from the N retention, and energy retention as fat (ER_f) was calculated from ER and ER_p as described by Henken et al. (1991).

From ER_p, ER_f, and ME intake, maintenance ME (ME_m) was calculated as follows :

$$ME_m = ME - (ER_p/0.54) - (ER_f/0.74) \quad [1]$$

where, 0.54 and 0.74 are the assumed values for the efficiency of utilization of metabolizable energy for protein and fat deposition, respectively (ARC, 1981).

Physical activity per chamber was continuously monitored by an ultrasonic burglar device using doppler effect according to the method used by Wenk and van Es (1976) and recorded in the same intervals as HP_{tot}. The principle of this method is that every surface change of animals due to movements result in a change in frequency of the reflected ultrasound waves emitted by the meters.

The 9-min data on HP_{tot} were related to activity per group and per day according to the following equation:

$$HP_{tot:ij} = \mu + D_i + \beta \times X_j + e_{ij} \quad [2]$$

where, $HP_{tot:ij}$ = heat production during day period i and 9-min period j; μ = overall mean; D_i = fixed effect of day period i (i = 1, 2); X_j = activity counts during 9-min period j; β = regression coefficient of heat production on activity counts; and e_{ij} = error term.

Heat production and physical activity exhibit circadian rhythms (Aschoff et al., 1974). Circadian rhythms in heat production, however, can only partially be explained by physical activity, which has been demonstrated in pigs (van der Hel et al., 1985; Henken et al., 1993) and calves (Schrama et al., 1994). Therefore, a fixed effect of day period with two levels was included in Equation [2]. The day was divided into a light period from 0700 to 1900 and a dark period from 1900 to 0700.

The heat production related to activity (HP_{act}) was calculated for each 9-min period as follows:

$$HP_{act:j} = b \times X_j \quad [3]$$

where, $HP_{act:j}$ = activity-related heat production during 9-min period j; X_j = activity counts during 9-min period j; and b = the estimated regression coefficient of HP_{tot} on activity from Equation [2].

The heat production not related to physical activity (HP_{cor}) was derived by subtracting HP_{act} from HP_{tot}. As with HP_{tot}, both HP_{act} and HP_{cor} were determined every 9-min throughout the balance period, except on days the chambers were opened.

Statistics

All balance data was analyzed with group as the experimental unit. The effect of immunization and balance period on the traits was tested by means of F-tests using a split-plot model (GLM procedure; SAS, 1989), with balance period values within groups taken as repeated measurements:

$$Y_{ijk} = \mu + I_i + e_{1,ij} + T_k + (I * T)_{ik} + e_{2,ijk} \quad [4]$$

where, Y_{ijk} = a specific trait at immunization procedure i, group j, and balance period k; μ = overall mean; I_i = the effect of immunization procedure i (i = 1, 2); $e_{1,ij}$ = error term 1, which represents the random effect of group j within immunization procedure i (j = 1, 2); T_k = the effect of balance period k (k = 1, 2); and $e_{2,ijk}$ = error term 2, which represents the random effect within group between time period.

The effect of immunization procedure was tested for significance against the random effect of group within immunization procedure (error term 1). The effect of time (balance period) and the interaction between time and immunization procedure were tested against the random effect between time period within group (error term 2).

Effects of immunization on the individually measured parameters including rectal temperature and antibody titers were tested against the animal effect nested within immunization procedure using the same model. Now that the day number was the time period, T_k = the effect of day period k (k = 1, . . . 5 for rectal temperature, and k = 1, . . . 6 for antibody titers, respectively).

RESULTS

An interaction was found between time and immunization procedure on total antibody titers to *Mycobacterium butyricum* ($p<0.001$). Ig total titers to *Mycobacterium butyricum* became different with time and were different ($p<0.01$) on d13 (1.76 vs 2.48) and d20 (1.81 vs 2.88) for the control and immunized group after immunization (figure 1). Rectal temperature was not affected by immunization, which was maintained at about 39℃ for both treatment groups throughout the experimental period (data not shown).

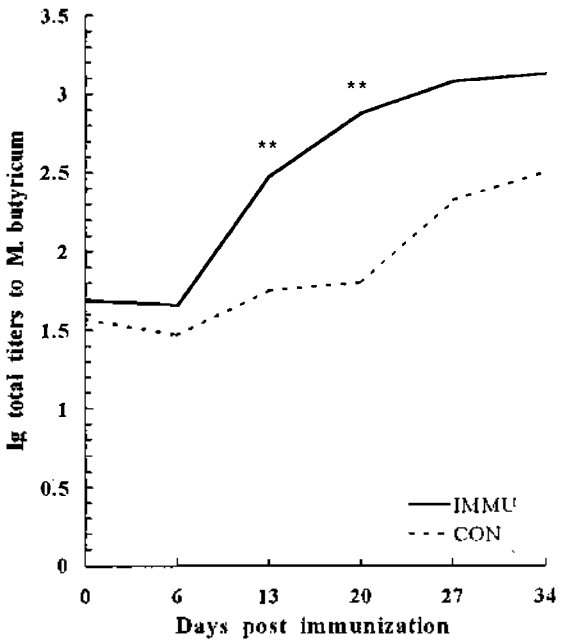

Figure 1. Ig total titers to *Mycobacterium butyricum* in control (CON) and immunization (IMMU) group. SEM = 0.164; ** $p<0.01$; immunization procedure×time interaction ($p<0.001$).

Effects of immunization on the performance, feed intake, and availability and partitioning of energy during the balance period of 2 weeks are shown in table 2 and 3. Only the means per treatment group were presented because the measured traits were not affected ($p>0.10$) by the interaction between the immunization procedure and time. As shown in table 2, there were no differences ($p>0.10$) between treatments in feed intake, average daily gain (ADG) and feed/gain ratio during the balance period. However, average daily feed intake was numerically higher in the immunized group than in the control group (0.34 vs 0.32 kg/d). ME intake was also

numerically higher in the immunized group than in the control group (860 vs 842 kJ · $kg^{-0.75}$ · d^{-1}), which was caused by numerically higher GE intake in the immunized pigs. The energy losses in manure were not affected (p>0.10) by the immunization of the pigs, as indicated by the similar ME/GE ratio of the CON (83.5%) and IMMU (82.9%) group.

Table 2. Least squares means of performance and availability of energy during balance period in weanling piglets as affected by immunization

Trait	CON[1]	IMMU[2]	SEM[3]	P value
No. of groups	4	4	-	-
No. of animals	12	12	-	-
Initial weight (kg)	7.7	7.8	0.274	0.916
Feed intake (kg/d)	0.32	0.34	0.036	0.773
ADG (kg/d)	0.26	0.28	0.03	0.656
Feed/gain	1.51	1.16	0.23	0.331
GE intake (kJ · $kg^{-0.75}$ · d^{-1})	1,008	1,038	95.7	0.830
ME intake (kJ · $kg^{-0.75}$ · d^{-1})	842	860	81.7	0.883
ME/GE (%)	83.5	82.9	0.94	0.693

[1] Control group immunized with Incomplete Freund's Adjuvant.
[2] Test group immunized with Complete Freund's Adjuvant.
[3] Standard error of the mean.

Table 3. Least squares means of the partitioning of energy during balance period in weanling piglets as affected by immunization

Trait	CON[1]	IMMU[2]	SEM[3]	p value
Heat production (kJ · $kg^{-0.75}$ · d^{-1})				
Total (HPtot)	591	592	22.7	0.993
Activity-related (HPact)	96	100	5.3	0.548
Non-activity-related (HPcor)	496	491	19.2	0.874
Retention (kJ · $kg^{-0.75}$ · d^{-1})				
Total energy (ER)	251	268	61.2	0.846
Protein (ERp)	153	156	21.6	0.916
Fat (ERf)	98	112	40.3	0.812
MEm (kJ · $kg^{-0.75}$ · d^{-1})	427	419	15.8	0.747

[1,2,3] See table 2.

The effect of immunization on the partitioning of energy was also assessed during the balance period of 2 weeks and the means per treatment group were presented in table 3. As shown in table 3, the immunization had no effect (p>0.10) on HP, ER, and ME_m. For CON and IMMU group, HP_{act} was 96 and 100 kJ · $kg^{-0.75}$ · d^{-1}, respectively, and expressed by the percentage of HP_{tot}, HP_{act} was 16.24 and 16.89%, respectively (p>0.10). The immunization did not impair production, as indicated by similar ER in the immunized (268 kJ · $kg^{-0.75}$ · d^{-1}) and control (251 kJ · $kg^{-0.75}$ · d^{-1}) piglets (p>0.10). There was no significant difference in the estimated ME_m between CON and IMMU group. Numerically, ME_m of IMMU group was even lower than that of CON group (419 vs 427 kJ · $kg^{-.75}$ · d^{-1}).

DISCUSSION

The present study was designed to investigate the effect of a chronic inflammation (cell-mediated immune response) on the energy metabolism and growth performance in weanling piglets.

Though Ig titers to *Mycobacterium butyricum*, which is present in CFA but not in IFA, were significantly different on d13 and d20 between treatment groups, overall titers were more or less low and the humoral response was less different between treatments than it should have been. Firstly, low humoral response might be partly explained by that *Mycobacterium butyricum* mainly induces cell-mediated immunity rather than humoral immunity (Tizard, 1982; Mosmann and Sad, 1996). Furthermore, granuloma formation was observed at the site of injection in IMMU group, with approximately 4 to 6 cm in length and 3 cm in width (data not shown), which did not occur in CON group. That granuloma formation was thought to be induced by the injection procedure. In the present study, we injected the immunogen subcutaneously rather than intramuscularly due to Dutch law regarding the use of experimental animals. It might be possible that the site of injection was encapsulated by some material such as fibroblast, which prevented the immunogen from delivering into the host body. Those findings were confirmed by the absence of a response in rectal temperature, since the increase of body temperature is well-characterized response especially to chronic inflammation. Therefore, the immunization in this study evidently induced a response, however, which might have been induced locally at the site of injection, and/or systemically with relatively weak status.

Average daily feed intake was numerically higher in piglets exposed to an inflammation response than in the control piglets (table 2), as was in the result of Gentry et al. (1997). Immunization or vaccination is generally expected to decrease feed intake, which is thought to be mediated by interleukin-1 (McCarthy et al., 1985). Thus the result of the present study and Gentry et al. (1997) is contrary to the theory that interleukin-1 reduces the feed intake.

The immunization in this study did not affect the energy losses in manure, as indicated by the similar ME/GE ratio in the immunized (82.9%) and the control (83.5%) piglets (table 2), which is consistent with the findings of Gentry et al. (1997) who found similar ME/GE ratio in the humoral immunization (83.1%) and the control (82.4%) group. The present results are also in agreement with the results of van Diemen et al. (1995b), where piglets were exposed to a subclinical challenge with Pasteurella multocida-toxin causing atropic rhinitis. No significant difference was found in ME_m between the immunized group and the control group, nor was the production impaired by immunization, with similar ER in both treatments (table 3). Those results

might be related with the absence of response in body temperature in this study. Numerically ME_m in the immunized piglets was even lower than that in the control piglets, which is contrary to what we expected.

In contrast to the results of Gentry et al. (1997) and van Diemen et al. (1995a), no reallocation of energy expenditure was present between activity and other maintenance processes in this study, with similar HP_{act}/HP_{tot} in the control (16.24%) and the immunized (16.89%) group (Table 3). They found that a humoral immunization with Keyhole limpet hemocyanine, ovalbumin and tetanus toxoid (Gentry et al., 1997) and subclinical challenge with Pasteurella multocida-toxin causing atropic rhinitis (van Diemen et al., 1995a, 1995b) did not result in a difference in ME_m but that still a reallocation of energy expenditure among the different maintenance processes was occured. They reported that the energy spent on physical activity was reduced in the challenged animals. In the study of Gentry et al. (1997), piglets which mounted a humoral immune response had lower HP_{act}/HP_{tot} ratio than control piglets (18.1 vs 21.7%). van Diemen et al. (1995a) reported that HP_{act} of the challenged pigs was 18 kJ · $kg^{-0.75}$ · d^{-1} lower than that of the control pigs (162 vs 180 kJ · $kg^{-0.75}$ · d^{-1}).

Several researchers have reported that sustained immune responses induced by multiple injections of a variety of immunogens might decrease growth rate and feed intake, and alter partitioning of nutrients, mostly from the studies with chicks (Murray and Murray, 1979; Klasing et al., 1987; Klasing and Barnes, 1988; Klasing et al., 1991). Most of those changes are thought to be mediated, at least in part, by cytokines released from stimulated leukocytes, including interleukin 1 and 6 (Klasing, 1984; McCarthy et al., 1985; Sipe, 1985; Klasing et al., 1987; Klassing, 1988), and tumor necrosis factor (Beutler and Cerami, 1986; Beutler and Cerami, 1988), as well as releasing hormones such as corticosteroids and thyroxin-stimulating hormone (Smith et al., 1982; Beisel, 1985; Blalock and Smith, 1985; Klasing, 1985). No effect of immunization, however, was observed on average daily gain, feed intake, and availability or partitioning of nutrients in weanling piglets in the present study.

Collectively, a chronic inflammation in the present study had no effect on energy metabolism and growth performance in weanling piglets, in spite of the difference in systemic antibody responses. The reason for the lack of an effect of immunization was considered to be due to locally induced immune response, resulting from the possible encapsulation at the site of injection, and/or to a low systemic immune stress which is within a functionally acceptable physiological range for the piglets.

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