Effect of Chronic Immune System Activation on the Rate, Efficiency, and Composition of Growth and Lysine Needs of Pigs Fed from 6 to 27 kg[1,2]

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ABSTRACT: The influence of a low and a high level chronic immune system (IS) activation on growth and dietary nutrient needs of pigs was evaluated. All pigs were of a single genetic strain and geographical site of origin, and the low and high IS pigs were created by physically isolating pigs from or continuously exposing pigs to major vectors of environmental antigen transmission. In each IS group, four littermate barrows in each of six litters were allotted at 25 ± 2 d of age to one of four dietary amino acid regimens (.60, .90, 1.20, or 1.50% dietary lysine. Dietary lysine concentrations were achieved by altering the ratio of corn to soybean meal resulting in lysine being the first-limiting amino acid in each diet. Pigs were individually penned in facilities maintained at 25.6 ± 2°C and allowed to freely consume feed from 6.2 to 26.5 kg BW. On the basis of the differences in serological antibody titers, lymphocyte $CD4^+$:$CD8^+$ ratios, and serum alpha-1-acylglycoprotein concentrations, low and high levels of IS activation were established and maintained during the study. Minimizing the degree of chronic IS activation resulted in greater feed intakes ($P < .09$), body weight and protein gains ($P < .01$), gain:feed ratios ($P < .01$), and body leanness (protein:lipid, $P < .01$). The level of IS activation did not influence the partial efficiency of energy utilization for body protein and lipid accretion. To allow their greater capacity for body growth and protein accretion to be expressed, the low IS pigs required greater dietary lysine concentrations and daily lysine intakes than high IS pigs.

Key Words: Pigs, Lysine, Immune System, Body Composition

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Introduction

Exposure of animals to pathogenic (i.e., bacteria, viral) or nonpathogenic (i.e., endotoxin) antigens results in cytokine release (Klasing, 1988). Cytokines such as interleukin-1 (**IL-1**) and tumor necrosis factor (**TNF**) activate the immune system (Dinarello, 1984) and alter metabolic processes in animals (Klasing, 1988). Metabolically, cytokine (IL-1, TNF) administration induces anorexia (Mrosovsky et al., 1989), depresses protein synthesis (Jepson et al., 1986), and stimulates protein degradation (Klasing et al., 1987) in skeletal muscle. Similarly, acute activation of the immune system via administration of nonpathogenic antigens results in lower voluntary feed intake, body growth rates, and efficiency of feed utilization in chicks (Klasing et al., 1987; Klasing and Barnes, 1988) and pigs (van Heugten et al., 1994). However, the effect of chronic immune system activation resulting from exposure to environmental antigens on the rate, efficiency, and composition of growth and dietary amino acid needs of pigs has not been evaluated.

The present study was conducted to determine the effect of level of chronic immune system activation on rate, efficiency, and composition of body growth; efficiency of utilization of dietary ME for body protein and fat accretion; and dietary lysine (**Lys**) needed to optimize these criteria in pigs fed from 6 to 27 kg BW.

Materials and Methods

Treatments. A split-plot experimental design was used. The whole-plot treatments consisted of a low

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level and a high level of chronic immune system (IS) activation. The subplot treatments consisted of four dietary amino acid regimens (.60, .90, 1.20, or 1.50% Lys). Low and high levels of IS activation were created with rearing schemes that resulted in pigs experiencing low and high levels of continuous exposure to environmental (pathogenic and nonpathogenic) antigens. Dietary regimens consisted of corn, soybean meal, dried whey, and dried skim milk mixtures in which the dietary Lys concentrations were achieved by altering the ratio of corn to soybean meal.

Animals. Within each IS group, six sets of five littermate barrows were used. All pigs were derived from a single genetic strain (Yorkshire × Landrace dam and Hampshire × Duroc sire) and herd. Lean (muscle with 10% fat, NPPC, 1983) growth potential of the genetic strain was estimated to be about .35 kg/d from 20 to 110 kg BW based on data previously collected on the strain at our research station. The herd from which the pigs were derived possessed antibody titers for *Actinobacillus pleuropneumoniae* (APP), *Mycoplasma hyopneumoniae* (MP), swine influenza virus (SIV), and transmissible gastroenteritis (TGE) virus, which indicated that bacterial and viral pathogens were present. Pigs were randomly allotted within litter to one of the four dietary L regimens.

Animal Care. Pigs were individually penned in .36 × 1 m solid-sided pens with woven wire flooring in rooms maintained between 23.8 and 26.6°C with minimal ventilation rates of .07 $m^3 \cdot min^{-1} \cdot pig^{-1}$. Each pig was allowed to consume feed and water ad libitum from a single hole stainless steel feeder and individual nipple waterer, respectively. Pig weights and feed consumption were determined at 4-d intervals throughout the duration of the trial. Feed wastage was collected on trays below the feeder, dried, weighed, and subtracted from feed disappearance to determine net feed consumption. Pigs were killed at 26.5 (± 2.3) kg by intracardial administration of sodium pentobarbital (1 mg/kg BW) for subsequent determination of body nutrient content. A fifth pig in each litter was killed at the initiation of the study (26 d of age) for determination of initial body composition. The experimental protocol was approved by the Iowa State University Animal Care Committee.

Development of Immune System Activation. Two management schemes were used to develop pigs with low and high levels of chronic immune system activation. The low IS pigs were developed using a medicated early-weaning (**MEW**) scheme. This rearing scheme minimizes disease transmission by enhancing the development of passive immunity in neonatal pigs and by physically isolating pigs from major vectors of antigen transmission (Harris, 1988). In this scheme, sows from which pigs were derived were vaccinated at 6 and 2 wk before farrowing for diseases that had previously been identified to exist in the herd of origin. These vaccinations included the following: *Mycoplasma hyopneumoniae* bacterin (Respifend™, Solvay, Mendota Heights, MN); *Bordetella bronchiseptica* (Rhinobac 3, NOBL, Sioux Center, IA); *Hemophilus pleuropneumoniae* bacterin (Pneumosuis III, Pfizer Animal Health, Lenexa, PA); and transmissible gastroenteritis, *Clostridium perfringens* type C, *Escherichia coli* bacterin toxoid (Scourshield D, Pfizer Animal Health). Sows were farrowed in sanitized (cleaned with hot water using a high pressure sprayer, disinfected with Bioguard-PFD 5, Bio-Lab, Inc., Decatur, GA) rooms. Neonatal pigs were treated i.m. with 1.5 mg/kg BW of ceftiofur (Naxcel, Upjohn, Kalamazoo, MI) and 22.7 mg/kg BW enrofloxacin (Baytril, Miles Ag Division, Shawnee Mission, KS) at 1, 3, 5, 8, and 11 d of age. Pigs were treated at weaning with 1.5 mg/kg BW ceftiofur, 22.7 mg/kg BW enrofloxacin, and with. 5 mg/kg BW of ivermectin (Ivomec™, Merck AgVet, Rahway, NJ). Pigs were weaned at 12 d of age (range 10 to 14 d) while they still possessed passive antibodies derived from their dam's colostrum. At weaning, pigs were placed in a sanitized facility that was physically isolated from major vectors of antigen transmission. Pigs were allowed to consume a milk-based diet (modified Day 13 [no antimicrobial agents or oat products], Merricks, Inc., Union Center, WI) ad libitum until 19 d of age.

High IS pigs were derived via a conventional rearing scheme. Specifically, sows were not vaccinated for prevalent antigens present in the herd of origin, sows were farrowed in a nonsanitized farrowing room, pigs did not receive injectable antibiotics unless they exhibited clinical signs of illness, and pigs were weaned at an average age of 19 d (range of 18 to 21 d) to increase the likelihood of antigen transfer from the sow to the neonate pig. Pigs were weaned into a nonsanitized (unit not cleaned with pressure sprayer after a previous 4-wk occupation of the room by 6- to 15-kg pigs derived from the herd of origin) facility located at the site of sow origin. During the experiment, groups of 7-wk-old pigs from another nursery unit at the site of origin were brought into the room at the start of the experiment and at 3-wk intervals during the trial to aid in maintenance of a chronic level of antigen exposure. Pigs in the low and high IS groups were allowed to consume the 1.50% Lys experimental diet ad libitum from 19 to 25 d of age.

Experimental Diets. Dietary amino acid regimens consisted of corn, dehulled soybean meal, spray dried whey, dried skim milk mixtures, with added minerals and vitamins (Table 1). The dietary lysine levels were achieved by altering the ratio of corn to soybean meal in the basal mixture. The diets were fortified with vitamins to achieve dietary levels equivalent to a minimum of 250% (except choline, 200%) of NRC (1988) estimated requirements for 5- to 10-kg pigs.

Table 1. Composition of experimental diets (as-fed basis)

Item	Dietary lysine, %			
	.60	.90	1.20	1.50
Ingredient, % of diet				
Yellow corn, ground	67.60	57.24	46.85	36.41
Soybean meal, dehulled	3.99	14.53	25.08	35.64
DL-Methionine, 99%	–	–	.01	.07
Spray-dried whey	20.00	20.00	20.00	20.00
Dried skim milk	5.00	5.00	5.00	5.00
Dicalcium phosphate	2.17	1.94	1.71	1.48
Ground limestone	.44	.49	.55	.60
Salt, iodized	.25	.25	.25	.25
Vitamin-trace mineral mix[a]	.55	.55	.55	.55
Analyzed composition,[b] %				
CP, %	12.0	16.2	20.4	24.7
Amino acid, %				
Lysine	.60	.90	1.20	1.50
Threonine	.58	.74	.90	1.06
Leucine	1.35	1.61	1.87	2.13
Isoleucine	.59	.77	.96	1.15
Valine	.67	.88	1.09	1.30
Histidine	.31	.41	.50	.60
Arginine	.56	.90	1.25	1.59
Calculated composition[c]				
ME, kcal/kg	3,169	3,169	3,175	3,179
Tryptophan, %	.16	.23	.29	.35
Methionine + cytine, %	.50	.61	.72	.88
Calcium, %	.90	.90	.90	.90
Phosphorus, %	.80	.80	.80	.80

[a]Provided the following (per kilogram of diet): 140 mg Fe, 120 mg Zn, 48 mg Mn, 14 mg Cu, .80 mg I, .30 mg Se, 5,500 IU vitamin A, 1,102 IU vitamin D_3, 37.5 IU vitamin E, 1.50 mg vitamin K (as menadione dimethylpyrimidinol bisulfate), 6.6 mg riboflavin, 17.6 mg panothenic acid, 33.1 mg niacin, 110.0 μg vitamin B_{12}, .03 mg biotin, .17 mg folacin, 400 mg choline, .82 mg of pyridoxine, .56 mg thiamine, and 167 mg ethoxyquin.

[b]Values determined from analysis of the single sources of corn, dehulled soybean meal, dried whey, and dried skim milk used in this study.

[c]Values based on NRC (1988) estimated nutrient composition of the ingredients used.

Minerals were fortified to achieve dietary levels equivalent to a minimum of 200% of NRC (1988) except for selenium (120%). Diets were formulated to meet a minimum of 110% of the ideal ratio of essential (Chung and Baker, 1992) and nonessential (Wang and Fuller, 1989) amino acids relative to Lys. Synthetic DL-methionine was added to the 1.20 and 1.50% dietary Lys diets to meet minimal methionine-cystine concentrations. Single sources of corn, dehulled soybean meal, dried whey, and dried skim milk were used throughout the trial to minimize variation in nutrient content and potential ingredient toxin levels. Each ingredient source was analyzed for protein and amino acid content. The analyzed amino acid contents of the ingredients were used to formulate the experimental diets.

Sample Collection and Analysis. Dry matter, N, ether-extractable lipid, and ash content were determined on the whole bodies of pigs killed at the initiation (12 pigs) and completion of the trial. Pigs were killed via lethal sodium pentobarbital injection, and the whole body including gut contents was then frozen at –20°C for subsequent analyses. Whole bodies were then ground in dry ice through a 2.54-cm die, mixed to ensure homogeneity of sample and reground through a .95-cm die. Two 500-g samples were collected and frozen at –20°C. Ground whole pig samples were then freeze-dried to determine DM content. Dried samples were allowed to air-equilibrate, ground through a 1-mm screen and then analyzed for Kjeldahl nitrogen, ether-extractable lipid, and ash in triplicate according to AOAC (1990) procedures.

Whole-body nutrient accretion rates were calculated based on a comparative slaughter technique. Because body nutrient content of low and high IS pigs killed at the initiation of the experiment did not differ, initial nutrient content of pigs in both IS groups was estimated based on initial BW of the experimental animals and average body nutrient content (expressed as a percentage of BW) of the initial pigs killed at 26 d of age (Table 2).

For amino acid analyses, ingredients were ground through a 1-mm die and hydrolyzed in 6 *N* HCL for 20 h under nitrogen at 105°C. Amino acids were separated (Gehrke et al., 1985) with an ion-exchange column (3 × 250 mm lithium gradient, Pickering Laboratories, Mountain View, CA) and detected by fluorometry after post-column reaction with *o*-phthaladehyde (Pickering Laboratories) and analyzed by HPLC (Shimazdv LC-6A, Columbia, MD). Tryptophan and methionine-cystine were not analyzed.

For determination of immune status, each pig was bled via an orbital sinus on d 1 and 4 of each 4-d period in which the pigs' body weight (± 1.0 kg) averaged 9.5, 17.5, and 25 kg. Serum were separated by centrifugation and stored at –20°C until analyzed. Whole blood aliquots were stored on ice and then processed within 5 h after collection.

Whole blood samples were collected for flow cytometry analysis of lymphocyte populations. Aliquots (10 μL) of whole blood from each pig were incubated for

Table 2. Initial body nutrient content of pigs in the low and high immune system (IS) activation groups at 6 kg BW[a]

Item	IS activation		SEM	*P* <
	Low	High		IS
Pig weight, kg	6.2	5.7	.75	.65
Body nutrient content, % of BW				
Protein	15.6	15.2	.72	.74
Water	74.1	73.3	9.3	.65
Lipid	6.3	7.9	.73	.19

[a]Five pigs per IS group.

30 min at 4°C with 30 μL of mouse anti-pig $CD4^+$ (T-helper lymphocytes), mouse anti-pig $CD8^+$ (cytotoxic-suppressor lymphocytes), or PBS (auto sample). Specificity of these monoclonal antibodies was previously described (Pescovitz et al., 1985). All monoclonal antibodies were diluted 1 to 100 mg/mL in PBS. Dilutions were based on previously determined optimal dilutions. After labeling with the primary antibody, cells were washed twice with 100 μL of PBS. The $CD4^+$ and $CD8^+$ samples were then incubated with 100 μL (1:100) of goat anti-mouse fluorescein isothiocyanate (Sigma Chemical, St. Louis, MO) for 30 min at 4°C. Samples were washed twice with 100 μL of PBS, and then red cells were lysed with 100 μL (1:25) of Immunolyse (Coulter, Hialeah, FL) and fixed with 10 μL of formaldehyde fixative (Coulter, Hialeah, FL). Cells were then resuspended in 100 μL of PBS. Control samples were incubated only with the second fluorescein-labeled antibody to determine background fluorescence and autofluorescence. Samples were analyzed for fluorescence using a 15 Ar laser, 488 nm flow cytometer (Coulter Epics, Hialeah, FL). Windows for each animal were set using its own control to exclude autofluorescence. Auto-fluorescent cells were excluded from analysis by gating. Less than 2% of the cells showed autofluorescence.

Two 1-mL serum samples were submitted to the Iowa State University Diagnostic Laboratory and analyzed for serum concentrations of antibody titers for: *Actinobacillus pleuropneumoniae*, swine influenza virus, and transmissible gastroenteritus virus according to APHIS (1981) procedures and for *Mycoplasma hyopneumoniae* by procedures outlined by Slavick and Switzer (1972).

Serum samples also were analyzed for alpha-1-acylglycoprotein (**AGP**) concentrations utilizing a radial immunodiffusion assay. Aliquots (5 μL) of serum (diluted 1:1 with PBS) were pipetted into agar plates containing antibody specific to porcine AGP (Development Technologies International, St. Frederick, MD). Plates were incubated for 48 h at 37°C. Samples were analyzed by measuring the precipitin ring diameter in the agar utilizing a logarithmic scale. A standard curve developed from purified porcine AGP was developed and utilized to determine serum concentrations. The validity and repeatability of the assay has been reported by Tamura et al. (1989).

Statistical Analyses. Data were analyzed as a split plot design (Steele and Torrie, 1980) using the GLM procedure of SAS (1994). Immune system activation was considered the main plot and was tested by an error term of replicate within IS. Dietary Lys was considered the subplot. Dietary Lys and the IS × Lys interaction were tested with the residual (replicate × Lys [IS]) mean square term. Orthogonal comparisons were made to test for Lys linear and quadratic effects (Steel and Torrie, 1980). The pig was considered the experimental unit. Changes in surface cell antigens and serum AGP concentrations over different stages of growth (average body weight [**ABW**]) were analyzed as a repeated measure within the split-plot design.

To estimate the partial efficiency of energy for body protein and lipid retention and maintenance needs of the pigs, the following multiple regression model was utilized: $y = a + b_1(x_1) + b_2(x_2)$ where y = daily ME intake (kcal/BW, $kg^{.75}$), a = daily maintenance needs (kcal/kg $BW^{.75}$, b_1 = partial energetic efficiency of protein gain (K_p), x_1 = daily energy retained as protein (kcal/BW, $kg^{.75}$), b_2 = partial energetic efficiency of lipid gain (K_f), and x_2 = daily energy retained as lipid (kcal/BW, $kg^{.75}$). The energy contents of retained body protein and lipid were assumed to be 5.76 and 9.5 kcal, respectively (ARC, 1981). The ME contents of the diets were estimated based on NRC (1988) values for the respective feed ingredients used. Data from pigs in the high IS group that received the 1.50% Lys diet were excluded from the analysis because the dietary Lys intakes of these animals were determined to be in excess of their needs at each stage of growth evaluated (Williams et al., 1997), and excess intakes of protein have been demonstrated to decrease ME utilization (NRC, 1988). Variance procedures using pooled sums of squares and pooled degrees of freedom from the two independent regressions were used to test for differences in efficiencies (slopes) of utilization of dietary energy (ME) for body protein and lipid accretion between high and low IS groups (Steele and Torrie, 1980).

One pig was removed from the low IS, 1.20% dietary Lys treatment group because of physical injury. One pig was removed from the high IS, 1.20% dietary Lys treatment group because of poor growth caused by proliferative enteritis. Least squares means are reported.

Results

Immune System Effects. Low IS pigs exhibited colostrally derived antibodies at the initiation of the study (6.2 kg BW) for APP, MP, SIV, and TGE (Table 3) but at 26.5 kg did not possess antibody titers for any of the antigens evaluated. High IS pigs did not possess colostral antibody titers at 6.2 kg BW but did possess positive titers for APP, MP, SIV, and TGE at 26.5 kg BW. Pigs in the low IS group had fewer CD4 positive T-lymphocytes, more CD8 positive T-lymphocytes, and lower $CD4^+$:$CD8^+$ ratios than high IS pigs at 9.5, 17.5, and 25 kg BW, and these responses were independent of dietary Lys (Table 3). Low IS pigs also had lower serum AGP concentrations than high IS pigs at each stage of growth monitored.

After a 6-d adjustment period (19 to 26 d of age), pigs were placed on their experimental diets at 6.2 ±.9 kg and were killed at an average weight of 26.5 ± 2.3 kg (Table 4). Over the duration of the trial, pigs in

Table 3. Sereological titers for prevalent antigens, serum CD4 and CD8 positive lymphocytes, and serum alpha-1-acylglycoprotein concentration in low and high immune system (IS) activation pigs at average body weights (ABW) of 9.5, 17.5, and 25 kg[a]

Item	IS Activation	Average body weight, kg 9.5	17.5	25	SEM	P < IS	ABW	IS × ABW
Serological titers for APP, MP, SIV, TGE[b]								
	Low	+	ND[c]	–				
	High	–	ND[c]	+				
Antigen receptors, % of total peripheral blood lymphocytes								
CD_4^+	Low	22.9	17.6	21.8	1.9	.01	.69	.22
	High	42.9	45.5	46.8				
CD_8^+	Low	38.9	32.4	35.6	1.9	.01	.83	.22
	High	22.4	26.0	25.2				
CD_4^+/CD_8^+	Low	.62	.84	.66	.16	.01	.63	.72
	High	2.20	1.97	2.01				
Serum alpha-1-acylglycoprotein, AGP, μg/mL								
	Low	1,111	1,112	911	83	.01	.01	.46
	High	1,499	1,542	1,401				

[a]Twenty-three individually penned pigs per IS group. Data pooled across dietary lysine concentration. Least squares means reported.
[b]APP = *Actinobaccilus pleuropneumoniae*; MP = *Mycoplasma hyponeumoniae*; SIV = swine influenza virus; TGE = transmissable gastroenteritis.
[c]Not determined.

the low IS group consumed more feed and Lys, gained body weight faster, and accrued more body weight per unit of feed than pigs in the high IS group (Table 4). Pigs in the low IS group also produced bodies with more protein and water and less lipid than high IS pigs (Table 5). Body ash content was similar in the two IS groups (Table 5). Because of their greater body growth rate and body protein content, low IS pigs accrued body protein faster than high IS pigs. Pigs in the low IS group also accrued body lipid faster than high IS pigs; however, lipid accretion as a proportion of total body weight gain was lower in low IS pigs as indicated by their greater protein accretion to lipid accretion ratio.

Estimates of dietary ME needed for maintenance and the energetic efficiency of ME utilization for body

Table 4. Effect of immune system (IS) activation and dietary lysine (Lys) regimen on feed intake, body weight gain, and gain:feed ratio of pigs fed from 6 to 27 kg BW[a]

Criterion	IS Activation	Dietary lysine, % .60	.90	1.20	1.50	SEM	P < IS	LL[b]	LQ[b]	IS × LL[b]	IS × LQ[b]
Pig weight, kg											
Initial	Low	6.6	6.7	6.3	6.2	.37	.31	.37	.84	.94	.67
	High	5.7	6.0	6.1	5.8						
Final	Low	25.0	26.9	27.7	27.6	.94	.63	.27	.98	.74	.49
	High	24.5	27.3	27.7	26.6						
Growth performance of pigs fed from 6.2 to 26.5 kg BW											
Daily feed, g	Low	896	1,025	1,052	1,002	36.2	.09	.23	.04	.15	.21
	High	889	954	889	911						
Daily Lys, g	Low	5.11	9.33	12.21	14.73	.29	.04	.04	.18	.01	.21
	High	4.18	6.92	8.78	11.48						
Daily gain, g	Low	400	556	644	663	18.5	.01	.01	.21	.95	.01
	High	357	495	510	504						
Gain/feed, g/kg	Low	445	544	613	662	16.1	.01	.01	.59	.16	.07
	High	395	522	581	565						

[a]Five or six individually penned pigs per IS activation-Lys treatment group. Least square means reported.
[b]Linear lysine (LL) and quadratic lysine (LQ) effects.

Table 5. Effect of immune system (IS) activation and dietary lysine (L) regimen on body nutrient content and accretion rates of pigs fed from 6 to 27 kg BW[a]

Criterion	IS Activation	Dietary lysine, % .60	.90	1.20	1.50	SEM	P < IS	LL[b]	LQ[b]	IS × LL[b]	IL × LQ[b]
Body nutrient content at 26.5 kg BW											
Protein, %	Low	12.92	14.37	15.70	16.40	.38	.14	.01	.87	.83	.07
	High	12.21	13.94	15.82	15.72						
Water, %	Low	59.82	64.67	67.61	69.11	.61	.14	.01	.79	.23	.05
	High	59.36	64.36	67.10	67.63						
Lipid, %	Low	21.48	15.46	11.95	10.85	.46	.08	.01	.27	.75	.01
	High	22.72	15.57	11.98	12.28						
Ash, %	Low	3.26	2.92	2.74	2.59	.21	.79	.06	.19	.15	.47
	High	3.05	2.65	2.71	2.94						
Body nutrient accretion rates from 6.2 to 26.5 kg BW											
Protein, g/d	Low	47.6	77.8	100.7	110.8	3.0	.01	.01	.27	.55	.01
	High	40.3	67.3	80.3	79.4						
Water, g/d	Low	220.1	343.4	424.8	449.9	12.5	.01	.01	.15	.42	.01
	High	220.7	310.6	339.4	336.0						
Lipid, g/d	Low	106.6	101.7	86.4	79.3	4.9	.10	.08	.57	.87	.05
	High	97.3	90.0	69.0	71.0						
Protein:lipid[c]	Low	.46	.77	1.17	1.41	.04	.09	.01	.28	.01	.03
	High	.41	.76	1.15	1.13						

[a]Five or six individually penned pigs per IS activation-Lys treatment group. Least square means reported.
[b]Linear lysine (LL) and quadratic lysine (LQ) effects.
[c]Protein deposited per unit of body lipid deposited.

protein (**kp**) or lipid (**kf**) accretion were not altered by IS status in animals consuming dietary Lys supplies equivalent to or below their daily needs (Table 6). Maintenance energy (ME) needs for the low and high IS pigs were estimated to be 102 and 115 kcal/kg $BW^{.75}$, respectively. The values of kp in the low and high IS pigs were estimated to be .47 and .49, respectively, and the values for kf were estimated to be .67 and .70, respectively.

Lysine Effects and Interactions. Over the duration of the study (6.2 to 25.6 kg BW), dietary Lys concentration did not alter daily feed intake (Table 4). As would be expected, increasing dietary Lys concentration resulted in a concomitant linear increase in daily Lys intake (Table 4). Over the duration of the study, daily body gain and gain:feed ratios increased as dietary Lys concentrations increased in both IS groups (Table 4); however, the low IS pigs responded to greater dietary Lys concentrations than high IS pigs, resulting in IS × Lys quadratic interactions. Both body growth rate and the efficiency of feed utilization were maximized by a dietary Lys concentration of 1.50% and daily Lys intakes of 14.7 g in low IS pigs compared with values of 1.20% and 8.8 g, respectively, in high IS pigs.

Table 6. Effect of immune system (IS) activation on energetic maintenance needs (a) and the partial efficiency (b) of utilization of metabolizable energy for body protein (K_p) and lipid (K_f) accretion in pigs fed from 6 to 27 kg BW[a,b]

IS Activation	a (SE)	b_1 (SE)[c]	b_2 (SE)[c]	R^2	P[d] < a	b^1	b^2
Low	102 (48)	2.11 (.33)	1.49 (.31)	.68	.54	.61	.82
High	115 (39)	2.03 (.54)	1.42 (.33)	.72			

[a]Seventeen individually penned pigs in the high IS group and 23 individually penned pigs in the low IS group included in the analysis.
[b]Model: $y = a + b_1(x_1) + b_2(x_2)$ where y = daily metabolizable energy intake (Mcal/BW, $kg^{.75}$), a = ME for maintenance (kcal/BW, $kg^{.75}$), b_1 = kilocalorie of ME required to deposit a kilocalorie of protein energy, x_1 = daily protein energy gain (kcal/BW, $kg^{.75}$), b_2 = kilocalorie of ME required to deposit a kilocalorie of lipid energy, and x_2 = daily lipid energy gain (kcal/BW, $kg^{.75}$).
[c]Standard error of estimate in parentheses.
[d]Probability values for low vs high IS.

Body protein and body water content in pigs at 26.5 kg BW increased and body lipid content decreased as dietary Lys concentration increased (Table 5). The daily accretion rate of body protein in pigs fed from 6.2 to 26.5 kg BW and the proportion of the body gain that was protein (protein:lipid) also increased as dietary Lys concentrations were elevated, whereas daily accretion rates of body lipids decreased (Table 5). The low IS pigs required greater dietary Lys concentrations (1.50%) and greater daily Lys intakes (14.7 g) to optimize these criteria than high IS pigs (1.20% and 8.8 g).

Discussion

On the basis of antibody titers for pathogenic antigens, T lymphocyte $CD4^+$:$CD8^+$ ratio, and serum alpha-1-acylglycoprotein concentrations, groups of pigs with a low and a high level of chronic IS activation were created and maintained throughout the study. The findings that the major pathogenic antigens present in the herd of origin were eliminated in the low IS group via the use of a medicated early-weaning rearing scheme are in agreement with the results of Harris (1988). The initial antibody titers present in the low IS group represent residual colostral antibodies resulting from the vaccination of the sow prepartally for these antigens.

The reduction in the number of CD4-positive T lymphocytes in the low IS group also indicates that immune cells (i.e., macrophages) in these pigs were presenting fewer foreign antigens (Matis, 1990), resulting in less cytokine release and cellular and humoral immune activation (Tonegawa, 1985). The greater $CD4^+$:$CD8^+$ ratio in the high IS pigs is in agreement with the higher $CD4^+$:$CD8^+$ ratio observed in coccidia infection in chicks (Lillehoj, 1994) and in animals with low levels of circulating thyroid hormones (Johnson et al., 1993) such as occurs in chronic respiratory infection in children (Hashimoto et al., 1994). The lower serum concentration of AGP in the low IS pigs also indicates a lower release of the pro-inflammatory cytokine IL-1 (Woloski et al., 1985) and a resulting lower immune response (Courtoy et al., 1981; Klasing, 1988). These findings are in agreement with the lower serum AGP observed in specific-pathogen-free pigs experiencing minimal antigen challenge compared with conventionally reared pigs that were infected with *Mycoplasma hyopneumoniae* and *Actinobacillus pleuropneumoniae* (Itoh et al., 1992).

The greater feed intake, body growth rate, efficiency of feed utilization, and proteinaceous tissue content of the low IS pigs was likely due to lower cytokine release and associated endocrine changes resulting from a lower chronic level of immune system activation. Administration of the pro-inflammatory cytokines has been shown to result in lower voluntary feed intake in rats (Mrosovsky et al., 1989) and pigs (Fink et al., 1995). This reduction in voluntary feed intake is associated with an IL-1-induced release of CRH (Navarra et al., 1991) and IL-8, which serve as a potent stimulant of the lateral hypothalamus (Plata-Salaman and Borkoski, 1993). The lower body growth rates and efficiency of feed utilization in the antigen-challenged animals are due in part to their lower feed intake; however, other metabolic shifts mediated by cytokines also play a role because administration of a non-pathogenic antigen (lipopolysaccharide) in chicks reduced body gains and gain:feed ratios by 17.1 and 17.0%, respectively, compared with those of pair-fed controls (Klasing et al., 1987). These metabolic shifts include increased skeletal muscle protein degradation (Klasing and Austic, 1984), decreased skeletal muscle protein synthesis (Jepson et al., 1986), increased liver and heart protein synthesis (Ballmer et al., 1991), and increased bone resorption (Cochran and Abernathy, 1988). Cytokines mediate these alterations in skeletal muscle protein synthesis and degradation by decreasing the release of anabolic hormones such as somatotropin (Honegger et al., 1991) and IGF-1 (Fan et al., 1994), increasing catabolic (glucocorticoid) hormone release (Navarra et al., 1991), and by direct inhibition of the muscle proteolytic inhibitor calpastatin (Chavis et al., 1994). Furthermore, thymic atrophy associated with cytokine release may result in decreased somatotropin release as the thymic peptide thymosin alpha-1 decreases somatostatin release from the hypothalamus (Milenkovic et al., 1992) and the thymic peptide thymosin fraction 5 increases somatostatin-releasing factor release from the hypothalamus (Badamchian et al., 1991).

Exposure to environmental antigens (i.e., sanitary vs unsanitary environments) has been reported to increase cytokine (IL-1) release and decrease the rate and efficiency of growth in chicks (Roura et al., 1991) and pigs (Wiseman et al., 1994). Administration of a nonpathogenic antigen (lipopolysaccharide) also results in an acute release of pro-inflammatory cytokines (Feldmann and Male, 1989) and a reduction in rate and efficiency of growth in chicks (Klasing and Barnes, 1988) and pigs (Van Heugten et al., 1994). Blocking the action of IL-1 by pretreatment with an IL-1 receptor antagonist prevents the skeletal muscle catabolism resulting from either IL-1 administration or sepsis resulting from cecal puncture (Zamir et al., 1994). On the basis of these data, the pro-inflammatory cytokine release that occurs in the immune response and the associated endocrine shifts account for the majority of the muscle catabolism rather than the direct effects of the pathogen per se.

As expected, the greater capacity of the low IS pigs to accrue body protein resulted in these pigs requiring greater dietary Lys concentrations and greater daily

Lys intakes to express their maximum rate of protein accretion compared with high IS pigs. Over the duration of the trial (6 to 27 kg BW), daily body protein accretion was maximized and daily lipid accretion minimized by dietary Lys concentrations of 1.50% and daily Lys intakes of 14.7 g in the low IS group compared with 1.20% and 8.8 g in the high IS group. These daily Lys intakes were 6 and 0 g greater respectively, than current NRC (1988) estimated Lys needs for pigs fed over the same stage of growth (6 to 27 kg BW). The daily weight gains and gain:feed ratios of the low IS pigs were 51% (663 vs 439 g) and 73% (662 vs 382 g/kg) greater, respectively, than the values assumed in establishing the NRC (1988) estimates.

The greater dietary Lys needs of the low IS pigs were due to their greater capacity for body protein accretion (180 vs 111 g/d), not changes in efficiency of lysine utilization for growth. In instances when the daily Lys intakes of the low and high IS pigs were similar (9.3 g/d, .90% Lys vs 8.8 g/d, 1.20% Lys) but at or below daily needs, body protein accretion rates were equal (78 vs 80 g/d), indicating a similar efficiency of dietary Lys utilization for body protein accretion. Furthermore, the additional body protein accrued per each additional gram of Lys ingested was similar in the low and high IS pigs (7.5 and 8.7 g/g, respectively) as dietary Lys intakes were increased from severely deficient (5.11 and 4.18 g/d, respectively) to less deficient or adequate intakes (12.21 and 8.78 g/d, respectively). Furthermore, the greater feed thus ME intakes of the low IS pigs accounted for only a portion of the observed increase in body protein accretion. In pigs consuming Lys intakes that optimized protein accretion in the low (1.50% L) and high (1.20% L) IS pigs, the low IS pigs consumed daily an additional 63 kcal of ME/kg$^{.75}$ BW. This additional ME intake would be estimated to result in an additional 12 g/d of body protein accretion (Stahly, 1986), whereas 31 g additional protein accretion actually occurred. The energetic costs of body maintenance and body protein and lipid accretion also were similar among the two IS groups. Estimates of ME maintenance needs compare favorably with literature estimates (110 kcal/kg BW$^{.75}$; ARC, 1981). The estimates of kp (.47 to .49) and kf (.67 to .70) in the present study were slightly lower than estimates (kp=.54, kf = .74) reported by ARC (1981). The lower partial efficiencies reported in this study may be a result of decreased efficiency of ME utilization associated with overfeeding of protein (NRC, 1988) This reduction in ME utilization because of excess dietary protein consumption is associated with the failure to retain the energy associated with the excretion of excess N as well as with higher rates of protein turnover and therefore higher rates of heat production related to protein catabolism and N excretion (Reeds et al., 1981; Adeola and Young, 1989).

On the basis of these data, low IS pigs require greater dietary Lys intakes because of their greater capacity for body protein accretion, not because of changes in efficiency of use of dietary amino acids and ME for body protein and lipid deposition. The reason that dietary Lys needs expressed as a percentage of the diet increased in low IS pigs is because the dietary amino acids needed for body protein accretion are increased more (40.1%) than that of dietary energy (19.7%) needed for body protein and fat accretion.

Implications

Technologies that minimize chronic activation of a pig's immune system by minimizing the animal's exposure to antigens allow a greater proportion of the pig's biological potential for body growth, efficiency of feed utilization, and carcass leanness to be achieved and alter the dietary amino acid needs of pigs. It is biologically and economically desirable to match nutritional inputs with the pig's biological capacity for proteinaceous tissue growth as defined by the animal's immune system status.

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