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REVIEW ARTICLE

Regulatory role for amino acids in mammary gland growth and milk synthesis

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Abstract The health and growth of mammalian neonates critically depend on the yield and composition of their mothers' milk. However, impaired lactogenesis occurs in both women in response to stress and hormonal imbalance and in primiparous sows which exhibit low voluntary feed intake and underdevelopment of mammary tissues. Because of ethical concerns over lactation research with women and children, swine is often used as an animal model to study mammary gland development and the underlying regulatory mechanisms. Available evidence from work with lactating sows shows that amino acids are not only building blocks for protein but are also key regulators of metabolic pathways critical to milk production. Particularly, arginine is the common substrate for the generation of nitric oxide (NO; a major vasodilator and angiogenic factor) and polyamines (key regulators of protein synthesis). Thus, modulation of the arginine-NO pathway may provide a new strategy to enhance the growth (including vascular growth) of mammary tissue and its uptake of nutrients, therefore improving lactation performance in mammals. In support of this proposition, supplementing 0.83% L-arginine (as 1% L-arginine-HCl) or 50 mg/day diethylenetriamine-NO adduct (NO donor) to diets of lactating primiparous sows increased milk production and the growth of suckling piglets. Future studies with animal models (e.g., pigs, sheep, cows, and rats) are necessary to elucidate the underlying mechanisms at molecular, cellular, tissue, and whole-body levels.

Keywords Amino acids · Arginine · Lactation · Milk · Neonates · Nitric oxide

Abbreviations

AA	Amino acids
DETA	Diethylenetriamine-NO adduct
NO	Nitric oxide
NRC	National Research Council

Introduction

Milk is the sole source of nutrients for nursing neonates, including human infants and piglets. Therefore, a mother's ability to produce milk determines the health and growth of preweaning babies, and may also have a long-term effect throughout adult life (Kim et al. 2000; Wu et al. 2006). Available evidence shows that impaired lactogenesis occurs in women in response to many factors, including malnutrition (either obesity or undernutrition), maternal and fetal stress (e.g., extreme environmental temperatures), and hormonal imbalance (Dewey 2001; Rasmussen 2007). Similarly, primiparous sows (sows in the first lactation period) have a limited ability to produce milk because they have underdeveloped mammary tissue, low voluntary feed intake during lactation, and a prolonged catabolic state during both gestation and lactation (Kim 1999; Trottier 1997). Because of ethical concerns over lactation research with women and children, swine is often used as an animal model to study mammary gland development and the underlying regulatory mechanisms.

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Amino acids (AA) are not only building blocks for protein but are also key regulators of metabolic pathways that are critical to whole body homeostasis (Jobgen et al. 2006; Wu and Meininger 2000) and lactogenesis (Boyd et al. 1995). In primiparous sows, limited food intake and suppressed flow of blood to lactating glands result in reduced provision of nutrients (including AA) to mammary tissues for their own growth and milk synthesis (Kim et al. 1999a). Of particular interest, arginine is the common substrate for the generation of nitric oxide (NO; a major vasodilator and angiogenic factor) and polyamines (key regulators of protein synthesis and lactogenesis) (Meininger and Wu 2002; Wu and Morris 1998). Thus, modulation of the arginine-NO pathway may provide a new strategy to enhance the growth (including vascular growth) of mammary tissue and its uptake of nutrients, therefore improving lactation performance in mammals. The major objective of this article is to review the literature on utilization of AA for mammary gland growth and present new data to support our hypothesis that the arginine-NO plays an important role in regulating milk production and neonatal growth.

Sow's milk production limits potential piglet growth

Sow's ability to produce milk greatly affects piglet growth and survival (Kim et al. 2000). Normal healthy piglets possess the ability to ingest a greater amount of milk than that available from sows. Growth of piglets reared by artificial milk feeding was 22–31% greater than the piglets nursed by sows (Boyd et al. 1995; Zijlstra et al. 1996). However, artificial milk feeding has not yet been accepted by the swine industry mainly due to high costs for dietary ingredients, facilities, and maintenance. Recent studies have identified that arginine (an essential AA for neonates) is remarkably deficient in sow's milk (Wu and Knabe 1994; Wu et al. 2007a, b) due to its extensive catabolism by lactating tissue (O'Quinn et al. 2002). Both growth and metabolic data indicate that arginine deficiency is a major factor limiting maximal growth of milk-fed piglets (Frank et al. 2007; Kim and Wu 2004; Wu et al. 2004). Thus, augmenting arginine availability may have great potential to improve lactation performance in mammals.

Important role for mammary tissue growth in milk production

Milk synthesis occurs in mammary epithelial cells, which take up nutrients from blood circulation and synthesize milk components (Trottier 1997). The newly synthesized milk is secreted to the mammary alveolar lumen and duct system and then released to piglets after an oxytocin surge (Boyd et al. 1995). Thus, the number of mammary cells and the amount of nutrients availability to those mammary cells are the critical determinants of milk production. Sows need a large amount of AA to support mammary tissue growth and milk synthesis during lactation (Kim et al. 1999b). AA serve as precursors for the synthesis of milk protein and fat (Boyd et al. 1995). Some AA (leucine, isoleucine, valine, and lysine) are inhibitors of arginase (Hrabak et al. 2008), an abundant enzyme that degrades arginine in mammary tissue (O'Quinn et al. 2002), therefore increasing the availability of arginine for milk protein synthesis.

Mammary tissue growth occurs during gestation (Ji et al. 2005, 2006) and continues in suckled glands during lactation (Kim et al. 1999b) whereas non-suckled glands undergo rapid involution (Kim et al. 2001) in sows. For example, the wet weight of individual suckled mammary gland increases by 55% and total amount of its DNA doubles between Days 5 and 21 of lactation (Kim et al. 1999b). The amounts of lysine and essential AA in sow's milk are 1.2 and 7.0 g/day, respectively, on Days 5 to 21 of lactation (Kim et al. 1999b). Trottier et al. (1997) reported that 49.0 g/day essential AA were taken up by sow's mammary glands but only about 14% of them were accreted largely as protein in milk. Thus, 86% of essential AA taken up by the lactating gland could be catabolized locally. However, except for arginine (O'Quinn et al. 2002) and branched-chain AA (Conway and Hutson 2000), pathways for the catabolism of other essential AA have not been established for mammary tissue.

The growth of mammary glands is maximal when sows are provided with 55 g lysine and 16.9 Mcal metabolizable energy daily during lactation (Kim et al. 1999a, c; Fig. 1). However, National Research Council (NRC 1998) recommended only 49 g/day lysine for lactating sows. The difference of 6 g/day lysine could be accounted for by the need for growth of mammary tissue during lactation, which was not considered by NRC (1998). There is much evidence that increasing the amount of nutrients available to mammary glands is critical to enhance AA uptake for milk production (Kim et al. 1999a; Guan et al. 2002). However, the low voluntary feed intake of primiparous sows impedes a sufficient supply of nutrients to mammary tissue for growth and development. Interestingly, the amount of AA taken up by the mammary gland does not change (Trottier et al. 1997) despite the increased number of its epithelial cells (Kensinger et al. 1986; Kim et al. 1999b) with advanced lactation, indicating a diminished rate of AA transport by these cells.

Increasing blood flow provides more nutrients to mammary tissue

The amount of nutrients available to mammary tissue can be enhanced by increasing either concentrations of

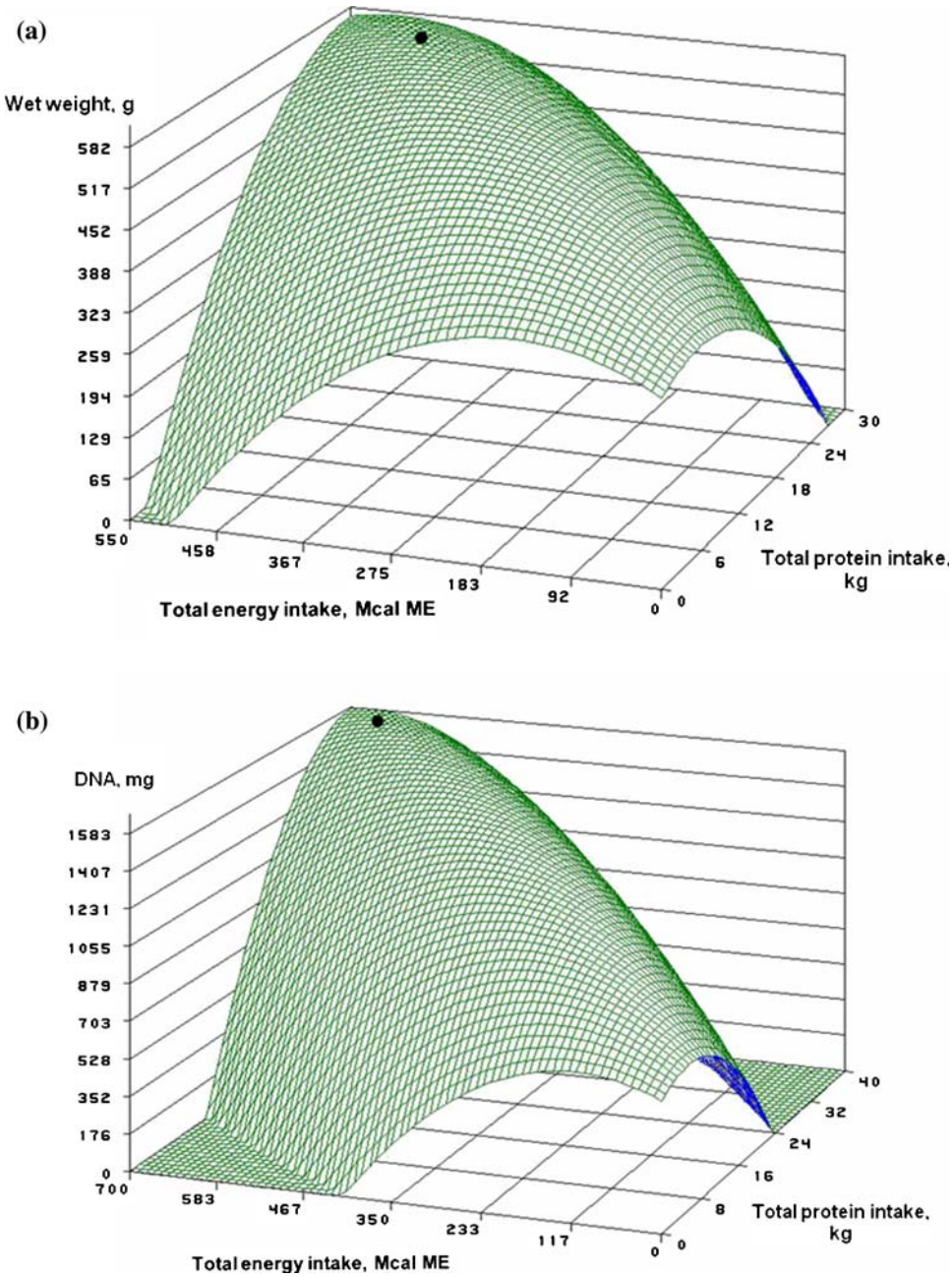

Fig. 1 **a** Response surface plot of the weight of suckled individual mammary glands from sows fed different levels of energy and protein. Weights of suckled individual mammary glands are affected by maternal protein and energy intake during lactation. **b** Response surface plot of the DNA amount in suckled individual mammary glands from sows fed different levels of energy and protein. DNA contents in suckled individual mammary glands are affected by maternal protein and energy intake during lactation. *Filled circle* maximum stationary point. Day of lactation when the maximum stationary point occurred was 25.3 (Adapted from Kim et al. 1999a)

nutrients in blood and/or the rate of its flow to the lactating gland (Renaudeau et al. 2002). As a stimulator of NO synthesis by endothelial cells, insulin is one of the major factors that increase blood flow (Scherrer and Sartori 1997). However, plasma concentrations of insulin are low in lactating primiparous sows (Mejia-Guadarrama et al. 2002), contributing to reduced blood flow to mammary tissue. In primiparous sows, because low voluntary feed intake is an obstacle to increasing the provision of dietary AA to the systemic circulation, enhancing blood flow to lactating glands can be an attractive alternative approach to augment milk production.

NO enhances blood flow to mammary glands

NO regulates blood flow in animals via a cGMP-dependent mechanism (Moncada et al. 1989). A short-term (6 h) arterial infusion of an NO donor (diethylamine NONOate with a half-life of 2.1 min) at the dose of 0.5 mg/h increased the rate of blood flow to mammary glands of 50–70 kg goats by 250% (Lacasse and Prosser 2003). This study also indicated that a short-term increase in mammary blood flow did not affect milk production by goats. However, because milk production is determined by the number of functional mammary epithelial cells, availability of

nutrients, and activities of milk-synthetic enzymes (Kim 1999), a short term increase of blood flow to the mammary gland may not be sufficient for enhancing the proliferation and number of these cells or augmenting cellular concentrations of substances (e.g., polyamines and proteins) that regulate lactogenesis.

Increasing NO availability through dietary supplementation with arginine improves lactation performance

Direct administration of the NO gas to target cells in vivo is not practical for lactating sows because of its extremely short half-life (<5 s) (Moncada et al. 1989), technical challenge, and potential toxicity at a high level (Fang et al. 2002). Thus, use of arginine facilitates the safe delivery of supplemental NO to animal tissues (Mateo et al. 2007; Wu and Meininger 2002). We found that supplementing 0.83% L-arginine (as 1% L-arginine–HCl) to the diets of primiparous sows enhanced litter weight gain and milk production by 21% in the first week of lactation and by 11% during a 21-day suckling period (Mateo et al. 2008). Notably, in our recent study, the arginine treatment increased the daily weight gain of low-birth-weight piglets (40%) to a greater extent than that of normal-birth-weight piglets (15%) (Table 1), likely because low-birth-weight piglets have a reduced ability to synthesize arginine due to both reduced mass and dysfunction of the small intestine (Wang et al. 2008). These findings have important implications for improving the growth and survival of piglets and human infants with prior experience of intrauterine growth retardation, a significant problem in both animal agriculture and human medicine (Wu et al. 2006).

Protein concentration was greater in the milk of arginine-supplemented primiparous sows than in control sows despite similar feed intake (Table 1). In addition, dietary arginine supplementation increased plasma concentrations of insulin and reduced plasma levels of urea (the major nitrogenous product of AA degradation) (Mateo et al. 2008). Taken together, these results indicate increased uptake of AA by lactating glands and increased efficiency of the utilization of dietary AA for milk protein synthesis in arginine-supplemented sows. Arginine-enriched (e.g., soybean, peanut and fish meals; NRC 1998) or citrulline-abundant foods (e.g., watermelon products; Wu et al. 2007a, b) are expected to have great potential to enhance NO production and cell proliferation in mammary tissue

Table 1 Growth performance of low- and normal-birth-weight piglets nursed by primiparous sows fed diets supplemented with or without L-arginine between Days 0 and 14 of lactation

Item	Control-fed sows		Arginine-supplemented sows	
	NBW piglets	LBW piglets	NBW piglets	LBW piglets
Body weight of piglets (kg)				
Day 0	1.36 ± 0.05	0.71 ± 0.03 *	1.38 ± 0.04	0.70 ± 0.03 *
Day 7	2.31 ± 0.08	1.19 ± 0.05 *	2.70 ± 0.10 †	1.45 ± 0.06 *†
Day 14	3.75 ± 0.14	1.86 ± 0.09 *	4.16 ± 0.17 †	2.31 ± 0.12 *†
Daily weight gain of piglets (g/day)				
Days 0 to 7	136 ± 5.6	69.0 ± 3.3 *	189 ± 8.7 †	106 ± 4.5 *†
Days 7 to 14	207 ± 9.3	95.8 ± 6.1 *	210 ± 9.0	123 ± 6.3 *†
Days 0 to 14	173 ± 7.9	82.3 ± 4.6 *	199 ± 8.4 †	115 ± 5.8 *†
Milk intake by piglets, ml/kg body weight				
Day 7	302 ± 18	294 ± 21	326 ± 24	312 ± 20
Day 14	253 ± 13	241 ± 16	267 ± 15	259 ± 18

LBW low birth weight, *NBW* normal birth weight

Gilts (Yorkshire × Landrace dams and Duroc × Hampshire sires) were bred at ~100 kg body weight and fed daily 2.0 kg of a sorghum- and soybean meal-based diet containing 14.0% crude protein, 0.80% arginine, 1.25% proline, and 0.61% lysine (Wu et al. 1995). Between days 0 and 14 of lactation, primiparous sows had free access to drinking water and the basal diet supplemented with either 1.0% L-arginine–HCl or 1.7% L-alanine (isonitrogenous control). Arginine or alanine was added to the basal diet at the expense of cornstarch. There were ten sows in each treatment group. On the day of farrowing, two normal-birth-weight (1.3–1.5 kg) piglets and two low-birth-weight (0.60–0.80 kg) littermates were chosen from each of ten sows in a treatment group for weekly measurements of body weight and milk consumption (Wu et al. 2004). Litter size was equalized to be nine per sow on Day 0. On Day 7, milk was obtained for analysis of amino acids (Wu and Knabe 1994), and protein concentration was 40.3 ± 0.6 and 43.8 ± 0.8 g/L ($P < 0.05$), respectively, for control and arginine-supplemented sows. Feed intake was 4.93 ± 0.17 and 5.04 ± 0.19 kg/day during the 14-day period of lactation, respectively, for control and arginine-supplemented sows ($P > 0.05$). Data are means ± SEM, and analyzed by two-way ANOVA (SAS, Cary, NC, USA) with sow as the experimental unit

* $P < 0.01$: different from the corresponding NBW piglets

† $P < 0.01$: different from the corresponding control (alanine-supplemented) group

(Wu and Meininger 2002). The outcome would be to stimulate vascular and alveolar tissue growth, the supply of nutrients to lactating glands, and milk production by sows and other mammals.

Delivery of NO through dietary supplementation with an NO donor improves lactation performance

Organic nitrates release NO through reactions catalyzed by glutathione-*S*-transferases, cytochrome P450 reductase, or microsomal proteins in cells (Miller and Megson 2007). However, nitrate intolerance caused by tissue thiol depletion is a major limitation of using organic nitrates as an NO donor (Packer et al. 1987). New NO donors without this limitation have been developed, which include diazeniumdiolates, *S*-ntrosothiols, mesoionic oxatriazoles, and diethylenetriamine-NO adduct (DETA). These NO donors are stable in the solid form and have long half-lives in vivo. Of particular interest, DETA has a half-life of 20 and 56 h in aqueous solution (Miller and Megson 2007) and 0.1 M phosphate buffer (pH 7.4; Hrabie et al. 1993), respectively. Thus, DETA can be an ideal source of NO for animals.

Intravenous infusion of DETA into rabbits at the dose of 0.1 mg/kg body weight substantially increased circulating levels of NO (Takano et al. 1998). A toxic level of DETA was reported to be 3.5 mg/kg body weight when it was infused intravenously into rats and rabbits (Gabikian et al. 2002). We found that supplementing DETA (50 mg/day) to the diets of primiparous sows between Days 7 and 21 of lactation enhanced the growth of nursing pigs by 11% (36.5 vs. 40.5 kg of litter weight) (Fig. 2). The dietary supplementation of DETA did not affect the maternal body weight loss or voluntary feed intake of sows (Table 2). Similar results were obtained from a subsequent titration study with 0, 25, and 50 mg/day of DETA (Fig. 3; Table 3). In both experiments, dietary supplementation of DETA had no adverse effect on the health of sows or piglets. Collectively, results of our study indicate that increasing NO provision can improve the efficiency of utilization of nutrients for milk production by lactating sows. It is likely that blood flow to mammary tissue and thus its uptake of nutrients from the circulation are enhanced in DETA-supplemented lactating sows.

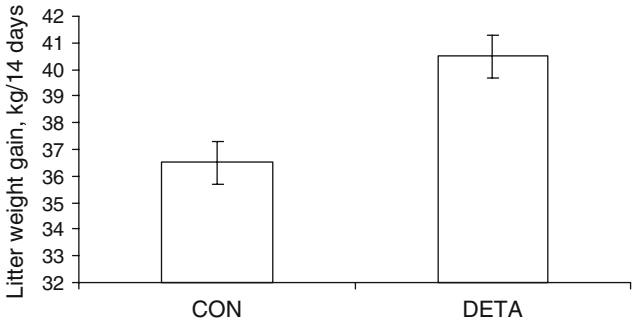

Fig. 2 Litter weight gain of the sows was increased by dietary supplementation of DETA between Days 7 and 21 of lactation. Primiparous sows (Camborough 22, Pig Improvement) with the average litter size of 11.5 ± 0.3 piglets were fed corn- and soybean meal-based diets (Mateo et al. 2008) supplemented with 0 (control) or 50 mg/day DETA (Sigma Aldrich Co., St Louis, MO, USA) between Days 7 and 21 of lactation. There were 5 and 4 sows in the control and DETA supplementation groups, respectively. Litter weight gains of piglets during the 14-day period of lactation differed ($P < 0.05$) between the two groups of sows, as analyzed by one-way ANOVA with sow as the experimental unit (SAS, Cary, NC, USA). CON, Control; DETA, 50 mg/day DETA

Table 2 Body weight, backfat thickness, and feed intake of primiparous sows fed diets supplemented with or without DETA between Days 7 and 21 of lactation

Item	DETA (mg/day)		SEM	*P* value
	0	50		
Number of sows	5	4		
Litter size	11.4	11.5	0.29	0.879
Body weight loss (kg/day)				
Days 7 to 14	1.39	0.68	0.36	0.367
Days 14 to 21	1.03	0.89	0.09	0.475
Days 7 to 21	1.21	0.79	0.44	0.354
Backfat loss (mm)				
Days 7 to 14	0.4	0.0	0.28	0.511
Days 14 to 21	0.4	0.5	0.24	0.853
Days 7 to 21	0.8	0.5	0.41	0.741
Feed intake (kg/day)				
Days 0 to 7	5.47	5.39	0.33	0.917
Days 7 to 14	6.71	6.63	0.39	0.927
Days 14 to 21	7.76	8.41	0.38	0.432
Days 7 to 21	7.24	7.52	0.37	0.725

Data are means with pooled SEM. Results were as analyzed by one-way ANOVA with sow as the experimental unit (SAS, Cary, NC, USA)

Conclusion and perspectives

Growth of nursing neonates depends on adequate milk yield from their lactating mothers. Mammary gland growth, which occurs during gestation and lactation, is critical to lactogenesis. Although AA play an important role in mammary gland growth and milk synthesis, optimal requirements of these nutrients for lactation have not been established for any species. As a common substrate for the synthesis of NO and polyamines, arginine regulates both angiogenesis and lactogenesis in mammary tissue. In support of this notion, supplementing an appropriate dose of

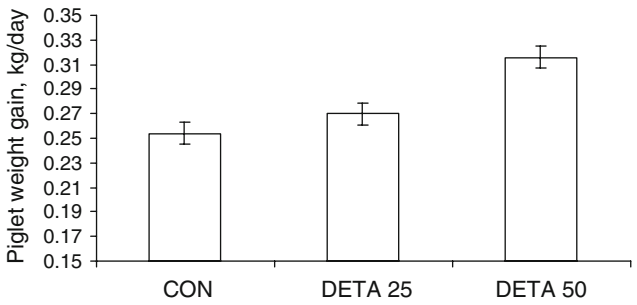

Fig. 3 Weight gain of piglets nursed by sows was increased in response to dietary supplementation of 50 mg/day DETA between Days 9 and 15 of lactation. Primiparous sows (Camborough 22, Pig Improvement) with the average litter size of 9.58 ± 0.19 piglets were fed corn- and soybean meal-based diets (Mateo et al. 2008) supplemented with 0 (control), 25 or 50 mg/day DETA (Sigma Aldrich Co., St Louis, MO) between Days 9 and 15 of lactation. There were four sows in each treatment group. The daily weight gain of piglets nursed by sows supplemented with 50 mg/day DETA was greater ($P < 0.05$) than that in the other two groups, as analyzed by one-way ANOVA with sow as the experimental unit (SAS, Cary, NC, USA). CON, control; DETA 25, 25 mg/day DETA; DETA 50, 50 mg/day DETA

Table 3 Body weight, backfat thickness, and feed intake of primiparous sows fed diets supplemented with or without DETA between Days 9 and 15 of lactation

	DETA (mg/day)			SEM	*P* value
	0	25	50		
Number of sows	4	4	4		
Litter size	9.75	9.50	9.50	0.36	0.856
Body weight loss (kg/day)					
Days 9 to 15	0.54	0.45	0.48	0.37	0.985
Feed intake (kg/day)					
Days 9 to 15	5.14	5.37	5.30	0.19	0.693

Data are means with pooled SEM. Results were analyzed by one-way ANOVA with sow as the experimental unit (SAS, Cary, NC, USA)

L-arginine or an NO donor to the diets of lactating primiparous sows effectively increases milk production and the growth of suckling piglets. We propose that increasing mammary gland growth (including vascular growth) and blood flow to mammary tissue is an effective strategy to improve lactation performance in mammals (including women and sows). Further studies with animal models (e.g., pigs, sheep, cows, and rats) are necessary to test this novel hypothesis. Additionally, it will be important to investigate how arginine and other AA may regulate expression and functions of key genes involved in mammary growth and milk synthesis.

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References

Boyd RD, Kensinger RS, Harrell RJ, Bauman DE (1995) Nutrient uptake and endocrine regulation of milk synthesis by mammary tissue of lactating sows. J Anim Sci 73(Suppl 2):36–56

Conway M, Hutson SM (2000) Mammalian branched-chain aminotransferases. Methods Enzymol 324:355–365

Dewey KG (2001) Maternal and fetal stress are associated with impaired lactogenesis in humans. J Nutr 131:3012S–3015S

Fang YZ, Yang S, Wu G (2002) Free radicals, antioxidants, and nutrition. Nutrition 18:872–879

Frank JW, Escobar J, Hguyen HV, Jobgen SC, Jobgen WS, Davis TA, Wu G (2007) Oral N-carbamylglutamate supplementation increases protein synthesis in skeletal muscle of piglets. J Nutr 137:315–319

Gabikian P, Clatterbuck RE, Eberhart CG, Tyler BM, Tierney TS, Tamargo RJ (2002) Prevention of experimental cerebral vasospasm by intracranial delivery of a nitric oxide donor from a controlled-release polymer. Stroke 33:2681–2686

Guan X, Bequette BJ, Calder G, Ku PK, Ames KN, Trottier NL (2002) Amino acid availability affects amino acid transport and protein metabolism in the porcine mammary gland. J Nutr 132:1224–1234

Hrabak A, Bajor T, Meszaros G (2008) The inhibitory effect of various indolyl amino acid derivatives on arginase activity in macrophages. Amino Acids 34:293–300

Hrabie JA, Klosie JR, Wink DA (1993) New nitric oxide-releasing zwitterions derived from polyamines. J Org Chem 58:1472–1476

Ji F, Wu G, Blanton JR Jr, Kim SW (2005) Changes in weight and composition in various tissues of pregnant gilts and their nutritional implications. J Anim Sci 83:366–375

Ji F, Hurley WL, Kim SW (2006) Characterization of mammary gland development in pregnant gilts. J Anim Sci 84:579–587

Jobgen WS, Fried SK, Fu WJ, Meininger CJ, Wu G (2006) Regulatory role for the arginine-nitric oxide pathway in metabolism of energy substrates. J Nutr Biochem 17:571–588

Kensinger RS, Collier RJ, Bazer FW (1986) Ultrastructural changes in porcine mammary tissue during lactogenesis. J Anat 145: 49–59

Kim SW (1999) Mammary gland growth and nutrient mobilization in lactating sows: a dynamic model to describe nutrient flow. PhD Thesis, University of Illinois at Urbana, Champaign

Kim SW, Wu G (2004) Dietary arginine supplementation enhances the growth of milk-fed young piglets. J Nutr 134:625–630

Kim SW, Hurley WL, Han IK, Stein HH, Easter RA (1999a) Effect of nutrient intake on mammary gland growth in lactating sows. J Anim Sci 77:3304–3315

Kim SW, Hurley WL, Han IK, Easter RA (1999b) Changes in tissue composition associated with mammary gland growth during lactation in the sow. J Anim Sci 77:2510–2516

Kim SW, Osaka I, Hurley WL, Easter RA (1999c) Mammary gland growth as affected by litter size in lactating sows: impact on lysine requirement. J Anim Sci 77:3316–3321

Kim SW, Hurley WL, Han IK, Easter RA (2000) Growth of nursing pigs related to the characteristics of nursed mammary glands. J Anim Sci 78:1313–1318

Kim SW, Easter RA, Hurley WL (2001) Regression of non-suckled mammary glands during lactation in sows as influenced by the stage of lactation, dietary nutrients, and litter size. J Anim Sci 79:2659–2668

Lacasse P, Prosser CG (2003) Mammary blood flow does not limit milk yield in lactating goats. J Dairy Sci 86:2094–2097

Mateo RD, Wu G, Bazer FW, Park JC, Shinzato I, Kim SW (2007) Dietary L-arginine supplementation enhances the reproductive performance of gilts. J Nutr 137:652–656

Mateo RD, Wu G, Moon HK, Carroll JA, Kim SW (2008) Effects of dietary arginine supplementation during gestation and lactation on the performance of lactating primiparous sows and nursing piglets. J Anim Sci 86:827–835

Mejia-Guadarrama CA, Pasquier A, Dourmad JY, Prunier A, Quesnel H (2002) Protein (lysine) restriction in primiparous lactating sows: effects on metabolic state, somatotropic axis, and reproductive performance after weaning. J Anim Sci 80:3286–3300

Meininger CJ, Wu G (2002) Regulation of endothelial cell proliferation by nitric oxide. Methods Enzymol 352:280–295

Miller MR, Megson IL (2007) Recent developments in nitric oxide donor drugs. Br J Pharmacol 151:305–321

Moncada S, Palmer RM, Higgs EA (1989) Biosynthesis of nitric oxide from L-arginine: a pathway for the regulation of cell function and communication. Biochem Pharmacol 38:1709–1715

NRC (1998) Nutrient requirements of swine, 10th edn edn. National Academy Press, Washington, DC

O'Quinn PR, Knabe DA, Wu G (2002) Arginine catabolism in lactating porcine mammary tissue. J Anim Sci 80:467–474

Packer M, Lee W, Kessler PD, Gottlieb SS, Medina N, Yushak M (1987) Prevention and reversal of nitrate tolerance in patients with congestive heart failure. N Engl J Med 317:799–804

Rasmussen KM (2007) Association of maternal obesity before conception with poor lactation performance. Annu Rev Nutr 27:103–121

Renaudeau D, Lebreton Y, Noblet J, Dourmad JY (2002) Measurement of blood flow through the mammary gland in lactating sows: methodological aspects. J Anim Sci 80:196–201

Scherrer U, Sartori C (1997) Insulin as a vascular and sympathoexcitatory hormone: implications for blood pressure regulation, insulin sensitivity and cardiovascular morbidity. Circulation 96:4104–4113

Takano H, Tang XL, Qiu Y, Guo Y, French BA, Bolli R (1998) Nitric oxide donors induce late preconditioning against myocardial stunning and infarction in conscious rabbits via an antioxidant-sensitive mechanism. Circ Res 83:73–84

Trottier NL (1997) Nutritional control of amino acid supply to the mammary gland during lactation in the pig. Proc Nutr Soc 56:581–591

Trottier NL, Shipley CF, Easter RA (1997) Plasma amino acid uptake by the mammary gland of the lactating sow. J Anim Sci 75:1266–1278

Wang JJ, Chen LX, Li DF, Yin YL, Wang XQ, Li P, Dangott LJ, Hu WX, Wu G (2008) Intrauterine growth restriction affects the proteomes of the small intestine, liver and skeletal muscle in newborn pigs. J Nutr 138:60–66

Wu G, Knabe DA (1994) Free and protein-bound amino acids in sow's colostrum and milk. J Nutr 124:415–424

Wu G, Morris SM Jr (1998) Arginine metabolism: nitric oxide and beyond. Biochem J 336:1–17

Wu G, Meininger CJ (2000) Arginine nutrition and cardiovascular function. J Nutr 130:2626–2669

Wu G, Meininger CJ (2002) Regulation of nitric oxide synthesis by dietary factors. Annu Rev Nutr 22:61–86

Wu G, Bazer FW, Tuo W (1995) Developmental changes of free amino acid concentrations in fetal fluids of pigs. J Nutr 125:2859–2868

Wu G, Knabe DA, Kim SW (2004) Arginine nutrition in neonatal pigs. J Nutr 134:2783S–2390S

Wu G, Bazer FW, Wallace JM, Spencer TE (2006) Intrauterine growth retardation: Implications for the animal sciences. J Anim Sci 84:2316–2337

Wu G, Collins JK, Perkins-Veazie P, Siddiq M, Dolan KD, Kelly KA, Heaps CL, Meininger CJ (2007a) Dietary supplementation with watermelon pomace juice enhances arginine availability and ameliorates the metabolic syndrome in Zucker diabetic fatty rats. J Nutr 137:2680–2685

Wu G, Bazer FW, Davis TA, Jaeger LA, Johnson GA, Kim SW, Knabe DA, Meininger CJ, Spencer TE, Yin YL (2007b) Important roles for the arginine family of amino acids in swine nutrition and production. Livest Sci 112:8–22

Zijlstra RT, Whang KY, Easter RA, Odle J (1996) Effect of feeding a milk replacer to early-weaned pigs on growth, body composition, and small intestinal morphology, compared with suckled littermates. J Anim Sci 74:2948–2959