Dietary nucleotides – the foundation for the future

by Dr Jules Taylor-Pickard, Solutions Deployment Team Manager, Alltech, Europe.

The American Institute of Nutrition held a seminar in 1994 entitled 'Dietary Nucleotides: A recently demonstrated requirement for cellular development and immune function'.

The purpose of the symposium was to consider research that had been accumulating over the previous two decades, suggesting that under certain circumstances dietary nucleotides were 'semi-essential' dietary requirements for humans and animals alike.

Previously, the nutritional requirement of the animal for nucleotides was thought to be supplied through 'de novo' synthesis within the cell when the salvage of nucleotide material from the breakdown of food and/or tissue within the body was inadequate. Quan (1992) depicted the maintenance of the nucleotide pools in the enterocyte, given either the presence or absence of dietary nucleotides.

In the absence of dietary nucleotide sources, dietary amino acids were required to maintain the pool, while this was less prevalent when there was a source of nucleotides given in the diet.

Uauy, Quan and Gil (1994) and Kulkarni, Rudolph and Van Buren (1994) presented their research at the symposium suggesting that in circumstances of disease challenge or where rapid/widespread intestinal repair was required, nucleotide supplementation of the diet conveyed a significant benefit to the recipient – in this instance, human babies.

Reduced immunity

Kulkarni et al (1994) suggested 'a nucleotide-free diet adversely affected the proliferative responses of T cells', thus reducing immunocompetence and the ability of the host to successfully survive a disease challenge.

Indeed these authors asserted that their 'studies clearly demonstrate that dietary nucleotides, in addition to energy and protein alone, are required to restore and sustain the cellular immune system in times of nutritional stress.'

The implication is that under maintenance conditions or limited growth and no disease challenge, 'de-novo' synthesis of nucleotides may be adequate to maintain the nutritional status of the host but that when growing quickly or fighting a disease challenge (stress conditions), the availability of dietary nucleotides conveys significant survival advantages to the host.

More recently, Sanchez-Pozo and Gil (2002) wrote 'in certain circumstances, and for some tissues, a lack of dietary nucleotides may impair important functions, suggesting a key nutritional role. Cellular proliferation …requires significant amounts of nucleotides…some tissues such as the lymphoid tissue or the intestine have a low biosynthetic capacity, probably being dependent on exogenous supply'.

Table 1. Nucleotide monophosphates in the milk from cow, goat, sheep and sow at different stages of lactation (Barness, 1994 and Mateo et al., 2004).

	Nuleotide monophosphate (umol/litre)			
	0-1 day	1-2 day	5-10 day	1 month
Adenine monophosphate				
Cow	39.7	61.8	41.9	27.5
Goat	37.8	47.0	62.7	61.0
Sheep	210.9	297.3	144.2	93.6
Sow	33.4	-	128.0	30.0
Guanine monophosphate				
Cow	ND	ND	ND	ND
Goat	ND	ND	ND	ND
Sheep	11.5	34.6	4.9	ND
Sow	54.0	-	140	71
Cytidine monophosphate				
Cow	31.9	52.5	47.4	33.2
Goat	40.6	64.5	53.3	49.1
Sheep	167.9	327.5	150.2	74.3
Sow	15.0	-	71.0	9.8
Uridine monophosphate				
Cow	186.3	390.0	31.2	ND
Goat	59.9	537.7	120.1	143.3
Sheep	1022.8	1133.0	584.6	250.9
Sow	5556.0	-	2631.0	1040.0

Item	Day of lactation					
	0	3	7	14	21	28
Total Milk Solids (%)	26.7	23.4	19.4	18.2	18.8	19.2
Adenine 5'monophosphate	4.0	11.3	12.8	6.8	4.3	3.0
Cytidine 5'monophosphate	1.5	7.1	7.1	3.5	2.3	1.0
Guanine 5'monophosphate	5.4	14.7	14.0	10.2	6.0	7.1
Inosine 5'monophosphate	1.1	1.8	2.6	1.4	0.9	0.4
Uradine 5'monophosphate	555.6	305.6	263.1	144.0	122.8	104.0

Table 2. Concentration of total milk solids and 5'monophosphate nucleotides in colostrum and milk from sows at different stages of lactation (Mateo et al., 2004).

Essential for new DNA

Domeneghini, Giancamillo, Arrighi and Bosi (2006) defined the conditions under which nucleotides may become essential nutrients as 'certain disease states in which a loss of gastrointestinal mass occurs and periods of limited nutrient intake or rapid growth'. This suggests that the period after weaning is a time when the piglet may benefit from the supply of exogenous nucleotides.

Nucleotides are the building blocks necessary for making new DNA and RNA.

There are five molecules referred to as nucleotides – adenosine, guanosine (both referred to chemically as purines) and cytosine, thymidine and uradine (collectively referred to as pyrimidines).

In the DNA helix, the rungs are made of a combination of two different nucleotides – guanosine and cytosine pair together while adenosine and thymidine form the second combination. In RNA uradine replaces thymidine in the molecular structure.

What all this means is that nucleotides are essential for the generation of new DNA – culminating in the generation of new cells which allow growth of new tissue or replacement of cells that have died or sloughed off (Koppel, 2004).

After birth young mammals avail of an abundant supply of nucleotides in their mother's milk. Barness (1994) presented figures (Table 1) indicating the levels of nucleotides in the milk of the cow, goat and sheep, while Mateo et al. (2004) reported the levels in sow's milk.

The data in Table 1 shows very marked differences in the quantity of the various nucleotides in the milk of each species, but the significance of this is as yet unknown.

Mateo, Peters and Stein (2004) reported the amount of nucleotides present in the milk of sows over a 28 day long lactation. Their results (Table 2) show that of the five nucleotides measured, uridine monophosphate (UMP) was quantitatively the highest but that the secretion concentration of all five followed the same pattern.

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UMP represents 98% of the nucleotides in colostrum and 86-90% of the nucleotides in milk from sows.

Mateo et al. (2004) have also suggested that 'the 5-monophosphate nucleotide concentration found in this study may serve as a starting point for nucleotide supplementation studies in weanling pigs'.

Mateo and Stein (2004) analysed the nucleotide levels in the raw materials used in baby piglet diets (Table 3) and showed that the dietary raw materials were substantially lower in all the nucleotides, with the exception of cystidine, than that present in sow's milk, concluding that the diets were therefore deficient in this regard.

Repair of DNA damage

Salobir, Rezar, Pajk and Levart (2005) conducted research to investigate the significance of dietary nucleotides in the repair of lymphocyte DNA caused by oxidative stress induced by high levels of dietary poly-unsaturated fatty acids.

The trial involved piglets starting at 11.9kg liveweight, fed to a level of feed that was very similar to that which would be expected in commercial practice.

The outcome of their work was that high levels of poly-unsaturated fatty acids in the diet did increase the rate of lymphocyte DNA damage but that nucleotide supplementation reversed this affect.

The research showed that the nucleotide supplementation did not prevent the damage in the cell due to lipid oxidation.

The authors concluded that 'the mode of action of supplemented nucleotides in prevention of DNA damage induced by high oxidative load is most likely the improved supply of nucleotides for the mechanisms of excision and repair of damaged parts of the DNA molecules of immune and possibly other cells.

The results also indicate that in the case of oxidative stress, the demand for nucleotides increases over the endogenous supply and that dietary sources are required 'for pigs of this weight'.

Response to infection

Yu, Wu, Yang, Liu, Lee and Yen (2002) studied the effect of adding glutamine and nucleotides in the diet of four week old weaned pigs, experimentally vaccinated against foot and mouth disease (FMD).

Their results suggested that nucleotide levels of 1000ppm resulted in faster growth in the four weeks after weaning and that average duodenal and jejunal villus height was higher when nucleotide and glutamine was added to the diet.

In addition their work showed that the glutamine-nucleotide supplemented diets led to a more rapid protection/immune response following FMD vaccination.

A difference, the authors suggest, may 'reduce the risk of piglets becoming infected with FMD virus.'

Interestingly, the supply of nucleotides at 1000ppm was more effective than when they were added to the diet at 500ppm.

Intestinal structure

Research has shown that piglets fed diets with added nucleotides retain longer villus length in the period after weaning than those fed the control diet. Indeed, Martinez-Puig, Manzanilla, Morales, Borda, Perez, Pineiro and Chetrit (2007) have shown that villus height fell from 448um in unweaned pigs to 275um in weaned control animals, but remained at 351um or 378um when either 500ppm or 1000ppm of nucleotide was added to the diet following weaning.

Cellular energy utilisation

Sanchez-Pozo and Gil (2002) reported that 'synthesis of nucleotides from amino acids and phosphoribosylpyrophophate is an energy consuming process and therefore the utilisation of exogenous nucleotides may be beneficial from a bioenergetic point of view.' This suggests that in circumstances where feed intake is low, de novo synthesis of nucleotides would further restrict the growth potential of the pig.

Table 3. Nucleotide concentrations in some commonly used feed ingredients (as fed basis).

Ingredient	Nucleotide (mg/g) AMP	CMP	GMP	IMP	UMP
Barley	0.001	0.002	0.001	0.001	0.000
Casein	0.000	0.001	0.000	0.000	0.000
Corn	0.002	0.003	0.003	0.001	0.000
Fish Meal	0.011	0.026	0.002	0.035	0.001
Naked oats	0.003	0.003	0.003	0.001	0.001
Plasma (spray dried)	0.002	0.002	0.002	0.001	0.000
Red blood cells (spray dried)	0.044	0.000	0.003	0.006	0.002
Soyabean meal	0.006	0.016	0.003	0.002	0.009
Soy protein concentrate	0.001	0.000	0.002	0.001	0.000
Dried whey	0.019	0.270	0.000	0.004	0.001
NuPro (Alltech Inc)	0.940	0.196	0.105	-	0.337

Treatment	Control	NuPro 4% in the diet from weaning to 21days post weaning
Number of pigs	79	91
Age at weaning (days)	20.4	18.8
Liveweight (kg)		
Weaning	5.97	5.25
21 days post weaning	9.25	9.99
40 days post weaning*	18.0	19.1

*A standard diet was fed to both groups from 21 days post weaning

Table 4. Trial results showing the benefits of using NuPro.

Commercial impact

The research quoted above suggests that exogenous supply of nucleotides will promote more efficient use of energy, improved immune response to infection, a reduction in the impact of oxidative stress and improved intestinal structure.

All of this should allow the pig eating diets with nucleotides incorporated in them to grow more quickly and efficiently.

A trial carried out at the National Committee for Pig Production in Denmark, showed that inclusion of NuPro from Alltech Inc (a feed ingredient rich in nucleotides) increased liveweight not only during the period in which it was included in the diet but thereafter as well.

Conclusions

The consensus of research over the last 30-40 years is that under conditions of nutrient deprivation, disease, stress and/or oxidative challenge, nucleotide supplementation of the diet can result in improved immune status, intestinal competence and physical growth.

The commercial challenge for the pig industry is to isolate the periods when nucleotide addition to the diet will result in financial advantage.

This challenge is made all the more difficult due to the lack of information within the individual research reports as to the quantity of the individual nucleotide molecules used in that particular study. ■

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