Effects and Functions of Copper on Nutrient Utilization in Growing Pigs

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Summary

Copper is involved in metabolic reactions and is important for oxidation-reduction reactions, transport of oxygen and electrons, and protection against oxidative stress. It is common to include high levels of Cu (i.e., 75 to 250 mg/kg) in nursery diets and, in some cases, grower-finisher diets may also include high levels of Cu to improve pig growth performance and health. However, the mechanism(s) by which dietary Cu exerts these positive effects on pig performance has never been fully elucidated. Results of recent experiments indicate that the consistently observed improvement in growth performance upon Cu supplementation is likely a result of the ability of dietary Cu to modulate intestinal microbial populations, stimulate secretion of neuropeptide Y and growth hormone, indirectly improve the immune response, and influence post-absorptive metabolism of lipids in pigs. However, the optimum amount and duration of feeding supplemental Cu in diets for pigs need to be further investigated. Future research also needs to focus on determining potential interactions of Cu with non-nutritive feed additives.

Introduction

Copper is involved in metabolic reactions including cellular respiration, tissue pigmentation, hemoglobin formation, and connective tissue development. Copper is an essential component of several metalloenzymes including ceruloplasmin, cytochrome C oxidase, lysyl oxidase, cytosolic Cu-Zn superoxide dismutase, extracellular Cu-Zn superoxide dismutase 3, monoamine oxidase, and tyrosinase (Manto, 2014). Copper, therefore, is important for oxidation-reduction reactions, transport of oxygen and electrons, and protection against oxidative stress. The requirement for Cu by pigs is influenced by dietary factors and age of the animal. Neonatal and growing pigs usually require 5 to 10 mg of Cu per kg of diet for normal metabolism and as pigs get older, the requirement for Cu decreases (NRC, 2012). The Cu that is included in pig diets usually originates from plant and animal based feed ingredients or from inorganic sources. Cereal grains, oilseed meals, and plant coproducts typically contain 4 to 30 mg/kg of Cu, but the amount of Cu present within each plant feed ingredient may vary depending on the variety, type of soil on which plants grow, maturity stage, and climatic conditions during growth (Underwood and Suttle, 1999). Supplemental Cu is provided by fortifying complete diets and premixes with inorganic Cu, which can be in the form of Cu sulfate ($CuSO_4$), Cu chloride, chelated Cu, Cu amino acid complexes, monovalent Cu oxide, and Cu hydroxychloride.

Although the requirement for Cu is low, it is common practice to include high levels of Cu (i.e., 75 to 250 mg/kg) in nursery diets, and in some cases, grower-finisher diets may also include high levels of Cu. The objective of this paper is to present the current understanding of nutritional value of Cu and effects of pharmacological levels of Cu on growth performance, intestinal health, nutrient digestibility, gut microbiome, and lipid metabolism of pigs. Gaps that need to be addressed to maximize inclusion of Cu in diets to improve growth performance will also be discussed.

Growth Promoting Levels of Cu

One of the alternatives for antibiotic growth promoters is dietary pharmacological levels of Cu. Supplementing Cu to diets fed to weanling pigs at 75 to 250 mg/kg may reduce post weaning diarrhea and improve average daily gain (**ADG**) and average daily feed intake (Cromwell et al., 1998; Hill et al., 2000; Perez et al., 2011). Reduction in diarrhea frequency and increased feed efficiency were also observed when a high concentration of Cu was included in diets for pigs (Espinosa et al., 2017). Supplemental Cu also increases feed efficiency of nursery pigs exposed to a heat stress challenge (Espinosa et al., 2019b).

Addition of Cu at 250 mg/kg in diets for weanling pigs containing 5% animal fat improved growth performance, and it was speculated that this is due to the ability of Cu to improve animal fat utilization (Dove and Haydon, 1992; Dove, 1993). Therefore, a recent experiment was conducted to determine the energetic value of dietary Cu in comparison with choice white grease (CWG; Espinosa et al., 2021). Pigs were fed diets with increasing concentrations of extracted fat by adding 2.0, 4.0, or 6.0% CWG to a diet based on corn, soybean meal, and distillers dried grains with solubles, which contained no CWG. Based on the improvement on feed efficiency that was observed upon supplementation of CWG to the diets, a prediction equation for the energetic value of each percent of CWG was generated. Two additional diets were formulated by adding 150 mg/kg of added Cu to the diet without added CWG and to the diet with 2% added CWG. Results indicated that supplementation of Cu to the diet without added CWG and to the diet containing 2% CWG improved feed efficiency of pigs. Based on the prediction equation, it was calculated that the improvement obtained by Cu supplementation was similar to the improvement in feed efficiency obtained by adding 2.8 to 3.8% CWG to the diets (Figure 1).

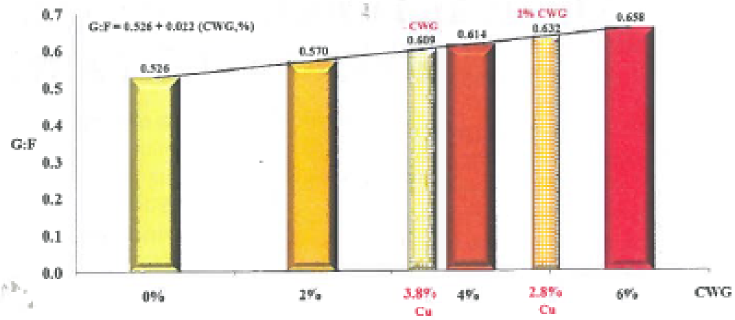

Figure 1. Choice white grease (CWG) equivalency of 150 mg/kg of Cu.

Effect of Cu on fat and energy digestibility

To understand how Cu increases feed efficiency in pigs, an experiment was conducted to test the hypothesis that supplemental Cu increases digestibility of fat and energy in pigs. In this experiment, 64 pigs were allotted to eight dietary treatments (Espinosa et al., 2021). A basal diet based on corn, soybean meal, and corn bran was formulated. Three additional diets were then formulated by adding 15, 30, and 45% distillers dried grains with solubles to the basal diet. The last four diets were formulated by adding 150 mg/kg of Cu to the first four diets. Results demonstrated that the apparent total tract digestibility (**ATTD**) of gross energy in diets containing supplemental Cu was not different from values for diets without supplemental Cu (Table 1). However, Cu improved the ATTD of fat by reducing the endogenous loss of fat (i.e., from 11.23 to 7.14 g/kg dry matter intake; Table 2). However, values for the true total tract digestibility of fat in diets without or with supplemental Cu were not different.

Effect of Cu on gut microbiome and health of pigs

One hypothesized mode of action for Cu is that Cu affects the bacteriostatic properties in the intestinal tract with a subsequent improvement in gastrointestinal health and immune function of pigs. Therefore, an experiment was designed to test the hypothesis that supplemental Cu changes concentration of microbial protein in the small intestine or

Table 1. Apparent total tract digestibility (ATTD) of dry matter (DM), gross energy (GE), and acid hydrolyzed ether extract (AEE) of pigs fed diets with increasing concentrations of distillers dried grains with solubles (DDGS) without or with 150 mg/kg Cu[1].

	No added Cu				150 mg/kg Cu					P-value		
Item	0% DDGS	15% DDGS	30% DDGS	45% DDGS	0% DDGS	15% DDGS	30% DDGS	45% DDGS	Pooled SEM	DDGS	Cu	DDGS × Cu
ATTD of DM	82.2	81.9	83.4	84.9	81.5	82.1	83.2	84.4	0.60	<0.001	0.399	0.882
ATTD of GE	82.3	81.7	82.8	84.4	81.6	81.7	82.4	83.4	0.69	0.002	0.204	0.819
ATTD of AEE	41.4	38.5	53.6	64.0	52.7	55.0	63.7	70.0	3.88	<0.001	<0.001	0.594

[1]Data are least squares means of 8 observations for all treatments.

Table 2. Regression coefficients of apparent total tract digested acid hydrolyzed ether extract (AEE; g/kg dry matter intake) on dietary AEE intake (g/kg dry matter) of pigs fed diets with increasing concentrations of distillers dried grains with solubles (DDGS) without or with 150 mg/kg Cu[1].

Item	Regression equation	Slope		Intercept		R^2	Estimated TTTD[2] of AEE	Estimated endogenous loss of fat[3]
		SE	P-value	SE	P-value			
DDGS	$y = 0.8282x - 11.23$	0.0660	<0.001	2.6737	<0.001	0.85	0.828	11.23[y]
DDGS + Cu	$y = 0.8185x - 7.14$	0.0404	<0.001	1.6305	<0.001	0.94	0.819	7.14[x]

[x,y]Means that do not have a common superscript tended to differ ($P < 0.10$).
[1]Regression analyses of apparent total tract digested AEE on dietary AEE intake was linear ($P < 0.01$).
[2]TTTD = true total tract digestibility.
[3]Gram per kilogram dry matter intake.

in the large intestine of pigs (Espinosa et al. 2019a). Results indicated that supplementation of Cu to diets reduced the concentrations of total volatile fatty acids and microbial protein in feces. Therefore, these observations indicate that the improved feed efficiency that was observed in pigs upon Cu supplementation is likely due to the effect of Cu in reducing selected microbial populations in the intestinal tract. This may have reduced the number of toxins and pathogenic microorganisms that could have negatively affected intestinal health, which may have reduced incidence of diarrhea and positively influenced immune response in pigs. Indeed, supplementation of Cu has been reported to positively influence cytokine concentrations and superoxide dismutase in blood serum of weanling pigs (Gonzales-Eguia, 2009; Espinosa et al., 2020a)

Effect of Cu on post-absorptive metabolism of lipids

In addition to the impact on intestinal health of pigs fed dietary Cu because of reduced microbial populations, the mode of action of Cu also was hypothesized to be related to systemic effects. Administration of high concentration of Cu via intravenous injection improved growth performance in previous experiments. This response was hypothesized to be attributed to the effect of Cu on increasing the mRNA expressions of growth hormone releasing hormone and neuropeptide Y in the hypothalamus of pigs (Li et al., 2008; Yang et al., 2011). In rabbits and fish, the effect of Cu on improving body mass gain is attributed to its role in increasing mRNA expression of fatty acid binding proteins and fatty acid transport proteins (Chen et al., 2016; Lei et al., 2017). To test the hypothesis that similar results can be obtained in pigs, another experiment was designed to investigate effects of Cu on feed efficiency and mRNA abundance of genes involved in lipid metabolism of pigs (Espinosa et al., 2020b). It was demonstrated that supplementation of Cu to diets increased mRNA abundance of lipoprotein lipase, fatty acid binding protein, and carnitine palmitoyl transferase 1B in the subcutaneous adipose tissue of pigs. Therefore, it was concluded that it is possible that the improved growth performance of pigs fed the Cu-supplemented diets is a result of improved lipid metabolism, which may have improved energy utilization.

Gaps

Supplementation of Cu to diets for weanling and young growing pigs has been a common practice due to its consistent improvement in growth performance. However, this may not be the case with finishing pigs as the response in growth performance is quite variable (Coble et al., 2018). Davis et al. (2002) demonstrated increased final body weight of finishing pigs fed diets supplemented with 175 mg/kg of Cu. However, Carpenter et al. (2017) and Forouzandeh et al. (2022) reported no positive effect of supplementing Cu at 130 to 250 mg/kg. In contrast, finishing pigs had increased ADG and feed efficiency when fed diets containing 20 mg/kg of supplemental Cu (Wen et al., 2022). Therefore, the optimum amount and duration of feeding supplemental Cu in diets fed to pigs also need to be further investigated.

Aside from Cu, other alternatives to antibiotic growth promoters are commonly used. These alternatives include probiotics, acidifiers, prebiotics, phytobiotics, and dietary pharmacological levels of Zn (Liu et al., 2018). Use of exogenous enzymes (e.g., xylanase and phytase) in pig diets is also rapidly increasing to enhance nutrient digestibility and pig performance. In some cases, commercial pig diets contain one or more of these feed ingredients; however, the mechanism of action and interactions among these products have not been fully elucidated. Therefore, further research needs to focus on determining potential interactions of Cu with non-nutritive feed additives.

Conclusion

Dietary inclusion of 75 to 250 mg/kg of Cu reduces diarrhea frequency and improves growth performance of pigs. Results of several experiments demonstrated that the consistent improvement in growth performance of young growing pigs upon Cu supplementation to diets is likely a result of the ability of dietary Cu to modulate intestinal microbial populations, stimulate secretion of neuropeptide Y and growth hormone, indirectly improve the immune response, and influence post-absorptive metabolism of lipids in pigs. To maximize the use of Cu in pig diets, potential interactions of Cu with non-nutritive feed additives, as well as the optimum amount and duration of feeding supplemental Cu in diets fed to pigs need to be further investigated.

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