

Impact of Microbial Phytase on Plasma Inositol in Weanling Pigs

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Abstract

Inositol is a ring-formed sugar that is needed for a number of physiological functions in the body including energy utilization, maintenance of the immune system, and integrity of cell membranes. Inositol can be synthesized by pigs from glucose and it has not been considered a limiting nutrient. However, results of recent research have demonstrated that pigs do not maintain pre-weaning levels of plasma inositol during the initial 4 to 6 weeks post-weaning and during this time, they may be immunologically compromised due to reduced plasma inositol. However, inositol is also present in phytate where it forms the ring-structure that chelates with up to 6 phosphate groups. Therefore, if phytase is added to diets, the ester bonds connecting the six phosphate groups to inositol will be hydrolyzed, which liberates the inositol in phytate. This inositol can then be absorbed, which enables weanling pigs to maintain plasma inositol at pre-weaning levels throughout the post-weaning period.

Introduction

In plant-based feed ingredients, most of the phosphorus (**P**) is bound to phytate (myo-inositol hexakisphosphate, IP₆; Cowieson et al., 2011; Lee et al., 2023). The portion of total P that is bound to phytate varies among feed ingredients. Corn contains 0.24 to 0.27% total P of which around 70% is phytate P, whereas soybean meal (**SBM**) contains 0.65% total P with approximately 60% as phytate P (Lee et al., 2023). Animal proteins, including spray-dried plasma and whey powder, contain no phytate because phytate is absent from animal tissues. Likewise, highly processed ingredients such as fermented SBM have reduced phytate-P compared with conventional SBM due to phytate degradation during fermentation (Rojas and Stein, 2012). Therefore, diets for weanling pigs typically contain less phytate than diets for growing pigs because they include animal protein sources and highly processed ingredients that contain little or no phytate. Because swine have low activity of endogenous phytase, the hydrolysis of phytate is limited and, therefore, the availability of P is reduced (Holloway et al., 2019). Phytase is the enzyme that hydrolyzes phytate to lower inositol phosphate, and exogenous phytase has been added to swine diets to increase P digestibility and reduce P excretion at a standard level of 500 phytase units (**FTU**)/kg (Moita and Kim, 2022).

Phytase and phytate

Phytate is the main storage form for P in plant ingredients (Cowieson et al., 2011) and it is composed of a complex structure with up to six phosphate molecules bound to a myo-inositol ring (Holloway et al., 2019). Pig diets may contain between 0.2 to 0.3% of phytate-P depending on the feed ingredients that are used in the diets and the processing conditions (Rodehutsord and Rosenfelder, 2016). Phytate is generally considered an anti-nutritional factor because it reduces the availability of nutrients to the pigs (Bedford and Walk, 2016). Phytate has 12 ionizable reactive sites, which results in a strongly negative charge at the pH range throughout the gastrointestinal tract and, therefore, phytate can chelate bind di- and trivalent cations such as Zn²⁺, Cu²⁺, Ni²⁺, Co²⁺, Mn²⁺, Fe²⁺, and Ca²⁺ in very stable complexes, reducing the availability of those minerals (Dersjant-Li et al., 2015). The extent to which any of those minerals inhibit the hydrolysis of phytate differs among cations, with Zn²⁺ having the greatest inhibitory effect, followed by Fe²⁺, Mn²⁺, Fe³⁺, Ca²⁺, and Mg²⁺. Differences among minerals are primarily associated with the stability of the phytate-mineral complex, solution pH, and the phytate-to-mineral molar ratio (Angel et al., 2002). As phytate remains relatively soluble under acidic conditions, complex formation is limited in the stomach and occurs primarily in the small intestine, where the higher pH favors the interaction between phytate and mineral ions (Angel et al., 2002). Because Ca is present in animal diets in greater concentrations than other cationic minerals,

phytate primarily forms complexes with Ca in the small intestine and can chelate up to six Ca atoms (Selle et al., 2009).

Phytate not only chelates minerals, potentially creating a deficiency, but also impairs digestion, which may reduce the digestibility of amino acids (AA) and energy (Bedford and Walk, 2016). One possible mechanism is that even at a low pH in the stomach, most of the dietary AA are positively charged, and as a result, insoluble protein-phytate complexes may be formed, reducing the efficiency of gastric digestion (Farhadi et al., 2019). In addition, to increase the solubility of these complexes, the pig may respond by increasing gastric acid secretion and lowering stomach pH (Yu et al., 2012). However, a more acidic environment may stimulate mucin secretion to protect the gastric epithelium (Onyango and Adeola, 2012), and because mucin is rich in threonine, serine, and proline (Lien et al., 1997), increased mucin production may increase endogenous AA losses and contribute to reduced AA digestibility.

Utilization of P from phytate and lower inositol phosphates requires the stepwise cleavage of phosphate groups from the inositol ring (Lagos et al., 2023). This hydrolysis is catalyzed by phytases and other phosphatases (Sandberg and Andlid, 2002). Phytases are not specific for phytate and can further catalyze the hydrolysis of lower inositol esters. Lower inositol phosphates can also be catalyzed by other phosphatases that cannot hydrolyze phytate (Rodehutschord and Rosenfelder, 2016). Standard phytase doses (e.g. 250-500 FTU/kg) may be sufficient to cleave phytate to IP₄, but insufficient to target full IP₄ hydrolysis, which may result in the accumulation of IP₄ or IP₃ in the intestinal tract (Mesina et al., 2019; Lagos et al., 2023). Previous data indicate that these lower esters retain antinutritional properties because they can bind minerals and interfere with proteolytic activity (Liu et al., 2009; Yu et al., 2012; Beeson et al., 2017). Therefore, further hydrolysis of IP₄ and IP₃ concentrations may contribute to improvements in nutrient digestibility and growth performance observed with high phytase inclusion rates.

The negative impact that phytate can have on nutrient utilization has increased interest in using phytase in concentrations greater than those required to meet the P requirement of pigs (Holloway et al., 2019). Increasing phytase inclusion beyond conventional levels facilitate the full hydrolysis of these lower esters and the release of the inositol ring (Moran et al., 2017; Laird et al., 2018; Moran et al., 2019; Lagos et al., 2023). Ileal concentrations of phytate decreased as phytase increased from 0 to 4,000 FTU/kg, whereas ileal inositol concentrations increased more than 35-fold, indicating extensive phytate breakdown (Lagos et al., 2023). These observations indicate that the benefits of high doses of phytase may be beyond improvements in P availability, as

the release of myo-inositol may provide additional physiological benefits to the pigs.

Role of inositol in the body

Inositols are a group of cyclic sugar alcohols that can exist in nine stereoisomeric forms, and among them, myo-inositol (referred to as inositol) is the most predominant and biologically important isomer in nature (Gonzalez-Uarquin et al., 2020; Quarta et al., 2025). Although inositol was historically classified as a member of the vitamin B complex and was often referred to as vitamin B₈, it is no longer considered a true vitamin because mammals can synthesize inositol endogenously from glucose (Regidor and Schindler, 2016; Antonowski et al., 2026). The synthesis begins with glucose entering the glycolytic pathway, where it is converted to glucose-6-phosphate. Glucose-6-phosphate is then converted to inositol-1-phosphate by the enzyme inositol-1-phosphate synthase, which represents the rate-limiting step in the inositol biosynthesis (Chen and Xiong, 2010; Sánchez-Hidalgo et al., 2021). Inositol monophosphatase then removes the phosphate group to generate free inositol (Antonowski et al., 2026). This synthesis occurs primarily in the kidneys, but other tissues such as liver, brain, and testis also synthesize inositol, but at much lower amounts compared with the kidneys (DiNicolantonio and O'Keefe, 2022). In addition to endogenous synthesis, pigs may obtain inositol from dietary ingredients, through the complete hydrolysis of phytate by phytase which releases free inositol that can be absorbed and utilized by the body, or by recycling from inositol phosphates and phosphatidylinositol (Gonzalez-Uarquin et al., 2020).

Inositol has a role in many physiological processes. Inositol is a precursor of phosphatidylinositol and its phosphorylated forms (i.e. PIP, PIP₂, PIP₃), which participate in signaling cascades such as the PI3K/Akt and PLC-IP₃/diacylglycerol pathways (Antonowski et al., 2026). The PI3K/Akt pathway regulates cellular growth, protein synthesis, glucose uptake, and insulin sensitivity (Manning and Cantley, 2007; Hers et al., 2011), whereas the PLC-IP₃/diacylglycerol pathway regulates intracellular Ca signaling through the generation of IP₃ and diacylglycerol. Upon activation, IP₃ stimulates Ca release from the endoplasmic reticulum, while diacylglycerol activates protein kinase C, together influencing hormone secretion, metabolism, immune responses, and other cellular processes (Nishizuka, 1992; Berridge, 1993). Inositol phosphates, including IP₃, IP₄, and IP₆ also function as signaling molecules involved in cell signal transduction and the regulation of diverse physiological processes such as muscle contraction, neurotransmission, and immune cell activation (Irvine and Schell, 2001).

Why is inositol important for weanling pigs

Weaning is one of the most stressful periods during the production cycle because it involves nutritional, environmental, physiological, and immunological changes. These changes result in reduced feed intake, impaired intestinal function, and activation of inflammatory responses, which can negatively affect growth performance (Pluske et al., 1997; Lallès et al., 2007). Recent research indicates that inositol may play an important role during this transition period because newly weaned pigs appear unable to maintain pre-weaning plasma inositol levels unless phytase is included in the diet (Moran et al., 2019; Lagos et al., 2021; Guan et al., 2025). Supplementation of microbial phytase increased phytate degradation and plasma inositol concentrations in weanling pigs. In pigs fed a diet without phytase, plasma inositol concentrations decreased from approximately 49 μM before weaning to 20 μM at 14 days post-weaning, which is a reduction of nearly 60%, whereas pigs fed phytase maintained plasma inositol concentrations within or above the pre-weaning range (Lagos et al., 2021). Pigs not receiving phytase did not recover pre-weaning plasma inositol concentrations until approximately 42 days after weaning (Lagos et al., 2021). Similar data have been reported from more recent experiments, which indicates that plasma inositol concentrations can be maintained at preweaning levels if pigs are fed diets containing phytase, whereas pigs fed diets without phytase experienced a reduction of approximately 50% in plasma inositol concentration (Guan et al., 2025; Mallea et al., 2025).

From the above experiments it was concluded that newly weaned pigs have a limited ability to maintain pre-weaning inositol status and may, therefore, benefit from phytase-derived inositol. Indeed, inositol may be a conditionally indispensable nutrient during the post-weaning period because the metabolic demand for inositol immediately after weaning may exceed the pig's capacity for endogenous synthesis (Moran et al., 2019). A dosing appears to be a result of a combination of the reduced anti-nutritional effects of phytate and increased generation of inositol, with these benefits being particularly evident during the immediate post-weaning period.

Whereas the positive effects of phytase-derived inositol on growth performance have been consistently observed, the physiological mechanisms associated with these responses have not been fully elucidated. One proposed mechanism involves the role of inositol in glucose metabolism and insulin signaling. Phytase supplementation increased the abundance of glucose transporter type 4 (GLUT4) in skeletal muscle plasma membranes (Lu et al., 2019). The GLUT4 is a glucose transporter primarily expressed in skeletal muscle and adipose tissue that responds to insulin stimulation. Under

similar concept has also been proposed for poultry, where inositol has been described as a semi-essential nutrient that may become limiting under certain physiological conditions despite the existence of endogenous synthesis pathways (Gonzalez-Uarquin et al., 2020). This indicates that periods of rapid growth or physiological stress may increase the dependence of pigs on dietary or phytase-derived sources of inositol.

Maintaining plasma inositol concentrations after weaning may have important implications for growth performance because increasing phytase inclusion not only elevates circulating inositol concentrations (Moran et al., 2019; Guan et al., 2025; Mallea et al., 2025) but also improves feed efficiency and growth performance in young pigs (Laird et al., 2016; Moran et al., 2017; Laird et al., 2018; Holloway et al., 2019; Lu et al., 2019; Moran et al., 2019; Lagos et al., 2021; Mallea et al., 2025). Supplementation of 2,500 FTU/kg phytase improved average daily gain (ADG) and gain to feed (G:F) ratio regardless of levels of dietary energy and amino acids demonstrating that the response was independent of nutrient deficiency and likely related to the extra-phosphoric effects of phytase. A linear increase in ADG and G:F was reported in weanling pigs as dietary phytase increased from 0 to 12,500 FTU/kg (Veum et al., 2006). Likewise, a dose-dependent improvement in ADG and G:F in weanling pigs supplemented with up to 15,000 FTU/kg phytase have been observed (Kies et al., 2006). Similar improvements in growth performance have also been observed under commercial production conditions, where supplementation with phytase at super-dosing levels improved feed efficiency and growth performance in weanling pigs, with the greatest responses observed at approximately 2,500 FTU/kg phytase (Moran et al., 2017). The enhanced growth performance may be partially explained by the complete hydrolysis of phytate and release of inositol (Moran et al., 2019; Lagos et al., 2021). Therefore, the improvements in growth performance associated with phytase super-

normal physiological conditions, insulin promotes the movement of GLUT4 to the plasma membrane, increasing glucose uptake from the bloodstream into tissues (Kahn, 1996). Because myo-inositol is involved in signaling pathways associated with insulin action, it has been proposed that some of the growth-promoting effects of inositol may be related to enhanced glucose uptake and utilization, as well as improved nutrient partitioning and protein accretion (Cowieson et al., 2015; 2017).

An additional implication of increased inositol availability may be the modulation of inflammatory responses. Pigs fed phytase had reduced plasma concentrations of tumor necrosis factor-alpha on day 28 after weaning compared with pigs fed the control diet (Mallea et al., 2025). Reduced concentrations of tumor necrosis factor-alpha indicate a reduced systemic

inflammatory status, which may allow nutrients and energy to be redirected from immune activation toward growth. Because activation of the immune system is energetically expensive, a reduction in inflammatory signaling may improve nutrient utilization and contribute to better feed efficiency. Inositol may also exert anti-inflammatory effects by reducing oxidative stress and suppressing activation of nuclear factor- κ B (NF- κ B), a key regulator of inflammatory responses (Quarta et al., 2025).

Phytase supplementation consistently increases plasma inositol concentrations in weanling, growing, and finishing pigs (Laird et al., 2016). However, improvements in growth performance have been observed mainly in weanling pigs, whereas increased availability of inositol in growing and finishing pigs has not consistently translated into improvements in ADG or G:F (Laird et al., 2016; Holloway et al., 2019). In poultry it was also observed that dietary inclusion of 0.1% inositol improved broiler feed efficiency, with the greatest response observed during the starter period, whereas improvements were less pronounced during the grower phase (Żyła et al., 2013).

Conclusions

Inositol has a number of important functions in the body, but in pigs more than six weeks post-weaning there is usually sufficient synthesis of inositol from glucose-6 phosphate to maintain plasma inositol at levels needed for normal body functions. However, it is apparent that newly weaned pigs do not have the ability to synthesize sufficient inositol and inclusion of microbial phytase, therefore, is needed to maintain pre-weaning levels of inositol in plasma. It is likely that at least 1,000 phytase units, and possibly more, is needed to liberate the inositol present in phytate, which allows pigs to absorb the inositol from phytate, and therefore, maintain pre-weaning levels of plasma inositol. By providing microbial phytase at generous levels in the post-weaning diets, pigs will not only maintain plasma inositol levels but also have improved growth performance and sometimes also reduced diarrhea.

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