METABOLISM AND NUTRITION

Myo-inositol: its metabolism and potential implications for poultry nutrition—a review

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ABSTRACT *Myo*-inositol (**MI**) has gained relevance in physiology research during the last decade. As a constituent of animal cells, MI was proven to be crucial in several metabolic and regulatory processes. *Myo*-inositol is involved in lipid signaling, osmolarity, glucose, and insulin metabolism. In humans and rodents, dietary MI was assessed to be important for health so that MI supplementation appeared to be a valuable alternative for treatment of several diseases as well as for improvements in metabolic performance. In poultry, there is a lack of evidence not only related to specific species-linked metabolic processes but also about the effects of dietary MI on performance and health. This review intends to provide information about the meaning of dietary MI in animal metabolism as well as to discuss potential implications of dietary MI in poultry health and performance with the aim to identify open questions in poultry research.

Key words: *myo*-inositol, phytate, metabolism, physiology, poultry nutrition

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INTRODUCTION

Inositol (cyclohexane-1,2,3,4,5,6-hexol) is a sugar cyclic polyalcohol whose epimerization of its hydroxyl groups generates 9 possible stereoisomeric forms (*myo*-inositol [**MI**], *scyllo*-inositol, *muco*-inositol, *D-chiro*-inositol, *L-chiro*-inositol, *neo*-inositol, *allo*-inositol, *epi*-inositol, and *cis*-inositol). Among these forms, *myo*-inositol (*cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol) is the predominant form occurring in nature (Turner et al., 2002; Pasta et al., 2015; Thomas et al., 2015). *Myo*-inositol has been suggested to be a member of the vitamin B group; however, this assumption was refuted because monogastric animals and humans could rely on their cellular biosynthesis (Regidor and Schindler 2016). Requirements for newborn human babies were generally met by body-own synthesis (Brown et al., 2009). However, dietary MI was found to effectively ameliorate certain endocrine diseases such as diabetes and insulin resistance (Croze and Soulange, 2013). Thus, MI may be considered as a semiessential substance, which could be limited at certain physiological and pathophysiological conditions.

It is synthesized *de novo* from glucose and by catabolism of phosphatidylinositol (**PI**), phosphoinositides (**PIP**), and inositol phosphates (**InsP**). Subsequently, it is utilized by the diacylglycerol pathway to generate new PIP (Di Daniel et al., 2009). Finally, in mammalians, MI is degraded in the kidney (Hankes et al. 1969; Chang et al., 2015a). In addition to the endogenous sources, MI absorbed by the gut epithelium was discussed as an essential source for MI in animal health and performance (Huber, 2016). *Myo*-inositol has strong physiological importance in a plethora of processes. Among its principal functions, MI participated in cellular signaling as a precursor of relevant biological compounds, including PIP and InsP (Beemster et al. 2002; Indyk et al., 2016). *Myo*-inositol also acted as an osmolyte in specific tissues, such as brain and kidney medulla, where osmolarity had a crucial biological meaning (Aouameur et al., 2007). It had also been postulated that MI is a modulator of glucose homeostasis and insulin regulation in humans and animal models of insulin resistance (Croze and Soulage, 2013). Several studies showed evidence for MI absorption existing in birds (Isaacks et al., 1982, 1989; Kohlmeier, 2003; Lee and Bedford, 2016; Sommerfeld et al., 2018b); however, the relevance of dietary MI in poultry metabolism is unknown. A few studies using MI as a dietary supplement resulted in variations of bone stability and general animal performance (Hegsted, 1941; Pearce,

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1975; Żyła et al., 2004, 2012, 2013a; Cowieson et al., 2013; Pirgozliev et al., 2017; Lee et al., 2017; Farhadi et al., 2017). Scientific interest in the role of MI in poultry metabolism emerged after recent studies showed that the enzyme phytase is able to release MI from *myo*-inositol-6-phosphate (**$InsP_6$**) in the gastrointestinal tract of poultry (Cowieson et al., 2015; Sommerfeld et al., 2018a; Pirgozliev et al., 2019). Knowledge about MI intestinal absorption, body-own transport, and metabolism in poultry is scarce, whereas more research has been conducted in other species including man. Therefore, the objective of this review was to summarize the published knowledge about MI metabolism in general and in particular for poultry and to discuss the potential implications of MI in poultry metabolism and nutrition.

PLANT AND ANIMAL SOURCES OF *MYO*-INOSITOL

Myo-inositol is contained in fresh fruits, vegetables, grains, meat, fish, eggs, milk, and many other foods (Clements and Darnell, 1980; Croze and Soulage, 2013). Hence, feed ingredients used in grain-based poultry nutrition provide some free MI; however, it had been widely reported that most of the MI in the organism that originated from the diet was obtained from gastrointestinal $InsP_6$ degradation (Holub, 1986; Selle and Ravindran, 2007; Kim et al., 2017). A recent study analyzed the content of the InsP in 7 tree nuts and in 3 grains that are rich in phosphorus and used for animal feeding (Duong et al., 2017). Tree nut species such as Brazil nuts, walnuts, pistachios, hazelnuts, and cashews contained high levels of total InsP (20.08, 6.64, 6.51, 5.15, and 5.02 μmol/g, respectively) in comparison to macadamia and pecan nuts (3.55 and 2.63 μmol/g; Duong et al., 2017). Seeds of different cereal grains contained InsP in different concentrations, but most were present in the form of $InsP_6$, whereas other InsP were present only in traces, except in seeds of barley (Rodehutscord et al., 2016a). For specific grain fractions, InsP levels of wheat aleurone and rice bran (63.85 and 97.36 μmol/g) were significantly higher than of corn germ (9.75 μmol/g). Percentage of $InsP_1$ and $InsP_2$ was higher in corn germ (3.4 and 4.6%, respectively) than in wheat aleurone (0.4 and 0.6%, respectively) and rice bran (0.1%). In these samples, total InsP levels ranged from 66.2 to 96.7% of the organic phosphorus content and from 58.4 to 80.3% of the total phosphorus content (Duong et al., 2017). Besides the sources and their intrinsic properties, factors such as soil type and agronomic details such as fertilization could also affect $InsP_6$ concentrations in plant seeds (Rodehutscord and Rosenfelder, 2016). While these InsP in the feed are an important source of MI for poultry, the dephosphorylation process in the digestive tract is not complete. Some differently phosphorylated InsP were found in the terminal ileum of broilers even when the diet contained high phytase supplements (Sommerfeld et al., 2018a,b). Hence, the amount of MI absorbed in the intestine cannot be predicted from InsP content of the feed.

MYO-INOSITOL TRANSPORT AND CELLULAR METABOLISM

Pathways of MI absorption, transport, and cellular metabolism are summarized in Figure 1. Chicken-specific knowledge about these pathways is also indicated.

Transepithelial Myo-*Inositol Absorption in the Intestine and Transport Into Tissues*

Dietary InsP were partially degraded by brush border membrane-associated endogenous phytases, phosphatases, pancreatic phospholipases, and microbial phytases, resulting in lower InsP and free MI in the digestive tract (Holub, 1986; Huber, 2016). Free MI was easily absorbed from the small intestine (Kohlmeier, 2003). It has been demonstrated in healthy humans that 99.8% of MI was absorbed in the gastrointestinal tract (Clements and Reynerston, 1977).

In rats, MI was transported by sodium and proton-dependent processes across the apical membrane of the enterocytes as the key step of MI absorption (Aouameur et al., 2007) as it was observed also in epithelial cells of rabbit kidney (Lahjouji et al. 2007). In chickens, mRNA of sodium/MI co-transporter 1 (**SMIT1**), sodium/MI co-transporter 2 (**SMIT2**), and H^+/MI co-transporter (**HMIT**) has been found in jejunum and ileum, which suggested that all 3 transporters could be involved in intestinal MI absorption (Walk et al., 2018). Most likely, the majority of MI was transferred into the bloodstream (Lewin et al., 1976) by an unknown secondary active transport system across the basolateral side of enterocytes driven by the sodium/potassium (Na^+/K^+)-ATPase (Holub, 1986).

After intestinal absorption, MI can reach body tissues via the bloodstream (Lewin et al. 1976); hypothetically, a portion of absorbed MI could be catabolized in the liver (Lee and Bedford, 2016). Basal MI concentrations in the blood of chicken ranged from 0.19 to 0.28 mmol/l (Oshima et al., 1964; Cowieson et al., 2015; Schmeisser et al., 2017; Sommerfeld et al., 2018b). All animal cells appeared to contain MI; however, its concentrations varied in different tissues (Battaglia et al., 1961). It has been reported that broilers supplemented with 3% MI (total diet) increased total weight of liver (Pirgozliev et al., 2019); however, until now, no data about MI concentrations in poultry tissues were reported. *Myo*-inositol concentrations in mouse liver and kidney were about 0.5 and 3.5 μmol/g wet weight, respectively (Croze et al., 2015). Intraperitoneal injection of radioactively labeled MI in male rats revealed that organs such as thyroid, brain, liver, spleen, kidney, reproductive tract, pituitary, and prostate gland actively accumulated MI (Eisenberg and Bolden, 1963;

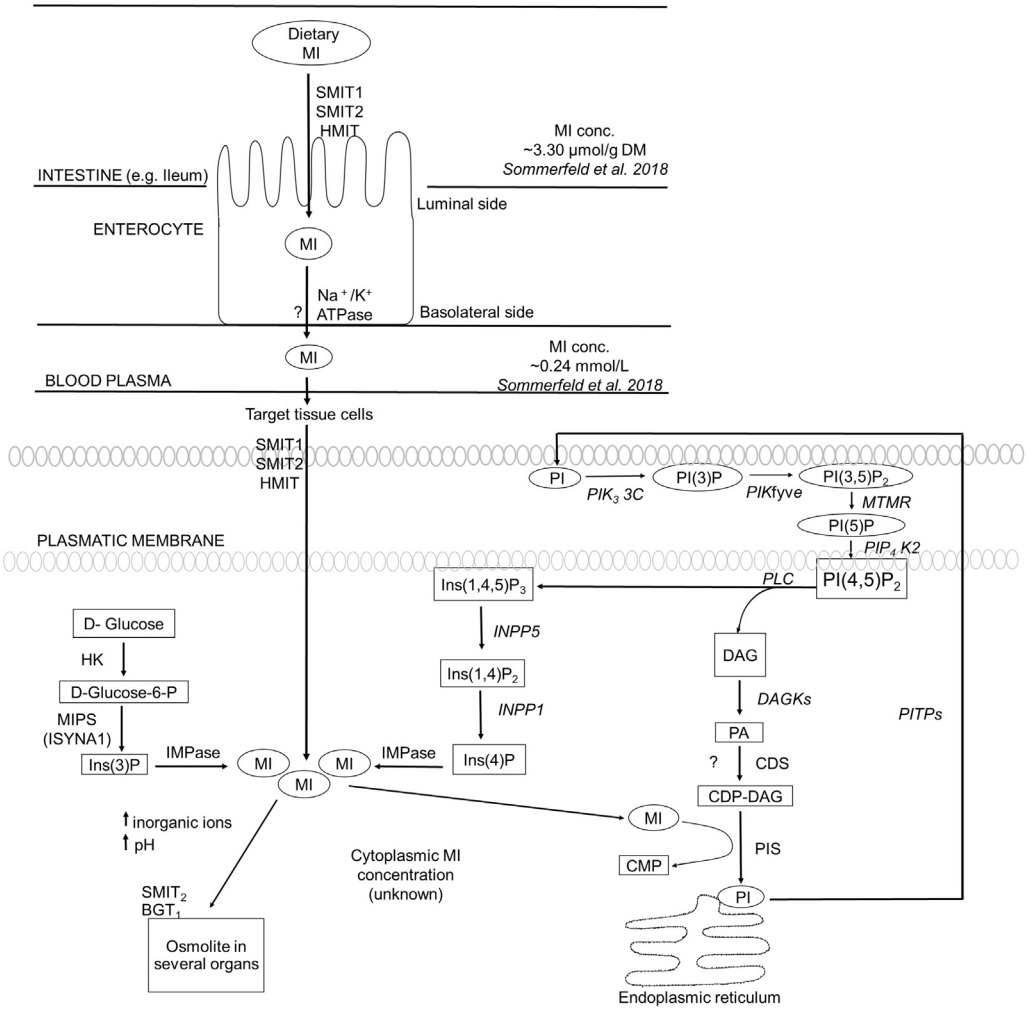

Figure 1. Absorption, transport, and cellular *myo*-inositol metabolism in KEGG *Gallus gallus* pathway (Kanehisa et al., 2017, 2019). MI is incorporated into the cell by 3 specific ways: (1) It is transported by SMIT1/2 or HMIT in the enterocyte and subsequently transported to target cells, (2) it is synthesized de novo from glucose metabolism, and (3) it is recycled from InsP phosphorylation. In the cytoplasm, free MI is utilized as osmolyte or transported to endoplasmic reticulum to be converted into PI to synthesize new $PI(4,5)P_2$; however, MI-associated pathways have been not characterized clearly in poultry. Concentrations of free MI in chicken have been reported at intestine and blood plasma; however, cellular values in different tissues remain unknown. Abbreviations: BGT1, betaine cotransporter 1; CDP-DAG, cytidine diphosphate diacylglycerol; CDS, CDP- diacylglycerol synthase; CMP, cytidine monophosphate; DAG, diacylglycerol; glucose-6-P, glucose-6-phosphate; DAGKs, diacylglycerol kinases; HK, hexokinase; HMIT, proton-linked myo-inositol transporter; IMPase, inositol monophosphatase; Ins(3)P, inositol 3-phosphate; Ins(4)P, inositol-4-phosphate; Ins(1,4)P2, inositol (1,4)-bisphosphate; I(1,4,5)P3, inositol-(1,4,5)tris-phosphate; INPP5, inositol-1,4,5-trisphosphate 5-phosphatase; INPP1, the inositol polyphosphate 1-phosphatase; MI, *myo*-inositol; PA, phosphatidic acid; MIPS (ISYNA1), inositol-3-phosphate synthase 1 isoform X1; Na+/K + -ATPase, sodium-potassium adenosine triphosphatase; pH, potential of hydrogen; MTMR, myotubularin-related protein; PI, phosphatidylinositol; PIP, phosphatidylinositol phosphate; PI(3)P, phosphatidylinositol 4-phosphate; PI(5)P, 1-phosphatidyl-1D-myo-inositol 5-phosphate; PI(3,5)P2, 1-phosphatidyl-1D-myo-inositol 3,5-bisphosphate; PI(4,5)P2, phosphatidylinositol-(4,5)bisphosphate; PIP4K2, phosphatidylinositol 5-phosphate 4-kinase type-2; PIS, phosphatidylinositol synthase; PITPs, phosphatidylinositol transfer proteins; PIK3 3C, phosphatidylinositol 3-kinase catalytic subunit type 3 isoform X2; PIKfyve, 1-phosphatidylinositol 3-phosphate 5-kinase isoform X1; PLC, phospholipase C; SMIT1/2, sodium-linked myo-inositol transporter 1 and 2.

Lewin et al. 1976). In contrast, adipose tissue and muscle accumulate less because of their limited *de novo* synthesis capacity (Lewin et al., 1976; Croze and Soulage, 2013), which will be explained in a later chapter. It is unknown the extent chicken tissues rely on MI biosynthesis. Entrance of MI into cells is transporter-dependent; SMIT1 and SMIT2 activity appeared to be induced by extracellular hyperosmolarity in cultured kidney cells (Bissonnette et al., 2008). Both transporters have been identified in many body tissues but predominantly in brain, intestine and kidney (Aouameur et al., 2007). The SMIT2, but not SMIT1, has been mainly located in kidney cortex where it potentially participated in MI reabsorption from the glomerular filtrate (Aouameur et al., 2007). The HMIT function (also known as GLUT 13) was restricted to brain inositol metabolism; however, mRNA (SLC2A13) has also been identified in rodent adipose tissue and kidney (Uldry et al. 2001) and in chicken intestine, kidney, and liver (Walk et al., 2018).

Cellular Synthesis of Myo-*Inositol*

As shown in Figure 1 and according to the KEGG's MI pathway for *Gallus gallus* (Kanehisa et al., 2017, 2019), chicken MI is derived from *de novo* synthesis

from glucose and generated from PIP and InsP (Di Daniel et al., 2009; Kanehisa et al., 2019). Regardless of the source, the ability of a cell to maintain sufficient levels of MI was crucial for the re-synthesis of PIPs and the maintenance and efficiency of signal transduction (Di Daniel et al., 2009). *De novo* synthesis of MI has been observed in rat liver, testis, kidney, and brain (Eisenberg and Bolden, 1963; Hauser and Finelli, 1963). As shown in Figure 1, MI was synthesized from D-glucose through 3 biochemical reactions. First, D-glucose was phosphorylated by hexokinase to glucose-6-phosphate; second, glucose-6-phosphate was isomerized by the NADH-dependent, cytosolic inositol-3-phosphate synthase to inositol 3-phosphate; and finally, inositol 3-phosphate was dephosphorylated to free MI by inositol-monophosphatase (**IMPase**) for further use in the PI synthesis pathway (Dinicola et al., 2017). Clements and Diethelm (1979) demonstrated this process was of quantitative importance; for instance, in human kidneys, around 4 g MI/d were synthesized.

Dephosphorylation of InsP was the other important route of cellular MI generation (Figure 1). The critical intermediates were Ins(1,4,5)P_3 and Ins(1,3,4)P_3, both isoforms of InsP_3. Briefly, each isoform of InsP_3 was dephosphorylated by the inositol-1,4,5-trisphosphate 5-phosphatase into Ins(1,4) P_2. Ins(1,4)P_2 was converted to Ins(4)P_1 by the action of the inositol polyphosphate 1-phosphatase. InsP_1 was then converted into free MI by IMPase (Downes and Macphee, 1990; Abel et al., 2001, Di Daniel et al., 2009). Free MI fueled the PI synthesis in the endoplasmic reticulum by PI synthase using cytidine diphosphate diacylglycerol (**CDP-DAG**) as educt (Downes and Macphee, 1990; Vance, 2015). Then, PI was transported to the plasmatic membrane by PI transfer proteins (Selitrennik and Lev, 2016; Muallem et al., 2017). In the plasmatic membrane, PI was phosphorylated to PIns(3)P, which in turn was converted into PIns(5)P and then into PIns(4,5)P_2 (Kanehisa et al., 2019). PIns(4,5)P_2 has been reported to be hydrolyzed to diacylglycerol (**DAG**) by phospholipase C. DAG phosphorylation by the DAG kinase to phosphatidic acid (Muallem et al., 2017) was a crucial step in generating new liponucleotide CDP-DAG via CDP-DAG synthase (phosphatidate cytidylyltransferase). All pathways are deposited as chicken-specific at https://www.genome.jp/kegg-bin/show_pathway?gga00562 (Kanehisa et al., 2017, 2019).

Linkages Between Myo-*Inositol and Glucose Metabolism*

Myo-inositol and glucose metabolism are interlinked. There is a competition for sodium availability of the transport processes of MI (SMIT) and glucose (sodium-linked glucose transporter 1) as it was observed that elevated glucose concentrations in medium reduced MI uptake in rabbit peripheral nerve tissue (Greene and Lattimer, 1982). Furthermore, in cultured rat glomerular mesangial cells, Haneda et al. (1990) reported that an increase of glucose concentrations in the medium from 0 to 55 mmol/L decreased intracellular MI from about 12 nmol/mg protein to about 5 nmol/mg protein linearly. Increasing concentrations of MI in medium also decreased jejunal sodium-dependent glucose absorption in an *ex vivo* everted sac model (Chukwuma et al., 2016).

Myo-inositol could act as insulin mimetics and could play a relevant role in insulin-related diseases (Kim et al., 2014). Dietary MI has been demonstrated to reduce postprandial glucose levels and increase peripheral insulin sensitivity proved by indices in humans (Ortmeyer, 1996; Corrado et al., 2011). Some studies indicated that also inositol phosphoglycans (phospholipid-derived putative second messengers of insulin) might have an insulin-mimicking effect. In regard to mammalian species, detailed information about effects of MI on insulin metabolism can be found elsewhere (Larner et al., 2010; Croze and Soulage, 2013; Unfer et al., 2017; Bevilacqua and Bizzarri, 2018).

In chickens, a study conducted by Cowieson et al. (2013) showed MI added to a diet low in Ca and P increased blood glucose, insulin, and glucagon concentrations in comparison to a control diet. These findings may be explained by the aforementioned competition between MI and glucose for sodium to enable a secondary active transport (Greene and Lattimer, 1982). Dietary MI was shown to increase both the expression of protein kinase B (PKB/Akt) and the translocation of GLUT4 in presence of insulin in skeletal muscle of mice (Dang et al., 2010; Croze et al., 2012).Together with the up-regulation of PInsP_3 through activation of the insulin receptor substrate proteins (Croze et al., 2012), it indicates that high concentrations of circulating MI could lead to increases in levels of insulin to activate the PI pathway.

Renal Myo-*Inositol Catabolism and Handling*

Catabolism of MI is essential for regulation of inositol homeostasis, and it occurs mainly in the kidney (Howard and Anderson, 1967; Hankes et al., 1969, Chang et al. 2015b) via *myo*-inositol oxygenase (**MIOX**; Thorsell et al., 2008). *Myo*-inositol oxygenase is a nonheme iron enzyme, which converts MI to D-glucuronic acid (Arner et al. 2001, González-Álvarez et al., 2017). The subsequent steps involve the conversion of D-glucuronic acid to D-xylulose-5-phosphate, which subsequently goes into the pentose phosphate pathway (Arner et al., 2004). End products are used for oxidative energy production (Hankes et al., 1969; Lewin et al., 1976). Renal *myo*-inositol handling included excretion of MI into the primary urine and reabsorption into the blood of about 98% of excreted MI (Sarashina et al., 2004).

Therefore, the kidney appears to be the most important organ in regulation of plasma inositol concentration in animals and humans (Holub, 1986). Higher

glucose concentrations appeared to upregulate MIOX enzyme activity (Nayak et al., 2005). This regulation could be based (1) on polymorphisms in the promoter regions of MIOX gene (Yang et al., 2010), (2) on activation of several transcription factors by different forms of stress induced by hyperglycemia (Nayak et al., 2011), and (3) on posttranslational modification of MIOX. The latter is based on an increased phosphorylation of MIOX by kinases such as protein kinase A and C and the 3-phosphoinositide-dependent protein kinase 1 (Nayak et al., 2011). A significant concomitant effect caused by glucose-induced MIOX activity in human and porcine kidney cell cultures was the impairment of mitochondrial integrity which was based on increases in reactive oxygen species, on a higher apoptosis rate and on the reduction in autophagy processes (Zhan et al., 2015). It has not been reported whether these pathways are relevant in birds as well, and further research is necessary to clarify MI breakdown in poultry.

Intracellular Myo-*Inositol Depletion*

Intracellular MI depletion depends on intestinal MI absorption, cellular MI synthesis, efflux from organ cells, and increases of renal MI excretion (Croze and Soulage, 2013; Dinicola et al., 2017). Causes of cellular MI depletion are mainly associated with the reduction of IMPase, myo-inositol-3-phosphate synthase (**MIPS**), and glycogen synthase kinase 3 activity (Llewelyn, 2003; Harwood, 2005). Consequences of cellular MI depletion are the reduction of PIP and DAG concentrations, the decreases of Na+/K+ -ATPase activity (Azab et al., 2007; Deranieh and Greenberg, 2009), and also the impairment of cell development, transformation, and differentiation (Oishi et al., 1990; Steele et al., 1993; Hamada et al., 1996).

Intracellular MI depletion was observed to be associated with intracellular osmotic stress. An increase in intracellular osmolarity provoked MI release, and under chronic conditions, this led to intracellular MI depletion (Croze and Soulage, 2013). Furthermore, inhibitory substances like lithium and valproic acid most likely caused intracellular MI depletion. Lithium is a mood stabilizer that increased serotonin accumulation in the central nervous system but also blocked MI synthesis by inhibition of phosphatases inositol-1,4 bisphosphate 1-phosphatase (**IPP**) and IMPase (Harwood, 2005). Valproic acid (a branched, short-chain fatty acid) has been related to the inhibition of MIPS, blocking the conversion of glucose-6-phosphate to MI (Deranieh et al., 2015). Interestingly, it has been hypothesized that valproic acid and the concomitant depletion of MI led to an increase in the level of the phospholipid cardiolipin (Ju and Greenberg, 2003). Cardiolipin has been shown to be essential for the osmotic stability of the mitochondrial membrane, the maintenance of the mitochondrial membrane potential, and the oxidative phosphorylation efficiency (Jiang et al. 2000; Deranieh and Greenberg, 2009).

PHYSIOLOGICAL MEANING OF *MYO*-INOSITOL

Besides its insulin-mimetics properties, dietary MI appeared to be of biological importance for several metabolic functions. A deficiency of dietary MI was related to enhanced intestinal mucosa inflammation and apoptosis and to diminished cell proliferation, antioxidant capacity, and intestinal bacterial activity in grass carps (Li et al., 2017, 2018). Dietary MI has also been considered crucial for lipid metabolism, bone formation, skeletal muscle metabolism, reproduction, and nervous system development in humans and animals. Furthermore, an artificial knock-out mouse model with total SMIT1 depletion (**SMIT$^{-/-}$**) was used to determine the impact of MI for biological functions. The SMIT$^{-/-}$ mice died soon after birth due to respiratory failure because of a lack of functional surfactant (Hallman et al., 1985) but also because of malfunction of respiratory nerves (Chau et al., 2005); however, neonatal mortality was prevented by prenatal maternal MI supplementation (Chau et al., 2005). The SMIT$^{-/-}$ mice also expressed deficiencies of MI in brain, kidney, skeletal muscle, liver, and sciatic nerve causing detrimental impact on nerve conduction velocity (Chau et al., 2005), prenatal skeletal development, and postnatal bone remodeling (Dai et al., 2011).

Effects of Dietary Myo-*Inositol on Lipid Metabolism*

Although relationships between dietary MI and lipid metabolism have not been fully understood yet, it was hypothesized in recent years that MI could be relevant for adipocyte differentiation and for fatty acid metabolism. Dietary MI deficiency was associated with increases of liver triglycerides (**TG**) concentration in male rats (Hayashi et al., 1974).

Murine preadipocyte 3T3-L1 cells incubated with 10, 50, and 200 μmol/L MI increased differentiation in a dose-dependent manner but also enhanced capacity for lipid storage, glucose uptake, and decreased lipolysis rate (Kim et al., 2014). This was confirmed earlier by Croze et al. (2012), detecting that dietary MI decreased nonesterifed fatty acids in plasma of mice. Furthermore, it was shown that dietary MI increased plasma adiponectin concentrations which correlated negatively with TG content in liver of rats (Okazaki et al., 2018). Higher lipid storage was associated with activation of transcription factors (CCAAT/enhancer-binding protein α, peroxisome proliferator-activated receptor γ, and sterol regulatory element-binding protein 1c, higher extent of tyrosine phosphorylation and increased insulin receptor substrate 1, fatty acid synthase, and GLUT4 expression) (Kim et al., 2014). These results suggested that MI is an insulin mimetic also promoting adipose tissue lipid storage capacity and preventing ectopic fat deposition (Plows et al., 2017). In poultry, controversial effects of MI on lipid metabolism were reported. Whereas,

Farhadi et al. (2017) showed MI supplementation (0.15% total diet) to a diet low in Ca and P did not change concentrations of total cholesterol and TG in 21-day-old broilers, Cowieson et al. (2013) showed that MI (0.15% total diet) added to a diet low in Ca and P decreased both total cholesterol and TG in comparison to a standard diet in 42 D old broilers. Differences in these results could be likely attributed to a plethora of reasons, one of them may be the duration of MI supplementation, which would suggests the importance of tracking dietary MI over lifespan as a key molecule for lipid metabolism in poultry; this from the fact basal total cholesterol and TG concentrations have shown to increase along broiler's life span (Prasad et al., 2009). Broilers supplemented with MI showed decreases in 5 phosphatidylcholines (PCaaC34:1, PCaaC36:1, PCaaC40:3, PCaaC36:1, PCaaC36:3) and 2 lysophosphatidylcholines (lysoPC C16:1 and lysoPC C18:1), both important components of cell membrane and plasma phospholipids (Gonzalez-Uarquin et al., 2019, accepted). It could be explained by the fact that more MI availability could increase the use of phosphatidic acid for PI synthesis at the expense of phosphatidylcholine. In hens, despite lack of conclusive evidence, dietary MI (0.1% total diet) added to a corn-based diet showed to decrease polyunsaturated fatty acids of 20 carbon atoms (C-20) and total lipids content in comparison to hens supplemented a diet low in nonphytate phosphorus (Żyła et al., 2012).

Effects of Dietary Myo-*Inositol on Bone Formation*

Myo-inositol could be associated with mineral absorption and bone mineralization. For example, in rats, supplementation of inositol alone by orogastric intubation (20 mg/100 g of BW) caused a 48% increase of ^{45}Ca accumulation in bone within 24 h (Angeloff et al., 1977). Moreover, supplementations with arginine silicate inositol complex (Arg: 49.47%; silicone: 8.2%; inositol: 25%) significantly improved bone mineral density as well as Ca, P, and Mg concentrations in tibia ash in control and heat-stressed quails (Sahin et al., 2006). However, potential mechanisms of MI effects are unknown. In transgenic SMIT1$^{-/-}$ mice, SMIT1 deficiency caused reductions in postnatal bone mass and changes in bone morphometry generated by an impairment in embryonic bone development and remodeling. Furthermore, postweaning dietary MI supplementation partially rescued bone defects in adult SMIT1$^{-/-}$ mice (Dai et al., 2011). *Myo*-inositol supplementation by maternal milk in SMIT1$^{-/-}$ mice restored skeletal malformation developed during their embryonic phase. Even in healthy subjects, dietary MI improved bone structure and increased BW (Dai et al., 2011).

In poultry, significant increases in blood alkaline phosphatase, an enzyme related to osteoblastic activity, were reported after 3% MI (total diet) supplementation (Pirgozliev et al., 2019), suggesting that MI could reform new InsP at the intestinal lumen provoking new synthesis of alkaline phosphatase (Farhadi et al., 2017). Lee et al. (2017) detected that dietary MI tended to decrease bone strength, while Żyła et al. (2013a), Farhadi et al. (2017), and Sommerfeld et al. (2018b) found no changes in tibia ash content and thereby, most likely no changes in bone strength. Perhaps, the inconsistency of data from poultry studies was caused by different basal MI concentrations in the diet or by different concentrations of phosphorus and calcium in the diet. In this regard, a supplementation of monocalcium phosphate increased egg production and egg mass in comparison to hens fed MI (Żyła et al., 2012). Moreover, Żyła et al. (2004) found that supplementation of 0.1% MI (total diet) resulted in significant decreases of P retention. Interestingly, when MI was supplemented together with a high Ca/P ratio diet, toe ash concentration increased significantly.

Effects of Dietary Myo-*Inositol on Skeletal Muscle Metabolism*

Myo-inositol could affect glucose transporter and therefore glucose uptake in muscle cells. For example, oral application of MI to mice 30 min before an oral glucose tolerance test resulted not only in an increase of GLUT4 transporter translocation into skeletal muscle cell membranes compared with control but also in a lower glucose and insulin concentration in plasma (Dang et al., 2010). In SMIT1$^{-/-}$ mice, individuals supplemented with MI from birth until 10 weeks of age had higher levels of MI in skeletal muscle than individuals supplemented with MI until weaning only (Chau et al., 2005). Chickens fed a moderately phosphorus-deficient diet plus supplementation of microbial 6-phytase (1000 FTU/kg) increased blood MI concentrations in comparison to chickens fed a nonsupplemented diet. Furthermore, a higher breast meat weight and an increased expression of genes associated with muscle development (calmodulin/calcineurin and insulin-like growth factor) were observed. However, this could not be solely related to MI because lower InsP and free phosphate (P_i) might also influence muscle metabolism (Schmeisser et al., 2017).

Effects of Dietary Myo-*Inositol on Reproduction*

Free MI concentrations were significantly higher in testes than in plasma (Setchell et al., 1968). An importance of MI for male reproduction was considered based on the following points: (1) high levels of MIPS and IMPase exist within the testis of patient diagnosed with asthenozoospermia (Chauvin and Griswold, 2004), (2) MI functions in the regulation of osmolarity in Sertoli cells and seminal fluid, and (3) spermatozoa concentrations increase in patients with oligoasthenoteratozoospermia by MI supplementation (Condorelli et al., 2017). Sperms incubated with MI for 2 h had a significantly higher motility and a higher mitochondrial

Table 1. Published studies on dietary *myo*-inositol in poultry.

Reference	Poultry type	MI % (total diet)	Lifespan	Main diet components	Measured variable	MI effects
Hegsted et al., 1941 Dam, 1944	Broiler chickens White leghorn chicks	0.1 0.15	Day 1 to 28 From day 1	Dextrin/casein/cartilage. Sucrose/casein/yeast or Lard/starch/casein.	BW gain. A staircase curve for exudate and encephalomalacia.	↑BW. ↓Encephalomalacia and exudates.
Pearce, 1975	Ross broiler chickens	0.25	Week 1 to 8	Corn (conventional). Wheat + choline. Wheat + inositol.	BW gain. Mortality by FLKS. Liver weight, lipid content, DM, and lipogenic enzyme activities.	↓BW but did not affect the incidence of FLKS nor liver lipid metabolism.
Żyła et al., 2004	Ross broiler chickens	0.1	Day 1 to 21	Corn–soybean + 0.27% NPP/0.65% Ca or 0.47 NPP/0.80% Ca.	Performance (BW gain and feed intake). Bone mineralization (toe ash). Phosphorus and Ca retention.	↑BW gain. ↓P retention (In birds fed just with the diet with 0.27% NPP and 0.65% Ca diet).
Żyła et al., 2012	Bovans Brown laying hens	0.1	Week 50 to 62	Corn and wheat/soybean.	Layer performance, eggshell quality, yolk cholesterol, and fatty acid deposition.	Added to corn–soybean diets: ↑ egg palmitoleic acid ↓egg total lipid content ↓ egg arachidonic, eicosatrienoic, and gadoleic fatty acids (In comparison to hens fed the negative control diet −3.65% Ca and 0.08& NPP).
Żyła et al., 2013a	Ross broiler chickens	0.1	First experimental period: Day 1 to 21 Second experimental period: Day 22 to 42	In the first period animals were fed with corn or wheat/soybean. For the second period, experiment proceeded only with broilers fed the low NPP corn-based, grower type diets.	Performance (body weight gain, feed intake, feed conversion ratio, and mortality). Bone mineralization (toe ash). Concentration of triglycerides and HDL cholesterol. 42-day-old broilers fed the corn-based starter and grower diets.	↑feed intake, BW gain and feed convertion ratio (In comparison to broilers fed the negative control diet). ↑the growth more efficiently in the starter than in the grower period.
Żyła et al., 2013b	Bovans Brown laying hens	0.1	Week 50 to 62	Corn/soybean.	Hematological indices (Hemoglobin, hematocrit, erythrocytes, leucocytes, lymphocytes, monocytes, heterophils, eosinophils, basophils, H/L3 as well as AGP levels.	↓basophils percent in the white blood cells in comparison to hens fed the NC diet.
Cowieson et al., 2013	Ross broiler chickens	0.15	Different measurements within day 1 to 42	Wheat/corn/soybean. Randomized positive Control - PC (adequated in P and Ca) Negative Control - NC (P and Ca reduced in 0.12 and 0.14%, respectively), Both of them supplemented with MI	Experiment 1: Performance (BW gain, feed intake and feed conversion ratio) Experiment 2: Performance (BW gain, feed intake and feed conversion ratio) Blood biochemistry (glucagon, insulin, glucose, total cholesterol, HDL cholesterol, and triglycerides)	Significant variations in feed intake and feed conversion ratio according to the age. Significant variations in BW and feed conversion ratio according to age. ↑insulin concentrations in birds fed the PC diet at the 42 d old. ↑glucagon and glucose concentration increased significantly in birds fed the NC diet at the 42 d old.
Lee et al., 2017	Cobb Broiler chickens	0.3	First phase: Day 0 to 21 Second phase: Day 22 to 42	Corn/soybean	Performance (feed intake, BW gain, and feed conversion ratio). Bone mineralization (Ash, Ca and Phosphorus)	MI supplementation had no significant effect on general performance respect to the other treatments. ↓significantly reduction in bone strength.

(*continued on next page*)

Table 1. (*continued*)

Reference	Poultry type	MI % (total diet)	Lifespan	Main diet components	Measured variable	MI effects
Pirgozliev et al., 2017	Ross Broiler chickens	2.5 5.0 7.0	Day 7 to 17	Corn/soybean 2.5 g/kg NPP	Performance (feed intake, daily weight gain, feed conversion efficiency). Dietary AMEn, AMEn intake, and AMEn: GE. DM digestibility, N, fat, P digestibility Excreta sialic acid concentration and sialic acid secretion.	↑feed intake, daily weight gain, AMEn intake and DM digestibility in quadratic (higher in animals supplemented with 0.25% MI). ↓concentration and secretion of sialic acid in excreta (the higher the level of MI, the lower the sialic acid concentration).
Farhadi et al., 2017	Ross Broiler chickens	0.15	First phase: Day 0 to 21 Second phase: Day 22 to 42	Corn/soybean + 0.45, 0.42 and 0.39% of nPP during starter, grower and finisher period, respectively (PC). Corn-soybean + 0.30, 0.27 and 0.24% of nPP during starter, grower and finisher, respectively (NC). Mi only was added to the NC diet.	Growth performance, nutrient digestibility, serum metabolites, tibia mineralization. Litter moisture content. Foot problems	↑significantly Ca, ALP, total protein, and gait score in comparison to NC, PC or both. ↓P content, crude protein digestibility, and tibia bone mineralization in comparison to NC, PC or both. ↓litter moisture % in comparison to NC diet but ↑compared with PC.
Sommerfeld et al., 2018b	Unsexed Ross Broiler chickens	0.38 0.35	Started phase: Day 0 to 11 Grower phase: Day 11 to 22	Wheat/Corn-soybean 1.5 g aP, 1.65 g Ca, + 0.3 g Na/kg feed.	Performance (Average daily gain, average daily feed intake and gain: feed ratio). Inositol phosphate degradation. Concentrations of MI in the digestive tract and blood. Bone mineralization, Prececal digestibility of amino acids (AA).	↑gain-feed ratio ↑MI concentration in crop, ileum, and blood plasma during the grower phase. ↑concentrations of $InsP_3$ and $InsP_4$ in crop digesta and $InsP_5$ in ileum digesta of 22-day-old broilers. ↓digestibility of the amino acids arginine, isoleucine, leucine, phenylananine, asparagine, glutamic acid, proline and tyrosine.
Pirgozliev et al., 2019	Male Ross broiler chickens	0.3 3.0	Day 7 to 21	Corn/soybean + 4.8 g/kg NPP (PC). Corn/soybean + 2.5 g/kg NPP (NC).	Performance (BW, average daily feed intake, average daily gain and gain: feed ratio). AME, DM retention, nitrogen retention and fat digestibility. Nutrient retention, liver N, fat, and vitamin E contents, MI and ALP concentrations in blood plasma.	MI inclusion at 3.0% significantly ↑ blood plasma MI and ALP concentrations. ↑liver weight and hepatic N retention in a dose dependent manner.
Farhadi et al., 2019	Ross broiler chickens	0.15	Day 1 to 23	Corn/soybean +4.8 g/kg NPP (PC). Started phase: (NPP: 0.45%). Grower phase: (NPP: 0.42%). Corn/soybean + 2.5 g/kg NPP (NC). Started phase: (NPP: 0.30%). Grower phase: (NPP: 0.27%).	pH of digesta and diets in gizzard and jejunum. Ca, P, Zn, and Fe solubility of digesta and diets in gizzard and jejunum.	↓ P gizzard solubility in comparison to animals fed the PC.

(*continued on next page*)

Table 1. (*continued*)

Reference	Poultry type	MI % (total diet)	Lifespan	Main diet components	Measured variable	MI effects
Gonzalez-Uarquin et al., 2019. (unpublished data)	Ross Broiler chickens	0.4	Day 1 to 21	Wheat/corn/soybean.	Blood plasma MI quantification. Targeted metabolomics approach in blood plasma (acylcarnitines, amino acids, biogenic amines, glycerophospholipids[1], sphingolipids and hexoses).	↑ blood plasma MI. ↑ serotonin and dopamine concentrations. MI supplementation also associated with decreases of acylcarnitines and glycerophospholipids.

This table shows information strictly related to dietary *myo*-inositol (MI) supplementation. For more details (e.g., diets, phytase supplementation and interactions between MI, phytase, and minerals), please see the original sources. Search was done with Google Scholar and PubMed using the following key words: "myo-inositol supplementation in poultry, avian, broilers, laying hens, layers, chicks, birds, and chickens," "dietary myo-inositol in poultry, avian, broilers, laying hens, layers, chicks, birds, and chicken".

Abbreviations: AGP, α-1 acid glycoprotein; ALP, alkaline phosphatase; AMEn, nitrogen-corrected apparent metabolizable energy; day-old, posthatching-day; AMEn:GE: metabolizability of gross energy; dP, digestible phosphorus; FLKS, Fatty liver and kidney syndrome; HDL, high-density lipoproteins; H/L[3], heterophils to lymphocytes ratio; MI, *myo*-inositol; NPP, nonphytate phosphorus.

[1]The glycerophospholipids mainly consists of phosphatidylcholines and lysophosphatidylcholines.

membrane potential, probably by increasing mitochondrial Ca^{2+} concentrations (Condorelli et al., 2011, 2012; Gulino et al., 2016). In human female patients with polycystic ovary syndrome, an oral dose of 2 g MI/twice a day increased the number of mature oocytes of top quality embryos and of successful pregnancies (Unfer et al., 2011). Data from laying hen studies are rare, and more research is needed in this field; however, dietary MI appeared to decrease egg production in comparison to a standard diet (Żyla, et al., 2012).

Effects of Dietary Myo-*Inositol on Peripheral Nerve Function*

Peripheral neuropathy, a damage of peripheral nerves, is common in diabetic patients and is accompanied by sensory loss and decreased nerve conduction velocity (Jolivalt et al., 2016). Effects of dietary MI on peripheral neuropathy remain unknown; however, it has been demonstrated that dietary MI supplementation maintained neuronal MI concentrations in diabetic rats and also improved sciatic motor nerve conduction velocity regardless of persistent hyperglycemia and elevated nerve sorbitol and fructose concentrations in diabetic rats (Greene et al., 1975). Furthermore, it has been observed that $SMIT1^{-/-}$ mice expressed dysfunctions in peripheral nerves such as brachial plexus, sciatic, facial, vagus, intercostal, and phrenic nerves, indicating that MI metabolism could be crucial in neuronal signaling, hypothetically through regulation of Ca^{2+} release (Takei et al., 1998; Chau et al., 2005).

Effects of Dietary Myo-*Inositol on Brain*

How dietary MI is associated with brain functions appears to be multivariate and remains unclear. Several mechanisms might be involved, such as the role of MI in osmotic balance (Macri et al., 2006; Dai et al., 2016), the role of PI, PIP, and InsP as important signaling molecules in cell regulation, and the role of molecules such as DAG, $InsP_3$, and $InsP_4$ as second messengers, among others. For mental health in humans, there was no conclusive evidence that dietary MI affected depression, anxiety, and obsessive-compulsive behavioral problems (Mukai et al., 2014). However, MI has been associated with amelioration of premenstrual dysphoric disorder in women (Gianfranco et al., 2011). Dietary MI was also associated with the functionality of the dopaminergic system, because dietary MI applied 12 wk increased significantly dopamine receptor (D_2) density in guinea pigs (Harvey et al., 2001). Furthermore, dietary MI applied 21 D was associated with increased plasma serotonin concentrations in broiler chickens (Gonzalez-Uarquin et al. 2019, accepted paper). Serotonin and dopamine are modulators of brain functions and behavioral patterns in animals and humans. In chicken, an increase in serotonin concentration was associated with a decrease in feather pecking and aggressive behavior (de Haas and van der Eijk, 2018). Even though a direct relationship between central

and peripheral serotonin has not been proved yet, significant correlations between cerebrospinal fluid and plasma have been observed in humans and rats (Audhya et al., 2012), indicating that dietary MI in poultry may be a promising candidate for functional feeding to improve animal health and welfare.

MYO-INOSITOL SUPPLEMENTATION IN POULTRY NUTRITION

Relevance of MI in poultry nutrition and physiology has received attention in recent years. Myo-inositol may be supplemented pure or through complete dephosphorylation of dietary $InsP_6$. Phytase supplementation has shown to increase MI concentrations in intestinal chymus and blood (Walk et al., 2014; Gautier et al., 2017; Farhadi et al., 2017; Beeson et al., 2017; Schmeisser et al., 2017; Walk et al., 2018; Sommerfeld et al., 2018b; Babatunde et al., 2019). Phytase supplementation also has been related with increases in the expression of the MI transporters-associated genes SLC5A11 (SMIT2) and SLC2A13 (HMIT) in jejunum and ileum, respectively (Walk et al., 2018). Studies on the effect of dietary MI on poultry health and performance are summarized in Table 1. Generally, the response to MI is inconsistent, but clearly, a better understanding is needed on the physiological effects of MI.

Further experimental data demonstrated that dietary MI was associated with increases of MI concentrations in intestinal chymus and in blood plasma (Sommerfeld et al., 2018b). However, conclusive evidence about its effects on health is insufficient because body MI concentrations depended on several factors such as production system, bird's age, diet type, and MI doses (Pirgozliev et al., 2017). Some studies have demonstrated that pure dietary MI supplementation did not affect P and Ca digestibility (Sommerfeld et al., 2018b; Pirgozliev et al., 2019). Combined supplementation of MI and phytase influenced metabolic conditions such as glucose and mineral homeostasis. For example, Cowieson et al. (2013) found that Ross 308 male broilers fed a diet with low available P plus 500 FTU/kg phytase and 0.15% MI supplementation significantly lower blood glucose concentrations (11.8 vs. 12.8 mmol/L) in comparison to the same feed without phytase. Furthermore, a dietary level of MI of 2.0, 5.0, and 7.5 g/kg of feed increased BW gain and nitrogen-corrected apparent metabolizable energy intake, whereas decreased total sialic acid excretion. When MI was supplemented in the presence of 500 FTU/kg phytase, a supplementation of 7.5 g/kg MI led to a reduction in P digestibility (Pirgozliev et al., 2017). Increases in Ca and P concentration of the diet may be associated with reductions in the efficacy of endogenous microbial or epithelial phosphatases, what could explain the decrease found in MI concentration in the intestinal digesta. Interestingly, these effects were counteracted by the addition of 1500 FTU phytase/kg feed (Sommerfeld et al., 2018a). Evidence of P × Ca × phytase interactions on InsP degradation is provided by several studies (Żyła et al., 2004; Tamim et al., 2004; Amerah et al., 2014; Dersjant-Li et al., 2015; Zeller et al., 2015; Beeson et al., 2017; and Sommerfeld et al., 2018a). However, insufficient work was done to allow an understanding of MI, Ca, and P relationships.

Many factors appear to influence the ability of MI to mitigate animal performance. It appeared that *in vivo* MI efficiency depended on (1) animal-related factors (e.g., species, age of animals, genetic background and endogenous, and microbial phosphatases), (2) dietary-related factors (e.g., MI content, type of substrates, intrinsic phytases or phosphatases, total Ca, P levels, and Ca:P ratio), and (3) MI-related factors (e.g., MI doses, and source). Exact knowledge about its functions and potential advantage in poultry production is lacking. *Myo*-inositol plays key roles in a number of different metabolic pathways, and a clearer understanding makes MI an important topic for future research in poultry.

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