

Myoinositol: mechanisms of action and role in the treatment of metabolic diseases, infertility and polycystic ovary syndrome

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ABSTRACT

Inositols are natural compounds present in animal and plant cells and play a key role in glucose metabolism, acting as second messengers of insulin. They have been shown to be able to counteract the downstream consequences of insulin resistance, exerting beneficial effects on metabolic diseases, infertility and polycystic ovary syndrome (PCOS). We summarize the mechanisms of action of inositol compounds, focusing on the most important functions of myoinositol and D-chiro-inositol in the treatment of metabolic syndrome, hyperlipidaemia, insulin resistance and PCOS.

Keywords

Inositol
Insulin resistance
Infertility
Metabolic disease

Introduction

Inositols are sugars and have a cyclic structure consisting of six carbon atoms with a hydroxyl group attached at each carbon. The inositol family comprises a group of molecules called inositol stereoisomers which exist in nine possible forms, all stemming from the same basic structure: myo-, scyllo-, epi, D-chiro-, L-chiro, neo, allo- and mucus cis-isomers [1]. Among these isomers, myoinositol (MI) is the most abundant in nature, being present in animal and plant cells, either in its free form as a component of phospholipids or in its form of inositol phosphate derivatives. It is a precursor of known compounds such as phosphorylated phosphoinositides, which are involved in signal transduction, including diacylglycerol and inositol triphosphate (IP3), a second messenger responsible for the regulation of many hormones such as insulin, thyroid stimulating hormone (TSH) and follicle-stimulating hormone (FSH) [2]. For this reason, MI is essential for the proper functioning of a wide range of cellular

functions, including cell growth and survival [3], the development and function of peripheral nerves [4], osteogenesis [5] and cell reproduction [6]. It is absorbed by the tissues through a co-inositol transporter that also mediates sodium-dependent glucose uptake (which competitively inhibits the intake of inositol) [7]. Another isomer of significant importance is D-chiro-inositol (DCI), involved in insulin signaling and glucose homeostasis, since numerous studies have shown that any anomalies in MI/DCI metabolism are associated with insulin resistance and long-term microvascular complications in patients with diabetes [8]. Indeed, in diabetic animal models and in human subjects, MI intracellular depletion with concomitant accumulation of intracellular sorbitol is commonly observed in the main sites of diabetic microvascular complications, such as the kidneys, the sciatic nerve and the retina [9].

Metabolic pathways involving inositol

Inositol plays an important role in glucose metabolism and acts as a second messenger of insulin action because binding of insulin to its receptor initiates a cascade of metabolic events which, through activation of the receptor substrate insulin-1 (IRS-1) and the action of the enzyme phosphatidylinositol-3-kinase (PI-3K), converts phosphatidylinositol-2-phosphate (PIP2) into phosphatidylinositol-3-phosphate (PIP3), activating protein kinase B (PKB), which is the metabolic pathway leading to glycogen synthesis [10, 11].

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Another important mechanism of action of inositol is the activation of pyruvate dehydrogenase kinase, isoenzyme 1 (PDK1), which acts on glucotransporter 4 (GLUT4), favouring glucose transportation through the plasma membrane into the cells of tissues that use it more as an energy substrate [11]. In addition, some of the actions of insulin may involve a low molecular weight mediator, such as DCI, which is a component of inositol phosphoglycan (DCI-IPG) and together with galactosamine regulates glucose metabolism [12]. Ultimately, inositol acts at multiple levels, playing a key role in promoting the action of insulin. Numerous experimental data suggest that inositol plays a significant role in the pathogenesis of insulin resistance, being a mediator of the action of insulin, which is necessary for the activation of key enzymes in glucose metabolism. Some experimental and clinical data have shown that in certain insulin-resistant conditions, there is impaired renal elimination of inositol and that supplementation with it is able to improve glucose metabolism [13].

Moreover, studies conducted on rhesus monkeys [14] and Goto-Kakizaki (GK) rats [15] have shown that MI depletion results in excessive excretion of MI and in decreased amounts of DCI in urine (a condition called inosituria). The same abnormal inositol pattern is observed in the insulin-sensitive tissues (liver, muscle, fat and kidney) of human [16] and animal [15] diabetic subjects. The excessive urinary excretion of MI reduces the plasma level and results in a decrease in the production of DCI (which derives from the epimerization of MI), reducing its intracellular availability, fundamental for its incorporation into IPG, a second messenger of insulin. Therefore, the reduced content of DCI in insulin target tissues reduces transduction of the insulin signal, contributing to the increased insulin resistance in the tissues. Low DCI plasma levels are, in fact, often observed in patients with polycystic ovary syndrome (PCOS), underscoring the correlation between plasma changes in DCI and insulin resistance [8].

Polycystic ovary syndrome

PCOS is the most common cause of infertility, ovarian dysfunction and menstrual irregularities, and affects 5–10% of women of reproductive age [17]. According to the Rotterdam criteria, elaborated in 2003 [18], PCOS is diagnosed if the patient meets two out of the three following characteristics: oligo-chronic anovulation, polycystic ovaries anatomically diagnosed by ultrasound, and biochemical and/or clinical hyperandrogenism [19]. Although insulin resistance

and hyperinsulinaemia are not included among the criteria, they are important aetiological factors associated with the typical clinical signs and hormonal disorders of PCOS.

Treatment of PCOS with insulin-sensitizing drugs, such as metformin, troglitazone and pioglitazone, has been shown to improve ovulatory function and reduce circulating androgens, corroborating the critical link between insulin resistance and the pathogenesis of this syndrome. Of these insulin-sensitizing agents, metformin is the most commonly used in the treatment of PCOS, although it is considered an off-label product when used in non-diabetic women with PCOS. However, metformin has many side effects, such as nausea, diarrhoea and weight gain, which significantly reduce patient compliance and its suitability [20–22].

Over the past two decades, several studies have reported the effectiveness of inositols, mainly the two stereoisomers MI and DCI, in improving the pathological conditions associated with PCOS [19]. DCI affects insulin-mediated ovarian androgen levels [23], while MI regulates glucose uptake and FSH levels in the ovaries [24–27].

Use of inositols in medically assisted reproduction

In the last few decades, problems connected with infertility and the use of assisted reproductive techniques have greatly increased. Many studies seeking to identify compounds able to improve the quality of oocytes [28] have focused on the effects of MI because its concentration in follicular fluid appears to be directly correlated with the quality of oocytes and embryos [29]. In addition, it has been observed that women treated with MI before hormonal stimulation require less FSH and fewer days for successful stimulation [30], have better quality oocytes [31–33] and embryos [34], and have a greater probability of successful implantation [35].

The results of several randomized controlled trials conducted in patients with PCOS [36] have confirmed that MI can be used to treat women undergoing in vitro fertilization (IVF) based on evidence demonstrating improved oocyte quality [37]. Studies have also been conducted on male subjects with oligoasthenoteratozoospermia (OAT), a serious medical condition where the number of sperm is reduced and their morphology and function are altered. These studies have shown that MI increases the activity of sperm [38], suggesting that its use in the treatment of semen samples during IVF cycles could have a positive impact on fertilization rate and embryo quality, thus leading to an increased chance of pregnancy.

Several experiments conducted on laboratory species also suggest that MI plays a vital role in oogenesis and promotes reproduction. In fact, therapy with MI before conception has demonstrated positive effects on the meiotic maturation of mouse oocytes [39] and improved the embryo implantation rates in cows [40], rabbits [41] and mice [42]). These observations led to the hypothesis that inclusion of MI in the culture media for human embryos might increase the number of high quality embryos during IVF cycles [37].

Experimental studies on obese, diabetic and metabolic-like syndrome models

A recent study evaluated the therapeutic effect of MI in hyperlipidaemic and insulin-resistant rats. The results showed that in hyperlipidaemic rats, MI administration resulted in significant reductions in total cholesterol and triglycerides, while in insulin-resistant diabetic rats, MI administration resulted in significant reductions in fasting blood glucose and plasma insulin levels compared with control. Inositol treatment significantly normalized the biochemical abnormalities induced by hyperglycaemia in insulin-resistant diabetic rats, supporting the role of MI in glucose disposal into adipose tissue by an insulin-dependent signalling cascade mechanism. Hence, MI could be used in the treatment of obesity-associated type 2 diabetes mellitus [43].

Furthermore, a combination of MI and DCI has recently been tested both in a pregnant obese mouse model and in a pregnant metabolic-like syndrome mouse model obtained from the offspring born to hypertensive dams lacking endothelial nitric oxide synthase, fed a high-fat diet. The treatment with combined inositol during pregnancy improved blood pressure, glucose levels determined with the glucose tolerance test, and leptin levels in pregnant dams with a metabolic-like syndrome phenotype but not in obese pregnant dams. In addition, inositol treatment was associated with lower gestational weight gain in the obese but not in the metabolic-like syndrome pregnant dams [2]. Inositol has a role in restoring maternal cardiovascular and metabolic status in pregnancy affected by obesity and metabolic syndrome.

Conclusion

In light of the evidence and considering that problems such as obesity, diabetes, PCOS and infertility have dramatically increased in the last decades, dietary supplementation with inositol isomers should be recommended to ameliorate these conditions, especially as women affected by such pa-

thologies could originate a vicious epigenetic cycle where maternal metabolic and cardiovascular diseases are passed down to their offspring. A hostile intrauterine environment causes specific changes in placenta pathways as demonstrated in animal models and in humans. However, larger double-blind trials in more heterogeneous populations are required to investigate the effect of the administration of DCI and MI in subjects with insulin resistance or with a genetic predisposition for one of the above conditions.

Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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