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Review

Potential role and therapeutic interests of *myo*-inositol in metabolic diseases

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ABSTRACT

Several inositol isomers and in particular *myo*-inositol (MI) and D-*chiro*-inositol (DCI), were shown to possess insulin-mimetic properties and to be efficient in lowering post-prandial blood glucose. In addition, abnormalities in inositol metabolism are associated with insulin resistance and with long term microvascular complications of diabetes, supporting a role of inositol or its derivatives in glucose metabolism. The aim of this review is to focus on the potential benefits of a dietary supplement of *myo*-inositol, by far the most common inositol isomer in foodstuffs, in human disorders associated with insulin resistance (polycystic ovary syndrome, gestational diabetes mellitus or metabolic syndrome) or in prevention or treatment of some diabetic complications (neuropathy, nephropathy, cataract). The relevance of such a nutritional strategy will be discussed for each context on the basis of the clinical and/or animal studies. The dietary sources of *myo*-inositol and its metabolism from its dietary uptake to its renal excretion will be also covered in this review. Finally, the actual insights into inositol insulin-sensitizing effects will be addressed and in particular the possible role of inositol glycans as insulin second messengers.

1. Introduction

myo-Inositol is a cyclitol naturally present in animal and plant cells, either in its free form or as a bound-component of phospholipids or inositol phosphate derivatives. It plays an important role in various cellular processes, as the structural basis for secondary messengers in eukaryotic cells, and in particular as inositol triphosphates (IP_3), phosphatidylinositol phosphate lipids (PIP_2/PIP_3) and possibly inositol glycans. For this reason, *myo*-inositol is essential or important for the smooth running of a wide range of cell functions, including cell growth and survival [1], development and function of peripheral nerves [2], osteogenesis [3] and reproduction [4–9] (See Fig. 1). *myo*-Inositol and D-*chiro*-inositol, another inositol isomer, could be also implicated in glucose homeostasis since abnormalities in their metabolism were associated to insulin-resistance and long-term diabetes microvascular complications in diabetic subjects. Furthermore, given as dietary supplements, both *myo*- and D-*chiro*-inositol showed insulin-mimetic

Abbreviations: AC, adenylyl cyclase; ACC, acetyl-coenzyme A carboxylase; AGEs, advanced glycation end products; AMP, adenosine monophosphate; cAMP, cyclic AMP; AMPK, 5′ AMP-activated protein kinase; AUC, area under the curve; BMI, Body Mass Index; CDP-DAG, cytidine diphosphate-diacylglycerol; DCI, D-chiro-inositol; ECM, extracellular matrix; FA, folic acid; FSH, follicle-stimulating hormone; GFR, glomerular filtration rate; GK, Goto Kakizaki (rat); GLUT-4, glucose transporter 4; GMD, gestational diabetes mellitus; G3PAT, glycerol-3-phosphate acyltransferase; GPI, glycosyl phosphatidylinositol; GS, glycogen synthase; GSK3, glycogen synthase kinase 3; HDL, high density lipoprotein; HK, hexokinase; HMIT, H^+/*myo*-inositol transporter; HOMA-IR, homeostasis model assessment of insulin resistance; IMPase, inositol monophosphatase; INS-2, insulin second messenger with a 4-*O*-(2-amino-2-deoxy-beta-D-galactopyranosyl)-3-*O*-methyl-D-chiro-inositol structure; IPs, inositol phosphates (including in particular: Ins-P: inositol monophosphate, IP3, inositol triphosphates, IP6, inositol hexakisphosphates or phytic acid); IPG, inositol phosphoglycan; IR, insulin receptor; IRS, insulin receptor substrate(s); LD50, median lethal dose; LDL, low density lipoprotein; LH, luteinizing hormone; LysoPI, lysophosphatidylinositol; MetS, metabolic syndrome; MI, *myo*-inositol; MIPS, 1-D-*myo*-inositol-phosphate synthase; MIOX, *myo*-inositol oxygenase; MNCV, motor nerve conduction velocity; mTOR, mammalian target of rapamycin; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PDH, pyruvate dehydrogenase; PDHP, pyruvate dehydrogenase phosphatase; PDK, phosphoinositide-dependent kinase; PI, phosphatidylinositol; PI3K, phosphatidylinositol-3-kinase(s); PIPs, phosphatidylinositol phosphate lipids (including PIP_2, phosphatidylinositol 4,5-bisphosphate and PIP_3, phosphatidylinositol (3,4,5)-trisphosphate); PKA, cyclic AMP-dependent protein kinase; PKB, Protein Kinase B; PKC, protein kinase C; PLC, phospholipase C; PLD, phospholipase D; PP2Cα, phosphoprotein phosphatase 2C alpha; PP-InsPs, pyrophosphate forms of inositol phosphates; RCT, randomized controlled trial; SHR, spontaneously hypertensive rat; SHBG, Sex Hormon Binding Globulin; SMIT1/2, sodium-dependant *myo*-inositol transporter 1/2; STZ, streptozotocin.

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effects in several animal models of insulin resistance [10–12] and in women with polycystic ovary syndrome [13], a metabolic and endocrine disorder associated with insulin resistance.

The aim of this review is to compile and discuss the results of the randomized controlled trials that tested the potential benefit of a dietary *myo*-inositol supplement in contexts of insulin-resistance or long-term diabetic complications. As an introduction and to further discuss the therapeutic interest of a *myo*-inositol supplement in those contexts, the dietary sources of *myo*-inositol, its metabolism from its oral intake to its catabolism by the kidney, and the abnormalities in inositol metabolism associated with insulin-resistance will be addressed. Finally, the putative and actually unclearly defined mechanisms of action of inositol derivatives as insulin sensitizers will be discussed on the basis of animal and clinical studies.

2. Biological forms and dietary sources

Inositol or cyclohexane-1,2,3,4,5,6-hexol is a polyol existing under nine stereoisomeric forms depending on the spatial orientation of its six hydroxyl groups (Fig. 2). *myo*-Inositol, or *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol, is the predominant isomeric form of inositol that we can find in nature and in our food. *myo*-Inositol was once considered to belong to the vitamin B family, however, because it is produced in sufficient amount by the human body from D-glucose, it is no more regarded as an essential nutrient. Human diet from animal and plant sources can contain *myo*-inositol in its free form, as inositol-containing phospholipid (phosphoinositides) or as phytic acid (inositol hexaphosphate or IP_6) [14]. Indeed, all living cells (animal, plant, bacteria, fungi) contain inositol phospholipids in their membranes, and phytic acid is the principal storage form of phosphorus in many plant tissues, especially bran and seed. Hence, the greatest amounts of *myo*-inositol in common foods are found in fresh fruits and vegetables, and in all foods containing seeds (beans, grains and nuts). Especially high phytic acid contents are found in almonds, walnuts and Brazil nuts (9.4, 6.7 and 6.3% of dry weight, respectively) [15] and oats and bran contain more *myo*-inositol than cereals derived from other grains. Among the vegetables, the highest contents are observed in the beans and peas, leafy vegetables being the poorest vegetable sources. Among the fruits, cantaloupe and citrus fruits (with the exception of lemons) have extraordinarily high contents of *myo*-inositol: for example, a portion of grapefruit juice (120 g) contains about 470 mg of *myo*-inositol [16]. The amount of

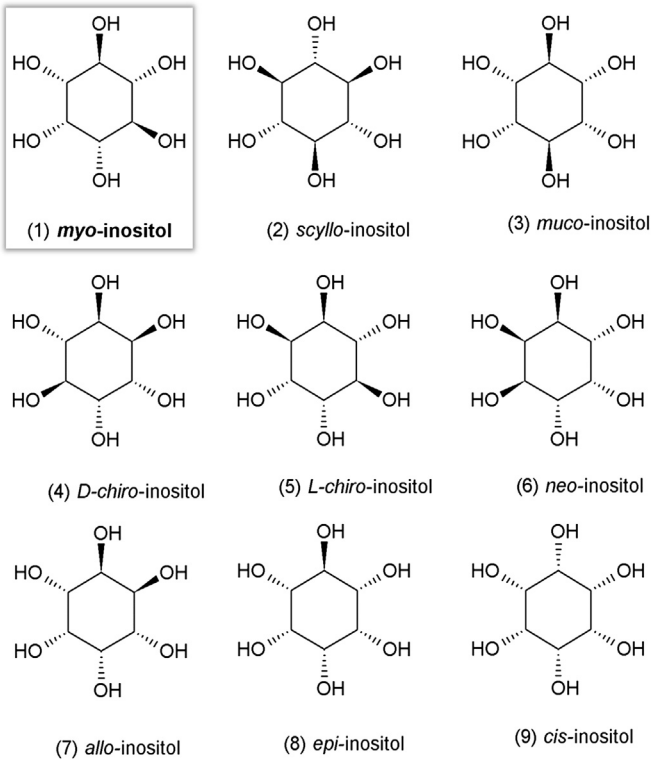

Fig. 2. Structures of the nine stereoisomers of inositol. Inositol exists under 9 stereoisomeric forms through epimerization of its hydroxyl groups. *myo*-Inositol (framed) is the most common isomer of inositol in foodstuffs and animal tissues.

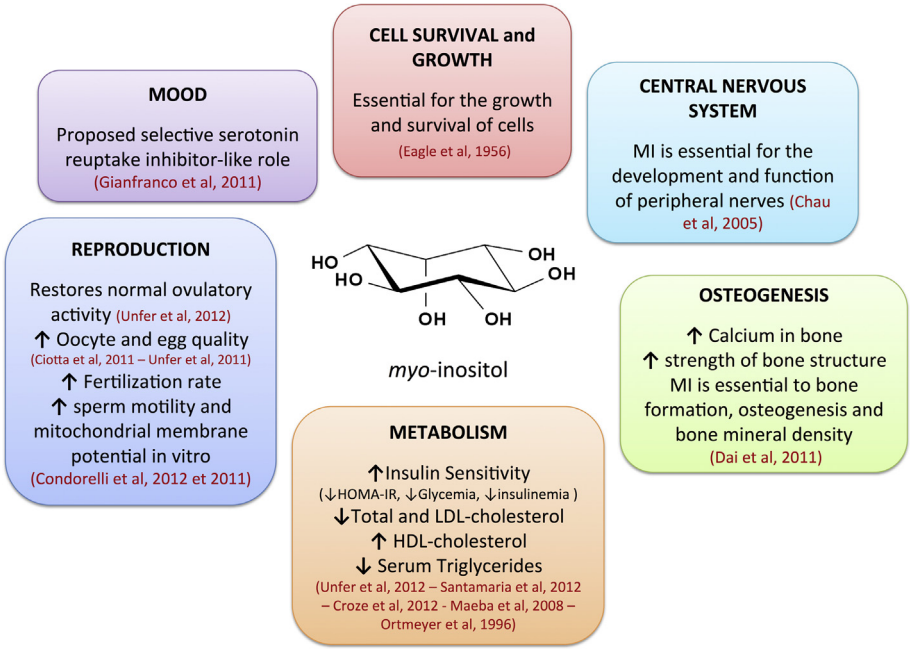

Fig. 1. Functions and benefits of a myo-inositol diet supplement for human health.