Микроэлементы в медицине 9 (3—4): 1—4

ПРОБЛЕМНАЯ СТАТЬЯ

ROLE OF CHROMIUM IN INSULIN FUNCTION
РОЛЬ ХРОМА В РАБОТЕ ИНСУЛИНА

D. Oberleas*
Д. Оберлис*

Texas Tech University, Lubbock, Texas, USA
Техасский технологический университет, Лаббок, США

KEYWORDS: chromium III, insulin, diabetes type 2, gestational diabetes

КЛЮЧЕВЫЕ СЛОВА: хром (III), инсулин, диабет II типа, гестационный диабет

ABSTRACT: Diabetes, Type II is probably the most misunderstood and mismanaged of all the chronic diseases. There is little common understanding of the physiology and biochemistry of the various metabolic components involved in the synthesis, utilization, diagnosis and therapies involved in the proper treatment of Diabetes, Type II. Diabetes has a genetic and nutritional origin but is promoted as resulting from a variety of risk factors, including obesity, high blood pressure and a multitude of irrelevant causes. Insulin is a protein of molecular weight 5700 and contains chains, A and B of slightly different size. If injected, insulin does not function independently and blood glucose does not enter the cells and metabolize to energy. A small peptide, ~1500 MW has been identified that contains 4 amino acids, 2 glycines, 4 glutamic acids, and 2 each of cysteine and aspartic acid. The exact sequence has not been published. The chemistry of chromium III is to form very stable complexes with water, urea, ammonia, halides, sulfate and particularly carboxylic acid as may be supplied by the glutamic acids. When one considers the logic of this combination only one conclusion can be drawn; chromium III is the stabilizing cation between insulin, and insulin receptors supported by the low-molecular weight chaperone. Furthermore gestational diabetes is most likely a transient chromium deficiency.

РЕЗЮМЕ: Диабет II типа, возможно, наименее понятное из всех хронических заболеваний. Недостаточно изучена физиология и биохимия компонентов обмена веществ, вовлеченных в процессы, обусловливающие течение, диагностику и лечение диабета II типа. Диабет имеет генетическое и диетарное происхождение, однако активируется под действием целого ряда факторов риска: ожирения, повышенного кровяного давления, а также множества других причин. Инсулин в организме не работает сам по себе. Для того чтобы глюкоза проникала в клетки и обеспечивала их энергией, существует небольшой пептид массой ~1500, содержащий остатки глицина, цистеина, глутаминовой и аспарагиновой кислот (точная последовательность не опубликована). Химическая функция хрома (III) — формировать устойчивые комплексы между водой, мочевиной, аммиаком, галогенидами, сульфатом и карбоновыми кислотами, в частности глутаминовой. Логика этой комбинации позволяет сделать вывод: хром (III) представляет собой стабилизирующий катион в соединении между инсулином и инсулиновыми рецепторами, осуществляемом низкомолекулярным шапероном. Более того, гестационный диабет, по всей видимости, является транзиторным проявлением дефицита хрома.

CHEMISTRY OF CHROMIUM

Chromium has an Atomic Number of 24 and an Atomic Mass of 51.99 (Mertz, 1969). Only the ground state 0, +2, +3, and +6 are common forms and of these, only Cr^{+3} has physiological activity and is the most stable oxidation state. Trivalent chromium has a coordination number of 6. It forms very stable complexes with water, ammonia, urea, halides, sulfate and many organic acids (Mertz, 1969). Its coordination with water is uniquely stable (Gärtner, Weser, 1986) (Table 1) and makes inorganic (Table 1) chromium salts less efficiently absorbed and thus a poorer

* Corresponding author: Donald Oberleas (prof.); Texas Tech University (Emeritus), 3404 88th Street, Lubbock 79423-2706, Texas, USA; E-mail: doberlea@aol.com

Table 1. ***Exchange rate of water in metal aquo-complexes***

Aquo-complex	$k_1(s^{-1})$
Cr^{3+}	5×10^{-7}
Al^{3+}	10^0
Fe^{3+}	3×10^3
Mg^{2+}	$> 10^4$
Ni^{2+}	3×10^4
Co^{2+}	1×10^6
Fe^{2+}	3×10^6
Mn^{2+}	3×10^7
Cu^{2+}	8×10^9

Source: Gärtner, Weser, 1986

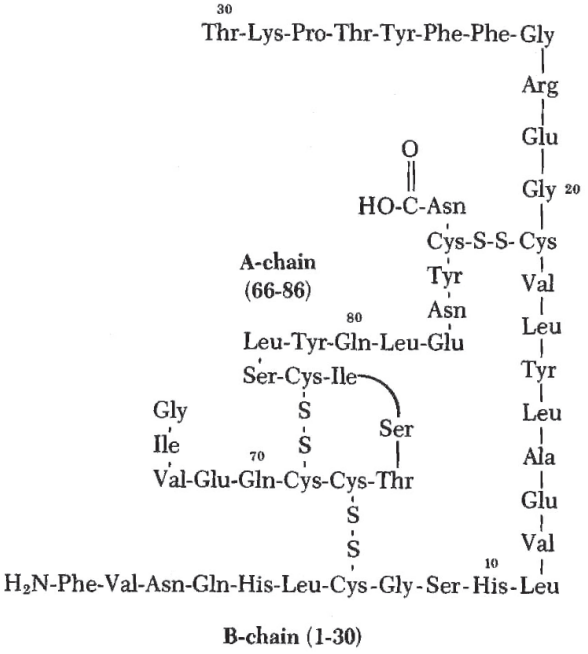

Fig. 1. *Insulin Molecule*

Note: Adapted from Orten, Neuhaus, 1986

candidate as a chromium supplement. This should be inferred from many of the early studies when only about 0.5% of oral doses of $CrCl_3$ were absorbed and the very rapid rate by which it travels through the intestinal tract (Oberleas et al., 1990). Chromium must be with a small organic anion, picolinate, aspartate, methionate, etc. that dissociates slowly to be effectively absorbed. Chromium^{+3} is the most stable oxidation state, is not readily oxidized or reduced and has a slow rate of exchange of ligands.

INSULIN

Insulin is a protein of molecular weight 5734 produced by the β-cells of the pancreas. It is synthesized as pre-proinsulin. It is stored as proinsulin in the β cells as granules. When secreted, a segment of peptide, referred to as C-peptide, is hydrolyzed to provide the active insulin. Its secretion is regulated by blood glucose and somatostatin, the later produced by the Δ-cells of the pancreas.

Insulin was the first protein whose amino acid sequence was described (Sanger, 1959) and a synthetic functional molecule has been synthesized. The molecule is first formed as a single protein, proinsulin, but is physiologically inactive. The C-chain, inactive portion of proinsulin, is split from the molecule to provide the active insulin (Fig. 1). In physiologically adequate subjects, plasma insulin level may increase with a half-time of 6.5—9 minutes in response to an increase in blood glucose. The function of insulin is to control the transfer of glucose through a glucose channel following a post-prandial influx of glucose (Orten, Neuhaus, 1975).

MECHANISM OF ACTION

In Diabetes, Type II, there is seldom a deficit of insulin (Yalow, Berson, 1960). The more common problem is a lack of utilization, sometimes referred to as insulin resistance. A chaperone type peptide has been discovered in several animal species and in cow colostrum that contains glutamic acid, aspartic acid, cysteine and glycine, amino acids that have characteristics which complex with chromium (Davis, Vincent, 1997a,b; Yammamoto et al., 1988). These characteristics are nearly the same for several species and are interchangeable physiologically. There are also 4 glutamic acid residues in insulin. Probably, there are 4 glutamic acid residues on the surface of the insulin receptor. Water is prevalent in the body and serves as the body's lubricant. In this set of circumstances, the greatest likelihood for chromium to function is to stabilize these three components, (insulin, chaperone and insulin receptor) in a precise manner to allow insulin to function appropriately. Without such precision of alignment, insulin, though circulating in the bloodstream cannot function efficiently. Two characteristics that have been demonstrated within this system are a gleam of light reaction within the insulin receptor (Debski, 2002; Saad, 1994) and the formation of hydrogen peroxide within the insulin receptor (Schlessinger, 2000). These receptors may number as few as 40 per cell for erythrocytes to as many as 200,000 per cell for adipocytes and

hepatocytes (Saad, 1994). Either one or both of these reactions or the combination could serve as a second messenger for the activation of phosphotyrosine phosphatase on the interior surface of the insulin receptor to open the glucose channel to allow glucose and amino acids into the cells for metabolism to energy. The model for this activity is illustrated in Figure 2.

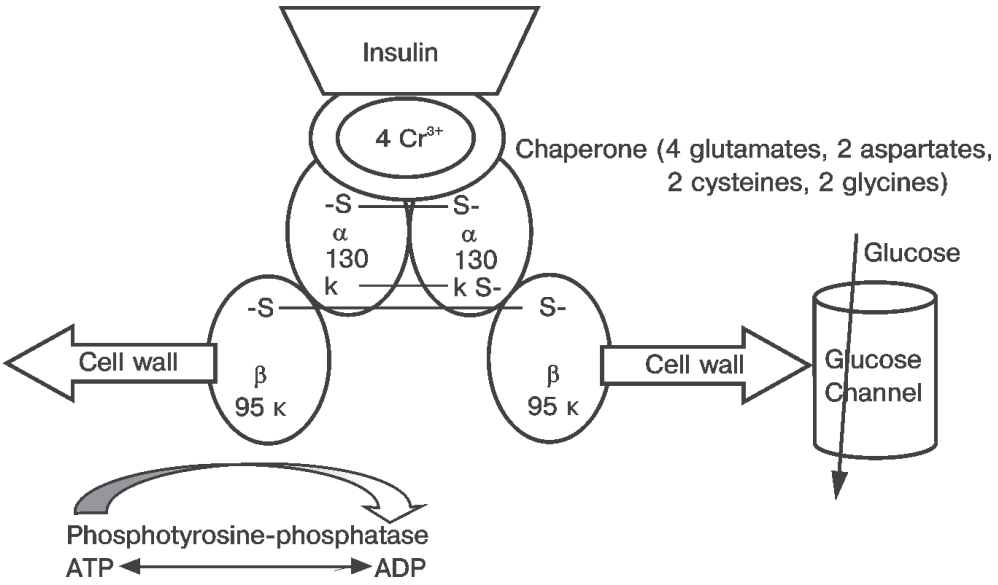

Fig 2. *Model for Insulin, Chaperone, and Insulin Receptor*

Gestational diabetes, affecting more than 5% of all pregnancies, is fraught with a variety of complications for mother and embryo. Historically, gestational diabetes, probably an early form of Type II Diabetes resulted in high maternal and infant mortality and morbidity. These mothers have low levels of circulating chromium and this may be described as transitional chromium deficiency (Anderson, 1998). Clinical conditions such as diabetic nephropathy, diabetic neuropathy, diabetic retinopathy and coronary-artery disease are always clinical conditions of pregnancy that need recognition and appropriate clinical evaluation and treatment, including chromium supplementation. The consequences of maternal diabetes or maternal chromium deficiency during pregnancy can have long-term consequences on the surviving embryos of such a pregnancy; clinical conditions as macrosomia (abnormally large size of the body), early delivery, growth retardation and Diabetes Type II in a surviving offspring. Risks of congenital fetal abnormalities involving more than one organ system have been reported. Common anomalies include cardiac defects, incomplete closure of the neural-tube, central nervous system abnormalities and caudal regression syndrome (Harms, 2006). Pre-eclampsia may exacerbate background placental insufficiency and compromise the fetus. Total parenteral nutrition solutions should be fortified with chromium at least 8 μg/kg body weight. This will prevent symptoms of hyperglycemia and other clinical consequences (Anderson, 1998).

SUMMARY

A brief study of the chemical characteristics of chromium, specifically the formation stable complexes but is not readily oxidized or reduced; thus is not altered or otherwise involved in any chemical change in physiology. It is necessary for insulin function. One mechanism is that insulin, a hydrophilic protein, must be stabilized over the insulin receptor with great precision in order to function. The stability is provided by the combination of insulin, the chaperone, and the insulin receptor each forming a complex, all stabilized by chromium $^{3+}$. Any disruption of this process either by substitution of an amino acid within the chaperone, insulin, or insulin receptor, or a deficiency of chromium will compromise the efficiency of the process.

Assuredly this is not a cure for Diabetes Type II but it is an effective long-term treatment that is without risk or undesirable side effects. The toxicity of chromium $^{3+}$ is about 350 times the estimated adequate intake. It is poorly absorbed and readily excreted and the effectiveness reduces blood glucose levels to a normal range. It should be taken twice daily to assure 24-hour coverage.

REFERENCES

Mertz W. Chromium occurrence and function in biological systems // Physiol. Rev. 1969. 49(2):163—239.

Gartner A., Weser U. Molecular and functional aspects of superoxide dismutase // Topics Curnt. Chem. 1986. 132(1):1—61.

Oberleas D. Li Y.C. Stoecker B.J. Henry S.A. Keim K.S. Smith J.C., Jr. The rate of chromium transit through the gastrointestinal tract // Nutr. Res. 1990. 10:1189—1194.

Sanger F. Chemistry of insulin. Sci. 1959. 129:1340—1344.

Orten J.M., Neuhaus O.W. Human Biochemistry (9th ed.). C.V. Mosby Co., St Louis, 1975. 426 p.

Yalow R.S., Berson S.A. Immunoassay of endogenous plasma insulin in man // J. Clin. Invest. 1960. 39:1157—1175.

Davis C.M., Vincent J.B. Isolation and characterization of a biologically active chromium oligopeptide from bovine liver // Arch. Biochem. Biophys. 1997b. 339(2):335—343.

Davis C.M., Vincent J.B. Chromium oligopeptide activates insulin receptor tyrosine kinase activity // Biochem. 1997a. 36:4382—4385.

Yamamoto A., Wada O., Suzuki H. Purification and properties of biologically active chromium complex from bovine colostrums // J. Nutr. 1988. 118(1):39—45.

Debski B. Personal Communication, 2002.

Saad M.J.A. Molecular mechanism of insulin resistance // Brazilian J. Med. Biol. Res. 1994. 27:941—957.

Schlessenger J. Cell signaling by receptor tyrosine kinases // Cell 2000. 103(2):211—225.

Anderson R.A. Chromium, glucose intolerance and diabetes // J. Am. Coll. Nutr. 1998. 17(6):548—555.

Harms R. Diabetes in pregnancy // Nutrition and Diabetes (Ed: Opara, E.). Taylor and Francis, Boca Raton, 2006. P. 267—280.