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Focused review

Controlling diabetes by chromium complexes: The role of the ligands

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ABSTRACT

Diabetes, particularly type II diabetes, is a severe disease condition which affects human health worldwide, with a dramatically increasing trend in Asian countries including China. Currently, no efficient drugs other than those with observable side effects are available. Chromium complexes, with the most known representative chromium picolinate, have been listed as one of most attractive health supplements to attenuate this disease condition in western countries. Recent efforts have been made to develop new chromium complexes with novel ligands. Although fair amounts of reviews have been published to emphasize the biological activity, preclinical and clinical information of chromium picolinate, this mini-review is trying to cover the entire picture of updated research efforts on various chromium complexes highlighting the role of ligands. Chromium phenylalanine sensitizes insulin cell signaling pathway via the activation of phosphorylation of Akt (protein kinase B (PKB)) and/or AMPK (AMP-activated protein kinase). The biological activities, toxicity, pharmacological features and clinical implications, including the effect of anti-oxidative capacities, protective effect on obese-induced heart dysfunction, and efficacy and safety of chromium supplementation in diabetes are discussed as well.

1. Introduction

The rapid prevalence of diabetes mellitus is becoming a global health problem as a result of population aging, urbanization and lifestyle changes [1]. Over the past three decades, the number of people with diabetes mellitus has dramatically increased, making it one of the most important public health challenges to all countries [2], estimated to rise to 439 million by 2030 [3]. Rather than a costly disease in developed countries decades ago, currently, diabetes mellitus is turning out to be a major burden in developing countries with 80% of cases of diabetes mellitus worldwide living in less developed countries and areas. Asian countries including China, India, Pakistan, Indonesia and Bangladesh are emerging as the major diabetes mellitus pool in the world [3]. In particular, 11.6% and 50.1% prevalence of diabetes and prediabetes, respectively, has been estimated in China [4].

Anti-diabetes drugs possess a tremendous market in pharmaceutical and health industry. The main products are metformin, DPP-4 inhibitors, GLP-1 receptor agonists, pioglitazone glucosidase inhibitors, sulfonylureas/glinides, acarbose, and SGLT-2 inhibitors. Metformin, with the weight neutral trait, lowers blood glucose levels, enhances glucose uptake into the skeletal muscle and reduces cancer incidence. However, the main contraindication to metformin is a GFR below 60 mL/min with the risk of lactic acidosis [5–7]. Other unpleasant side effects, including hypoxic comorbidities are further contraindications. DPP-4 inhibitors, the gliptins sitagliptin, vildagliptin, or saxagliptin have a broader therapeutic application and a low risk of causing hypoglycemia [8]. GLP-1 receptor agonists tend to cause weight loss, particularly when compared to insulin or sulfonylureas [9]. However, in rodents treatment with the long-acting GLP-1 receptor agonist Exendin resulted in acinar cell death and inflammation and in accelerated metaplasia and lesion formation of pancreatic intraepithelial neoplasia [10,11]. The thiazolidinediones including rosiglitazone and pioglitazone have a very favorable pattern of action since they enhance insulin sensitivity of the skeletal muscle and liver, inhibit hepatic gluconeogenesis and are anti-inflammatory in various organs [12]. However, these thiazolidinediones drugs cause fluid retention with associated peripheral edema due to altered renal sodium and water reabsorption, the higher rate of fractures and the weight gain [13,14]. Acarbose inhibits intestinal alpha-glucosidases, lowers the insulin requirement without causing hypoglycemia, and causes neither weight loss nor weight gain. However, gastrointestinal side effects such as flatulence and diarrhea, and pneumatosis cystoides intestinalis are often seen in the application of these drugs [15,16]. Sulfonylureas like glibenclamide, tolbutamide and glimepiride have been broadly used for treating diabetes since the 1950s. Increased insulin levels reduce blood glucose concentration but lead to weight gain, a most undesired effect in the T2D. Hypoglycemia and high cardiovascular risk are other important adverse effects [17–19]. SGLT-2 inhibitors are newly developed anti-diabetic drugs. The first drug, Canagliflozin, has been approved by the FDA in 2013 for clinical use. These inhibitors lessen renal glucose resorption and thus cause glycosuria and a resulting insulin-independent reduction in the blood glucose concentration with weight loss [20]. However, several side effects of this class of drugs have been

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seen such as urinary tract infections, genital mycotic infections, increased urination and episodes of hypotension. Thus, novel methods to treat diabetes are needed to be developed.

Chromium is an essential nutrient required for glucose and lipid metabolism [21] and improves insulin sensitivity by enhancing intracellular signaling [22,23]. Nevertheless, it is worth mentioning whether chromium that is essential is still controversial since there are neither known metabolic pathways nor known proteins requiring chromium. However, supplemental trivalent chromium taken appears to be a useful tool in the world's fight against epidemic-like appearances of various manifestations of the metabolic syndrome, especially obesity and diabetes. Laboratory and clinical studies indicate that certain forms of trivalent chromium have various capabilities such as overcoming insulin resistance, ameliorating diabetes, suppressing free radical formation and decreasing SBP. Although the first and most popularly used chromium complex, CrPic has been marketed for decades, novel complexes of trivalent chromium with unique ligands have been continuously prepared and investigated, indicating that the ligand plays an important role on improving the performance of this kind of chromium complexes. Thus, this review summarizes bioactivity, bioavailability and toxicity of several newly developed chromium complexes highlighting the importance of ligands. The chemical structures of chromium complexes and their ligands are listed in Fig. 1.

2. Chromium picolinate

CrPic, the complex of chromium and picolinic acid, is the most extensively studied anti-diabetic and anti-obese chromium complex. Although its molecular mechanism and biological activities have been extensively summarized [24], we mainly highlight the ligand picolinate and the recent progress of its complex afterwards.

Pic is a very important metabolite in neuroscience and brain tumors. It has been shown that Pic is able to block the neurotoxic, serving as a neuro-protective agent [25]. One recent study has shown that cerebrospinal fluid Pic levels are higher in old people than that in young people although circadian even plays a more important role on this [26]. It is interesting that Pic has been shown to have selective toxicity on simian-virus transformed cells in Petri dish experiment [27] and antitumor activity in mice as well [28]. As a key metabolite in kyurenine pathway, the effect of Pic has been summarized in one recent review [29].

Fan et al. reported that CrPic treatment is able to protect hepatocellular injury [30]. Another report shows that CrPic is able to enhance the Cr translocation through AMPK pathway in 3T3-L1 adipocytes [31]. Also, CrPic improves the glucose uptake in insulin-resistant 3T3-L1 adipocytes via the activation of P38 pathway [32]. The same group has reported their findings that CrPic exerts the effect via activation of AMPK pathway using western blot, ELISA and RT-PCR techniques [33].

Interestingly, it has been shown that the traditional Chinese medicine, Tianmai Xiaoke tablet consists of CrPic, which improves blood glucose through activating insulin-signaling pathway and inhibiting PTP1B and PCK2 in diabetic rats [34].

Staniek et al. have shown that $CrCl_3$, CrPic and chromium propionate have effects on the Zucker obese and Zucker diabetic fatty rats [35]. CrPic administration has effects on the brain of diabetic rats, mainly via NF-kB and Nrf/HO1 pathway [36]. Interestingly, the data have shown that Cr histidinate is superior to CrPic in reducing NF-kB expression and increasing Nrf2 expression in the brain of diabetic rats. The same group evaluated the effects of CrPic on serotonergic properties and carbohydrate metabolism in diabetic rats [37]. Sealls et al. have shown that CrPic is able to modulate cellular cholesterol homeostasis and impair ABCA1 functions under the conditions of hyperinsulinemia [38]. Wang et al. show that picolinate induces translocation of CD36 to the plasma membrane through the signaling pathways in 3T3-L1 adipocytes [39]. CrPic is able to augment insulin-stimulated protein synthesis. At the molecular level, insulin significantly increased the mRNA levels of insulin-like growth factor 1 and insulin-like growth factor 1 receptor [40]. It has been shown that CrPic increases the glucose uptake in the insulin-resistant 3T3-L1 adipocytes, which is related to the activation of p38 MAPK, independent of the effect on GLUT4 translocation [32]. Further, Qiao et al. has shown that CrPic improves glucose uptake and metabolism through up-regulating the mRNA levels of

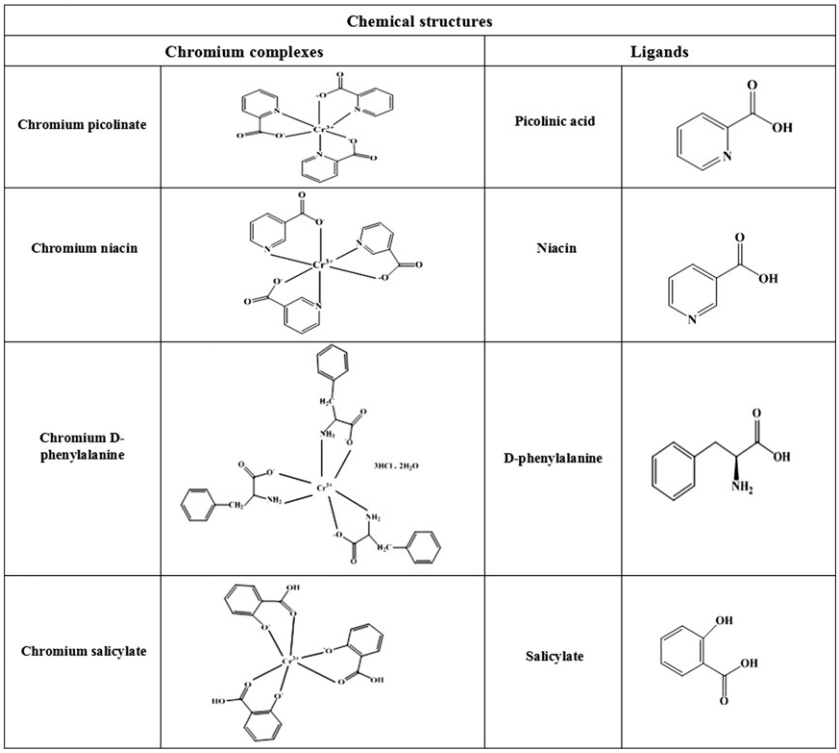

Fig. 1. Chemical structures of chromium complexes and their ligands.