Diabetes mellitus (DM) dates back to approximately 1550 B.C. The discovery of “insulin”, which was extracted from a dog’s pancreas by Canadian researchers Banting and Best in 1921, established a base for the molecular mechanism of the clinical treatment of DM. Insulin-dependent DM, which is characterized by the absence of insulin synthesis and secretion in the pancreas, is called type 1 DM, and it can be clinically treated only by administering insulin injections daily. Subsequently, non-insulin-dependent DM, which cannot be treated with insulin injection, was discovered and is called type 2 DM. Exercise therapy and diet control along with the administration of oral synthetic medicines are used for the treatment of this condition.

Type 1 DM is observed in 5% of the total patients with DM and is more likely to develop in infants and youth; in contrast, type 2 DM is observed in 95% of the total patients with DM and is more likely to develop in middle-aged patients that suffer from obesity and spiritual stress [1,2]. Long-term administration of oral synthetic medicines in patients with type 2 DM causes the pancreatic cells to discontinue insulin synthesis because of a reduced insulin demand by the body; this eventually necessitates the need for insulin injections.

Daily insulin injections are associated with physical and spiritual burden especially in infants and youth. In addition, the long-term administration of insulin injec-
tions leads to the formation of antibodies of insulin in some patients; this renders the insulin injections ineffective in lowering the high blood glucose levels in these patients. On the other hand, oral antidiabetic medicines have been known to cause several adverse effects.

In order to overcome the adverse effects of insulin injections and oral antidiabetic medicines and replace them, the development of new antidiabetic medicines with a novel mechanism of action is being anticipated worldwide.

Discovery of Vanadium as a Medicine for the Treatment of Diabetes

In 1899, 22 years before the discovery of insulin by Banting and Best, French physicians reported the effectiveness of sodium metavanadate NaVO₃, which is a +5 oxidation state of vanadium (atomic number 23), in improving the diabetic state of patients by lowering the urinary glucose excretion [3]. It is impossible to ascertain the reason for undertaking such a risky trial (experiment) at the end of 19th century; however, this could be better understood based on the fact that at time, vanadium was expected to cure all kinds of diseases and was called “panacea”, “cure-all”, or “elixir”.

The clinical effect of vanadium with respect to its lipid and glucose metabolism has been known since 1979 [4,5]. In 1985, after investigating the in vitro insulinomimetic effect of vanadium ions in cell systems [6,7], NaVO₃ was found to be effective in lowering the high blood glucose levels in diabetic rats and consequently improving their cardiac function [8]. Subsequent to this finding, in 1987, a solution of 0.8 mg mL⁻¹ NaVO₃ dissolved in 80 mM NaCl, which was fed as drinking water to streptozocin-induced type 1 DM rats (STZ-rats), was reported to normalize their high blood glucose levels 4 days after administration [9]. These findings demonstrated that vanadate ion had hypoglycemic effects in mammals. Thus, several types of vanadate complexes with organic ligands have been prepared and their antidiabetic effects have been extensively studied [10].

Anti-diabetic Vanadyl (+4 Oxidation State of Vanadium) Complexes

The vanadate ion (+5 vanadium) has been known to exhibit toxicity in rats that is several times higher than the vanadyl (+4 vanadium) ion [11]. In addition, the vanadyl form was found to be in a stable bio-state condition in the organs of the animals that were administered vanadic (+3 vanadium), vanadyl and vanadate compounds. Therefore, we exclusively used the vanadyl ion as VOSO₄. When VOSO₄ was administered daily to the STZ rats by intraperitoneal (ip) injections at a dose of 9.3 mg kg⁻¹ body weight for 12 days, the hyperglycemia improved within a few days. The normoglycemic effect of VOSO₄ continued as long as the compound was administered [12]. However, when the same dose of VOSO₄ was administered orally to the STZ rats, the hyperglycemia was not improved. Based on these observations, we and others have attempted to prepare vanadyl complexes with different types of organic ligands, and less toxic ligands have been selected in order to enhance their bioavailability in animals [13-19].

In 1990, we first proposed orally active vanadyl complexes such as vanadyl-methylcysteinate (VO(cym)₂), -oxalate (VO(ox)₂), -salicylaldehyde (VO(sal)₂), -malonate (VO(mal)₂), and binuclear vanadyl-tartrate ([VO₂(tart)₂]) that were effective in normalizing hyperglycemia in STZ rats when administered once daily [20].

These blood glucose normalizing effects were also maintained as long as the complexes were administered. These findings suggested the possibility of designing new and more effective hypoglycemic complexes by altering the coordination environment around the vanadyl ion, because the above mentioned complexes have the coordination environments of either VO(S₂N₂) or VO(O₄).

In fact, following our report in 1990, a complex with a VO(O₄) coordination environment, vanadyl-maltololate (VO(ma)₂), was proposed by Canadian groups in 1992 [21].

We also proposed new complexes such as vanadyl-pyrrolinedithiocarbamate (VO(pdc)₂) with a VO(S₄) coordination environment in 1994 [22,23], vanadyl-
picolinate (VO(pa)_2) with a VO(N,O)_2 coordination environment in 1995 [24], vanadyl-amino acid complexes with a VO(N,O)_2 coordination environment in 1998 [25,26], vanadyl-metofomine (VO(metf)_2) with a VO(N)_2 coordination environment by Canadian groups in 1999 [27], vanadyl-oxypyridine thiolate (VO(opt)_2) with a VO(S,O)_2 coordination environment in 1999 [28,29], and vanadyl-porphyrin (VO(por)_2) complexes such as VO(tmpyp) and VO(tpps) with a VO(N)_4 coordination environment since 2004 [30-32].

Among these complexes, VO(pa)_2 complex has an advantage to find more active complexes on the basis of the study on structure-activity relationship with the VO(pa)_2 complex as the leading complex.

Structure-Activity Relationship of the Vanadyl-picolinate Complexes

Since the discovery of the in vitro insulinomimetic activities of VO(pa)_2 complex using isolated rat adipocytes and its in vivo antidiabetic activities in 1995 [24], several types of VO(pa)_2-related complexes have been prepared in order to find more active complexes than the leading complex.

In 1997, the daily oral administrations of vanadyl-6-methylpicolinate (VO(6mpa)_2) in type 1 and type 2 diabetic animals was identified to be more effective than VO(pa)_2 in terms of its in vitro insulinomimetic activity and in vivo hypoglycemic effects [33,34]. This complex exhibited a remarkable long-term hypoglycemic effect even after administration of the complex to the animals was discontinued.

Based on this observation, a new halogenated complex, vanadyl-5-iodopicolinate (VO(5ipa)_2) was prepared in 2001 [35]. This was followed by the discovery of vanadyl-3-methyl-picolinate (VO(3mpa)_2) and 4-chloropicolinate (VO(4cpa)_2) [36].

Unfortunately, good crystals of VO(pa)_2-related complexes that are suitable for the 3-dimensional X-ray structure analysis had not been obtained for many years. However, fortunately, a good crystal of vanadyl-6-ethylpicolinate (VO(6epa)_2) was obtained in 2002, and it was observed to have a distorted octahedral geometry [37]. In this crystal, the 2 independent molecules of 2 [VO(6epa)_2(H_2O)] · 4H_2O are in an asymmetric unit. Each vanadium center in the complex is coordinated by 2 carboxylate oxygen atoms, 2 pyridine nitrogen atoms, 1 vanadyl oxygen atom, and 1 water oxygen atom. The 2 carboxylate oxygen atoms and the 2 pyridine nitrogen atoms of the 2 6-epa ligands lie in an equatorial plane and coordinate to the vanadium center in trans arrangements. The water oxygen atom occupies an axial position and binds trans to the vanadyl oxo moiety.

In 2002, new complexes such as vanadyl-3-hydroxypicolinate (VO(3hpa)_2) and 6-hydroxypicolinate (VO(6hpa)_2) were proposed [38]. Interestingly, during the crystallization process of the former complex, 2 new complexes were discovered: [VO(3hpa-O,O)(3hpa-O,
N(H₂O)·3H₂O (A) and cyclic tetranuclear [VO(m-3hp-a-O,O’N)(H₂O)₄] (B) [39,40].

In complex (A), 1 of the ligands contains deprotonated phenoxy and protonated pyridinium functionalities, and binds to the vanadyl ion through the phenolate and carboxylate oxygen atoms; the other ligand binds to the metal ion through the pyridine nitrogen and carboxylate oxygen atoms. Complex (B) comprises 4 distorted octahedral 6 coordinate vanadium centers as VO₅N. Each ligand is tetradentate, bidentate to each of the 2 vanadyl moiety that it bridges, and the 2 remaining oxygen atoms are vanadyl o xo and a water oxygen atom. The carboxylate group of the ligand bridges the adjacent vanadyl ions to form an unusual cyclic arrangement of 4 octahedrals (VO₅N). Interestingly, vanadyl ions in both (A) and (B) have the same arrangement of coordinated atoms. The formations of these 2 types of complexes has been assumed by means of a solution speciation study [41,42].

Newer types of complexes were discovered in 2003. Vanadyl-5-carboalkoxy picolinate (VO(5Ropa)₂(H₂O), R = methyl, ethyl, isopropyl and butyl) complexes with water and one of the picolinate ligands in an equatorial position, and the second ligand occupies the equatorial and axial positions of the nitrogen and oxygen atoms, respectively. When this complex was reacted with NH₄VO₃, it yielded (NH₄)(VO₂(5mopa)₂), in which the nitrogen atoms of the ligands are trans to the doubly-bonded, cis-positioned o xo groups [43].

As described above, many types of VO(pa)₂-related complexes have been proposed. However, from those results, the important factor, which one either the electronic effect or position of the functional group contributes to the biological activity of the complex, has not been identified. We have prepared several VO(pa)₂-related complexes with different types of functionalities at different positions of picolinate ligand by testing their physicochemical properties and their insulinomimetic and antidiabetic activities in order to analyze these factors. Based on the obtained results, it was revealed that the position of the functional group in the picolinate ligand was more important than its electronic effect. This observation demonstrated the importance of a functional group at the 4th position [17].

x = electro-donating or electro-withdrawing functional group

To relate the insulinomimetic and antidiabetic activities of these complexes with their structures in solution, intensive speciation studies have been performed [43-45].

Use of the Vanadyl Ion in the Development of New Drug Delivery Systems

Vanadyl sulfate VOSO₄ has been tested in the treatment of both type 1 and 2 diabetic patients. In fact, treatment with VOSO₄ improved DM as well as hepatic, peripheral, and muscle insulin sensitivity. However, the bioavailability of VOSO₄ is low. Alternatively, we are now proposed the use of drug delivery systems (DDS) to enhance vanadium uptake in animals given VOSO₄ either by enteric coating or by the formation of a complex between VOSO₄ and a high molecular-weight material such as poly(γ-glutamic acid).

When VOSO₄ was administrated to type 2 diabetic patients, mild gastrointestinal symptoms and side effects were observed to develop in a few of the patients [46]. In order to determine safer and more effective dosages, we developed an enteric-coated capsule containing solid VOSO₄ (ECC/VS) and found that the bioavailability of ECC/VS (9.8%) was almost double that of the VOSO₄ solution (4.8%). Thereafter, ECC/VS was chronically administrated to treat STZ rats, and an equivalent blood glucose-lowering effect was observed at half the dose of VOSO₄ alone [47]. In addition, the total serum levels of
vanadium was also observed to be almost the same after chronic administration of ECC/VS as that with VOSO\(_4\) alone [48]. These results indicate that the plasma vanadium level correlates well with the hypoglycemic activity of VOSO\(_4\) and its administration doses are reduced by the ECC.

Additionally, we are proposing a novel DDS consisting of VOSO\(_4\) and poly(γ-glutamic acid) (γ-PGA) for treating type 1 DM animals. We analyzed the structure of VO-γ-PGA in solution as well as in the solid state and proposed that the equatorial coordination environment of the vanadyl ion is either carboxylate(O)-VO-(OH\(_2\))\(_3\) or 2 carboxylate(O\(_2\))-VO-(OH\(_2\))\(_2\) [49].

We then examined the \textit{in vitro} insulinomimetic activity of VO-γ-PGA in isolated rat adipocytes and found that its activity was significantly higher than that of VOSO\(_4\) alone. This complex exhibited significant hypoglycemic activity within a minimum of 4 h after the oral administration of a single dose, and this effect lasted for a minimum of 24 h. In addition, when 5-10 mg V\(^{-1}\) kg body weight of the complex was administered for 16 days, it normalized the hyperglycemia in the STZ mice within 3 days. This improvement in the diabetic state of STZ mice induced by the complex was substantiated further by the results of the oral glucose tolerance test (OGTT) and the determination of hemoglobin A\(_1c\) (HbA\(_1c\)) levels and blood pressure.

**Perspective**

Even since we commenced our research on the development of antidiabetic metal complexes that can be administered orally and are capable of replacing insulin injections and synthetic organic medicines for the treatment of type 1 and 2 DM, respectively, in 1990, a variety of metal complexes have been proposed worldwide on the basis of bioinorganic chemistry or bio-coordination chemistry in the span of these 16 years. Several types of antidiabetic metal complexes, in particularly, vanadyl complexes, have been discovered by investigation the following: \textit{in vitro} insulinomimetic activity in isolated rat adipocytes, \textit{in vivo} hypoglycemic activity in both type 1 and 2 diabetic animal models, metallokinetics using the \textit{in vivo} blood circulation monitoring-electron paramagnetic resonance (BCM-EPR) method and \textit{in vivo} metal monitoring in the blood of animals using the neutron activation analysis (NAA) and inductively coupled plasma (source) mass spectrometry (ICP-MS), and evaluating the dosage form of the complex after determining the structure of the complexes using many different types of spectroscopies, X-ray analysis, and solution speciation studies.

In the 16-year period, we proposed a variety of potent complexes that can be developed as clinically useful agents in the future. However, it is necessary to understand the toxicology of these complexes in order to be able to determine the concentrations at which they can cause acute and chronic toxicities. In addition, it is necessary to understand the true molecular mechanism of these complexes because this information can be effectively used for developing more active complexes and for fine-tuning the active structures of the complexes [20,50-53].

When we think of how researchers achieved the insurmountable task of developing cisplatin (cis,cis-diaminedichloroplatinum(II)) as a clinical antitumor agent, we should realize that the development of vanadyl complexes as viable antidiabetic agents depends on our future enthusiasm and efforts.

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