Metal-Based Anti-diabetic Drugs: Advances and Challenges†

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Supporting Information

Table S1. Main types of drugs used in the treatment of human type 2 diabetes.[21, 22, 24]

Drug type [a]	Clinical status [b]	Representatives	Mode of action	Dose,[c] mg/day	Main side effects	Refs.
Biguanides	1957	metformin	increasing insulin-independent glucose metabolism in the liver	1000-2000	GI discomfort	27-29
Thiazolidine-diones	1997	rosiglitazone, pioglitazone	increasing glucose metabolism in fat tissue	2-30	weight gain, fluid retention	30, 31
Sulfanylureas	1946	glibenclamide, glimepiride	stimulating insulin production in the pancreas	1-10	hypoglycaemia, weight gain	32, 33
DPP-4 inhibitors	2006	sitagliptin	stimulating insulin production in the pancreas	100	GI discomfort	34-36
GLP-1 agonists	2005	exenatide	stimulating insulin production in the pancreas	0.010 [d]	nausea, pancreatitis	37-39
Glucosidase inhibitors	1995	acarbose	delaying glucose absorption from the small intestine	25-100	GI discomfort	40-42
Dopamine receptor agonists	2008	bromocriptine	activating general glucose metabolism though CNS action	2-5	nausea, reduced blood pressure	43
SGLT2 inhibitors	phase III trials	dapagliflozin	decreasing glucose re-absorption in the kidneys	10-20	urogenital infections	44

[a] Abbreviations: DPP-4 = dipeptyl peptidase IV; GLP-1 = glucagon-like peptide 1; SGLT2 = sodium glucose co-transporter 2; CNS = central nervous system; GI = gastrointestinal. [b] The year of approval for clinical use in the USA for each type of drugs (not necessarily for the representative compounds).[21, 24] [c] Typical daily doses.[24] Unless stated otherwise, the drugs are administered orally.
[d] Administered by subcutaneous injection.[24]

Table S2. Typical anti-diabetic activities of metal- and non-metal-based drugs in animal models

Model [a]	Compound [b]	Time, days	Total dose, mmol kg^{-1} [c]	Glucose, mM [d] Vehicle	Drug	Additional observations [e]	Ref.
STZ rats	Metformin	42	25	21 ± 3	12 ± 1	↓HbA1c; ↑glucose tolerance	60
STZ rats	$Na_3[V^VO_4]$	42	23	20.2 ± 0.1	8.7 ± 0.4	improves cardiac function	58
STZ rats	**1a** ($[V^{IV}O(ma)_2]$	28	10.4	23.2 ± 1.5	7.0 ± 0.8	no change in Ins, Ch, and TG	61
STZ rats	**4**	17	1.35	23 ± 2	12 ± 2	↓FFA; ↓TG	88
STZ rats	$Na_2[Mo^{VI}O_4]$	42	5.5	23.2 ± 1.5	13.2 ± 1.4	↓BW; ↓FFA; improves cardiac function	154
STZ rats	$[Mo^{VI}O_2(ma)_2]$	42	6.3	23.2 ± 1.5	16.3 ± 1.3	↓BW; ↓FFA	154
ZDF rats	Metformin	42	302	12.6 ± 1.4	7.0 ± 0.3	↓BW; ↓ Ins; ↓FFA; ↓TG	67
ZDF rats	Rosiglitazone	42	0.42	28 ± 3	7 ± 1	↑ Ins sensitivity	64
ZDF rats	$Na_3V^VO_4$ + tea extract [f]	105	21	25.0 ± 0.3	10 ± 1	↑ Ins; ↑ TG	65
ZDF rats	**1a**	42	5.5	28 ± 3	7 ± 1	↑ Ins sensitivity; activates Ins receptor	64
ZDF rats	**6** ($[Cr^{III}(pa)_3]$)	48	0.37	32 ± 2	29 ± 2 [g]	↓ HbA1c; ↓ lipid peroxidn.	139

Table 3 (end)

Model [a]	Compound [b]	Time, days	Total dose, mmol kg^{-1} [c]	FPG, mM [d] Vehicle	Drug	Additional observations [e]	Ref.
ZDF rats	Cr(III) dinicocysteinate	48	0.37	32 ± 2	23 ± 2	↓ HbA1c; ↓ lipid peroxidn.	139
ZDF rats	**7**	126	2.4	14.5 ± 2.1	13.0 ± 2.0 [g]	↑ Ins sensitivity; ↓ Ch; ↓ TG	151
ZDF rats	$Na_2[W^{VI}O_4]$	60	~37 [h]	25 ± 3	11 ± 1	↑ gluc. tol.; ↓ TG; improves liver function	155
KKA^y mice	**1c**	28	1.6-3.8	24 ± 3	12 ± 2	↓ blood pressure	77
KKA^y mice	**8**	24	5.5	27 ± 2	12 ± 2	↓ HbA1c; ↓ Ins; ↓ leptin	163 164
KKA^y mice	**9**	28	7.9	28 ± 3	13 ± 3	↓ HbA1c; ↓ Ins	165

[a] Streptozotocin-(STZ)-induced animal models of diabetes develop type 1 diabetes due to the destruction of β-cells in the pancreas.[59] Zucker diabetic fatty (ZDF) rats are an animal model in which diabetes develops in obese homozygous males (but not in their lean littermates) at over 10 weeks of age due to a mutation in a single gene.[66] KKA^y mice are used as an animal model in which type 2 diabetic traits are inherited by polygenes and are present in the latent form since the early age.[76] [b] Designations of the complexes (**1**-**9**) correspond to Chart 1; ma = maltolato(−); pa = 2-pyridinecarboxylato(−). [c] Total dose per kg of body weight received during the treatment (calculated in mmol of metal ion in the case of polynuclear complexes such as **4** or **7**). Unless stated otherwise, the drugs were delivered daily by oral gavage or with food or in drinking water. [d] Average fed plasma glucose (FPG) levels and standard deviations at the end of the treatment. Vehicle-treated diabetic animals were used as age-matched controls. Typical plasma glucose levels for age-matched non-diabetic animals (both vehicle- and drug-treated) were 7 ± 1 mM (not shown in the table). [e] Designations: HbA1c = glycated hemoglobin levels; gluc. tol. = glucose tolerance (rate of glucose clearance following glucose challenge); BW = body weight; Ins, Ch, TG and FFA are plasma levels of insulin, cholesterol, triglycerides and free fatty acids, respectively.

[f] Dissolution of vanadate in black tea extract instead of water greatly reduced the gastrointestinal inflammation caused by the treatment.[65] [g] Not significantly different ($p > 0.05$) compared with the vehicle-treated animals.[139, 151] [h] The drug was delivered in drinking water (2.0 mg $Na_2[WO_4]$ per mL).[155] The calculated dose is based on the average water uptake (~30 mL)[64] and average weight (~300 g)[155] of treated diabetic ZDF rats.

Table S3. Typical acute glucose-lowering activities of metal complexes in animal models

Compound [a]	**Model** [b]	**Dose,** [c] **mmol kg^{-1}**	**Time,**[d] **h**	**Glucose,**[e] **mM**		**Ref.**
				Baseline	**Treatm.**	
1a,b	STZ rats	0.60 o. g.	24	22 ± 1	9 ± 1	62
1a	STZ rats	0.10 i. p.	24	25 ± 2	11 ± 4	62, 71
2	STZ rats	0.10 i. p.	8-12	25 ± 2	11 ± 4	71
3	non-diabetic or BB rats	0.0060 i. v.	0.5-1.0	decrease by ~30%		87, 241
5	STZ rats	0.0050 o. g.	6	decrease by 6-10 mM		92
$[V^{IV}O(pa)_2]$	STZ mice	0.20 i. p.	12	27 ± 5	15 ± 5	169
$[Cu(pa)_2]$	STZ mice	0.047 i. p.	12	27 ± 5	10 ± 2	169

[a] Structures of the complexes **1a**,**b**, **2**, **3** and **5** are shown in Chart 1; pa = 2-pyridinecarboxylato. [b] Streptozotocin-(STZ)-induced animal models of diabetes develop type 1 diabetes due to the destruction of β-cells in the pancreas; and BB rats are genetically type 1 diabetic animals.[59] [c] Single dose (in mmol metal per kg body weight). Administration routes: o. g. = oral gavage; i. p. = intraperitoneal injection; i. v. = intravenous injection. [d] Time after the drug administration in which maximal activity is achieved. [e] Average values and standard deviations for plasma glucose (in the fed state).

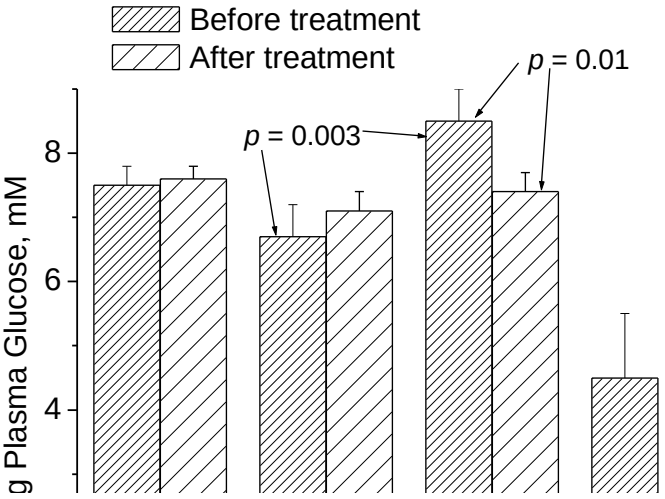

Figure S1. Changes in fasting plasma glucose (PG) levels observed in human clinical trials of Cr(III) picolinate (**6** in Chart 1) for type 2 diabetes.[115] Patients were treated either with **6** (1.0 mg Cr per day, $n = 70$) or with placebo ($n = 67$) for 24 weeks.[115] Responders to the Cr treatment ($n = 32$) had significantly higher ($p = 0.003$) initial PG levels that the non-responders ($n = 38$). After the treatment, the PG levels in the responding group significantly decreased ($p = 0.01$), but not to the normal range (4.5 ± 1 mM),[3] but to the values slightly above those for the non-responding group.[115] Similar differences between Cr-responding and non-responding groups were observed for the glycated hemoglobin levels, glucose clearance rates after challenge, and insulin sensitivity.[115]

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