SUPPLEMENTARY DATA

Radiomanganese PET Detects Changes in Functional β-cell Mass in Mouse Models of Diabetes

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Short title: $^{52}Mn^{2+}$-PET imaging of functional β-cell mass in vivo

Authorship note: R.H. and S.A.G. contributed equally to this work.

Conflict of interest: The authors declare that no conflict of interest exists.

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Mice

All animal experiments were approved by the Institutional Animal Care and Use Committees of the University of Wisconsin-Madison and the William S. Middleton Memorial Veterans Hospital. Male ICR (Envigo) and C57BL/6J wildtype and *ob/ob* mice (The Jackson Laboratory) were employed in this work. All mice were approximately ten weeks of age at the time of the experiments. Mice had access to food and water *ad libitum,* except under fasting condition when access to food was restricted for 6-12 hours.

$^{52}Mn^{2+}$ Production

$^{52}Mn^{2+}$ was produced as previously described (1). Production yields of up to 5.92 MBq/μAh (355 MBq/h @ 60 μA) were achieved using a chromium pellet pressed into a silver disc substrate. $^{52}Mn^{2+}$ was eluted in <1mL of 0.01 M NaOAc buffer (pH ~6.5) from a ~150 mg AG 1×8 column which had been conditioned with ethanol. As previously described (2), thin layer chromatographs confirmed the Mn^{2+} oxidation state following elution. End of bombardment radionuclidic purity was measured to be >99.5% by efficiency-calibrated high-purity germanium (HPGe) gamma spectrometry measurements. The only radionuclidic impurity observed was <0.5% of ^{54}Mn ($t_{1/2}$= 312.1 d), which does not decay by positron emission.

Islet Isolation

Mouse pancreatic islets were isolated by collagenase digestion as previously reported in (3). Briefly, mice were sacrificed via CO_2 asphyxiation followed by cervical dislocation. The common bile duct was perfused with 4 mL of an ice-cold solution containing type XI collagenase (0.5 mg/mL; Sigma Aldrich) and bovine serum albumin (BSA; 0.2 mg/mL; Sigma Aldrich) in Hank's Balanced Salt Solution (HBSS; Invitrogen). After inflation, the pancreas was removed to a glass vial containing 5 mL of collagenase solution, and incubated in a shaking water bath at 37°C for approximately 20 min. The digests were centrifuged at 50*g* for 2 min and islet pellets were washed three times with 30 mL ice-cold HBSS/BSA. The pellet was re-suspended and the islets were handpicked into 35 mm petri dishes. Following isolation, islets were placed in RPMI1640 media supplemented with penicillin (100 U/mL; Invitrogen), streptomycin (100 μg/mL; Invitrogen), and 10% (wt/vol) FBS (Sigma) and incubated overnight at 37°C in a 5% CO_2 atmosphere.

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Pharmacological Disruption of $^{52}Mn^{2+}$ Uptake in Isolated Islets

Batches of 50 islets were transferred into 0.45 μm-filtered 1 mL centrifuge vials (Thermo Fisher Scientific), and incubated with 500 μL of Krebs-Ringer buffer (KRB: 118 mM NaCl, 5.4 mM KCl, 2.4 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1 mM KH_2PO_3, 20 mM HEPES; pH 7.4) containing 1 mM glucose for 30 min at 37°C. After removing the supernatant by centrifugation at 50*g* for 5 min, 250 μL of KRB containing 16.7 mM glucose, diazoxide (50 μM; Tocris Biosciences), or tolbutamide (250 μM; Selleckchem) were added, and the vials were spiked with 370 kBq (10 μCi) of $^{52}Mn^{2+}$. After 15 min of incubation, the islets were washed three times with KRB. $^{52}Mn^{2+}$ radioactivity in the islet pellets was quantified using an automated gamma counter (Perkin Elmer).

Ex vivo $^{52}Mn^{2+}$ Biodistribution Analysis

Ex vivo biodistribution studies were performed in all groups of mice to validate the results of $^{52}Mn^{2+}$-PET imaging and obtain a more complete profile of tissue $^{52}Mn^{2+}$ uptake. Following the last imaging time point, mice were euthanized by CO2 asphyxiation and 15 organs of interest were removed, wet-weighed, and counted in an automated gamma-counter (Wizard 2480, Perkin Elmer). The tissue uptake of $^{52}Mn^{2+}$ was reported as SUV (mean ± S.D.).

Measurement of β-cell Mass

Similar as our previous report (4), mice were euthanized under anesthesia with CO_2 followed by cervical dislocation. The pancreas was immediately dissected, weighed, and fixed in 10% formalin on ice for 30 minutes. Pancreata were then washed in PBS and transferred through a series of solutions, beginning with 30% sucrose in PBS, 1:1 30% sucrose:OCT, and OCT before cryopreservation in OCT and storage at -80°C. 10-micron serial sections were cut on positively charged slides, with 9 sections per stop position (3/slide) and two stop positions per pancreas separated by at least 200 microns. For each pancreas, one slide per position was post-fixed, quenched of peroxidase activity with 3% H_2O_2, and immunohistochemically labeled using guinea pig anti-insulin primary antibody (Dako A056401-2), diluted 1:500 in antibody diluent, and co-stained with hematoxylin (Sigma, GHS280). Slides were imaged using an automated pan-and-stich microscope at 10× (Evos). β-cell fractional area was determined by quantifying the percent of insulin-positive pancreas area as a total of the full pancreas area for each section, followed by averaging of 2 distinct sections per mouse. Images were analyzed using ImageJ (64-bit) software (National Institutes of Health, Bethesda, MD) with shading correction. β-cell mass was calculated by multiplying β-cell fractional area by the pancreatic wet weight.

Islet Ca^{2+} Imaging

For measurements of cytosolic Ca^{2+}, islets were pre-incubated in 2.5 μM FuraRed (Molecular Probes) for 45 min at 37°C. Islets were then placed in an RC-41LP glass-bottomed chamber mounted in a QE-1 platform (Warner Instruments) on a Nikon Ti-Eclipse inverted microscope equipped with a 20×/0.75NA SuperFluor objective (Nikon Instruments). The chamber was perfused with standard external solution with glucose (in mM: 135 NaCl, 4.8 KCl, 5 $CaCl_2$, 1.2 $MgCl_2$, 20 HEPES; pH 7.35). The flow rate was 0.5 ml/min and temperature was maintained at 33°C using inline solution and chamber heaters (Warner Instruments). Excitation was provided by a SOLA SEII 365 (Lumencor) set to 10% output. Excitation (430/20 nm and 500/20 nm) and emission (630/70 nm) filters (ET type, Chroma Technology Corporation) were used in combination with an FF444/521/608-Di01 dichroic (Semrock). Fluorescence emission was collected with a Hamamatsu ORCA-Flash4.0 V2 Digital CMOS camera at 0.125 Hz. A

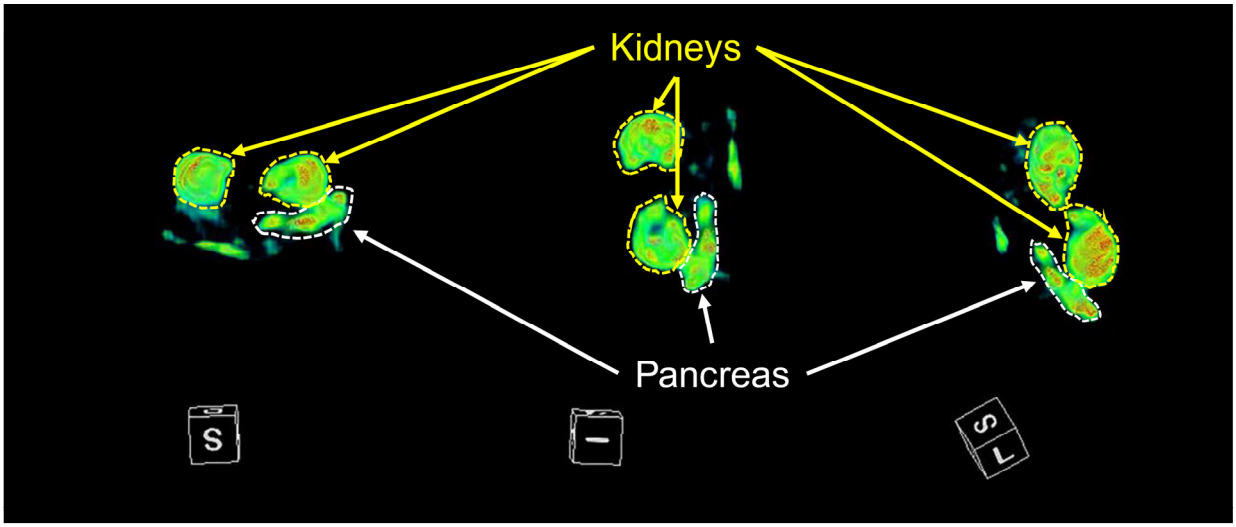
single region of interest was used to quantify the average response of each islet as the excitation ratio (R430/500) using Nikon Elements and MathWorks MATLAB software as in (3).

Statistics

A minimum sample size of three (n=3) was used in all *in vitro* and *in vivo* experiments. The uptake of $^{52}Mn^{2+}$ in the different tissues was reported as SUV (mean ± S.D.) and the differences between groups were evaluated for significance using a two-tailed Student's t-test. Differences were considered statistically significant at $P < 0.05$.

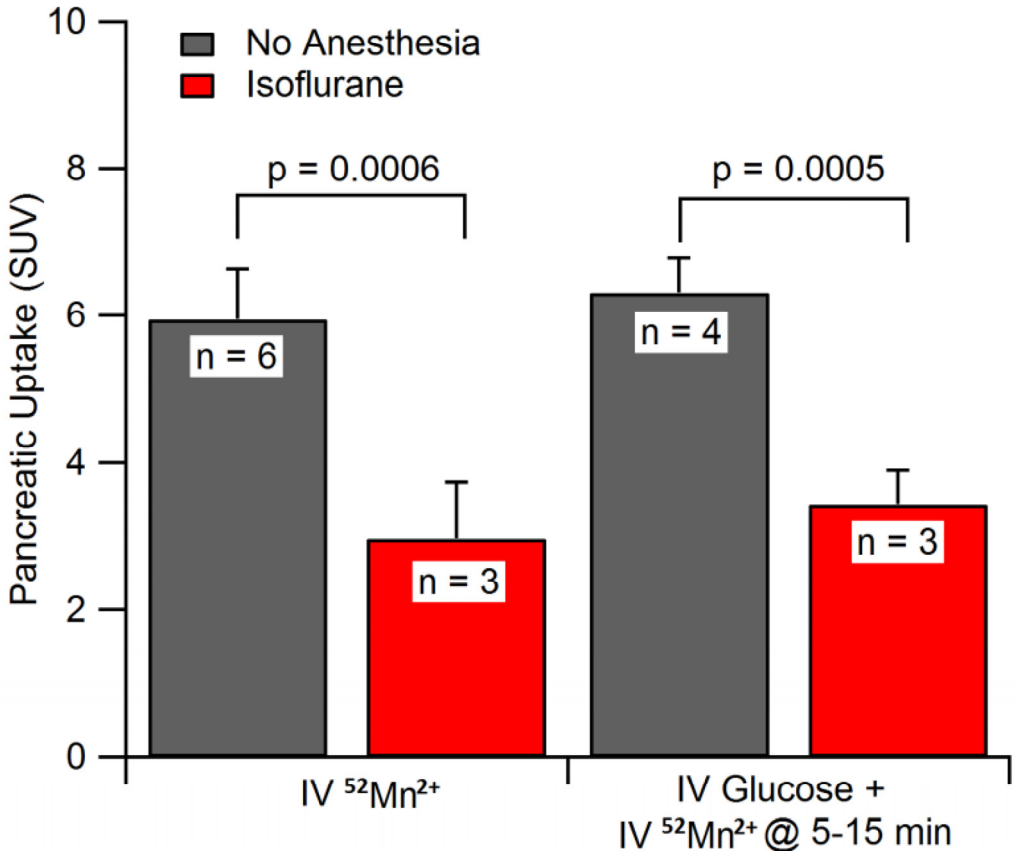
SUPPLEMENTARY DATA

Supplementary Figure S1 Three-dimensional rendering of the pancreas and kidneys PET signal in ICR mice injected a rapid IV $^{52}Mn^{2+}$ bolus. Three different view angles are presented showing the separation between pancreas and the left kidney. The animal subject shown here is the same displayed in Figure 1 of the main text.



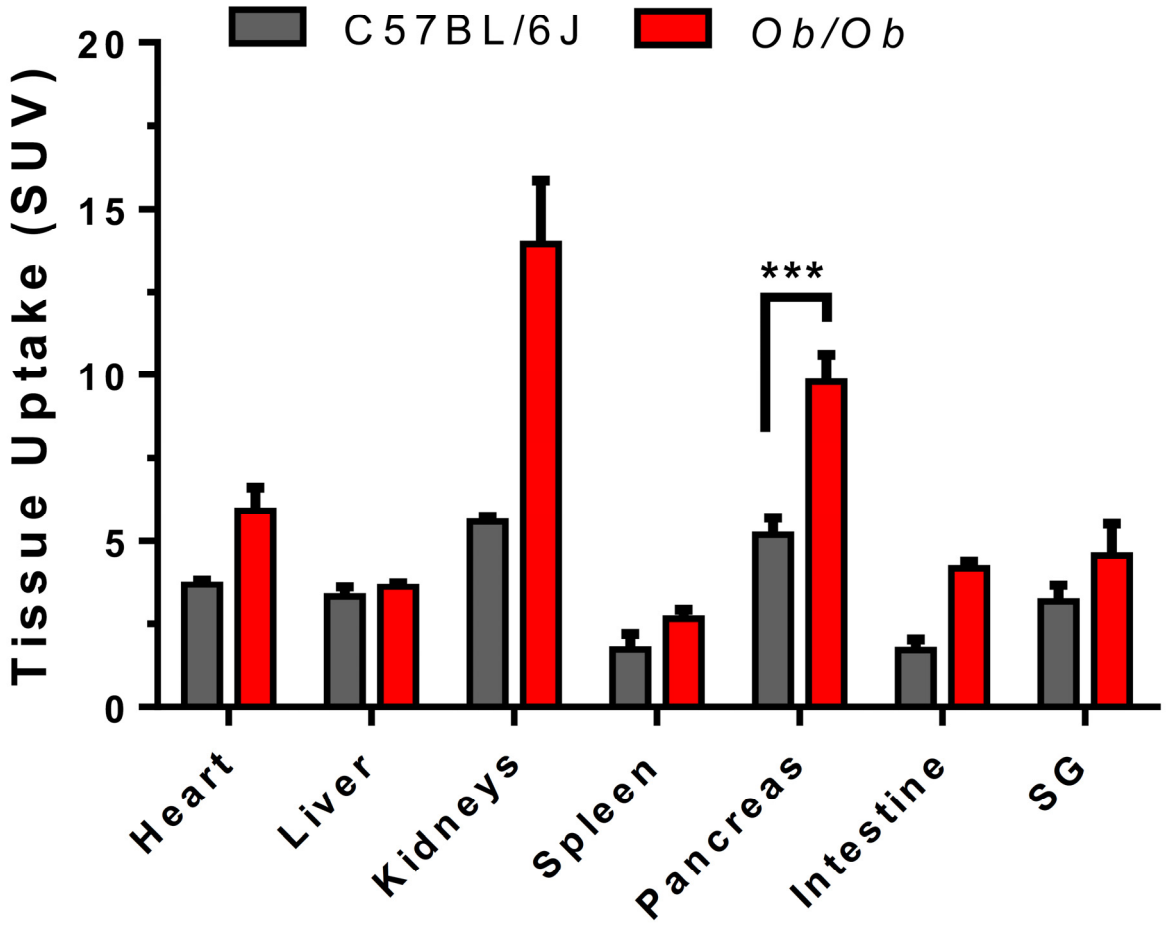
SUPPLEMENTARY DATA

Supplementary Figure S2. Impact of isoflurane on pancreatic uptake of $^{52}Mn^{2+}$ in mice. ICR mice (3-6 per group) received either an intravenous bolus of $^{52}Mn^{2+}$, or an intraperitoneal injection of glucose (1 mg/kg) followed by an intravenous infusion of $^{52}Mn^{2+}$ from 5 to 15 minutes following glucose administration. A subset of these treatments was anesthetized with 2% isoflurane during injections, whereas the rest of the mice were not anesthetized. One hour following $^{52}Mn^{2+}$ administration, mice were euthanized and *ex vivo* biodistribution studies were performed via gamma counting. Pancreatic uptake of $^{52}Mn^{2+}$ was found to be significantly lower in both groups under isoflurane anesthesia, when compared to non-anesthetized controls, suggesting that isoflurane prevents voltage-dependent calcium channel (VDCC) mediated $^{52}Mn^{2+}$ influx.



SUPPLEMENTARY DATA

Supplementary Figure S3 *Ex vivo* biodistribution of lean (C57BL/6J) and obese (ob/ob) mice, one-hour post injection of $^{52}Mn^{2+}$. Significantly higher $^{52}Mn^{2+}$ uptake can be noted in obese mice compared to the lean controls (***$P < 0.0001$; n=3).



SUPPLEMENTARY DATA

Supplementary Table S1. Quantitative results of longitudinal PET imaging studies in ICR mice administered a $^{52}Mn^{2+}$ intravenous bolus (n = 4)

	Organ/tissue uptake					
Time (days)	**Heart/blood**	**Liver**	**Kidneys**	**Muscle**	**Pancreas**	**S Gland**
0.042	2.11 ± 0.20	3.27 ± 0.34	5.13 ± 0.02	0.38 ± 0.03	5.13 ± 0.37	2.30 ± 0.26
0.125	1.88 ± 0.19	3.37 ± 0.47	5.21 ± 0.32	0.38 ± 0.02	5.11 ± 0.50	2.53 ± 0.44
0.5	1.21 ± 0.16	3.51 ± 0.29	4.90 ± 0.19	0.35 ± 0.05	4.89 ± 0.17	2.77 ± 0.19
1	0.93± 0.11	3.15 ± 0.28	4.59 ± 0.27	0.33 ± 0.03	4.84 ± 0.18	2.69 ± 0.05
3	0.80 ± 0.08	1.94 ± 0.17	3.32 ± 0.14	0.27 ± 0.05	4.40 ± 0.34	2.85 ± 0.09
5	0.72 ± 0.05	1.49 ± 0.05	2.60 ± 0.03	0.26 ± 0.03	3.65 ± 0.37	3.18 ± 0.33
7	0.69 ± 0.00	1.08 ± 0.10	1.96 ± 0.21	0.20 ± 0.02	2.98 ± 0.25	3.02 ± 0.13
9	0.64 ± 0.02	0.83 ± 0.06	1.56 ± 0.20	0.18 ± 0.02	2.26 ± 0.23	2.70 ±0.10
11	0.58 ± 0.03	0.70 ± 0.02	1.28 ± 0.14	0.19 ± 0.01	1.80 ± 0.23	2.63 ± 0.15
13	0.54± 0.03	0.62 ± 0.01	1.13 ± 0.06	0.19 ± 0.01	1.65 ± 0.31	2.50 ±0.08

Mean ± SD values are reported as standardized uptake value (SUV)

SUPPLEMENTARY DATA

Supplementary Table S2. *Ex vivo* biodistribution of $^{52}Mn^{2+}$ at day 13 after intravenous administration in healthy ICR mice. n = 4.

Organ/tissue	$^{52}Mn^{2+}$ uptake (SUV)*	$^{52}Mn^{2+}$ uptake (%ID/g)*
Blood	0.01 ± 0.01	0.06 ± 0.02
Skin	0.16 ± 0.05	0.56 ± 0.18
Muscle	0.26 ± 0.04	0.93 ± 0.14
Bone	0.50 ± 0.09	1.78 ± 0.28
Heart	1.19 ± 0.08	4.25 ± 0.18
Lung	0.22 ± 0.06	0.80 ± 0.22
Liver	0.72 ± 0.04	2.57 ± 0.14
Kidney	1.85 ± 0.04	6.57 ± 0.23
Spleen	0.35 ± 0.10	1.23 ± 0.34
Pancreas	2.62 ± 0.44	9.30 ± 1.29
Stomach	0.76 ± 0.18	2.68 ± 0.61
Intestine	0.14 ± 0.02	0.49 ± 0.07
Salivary	2.84 ± 0.13	10.13 ± 0.38
Tail	0.14 ± 0.01	0.54 ± 0.05
Brain	0.52 ± 0.01	1.87 ± 0.07
***Mean ± SD**		

SUPPLEMENTARY DATA

Supplementary Table S3. Quantitative results of PET imaging in ICR mice 1 h post administration of $^{52}Mn^{2+}$ under various conditions to stimulate or inhibit insulin release.

Organs	Baseline (n=3)	Diazoxide (n=3)	Nifedipine (n=3)	Glibenclamide (n=4)	STZ-diabetic (n=3)
Heart/blood	2.11 ± 0.20	2.58 ± 0.22	2.61 ± 0.30	2.50 ± 0.60	1.97 ± 0.50
Liver	3.27 ± 0.34	3.11 ± 0.50	2.06 ± 0.56	3.20 ± 0.87	2.89 ± 1.70
Kidneys	5.13 ± 0.02	4.66 ± 1.48	3.52 ± 0.43	5.70 ± 1.35	3.80 ± 0.78
Muscle	0.38 ± 0.03	0.40 ± 0.07	0.44 ± 0.07	0.44 ± 0.04	0.23 ± 0.06
Pancreas	5.13 ± 0.38	2.85 ± 0.92	2.36 ± 0.61	6.47 ± 1.36	2.04 ± 0.81
Salivary Gland	2.30 ± 0.26	2.46 ± 0.97	2.15 ± 0.22	2.25 ± 0.14	1.51 ± 1.01

Mean ± SD values are reported as standardized uptake value (SUV)

SUPPLEMENTARY DATA

Supplementary Table S4. One-hour post injection e*x vivo* biodistribution data in ICR mice administered $^{52}Mn^{2+}$ under various conditions to stimulate or inhibit insulin release.

Organs	Baseline (n=3)	Diazoxide (n=3)	Nifedipine (n=3)	Glibenclamide (n=4)	STZ diabetic (n=3)
Heart	4.01 ± 0.26	4.96 ± 0.46	5.42 ± 0.81	5.29 ± 1.19	1.97 ± 0.50
Liver	3.63 ± 0.13	3.17 ± 0.83	1.84 ± 0.45	3.26 ± 0.70	2.89 ± 1.70
Kidneys	8.12 ± 0.88	6.42 ± 2.67	4.55 ± 0.84	8.10 ± 1.22	3.80 ± 0.78
Spleen	1.74 ± 0.22	1.75 ± 0.47	0.52 ± 0.13	1.68 ± 0.40	0.23 ± 0.06
Pancreas	6.31 ± 0.51	4.43 ± 1.08	3.20 ± 0.61	7.53 ± 1.29	2.04 ± 0.81
Intestine	1.96 ± 0.32	2.40 ± 0.99	1.94 ± 0.14	2.25 ± 0.64	1.51 ± 1.01
Salivary Gland	2.90 ± 0.67	2.97 ± 0.62	2.35 ± 0.16	2.68 ± 0.46	1.97 ± 0.50

Mean ± SD values are reported as standardized uptake value (SUV)

SUPPLEMENTARY DATA

Supplementary Table S5. *In vivo* PET and *ex vivo* biodistribution data in C57BL/6J and obese (*ob/ob*) mice one-hour after intravenous administration of $^{52}Mn^{2+}$. n = 3.

	***In vivo* PET Data**			***Ex vivo* biodistribution**	
Organs	C57BL/6J (n=3)	*Ob/Ob* (n=3)	**Organs**	C57BL/6J (n=3)	*Ob/Ob* (n=3)
Heart/blood	1.93 ± 0.10	3.32 ± 0.13	**Heart**	3.68 ± 0.15	5.93 ± 0.69
Liver	3.40 ± 0.73	3.68 ± 0.25	**Liver**	3.33 ± 0.29	3.63 ± 0.10
Kidneys	5.08 ± 0.37	9.43 ± 0.44	**Kidneys**	5.58 ± 0.16	13.94 ± 1.91
Muscle	0.38 ± 0.06	0.26 ± 0.09	**Spleen**	1.74 ± 0.46	2.65 ± 0.27
Pancreas	4.89 ± 0.68	7.27 ± 1.03	**Pancreas**	5.19 ± 0.52	9.79 ± 0.83
Salivary Gland	2.40 ± 0.20	3.11 ± 1.05	**Intestine**	1.72 ± 0.33	4.17 ± 0.21
			Salivary Gland	3.18 ± 0.49	4.57 ± 0.95

Mean ± SD values are reported as standardized uptake value (SUV)

SUPPLEMENTARY DATA

Supplementary Table S6. Quantitative results of longitudinal PET imaging studies in ICR mice administered a $^{52}Mn^{2+}$ intravenous bolus (n = 4)

	Organ/tissue uptake					
Time (days)	**Heart/blood**	**Liver**	**Kidneys**	**Muscle**	**Pancreas**	**S Gland**
0.042	7.50 ± 0.61	11.63 ± 1.12	18.30 ± 0.53	1.37 ± 0.12	18.30 ± 1.71	8.20 ± 0.92
0.125	6.70 ± 0.62	12.00 ± 1.41	18.57 ± 1.42	1.37 ± 0.06	18.23 ± 2.21	9.00 ± 1.35
0.5	4.30 ± 0.61	12.50 ± 0.69	17.47 ± 0.21	1.27 ± 0.15	17.43 ± 0.87	9.87 ± 0.49
1	3.33 ± 0.42	11.20 ± 0.72	16.33 ±0.72	1.17 ± 0.12	17.23 ± 0.40	9.60 ± 0.30
3	2.83 ± 0.21	6.90 ± 0.46	11.83 ± 0.45	0.96 ± 0.15	15.70 ± 1.59	10.17 ± 0.38
5	2.57 ± 0.15	5.30 ± 0.10	9.27 ± 0.25	0.93 ± 0.06	13.03 ± 1.56	11.20 ± 0.85
7	2.47 ± 0.06	3.83 ± 0.29	7.00 ± 0.87	0.73 ± 0.07	10.63 ± 1.17	10.77 ± 0.71
9	2.30 ± 0.10	2.93 ± 0.15	5.57 ± 0.84	0.64 ± 0.05	8.07 ± 0.90	9.63 ± 0.32
11	2.07 ± 0.15	2.50 ± 0.10	4.57 ± 0.61	0.66 ± 0.02	6.43 ± 0.95	9.37 ± 0.55
13	1.93 ± 0.06	2.20 ± 0.10	4.03 ± 0.31	0.66 ± 0.05	5.90 ± 1.20	8.90 ± 0.26

Mean ± SD values are reported as percent injected dose per gram (%ID/g)

SUPPLEMENTARY DATA

Supplementary Table S7. Quantitative results of PET imaging in ICR mice 1 h post administration of $^{52}Mn^{2+}$ under various conditions to stimulate or inhibit insulin release.

Organs	Baseline (n=3)	Diazoxide (n=3)	Nifedipine (n=3)	Glibenclamide (n=4)	STZ-diabetic (n=3)
Heart/blood	7.50±0.61	8.27±1.75	10.93±0.76	8.25±1.68	7.63±1.94
Liver	11.63±1.12	9.77±0.42	8.53±1.63	10.55±2.39	11.83±8.63
Kidneys	18.30±0.53	14.53±3.27	14.73±0.99	18.73±2.65	14.80±3.82
Muscle	1.37±0.12	1.29±0.37	1.83±0.15	1.45±0.10	0.86±0.14
Pancreas	18.30±1.71	9.03±2.74	9.87±2.42	21.28±2.43	7.70±2.49
Salivary Gland	8.20±0.92	7.97±3.69	9.03±1.10	7.48±0.29	5.53±3.20

Mean ± SD values are reported as standardized uptake value (%ID/g)

SUPPLEMENTARY DATA

Supplementary Table S8. One-hour post injection e*x vivo* biodistribution data in ICR mice administered $^{52}Mn^{2+}$ under various conditions to stimulate or inhibit insulin release.

Organs	Baseline (n=3)	Diazoxide (n=3)	Nifedipine (n=3)	Glibenclamide (n=4)	STZ diabetic (n=3)
Heart	13.10±1.90	15.85±3.02	22.72±3.12	17.46±3.10	15.13±3.33
Liver	8.01+0.33	9.87+1.62	7.63+1.24	10.79+2.22	15.11+11.18
Kidneys	30.77±4.67	19.92±6.50	19.04±3.15	26.85±3.34	22.85±6.62
Spleen	5.85±0.69	5.42±0.94	2.18±0.42	5.52±0.85	3.39±1.36
Pancreas	21.62±2.49	14.03±3.27	13.33±1.64	24.85±2.05	10.14±3.92
Intestine	9.23±0.74	7.44±2.56	8.17±0.69	7.55±2.58	8.33±4.19
Salivary Gland	10.03±1.78	8.81±3.80	9.86±0.83	8.85±0.63	7.11±4.45

Mean ± SD values are reported as percent injected dose per gram (%ID/g)

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Supplementary Table S9. *In vivo* PET and *ex vivo* biodistribution data in C57BL/6J and obese (*ob/ob*) mice one-hour after intravenous administration of $^{52}Mn^{2+}$. n = 3.

	***In vivo* PET Data**			***Ex vivo* biodistribution**	
Organs	C57BL/6J (n=3)	*Ob/Ob* (n=3)	**Organs**	C57BL/6J (n=3)	*Ob/Ob* (n=3)
Heart/blood	8.57±0.60	7.33±0.50	**Heart**	16.36±0.74	13.10±1.90
Liver	15.07±2.97	8.10±0.36	**Liver**	14.75±1.01	8.01±0.33
Kidneys	22.53±1.31	20.80±1.61	**Kidneys**	24.79±1.13	30.77±4.67
Muscle	1.70±0.30	0.58±0.20	**Spleen**	7.72±1.95	5.85±0.69
Pancreas	21.70±2.86	16.07±2.67	**Pancreas**	23.03±1.94	21.62±2.49
Salivary Gland	10.63±0.91	6.80±2.08	**Intestine**	7.62±1.42	9.23±0.74
			Salivary Gland	14.12±2.35	10.01±1.78

Mean ± SD values are reported as standardized uptake value (%ID/g)

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