Electronic Supplementary Material (ESI) for Analytical Methods

Supporting Information

The two datasets used in this article were listed:

The first metabolomics data contained three classes, healthy control C57 mice, female C57-AMPK gene knocked-out mice and male C57-AMPK gene knocked-out mice. The concentrations of 42 compounds were listed in Table 1.

Table 1. Qualitative and quantitative metabolic profile of three group mice.

id	t_r[a] (min)	endogenous metabolites	C57	AMPK-male	AMPK-female
1	5.922	Aminoethane	0.2456±0.0705	0.1905±0.0567	0.1958±0.0551
2	6.593	Ethylene glycol	0.0182±0.0020	0.0530±0.0428	0.0746±0.0626
3	6.84	N,N-diethylacetamide	0.0657±0.0087	0.0476±0.0202	0.0557±0.0107
4	7.716	Lactic acid *	0.0872±0.0374	0.0952±0.0592	0.1482±0.2155
5	7.934	Acetic acid	0.0856±0.0333	0.0229±0.0140	0.0412±0.0203
6	10.01	phosphate	2.1278±0.9173	1.4730±0.7381	1.3767±0.9361
7	10.2	l-Threonine	0.0173±0.0098	0.0108±0.0068	0.0096±0.0065
8	10.297	Phenylacetic acid	0.0047±0.0023	0.0159±0.0103	0.0147±0.0097
9	10.382	Succinic acid *	0.0311±0.0129	0.0098±0.0031	0.0119±0.0086
10	10.447	1,2-Hydroquinone	0.0120±0.0072	0.0078±0.0047	0.0067±0.0039
11	10.503	Glyceric acid	0.0961±0.0266	0.0400±0.0232	0.0183±0.0087
12	10.723	(R*,R*)-2,3-Dihydroxybutano	0.0167±0.0053	0.0037±0.0014	0.0053±0.0029

		ic acid			
13	11.357	2,4-Dihyoxybutanoic acid	0.0147±0.0051	0.0155±0.0080	0.0166±0.0047
14	11.583	(R*,S*)-3,4-Dihydroxybutanoic acid	0.0304±0.0098	0.0132±0.0064	0.0178±0.0107
15	11.797	N-(1-oxobutyl)- Glycine	0.0653±0.0244	0.0319±0.0186	0.0274±0.0151
16	12.341	Isovaleroglycine	0.0356±0.0134	0.0160±0.0079	0.0107±0.0073
17	12.483	D- Threitol	0.0714±0.0273	0.0290±0.0130	0.0251±0.0151
18	12.645	N-Crotonylglycine	0.0240±0.0146	0.0207±0.0129	0.0148±0.0099
19	12.973, 13.203	2,3,4-Trihydroxybutyrate	0.1276±0.0162	0.0631±0.0343	0.0412±0.0250
20	14.53	N-(1-oxohexyl)-glycine	0.0960±0.0319	0.0421±0.0273	0.0232±0.0081
21	14.58	3-Hydroxyphenylacetic acid	0.0326±0.0100	0.0140±0.0081	0.0134±0.0088
22	14.713	D-Xylose	0.0408±0.0150	0.0182±0.0044	0.0193±0.0053
23	14.823, 15.057	D-Ribose	0.0926±0.0370	0.0252±0.0142	0.0250±0.0179
24	15.509, 15.733	Arabitol	0.0287±0.0164	0.0283±0.0179	0.0278±0.0215
25	16.023	6-Deoxy-D-Galactose,	0.0336±0.0083	0.0177±0.0100	0.0149±0.0104
26	16.087	Mannonic acid	0.0505±0.0177	0.0211±0.0143	0.0168±0.0138
27	16.2	cis-Aconitic acid*	0.0535±0.0288	0.0105±0.0079	0.0168±0.0147
28	16.357	Phosphoric acid	0.0414±0.0202	0.0230±0.0141	0.0212±0.0168
29	17.177	Isocitric acid*	0.0348±0.0121	0.0140±0.0093	0.0248±0.0138
30	17.563	Hippuric acid	0.0470±0.0126	0.0180±0.0074	0.0156±0.0096
31	17.85, 17.96	D-Fructose*	0.0512±0.0286	0.0371±0.0145	0.0480±0.0131
32	18.087	N-phenyl glycine*	0.0596±0.0214	0.0455±0.0272	0.0389±0.0287

33	18.197, 18.147	D-Glucose*	0.3785±0.1618	0.1741±0.0654	0.1859±0.0736
34	18.507	Altronic acid	0.0302±0.0069	0.0185±0.0100	0.0102±0.0074
35	18.577, 18.65	D-Sorbitol*	0.0896±0.0269	0.0254±0.0187	0.0300±0.0275
36	18.983, 19.533	Galactonic acid	0.0613±0.0282	0.0617±0.0328	0.0441±0.0351
37	19.99	Palmitic acid	0.0084±0.0009	0.0067±0.0017	0.0071±0.0025
38	20.403	Myo-Inositol	0.0347±0.0228	0.0097±0.0037	0.0134±0.0129
39	25.465	D-Turanose	0.0216±0.0138	0.0197±0.0090	0.0510±0.0099
40	25.653, 25.783	D-（+）-lactose monohydrate*	1.0400±0.3349	0.7475±0.2366	0.6559±0.3286
41	25.927	Lactose*	0.0142±0.0043	0.0143±0.0075	0.0190±0.0163

*: Identified by standard substances; [a]: Retention time;

The second data contained 25 mice. i.e., 20 KK-Ay mice with diabetes and 5 C57 mice as healthy control group. 20 KK-Ay diabetic mice were further classified into four classes, 5 mice in each class. Each group was treated with repaglinide with different periods ranging from 14^{th} week to 22^{nd} week. 42 compounds were considered as endogenous metabolites to represent each sample. The concentrations of 42 compounds were listed in Table 2.

Table 2 Quantitative metabolic profile of the repaglinide treated diabetic KK-A^y mice and C57BL/6J mice (relative quantity of each metabolite to internal standard).

id	t_r^a (min)	endogenous metabolites	14th week	17th week	20th week	22nd week	healthy
1	6.833	N,N-diethyl-acetamide	6.59±0.70	6.85±1.14	7.54±0.48	8.06±0.45	5.19±0.84
2	7.14	N-ethyl-acetamide	15.42±2.70	14.72±2.93	16.32±0.69	20.17±2.03	11.90±1.42
3	7.667	Lactic acid	30.09±11.02	165.99±46.18	46.61±26.27	66.03±11.22	6.25±3.97
4	7.75	Dimethylsilanediol	6.59±1.16	6.67±1.02	5.70±2.17	6.63±3.15	3.83±0.68
5	7.883	Glycollic acid	3.24±0.86	3.03±1.73	4.07±1.39	4.09±1.03	7.45±1.62

6	8.557	N-formyl-glycine	6.10±0.79	12.99±2.01	16.65±3.09	9.59±7.84	9.81±1.62
7	8.993	Valine	8.46±5.08	15.88±2.27	15.26±2.62	6.78±7.25	7.49±0.44
8	10.32	Butanedioic acid	6.58±7.26	4.04±0.75	3.33±0.18	5.80±3.12	7.70±3.62
9	10.37	o-Dihydroxybenzene	1.03±0.26	0.64±0.22	0.78±0.48	1.38±0.92	0.51±0.18
10	10.427	2,3-Bis(hydroxy)propionic acid	1.13±0.16	0.93±0.53	0.99±0.41	1.44±0.25	9.26±2.15
11	11.247	Pentanedioic acid	1.83±0.29	1.98±0.30	4.60±2.82	2.37±0.58	0.79±0.30
12	12.163	Malic acid	2.80±1.11	1.46±0.41	1.49±0.86	1.78±0.47	0.94±0.51
13	12.37	Threitol	3.87±0.47	2.84±0.90	4.58±0.84	4.01±1.01	6.77±0.46
14	12.857	2,3,4-Trihydroxybutyric acid*	2.15±0.85	1.41±0.34	1.93±0.31	1.73±0.77	5.74±0.74
15	13.083	2,3,4-Trihydroxybutyric acid*	1.41±0.41	1.42±0.69	2.00±0.71	1.67±0.55	6.20±0.97
16	13.373	α-Hydroxyglutaric acid	3.93±1.99	5.01±1.13	3.38±1.13	2.94±1.89	6.91±6.44
17	14.523	2-Phenyl-1,2-bis(hydroxy)propane	1.58±0.25	1.91±2.85	0.79±0.70	2.00±1.08	0.42±0.21
18	15.377	Arabitol	1.99±0.24	1.47±0.67	2.86±1.39	2.11±0.57	2.36±0.47

19	15.597	Xylitol	1.17±0.18	1.45±1.18	1.62±0.59	1.80±0.71	2.37±0.36
20	15.893	2,3-Butanediol	1.68±0.56	1.08±0.58	0.34±0.17	1.42±0.70	0±0[d]
21	15.967	Pentonic acid	1.52±0.43	0.54±0.34	1.17±1.15	1.72±1.05	3.56±0.20
22	16.1	1-Propene-1,2,3-tricarboxylic acid	3.79±1.19	2.15±1.36	3.44±2.00	2.32±1.16	6.95±1.02
23	17.493	1,5-Anhydro-d-glucitol[1]	42.31±5.74	15.12±11.53	5.20±3.45	0±0[b]	3.48±0.88
24	17.73	d-Ribose	9.12±4.39	0.48±0.26	2.25±2.94	0.71±0.25	0.84±0.38
25	17.85	Xylitol	6.42±1.70	3.07±1.98	3.02±2.11	0.74±0.26	4.01±1.35
26	18.227	d-Glucose[2]	1154.25±145.85	884.53±157.43	223.74±111.73	8.52±1.02	4.05±0.44
27	18.403	d-Galactose[3]	379.15±54.26	354.68±128.86	68.94±41.86	1.64±0.21	2.76±0.14
28	18.56	d-Mannose	5.77±3.86	4.99±1.74	6.70±2.90	4.63±4.08	10.60±2.81
29	18.877	Ribonic acid	3.09±2.07	2.63±0.70	2.78±0.86	0.63±0.23	10.77±0.88
30	19.04	Glucopyranose	41.78±17.67	66.13±60.23	3.42±3.68	0.05±0.12	0±0[e]
31	19.418	Tartaric acid	3.40±1.08	2.70±1.60	1.40±0.76	0.67±0.80	1.18±0.06

32	19.91	Hexadecanoic acid	2.18±0.83	2.77±1.10	3.73±2.03	0.53±0.91	0.39±0.17
33	20.277	Myo-inositol	4.39±1.37	3.46±1.27	2.88±0.87	2.65±1.29	1.79±0.40
34	21.584	9,12-Octadecadienoic acid	1.36±0.32	0.85±0.35	1.34±1.05	0±0[c]	0±0[f]
35	25.143	α-d-Glucopyranoside	49.0±23.9	9.69±9.12	21.52±23.40	19.73±21.06	5.52±3.65
36	25.54	d-Turanose[#]	56.9±12.9	63.02±8.29	56.97±5.63	39.15±17.90	85.91±26.03
37	25.667	Maltose	13.4±4.43	13.79±2.43	13.13±2.64	8.20±4.79	20.89±6.80
38	25.733	2-Deoxy-galactopyranose	2.13±0.85	0.60±0.37	0.57±0.35	4.02±6.57	1.29±0.43
39	25.903	d-Turanose[#]	25.7±6.98	8.03±7.20	11.51±8.56	9.62±11.23	1.98±1.10
40	26.04	Melibiose	3.07±0.89	4.61±2.70	2.07±1.05	2.11±1.44	0.19±0.06
41	26.107	Allonic acid	3.16±1.02	2.91±3.73	1.98±1.54	2.30±1.73	0.36±0.13

1,2,3: Identified by standard substances; a: Retention time;

b,c,d,e,f: No target product was detected

*,#:Can't identified by NIST05.