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Material and methods

Human Subjects

Patients with CKD patients admitted to the XiangYa Hospital were identified by nephrologists of the Central South University at Changsha, Hunan, China. Normal individuals were free of kidney disease. CKD patients were selected on the basis of displaying kidney damage (structural or functional abnormalities of the kidney) with glomerular filtration rate <60 mL/min per 1.73 m2 for >3 months. Clinical data for normal individuals and patients with mild or severe CKD are listed in the Table 1.

The research protocol, which included informed consent from the subjects, was approved by the Central South University Committee for the Protection of Human Subjects（No.201512551）.

Animals

Eight- to 10-week-old C57BL/6 wild-type (WT) mice were purchased from Harlan Laboratories (Indianapolis, IN). A2B adenosine receptor (ADORA2B)–deficient mice with C57BL/6 background were generated and genotyped as described previously[1, 2]. A novel line of mice with erythrocyte-specific deletion of Adora2b was generated by crossing mice homozygous for a floxed Adora2b allele with mice expressing Cre recombinase under the control of erythropoietin receptor (EpoR) gene regulatory elements[1]. All protocols involving animal studies were reviewed and approved by the Institutional Animal Welfare Committee of the University of Texas Health Science Center at Houston.

Blood Collection and Preparation

Human and mouse blood were collected and stored as described earlier[1, 2]. Approximately 4 mL human blood was collected with heparin as an anticoagulant for 2,3-BPG measurement with a commercial assay (Roche, USA) as previously described[1]. For plasma adenosine assay, 1 mL EDTA-collected blood was divided into aliquots in tubes containing 10 μ mol/L dipyridamole (an inhibitor of equilibrative nucleoside transporters) and 10 μ mol/L eoxycoformycin (an inhibitor of adenosine deaminase). Approximately 1 mL mouse blood was collected and used for 2,3-BPG and plasma adenosine measurement, similar to human blood described above[1, 2]. Approxiamately 1ml of blood was withdrawn from a forearm vein of study participants, collected in 1.5ml tubes and stored at −80°C after collection for further analysis.

Metabolomics

Untargeted metabolomics profiling of all samples were performed by Metabolon Inc., as previously described [3]. Briefly, Blood samples were processed by using the automated MicroLab STAR® system from Hamilton Company. Recovery standards were added prior to the first step in the extraction process for QC purposes. Protein was precipitated by a series of organic and

aqueous extractions via a methanol crash, the samples were shaken then centrifuged. The resulting supernatant was split into equal aliquots for analysis on the Liquid chromatography/Mass Spectrometry (LC/MS, LC/MS/MS2) or Gas chromatography/Mass Spectrometry (GC/MS) platforms. For the LC/MS and- LC/MS/MS analysis, sample extracts were reconstituted in acidic or basic LC-compatible solvents and separated by a Waters ACQUITY UPLC and analyzed by on a Thermo-Finnigan LTQ mass spectrometer, which consisted of an electrospray ionization (ESI) source and linear ion-trap (LIT) mass analyzer. For GC/MS analysis, samples were re-dried under vacuum desiccation for a minimum of 24 hours prior to being derivatized under dried nitrogen using bistrimethyl-silyl-triflouroacetamide (BSTFA). The GC column was 5% phenyl and the temperature ramp is from 40° to 300° C in a 16 minute period. Samples were analyzed on a Thermo-Finnigan Trace DSQ fast-scanning single-quadrupole mass spectrometer using electron impact ionization. The instrument was tuned and calibrated for mass resolution and mass accuracy on a daily basis. The information output from the raw data files was automatically extracted by the informatics system developed by Metabolon. The informatics system consisted of four major components, the Laboratory Information Management System (LIMS), the data extraction and peak-identification software, data processing tools for QC and compound identification, and a collection of information interpretation and visualization tools for use by data analysts.

The metadata of this study had been uploaded to the Metabolomicsworkbench public database, Study ID (ST001153).
https://www.metabolomicsworkbench.org/data/MWTABMetadata4.php?Mode=Study&DataMode=AllData&StudyType=MS&F=Tingting_UT_20190218_135726_mwtab_analysis_1.txt

For statistical analysis and data display, metabolites were deleted if its value was missing in any sample. Fold change of each metabolite median value between Ang II infused group and Saline group was conducted to compare data between the experimental groups. Unpaired 2-tailed Student's t test were used to evaluate the difference between two groups and P values were shown ($P<0.05$ was considered as statistically significant, green background). All the statistics were performed in Microsoft excel 2016. R package "heatmap" Version 1.0.8 in the freely available program R (http://cran.r-project.org/) was used to draw the heatmap.

Chronic Ang-II infusion into mice

Mice were anesthetized with isoflurane (2%), and osmotic minipumps (Alzet model 2001; Alza, Palo Alto, CA) were implanted subcutaneously in the nape of the neck. Ang II (Sigma, MI, USA) was delivered at a rate of 140ng/kg/min into 12-week-old mice for 7 or 14-days. Control mice were infused with PBS[4].

***In vivo* treatment of mice with AICAR, Compound C and Ang II**

7-days Ang II chronic infused WT mice were divided into 3 groups. One group was intraperitoneally (i.p.) injected with AICAR (200 mg/kg daily) (TOCRIS, USA) for 7 days[4], the second group was i.p. injected with PBS for 7 days and the third group was i.p. injected with Compound C (20 mg/kg) for 7 days (TOCRIS, USA)[1, 6]. 14-days Ang II chronic infused *EpoR-Cre*$^{+}$ and *Adora2b*$^{f/f}$*-EpoR-Cre*$^{+}$ were treated with or without AICAR (200 mg/kg daily) (TOCRIS, USA) for 14 day.

Mouse blood pressure measurements

Systolic blood pressure was measured by a carotid catheter-calibrated tail-cuff system (CODA, Kent Scientific, Torrington, CT) before and after mini-pump implantation as described[3, 6]. Specifically, blood pressure was monitored on day 0 which was considered as baseline and continuously measured on the day 3rd, 7th, 10th, and 14th of the 2-week experimental period. After an initial acclimatization of the mice for five cycles, blood pressure was monitored over a period of 20 cycles and averaged for the final blood pressure measurement. To minimize the circadian effects, blood pressure measurement and urine collection were conducted at the same time each day.

Quantification of renal adenosine levels

Mice were anesthetized, and the kidneys were rapidly removed and frozen in liquid nitrogen. Adenosine was extracted from frozen kidney tissue using 0.4N perchloric acid, separated and quantified using reversed phase HPLC as described previously[4].

Mouse urine collection and analysis

Twenty-four–hour urine was collected using metabolic cages (Nalgene). The concentration of albumin and creatinine in the urine were determined using a commercially available kit (Exocell). The ratio of urinary albumin to urinary creatinine was used as an index of urinary protein[7].

Measurement of erythrocyte 2,3-BPG mutase activity

Frozen erythrocyte pellets were used for protein extraction following the protocol as mentioned above. Erythrocyte protein extract were subsequently utilized for measurement of 2,3-BPG mutase activity as described previously with modification10. Briefly, erythrocyte protein extract was incubated in 100 µl prepared reaction mixture (100 mM Triethanolamine pH 7.6, 1 mM MgSO4, 4 mM ATP, 3 mM 3-phosphoglycerate, 10 unit phosphoglycerate kinase for 20 minutes at 300C. Then, the reaction was terminated by adding 25µl of Trichloroacetic acid, and subsequently centrifuged at 10,000gX for 5 minutes. 100 µl of the supernatant was mixed with 17 µl of 1.8 M Tris base, and the 2,3-BPG level of the mixture was measured by using a commercial assay (Roche, USA) as previous[8].

2,3-BPG analysis and erythrocyte oxygen release capacity (P50) measurement.

2,3-BPG in 20 ml RBC pellets from human and mouse was isolated with 100 ml, 0.6M cold perchloric acid on ice, vortexed and subsequently sonicated for 10 s with output 6 (W-220F, Heat Systems-Ultrasonic, Inc.). The homogenate was centrifuged at 20,000g for 10 min). A volume of 80 ml supernatant was transferred to a new tube and neutralized with 10 ml, 2.5M K_2CO_3, then centrifuged at 20,000g for 5min. A volume of 20 ml supernatant was used to quantify 2,3-BPG using a commercially available kit (Roche, Nutley, NJ)[1, 8] For human samples, arterial blood gases were measured and the Hill equation was used to calculate P50 (ref. 58. For mouse samples, 10 ml of whole blood aliquot were mixed with 4.5 ml Hemox Buffer (TCS Scientific Corporation, PA), 10 ml anti-foaming reagent ((TCS Scientific Corporation, PA) and 20 ml 22% BSA in PBS. The mixture was then injected into the Hemox Analyzer (TCS Scientific Corporation, PA) for measurement of oxygen equilibrium curve at the temperature of 37 ºC[1, 2].

Real- time PCR of kidneys of mice

RNA was extracted using Trizol reagent (Invitrogen). Transcript levels were quantified using real-time quantitative RT-PCR. Syber green was used for analysis of prepro-ET-1, EDNRA, Col I, FN, GAPDH using the following primers: mouse: prepro-ET-1 F:5'-ctcttctgacccctttgcag-3', R: 5'-agctccttggaaagtcacga-3', Ednra F:5'-caaccattacgccacagatg -3', R: 5'-caggaaagacccattggcta-3', Col I F:5'-tctcctggcaaagacggactcaac-3' , R: 5'-tgcggatgttctcaatctgctgac-3' , FN F: 5'-ccacccccataaggcatagg-3', R: 5'-gtaggggtcaaagcacgagtcatc-3', Gapdh F:5'-tgacctcaactacatggtctaca-3' , R: 5'-cttcccattctcggccttg-3'. PCR was performed on an ABI Prism 7700 sequence Detector (Applied Biosystems) under the following conditions: 95°C, 10 min; 95°C, 30 s; 60°C, 30 s; 72°C, 1min; 40 cycles, 95°C, 1min, 60°C, 30 s, 95°C, 30 s. Each cDNA sample was run in triplicate. For data analysis, the $2^{-\Delta\Delta Ct}$ method was used. For each gene, the fold changes were calculated as difference in kidney expression[7].

Tissue hypoxia detection measurement in the kidney

Tissue hypoxia levels were assessed by Hypoxyprobe immunohistochemistry as described before[1, 10]. Briefly, animals were administered Hypoxyprobe (Hypoxyprobe, Inc.) via intraperitoneal injection (60 mg/kg body weight). One hour after injection, kidney tissues were harvested, and fixed overnight in 4% buffered formalin, and embedded in paraffin. According to the manufacturer's instructions (Hypoxyprobe-1 Omni-Kit), sections of 4μm were cut and mounted on glass slides, deparaffinized through serial baths in xylene and rehydrated in a graded series of alcohol and distilled water. Endogenous peroxidase activity was quenched by 10 min of incubation in a 3% hydrogen peroxide/methanol buffer. Antigen retrieval was enhanced by autoclaving slides in sodium citrate buffer (pH 6.0) at 95°C for 15 min. After blocking with a Biotin Blocking System (Dako), the slides were then incubated with rabbit anti-PAb2627AP in a humidified chamber at 4°C overnight. After the primary antibody incubation, anti-rabbit IgG ABC staining system kit (VEACTASTAIN ABS-AP, VECTOR LAB) was used according to the stained with alkaline phosphatase substrate kit (VEACTASTAIN ABS-AP, VECTOR LAB) and

counterstained with hematoxylin. Quantification of the IHC staining was performed using the Image-Pro Plus software (Media Cybernetics, Bethesda, MD). The density of the red staining was measured. The average densities of 20 areas per samples were determined and the SEM is indicated.

ELISA measurement of erythrocyte phosphorylation of AMPKα at Thr172

Erythrocyte protein extract from human and mouse blood were collected as described above[8]. Next, phosphorylation levels of erythrocyte AMPKα at Thr172 were quantitatively measured by using commercially available ELISA kits (A Solid phase sandwich ELISA, Cell Signaling) [1].

Immunofluorescence analysis of HIF-1α expression in mouse kidneys

Immunofluorescence for HIF-1 α was carried out with the formalin fixed tissues. Sections (4μm) deparaffinized through serial baths in xylene and rehydrated in a graded series of alcohol and distilled water. After antigen retrieval and blocking as above, the slides were then incubated with mouse anti-HIF-1 α antibody (Novus Biologicals, 1:100 dilution) in a humidified chamber at 4°C overnight. After the primary antibody incubation, anti-rabbit secondary antibody was used for 1 hour preventing from light. Quantification of the immunofluorescence staining was performed using the Image-Pro Plus software (Media Cybernetics, Bethesda, MD). The density of the red colors was measured. The average densities of 20 areas per kidneys were determined and the SEM is indicated.

Statistical analyses

All data were expressed as mean ± SEM. Unpaird student's t tests were applied in two-group analysis. Differences between the means of multiple groups were compared by the one-way analysis of variance (ANOVA), followed by a Tukey's multiple comparisons test. Comparison of the data obtained at different time points was analyzed by 2-way repeated measures, followed by the Tukey post hoc test. Linear correlations were analyzed by Pearson's correlation coefficient. A value of $P < 0.05$ was considered significant. Statistical programs were run using GraphPad Prism 5 software (GraphPad Software, San Diego, CA).

Supplemental reference

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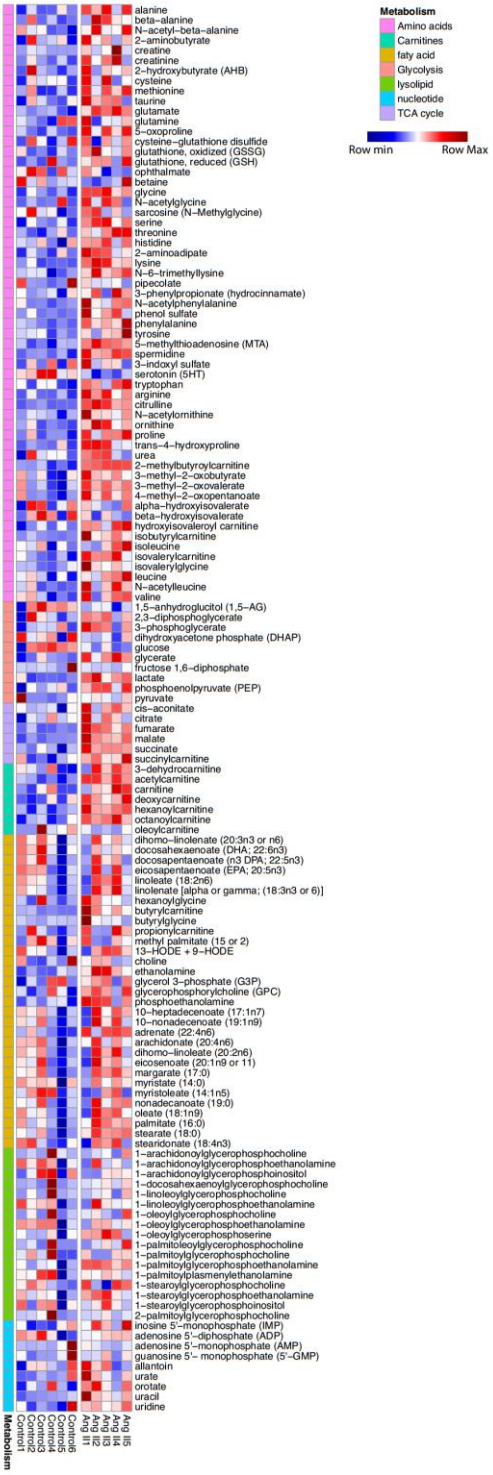
Supplementary Figure 1



Heatmap showing relative abundance of metabolites in selected metabolism pathways in the whole blood of WT mice with Saline (Control） or Ang II infusion (Ang II). N=6 mice for control group, N=5 mice for Ang II group.

Supplemental Table 1

Metabolites	PATHWAY	Control Median	Ang II Median	Fold Change	P value
alanine	Amino acid	51,645,514.0	89,689,184.0	1.737	0.004
beta-alanine	Amino acid	108,507.9	156,393.2	1.441	0.077
N-acetyl-beta-alanine	Amino acid	25,632.6	29,551.9	1.153	0.049
2-aminobutyrate	Amino acid	941,249.1	1,141,596.0	1.213	0.205
creatine	Amino acid	961,813.3	1,336,434.5	1.389	0.104
creatinine	Amino acid	27,660.0	51,188.0	1.851	0.036
2-hydroxybutyrate (AHB)	Amino acid	601,363.3	864,309.6	1.437	0.321
cysteine	Amino acid	2,248,681.8	2,358,157.5	1.049	0.153
homocysteine	Amino acid	67,271.3	106,889.4	1.589	0.091
methionine	Amino acid	2,984,908.2	5,716,055.5	1.915	0.011
N-acetylmethionine	Amino acid	5,680.7	10,924.6	1.923	0.001
taurine	Amino acid	189,982.5	255,095.0	1.343	0.057
glutamate	Amino acid	1,032,461.3	1,284,100.1	1.244	0.000
glutamine	Amino acid	589,665.2	623,901.3	1.058	0.635
5-oxoproline	Amino acid	238,453.9	359,737.6	1.509	0.001
cysteine-glutathione disulfide	Amino acid	472,878.8	503,564.1	1.065	0.805
glutathione, oxidized (GSSG)	Amino acid	14,045,026.5	15,698,076.0	1.118	0.020
glutathione, reduced (GSH)	Amino acid	38,755.6	87,953.2	2.269	0.191
ophthalmate	Amino acid	334,512.9	284,034.6	0.849	0.171
betaine	Amino acid	1,383,484.6	1,287,533.4	0.931	0.698
dimethylglycine	Amino acid	479,846.2	382,609.1	0.797	0.269
glycine	Amino acid	23,825,972.0	40,342,652.0	1.693	0.000
N-acetylglycine	Amino acid	142,938.0	232,250.0	1.625	0.152
sarcosine (N-Methylglycine)	Amino acid	560,106.0	633,402.0	1.131	0.445
serine	Amino acid	8,360,846.3	13,692,420.0	1.638	0.002
threonine	Amino acid	195,553.1	285,982.3	1.462	0.005
histidine	Amino acid	42,039.0	52,350.4	1.245	0.074
2-aminoadipate	Amino acid	713,663.5	1,099,584.4	1.541	0.008
lysine	Amino acid	1,323,607.7	2,869,885.3	2.168	0.001
N-6-trimethyllysine	Amino acid	1,438,829.9	1,604,961.1	1.115	0.005
pipecolate	Amino acid	386,585.2	539,359.2	1.395	0.666
2-(4-hydroxyphenyl)propionate	Amino acid	174,065.9	288,672.0	1.658	0.036
3-(4-hydroxyphenyl)lactate	Amino acid	16,166.2	19,226.2	1.189	0.095
3-phenylpropionate (hydrocinnamate)	Amino acid	70,534.0	121,541.3	1.723	0.094
N-acetylphenylalanine	Amino acid	44,478.8	68,197.4	1.533	0.012
phenol sulfate	Amino acid	35,895.8	186,346.4	5.191	0.012
phenylacetylglycine	Amino acid	12,508.3	13,741.2	1.099	0.480

phenylalanine	Amino acid	9,055,644.5	11,603,604.0	1.281	0.003
tyrosine	Amino acid	3,730,607.3	4,483,908.0	1.202	0.077
5-methylthioadenosine (MTA)	Amino acid	101,348.6	169,920.3	1.677	0.000
spermidine	Amino acid	1,849,450.6	2,735,224.3	1.479	0.000
3-indoxyl sulfate	Amino acid	64,524.2	85,716.0	1.328	0.550
C-glycosyltryptophan	Amino acid	18,847.0	22,269.9	1.182	0.151
kynurenine	Amino acid	88,597.4	98,994.2	1.117	0.216
N-acetyltryptophan	Amino acid	10,259.2	14,277.2	1.392	0.004
serotonin (5HT)	Amino acid	170,394.7	120,044.5	0.705	0.006
tryptophan	Amino acid	6,031,931.0	8,028,306.0	1.331	0.011
arginine	Amino acid	2,072,133.3	4,930,608.0	2.379	0.001
citrulline	Amino acid	190,260.2	320,091.4	1.682	0.000
homocitrulline	Amino acid	18,114.7	25,103.2	1.386	0.096
N-acetylornithine	Amino acid	263,479.7	308,241.6	1.170	0.023
ornithine	Amino acid	1,805,053.1	2,957,174.0	1.638	0.005
proline	Amino acid	1,124,065.5	1,639,845.6	1.459	0.004
trans-4-hydroxyproline	Amino acid	691,670.1	1,725,347.3	2.494	0.007
urea	Amino acid	193,751,448.0	229,500,096.0	1.185	0.264
2-methylbutyroylcarnitine	Amino acid	31,371.8	44,470.9	1.418	0.000
3-methyl-2-oxobutyrate	Amino acid	58,766.5	73,398.3	1.249	0.062
3-methyl-2-oxovalerate	Amino acid	116,124.9	191,409.5	1.648	0.011
4-methyl-2-oxopentanoate	Amino acid	112,158.9	234,815.7	2.094	0.009
alpha-hydroxyisovalerate	Amino acid	1,088,150.8	970,529.8	0.892	0.823
beta-hydroxyisovalerate	Amino acid	121,578.1	72,889.9	0.600	0.289
hydroxyisovaleroyl carnitine	Amino acid	59,983.4	92,951.5	1.550	0.004
isobutyrylcarnitine	Amino acid	43,242.9	69,573.2	1.609	0.010
isoleucine	Amino acid	9,711,431.0	10,295,614.0	1.060	0.198
isovalerylcarnitine	Amino acid	44,779.2	61,666.1	1.377	0.002
isovalerylglycine	Amino acid	67,734.1	86,207.5	1.273	0.038
leucine	Amino acid	14,116,956.0	16,784,376.0	1.189	0.042
N-acetylleucine	Amino acid	81,063.2	142,304.6	1.755	0.017
valine	Amino acid	4,311,549.0	5,479,219.5	1.271	0.056
erythronate	Carbohydrate	94,956.0	130,737.0	1.377	0.136
N-acetylneuraminate	Carbohydrate	300,330.0	324,302.1	1.080	0.518
fructose	Carbohydrate	1,302,043.0	1,373,237.6	1.055	0.268
mannose	Carbohydrate	4,275,592.8	2,834,863.3	0.663	0.117
1,5-anhydroglucitol (1,5-AG)	Carbohydrate	2,119,225.2	1,776,432.8	0.838	0.160
2,3-diphosphoglycerate	Carbohydrate	3,140,983.0	4,116,786.3	1.311	0.031
3-phosphoglycerate	Carbohydrate	2,361,776.9	3,100,091.8	1.313	0.070
dihydroxyacetone phosphate (DHAP)	Carbohydrate	344,899.0	251,529.0	0.729	0.340
glucose	Carbohydrate	251,990,568.0	164,908,704.0	0.654	0.150
glycerate	Carbohydrate	180,827.5	249,222.1	1.378	0.003

fructose 1,6-diphosphate	Carbohydrate	101,689.5	105,205.2	1.035	0.495
lactate	Carbohydrate	77,210,592.0	198,715,808.0	2.574	0.001
phosphoenolpyruvate (PEP)	Carbohydrate	1,092,893.4	1,506,538.5	1.378	0.020
pyruvate	Carbohydrate	77,738.3	165,925.9	2.134	0.997
threonate	Cofactors and vitamins	376,297.0	468,322.0	1.245	0.241
heme	Cofactors and vitamins	1,068,121.8	1,308,941.1	1.225	0.891
adenosine 5'diphosphoribose	Cofactors and vitamins	185,730.5	190,668.3	1.027	0.491
nicotinamide	Cofactors and vitamins	7,164,177.8	7,820,276.5	1.092	0.129
trigonelline (N'-methylnicotinate)	Cofactors and vitamins	150,133.9	234,141.3	1.560	0.009
pantothenate	Cofactors and vitamins	106,178.7	172,645.2	1.626	0.000
alpha-tocopherol	Cofactors and vitamins	46,681.0	59,133.0	1.267	0.119
cis-aconitate	Energy	145,094.4	186,705.1	1.287	0.053
citrate	Energy	7,657,857.5	9,022,458.0	1.178	0.153
fumarate	Energy	216,976.6	402,840.7	1.857	0.000
malate	Energy	702,244.5	1,151,349.1	1.640	0.000
succinate	Energy	52,240.9	80,670.7	1.544	0.003
succinylcarnitine	Energy	109,840.5	129,338.0	1.178	0.021
acetylphosphate	Energy	1,331,728.1	1,484,740.9	1.115	0.583
phosphate	Energy	189,109,288.0	195,629,712.0	1.034	0.844
pyrophosphate (PPi)	Energy	892,249.5	1,019,729.9	1.143	0.645
alpha-muricholate	Lipid	54,437.4	12,578.4	0.231	0.267
cholate	Lipid	34,174.0	10,247.4	0.300	0.260
tauro-beta-muricholate	Lipid	29,586.5	25,484.8	0.861	0.336
taurocholate	Lipid	27,506.7	69,886.8	2.541	0.478
taurodeoxycholate	Lipid	7,247.4	18,261.9	2.520	0.243
tauroursodeoxycholate	Lipid	287,213.3	10,475.7	0.036	#DIV/0!
3-dehydrocarnitine	Lipid	1,238,776.3	1,702,888.3	1.375	0.098
acetylcarnitine	Lipid	3,554,340.9	5,156,765.5	1.451	0.000
carnitine	Lipid	990,437.1	1,099,840.3	1.110	0.056
deoxycarnitine	Lipid	225,939.2	273,921.1	1.212	0.006
hexanoylcarnitine	Lipid	26,710.6	46,227.5	1.731	0.000
octanoylcarnitine	Lipid	52,835.5	74,658.5	1.413	0.001
oleoylcarnitine	Lipid	30,457.4	23,731.9	0.779	0.326
12-HEPE	Lipid	1,781,332.7	2,039,065.4	1.145	0.640
12-HETE	Lipid	2,324,695.0	1,244,194.4	0.535	0.043
dihomo-linolenate (20:3n3 or n6)	Lipid	365,006.1	356,495.6	0.977	0.608
docosahexaenoate (DHA; 22:6n3)	Lipid	3,626,191.1	3,537,821.0	0.976	0.913
docosapentaenoate (n3 DPA; 22:5n3)	Lipid	582,000.3	644,838.1	1.108	0.706
eicosapentaenoate (EPA; 20:5n3)	Lipid	1,175,129.0	945,899.5	0.805	0.545
linoleate (18:2n6)	Lipid	13,982,038.0	18,403,560.0	1.316	0.224

linolenate [alpha or gamma; (18:3n3 or 6)]	Lipid	1,384,669.3	1,894,397.0	1.368	0.142
hexanoylglycine	Lipid	25,601.6	37,814.9	1.477	0.242
butyrylcarnitine	Lipid	91,626.1	187,728.1	2.049	0.009
butyrylglycine	Lipid	53,052.7	82,162.3	1.549	0.190
propionylcarnitine	Lipid	365,491.2	444,291.0	1.216	0.222
malonylcarnitine	Lipid	43,009.7	37,712.4	0.877	0.383
17-methylstearate	Lipid	25,163.8	26,005.8	1.033	0.962
methyl palmitate (15 or 2)	Lipid	326,902.6	300,732.6	0.920	1.000
azelate (nonanedioate)	Lipid	5,573.8	7,604.8	1.364	0.061
13-HODE + 9-HODE	Lipid	250,855.0	317,283.0	1.265	0.292
2-hydroxystearate	Lipid	29,990.7	39,469.7	1.316	0.221
choline	Lipid	888,145.5	969,200.5	1.091	0.994
ethanolamine	Lipid	89,898.5	152,686.9	1.698	0.003
glycerol 3-phosphate (G3P)	Lipid	850,548.5	1,055,539.6	1.241	0.405
glycerophosphorylcholine (GPC)	Lipid	491,107.6	550,026.0	1.120	0.067
phosphoethanolamine	Lipid	283,025.3	459,869.5	1.625	0.007
chiro-inositol	Lipid	261,053.0	364,294.5	1.395	0.522
myo-inositol	Lipid	6,069,591.5	6,165,021.0	1.016	0.692
pinitol	Lipid	147,703.2	204,861.0	1.387	0.055
1,2-propanediol	Lipid	800,759.6	817,265.0	1.021	0.662
3-hydroxybutyrate (BHBA)	Lipid	3,816,605.6	7,640,417.0	2.002	0.000
10-heptadecenoate (17:1n7)	Lipid	291,744.5	340,506.9	1.167	0.295
10-nonadecenoate (19:1n9)	Lipid	74,346.7	89,838.9	1.208	0.320
adrenate (22:4n6)	Lipid	139,643.5	327,011.0	2.342	0.007
arachidonate (20:4n6)	Lipid	1,673,147.3	1,683,761.3	1.006	0.357
dihomo-linoleate (20:2n6)	Lipid	353,385.3	464,331.5	1.314	0.287
eicosenoate (20:1n9 or 11)	Lipid	730,483.3	976,684.2	1.337	0.414
margarate (17:0)	Lipid	647,502.4	849,179.1	1.311	0.131
myristate (14:0)	Lipid	2,443,644.6	2,375,114.3	0.972	0.555
myristoleate (14:1n5)	Lipid	57,399.7	33,530.7	0.584	0.439
nonadecanoate (19:0)	Lipid	97,539.7	138,763.3	1.423	0.220
oleate (18:1n9)	Lipid	15,455,619.5	21,619,338.0	1.399	0.194
palmitate (16:0)	Lipid	20,414,287.0	26,105,430.0	1.279	0.052
palmitoleate (16:1n7)	Lipid	3,525,606.5	4,286,330.5	1.216	0.943
stearate (18:0)	Lipid	9,465,239.0	12,943,878.0	1.368	0.023
stearidonate (18:4n3)	Lipid	112,550.4	154,902.6	1.376	0.801
1-arachidonoylglycerophosphocholine	Lipid	68,195.8	83,390.6	1.223	0.644
1-arachidonoylglycerophosphoethanolamine	Lipid	250,715.3	203,755.2	0.813	0.870
1-arachidonoylglycerophosphoinositol	Lipid	62,830.3	57,783.3	0.920	0.591
1-docosahexaenoylglycerophosphocholine	Lipid	109,913.8	140,244.9	1.276	0.932
1-linoleoylglycerophosphocholine	Lipid	442,435.3	554,016.0	1.252	0.627
1-linoleoylglycerophosphoethanolamine	Lipid	150,712.5	140,955.3	0.935	0.648

1-oleoylglycerophosphocholine	Lipid	146,450.3	172,716.6	1.179	0.960
1-oleoylglycerophosphoethanolamine	Lipid	208,725.6	187,903.8	0.900	0.902
1-oleoylglycerophosphoserine	Lipid	59,903.5	77,825.0	1.299	0.057
1-palmitoleoylglycerophosphocholine	Lipid	35,636.0	46,853.1	1.315	0.833
1-palmitoylglycerophosphocholine	Lipid	799,570.2	926,561.4	1.159	0.781
1-palmitoylglycerophosphoethanolamine	Lipid	168,400.4	234,568.7	1.393	0.014
1-palmitoylglycerophosphoinositol	Lipid	27,022.0	19,866.1	0.735	0.274
1-palmitoylplasmenylethanolamine	Lipid	105,264.7	106,560.3	1.012	0.840
1-stearoylglycerophosphocholine	Lipid	253,471.1	355,529.1	1.403	0.652
1-stearoylglycerophosphoethanolamine	Lipid	131,110.7	158,706.9	1.210	0.098
1-stearoylglycerophosphoinositol	Lipid	64,657.1	59,587.1	0.922	0.624
2-arachidonoylglycerophosphoethanolamine	Lipid	52,347.1	44,548.8	0.851	0.427
2-docosahexaenoylglycerophosphoethanolamine	Lipid	76,424.2	53,897.3	0.705	0.376
2-linoleoylglycerophosphocholine	Lipid	75,808.5	79,017.0	1.042	0.576
2-oleoylglycerophosphoethanolamine	Lipid	22,581.7	21,139.3	0.936	0.955
2-palmitoylglycerophosphocholine	Lipid	65,439.2	71,119.3	1.087	0.581
2-palmitoylglycerophosphoethanolamine	Lipid	19,815.5	21,900.0	1.105	0.773
caprate (10:0)	Lipid	285,569.7	206,051.6	0.722	0.333
caproate (6:0)	Lipid	34,066.4	36,489.7	1.071	0.434
caprylate (8:0)	Lipid	78,903.1	69,578.4	0.882	0.730
heptanoate (7:0)	Lipid	25,865.4	17,753.7	0.686	0.017
laurate (12:0)	Lipid	1,088,136.3	534,824.1	0.492	0.150
pelargonate (9:0)	Lipid	688,278.8	478,440.6	0.695	0.449
1-stearoylglycerol (1-monostearin)	Lipid	57,578.5	127,264.9	2.210	0.026
palmitoyl sphingomyelin	Lipid	3,726,457.8	4,504,461.0	1.209	0.297
campesterol	Lipid	527,258.7	709,364.3	1.345	0.542
cholesterol	Lipid	36,469,212.0	41,266,288.0	1.132	0.361
methylphosphate	Nucleotide	487,775.9	637,984.5	1.308	0.089
inosine 5'-monophosphate (IMP)	Nucleotide	1,068,879.4	1,300,183.0	1.216	0.067
adenosine 5'-diphosphate (ADP)	Nucleotide	178,876.5	178,610.8	0.999	0.625
adenosine 5'-monophosphate (AMP)	Nucleotide	406,301.0	609,880.7	1.501	0.494
guanosine 5'- monophosphate (5'-GMP)	Nucleotide	110,458.6	117,056.4	1.060	0.705
allantoin	Nucleotide	176,673.8	186,126.2	1.054	0.469
urate	Nucleotide	105,488.7	194,277.0	1.842	0.148
orotate	Nucleotide	47,824.2	72,133.4	1.508	0.104
pseudouridine	Nucleotide	17,466.3	24,642.9	1.411	0.009
uracil	Nucleotide	53,411.4	110,755.2	2.074	0.021
uridine	Nucleotide	19,621.9	35,328.5	1.800	0.234
alanylalanine	Peptide	92,170.3	138,611.0	1.504	0.059
gamma-glutamylisoleucine	Peptide	73,993.0	74,905.0	1.012	0.178
gamma-glutamylleucine	Peptide	249,140.7	304,864.1	1.224	0.164

gamma-glutamylphenylalanine	Peptide	108,877.6	133,112.0	1.223	0.311
gamma-glutamylthreonine	Peptide	39,585.8	45,653.2	1.153	0.178
gamma-glutamyltyrosine	Peptide	48,921.7	60,243.0	1.231	0.305
gamma-glutamylvaline	Peptide	262,954.1	293,628.1	1.117	0.085
benzoate	Xenobiotics	1,477,743.8	1,072,581.0	0.726	0.395
hippurate	Xenobiotics	146,049.5	187,332.9	1.283	0.090
glycerol 2-phosphate	Xenobiotics	184,453.4	229,914.4	1.246	0.039
glycolate (hydroxyacetate)	Xenobiotics	1,058,732.0	1,039,944.5	0.982	0.841
iminodiacetate (IDA)	Xenobiotics	4,988,213.5	7,384,151.0	1.480	0.005
Isobar: 2-propylpentanoic acid, 2-ethylhexanoic acid	Xenobiotics	161,704.1	132,803.9	0.821	0.733
EDTA	Xenobiotics	4,529,309.3	4,682,878.0	1.034	0.228
cinnamoylglycine	Xenobiotics	38,667.8	52,321.4	1.353	0.118
ergothioneine	Xenobiotics	1,204,562.1	1,571,682.1	1.305	0.022
homostachydrine	Xenobiotics	546,046.5	694,373.1	1.272	0.055
stachydrine	Xenobiotics	1,298,419.7	1,681,150.4	1.295	0.006
erythritol	Xenobiotics	139,496.7	184,270.6	1.321	0.152

List of all the 218 metabolites been identified through metabolic screening in the whole blood of WT mice with Saline (Control） or Angiotensin II infusion (Ang II). Median values were calculated from each group and then fold change of the each individual metabolite in Ang II group was conducted compared to control. N=6 mice for control group, N=5 mice for Ang II group. $P<0.05$ as significant changes.