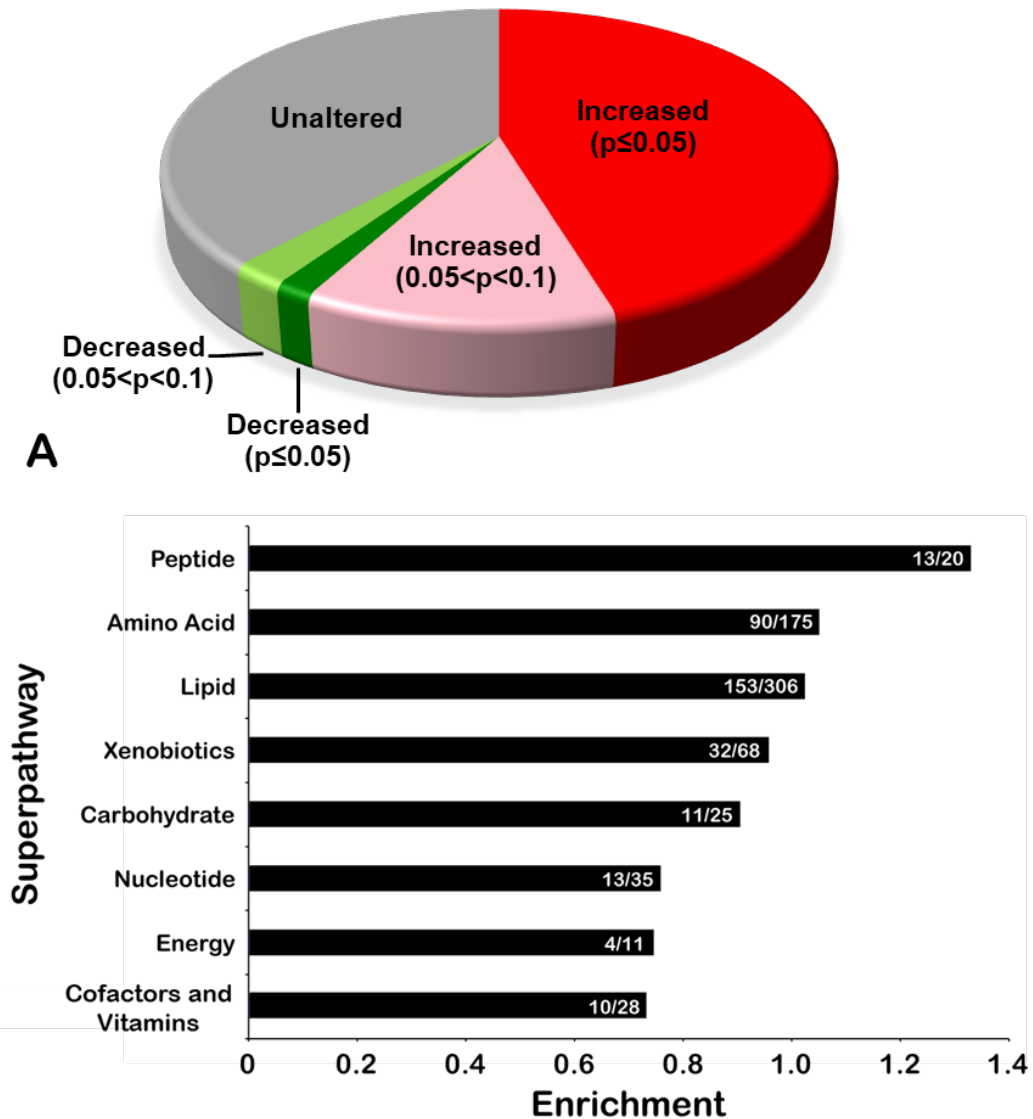


SUPPLEMENTAL DATA

Gut-derived uremic toxin handling in vivo requires OAT-mediated tubular secretion in chronic kidney disease

Kevin T. Bush, Prabhleen Singh, and Sanjay K. Nigam



Supplemental Figure S1. Subtotal nephrectomy (STN) has dramatic effect on systemic metabolism. (A)

Pie chart showing the effects of STN on the plasma concentrations of the 668 metabolites of known identity on the metabolomics platform. More than half of the 668 metabolites were found to have an increased plasma concentration (dark red and light red wedges) when compared to the sham-operated control animals. The majority of the increased metabolites (~78%) displayed significant ($p \leq 0.05$; dark red) changes in plasma concentration. **(B)** Metabolite enrichment analysis of the altered metabolites in the STN animal revealed their presence in all 8 metabolic superpathway categories described in the analysis. The majority of these metabolites (almost 75%) were found to be components of either the lipid (~47%) or the amino acid (~28%) superpathways.

Supplemental Table S1			
Uremic Solutes/Toxins Found in Literature			
Solute	Present on Metabolomics Platform	Increased in Plasma	
		STN	STN + Probenecid
L-Cystine	✓	✓	✓
N-Formyl-L-methionine	✓	✓	✓
glucuronate	✓	✓	✓
Xanthurenic acid	✓	✓	✓
Hydroxyphenyllactic acid	✓	✓	✓
Isobutyrylglycine	✓	✓	✓
N-acetyl-beta-alanine	✓	✓	✓
N-formylanthranilic acid	✓	✓	✓
gamma-glutamylvaline	✓	✓	✓
Uracil	✓	✓	✓
Sebacic acid	✓	✓	✓
Isobutyryl-L-carnitine	✓	✓	✓
Thymidine	✓	✓	✓
Indolelactic acid	✓	✓	✓
4-Pyridoxic acid	✓	✓	✓
Phenylacetylglycine	✓	✓	✓
L-gamma-glutamyl-L-isoleucine	✓	✓	✓
Hydroquinone	✓	✓	✓
3-hydroxyindolin-2-one sulfate	✓	✓	✓
Cytidine	✓		✓
Thymine	✓		✓
Ureidopropionic acid	✓		✓
L-Kynurenine	✓		✓
Threonic acid	✓		✓
dodecanedioate	✓		✓
L-Octanoylcarnitine	✓		✓
laurylcarnitine (C12)	✓		✓
thioprolin	✓		✓
Beta-Alanine	✓	✓	
Indoxyl sulfate	✓	✓	✓
7-Methylguanine	✓	✓	✓
indole-3-carboxylic acid	✓	✓	✓
Kynurenic acid	✓	✓	✓
5'-Methylthioadenosine	✓	✓	✓
picolinate	✓	✓	✓
4-Acetamidobutanoic acid	✓	✓	✓
Cysteine	✓	✓	✓
2-Aminobenzoic acid	✓	✓	✓
cholate	✓	✓	✓
gamma-glutamylthreonine	✓	✓	✓
gamma-glutamylphenylalanine	✓	✓	✓
hexanoylglycine	✓	✓	✓
3-methyladipate	✓	✓	✓
S-(3-hydroxypropyl)mercapturic acid (HPMA)	✓	✓	✓
gulonate	✓	✓	✓
6-hydroxyindole sulfate	✓	✓	✓
3-hydroxyadipate	✓	✓	✓
Angiogenin	✓	✓	✓
Adenine	✓		✓
Hypotaurine	✓		✓
Putrescine	✓		✓
Orotic acid	✓		✓
Oxalic acid	✓		✓
N-Acetyl-L-phenylalanine	✓		✓
Ophthalmic acid	✓		✓
N2,N2-Dimethylguanosine	✓		✓
2-Aminoisobutyric acid	✓		✓
Undecanedioate	✓		✓
N-acetylkynurenine	✓		✓
Glycine	✓	✓	
Creatinine	✓	✓	
3-hydroxy-3-methylglutarate	✓	✓	
L-Arabinose	✓	✓	
fructose	✓	✓	
Gluconic acid	✓	✓	
Allantoin	✓	✓	
Myoinositol	✓	✓	

N6,N6,N6-Trimethyl-L-lysine	✓	✓	
Pantothenic acid	✓	✓	
Salicylic acid	✓	✓	
Citric acid	✓	✓	
N-Acetyl-L-alanine	✓	✓	
N-acetylleucine	✓	✓	
N-Acetyl-L-methionine	✓	✓	
N-Acetylvaline	✓	✓	
Urea	✓	✓	
carosine	✓	✓	
Quinolinic acid	✓	✓	
Citrulline	✓	✓	
Dimethylglycine	✓	✓	
Isocitric acid	✓	✓	
argininosuccinate	✓	✓	
1-Methyladenosine	✓	✓	
2-Isopropylmalic acid	✓	✓	
3-Methylhistidine	✓	✓	
4-Guanidinobutanoic acid	✓	✓	
5-hydroxylysine	✓	✓	
Pimelic acid	✓	✓	
imidazole lactate	✓	✓	
N-Acetylglutamic acid	✓	✓	
Suberic acid	✓	✓	
Hippuric acid	✓	✓	
Salicyluric acid	✓	✓	
Maleic acid	✓	✓	
Erythritol	✓	✓	
phenyllactate (PLA)	✓	✓	
Homocitrulline	✓	✓	
Cysteine-S-sulfate	✓	✓	
N-Acetyl-L-aspartic acid	✓	✓	
Indoleacetic acid	✓	✓	
Creatine	✓	✓	
1-Methylhistidine	✓	✓	
Hydroxyproline	✓	✓	
Methylimidazoleacetic acid	✓	✓	
N-Acetylneuraminic acid	✓	✓	
Phenol sulphate	✓	✓	
N-Acetylornithine	✓	✓	
allantoic acid	✓	✓	
Pseudouridine	✓	✓	
N-Acetylthreonine	✓	✓	
N-acetylasparagine	✓	✓	
N-acetylglutamine	✓	✓	
N-Acetylhistidine	✓	✓	
N-a-Acetyl-L-arginine	✓	✓	
Proline betaine	✓	✓	
N-acetylproline	✓	✓	
Isovalerylglycine	✓	✓	
Alpha-N-Phenylacetyl-L-glutamine	✓	✓	
Polyhydroxyproline	✓	✓	
N4-Acetylcytidine	✓	✓	
N6-Carbamoyl-L-threonyl-adenosine	✓	✓	
Orotidine	✓	✓	
Pyrocatechol sulfate	✓	✓	
4-Hydroxyhippuric acid	✓	✓	
ectoine	✓	✓	
4-vinylphenol sulfate	✓	✓	
4-Ethylphenyl sulfate	✓	✓	
p-Cresol sulfate	✓	✓	
N6-carboxymethyllysine	✓	✓	
N2-acetyllysine	✓	✓	
N6-Acetyl-L-lysine	✓	✓	
Asymmetric dimethylarginine	✓	✓	
malonylcarnitine	✓	✓	
N-Acetylserine	✓	✓	
Levoinositol	✓	✓	
2,3-dihydroxyisovalerate	✓	✓	
carboxyethyl-GABA	✓	✓	
Trimethylamine N-oxide	✓	✓	
N1-Methyl-2-pyridone-5-carboxamide	✓	✓	
hydantoin-5-propionic acid	✓	✓	
2-Oxindole-3-acetate	✓	✓	

prolylglycine	✓	✓	
Imidazolepropionic acid	✓	✓	
Erythronic acid	✓	✓	
6-oxopiperidine-2-carboxylate	✓	✓	
N-Acetyl-1-methylhistidine	✓	✓	
N-Acetyl-3-methylhistidine	✓	✓	
2-Aminophenol sulphate	✓	✓	
Acetylcarnosine	✓	✓	
formiminoglutamate	✓	✓	
5-(galactosylhydroxy)-L-lysine	✓	✓	
N2,N5-diacetylmithine	✓	✓	
4-acetylphenol sulfate	✓	✓	
Glutaryl carnitine	✓	✓	
O-sulfo-L-tyrosine	✓	✓	
3-(3-hydroxyphenyl)propionate sulfate	✓	✓	
guaiacol sulfate	✓	✓	
4-Methylcatechol sulfate	✓	✓	
N-Acetyl-D-glucosamine	✓	✓	
N-methylpipecolate	✓	✓	
ferulic acid 4-sulfate	✓	✓	
Methylguanidine	✓	✓	
N-acetyltaurine	✓	✓	
arabitol/xylitol	✓	✓	
1-Methylinosine	✓	✓	
3-hydroxycinnamate sulfate	✓	✓	
N-acetylcitrulline	✓	✓	
3-hydroxypyridine sulfate	✓	✓	
2-acetamidophenol sulfate	✓	✓	
N-acetylhistamine	✓	✓	
2,8-quinolinediol sulfate	✓	✓	
C-glycosyltryptophan	✓	✓	
p-Cresol glucuronide	✓	✓	
Phenol glucuronide	✓	✓	
indoxyl glucuronide	✓	✓	
4-ethylphenol glucuronide	✓	✓	
catechol glucuronide	✓	✓	
caffeic acid sulfate	✓	✓	
2-Oxoarginine	✓	✓	
Argininic acid	✓	✓	
2,3-dihydroxy-2-methylbutyrate	✓	✓	
(N(1) + N(8))-acetylspermidine	✓	✓	
5,6-dihydrouridine	✓	✓	
1-ribosyl-imidazoleacetate	✓	✓	
N-acetyl-2-aminooctanoate	✓	✓	
hydroxyasparagine	✓	✓	
5-methylthioribose	✓	✓	
N-acetyl-isoptreanine	✓	✓	
Glutaric acid	✓		
Spermidine	✓		
alpha-ketoglutarate	✓		
Cytosine	✓		
Niacinamide	✓		
Uridine	✓		
Galactitol	✓		
Inosine	✓		
Succinic acid	✓		
Pyroglutamic acid	✓		
Methylmalonic acid	✓		
Sucrose	✓		
Uric acid	✓		
Fumaric acid	✓		
3-methoxytyrosine	✓		
Xanthosine	✓		
carnitine	✓		
Choline	✓		
D-Xylose	✓		
Methylsuccinic acid	✓		
gentisate	✓		
Azelaic acid	✓		
Methionine sulfoxide	✓		
Adipic acid	✓		
3-hydroxysebacate	✓		
4-imidazoleacetate	✓		
N-acetyltyrosine	✓		

2-Ethylhydracrylic acid	✓		
Propionylcarnitine	✓		
N-acetyltryptophan	✓		
Beta-Guanidinopropionic acid	✓		
Tiglylcarnitine	✓		
4-Trimethylammoniobutanoic acid	✓		
Cinnamoylglycine	✓		
3-Hydroxyhippuric acid	✓		
2-hydroxydecanoate	✓		
benzoylcarnitine	✓		
Guanidoacetic acid	✓		
2-Methylbutyroylcarnitine	✓		
N-acetylmethionine sulfoxide	✓		
Sorbitol	✓		
2-methylcitrate/homocitrate	✓		
maleonylcarnitine	✓		
ribulonate/xylulonate	✓		
p-Hydroxyphenylacetic acid			
cis-Aconitic acid			
Dimethylamine			
Deoxyadenosine			
Homovanillic acid			
Homogentisic acid			
Hypoxanthine			
Methylamine			
L-Fucose			
L-Dopa			
Alpha-Lactose			
Phenylacetic acid			
Norepinephrine			
Phenol			
Riboflavin			
Pyrophosphate			
Vanillylmandelic acid			
Xanthine			
Citramalic acid			
2-Furoylglycine			
3-Hydroxyphenylacetic acid			
Vanillic acid			
4-Hydroxybenzoic acid			
Arabinonic acid			
3-Methylglutaryl carnitine			
3-Methoxy-4-hydroxyphenylethyleneglycol sulfate			
DL-Homocystine			
Citraconic acid			
Levoglucosan			
Decanoylcarnitine			
Ortho-Hydroxyphenylacetic acid			
Isovalerylcarnitine			
Malonic acid			
Methionine			
Levulinic acid			
Alpha-Hydroxyisobutyric acid			
Homocysteine			
5-Hydroxyindoleacetic acid			
Mannitol			
Neopterin			
Trimethylamine			
S-Adenosylhomocysteine			
Tartaric acid			
Pyrocatechol			
trans-Aconitic acid			
Tiglylglycine			
Pyruvaldehyde			
Spermine			
Cyclic GMP			
Melatonin			
Thiocyanate			
1-Methylguanosine			
Guanidine			
D-Arabitol/L-Arabitol§			
5-Hydroxytryptophol			
1,3-Dimethyluric acid			
p-Cresol			

3-Methylxanthine			
Gamma-CEHC			
Phthalic acid			
1,3,7-Trimethyluric acid			
3-Hydroxybenzoic acid			
Androsterone sulfate			
Quinic acid			
1-Methyluric acid			
Benzyl alcohol			
Guanidinosuccinic acid			
8-Hydroxy-deoxyguanosine			
Symmetric dimethylarginine			
D-Cysteine			
L-Gulonolactone			
Taurocyamine			
2-Hydroxyethanesulfonate			
3-Aminoisobutanoic acid			
Pentosidine			
N6-Methyladenosine			
D-Threitol			
N1-Methyl-4-pyridone-3-carboxamide			
4-Hydroxynonenal			
5-Acetylamino-6-amino-3-methyluracil			
2,5-Furandicarboxylic acid			
Hexanal			
Scyllitol			
Malondialdehyde			
6-Sialyl-N-acetyllactosamine			
Indoxyl glucuronide			
1,7-Dimethyluric acid			
7-Methyluric acid			
Decanal			
L-3-Hydroxykynurenine			
Homovanillic acid sulfate			
Ethylamine			
Indoleacetyl glutamine			
Saccharin			
Indole-3-methyl acetate			
2-Octenal			
2-Nonenal			
Heptanal			
2-Hexenal			
2-Heptenal			
1-[(5-Amino-5-carboxypentyl)amino]-1-deoxyfructose			
4-Decenal			
Acrolein			
5-Hydroxyindole			
Nonanal			
L-Xylonate			
3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid			
21-Hydroxypregnenolone disulfate			
2-Hydroxyacetaminophen sulfate			
2-Methoxyphenol sulfate			
2-Methoxyresorcinol			
3-[3-(sulfooxy)phenyl]propanoic acid			
3-Deoxyglucosone			
3-Methylcatechol sulfate			
4-HO-decenal			
4-HO-hexenal			
4-HO-Nonenal			
4-HO-octenal			
4-Pyridone-3-carboxamide-1-β-d-ribose			
4-Vinylphenol sulfate			
Acisoga			
Alpha-CEHC glucuronide			
C-mannosyltryptophan			
Gamma-CEHC glucuronide			
Glyoxal			
Hydroquinone sulfate			
Indican			
Insulin-like growth factor 1			
Interleukin-10			
Leptin			
Methionine-enkephalin			

N-acetyl alliin			
N ξ -(carboxymethyl)lysine			
Osteocalcin			
Oxamate			
Phenylcarnitine			
Pyroglutamine			
Pyroglutamylvaline			
Retinol Binding Protein			
Salicylic glucuronide			
Vascular endothelial growth factor			
α 1-Acid glycoprotein			
β -Lipotropin			
PMID: 14615964, 17015248, 18698804, 18854818, 19234110, 20218618, 20870466, 21784895, 22300547, 22961385, 23614584, 26317986, 27701177, 28379433, 28396122, 30087103			

Supplemental Table S1. List of uremic solutes compiled from literature search (reference PMIDs are shown in the final row of the table). A check mark in Column 2 indicates that uremic solute is found on the Metabolon platform used in the study. A check mark in Column 3 indicates that this uremic toxin accumulated in the plasma of the STN animal, while a check mark in Column 4 indicates plasma accumulation in the STN animal treated with probenecid. The absence of a check mark indicates that no significant accumulation was detected for that metabolite.