Abbreviations used in the article

NQR - Na(+)-transporting NADH:ubiquinone reductase; TrpRS - tryptophanyl-tRNA synthetase; MAO - monoamine oxidase; ADAS – Alzheimer's disease associated sequence; AD – Alzheimer's disease; C&A - American Indian Cheyenne & Arapaho; NNI - non-native individuals; T2D - type 2 diabetes; CRC - colorectal cancer; Trp – tryptophan; Q – ubiquinone; SP - shikimate pathway; WARS – gene of tryptophanyl-tRNA synthetase; NFT - neurofibrillary tangles of filaments; AAA - aromatic amino acid/s; AAAD - aromatic amino acid decarboxylase; PEA – phenethylamine; INF - interferon, IDO - indoleamine-2,3-dioxygenase; MS – mass spectrometry; IAA - indole-3-acetic acid; NCBI - The National Center for Biotechnology Information; mAb - monoclonal antibodies; 4-HBA - 4-hydroxybenzoate; Kyn – kynurenate; TDO - tryptophan 2,3-dioxygenase; NAFLD - non-alcoholic fatty liver disease; IBD - inflammatory bowel disease; UC - ulcerative colitis; CD - Crohn's disease; AS - ankylosing spondylitis; HE - hepatic encephalopathy; RAU - aphthous ulcer; IBS - irritable bowel syndrome; 18F-FDG - 18F-fluorodeoxyglucose; SFB – spore forming bacteria; MAOI – monoamine oxidase inhibitor; PD – Parkinson's disease; CKD - chronic kidney disease; TCP – tranylcypromine; dbGaP - database of Genotypes and Phenotypes; AC – activated charcoal; HD - hemodialysis patients; SD – standard deviation; BA – biogenic amines; ASD - autism spectrum disorders; CH - chronic cluster headaches.

Supplementary Tables S1-S4; Figure S1; Supplemental file 1: Link of Trp to Q

Table S1 Prevalence of ADAS (89% and 100% nucleotide identity) in different human gut metagenomics studies.

COUNTRY	PARTICIPANTS	ADAS+ individuals	DIAGNOSIS or STATUS
MO, USA	2	1	obese co-twin
Canada	24	2	healthy, after Cefprozil
OK, USA	37	4	American Indian
UK	6	1	healthy
Denmark	13	3	morbidly obese
Germany	16	3	obese and NAFLD, inulin
Sweden	12	2	atherosclerosis
Sweden	13	1	healthy control
Australia	12	3	healthy, western diet
MO, USA	84	1	preterm infants
Europe	~100	4	infants
Europe	~100	9	mothers after birth
TX, MO, USA	300	4	healthy
China	54	1	healthy control
China	74	6	CRC
Washington, DC, USA	52	1	healthy control
Washington, DC, USA	52	14	CRC
AL, USA	6	1	donor, transplant to recurrent Clostridium difficile infection
MA, USA	19	1	CD; after fecal transplant
Germany	59	1	control; 31 PD, 28 controls
China	211	1	ankylosing spondylitis patient; 97 AS, 114 controls

Table S2. Chromosomal and gene abnormalities induced by tryptamine

Species	cells/organs	Abnormalities description	References
Human	HeLa cells, cervical cancer, prolonged treatment	TrpRS gene dose decrease	Present study
Hamster Chinese	SV40-transformed 631 embryonic cells, prolonged treatment	TrpRS gene dose decrease	Present study
Bovine animal	Kidney cells MDBK, prolonged treatment	Additional material in aberrated marker chromosome, frequency of its duplication 96%	[1, 2]
Hamster Djungarian	SV40-transformed DM 15 fibroblasts, prolonged treatment	Additional material, chromosomes 5 and 7, short arm	[3]
Nucleic acid base, cytosine base	Crystal structure, X-ray	Stacking interaction, probable single nucleotide polymorphisms	[4]
Salmonella typhimurium	Bacterial cells	Mutagenic products of nitrosation of tryptamine	[5, 6]
Rat	Cultured hepatocytes	DNA adducts	[7]
Rat	Liver tissue homogenate S9	Suppress DNA synthesis	[7]
Salmonella typhimurium	S-9 fractions from mice	Counteract genotoxicity of cooked-food mutagens	[8]

Table S3. Concentrations of fecal biogenic amines (μmol/g of fecal dry matter) for cats fed select fibers [9].

BA	Treatment with Fibers		
	Cellulose	FOS	Pectin
Histamine	0.23	0.29	0.29
Tryptamine	1.17	5.77	6.02
Tyramine	1.38	0.24	1.71

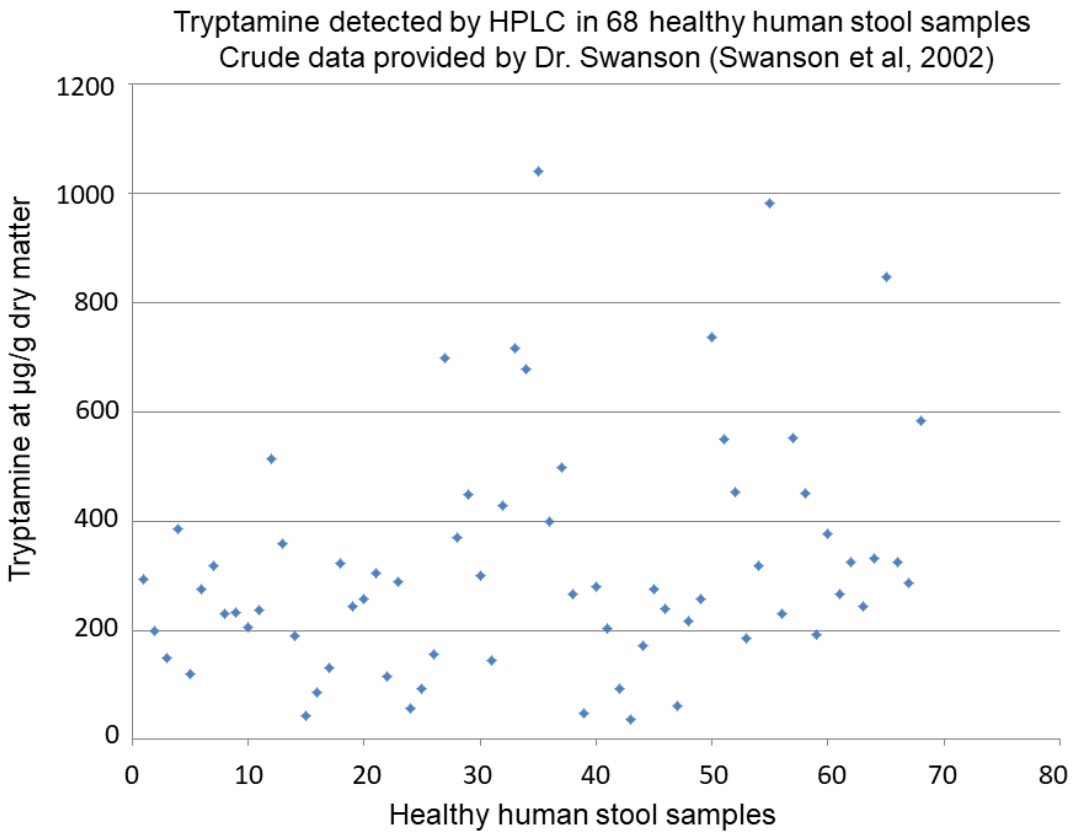
Cellulose, fructooligosaccharides (FOS), or pectin incorporated into the diets at 4% before extrusion. Cellulose is a very lowly fermentable, insoluble fiber. For this reason, it also served as the control. Cats were offered their assigned diet twice daily. Intake, gram/day of dry matter was at 70.3 (cellulose), 68.7 (FOS) and 66.6 (pectin).

Table S4. **Tryptamine and ADAS in Human Groups or Diseases**

Group/Diagnosis	ADAS	Tryptamine, human cases vs controls
C&A	89%-100%	increase, stool [10]
CRC	89%	increase, stool [11]
CKD	n/d	increase, stool [12]
CKD+AC	n/d	decrease, stool [12]
PD	72-75%	increase, urine [13]
Cataract	n/d	increase, cataractous lenses [14]
cirrhotic/HE	n/d	increase, brain tissue [15]
AD	100%	n/d [16]
IBD/IBS	89%	increase, stool [17]
Gastroenteritis (diarrhea), infants		increase, fecal [18]
RAU	n/d	increase, saliva [19]
Formula-fed infants	n/d	increase, fecal [20]
Autism (severe/mild)	n/d	increase, stool [21]
Autism	n/d	increase IAA, urine [22]
CH	n/d	increase, plasma [23]
NAFLD	88%	increase HE, brain [15]

n/d – no data available

Figure S1. Large interindividual variation of tryptamine content (µg/gram of dry matter) in stool samples of 68 healthy humans



HPLC detection and quantification of tryptamine in human stool samples (IL, U.S.A.) was reported earlier along with a mean tryptamine content (mean value 2.00 ± 1.24 µmol/g dry matter) [24]. The unreported crude data on human fecal tryptamine were kindly provided by Drs G.C. Fahey and K.S. Swanson. To the best of my knowledge, these presented data are the only available tryptamine quantification in stool samples of adult humans. In other reported studies, tryptamine was detected but not quantified in stool samples (http://www.hmdb.ca/metabolites/HMDB0000303).

Supplemental file 1: Link of tryptophan (Trp) to ubiquinone (Q)

Density-dependent production of toxic factors regulated by the Pseudomonas quinolone signal (2-heptyl-3-hydroxy-4-quinolone; PQS) has been proposed to be involved in P. aeruginosa virulence. PQS biosynthesis requires conversion of the central metabolite chorismate to anthranilate by anthranilate synthase. This reaction is also the first step in Trp biosynthesis with usage of two functional anthranilate synthases TrpEG and PhnAB of P. aeruginosa [25]. Quinolones are inhibitors of ubiquinone functions in the mitochondrial respiratory chain [26]. The 1H-quinolin-2-one (2(1H)-quinolone) was detectable in six NNI (26%) and five C&A (13.1%) including one $ADAS^+$ individual (23 NNI and 35 C&A). The 2,8-quinolinediol was detectable in 10 NNI (43.47%) and 13 C&A (37.14%) including $ADAS^+$/T2D/obese individual and four individuals with T2D/obesity (BMI ≥ 30). Quinolines are excreted in increased quantities following the administration of Trp. However, the urinary quinoline derivative 2,8-quinolinediol was identified in rats that were fed diets containing corn [27].

The exogenous ubiquinone homologues Q2, Q4, Q6 and Q10 were able to cross the pig heart mitochondrial membrane to interact (to be reduced) with a transmembrane NADH-Q reductase [28]. Furthermore, in beef heart mitochondria, the oxidation of NADH occurs strictly from the matrix side of the membrane [29] The length of the isoprenoid side chain (n) of Q varies depending on the species and ranges from n = 6 in yeast (S. cereuisaie) to n = 10 (humans) [30]. It means that exogenous bacterial E. coli Q8 [31], Protobacteria bacterium Q7 or yeast Q2, Q3, Q5, Q7 [32] can interact with human mitochondrial NADH-Q reductase, which normally, binds its substrate Q10. Respiratory complex I (NADH:ubiquinone oxidoreductase), one of the largest membrane-bound enzymes in mammalian cells, powers ATP synthesis by using the energy from electron transfer from NADH to Q10 to drive protons across the energy-transducing mitochondrial inner membrane. The kinetics of complex I catalysis with Q of varying isoprenoid chain length, from 1 to 10 units were studied. Structural data show the hydrophobic channel for Q10 is interrupted by a highly charged region at isoprenoids 4–7. Q10 has both the highest binding affinity and the fastest binding rate [33]. Coenzyme Q(0), a strong electrophile, is toxic to insulin-producing cells [34] and human breast cancer cells [35]. The Na+-dependent NADH:quinone oxidoreductase of anaerobic Klebsiella pneumoniae interacts with Q1 in micromolar concentrations [36]. A role of the Q tail is not simply the enhancement of the hydrophobicity of the molecule. The molecular recognition of the tail by the Q redox site differs among the respiratory enzymes [37]. Thus, it can be suggested that microbial Q of varying isoprenoid chain length of tail but shorter than 10 can interrupt the activity of human respiratory complex I.

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